The Use of Three-Dimensional Surface Imaging and Assessment of Aesthetics in Breast Cancer Surgery

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MD(res) Thesis

I declare that that the work presented in the thesis is my own

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Abstract

Aesthetic outcome from breast cancer surgery influences long-term psychosocial wellbeing. There is no gold standard measure. An objective measure is required in order to communicate and compare results ultimately to raise standards for patients.

Simulation of aesthetic outcome can cross language and literacy barriers, explaining complex ideas simply which may help to prepare women for their surgery and consequently, by managing expectations translate into better satisfaction long-term.

The over-arching hypothesis was that 3D surface imaging (3D-SI) can be applied to both evaluate and model aesthetic outcome in oncoplastic breast surgery.

An objective aesthetic outcome tool for breast conserving treatment (BCT) was developed using measures from 3D-SI, designed to replace panel assessment and for use in conjunction with patient reported outcome measures (PROMs).

An expert panel scale was constructed using Delphi methodology for the reconstruction population for use in the development of an objective tool. Subscales include volume, symmetry, breast mound position, nipple position and shape in addition to a global scale. It was used to report aesthetic outcomes for the Primary Radiotherapy And Diep flAp reconstruction (PRADA) study.

A simulation model for BCT was designed. A randomised controlled trial demonstrated significantly better preparedness for aesthetic outcome having viewed a simulation pre-operatively compared to 2D photographs or a verbal description.

A low burden online patient recruitment and data collection platform was shown to be feasible, accurate, and acceptable to patients. It is scalable for use within a large multicentre study to develop an objective aesthetic outcome tool and simulation model for the reconstruction population.

3D-SI demonstrates capabilities to provide a robust method to report aesthetic outcome. The role of simulation is encouraging and research into the long-term influence on patient satisfaction is ongoing.

Future research within the reconstruction population and the development of cheaper, portable 3D-SI devices will enable widespread use.

Summary

I have taken two studies from inception to completion (Chapters 4 and 5), one from inception to the primary endpoint with ongoing follow-up expected for five years (Chapter 3) and I have completed the recruitment, data collection and analysis (ethical approval was in place) for a further two projects (Chapters 2 and 6). I have been awarded grants from the Association of Breast Surgery, the University of London, The Royal Marsden Charity and the Biomedical Research Centre. Each project has been presented internationally (with a poster presentation prize at ABS 2019) and each chapter has at least one manuscript for publication (2 published).[1, 2] I have been sponsored by the National Institute for Health Research Biomedical Research Centre, the Royal Marsden NHS Foundation Trust and Institute of Cancer Research.

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Dedications

My supervisor Jennifer Rusby, who continues to encourage, inspire and challenge me. By placing her confidence in me, she has shown me what I am capable of.

Carol Pitches who has taught me what books cannot.

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Abbreviations

2D	Two-dimensional
3D	Three dimensional
3D-SI	Three-dimensional surface imaging
AP	Antero-posterior
BAT	Breast Analysis Tool
BCCT.core	Breast Cancer Treatment Cosmetic result
BCT	Breast Conserving Therapy
BMI	Body mass index
BRC	Biomedical Research Centre
BSI	Breast Symmetry Index
CI	Confidence Interval
CRF	Case Report Form
CT	Computer tomography
DIEP	Deep inferior epigastric perforator
EORTC	European Organisation for the Research and Treatment of Cancer
ER	Oestrogen receptor
ICC	Intra-class correlation coefficient
IMF	Inferior mammary fold
IQR	Inter quartile range
κ	Kappa
LD	Latissimus Dorsi
LMIMF	Lateral to medial mammary fold
MOT	Medical Outcomes Trust
MRI	Magnetic resonance imaging
NH	Nipple height
NICE	National Institute of Clinical Excellence
NMBRA	National Mastectomy and Breast Reconstruction Audit
N-N	Nipple-Nipple
PIS	Patient Information Sheet
PMRT	Post mastectomy radiotherapy
PPI	Public and Patient Involvement
PR	Progesterone receptor
PRADA	Primary Radiotherapy And Diep flAp reconstruction study
PROMs	Patient Reported Outcome Measures
QoL	Quality of Life
REC	Regional Ethics Committee
RMS	Root mean squared
SD	Standard deviation
SN-N	Sternal notch to nipple
TRAM	Transverse rectus abdominis myocutaneous
Wκ	Weighted kappa

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Chapter 1 Introduction

1.1 Background

Breast cancer is a common and emotive diagnosis with 55,122 new cases diagnosed in the UK in 2015.[3] Aesthetic outcome after breast cancer surgery has a well-documented influence on patients' psychosocial wellbeing and quality of life.[4-10] With excellent survival expectations of 96% at one year and 78% at ten years,[11] more women survive to experience the long-term impact of treatments, emphasising the importance of aesthetic outcome as a patient-centred survivorship priority. The acceptance of its worth is reflected in the 2002 NICE guidelines, that all women undergoing mastectomy in the UK should be offered reconstruction.[12] Surgeons and clinical oncologists should now focus on excellent aesthetic outcome in addition to excellent disease control.

The two overarching themes of this thesis are the use of three-dimensional surface imaging (3D-SI) within 1) the *objective evaluation* and 2) the *simulation* of aesthetic outcome of breast cancer surgery.

1.2 Aesthetic evaluation

An association between aesthetic outcome, quality of life and psychosocial well-being has been well described.[4-10] In 2017 Volders et al reported that the negative effects of aesthetic outcome on quality of life can persist for many years.[13] Poor aesthetic outcome, as judged by either patient or expert, is correlated with inferior quality of life scores.[10, 13, 14]

There is no gold standard measure for aesthetic outcome. The intricacies of aesthetic evaluation are subtle and challenging to articulate. The complexities are reflected in the poor agreement between patient, physician, and objective scales.[15-17] Anthropometric assessment, subjective rating scales, and photographic measurements have all been used to evaluate aesthetic outcome from breast surgery, none has been widely accepted and each comes with its own well-described limitations.[18]

Almost two thirds of women with surgically managed breast cancer undergo breast conserving therapy (BCT), with 28,500 breast conserving operations performed annually in the UK. The development of oncoplastic techniques and introduction of neoadjuvant chemotherapy enables a larger proportion of women to consider breast conservation than in the past. BCT is maintenance of symmetry, which may necessitate a contralateral symmetrising operation.[11]

Between 2008 and 2009, 16,485 women underwent mastectomy in England. Of these, 3,389 had immediate breast reconstruction and 1,731 women underwent a delayed reconstruction.[18] A third of patients who are suitable for breast reconstruction take this up.[19] This aesthetic outcome of breast reconstruction is applicable, therefore, to a large number of women.

1.3 Panel assessment

Panel assessment is the most widely accepted technique to measure aesthetic outcome in breast surgery but is far from ideal. Inherent bias, cost, logistical challenges and un-standardised scales render the communication and comparison of results challenging.

A review by Potter et al highlighted multiple inconsistencies between assessment methods including personnel involved (healthcare professionals, patients, both), profession (largely surgeons, some involvement of clinical nurse specialists, occasional lay person representation), method (clinical/photographic), number and type of views (if photographic), number and type of reporting methods (scales and subscales), blinding of observers, and aspects of cosmesis assessed (volume, symmetry, shape etc).[18] Potter et al provide an informative summary of methods in current use. For those involving photographic assessment, 88% reported the use of a panel (median panel size 4), 69% of the panels involved an oncoplastic surgeon, with fewer than half involved assessors being independent of the surgical team (46%). A global scoring system was employed in 53% with a 4 point-scale most commonly used (44%), followed by a 10-point scale (26%). Subscales were used in 43% of photographic assessment, 4-5 subscales were most frequently utilised. The most prevalent global scales were Baker,[20] Kroll,[21] and Harris,[22] and subscale was Lowery.[23] The multiple disparities render meaningful comparison of results impracticable.

The most widely adopted scale for use within BCT is the Harvard Cosmesis Scale, developed by Harris et al in the 1970s.[22] It reports symmetry between breasts using a 4-point Likert scale from 1, poor to 4, excellent (Figure 1).

Harvard Cosmesis Scale	
Excellent (4)	Treated breast nearly identical to untreated breast
Good (3)	Treated breast slightly different from untreated breast
Fair (2)	Treated breast clearly different from untreated breast but not seriously distorted
Poor (1)	Treated breast seriously distorted

Figure 1 Harvard Cosmesis Scale[22]

When an expert international panel used the Harvard Scale to assess a BCT cohort, consensus was reported in only 60% of cases (defined as two thirds of the panellists in agreement). Intra-observer agreement was reported as fair to moderate (κ0.4, wκ 0.57).[24] Even when a panel was selected based upon agreement of their scores with consensus, their individual Harvard score switched category to match consensus a third of the time.[25]

Cardoso et al report improved intra-observer agreement in panel assessment when 4 photographic views were used as compared to one AP view.[25] The reported agreement when comparing panel score using 2 versus 3 dimensional images for panel assessment in a BCT population was fair to moderate (κ = 0.30 and wκ = 0.43), [26] however inter-rater and inter-panel agreement was reported to be lower when 3D-SI are used. This may reflect the additional information presented by 3D-SI representing the finer details of aesthetic outcome, which are understandably, open to further diversities of opinion. Heil et al demonstrated slight to fair inter-rater agreement (MK 0.1-0.3) and moderate to substantial intra-panel agreement (κ 0.4 – 0.5, wκ 0.6-0.7) using the Harvard scale.[27]

In a study by Merie et al, physician and patient reported cosmesis, panel evaluation, and objective measures (BCCT.core) showed poor agreement. The only comparison achieving a greater than 'fair' agreement (κ >0.2) was BCCT.core versus panel which showed moderate agreement (κ 0.57).[15] A cosmetic assessment subgroup from the TARGIT-A trial reports little agreement between cosmetic assessment by doctors, nurses, patients, and objective systems (BCCT.core) over a 5 year follow up. Doctor and patients' score were overall most closely correlated. The variation between raters was reported to be 25%. Doctors followed by nurses, patients, then objective measures (BCCT.core) were reported to score aesthetic outcome most favourably.[28]

A literature review by Maas et al in 2015, reported upon 12 professional aesthetic outcome scales for breast reconstruction.[29] No scale has been widely adopted and each scale assesses different aspects of aesthetics. The most commonly referenced scale in the literature reviewed was Vrieling's, which includes

assessment of scar, size, shape, nipple position, shape of areola, skin colour, and global assessment of the reconstructed breast compared to the other breast. A 4-point Likert scale is used to score each item from 0 (excellent) to 3 (poor). [30]

In the review, each scale identified was assessed by the Scientific Advisory Committee's modified Medical Outcomes Trust (MOT) criteria. This included; conceptual framework formation, reliability and responsiveness, validity, interpretability, burden, and agreement with patient assessment (Figure 2).

Characteristic	Definition	Criteria for scoring
Development of conceptual framework	The scale includes a process that involves qualitative interviews with patients, item generation and preliminary scale formation, and several iterations of redraft based on feedback from patients and surgeons	1 = Patients undergoing post-mastectomy breast reconstruction 0 = Cosmetic augmentation, breast conserving therapy or other
Reliability	The degree to which scores reflect the underlying phenomenon and not measurement error. A reliable measure is also reproducible. The most appropriate statistics to determine test-retest concordance is the intraclass correlation coefficient. A good measure to test the internal consistency is Cronbach's alpha	1 = κ of 0.40–0.75 fair to good agreement and $\kappa > 0.75$ excellent agreement Cronbach $\alpha > 0.71$ 0 = $\kappa < 0.40$ indicates poor agreement Cronbach $\alpha \leq 0.70$
Validity	The degree to which an instrument measures what it is purported to measure. To demonstrate construct validity, research findings need to support the proposed hypothesis	1 = Spearman $\rho > 0.71$ 0 = Spearman $\rho \leq 0.70$
Responsiveness	The ability of an instrument to distinguish clinically important changes from measurement error over time, even if these changes are small	1 = Responsiveness ratio ≥ 1.96 0 = Responsiveness ratio < 1.96
Interpretability	Information on the means and standard deviations (SD) in patient subpopulations and an anchor-based approach that uses an external criterion to operationalize a minimally important change (MIC) are important elements of an interpretable scale	1 = if means or SD in the groups or reference population have been calculated or if MIC have been calculated for the scale 0 = if means or SD in the reference population is unknown, or if MIC is unknown
Burden for professional and patient	This criteria evaluates the overall time burden required for the professional and patient to complete the professional aesthetic assessment scale	1 = Burden low 0 = Burden high
Patient reported outcome	The correlation between the patient and the professional evaluation of the aesthetic result	1 = high positive correlation, >0.71 0 = minimal correlation, ≤0.70

Figure 2 Medical Outcomes Trust (MOT) criteria for the evaluation of panel scales to assess aesthetic outcome from oncoplastic breast surgery. Maass et al[29]

The highest scoring scale by modified MOT criteria was the 10-point professional outcome scale, also known as the Visser scale. This scale was most closely related to patient reported outcomes of aesthetic satisfaction and had demonstrable validity. Despite scoring the highest, a wide range of inter- and intra- observer agreement was reported (0.17-1.0 and 0.06-0.8 respectively).[29] A recent publication by O'Connell et al reported poor inter- observer agreement

of subscales ($w\kappa$0.2) using the 10-point (Visser) scale. Global scales demonstrated better agreement, still only 'moderate' by weighted kappa (0.4).[31]

Maass highlighted deficiencies shared by all of the scales including lack of responsiveness, and interpretability. Both of these features are essential to ensure clinical meaningfulness, in that numerical values can be given qualitative meaning.

'Live assessment' reports more favourable outcomes versus photographic panel evaluation, which highlights the difficulty in separating interaction between clinician and patient from an objective evaluation of aesthetic outcome. In a study by Merie et al, 'live assessment' by clinicians and patients reported a higher proportion of excellent or good aesthetic outcomes than corresponding panel assessment (93%, 94%, and 74% respectively).[15]

1.4 Patient reported outcome measures (PROMs)

Clinicians and patients may place differing values on various aspects of what constitutes a good aesthetic outcome. Potter et al outlined a core outcome set for breast reconstruction based on Delphi methodology in which 'patient satisfaction with cosmetic outcome' was rated highly amongst medical professionals and patients alike.[32] The opinion of the patient is the most important, but may lack objectivity secondary to influences from treatment experience, healthcare providers, or oncological outcome.[33] Indeed, patient reported satisfaction with outcome is only moderately related to self-reported cosmesis score ($w\kappa$ 0.54).[34] PROMs are consistently reported to be discordant from professional opinion regarding aesthetic outcome,[31, 34-36] the former frequently being more favourable.[15, 37, 38] Although PROMs are one of the most clinically important markers of outcome, they do not preclude the need for an objective aesthetic outcome tool and the two should co-exist.

A review of patient reported outcomes by Pusic et al in 2006, called for a valid, reliable, and responsive instrument to thoroughly assess the influence of breast cancer surgery on psychological wellbeing.[39] Her group at the Memorial Sloan Kettering Cancer Centre developed a tool which is increasing in popularity for use in oncoplastic breast surgery: the BREAST-Q.[39, 40] Overlapping

questionnaires have been validated for BCT, simple mastectomy, reduction and breast reconstruction. Each questionnaire is separated into two overarching themes: 1) patient satisfaction and 2) health related quality of life and each theme into domains. Each domain has a variable number of questions to be scored using a Likert scale. The patient responses are converted to provide a total score (out of 100) for each scale, a Q-score. The BREAST-Q can be used in its entirety or an investigator can select different scales relevant to a specific area of interest [Appendix 1 and 2].

The most recent BREAST-Q module is for BCT. Two studies have recently been published with similar findings. O'Connell et al report on a series of 200 women 1-6 years after BCT with a median Q-score for 'satisfaction with breasts' of 68, and 82 for psychosocial wellbeing.[35] Dahlbäck et al corroborate these findings in a series of over 300 women with a median 'satisfaction with breasts' Q-score of 66 after BCT, and psychosocial wellbeing Q-score of 82.[41] Longitudinal studies of PROMs are lacking and will help inform us of how satisfaction and quality of life change with time.

O'Connell et al looked at the association between clinicopathological features and patient satisfaction using the BREAST-Q, concluding that high BMI, delayed wound healing, and axillary surgery have an influence on patient reported satisfaction with breasts in a BCT population, further highlighting potential confounding elements for patient reported satisfaction.[35]

Over one third of patients having surgery for breast cancer undergo mastectomy.[42] Heterogeneity between reported measures of patient satisfaction creates difficulty in understanding the impact of reconstruction on psychosocial wellbeing. Existing literature reports that 93% of women are satisfied with aesthetic outcome from reconstruction clothed but only 59% with their appearance unclothed.[19] More women with a reconstruction report social confidence than patients without (mastectomy alone), 92% versus 85%, and more women feel emotionally healthy most of the time, 88% versus 75%. [19] Techniques that spare the skin envelope, with or without sparing the nipple-areola complex, have a higher reported level of patient satisfaction than total mastectomy.[14] Conversely, Reaby et al reported a more positive body image for

women with simple mastectomy than women in the general population, illustrating the complexities that surround the psychology of aesthetics.[8]

Body image is a complex psychological state. An excellent reconstruction, as judged by expert opinion, may not be reflected in patient satisfaction and similarly patient satisfaction may not respond as expected to cosmetic adjustments to the reconstruction. This strengthens the need to measure patient satisfaction as well as an independent evaluation of aesthetic outcome, and to ensure that both are reported in parallel.

1.5 The need for an objective measure of aesthetic outcome

The core outcome set developed by Potter et al includes 'women's satisfaction with outcome', but although an objective evaluation of aesthetic outcome was ranked highly by patients and professionals alike, it was excluded from the Delphi consensus process after the second round and was not included in the core outcome set.[32] The patients view of aesthetic outcome is clearly important and should be included in the outcome analysis for oncoplastic breast surgery, however, it is open to influence from many external factors such as relationship with the clinical team,[33] how the patient feels others view her, how she feels about her own reconstruction, body mass index, surgical complications,[35] type of axillary surgery and her position along the reconstructive pathway.[33] In a study by Dikmans et al participants report taking into consideration nipple sensation, breast pain, hypersensitivity, numbness, rigidity and breast movement into consideration when asked to evaluate the cosmetic outcome of their reconstruction.[43] PROMs are consistently reported to be discordant from expert opinion, [31, 34-36] often reported more favourably, [15, 37, 38] and have been demonstrated to have poor correlation with objective measures (r=0.18, -0.2).[44] These factors combined highlight that PROMs are not robust enough to compare technical elements of surgical innovation, benchmark performance or for quality assurance. For example, a women who has an excellent relationship with her surgeon who is skilled at managing patient expectations may report an excellent aesthetic outcome in the absence of such, and conversely, a poor relationship with the clinical team may reflect badly in the patient reported aesthetic outcome, where in fact it is technically good. McCulloch et al describe three elements to

outcome reporting as part of the IDEAL framework which includes surgical, patient report outcome, and technical outcome.[45] Aesthetic outcome should be included in both technical (objective evaluation) and patient reported outcome (PROMs) with important yet different elements addressed by each.

1.6 Assessing reliability and validity of measurement instruments

The quality of measurement instruments falls largely into two domains, reliability and validity. Reliability details how consistently a test performs in time and space. The validity of a test informs the user of its property to measure what it sets out to. The two domains can be further separated into many sub-sections. In relation to an objective aesthetic evaluation tool the most relevant subdomains for reliability include stability (test-retest, intra-observer variability), internal consistency (do all of the components measure the same construct), and equivalence (inter-observer variability).[46-48] The most relevant subdomains for validity include content (degree to which a test contains all the necessary items), concurrent (can be evaluated simultaneous to the gold standard) and construct (agreement with gold standard).[49, 50] Each domain should be considered when designing a tool and reported upon in order to aid selection of valid and reliable methods for quality assurance.

1.7 Objective measures

Attempts have been made to objectively evaluate the aesthetic outcome of breast surgery, however, each method has limitations.[51-52]

Traditionally measures of breast volume have involved direct measures which are time consuming, assessor-dependent, and can be awkward for patients. The Archimedes principle of water displacement has been directly applied to measuring breast volume by submerging the breast into a flask of water and measuring the rise.[51] Grossman-Roudner disks involves placing the breast into different sized adjustable disks that transform into cones with volume measures along one edge to estimate volume.[53]

Thermoplastic casting is a method where heat sensitive plastic is used to create a cast over the breast which is subsequently filled with water to measure volume,

depending on the material used, some disks reach 55°C which is uncomfortable for the patient.[54] Anthropometric measures can be used to calculate volume using a formula suggested by Qioa et al:

$$\text{breast volume} = \pi/3 \times MP^2 \times (MR + LR + IR - MP)$$

where MP; mammary projection, MR; medial breast radius, LR; lateral breast radius, IR; inferior breast radius.

Mammographic volume estimates have also been used in the past by measuring the breast width (W), breast height (H), and compression thickness in craniocaudal view (C) and substituting them into the equation reported by Kalbhen et al:[52]

$$\text{breast volume} = \pi/4 \times (W \times H \times C)$$

where W; width, H; height, C; cc compression thickness

A systematic review summarised and compared the level of accuracy between the different methods for volume assessment, but it is beyond the scope of this thesis.[55]

1.7.1 Breast Retraction Assessment (BRA)

Breast Retraction Assessment (BRA) was developed by Pezner in the 1980s to measure post-BCT changes to the breast.[56] The patient stands behind a clear acrylic sheet with a 1cm square grid, aligned to the Y-axis (bisecting the torso). The co-ordinates of both nipples are documented using X and Y values and using Pythagorean theorem, the BRA is calculated:

$$BRA = (XR-XL)^2 + (YR-YL)^2$$

Pezner's technique was an important start in the search for an objective method of assessment, however, it only considered 2 dimensional measures from a single view. Van Limbergen used a similar technique but added further measurements including lower breast contour and upward nipple retraction. These techniques were both time-consuming and did not take into consideration the breast as a whole, or account for volume differences.[57] A further progression included an attempt to combine objective and subjective rating to give an overall score, as described initially by Noguchi et al, who used Moire's topography combined with subjective panel assessment to provide a score.[58] This was an improvement over BRA, as it considered the entire breast.

1.7.2 Breast Cancer Conservative Treatment. cosmetic results (BCCT.core) software

BCCT.core uses manually placed landmarks on digital 2-dimensional photographs to calculate measures used to score overall aesthetic outcome from BCT (Figure 3). It considers asymmetry, scar, and colour differences between operated and non-operated breasts. BCCT.core is the most frequently referenced objective measure for BCT in the literature which may reflect its simplicity, low burden, and low requirements for specialised equipment.[59] It is reported to have excellent intra-observer variability (ICC 0.93), which is unsurprising as this reflects simple positioning of landmarks on a single AP view of a digitised 2D photograph, therefore, small margins of error are to be expected.[60]

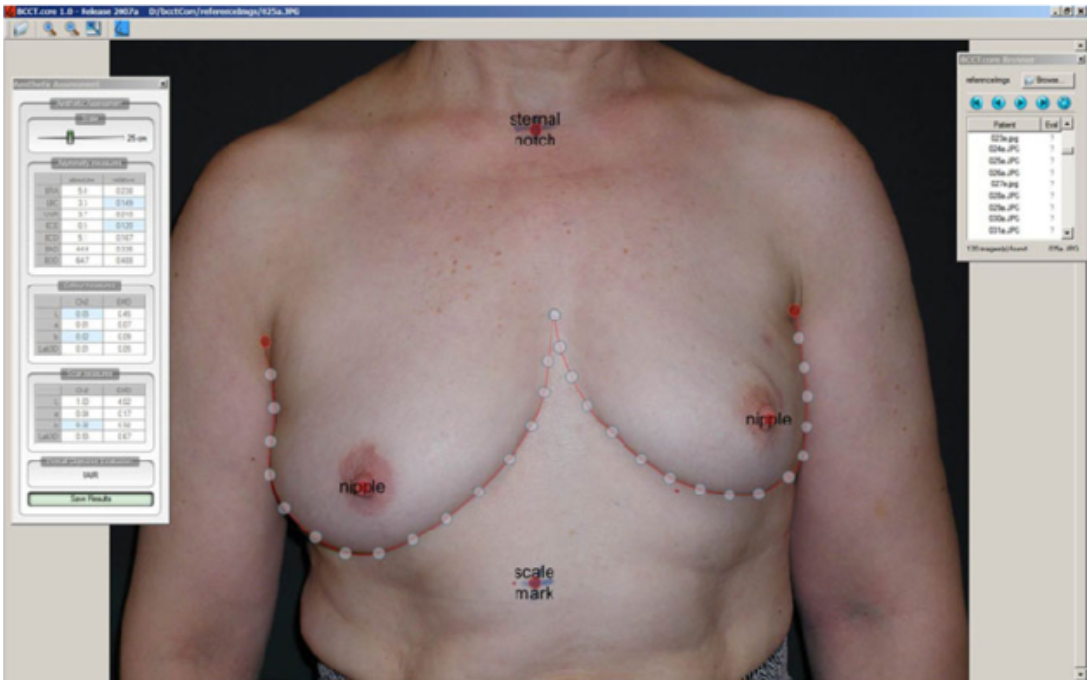

Figure 3 A screen shot from the BCCT.core software. Cardoso et al 2012[61]

The reported correlation between subjective aesthetic assessment (panel) and BCCT.core is variable in the literature (wκ 0.24 – 0.69). [15, 24, 27, 62, 63] The strongest association was reported by Lagendijk et al, who compared the scores from the panel assessment created by Cardoso et al with BCCT.core (ICC 0.69).[60] Panel was reported to score consistently higher than BCCT.core.[60]

PROMs have variable correlation with the BCCT.core score. EORTC QLQ-C30 and QLQ-BR23 have no reported association with BCCT.core.[13] However Lagendijk et al found a significant, albeit weak correlation between BCCT.core score and BREAST-Q *'satisfaction with breasts'* domain (r=0.178, p=0.01).[60]

The limitations of the BCCT.core is that only one view is assessed, therefore the breast is represented as a 2-dimensional object which may oversimplify aesthetic assessment. The developers published a comparison between four views versus one, concluding that there is no advantage.[25] Recently the developers included a three-dimensional element to the BCCT.core (BCCT.core3d) using Microsoft Kinect software. Agreement between panel assessment and BCCT.core for the original 2-dimensional software and the 3-dimensional model was performed. They reported no significant difference in

agreement between 2D or 3D panel, with either BCCT.core(2d) or BCCT.core3d and almost perfect agreement between BCCT.core and BCCT.core3d scores (κ = 0.85 and wκ 0.89) concluding that the addition of 3-dimensions to the assessment was an unnecessary complexity.[26]

1.7.3 Breast Analysing Tool (BAT) - Breast Symmetry Index (BSI)

The concept of the BSI was to provide objective analysis of breast symmetry using 2-dimensional photography, independent of image illumination, and user expertise. The system is based on the user placing landmarks including breast borders and nipple position on a 2D image. The automated model then measures and compares distances between points from one side to the other using the BAT software. This model can analyse symmetry of breast circumference, nipple position, area, and scars, however, is based on only 2-dimensions, therefore, volume, surface symmetry, and projection are omitted.

BAT is reported to have excellent inter-rater reliability (ICC 0.988).[64] The authors attribute this to the inclusion of lateral images in addition to the AP view. It is reported to have strong positive correlation with subjective assessment using the Harvard Scale, ($r=0.834$ $p< 0.01$) which is expected considering both measure symmetry and it is the scale on which the tool was modelled.[65]

BAT reports asymmetry only, while BCCT.core considers scar and skin colour. Despite being less accurate in low-lighting conditions, BCCT.core was reported to have better association with panel assessment than BAT.[63]

There has been some success with regard to measuring aesthetic outcome using 2-dimensional imaging including BCCT.core and BSI.[24, 64, 66, 67] Both reported excellent inter-rater agreement, but variable agreement with panel assessment (BSI wκ0.41- 0.5, BCCT.core wκ0.43-0.71). [63, 68] Both compare breast symmetry but do not record differences in volume, surface symmetry and projection and are therefore unable to assess the breast in three dimensions.

1.8 3-Dimensional surface imaging systems

Three-dimensional imaging has been in existence since the 1940s, with examples including Moire topography, liquid crystal scanning, laser scanning, and digital subtraction techniques. Within the past couple of decades, the development of more accurate and reproducible images and systems with faster capture and processing speeds has enabled 3D-SI technology to be applied in clinical practice. Tzou et al (2014), reviewed hardware and software products of 5 companies to highlight the clinical pros and cons of each,[69] things have progressed further since that article was published.

In general terms 3D-SI systems work from two main principles, structured light and stereophotogrammetry. Structured light method works on the principle of predicting the 3D surface of a structure by measuring the deformation of a projected pattern using a calibrated camera.[70] Examples of this technology include the EVA scanner (Artec 3D, Luxemburg) and the Sensor 3D (Occipital Inc., Boulder, CO, USA). Stereophotogrammetry uses 3 methods; active, passive, and hybrid. Active stereophotogrammetry works on the principle of structured light by projecting a pattern onto the surface, then captures the deformation using 2 or more cameras at differing angles. A 3D image is created by triangulation. An example of this type of system is the 3dMD TMS system (3dMD, Atlanta, USA). Passive stereophotogrammetry compares images from two or more cameras without the use of a projected pattern. The absence of a pattern renders identification of corresponding points more ambiguous. An example of this type of system is the VECTRA® XT (Canfield Scientific Inc., Fairfield, NJ, USA). Hybrid stereophotogrammetry combines both methods in order to produce the most accurate 3D-SI.[69]

1.9 VECTRA® XT

The VECTRA® XT 3D imaging system by Canfield (Canfield Scientific Inc., Fairfield, NJ, USA) is a 3D photographic image capture system. Based on passive stereophotogrammetry it uses skin texture to compute geometry and produce a 3D-SI. Six mounted cameras take simultaneous images, which are then integrated into a 3D image viewable on a workstation. VECTRA® XT is the available 3D surface imaging technology at the Royal Marsden. It has

demonstrable ability in pre-operative planning,[71, 72] evaluation of outcome,[73-75] and the simulation of aesthetic surgery. 3D measures including volume and symmetry have been validated in vivo using VECTRA[76, 77] and it is held as a gold standard by which other systems have been measured.[78, 79] The VECTRA XT is easy to use, has a fast capture speed (3.5ms) and processing speed (80 seconds) and does not require an experienced photographer (Figure 4).

Figure 4 VECTRA® XT 3D imaging system by Canfield (Canfield Scientific Inc., Fairfield, NJ, USA). Reproduced with permission from Canfield Scientific

1.10 3D over 2D objective evaluation

3-Dimensional Surface Imaging (3D-SI) has the potential to overcome the limitations of the alternative methods for evaluating aesthetics. It does not require a medical photographer and is more convenient for the patient with one capture providing all the necessary views including the cranial and caudal views which help visualise projection and the infra-mammary fold (IMF). It delivers linear mammometrics in addition to calculating volume and surface symmetry (Figure 5) which is not deliverable using 2D imaging systems. A study by Volders et al looking at BCCT.core, panel evaluation and PROMs reported BCCT.core to be insensitive to changes over time compared with the other two methods.[13] This may be secondary to its over-simplified 2D ranking of aesthetic outcome, and evaluation of the breast in three dimensions may prove to be more sensitive to changes over time.

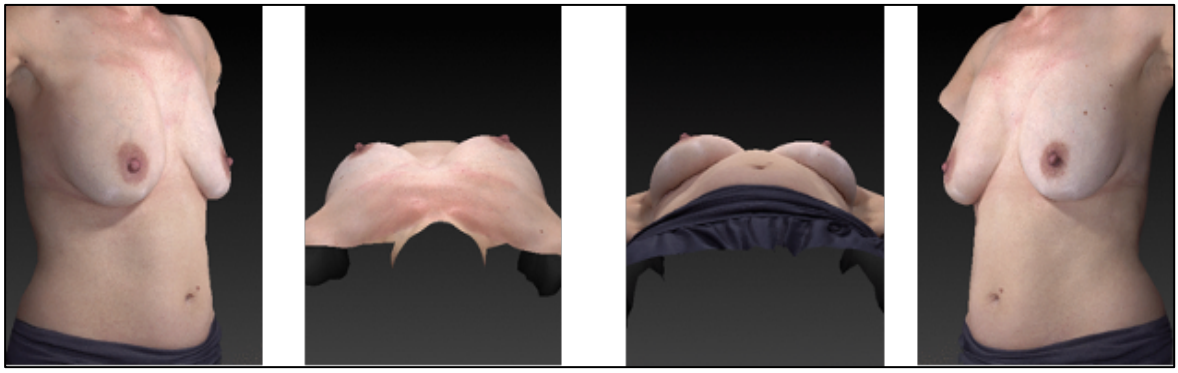

Figure 5 3D-SI views using Mirror™ software and Vectra XT ®. Left to right; right oblique, cranial or projection view (cleavage), caudal (infra mammary fold), left oblique

In 2006, Tepper et al highlighted potential applications of 3D-SI technology within breast surgery (aesthetic and reconstructive) including pre-operative planning (measuring existing asymmetry, implant selection, volume calculations, and volume distribution analysis), post-operative evaluation, monitoring and quantifying complications (oedema), comparing techniques, and examining changes over time.[80] The majority of these topics have subsequently been investigated and published upon.

Natural breast asymmetry exists and the ability to quantify it objectively may assist surgical planning and aid the evaluation of outcome.[81] 3D-SI has been used to objectively assess symmetry in the natural breast.[82] Additional considerations highlighted by Wang et al include statistically significant changes in breast volume (quantified with 3D-SI) between the pre-and post-ovulatory phase of the menstrual cycle.[83] In addition the same group reported significant differences in 3D-SI derived linear measures in inspiration compared to expiration, however, they could not find significant differences in volume calculations throughout the respiratory cycle.[84] This highlights the importance of using a standardised photography protocol to minimise error.

1.11 3D-SI in BCT

In 2008, Moyer et al used 3D-SI to analyse symmetry after breast conserving surgery, and described the relationship of symmetry to amount of tissue resected rather than patients' age at time of operation, tumour size, location, or need for re-operation. [85] However, the study was small including only 23 surgical patients. A further study used 3D-SI as one part of a combined assessment tool to compare BCT for two different ethnic groups. [86]

O'Connell et al presented a case for the use of 3D-SI for objective aesthetic evaluation. In their study of 200 BCT patients, objective measures for volume and shape symmetry were strongly associated with panel assessment (Harvard scale, p=0.028 and p= <0.001 respectively). Correlation was observed between the BREAST-Q satisfaction with breasts domain and both volume and shape symmetry, albeit weak (r= 0.187, p=0.008 and r=0.229 p=0.001 respectively).[87]

1.12 3D-SI in breast reconstruction

1.12.1 Volume considerations

Ma et al used pre-operative 3D-SI derived volume measurements (VECTRA® XT) to guide expansion volumes in two stage implant based breast reconstruction.[71] They reported a strong correlation between the volumes of the final implant and the contra-lateral breast (r=0.997, p<0.001). A mean post-operative volume asymmetry of 5% (compared to 10% pre-operative asymmetry) was reported and they concluded that 3D-SI is a useful adjunct in

guiding expansion volumes. The population in this study had an average age of 37, BMI of 21, and minimal ptosis so their conclusions may not be extrapolatable to the general population.

1.12.2 Outcome evaluation

Cohen et al described the use of 3D-SI in the comparison of aesthetic outcome between autologous and implant based unilateral reconstruction using VECTRA®.[88] For the implant group an average difference in breast volume of 27.1+/-22.2cc (p=0.48) and a difference in projection of 0.8+/- 0.3mm is reported between breasts (p=0.87) with the reconstructed breast being on average larger and more projected. The autologous group had an average volume difference of 29.5+/- 24.7cc (p=0.55) and a difference in projection of 4.4+/-1.2mm (p=0.28) with the reconstructed breast being on average larger and less projected. They concluded that both methods produce satisfactory volume, projection symmetry compared to the contralateral un-operated breast albeit larger volumes for both compared to the un-operated breasts, which did not reach statistical significance.

Koban et al described the use of 3D-SI to evaluate the relative change in nipple-areola complex dimensions following mastectomy and liposuction for gynaecomastia between two techniques. They deemed 3D-SI a useful tool for evaluating the nipple, however, less so for volume calculations. Pre-operative 3D-SI derived volume measurements were significantly different to intra-operative mastectomy and liposuction volumes,[74] which may have been due to difficulty calculating male breast volumes using 3D-SI, measuring liposuction volumes or liposuction extending beyond the breast footprint skewing results. Tremp et al also report 3D-SI to be useful in the evaluation of the post-operative nipple-areola complex in terms of volume, projection, and diameter of nipple reconstructions over time.[89]

Kasielska-Trojan et al used 3D-SI derived volumes to aid implant selection in a case series of 7 patients undergoing corrective surgery for Poland syndrome. They also used 3D-SI in the post-operative evaluation of volume symmetry and NAC position and compared the objective measures to patient reported

satisfaction. They concluded that patients were able to detect volume asymmetry at a volume difference of 40-50cc, and NAC asymmetry when there was a >2cm deviation of nipple position between sides.[90] Despite the small numbers, this study highlights a potential further area of study in the use of 3D-SI derived measures to better understand patient reported aesthetic outcomes.

Killars et al compared pre-operative 3D-SI derived breast volumes and final implant volumes for single- and 2-stage implant-based reconstruction. 61 reconstructions were analysed, 28 single-stage and 33 two-stage, around half were risk reducing operations and none of the participants underwent radiotherapy. They concluded that the single-stage approach results in an implant volume of equal size to the pre-operative calculated volume, whereas a 2-stage approach resulted, on average, in a larger implant volume.[91] Patient satisfaction was not significantly different between the two approaches.

Tsay et al also used 3D-SI to compare the outcome of different operative techniques. They compared implant-based breast reconstruction with and without the use of acellular dermal matrix in terms of volume distribution, lower-pole distance, and projection 1-3 months and 6-9 months post-surgery. Patients choosing immediate reconstruction consented to the use of ADM and those choosing tissue expander reconstruction consented to the use of ADM at the discretion of the operating surgeon (if the inferior border of pectoralis major was >2cm from the IMF, ADM was used). In the absence of ADM, submuscular implant placement was performed with routine elevation of serratus to ensure implant coverage. They reported a significant difference in volume distribution between groups in the early but not late follow-up, and a significant difference in projection (distance from the point of maximum projection to the chest wall on the X axis) and lower pole curvature (measured from the point of maximum projection to the IMF in the Y axis) between groups overtime (with the ADM group having more projection and higher lower pole curvature).[75] This information could be used for both operative planning and in pre-operative counselling to aid shared decision making and expectation management.

1.12.3 Quantifying how the breast changes over time

Breast morphology changes naturally over time with influencing factors such as pregnancy, lactation, breast feeding, gravity, and tissue quality. Post-surgical or radiotherapy changes are superimposed on these. 3D-SI has been utilised to map this process over a relatively short period of time post-operatively after augmentation and breast reduction with respect to IMF height, nipple-to-sternal notch (N-SN) distance, nipple-to-IMF distance, and volume loss. [86, 92-94] For example, Munhoz et al employed 3D-SI to quantify changes in lower pole stretch over time following augment mastopexy in patients with pre-operative grade II-III ptosis.[95]

Better understanding of how both the operated and non-operated breasts change over time may prove beneficial in the pre-operative phase (patient counselling), intra-operative planning (adjusting for 'breast settling' or expected radiotherapy induced change), timing of symmetrisation surgery depending on when the operated breast has reached a 'steady state', and outcome evaluation (benchmarking at specified time-intervals). There has been no validation to date of the accuracy of VECTRA in measuring changes over time.

1.12.4 Validation

Steen et al compared anthropometric measures (their gold standard) to the linear measures derived from VECTRA® XT for 28 women who were being assessed for breast augmentation. The population had an average age of 23, an average BMI of 20 with A-B cup breasts and were nulliparous. The reported ranges for anthropometric and VECTRA measures were similar for all distances. Nipple to sternal notch and nipple to midline were the most accurate with a mean error of 0.05cm (SD 0.65) and 0.2cm (SD 0.02) respectively. Base width and Nipple- to IMF distance were less accurate with a mean error of 1.26cm and 1.22cm respectively.[77] This may be due to ill-defined borders on the 3D-SI, but in addition, the nipple to IMF anthropometric measure is dynamic i.e. the breast can be manipulated, whereas, on a 3D-SI the true IMF may be hidden by ptotic breast tissue creating a margin of error. The population in this study are likely to have had less ptosis than an older, breast cancer population. The nipple to

IMF distance is important when considering pre-operative planning as it may influence pocket and implant size and impact volume distribution if over or underestimated.

Methods for measuring breast volume and symmetry using VECTRA® XT have recently been validated in vivo and in vitro by O'Connell et al.[76] They reported a mean relative difference between observers of 0.43 mm (range 3.5 to 15.5 mm) for symmetry, and 5.78% for volume difference in vivo. Eder et al found symmetry assessment using 3D-SI observer independent and significantly more accurate than BCCT.core in a breast reconstruction population.[96]

Chen et al used the EVA hand-held scanner (Artec 3D, Luxemburg) to compare volume measurements with MRI and mastectomy specimens (using the water displacement method) for 20 mastectomies (19 women). They described excellent correlation between MRI and 3D-SI volume measures compared with the mastectomy volume ($r = 0.925$, $r = 0.915$ respectively) with both MRI and 3D-SI overestimating volume.[97] Howes et al compared 3D-SI and MRI derived volumes for women undergoing external expansion and fat grafting following BCT or Mastectomy using the Cyberware 3D laser scanner with Cyslice Software (Headus, Australia). On analysis of 72 scans they found no significant difference between MRI and 3D-SI volume measures ($p=0.35$), very good correlation ($r = 0.889$) and no proportional bias (Bland Altman analysis).[98]

Utsunomiya et al compared 3D-SI derived volume measures (Microsoft Kinect Scanner, Kinect V1, Microsoft corporation, Washington, USA), mastectomy specimen volume (using the water displacement method), and final implant volume for 48 women undergoing two-stage implant based breast reconstruction.[99] A strong correlation was reported between the three measures (0.81-0.91, $p<0.01$). They derived a formula to aid in the calculation of final fill volume using pre-operative 3D-SI volume measurements.

Oranges et al validated a cheaper hand-held system (Sensor 3D scanner, Occipital Inc., Boulder, CO, USA) against the VECTRA® M5 (Canfield, NJ, USA) and the EVA 3D scanner (Artec, Luxemburg) concluding acceptable accuracy for linear measures.[78] They did not validated volume or surface symmetry and

they used a plastic torso rather than human participants which negates the challenges such as ptosis, body habitus, and ill-defined breast borders.

Koban et al compared the capabilities of a cheaper, hand-held, consumer device (3D Sense ™) with the VECTRA® XT medical imaging device in vivo concluding high correlation (r = 0.994) and agreement between the two devices both in terms of linear measures, volume (-5.11 ± 32.10 mL), and surface symmetry calculations (1.62 ± 0.8mm rms). Mirror software ™ (Canfield, USA) was used for the analysis of all images.[79]

1.13 Simulation

3D simulation provides a visual experience for patients and a personalised approach to their care. It is a way of communicating complex ideas simply, crossing language and literacy barriers, reducing the patient perception to expectation gap and improving communication in the pre-operative planning stage of surgery. Although used fairly routinely in the aesthetic industry, there is a paucity of literature on the use of simulation using 3D-SI within breast cancer surgery.

In the cosmetic surgery industry, particularly within breast and facial surgery, simulation is widely used to facilitate patient decision-making.[100, 101] In a recent survey of members of the American Academy of Facial Plastic and Reconstructive Surgery, 63% of surgeons already use simulation as part of their rhinoplasty consultation.[102] Patients appreciate the use of simulation in the pre-operative decision making consultation for aesthetic surgery with a reported 70% of patients undergoing rhinoplasty stating they would decline surgery in its absence.[103] Patients also report a higher satisfaction with 3D simulation over 2D simulation for rhinoplasty.[104] Persing et al used panel evaluation to examine the accuracy of 3D rhinoplasty simulation using VECTRA and deemed actual aesthetic results to be superior to simulation.[103] The group also conclude that experienced surgeons are necessary to translate the simulation into an achievable plan. Markey et al at MD Anderson have completed extensive work looking at the use of 3D-surface imaging to simulate facial disfigurement in cancer patients. Their model included the manual annotation of 61 fucidal points for analysis. They categorised facial disfigurement into 13 groups and were able

to model the patterns onto 3D-SIs of healthy subjects to simulate post-operative appearance. The group are using their simulations to study human perception of disfigurement rather than for pre-operative preparation for surgery or as a decision-making tool.[105]

Simulation has been reported to be highly reproducible for breast augmentation, [106-108] and a useful tool for implant selection.[81, 109-111] Patients have found pre-operative simulation for breast augmentation helpful and reported satisfaction with their pre-operative decisions.[110] It has been shown to be useful for measuring the anticipated volume changes in aesthetic surgery. [81, 106, 112]

Derunz et al, used Crisalix (Switzerland) to simulate breast augmentation for 38 women. After surgery, 66% of the women absolutely agreed that the simulation represented their actual outcome and 24% partially agreed. 93% felt the simulation helped them chose their implant size, and 97% found the simulation useful. Vorstenbosch et al also used Crisalix to simulate breast augmentation and asked an expert panel to comment upon its accuracy compared to post-operative 3D-SI. The results highlighted baseline breast type as an influencing factor for simulation success.[108] The simulation was deemed to predict overly optimistic results for women with ptotic breasts, and the opposite for women with tuberous breasts. The most accurate simulations were for women with symmetrical breasts at baseline.[108]

3D-SI has been used to create 3D-printable moulds for intra-operative use to aid autologous flap size, shape and orientation.[72, 97, 113] Tomita et al describe the use of a 3D-printable mould for 8 women undergoing a 2-stage unilateral autologous reconstruction with symmetrising mastopexy.[113] The 3D-mould was created of the mirrored contralateral breast 6 months after the first stage (mastectomy and tissue expander with contralateral mastopexy) which was then used as a guide intra-operatively for volume and shape of DIEP flap. They reported ‘excellent’ or ‘good’ aesthetic outcome (evaluation by two health care professionals on a 4-point Harvard scale)[22] for all women at a mean follow up of 14.6 months (range 6-27 months). They highlighted potential advantages of this technique for trainees and less experienced surgeons although conceded to the disadvantages of an additional operation.

Chen et al reported the use of a 3D-mould for single-stage immediate unilateral reconstruction,[97] and Chae et al described a positive experience using a 3D-mould to guide projection for delayed unilateral DIEP reconstruction using the St Andrews coning technique, highlighting the role of a printable mould to estimate flap volumes in pre-operative planning potentially reducing operating times.[114] It is difficult to draw conclusion as to whether printable moulds offer any advantage over and above a competent surgeon, and indeed if there were a discrepancy between the experienced surgeon and the 3D printable mould, which outcome is 'correct'.

Some groups have looked at complex modelling of the outcome of BCT using biomechanics and wound healing models based on MRI imaging, but these methods involve complex mathematics, are time consuming, expensive, and not yet at a stage to be used in a clinical setting.[115-117]

In many breast units, the standard pre-operative preparation for a woman undergoing BCT includes a verbal description of likely aesthetic changes. Often women undergoing breast reconstruction are shown photographs of other women who have had similar operations. The patient steering committee developed to guide studies within 3D-SI at the Royal Marsden have explained that looking at other women's post-operative photographs did not always give them a sense of how *they* would look, and some reported that it felt inappropriate and awkward. The concept of using simulation as part of a pre-operative discussion within breast cancer surgery was generated by our patient steering group as a desirable area of study. They felt that a visual aid to the surgeons' description would have helped to prepare them for the surgical outcome. Many women who had undergone BCT commented that their actual outcome was far superior to the imagery created during the pre-operative consultation where many influencing factors including a recent cancer diagnosis, anxiety and fear influenced how they perceived and processed verbal information.

1.14 Shared decision-making

Shared decision-making has been a focus of NHS England since 2013 when it took over the Shared Decision-Making Programme from the Quality, Innovation, Productivity and Prevention (QIPP) Right Care Programme. [118] NHS England defines SDM as;

'a process in which patients, when they reach a crossroads in their health care, can review all the treatment options available to them and participate actively with their health care professional in making that decision'.

SDM is considered a standard of care in breast cancer. Literature focussing on patients' experience of SDM within breast cancer treatment has described reduced levels of stress, improved knowledge, and a preferred personalised decision-making approach. [119, 120]

3D simulation of outcome could add value as a tool to improve patient preparedness for breast cancer surgery, manage expectations, and ultimately enrich the patient pathway by engendering a shared decision-making approach.

1.15 Gap analysis

The use of 3D-SI for the objective evaluation of aesthetic outcome has not been described within breast cancer surgery. Isolated measures derived from 3D-SI have been used to assess surgical outcome such as volume symmetry and projection for breast reconstruction, but no comprehensive tool has been developed and compared to the current gold standard of panel evaluation.

The Harvard scale for aesthetic evaluation is widely accepted for panel evaluation within BCT, where the maintenance of symmetry is the overarching goal. The same is not true for the reconstruction population, where many scales are referenced in the literature, all with common deficiencies. A contemporary, agreed scale for breast reconstruction is required prior to the development on

an objective aesthetic outcome tool for this population in order to have a gold standard upon which to base it.

The use of 3D-SI pre-operative simulation as a decision-making tool is described for aesthetic breast and facial surgery. Its use within breast cancer surgery pertains to the use of 3D printable moulds in operative planning to guide reconstruction, however, it has not been used as an adjunct to pre-operative discussion as preparation for aesthetic results from surgery or as a decision-making tool. Simulation using 3D-SI has been investigated within head and neck oncology and facial disfigurement simulation, however, has been used to investigate human perception of facial disfigurement rather than pre-operative preparation for aesthetic outcome. The accuracy of the simulations used within breast surgery is largely reported by panel evaluation or PROMs but there has been no publications on the comparison of simulated images with reality over time using objective measures derived from 3D-SI.

BCT is a simpler population to study with regards to aesthetic evaluation and simulation of aesthetic outcome given the more straightforward aesthetic goal of maintaining symmetry compared to the broad and complex aesthetic goals that are possible with reconstructive surgery i.e. volume symmetry, shape symmetry and dynamic shape symmetry, autologous versus implant reconstruction, and unilateral versus bilateral reconstruction. Prior to the development of an objective outcome tool or a simulation method in the reconstruction population, proof of principle is required, and the BCT population is the most logical starting point.

Hypotheses, Aims, and Objectives.

The over-arching hypothesis is that 3D-SI can be applied to both evaluate and model aesthetic outcome in oncoplastic breast surgery.

1.16 Project 1

Hypothesis

3-Dimensional Surface Imaging (3D-SI) can be used to objectively evaluate aesthetic outcome after Breast Conserving Therapy (BCT).

Aims

1. To develop an objective aesthetic outcome tool for BCT using measures derived from 3D-SI.

2. To validate the objective aesthetic outcome tool in a subsequent BCT cohort.

Objectives

1. To use multivariate analysis to identify objective 3D-SI measures that can jointly predict Harvard Panel score to build a tool to measure aesthetic outcome

2. To determine the reliability of the panel assessment.

3. To investigate the strength of association between the observed and predicted panel score.

4. To establish the agreement between the observed and predicted panel score.

5. To validate the model in a separately recruited cohort.

1.17 Project 2

Hypothesis

Simulation of aesthetic outcome using 3D-SI can improve patient preparedness for their aesthetic outcome after surgery and may influence their satisfaction by managing expectations.

Aims

1. To assess, in a randomised controlled trial, the value of 3D-SI in the simulation of aesthetic outcome of BCT compared with standard techniques to provide information to patients and improve preparedness for surgery

2. To compare patient perception of post-operative outcome with their pre-operative expectation.

3. To assess the objective differences using linear and 3D measures between the simulated 3D-SI and the actual post-operative 3D-SI.

4. To describe longitudinal PROMs in the form of the BCT BREAST-Q.

Objectives

1. Evaluate between-group differences of visual analogue scale (VAS) scores administered pre-operatively for the question "*How confident are you that you know how your breasts are likely to look after treatment?"*

2. Evaluate between-group differences of VAS scores administered at 3- and 12-months post treatment for the question "How well do you think the information about how your breasts are likely to look after surgery (discussion, 2D photographs, or 3D simulation) reflects how they actually look today?"

3. Compare simulated 3D-SI with post-operative 3D-SI taken 3-months and one-year post treatment using linear and 3D measures.

4. Report Q-scores for the BREAST-Q BCT module administered pre-operatively and 3-6month and 1-year post BCT.

1.18 Project 3

Hypothesis

Research involving 3D-SI and PROMs is amenable to novel online research methods for recruitment and participant-reported data collection to facilitate accessible research.

Aims

1. To develop an online research platform for use in a multi-centre study

2. To assess the acceptability, feasibility, and accuracy of a novel online research methodology within a pilot study for an implant reconstruction population.

3. To report upon the reliability of 3D-SI measures using VECTRA XT® in an implant reconstruction population.

Objectives

1. Assess recruitment rate to a study of this design.

2. Understand discontinuation rates and time taken to complete the online process.

3. Describe the accuracy of participant-reported clinical information compared with electronic patient records.

4. Evaluate inter- and intra- observer variability for linear measures derived from 3D-SIs for an implant-based reconstruction population.

5. Appraise the feasibility of online PROMs in the form of the BREAST-Q post-operative reconstruction module.

1.19 Project 4

Hypothesis

A Delphi process can be used to reach consensus to define an expert aesthetic scoring system for use in panel assessment of 3D-SIs of women who have undergone breast reconstruction.

Aims

1. Derive a contemporary panel assessment scale for use in a reconstruction population.

2. Test the reliability of the Delphi derived panel scale.

Objectives

1. Identify key items for evaluation in a reconstruction specific panel scale using a Delphi consensus process.

2. Report upon intra-panellist, inter-panellist and intra-panel reliability of the Delphi derived panel scale.

3. Evaluate the correlation between the Delphi derived panel evaluation and Patient Reported Outcome Measures.

1.20 Project 5

Hypothesis

3D-SI and patient reported outcome measures can be used to compare aesthetic outcome between Deep Inferior Epigastric Perforator (DIEP) flap reconstruction with neoadjuvant radiotherapy and DIEP flap reconstruction with post-mastectomy radiotherapy (PMRT).

Aims

1. Describe aesthetic outcome in the form of PROMs and Panel evaluation for the aesthetic subgroup from the Primary Radiotherapy and Diep flap (PRADA) study.

2. Compare aesthetic outcome between the PRADA aesthetic sub-group and a historic cohort (DIEP and PMRT).

Objectives

1. Perform panel evaluation for the PRADA aesthetic subgroup using the Delphi derived panel method (Project 3) for 3 - and 12- month post-operative 3D-SI.

2. Report PROMs in the form of the BREAST-Q reconstructive module from pre-operative, to 3- and 12-months post-operatively for the PRADA aesthetic sub-group.

3. Compare outcome (measured by panel evaluation and PROMs) between PRADA aesthetic sub-group and historic cohort (DIEP and Post mastectomy radiotherapy).

Chapter 2 The Use of 3-dimensional Surface Imaging in creating an objective aesthetic outcome measure for breast conserving therapy (BCT)

RMH R&D Reference	CCR 4252
IRAS	164043
REC	15/LO/0010
ClinicalTrials.Gov ID	NCT 02304614

2.1 Introduction

As discussed in Chapter 1, breast cancer is common, and two thirds of women managed surgically for breast cancer undergo BCT Aesthetic outcome after BCT has a well-documented influence on patients' psychosocial wellbeing and quality of life.[4-7, 9, 10, 13, 121, 122] Excellent survival expectation means more women are living with the long term impact of treatment, highlighting the importance of aesthetic outcome as a core survivorship focus.

There is no gold standard measure for aesthetic outcome. Patient Reported Outcome Measures (PROMs) are becoming an aesthetic evaluation method in their own right but lack objectivity and consistently report aesthetic outcome more favourably than panel assessment which highlights the need for an objective method of evaluation *in addition to PROMs*.[15, 31, 35, 38, 123, 124] Although anthropometric assessment, subjective rating scales, and photographic measurements have all been used to evaluate aesthetic outcome from breast surgery, none has been widely accepted and each comes with its own well-described limitations.[51-57, 125] The complexity of the perception of aesthetics is reflected in poor agreement between patient, physician, and objective scales.[15, 16, 32, 122]

Panel assessment is the most widely accepted technique to measure aesthetic outcome in breast surgery, but is inherently biased, costly, time-consuming, and un-standardised. The aesthetic goal of BCT is to achieve or maintain symmetry

which is reflected in the most widely adopted scale, the Harvard Cosmesis Scale, developed by Harris et al in the 1970s.[22] Panellists score symmetry between the breasts using a 4-point Likert scale from 1 which is poor to 4 which is excellent.

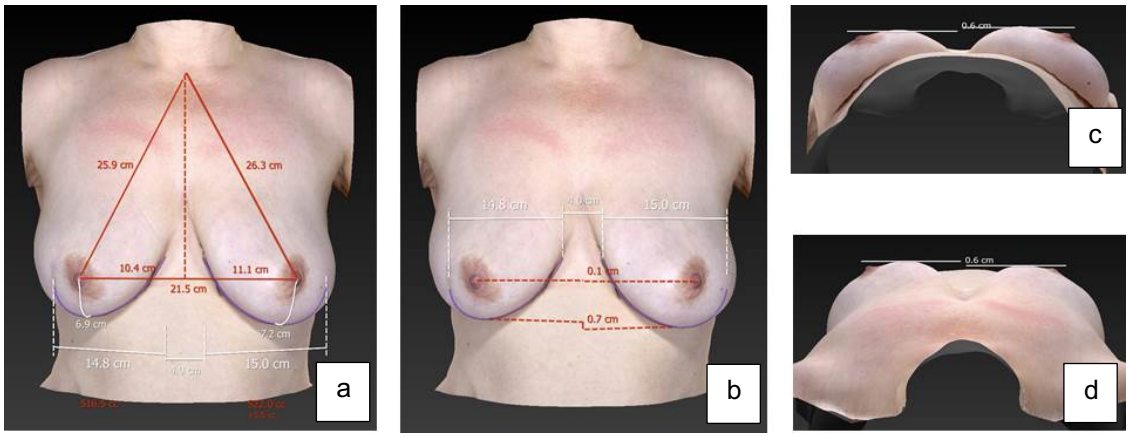

Figure 6 3D-SI in Mirror® illustrating the objective linear measures delivered automatically by the software following landmark positioning (a-d) and cranial and caudal views (c & d)

3-Dimensional Surface Imaging (3D-SI) has the potential to overcome the limitations of the alternative methods for evaluating aesthetics (Figure 6), as discussed in Chapter 1. 3D-SI derived measures could replace panel assessment negating the subjective variability, inherent bias and associated logistical challenges.

Objective evaluation of aesthetic outcome is essential for the communication and comparison of results e.g. between current and emerging techniques. It informs us of individual performance and can be used to benchmark performance between centres, regions, and at a national level. Robust reporting methods strengthen evidence on which to base decisions and guidelines. This project describes the development of an objective aesthetic evaluation model based on measures derived from 3D-SI.

2.2 Hypothesis and specific aims

2.2.1 Hypothesis

3-Dimensional Surface Imaging (3D-SI) can be used to objectively evaluate aesthetic outcome after Breast Conserving Therapy (BCT).

2.2.2 Aims

1. To develop an objective aesthetic outcome tool for BCT using measures derived from 3D-SI.
2. To validate the objective aesthetic outcome tool in a subsequent BCT cohort.

2.2.3 Objectives

1. To use multivariate analysis to identify objective 3D-SI measures that can jointly predict Harvard Panel score to build a tool to measure aesthetic outcome.
2. To determine the reliability of the panel assessment.
3. To investigate the strength of association between the observed and predicted panel score.
4. To establish the agreement between the observed and predicted panel score.
5. To validate the model in a separately recruited cohort.

2.3 Methodology

Study design

The protocol was reviewed and approved by London-Riverside NRES committee (Ref 15/LO/0010) and is available at clinic trial.gov [NCT02304614]. An observational study of women 1-5 years after unilateral BCT was performed to develop an objective aesthetic outcome tool using measures derived from 3D-SI. Eligible potential participants were identified by working consecutively and chronologically through the open access follow up (OAFU) surveillance mammography register. Invitation to participate was by letter containing a participant information sheet (Appendix 3 and 4) with a follow-up telephone call by a member of the study team to endorse the study. Participants attended for a 3D-SI at the same time as their screening mammogram. The 3D-SIs were scored for aesthetic outcome by an expert panel and objective measurements for the operated versus unoperated breast were performed independently as described in the sections below. No pre-operative images were available for comparison. Comparison between objective measures and panel score identified associations, and a model was built based on the relationships in a training set and validated using an independently recruited cohort from the same institution (validation set).

Inclusion criteria:

- Age over 18 years
- Unilateral BCT for DCIS or invasive cancer
- Capacity to consent
- Able to stand for a 3D-SI

Exclusion Criteria

- Contralateral Surgery
- Previous ipsilateral surgery
- Removal of nipple without reconstruction

2.3.1 Objective measures

The 3D-SIs were captured using VECTRA ® XT (Canfield Scientific) with a pre-defined protocol described in a publication from our institution.[76] Objective measures were derived using Mirror ® software (Canfield Scientific). Validated methods were used to calculate volume and surface symmetry which were represented as an average of three measures.[76] The upper proportion was defined as the proportion of breast above the nipple (a linear measure). Independent measures e.g. nipple to sternal notch (N-SN) distance were presented as percentage difference between a patient's breasts, and comparative measures e.g. surface asymmetry, projection, nipple height difference, and infra-mammary fold (IMF) height difference, as absolute values. Landmarks for linear measures were sited using a predefined protocol (Appendix 5). Mirror software has the ability to recognise surface anatomy and site surface landmarks enabling automatic delivery of liner measures. Often the landmarks require manual adjustment to improve accuracy. Volume and surface symmetry measures require some manipulation of the images (as described previously by O'Connell et al).[76] It takes less than 5 minute per image to complete the semi-automated analysis.

2.3.2 Panel assessment

The Panel comprised three consultant oncoplastic surgeons, a consultant radiation oncologist, and one senior breast care nurse. Panellists were blinded to patient, operating surgeon and treating radiation oncologist identity. The Harvard cosmesis scale was used to assess AP, oblique, lateral, cranial and caudal views of 3D-SIs. The Harvard scale (1-4) is based upon symmetry: 1, poor (treated breast seriously distorted), 2, fair (treated breast clearly different from the untreated breast but not significantly distorted), 3, good (treated breast slightly different from the untreated breast), and 4, excellent (treated breast nearly identical to the untreated breast) (Figure 7). The Likert scale was available throughout for reference. Individual panellist's scores were recorded before a consensus panel score was agreed by discussion. The average of the individual panellist's scores was calculated for each image. Ten random images were

presented more than once to test for internal consistency in the consensus scores for both the training and the validation set. The same panel was used to validate the model due to the inherent inconsistencies between panels rendering comparison between different panels unreliable. Examples of images from the training set receiving poor, fair, good and excellent scores were shown at the start of the assessment of the validation set to benchmark the panel.

Harvard Cosmesis Scale	
Excellent (4)	Treated breast nearly identical to untreated breast
Good (3)	Treated breast slightly different from untreated breast
Fair (2)	Treated breast clearly different from untreated breast but not seriously distorted
Poor (1)	Treated breast seriously distorted

Figure 7 Harvard Cosmesis Scale for the evaluation of aesthetic outcome from oncoplastic breast surgery

2.3.3 Statistical analysis

The training set was analysed using linear regression to determine the relationship between each individual measurement and mean observed Harvard panel score. Then, a forward, stepwise, multiple, linear regression model (at $p<0.05$ variable inclusion) was fitted to identify the measurements which, together, best predicted the mean observed Harvard panel score. The fitted model coefficients (intercept and slopes) were used to predict panel scores for the validation dataset. The association between the mean observed and predicted panel score was assessed using scatter graphs and the correlation co-efficient (r) were reported for both sets separately. Bland-Altman was used to assess agreement between mean observed and predicted panel scores and the mean difference and limits of agreement were reported.

Intra-panel agreement was assessed for repeated images and reported as weighted kappa ($w\kappa$) for both sets. $w\kappa < 0$ indicates no agreement and 0–0.20

slight, 0.21–0.40 fair, 0.41–0.60 moderate, 0.61–0.80 substantial, and 0.81–1 almost perfect agreement.[126]

2.4 Results

2.4.1 Recruitment

The training set was recruited by Rachel O'Connell as part of her MD thesis.[127] Recruitment for the training set was from April 2015 to October 2015. Recruitment for the validation set was from June 2016 to March 2017.

3D-SIs from 190 women were used for the training set and a further 100 women were recruited for the validation set. Clinico-pathological data for both sets were comparable (Table 1). Surgery was performed between 2009 and 2014 for the validation set and 2010 and 2016 for the validation set. The median time (in months) from surgery to participation was 36 (IQR18-49) for the training set and 34 (IQR23-47) for the validation set. The tumour was located in the upper outer quadrant for the majority of women in both groups and most women had a standard wide local excision with no complex tissue rearrangement. All women in the training and 94% of women in the validation set had adjuvant radiotherapy. The mean pre-operative tumour size (measured on ultrasound) for the training and validation set was 14mm and 16mm respectively. The median weight of excision specimen was 32g in the training set and 44g in the validation set.

Clinico-pathological data	Training Set n=190	Validation Set n=100
Pre-operative data		
Age at time of surgery (years), mean (SD)	61(11)	59(11)
Time from surgery to study participation (months), median (IQR)	36(18-49)	34(23-47)
Ethnic origin (%)		
White	178(95)	91(91)
Non-white	9(5)	9(9)
Smoking status (%)		
Never	119(60)	58(58)
Current	16(8)	16(16)
Ex-smoker	60(32)	25(25)

BMI at surgery (kg/m^2), mean (SD)	27(5)	28(5)
Location of tumour on pre-operative imaging (%)		
Upper Outer	104(55)	50(50)
Central	8(3)	2(2)
Lower inner	27(14)	14(14)
Lower outer	20(11)	18(18)
Upper Inner	34(18)	15(15)
		1 – unknown
US size (mm), mean (SD)	14(9)	16(9)
Mammographic size (mm), mean (SD)	16(11)	18(10)
Neoadjuvant therapy (%)		
None	167(88)	92(92)
Endocrine	9(5)	2(2)
Chemotherapy	14(7)	6(6)
Intra-operative data		
Experience of operating surgeon		
Consultant	105(55)	47(47)
Trainee with consultant scrubbed	41(22)	17(17)
Trainee with consultant un-scrubbed	44(23)	36(36)
Type of surgery (%)		
WLE	172(91)	90(90)
Other complex	18(9)	10(10)
Axillary surgery (%)		
Nil	16(8)	10(10)
SLNB or sampling	145(76)	74(74)
ALND	29(16)	16(16)
Re-excision of margins (%)		
No	160(84)	88(88)
Yes	30(16)	12(12)
Pathology data	Training Set n=190	Validation Set n=100
Tumour pathology size (mm), mean (SD)	22(13)	24(16)
Weight of tumour (g), median (IQR)	32(20-48)	44 (22-59)

Tumour type on final pathology (%)		
IDC+DCIS	120(63)	68(68)
IDC	26(14)	17(17)
DCIS	15(8)	6(6)
ILC	25(13)	4(4)
Other Invasive	4(2)	5(5)
Grade of invasive tumours (%)		
1	40(23)	19(20)
2	88(50)	43(22)
3	43(25)	27(29)
Not recorded	4 (2)	4(4)
ER status of invasive tumours (%)		
Positive	157(90)	82(88)
Negative	18(10)	11(12)
PR status of invasive tumours (%)		
Positive	135(77)	65(70)
Negative	40(23)	28(30)
HER2 status of invasive tumours (%)		
Negative	165(94)	87(94)
Positive	9(5)	6(6)
Not recorded	1(1)	
Triple negative (%)	12(7)	9(10)
Nodal status (%)		
Negative	131(69)	72 (72)
Positive	43(23)	18(18)
No axillary surgery	16(8)	10(10)
Adjuvant therapy		
Adjuvant chemotherapy (%)		
No	155(82)	72(72)
Yes	35(18)	28(28)

Adjuvant endocrine Therapy (%)		
No	29(15)	22(22)
Yes	161(85)	78(78)
Adjuvant radiotherapy(%)		
No	0(0)	6(6)
Yes	190(100)	94(94)
Boost	50(26)	28(28)
SCF & Axilla	11(6)	7(7)
Post-operative complications		
Delayed wound healing (>30 days) (%)		
No	183(95)	100 (100)
Yes	7(5)	0(0)

Table 1 Clinicopathological data for the training (n=190) and validation (n=100) sets

2.4.2 Training set

Almost perfect intra-panel consistency ($w\kappa = 0.87$) was observed for 10 repeated images in the training set, with 7/10 consensus scores agreeing and 3/10 varying by one point. In the validation set, the intra-panel agreement was similar ($w\kappa = 0.84$) with 6/10 consensus scores agreeing and 4/10 varying by one point.

A significant relationship was identified between all but one (nipple-to-nipple distance) of the 3D-SI-derived measures and the mean panel score (Table 2). All were carried forward into the multivariate analysis and seven were found to be *independently* associated with mean panel score. Six of these variables were included in the multivariate model. The upper proportion difference was considered to produce similar measurements to nipple-to-sternal-notch (N-SN) distance and was considerably more time consuming to measure so was excluded. The variables in the multivariate model and their significance are reported in Table 2.

Univariate Analysis			
Variable	**Constant (95% CI)**	**Coefficient (95% CI)**	**P value**
Upper proportion difference	3.21 (3.04 – 3.39)	-0.059(-0.082: -0.035)	<0.001
N-M difference (%)	3.04 (2.87 – 3.21)	-0.015(-0.027: -0.003)	0.011
N-IMF difference (%)	3.09 (2.94 – 3.25)	-0.014(-0.022: -0.007)	<0.001
N-SN difference (%)	3.38 (3.22 – 3.54)	-0.079(-0.099: -0.059)	<0.001
Breast base width difference (%)	3.07(2.89 – 3.25)	-0.043(-0.073: -0.013)	0.005
M-MMF distance (cm)	2.62 (2.37 – 2.87)	0.097(0.001 : 0.184)	0.030
NH difference (cm)	3.31 (3.16 – 3.46)	-0.256(-0.324: -0.188)	<0.001
IMF difference (cm)	3.30 (3.15 – 3.45)	-0.355(-0.449 : -0.262)	<0.001
Projection difference (cm)	3.08 (2.92 – 3.25)	-0.344(-0.547 : -0.141)	0.001
N-N distance (cm)	3.74 (2.75 – 4.72)	-0.036(-0.078: 0.005)	*0.083*
Volume symmetry (%)	1.22 (0.37 – 2.07)	0.019(0.009: 0.029)	<0.001
Surface asymmetry (mm)	3.87 (3.64 – 4.10)	-0.156(-0.189 : -0.123)	<0.001
Multivariate Analysis			
		Coefficient (95% CI)	**P Value**
Constant	3.137(2.372 : 3.902)	-	-
N-SN difference (%)	-	-0.047 (-0.068 : -0.026)	<0.001
Breast base width difference (%)	-	-0.028 (-0.052 : -0.004)	0.021
IMF difference (cm)	-	-0.162 (-0.267 : -0.057)	0.003
Projection difference (cm)	-	-0.255 (-0.424 : -0.086)	0.003
N-N distance (cm)	-	0.041 (0.007 : 0.075)	0.017
Surface asymmetry (mm)	-	-0.072 (-0.116 : -0.028)	0.001

Table 2 Univariate and multivariate analysis comparing 3D-SI measures with mean Harvard panel score. The model was built using forward stepwise multiple linear regression for the training set (at 5% alpha level) (n190). The variables shown to be *independently* associated with panel score are included in the table. RMS, root mean squared; IMF, Inframammary fold; N-M, nipple-midline; N-IMF, nipple – inframammary fold; M-MMF, medial – medial mammary fold; NH, nipple height; N-N, nipple-nipple

A good correlation (r=0.68) was seen between predicted and mean observed panel score for the training set (

Figure 8). The Bland-Altman plot (Figure 9) demonstrates a mean difference of 0 (95% CI: -0.08 to 0.08) and limits of agreement of -1.17 to 1.17.

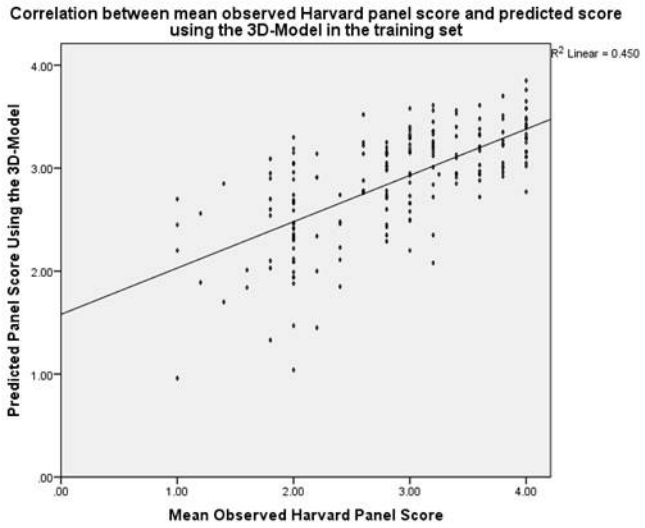

Figure 8 Correlation between predicted and mean observed panel score for the training set (n=190). Correlation co-efficient (r) = 0.68

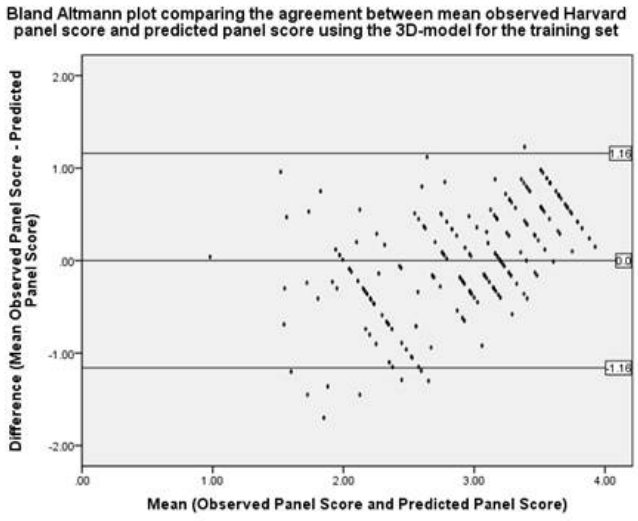

Figure 9 Bland-Altman plot for the training set: the mean of the panel scores (predicted and mean observed) against the difference(n=190). The middle horizontal line represents the mean difference between mean observed panel score and predicted panel score and the upper and lower horizontal lines represent limits of agreement

2.4.3 Validation set

A summary of the six independent variables and the mean observed Harvard panel scores for the training and validation set and predicted panel score using the multivariate model are summarised in Table 3. A good correlation was found between the predicted and mean observed panel score for the validation set (r=0.65). This is represented in Figure 10. The Bland-Altman plot (Figure 11) demonstrated a mean difference of -0.055 (95% CI: -0.166 : 0.056) and limits of agreement of -1.17 to 1.06.

	Training set n=190 Mean (SD)	**Validation set n=100 Mean (SD)**	
Measures from 3D-SI			
Surface Asymmetry (mm)	6.40 (2.86)	7.11 (2.97)	-
NSN difference (%)	6.47 (4.97)	5.44 (4.35)	-
IMF height difference (cm)	1.21 (1.07)	1.12 (1.03)	-
Projection difference (cm)	0.61 (0.54)	0.61 (0.52)	-
N-N distance (%)	23.76 (2.74)	23.99 (2.80)	-
Breast width difference (%)	4.62 (3.72)	5.31 (3.42)	-
Harvard Panel Score	**Observed score training set**	**Observed score validation set**	**Predicted score for validation set**
Median	3	3	3
Range	1 - 4	1 – 4	1 – 4
IQR	2 – 3.6	2.2 – 3.6	2.57 – 3.25
Mean (SD)	2.87 (0.79)	2.93 (0.78)	2.87 (0.54)

Table 3 A summary of the 3D-SI measures, mean observed Harvard panel scores and predicted panel score using the multivariate model. NSN; nipple-sternal notch, IMF; inframammary fold, N-N; nipple- nipple, IQR; interquartile range, SD; standard deviation.

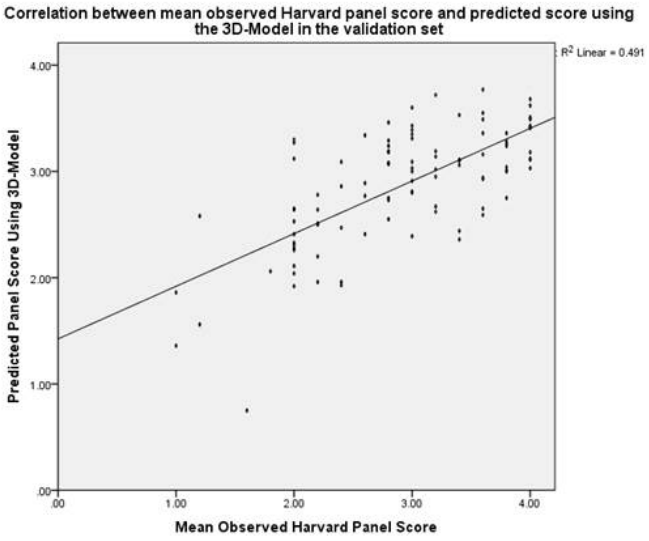

Figure 10 Correlation between predicted and mean observed panel score for the validation set (n=100) r=0.65

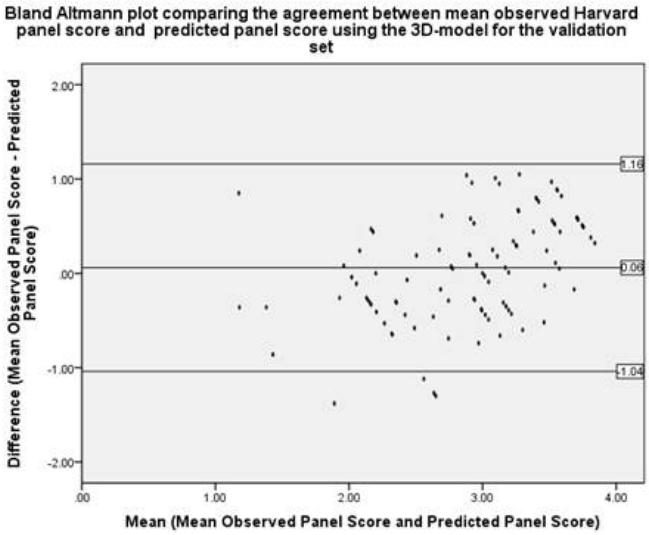

Figure 11 Bland-Altman plot for the validation set: the mean of the panel scores (predicted and mean observed) against the difference (n=100). The middle horizontal line represents the mean difference between mean observed panel score and predicted panel score and the upper and lower horizontal lines represent limits of agreement

2.4.4 Calibrated model

The Bland-Altman plots illustrate that the model over-predicts for lower panel scores, and under-predicts for higher panel scores, tending towards the mean (Figure 9 and Figure 11). Histograms corroborate this finding by illustrating a clustering of predicted scores around the median with very few predicted scores at the extremes (Figure 12). In order to improve the spread of predicted scores, to better reflect the observed distribution of scores and improve clinical utility, the model was calibrated post-hoc to the observed frequency distribution of panel score in the training set.

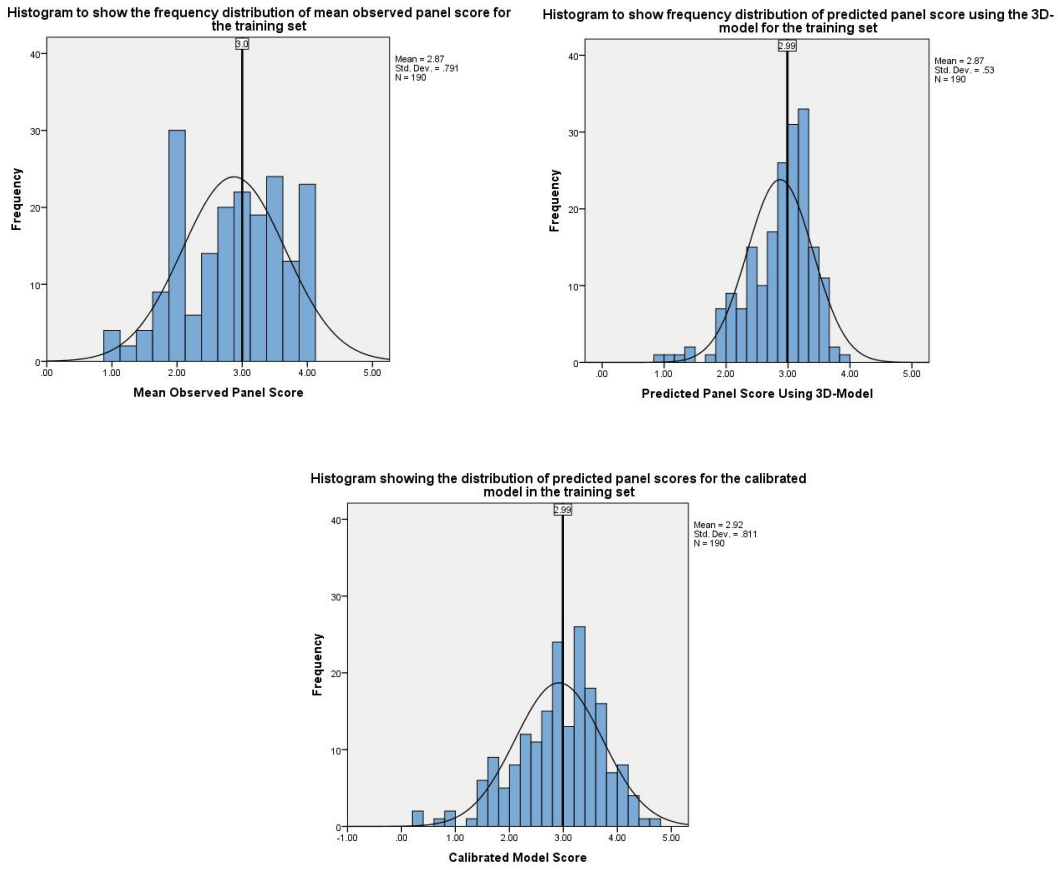

Figure 12 Histograms to show the frequency distribution of the mean observed Harvard panel scores (top left), 3D-Model (top right), and the calibrated model (bottom) for the training set (n=190)

Calibration was performed by firstly dividing the scores from the 3D-Model into three groups; those that fall above, equal to, or below the median. Different multiplication factors were then substituted into the equations in Figure 13 and were either added to (values falling above the median) or subtracted from (for values falling below the median) to spread the data. Predicted values that fell at the median score remained the same. The most appropriate multiplication factors were determined by analysing the change in spread of the data as illustrated in Table 4.

	Calibration model 1	Calibration model 2	Calibration model 3	Calibration model 4	Calibration model 5	Calibration model 6
y	2.5	1.2	1.3	1.4	1.3	1.35
z	1.5	0.7	1.1	1.2	1.2	2
Median	2.97	2.99	3.27	2.98	2.98	2.98
Minimum	-2.09	0.56	1.66	0.15	0.35	0.25
Maximum	4.27	3.59	2.99	4.02	4.02	4.69
Quartile 1	1.96	2.50	2.21	2.42	2.46	2.44
Quartile 3	3.36	3.17	2.83	3.29	3.29	3.49
Mean	2.54	2.78	2.49	2.79	2.82	2.92
Standard Deviation	1.19	0.57	0.38	0.71	0.68	0.81

Table 4 Descriptive statistics illustrating the development of multiplication factors for use in the calibration model. c, calibrated model score; m, median; k, 3D-Model score, z, multiplication factor for values falling above the median, y, multiplication factor for values falling below the median

For values above the median

$$c = m + [k - m] \times z$$

For values below the median

$$c = m - [m - k] \times y$$

Figure 13 Equations used to calibrate the 3D model where c; calibrated score, m; median, k; model score and y and z are multiplication factors for values above and below the median respectively

The correlation between the calibrated model and the mean observed panel scores is similar to that of the 3D-Model (r = 0.67 and 0.69 for the training and validation sets respectively) (Figure 14). Bland Altman analysis of the calibration model demonstrated the mean difference and limits of agreement for the calibrated model and the training and validation sets (Figure 15). Histograms demonstrate improved distribution of scores for the calibrated model compared to the 3D-Model with reference to the distribution of mean observed panel score (Figure 12). This is reflected in the broader IQR observed in the calibrated model versus 3D model in Table 5, which better reflects the IQR in actual panel scores.

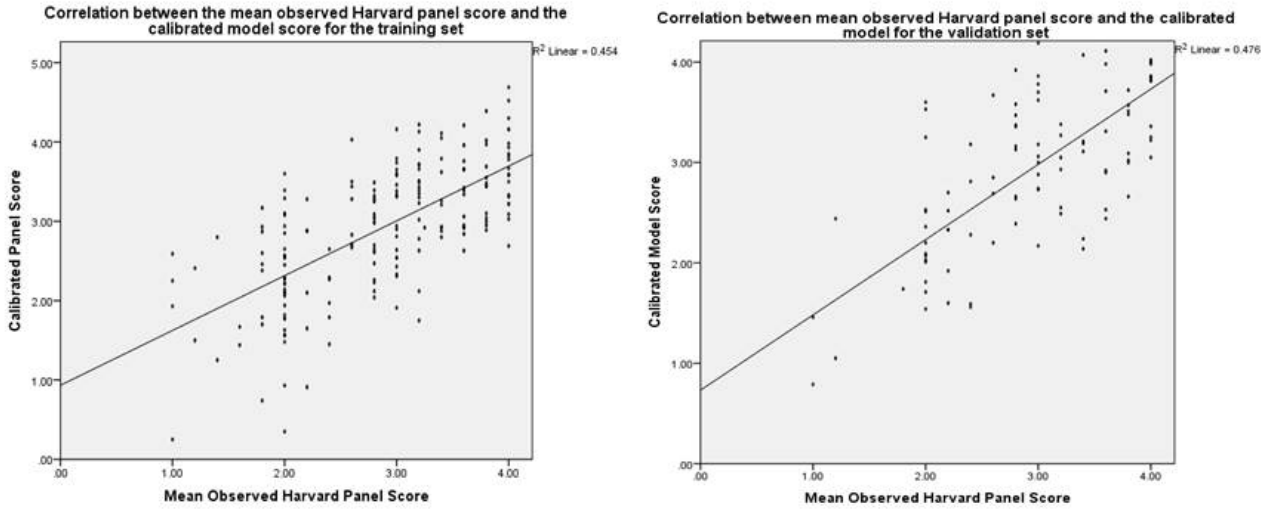

Figure 14 Scatter plots illustrating the correlation between observed Harvard panel score and the calibrated model for the training set (left) and the validation set (right). Correlation co-efficient (r) = 0.67 and 0.69 respectively

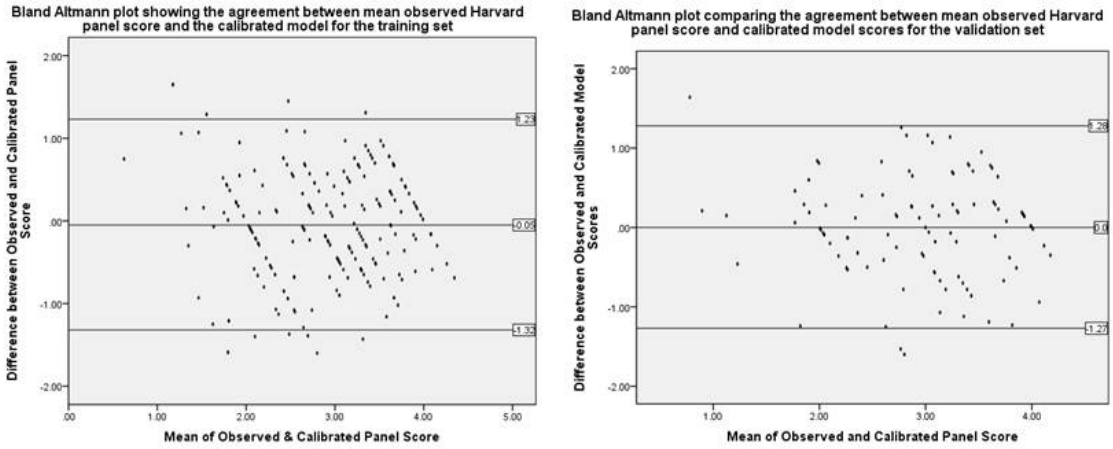

Figure 15 Bland-Altman plots illustrating the agreement between mean observed Harvard panel score and the calibrated model in the training set (left) and validation set (right). The middle horizontal lines represent the mean difference between mean observed panel score and the upper and lower horizontal lines represent limits of agreement

	Observed	Observed	3D-Model	3D-Model	Calibrated Model	Calibrated Model
	Training	Validation	Training	Validation	Training	Validation
Min	1	1	0.96	0.75	0.25	-0.04
Max	4	4	3.85	3.77	4.69	4.54
Mean	2.87	2.93	2.87	2.87	2.92	2.93
SD	0.79	0.78	0.53	0.55	0.81	0.85
Median	3.0	3.0	2.99	3.02	2.98	3.03
Q1	2	2.2	2.56	2.54	2.44	2.38
Q3	3.6	3.6	3.24	3.29	3.49	3.57

Table 5 Descriptive statistics for the mean observed panel scores, 3D-model, and calibrated model for the training and validation sets.

In the training set, the calibrated model correctly predicted panel score to within 0.5 points of the mean observed Harvard panel score in 99 (52%), within 1 point in 166 (87%), within 1.5 points in 187 (98%) and all patients within 2 points. In the validation set the calibrated model correctly predicted panel score to within 0.5 points of the mean observed Harvard panel score in 57 (57%), within 1 point in 86 (86%), within 1.5 points in 97 (97%) and all patients within 2 points. In-depth analysis of cases where the model over-predicted by more than 1.5 points found cases in which focal volume deficits detracted from the overall aesthetic result. These may not have been captured by the overall asymmetry score delivered during 3D-SI analysis (Figure 16).

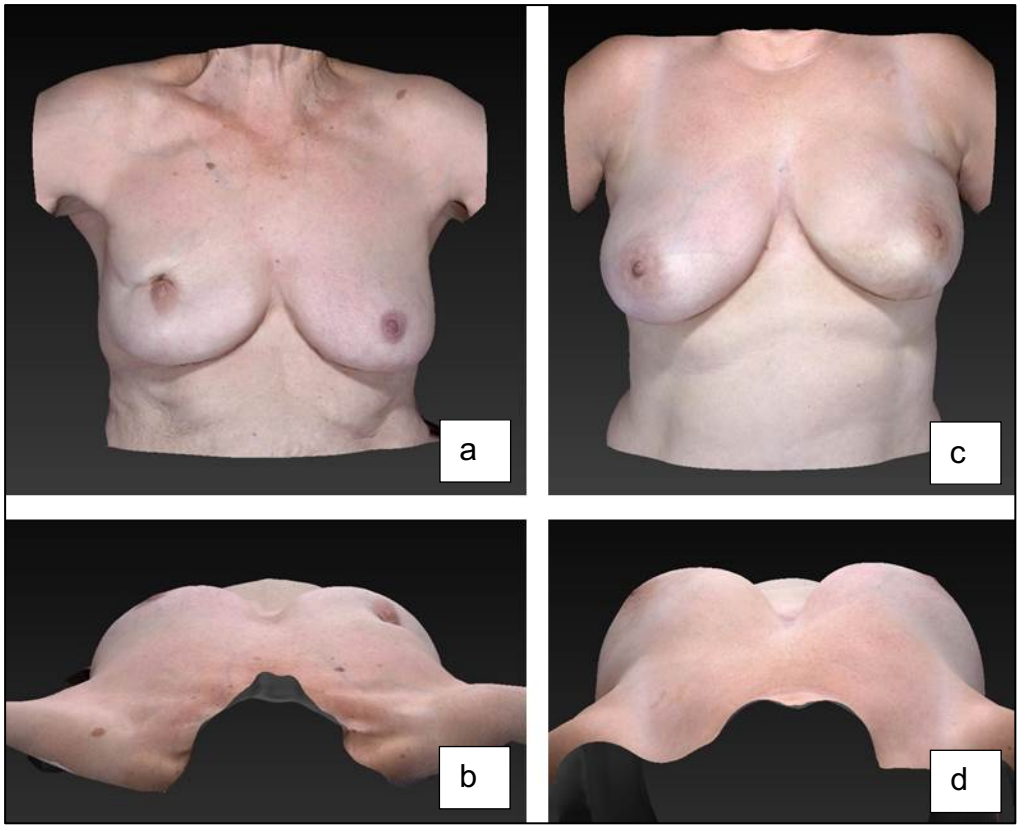

Figure 16 3D-SI in Mirror ™. Images a&b; Observed Harvard panel score of 1.4 and 3D-Model score of 2.8. A focal deficit in the upper outer right breast detracts from the overall aesthetic result, however, may not be captured in the overall asymmetry score (rms) delivered by 3D-SI analysis. Images c&d; observed Harvard panel score of 2.4 and 3D-Model score of 2.3. Global volume and surface asymmetry between operated and non-operated breast is accurately detected by 3D-SI analysis .

A summary of the ideal reliability and validity measures and the progress made towards each domain for the calibrated model are illustrated in Table 6 and Table 7. Further testing of the model with a second investigator may help improve the understanding of inter-rater variability.

Type of reliability	Definition	Statistical test	Objective outcome tool
Stability	Consistency of repetitions. How stable the test is throughout time	Test – retest	The model was developed using a training set and then repeated on an independently recruited cohort and the correlation with panel score remained stable r=0.67 and r=0.69 The measures were not repeated twice for the same cohort.
Internal Consistency	Measures if the domains of an instrument measure the same characteristic	Cronbach's alpha	Cronbach's alpha for the linear measures used in the tool were all >0.9 (section 4.4.6 Table 17)
Equivalence	Concordance between two or more raters using the same instrument	Inter-observer variability. Weighted kappa ($w\kappa$)	Not completed within this study. A second investigator could re-measure the images and repeat the multivariate modelling to assess the inter-observer variation of the model – although we know the interobserver variability for the measures used is low (see section 4.4.6)

Table 6 Reliability measures for the calibrated model and progress towards each domain

Type of validity	Definition	Example	Statistical test	Objective outcome tool
Content validity	The degree to which a test contains all the necessary items to represent the concept to be measured	Are all the relevant objective measures contained within the test	Linear regression analysis to identify objective measures that are independently associated with aesthetic outcome i.e. panel score	Multivariate analysis model created where each item was independently associated with panel score ($p<0.05$) (section 2.4.2 Table 3)
Concurrent validity	Can be evaluated using the gold standard at the same time.	The panel assessment is performed alongside the objective outcome tool	Correlation	r=0.67-69 for the training and validations sets respectively (section 2.4.4 figure 13)
Construct validity	The extent to which a set of variables represent the construct to be measured	How well does the objective outcome tool predict the panel score?	Agreement	Mean difference of the calibrated model and the panel score was -0.05. The limits of agreement were -1.32 – 1.23. (section2.4.4 figure 14e)

Table 7 Validity measures for the calibrated model and progress towards each domain

Discussion

This chapter describes the development of a six-variable objective aesthetic outcome model for Breast Conserving Therapy (BCT) which can predict and could ultimately replace panel assessment. The model accurately measures and reports aesthetic outcome incorporating evaluation of views unique to three-dimensional photography enabling surface symmetry and projection to be incorporated into the assessment, a potential advantage over 2D images.

Many attempts have been made to objectively evaluate aesthetic outcome of breast surgery; however, each method has its limitations.[18, 29] The Breast Cancer Conservative Treatment. cosmetic results (BCCT.core) model is the most widely cited in the literature.[24, 25, 63, 66] The BCCT.core model evaluates breast asymmetry in two dimensions so measures such as volume, 3D surface symmetry, and projection cannot be evaluated. The breast is a 3-dimensional structure, therefore, is not comprehensively assessed in two dimensions. 3D-SI has the ability to measure volume and shape symmetry providing an additional component to objective aesthetic evaluation.[76]

Cardoso et al have published results for a 3D-version of the BCCT.core model based on the capabilities of Microsoft Kinect. They concluded the addition of the third dimension is not necessary, based on the lack of improvement in the association between model and panel score.[26] The conclusion was based on the addition of a single 3D parameter to BCCT.core, volume symmetry, which was not found to be independently associated with panel score on multivariate analysis in this study. Additional capabilities of 3D measures, such as surface symmetry and projection were not included, so the conclusion was perhaps drawn upon an oversimplified application of 3D technology. Another advantage of the 3D-model described in this paper is that it produces a score on a continuous scale, enabling more detailed feedback on performance i.e. a score of 2.4 or 1.5 would be delivered rather than a score of 2, which would be applicable to both.

Clinicians and patients may have divergent views of what constitutes a good aesthetic outcome. Potter et al outlined a core outcome set for breast

reconstruction based on Delphi methodology in which 'patient satisfaction with cosmetic outcome' was rated highly amongst medical professionals and patients alike.[32] Patient Reported Outcome Measures (PROMs) are an important evaluation of aesthetic outcome but lack objectivity, are affected by the treatment path leading to the final outcome and are consistently discordant from professional assessment, being frequently reported more favourably.[27, 33, 38, 122, 124] Dahlbäck et al have emphasised the importance of PROMs in aesthetic evaluation demonstrating a stronger predictive ability for longer term health related quality of life as compared to objective measures or panel assessment.[122] The objective model described in this paper is not designed to replace PROMs, and PROMs cannot obviate the need for an objective model which is designed to produce an independent and unbiased evaluation of aesthetic outcome. The two methods of aesthetic evaluation must co-exist and development into a combined outcome set for BCT may be considered a further area of study.

A very good intra-panel agreement using the Harvard scale ($w\kappa = 0.87$, $w\kappa = 0.84$ for test and validation sets respectively) is reported. However, the reported internal consistency of panel assessment is variable in the literature illustrating one of the limitations of this evaluation method.[24, 27, 30, 62, 122] Even when a panel was selected from a group of experts based upon the agreement of their previous scores with the consensus opinion, their individual Harvard score switched category to match consensus 30% of the time.[25] The logistics of arranging a panel assessment are complex and inefficient both in terms of time and cost. Objective assessment can be performed on a case by case basis with greater flexibility and potentially reduced burden on time and resources.

The surface asymmetry measure in Mirror® gives an average over the entire breast surface (root mean squared), thereby giving a representative result when there is global surface asymmetry or surface asymmetry affecting a moderate area of the breast. However, for very small areas of volume deficit in an otherwise symmetrical breast, the focal surface asymmetry will be countered by the remaining global surface symmetry, so can be 'hidden' in the measure. The ability of the model to detect, measure and report upon a focal volume deficit is

an area for development which may help to refine the accuracy of the model in this small subset of patients.

To improve the applicability into everyday practice, the software requires development to enable automated calculation of the outcome score. In addition, there is some difficulty imaging women with very large volume breasts and on occasion the lateral view is cropped to the mid-axillary line to enable capture of the anterior contour of the breasts. The automatic placement of surface landmarks is less reliable for larger breasts and moderate ptosis, requiring manual adjustment or placement, which decreases the efficiency of measuring. However, manually placing landmarks is still very quick and the software provides diagrams to guide placement so prior training is not essential.

The model was based upon and tested against a clearly defined method of expert panel assessment with very-good internal consistency, a large dataset of 3D-SIs and included an independently recruited cohort for validation. Validation at a different centre, or within a prospectively collected cohort is an area for future work. A prospective study would also eliminate selection bias. For now, it is encouraging that the median Q-score for “satisfaction with breasts “ for the training set using the BREAST-Q BCT module was 68 (IQR 55-80) out of 100, where 100 is best. This is concordant with other contemporary analyses where the median Q-scores 3-6 years after surgery ranged from 65 to 68.[122]

It may be possible to extend the principle used within this study to a reconstruction population, however, a large multicentre study would be required in order to generate a 3D-SI library large enough to reflect the diversity in practice in the UK. Survivorship is a rapidly expanding area of interest, and continued development of portable, cheaper 3D capture systems has the potential to revolutionise aesthetic evaluation by the integration of 3D-SI into research and clinical practice.

2.5 Conclusion

A six-variable objective aesthetic outcome model for BCT has been described and validated. This can predict and could replace panel assessment, facilitating independent and unbiased evaluation of aesthetic outcome to communicate and

compare results, benchmark practice, and drive standards. The model is not ready for adoption into clinical practice yet as further validation at a different centre or a prospective cohort is required to establish whether the model is generalisable. Automation of the calculation using the 6 measure would also be required prior to widespread use to improve time efficiency, ease of use, and minimise error.

2.6 Acknowledgements

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The views expressed are those of the authors and not necessarily those of the NIHR or the Department of Health and Social Care.

We would like to formally acknowledge the contributions of the participants, Miss Rachel O'Connell and medical photographer Dennis Underwood to this study.

The protocol was reviewed and passed by London-Riverside NRES committee Ref 15/LO/0010. The study is registered on a publicly accessible database, clinicaltrial.gov, NCT02304614.

Informed consent was obtained from all individual participants included in the study.

Chapter 3 The Use of 3D Surface Imaging to Simulate Outcome after Breast Conserving Therapy: A Randomised Controlled Trial.

RMH R&D Reference	CCR 4660
IRAS	218564
REC	17/LO/0399
ClinicalTrials.Gov ID	NCT03250260

3.1 Introduction

3D simulation provides a visual experience for patients and a personalised approach to care. It is a way of displaying complex ideas simply, crossing language and literacy barriers and improving communication in the pre-operative planning stage of surgery. 3D simulation of aesthetic outcome could add value as a tool to improve patient preparedness for breast cancer surgery by reducing the gap between patient perception and expectation and enrich the patient pathway by improving shared decision-making.

In the cosmetic surgery industry, particularly within breast and facial surgery, 3D-SI and simulation is widely used to facilitate patient decision-making.[100, 101] Simulation was reported to be highly reproducible for breast augmentation, [106-108] and proved a useful tool for implant selection.[81, 109-111] Patients found pre-operative simulation helpful and reported satisfaction with augmentation choice.[110]

The simulation software available uses pre-defined algorithms to model outcome from aesthetic surgery i.e. implant augmentation, lipofilling, and mastopexy. There is no software currently available to model breast reconstruction or BCT using 3D-SI. Some groups have looked at complex modeling of the outcome of BCT using biomechanics and wound healing models based on MRI imaging, but

these methods involve complex mathematics, are time consuming, expensive, and not yet at a stage to be used in a clinical setting.[115-117]

In many breast units, the standard pre-operative preparation for a woman undergoing BCT includes a verbal description of likely aesthetic changes. Often women undergoing breast reconstruction are shown photographs of other women who have had similar operations. Women themselves have explained that looking at other women's post-operative photographs did not always give them a sense of how *they* would look, and some reported that it felt inappropriate and awkward. The concept of using simulation as part of a pre-operative discussion within breast cancer surgery was generated by our patient steering group as a desirable area of study.

Confidence approaching an operation may be increased if a woman has reviewed simulated images of her own appearance, and this may translate to better satisfaction with outcome in terms of satisfaction with the breasts. Conversely, however, if the simulation gives a woman an artificially high expectation then she may be more disappointed than had she not seen it.

The aim of this study was to establish, using a randomised controlled trial, which preparation method best prepares women for their likely aesthetic outcome after BCT; verbal description, showing others' photographs, or 3D simulation.

3.2 Hypothesis and specific aims

3.2.1 Hypothesis

Simulation of aesthetic outcome using 3D-SI can improve patient preparedness for their aesthetic outcome after surgery and may influence satisfaction by managing expectations.

3.2.2 Aims

1. To assess, in a randomised controlled trial, the value of 3D-SI in the simulation of aesthetic outcome of BCT compared with standard techniques to provide information to patients and improve preparedness for surgery.
2. To compare patient perception of post-operative outcome with their pre-operative expectation.
3. To assess the objective differences using linear and 3D measures between the simulated 3D-SI and the actual post-operative 3D-SI.
4. To describe longitudinal PROMs in the form of the BCT BREAST-Q.

3.2.3 Objectives

1. Evaluate between-group differences of visual analogue scale (VAS) scores administered pre-operatively for the question "*How confident are you that you know how your breasts are likely to look after treatment?"*
2. Evaluate between-group differences of VAS scores administered at 3 and 12 months post treatment for the question "How well do you think the information about how your breasts are likely to look after surgery (discussion, 2D photographs, or 3D simulation) reflects how they actually look today?"
3. Compare simulated 3D-SI with post-operative 3D-SI taken 3 months and one year post treatment using linear and 3D measures.
4. Report Q-scores for the BREAST-Q BCT module administered pre-operatively and 3 months and 1 year post BCT.

3.3 Methodology

3.3.1 Study Design

A randomised controlled trial (RCT) to compare the efficacy of 3D simulation, 2D photography, and standard care in terms of patient preparedness for aesthetic outcome following BCT.

3.3.2 Interventions

Women were randomised into one of three groups: standard care, viewing 2D photographs of other women who have undergone similar surgery in the past or viewing a real-time simulation of an average outcome from BCT using their own 3D-SI (Appendix 8 participant information sheet). All women received standard care with their surgeon (a description of likely aesthetic outcome). Women in the 2D photograph group viewed images of two women, using three views (AP, left and right oblique) matched for age, BMI, tumour location and breast volume (as far as possible) from an image library of 135 women who had undergone BCT at Royal Marsden Sutton within the previous 1-5 years with a Harvard cosmesis score of 2 or 3 (out of 4). The simulation group saw a real time simulation of an average appearance after BCT simulated onto their own 3D-SI.

3.3.2.1 Simulation model

The simulation method was based on pre-existing software for simulating mastopexy outcome within Mirror™ Software, and the VECTRA XT® capture system (Canfield Scientific, New Jersey, USA). The model was based upon average changes from the un-operated to the operated breast measured for a series of breast conservation patients [NCT 02304614] for a population with Harvard panel scores of 2 and 3 (n=135) i.e. the best and worst aesthetic outcomes were excluded. Mirror™ software is designed to simulate implant augmentation and mastopexy, and although there are many options for manipulating these operations, it is not currently possible to reduce certain objective measures by a pre-defined amount. Nipple-Sternal Notch (N-SN) distance can be manipulated in the mastopexy function so this was used for the simulation. N-SN distance was reduced by 5% and moved maximally laterally.

A circumareolar scar pattern was used to standardise the type of simulation used, other options included inverted T or wise pattern.

The simulation was performed on the native breasts of the development series of patients and compared visually to the treated breast (actual outcome). The accuracy of the simulation to display an average outcome from BCT was deemed acceptable for the purpose of this trial by two reviewers, to provide proof of principle that simulation is helpful prior to embarking on expensive and time-consuming software developments.

3.3.2.2 Simulation Methodology

The retrospective BCT cohort (n=190) were categorised by their panel score (4 = 49, 3 = 80, 2 = 55, 1 = 7), and those with panel score of two or three were then selected (n= 135). The change in objective measures between the non-operated and operated breast were calculated and mean values taken for each measure (Table 8). We acknowledge that natural asymmetry of the breasts will not be accounted for in this model, but in the absence of a large set of pre- and post-operative 3D-SI, we accepted this. For the reasons given above, manipulation of nipple-sternal notch (N-SN) distance was used for the simulation.

Measure	Mean change from non- operated to operated breast
Nipple to midline difference (%)	9
Nipple to IMF difference (%)	3
Nipple to sternal notch difference (%)	-5
Nipple height difference (cm)	0.3
IMF height difference (cm)	0.9
Projection (cm)	-0.2
Volume difference (%)	-4
Surface asymmetry (mm, rms)	3.76

Table 8 Mean change in objective measures from operated to non-operated breast for the retrospective BCT cohort. IMF; infra-mammary fold, RMS; root mean squared

The un-operated breasts of 10 3D-SIs randomly chosen from the retrospective BCT cohort were subject to the simulation method derived from the mastopexy model. The N-SN distance was reduced by 5% in the model. Objective measures from the simulation were compared to the unoperated breast in terms of percentage change and subsequently inspected alongside the changes seen in the retrospective BCT cohort as already described (Table 9).

Measure	Change in objective measure for simulation	Predicted Change
Nipple to midline difference (%)	3	9
Nipple to IMF difference (%)	4	3
Nipple to sternal notch difference (%)	-2	-5
Nipple height difference (cm)	0.4	0.3
IMF height difference (cm)	0.6	0.9
Projection (cm)	-0.18	-0.2
Volume difference (%)	-8.8	-4
Surface asymmetry (mm, rms)	2.5	3.76

Table 9 The differences between simulated breast measurements and those seen in the retrospective cohort (predicted change). IMF; inframammary fold

Table 9 illustrates that the simulation method produced measures similar to the changes seen in the retrospective cohort. Prior to showing the simulation to participants it was stressed that the images they were about to see were based on average changes seen in women having similar but not identical treatment, therefore, it was designed to give an idea of the average post-treatment outcome but will not represent exactly how they will look. They may have an aesthetic outcome that is better or worse than the images they were going to view.

3.3.3 Target population

Women over 18 years of age with early breast cancer who were planned to undergo BCT at the Royal Marsden Hospital, Sutton.

3.3.4 Inclusion criteria

- Unilateral BCT
- Intention to undergo radiotherapy
- Wide local excision or mammoplasty

3.3.5 Exclusion criteria

- Previous breast surgery
- Intent to undergo symmetrisation
- Lacks capacity
- Unable to attend for follow-up

3.3.6 Implementation

Potential participants were identified pre-operatively by the clinical team of four consultant oncoplastic breast surgeons. The study was introduced by a member of the clinical team (either a breast care nurse or the surgeon) in consultation and the patient information sheet along with an infographic was issued. Potential participants received a follow-up telephone call by one of two clinical research registrars to endorse the study and arrange an initial study consultation. One of the same two research registrars conducted the initial study consultation which included the consent process, filling of the baseline pre-operative BCT BREAST-Q, randomisation, a baseline 3D-SI, preparation method (as per randomisation) and finally the baseline VAS (primary endpoint), all of which took on average 20 minutes.

3.3.7 Bias minimisation and blinding

The language used during the telephone consultation was guided by a performance coach with the intention of providing adequate information about the study and relaying clinical equipoise between groups. The number of

investigators performing the telephone calls and recruitment was limited to two registrars to reduce variability in delivery.

It was not possible to blind the patient or the investigator to the group at this consultation, however, the VAS were measured on mass at the end of the trial by one investigator blinded to the randomisation group to reduce bias. The BREAST-Q was administered prior to randomisation.

In attempt to reduce bias from seeing the 3D-SI technology and receiving extra time from a member of the clinical team (an intervention in itself) every participant went through the process of having a 3D-SI and spent time with the investigator to explain the average aesthetic changes observed with BCT. Women in the 2D and simulation groups then went on to experience their preparation method in addition.

3.3.8 Outcome measurements

3.3.8.1 Primary outcome

Preparedness for aesthetic outcome after BCT

The primary endpoint was the difference between groups' median score on a 10cm Visual Analogue Scale (VAS) administered pre-operatively for the question:

'*How confident are you that you know how your breasts are likely to look after treatment?'*

3.3.8.2 Secondary outcomes

Patient reported satisfaction with preparation method (i.e. randomisation group).

Measured using a post-operative VAS at 3-6 months and one year post treatment to assess how the pre-operative preparation compared to their observed aesthetic results.

The post-operative VAS was for the question:

"How well do you think the information about how your breasts are likely to look after surgery (discussion, 2D photographs, or 3D simulation) reflects how they actually look today?"

Objective evaluation of simulation accuracy

Linear measures and volume analysis for the operated breast at 3 and 12 months post BCT and for the simulated image were compared. The change in measures from baseline for the operated breast at 3 and12 months post BCT and for the simulated image were compared for accuracy.

Longitudinal PROMs

The BREAST-Q BCT module was administered at baseline, 3- and 12- months post BCT. Q-scores for 'satisfaction with breasts', 'psychosocial well-being', and 'sexual well-being' were reported. Between group differences and how PROMs change over time were evaluated.

3.3.9 Follow-up

3D-SI are performed at 2 weeks post-surgery, pre-radiotherapy, 3-6 months post BCT and annually to five years (following the mammography schedule). The follow up VAS will be administered at 3-6 months post BCT and at one year. The BREAST-Q will be administered at 3-6 months post-BCT then annually to five years.

3.3.10 Sample size calculation

The primary endpoint was based on a visual analogue scale. A difference of 15mm or greater between any two groups, was considered clinically significant. This was based on clinical judgement and feedback from patient representatives. With an estimated standard deviation of 20mm, a Bonferroni corrected alpha of 0.017 to allow for 3 comparisons and an 80% power the study, 39 patients were required per arm giving a total of 117 patients. Although it was predicted that 15% of patients might be lost due to mastectomy or discontinuation later, this would not affect the primary outcome measure and therefore did not need to be accounted for in the power calculation.

3.3.11 Randomisation

Women were recruited and randomised pre-operatively by the Institute of Cancer Research Clinical Trials Unit. Randomisation was stratified for BMI, intent to undergo axillary lymph node dissection (ALND) and operation type (Wide Local Excision or therapeutic mammoplasty) as these factors are reported to influence patient satisfaction with breasts after BCT.[35]

3.3.12 Blinding

As explained, it was not possible to blind participants or investigators to the randomisation groups at the initial consultation. One research registrar carried out the outcome evaluation (i.e. analysis of VAS, BREAST-Q, and objective measures) and was blinded to randomisation group at this stage.

3.3.13 Statistical analysis

Primary endpoint

A Kruskal-Wallis test was used to compare baseline VAS scores between the 3 groups with a 5% significance level, with further post-hoc tests to find the statistically significant differences. Patients who did not go on to have BCT and instead had mastectomy were included in the primary endpoint analysis.

The same analysis was used for the VAS at 3 and 12 months (VAS 2 and 3) although follow-up is ongoing therefore the results must be interpreted with caution.

Comparing the simulation to reality at 3 months and 1 year post BCT using linear and 3D measures from 3D-SI

The change in the operated breast from baseline to 3 and 12 months post BCT and for the simulated image were analysed using objective linear and 3D measures and compared.

Objective measures were used to compare the simulated image of the operated breast to the actual appearance at both 3 and 12 months post-BCT. The correlation co-efficient (r), limits of agreement, and mean differences were

calculated to compare the simulated image to reality. Scatter and Bland Altman plots were used to illustrate correlation and agreement for nipple-to-sternal notch distance and volume between the simulated images and reality at 3 and 12 months post-BCT.

Follow-up is ongoing so statistical testing was not performed on these data as the results may be misleading. The study will run for 5 years and 3D-SI is performed annually enabling further longitudinal analysis on how both the operated and non-operated breasts change over time.

Analysis of the BREAST-Q

The descriptive statistics for the Q-score for 'satisfaction with breasts', 'psychosocial well-being', and 'sexual well-being' were reported at baseline and 3 and 12 months post BCT.

Between-group differences for the 'satisfaction with breasts' domain were analysed at baseline using a Kruskal-Wallis test.

The post-operative BREAST-Q results were reported using descriptive statistics for the purpose of this thesis and significance testing will not be reported as follow-up is ongoing, hence, may be misleading. The study continues to 5 years and the BREAST-Q is repeated annually with the intention to gain valuable insight into how PROMs change over time in a BCT population.

3.4 Results

3.4.1 Recruitment

The Study opened in May 2017 and the final patient was recruited in October 2019. Cumulative recruitment is illustrated in Figure 17. The discontinuation rates are illustrated in Figure 18. Participant progress through the study is displayed in Figure 19.

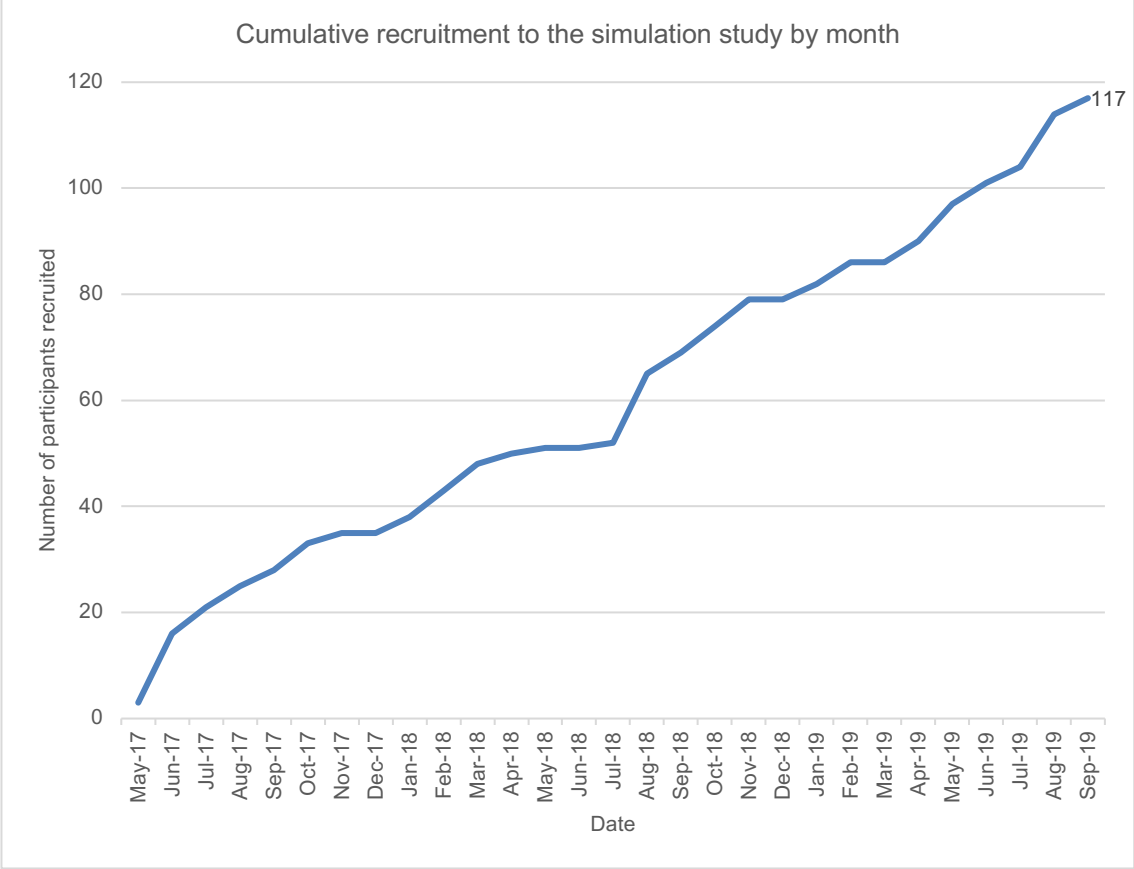

Figure 17 Cumulative recruitment to the simulation study by month

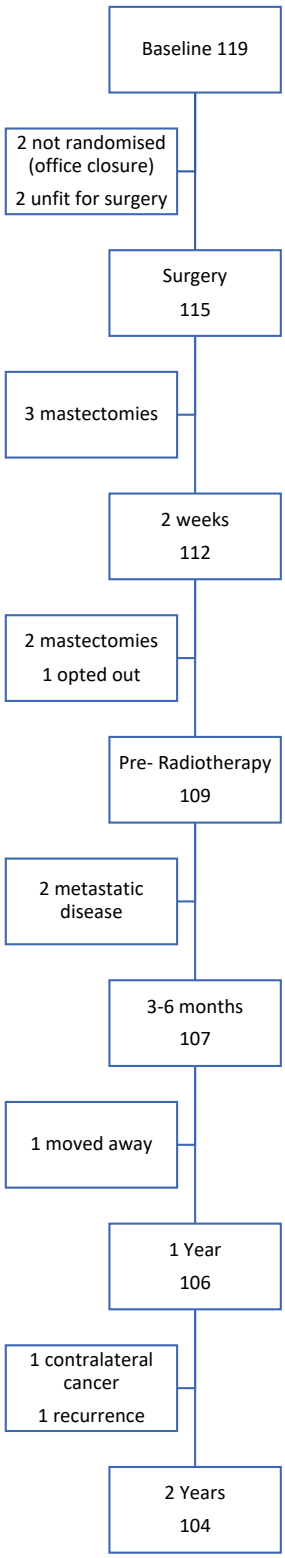

Figure 18 Study population and explanation of 'discontinuations' (as of October 2019)

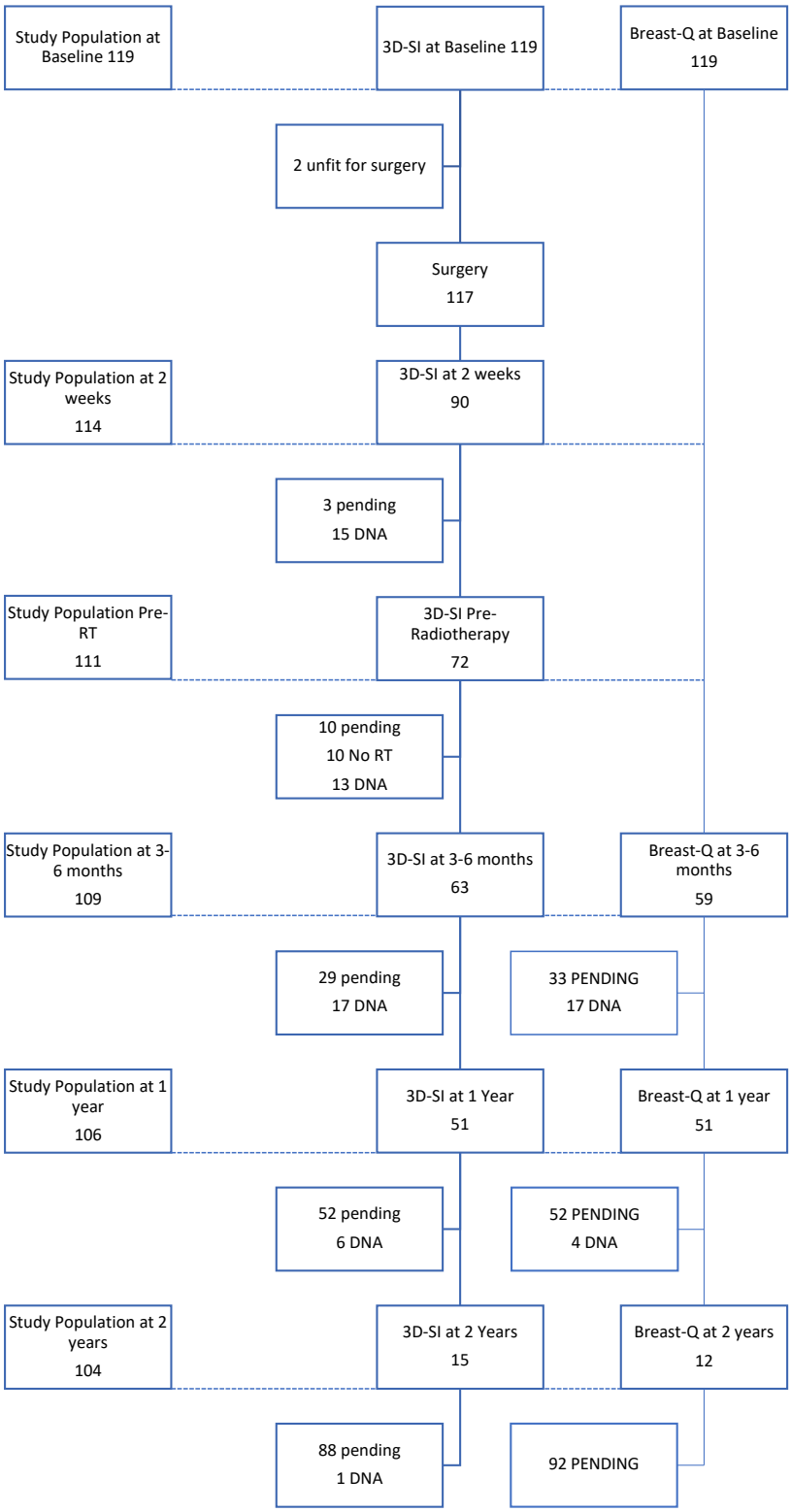

Figure 19 Participant progress through the study (as of October 2019)

3.4.2 Baseline data

The demographics and clinico-pathological data for the study population are illustrated in Table 10. The participants had an average age of 59 years, BMI of 29kg/m^2 and were mainly White British, reflecting our local population. Two participants were deemed unfit for surgery after randomisation and hence are not included in the histopathological data but are included in the primary endpoint. The majority of women underwent standard wide local excision (76%) and sentinel lymph node biopsy (SLNB) (90%). 13(11%) had re-excision of margins, 5(4%) of whom progressed to mastectomy (hence were included in the primary endpoint but not for the remaining outcomes). 86% of participants underwent radiotherapy, of the 16 women that did not, 6 participated in the PRIMETIME study [NCT00088168], 3 had mastectomy, 3 declined, 3 had DCIS (and radiotherapy not indicated in the light of the histopathology), and 1 had a new diagnosis of metastatic colorectal cancer shortly after surgery and became palliative.

Demographics	
Age Mean (sd)	58.88 (10.00)
BMI Mean (sd)	28.79 (6.11)
Ethnicity n (%)	
White British	93 (79)
White Other	12 (10)
Asian	5 (4)
Black -Caribbean	4 (3)
Mixed White and Asian	1 (1)
Black African	1 (1)
Black other	1 (1)
Smoking status n (%)	
Non-smoker	61 (52)
Ex-smoker	42 (36)
Smoker	14 (12)

Clinicopathological Information	
Laterality of Cancer n (%)	
Right	65 (56)
Left	52 (44)
Tumour Location n (%)	
Upper Outer Quadrant	51 (44)
Upper Inner Quadrant	17 (15)
Upper Central	12 (10)
Lateral	11 (9)
Lower Outer Quadrant	8 (7)
Lower Inner Quadrant	6 (5)
Lower Central	5 (4)
Central	4 (3)
Medial	3 (3)
Tumour Size at Diagnosis (straight to surgery population)	
Size on Mammogram mm Mean (sd)	20 (12.89)
Size on USS mm Mean (sd)	18 (11.27)
Size on MRI (n=13) mm Mean (sd)	26 (12.34)
Tumour Size (neoadjuvant study population)	
Mammogram at diagnosis (mm) Mean (sd)	30 (16.59)
Ultra-sound (mm) Mean (sd)	30 (9.56)
MRI (n= 1) (mm) Mean (sd)	36
Pre-op USS size (mm) Mean (sd)	11 (9.11)
Neoadjuvant Treatment	
Total n (%)	15 (13)
Chemotherapy n (%)	12 (10)
Endocrine n (%)	3 (3)

Surgical Information	
Type of Surgery n (%)	
Wide Local Excision	76 (65)
Mammoplasty	39 (33)
No surgery (deemed unfit at pre-assessment)	2 (2)
Type of mammoplasty n (%)	
Wise pattern mammoplasty	7 (18)
Nipple re-centralisation	7 (18)
Round Block	6 (15)
Lateral	6 (15)
SPAIR	4 (10)
Vertical scar mastopexy	4 (10)
Benelli	2 (5)
J mammoplasty	2 (5)
Le Jour	1(3)
Axillary Surgery n (%)	
SLNB	90 (78)
ALND	7 (6)
None	16 (14)
TAD	2 (2)
Re-excision of margins n (%)	
No	104 (90)
Yes	13 (11) (5 [4%] completion mastectomies)
No surgery	2 (2)
Contralateral symmetrisation	8 (7)

Histopathology	
Tumour Type n (%)	
Ductal	90 (78)
Lobular	8 (7)
Other	2 (2)
No invasive component	15 (13)
Grade of Invasive Tumour n (%)	
1	18 (18)
2	53 (53)
3	28 (28)
Microinvasion	1 (1)
Presence of DCIS n (%)	
Yes	96 (83)
No	19 (17)
Grade of DCIS n (%)	
Low	12 (13)
Intermediate	48 (50)
High	36 (37)
Specimen weight (g) Mean (sd)	70 (128.5)
Invasive Tumour Size (mm) Mean (sd)	24(15.04)
Total tumour size Including DCIS (mm) Mean (sd)	27 (15.22)
Nodal Disease n (%)	
Negative	71 (62)
Positive	25 (22)
Micrometastasis	3 (3)
No Axillary Surgery	16 (14)

Hormone receptor status for invasive tumours	
ER n (%)	
Positive	88 (88)
Negative	11 (11)
Unknown	1 (1)
PR n (%)	
Positive	78 (78)
Negative	21 (21)
Unknown	1 (1)
HER2 n (%)	
Positive	15 (15)
Negative	84 (84)
Unknown	1 (1)
Adjuvant Treatment	
Radiotherapy (%)	
Yes	99 (86)
No	16 (14)
Endocrine n (%)	
Yes	91 (79)
Tamoxifen	25 (28)
Letrozole	66 (73)
No	24 (21)
Chemotherapy n (%)	
No	87 (76)
Yes	28 (24)
Surgical Complications	
Stitch Abscess n (%)	2 (2)
Seroma requiring drainage n (%)	1 (1)
Wound infection requiring antibiotics n (%)	1 (1)
Delayed wound healing (>30 days) n (%)	1 (1)
Evacuation of haematoma in theatre n(%)	1 (1)

Table 10 Demographics and clinicopathological data for the simulation study population

3.4.3 Visual analogue scales

The descriptive statistics for the three VASs administered during the study are illustrated in Table 11. Higher score for VAS 1 are observed in groups 2 and 3 and in additional, narrower inter-quartile ranges. There is little difference between groups for VAS 2 & 3, but these data are incomplete, and follow-up is ongoing.

	Control	2D-Photography	3D-Simulation	*Between group differences (Kruskall-Wallis Test)*
VAS 1 (Baseline)				
N116 (1 not able to view sim)	41	39	36	*<0.001*
Median (mm) (IQR)	52(26-78)	80(57-87)	89(82-95)	
VAS 2 (3-6 months)				
n	17	21	21	*0.23*
Median (mm) (IQR)	83(57-97)	90(72-99)	94(79-100)	
VAS 3 (1 year)				
n	15	17	17	*0.66*
Median (mm) (IQR)	81(66-94)	90(70-95)	84(78-100)	

Table 11 Comparison of median visual analogue scale (VAS) scores at different time-points. The VAS at baseline (VAS 1) was in answer to the question "How confident are you that you know how your breasts are likely to look after treatment?" and the VAS at 3-6 months and 1 year (VAS 2&3) was in answer to the question "*How well do you think the information about how your breasts are likely to look after surgery (discussion, 2D photographs, or 3D simulation) reflects how they actually look today?"*

3.4.3.1 Primary endpoint

The total number of participants for the primary endpoint was 116 because it was not possible to perform a simulation using the Mirror™ software for one participant. The simulation group report significantly higher VAS scores than group one and two (p=<0.001 and p= 0.012 respectively). No significant difference was observed between the group one and group two (standard verbal discussion and 2D photographs) (p = 0.061) (Figure 20).

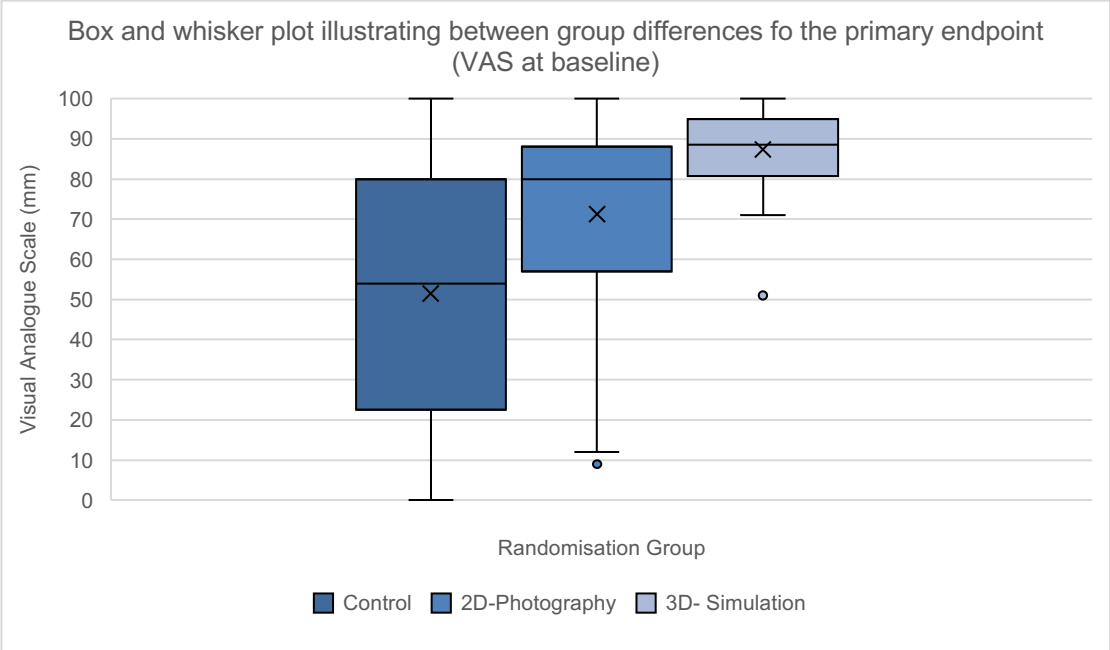

Figure 20 Box and whisker plot demonstrating between-group differences for the primary end point VAS in answer to the question "How confident are you of how your breasts will look after treatment?" administered pre-operatively (p<0.01). n=116 (1 failed simulation).Pairwise comparison with Bonferroni correction 1V2 p=0.061, 1V3 p<0.001, 2V3 p=0.004. X; mean, o ; outliers

3.4.3.2 VAS 2 & 3

As of October 2019, 60 participants had completed 'VAS 2' and 49 'VAS 3' for the question "How well do you think the information about how your breasts are likely to look after surgery (discussion, 2D *photographs, or 3D simulation) reflects how they actually look today?".* No statistically significant difference was observed between groups for either VAS 2 or 3 (Figure 21 and Figure 22),

however, these data are incomplete and follow-up is ongoing, therefore no firm conclusion can be drawn from these results.

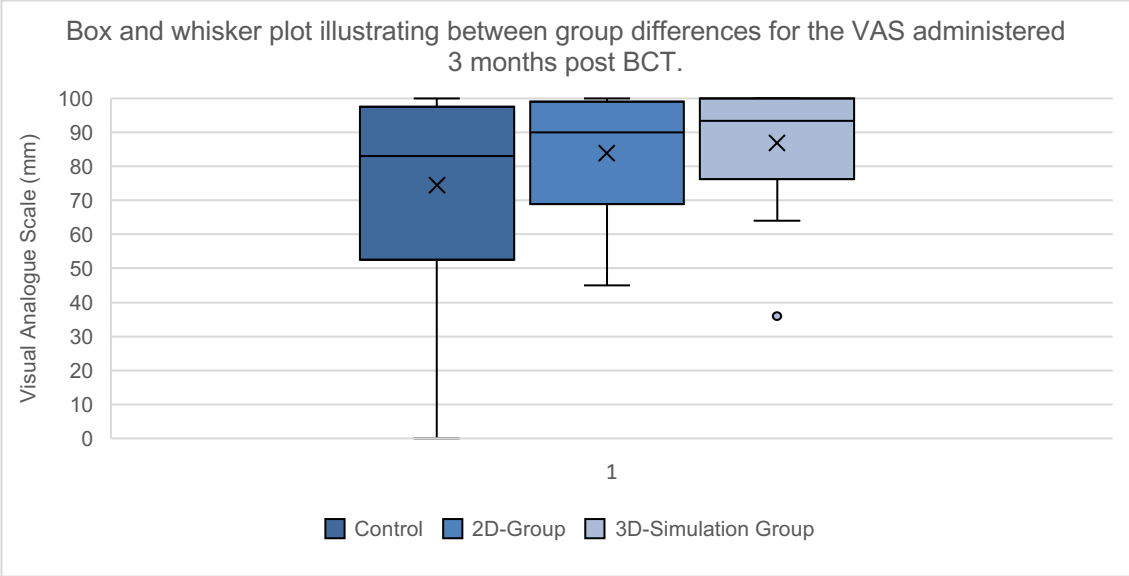

Figure 21 Box and whisker plot illustrates no between-group differences of VAS 2 administered 3-6 months post BCT in answer to the question "How well do you think the information about how your breasts are likely to look after surgery (discussion, 2D *photographs, or 3D simulation) reflects how they actually look today?"* (p=0.83) X; mean, ○ ; outliers

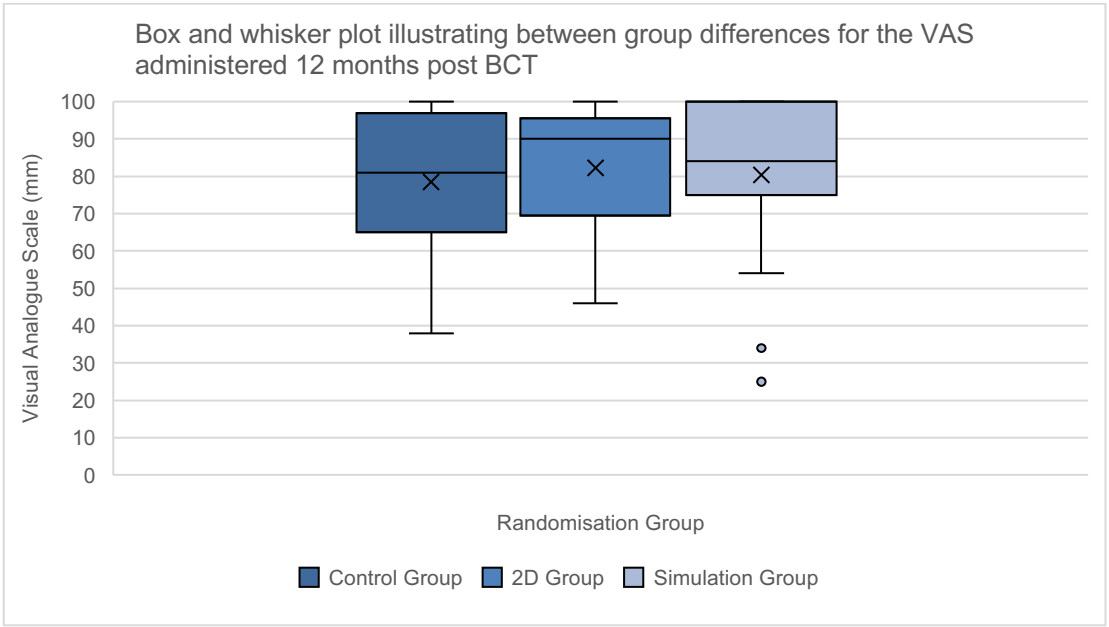

Figure 22 Box and whisker plot illustrates no between-group differences of VAS 3 administered 1-year post BCT in answer to the question "*How well do you think the information about how your breasts are likely to look after surgery (discussion, 2D photographs, or 3D simulation) reflects how they actually look today?"* (p=0.305) X; mean,○ ; outliers

3.4.4 3D-SI measures

Simulation was performed for all participants from their baseline image using the pre-defined method, but only the participants in the simulation group were shown their simulation (example simulation is illustrated in Figure 23). 16 images could not be simulated due to software difficulty. The majority had a high BMI with central adiposity, large volume breasts, or significant ptosis. One of the 16 was in the simulation group (Figure 24).

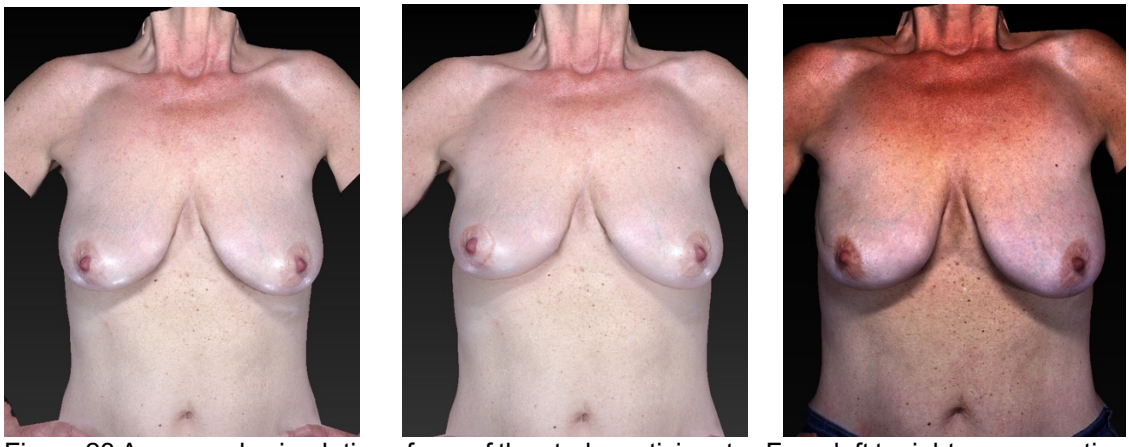

Figure 23 An example simulation of one of the study participants. From left to right, pre-operative AP view, simulated AP view, reality at 24 months AP view

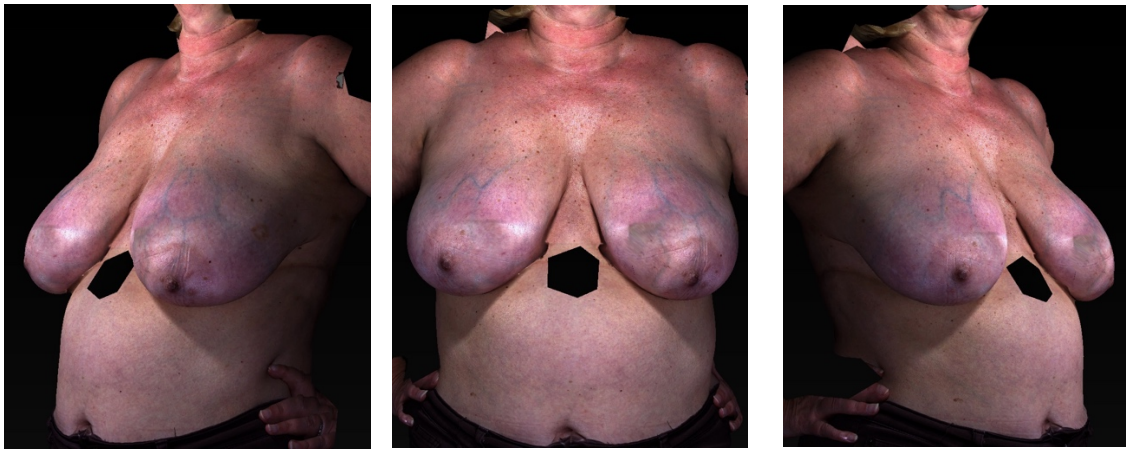

Figure 24 3D-SI of the participant whose images could not be simulated. Note an elevated BMI, defect in capture of the anterior abdominal wall secondary to central adiposity, and ptosis

At the time of analysis in October 2019, 56 participants had attended for the 3-month image, and 43 for the 12-month image. Women who had undergone mastectomy were not included in the analysis, neither were the two women who did not undergo surgery. The two participants who were not randomised because of a technical problem at the ICR randomisation service were included, as randomisation group was not relevant for this part of the analysis.

Measure	Difference between SIM and baseline for the operated breast (n=103)	Difference between 3 months and baseline for the operated breast (n=56)	Difference between 12 months and baseline for the operated breast (n=43)
Single breast measures			
Nipple to sternal notch distance (cm) Mean (sd)	1.61 (3.58)	0.59 (1.94)	0.81(3.57)
Volume (cc) Mean (sd)	11.70 (114.99)	4.67 (95.88)	30.05 (170.39)
Nipple to midline distance (cm) Mean (sd)	-0.29 (1.85)	0.23 (0.96)	0.58 (1.63)
Nipple to IMF distance (cm) Mean (sd)	-0.68 (1.69)	-0.2 (0.83)	0.089 (1.45)
Breast base width i.e. lateral to medial mammary fold (cm) Mean (sd)	0.44 (2.6)	0.25 (1.22)	0.69 (2.58)
Nipple to Nipple distance (cm) Mean (sd)	-0.61 (0.48)	1.31 (5.28)	0.99 (4.21)
Between breast measures			
Medial to medial mammary fold distance (cm) Mean (sd)	-0.26 (1.37)	0.16 (0.97)	0.14 (0.96)
Projection difference (cm) Mean (sd)	-0.16 (0.44)	-0.14 (0.6)	-0.13 (0.57)
Nipple height difference (cm) Mean (sd)	1.42 (0.81)	1.30 (1.64)	1.29 (1.54)
IMF height difference (cm) Mean (sd)	1.42 (0.81)	0.51 (1.56)	0.65 (1.54)

Table 12 Changes in measures (from 3D-SI) from baseline to the simulated, 3- and 12-month images

Table 12 illustrates the change in measures from baseline to the simulated and 3- and 12-month images. The most striking difference between simulation and reality is the change in volumes. The simulation on average, results in an 11cc reduction in volume compared to baseline, compared to a 4cc reduction at 3months and 30cc at one year. The difference between the 3- and 12-month volumes could be partially down to the presence of oedema at 3 months creating an artificially larger volume for comparison. The standard deviation in volume change may represent the range of oncoplastic procedure in the cohort given that 39% underwent mammoplasty or more complex tissue re-arrangement. The means of the remaining linear values were accurate to within a couple of centimetres. Of note, the simulation model moved the nipple laterally, however, the results from this cohort suggest the nipple on the post-operative breast has moved very marginally medially i.e. the nipple midline, nipple to nipple, and medial mammary fold distances are all shorter for the 3-and 12-month images than for baseline, but marginally longer for the simulated image. The values are small, so the relevance is debatable.

Measure	Correlation co-efficient (3 months and simulation) (n=56)	Correlation co-efficient (12 months and simulation) (n=43)
Single breast measures		
Nipple-sternal notch distance (cm)	0.86	0.83
Volume (cc)	0.94	0.83
Nipple- midline distance (cm)	0.87	0.82
Nipple-IMF Distance (cm)	0.65	0.67
Breast base width i.e. lateral to medial mammary fold (cm)	0.80	0.74
Nipple to nipple distance (cm)	0.92	0.88
Medial to medial mammary fold	0.39	0.24
Between breast measures		
Projection between breasts (cm)	0.56	0.60
Nipple height difference between breasts (cm)	0.37	-0.02
IMF height difference between breasts (cm)	0.30	-0.06

Table 13 Correlation of 3D measures between the simulated images and actual results at 3 and 12 months post-BCT. IMF; inframammary fold

Table 13 illustrates a strong positive correlation at 3 and 12 months between the simulated and actual measures for nipple to sternal notch distance(r=0.86, r=0.83), volume, nipple to midline distance (r=0.94, r=0.83), breast base width (r=0 0.8, r=0.74) and nipple to nipple distance (0.92, 0.88) and a moderate correlation form nipple to IMF distance (r=0.65, r=0.67) and projection (r=0.56, r=0.6). Nipple and IMF height difference in addition to medial to medial mammary fold distance have (at best) a weak correlation with the simulated values. The small values and narrow range of change from baseline may help explain this relationship. The correlation between the simulated image and reality and 3 and 12 months for N-SN distance and volume are illustrated in Figures 25-28.

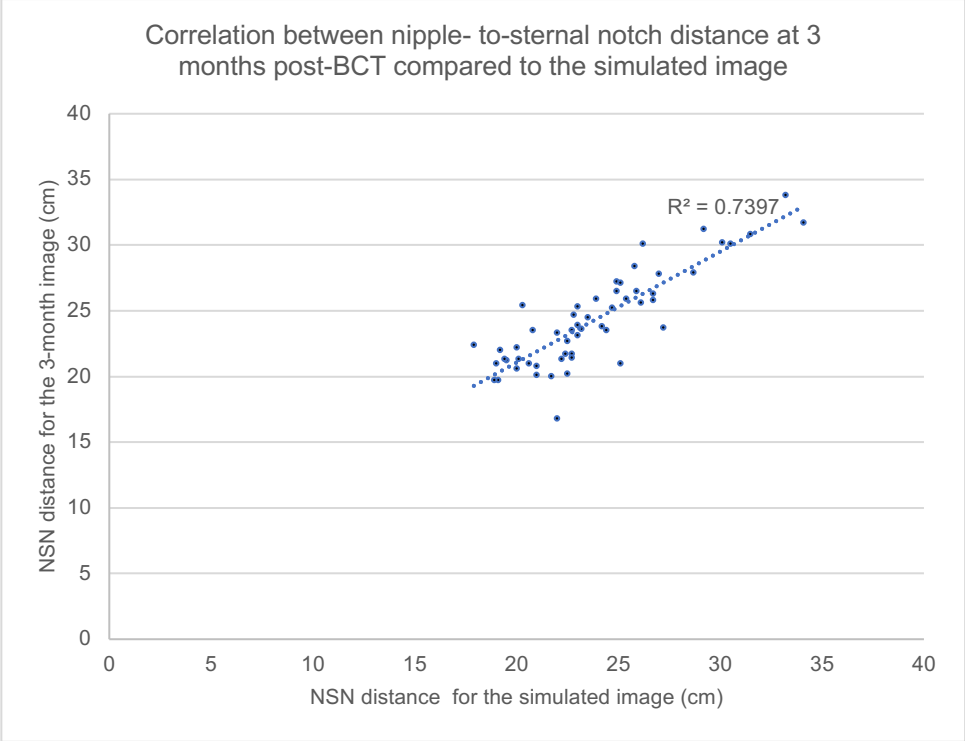

Figure 25 Correlation between Nipple-Sternal-Notch distance at 3 months post-BCT and the simulated image. (r=0.86) Dotted line represents the linear agreement, with R^2 demonstrating the strength of linear agreement where 1 is perfect agreement and 0 is no agreement

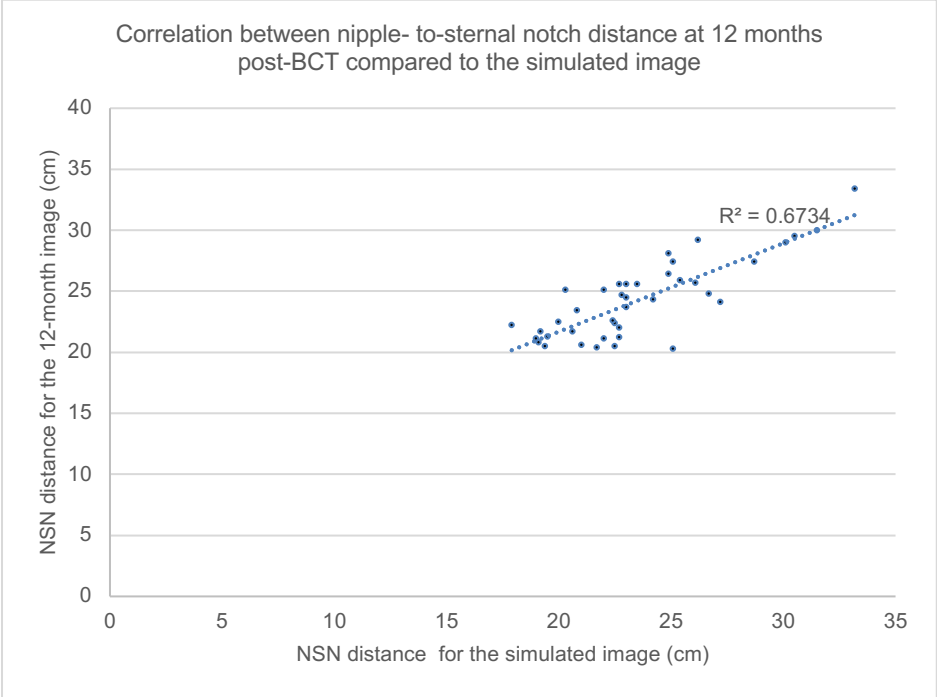

Figure 26 Correlation between Nipple-Sternal-Notch distance at 12 months post-BCT and the simulated image (r=0.83). Dotted line represents the linear agreement, with R^2 demonstrating the strength of linear agreement where 1 is perfect agreement and 0 is no agreement

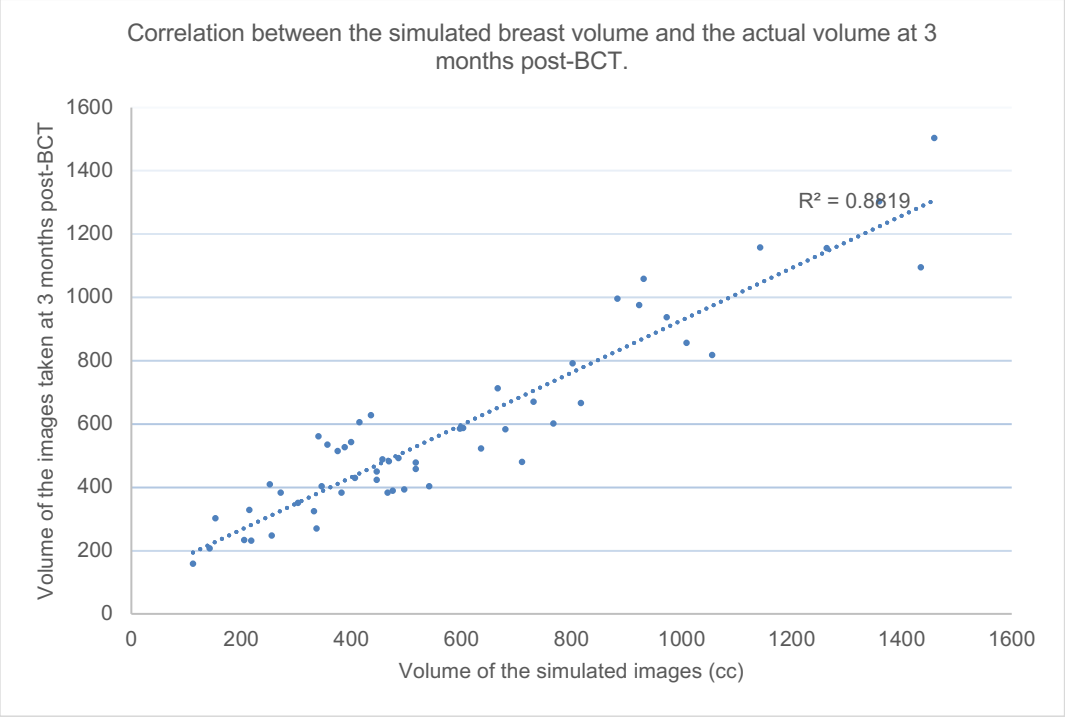

Figure 27 Correlation between volume at 3 months post-BCT and the simulated image (r=0.94). Dotted line represents the linear agreement, with R^2 demonstrating the strength of linear agreement where 1 is perfect agreement and 0 is no agreement

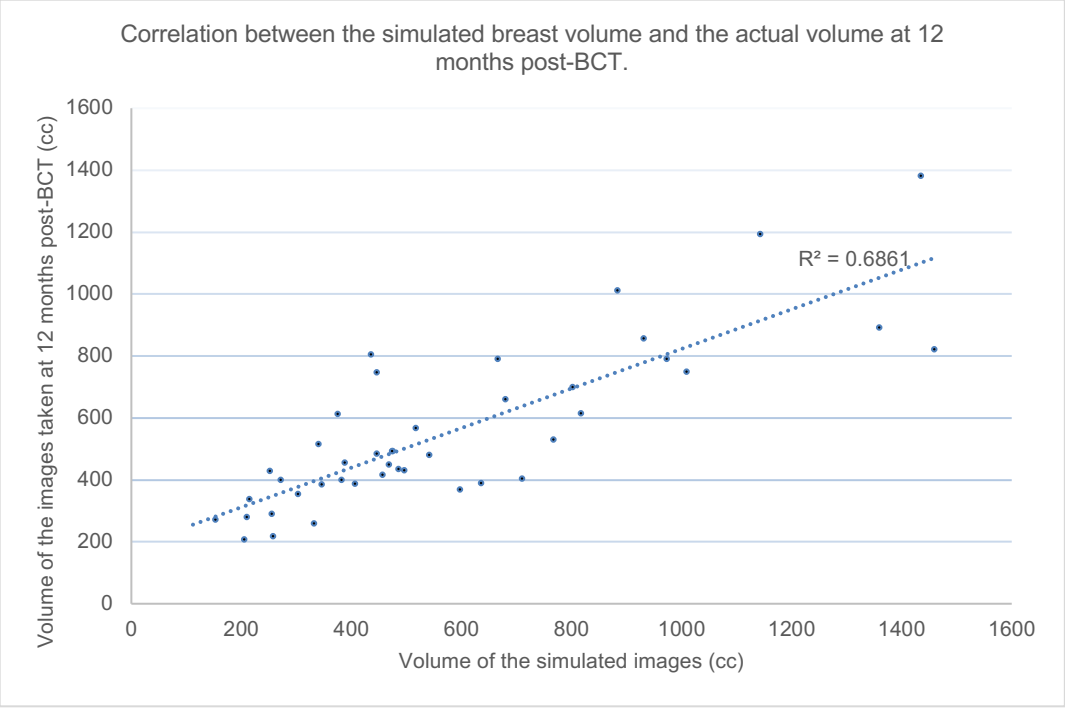

Figure 28 Correlation between volume at 12 months post-BCT and the simulated image r=0.83). Dotted line represents the linear agreement, with R^2 demonstrating the strength of linear agreement where 1 is perfect agreement and 0 is no agreement

	Mean difference	Standard deviation	Lower limit of agreement (mean difference-1.96 x standard deviation)	Upper limit of agreement (mean difference+1.96 x standard deviation)
Single breast measures				
Nipple-sternal notch distance (cm)				
3 months and simulation (n=56)	0.47	1.93	-3.33	4.27
12 months and simulation (n=43)	0.71	2.01	-3.23	4.65
Volume (cc)				
3 months and simulation (n=56)	0.16	117.35	-229.84	230.17
12 months and simulation (n=43)	-24.46	188.24	-393.40	344.49
Nipple- midline distance (cm)				
3 months and simulation (n=56)	-0.75	0.93	-2.57	1.07
12 months and simulation (n=43)	-0.94	1.06	-3.01	1.13
Nipple-IMF Distance (cm)				
3 months and simulation (n=56)	-0.80	1.54	-3.83	2.22
12 months and simulation (n=43)	-0.98	1.52	-3.96	1.99
Breast base Breast base width i.e. lateral to medial mammary fold (cm)				
3 months and simulation (n=56)	-0.30	2.60	-5.39	4.79
12 months and simulation (n=43)	-0.07	1.80	-3.60	3.46
Nipple to nipple distance (cm)				
3 months and simulation (n=56)	-0.95	1.28	-3.46	1.55
12 months and simulation (n=43)	-1.05	1.49	-3.98	1.87
Medial to medial mammary fold distance				
3 months and simulation (n=56)	-0.95	1.28	-3.46	1.55
12 months and simulation (n=43)	-1.05	1.49	-3.98	1.87

	Mean difference	Standard deviation	Lower limit of agreement (mean difference-1.96 x standard deviation)	Upper limit of agreement (mean difference+1.96 x standard deviation)
Between breast measures				
Projection between breasts (cm)				
3 months and simulation (n=56)	-0.01	0.66	-1.30	1.27
12 months and simulation (n=43)	0.01	0.50	-0.97	0.99
Nipple height difference between breasts (cm)				
3 months and simulation (n=56)	-0.01	1.66	-3.26	3.23
12 months and simulation (n=43)	-0.03	2.14	-4.22	4.16
IMF height difference between breasts (cm)				
3 months and simulation (n=56)	-0.82	1.81	-4.37	2.74
12 months and simulation (n=43)	-0.74	1.95	-4.57	3.08

Table 14 Summary of the agreement between 3D-measures from the simulated image and the actual results at 3 and 12 months post-BCT. IMF; inframammary fold

Table 14 illustrates the agreement between the simulated images and reality at 3 and 12 months. Aside from volume at 12 months, the measures all have a mean difference close to zero implying no systematic bias in the simulation. The mean difference of -24cc for volume at 12 months suggests the simulation is underestimating volume reduction with surgery. Volume also has wide limits of agreement meaning that the simulation may be quite different from reality for an individual patient.

Bland Altman plots illustrate the agreement between the simulated image and reality for volume and nipple-sternal notch difference at 3 and 12 months post BCT (Figure 29, Figure 30, Figure 31 and Figure 32 respectively).

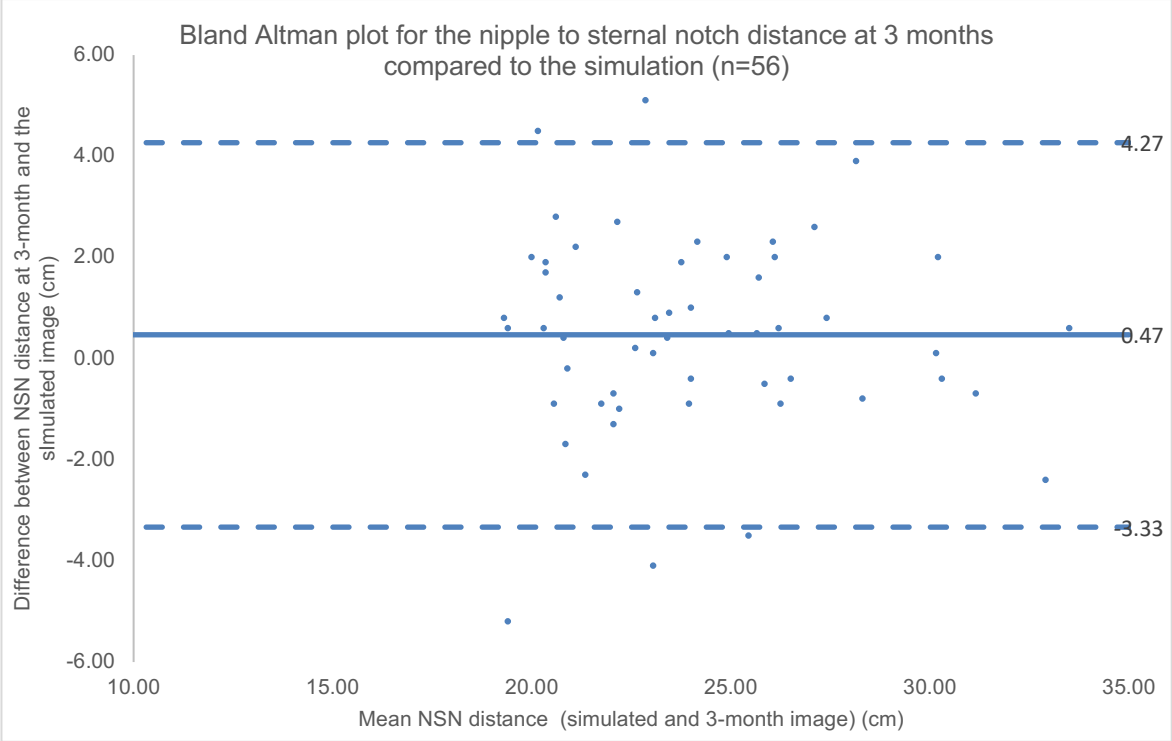

Figure 29 Bland Altman plot to illustrate the mean difference and limit of agreement for nipple to sternal notch (NSN) distance between the simulated image and the image taken at 3 months post-completion of BCT. The solid horizontal line represents the mean difference and the two broken lines represent the upper and lower limits of agreement

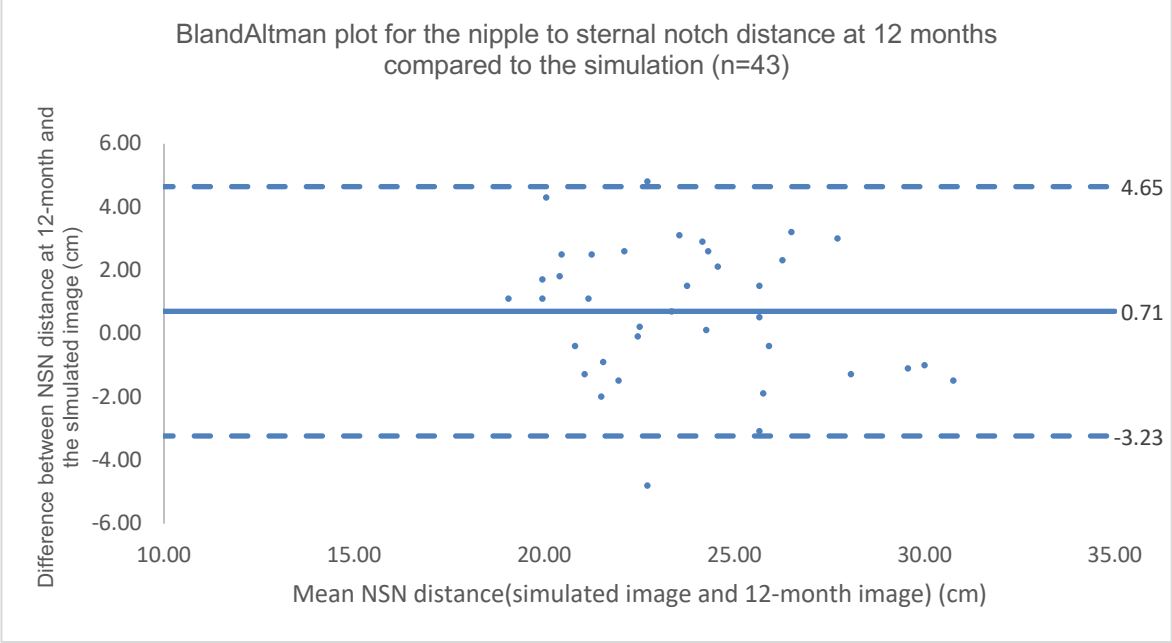

Figure 30 Bland Altman plot to illustrate the mean difference and limit of agreement for nipple to sternal notch (NSN) distance between the simulated image and the image taken at 12 months post-completion of BCT. The solid horizontal line represents the mean difference and the two broken lines represent the upper and lower limits of agreement

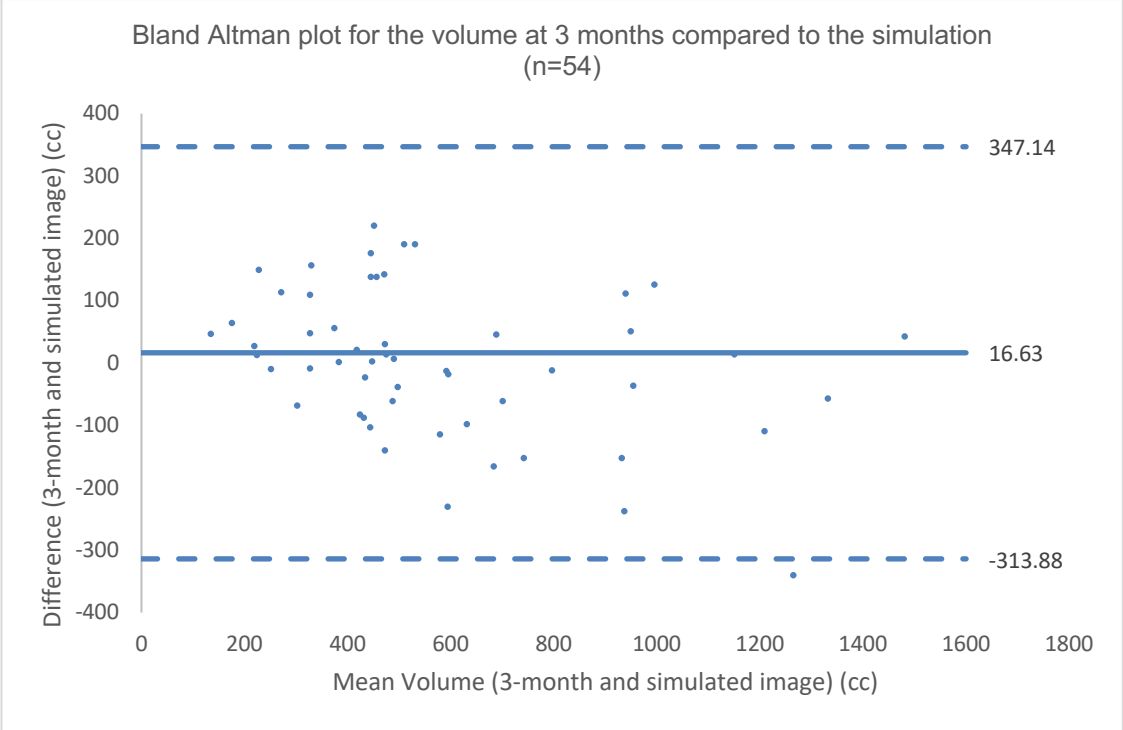

Figure 31 Bland Altman plot to illustrate the mean difference and limit of agreement in volume between the simulated image and the image taken at 3 months post-completion of BCT. The solid horizontal line represents the mean difference and the two broken lines represent the upper and lower limits of agreement

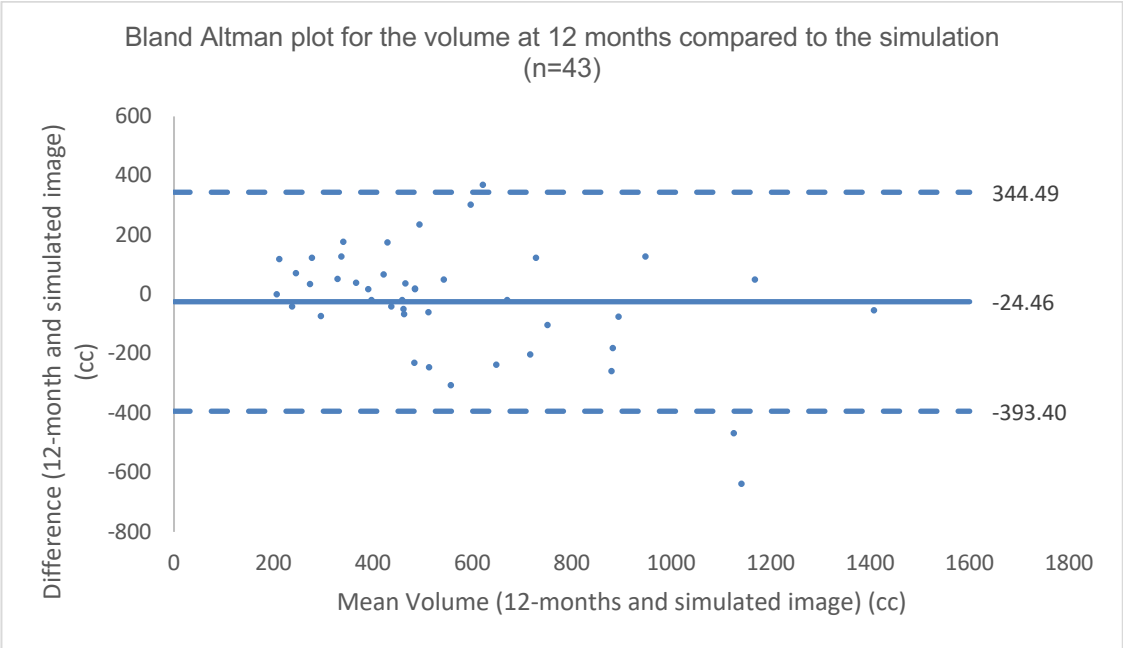

Figure 32 Bland Altman plot to illustrate the mean difference and limit of agreement in volume between the simulated image and the image taken at 12 months post-completion of BCT. The solid horizontal line represents the mean difference and the two broken lines represent the upper and lower limits of agreement

3.4.5 BREAST-Q

The Q-scores for the baseline BREAST-Q are shown in Figure 33. No significant differences for the 'satisfaction with breasts' domain were found between groups at baseline (p=0.34), 3-months (p=0.843) or 12 months (p=0.5). There were no significant differences between groups for psychosocial or sexual wellbeing at any time-point (Table 15).

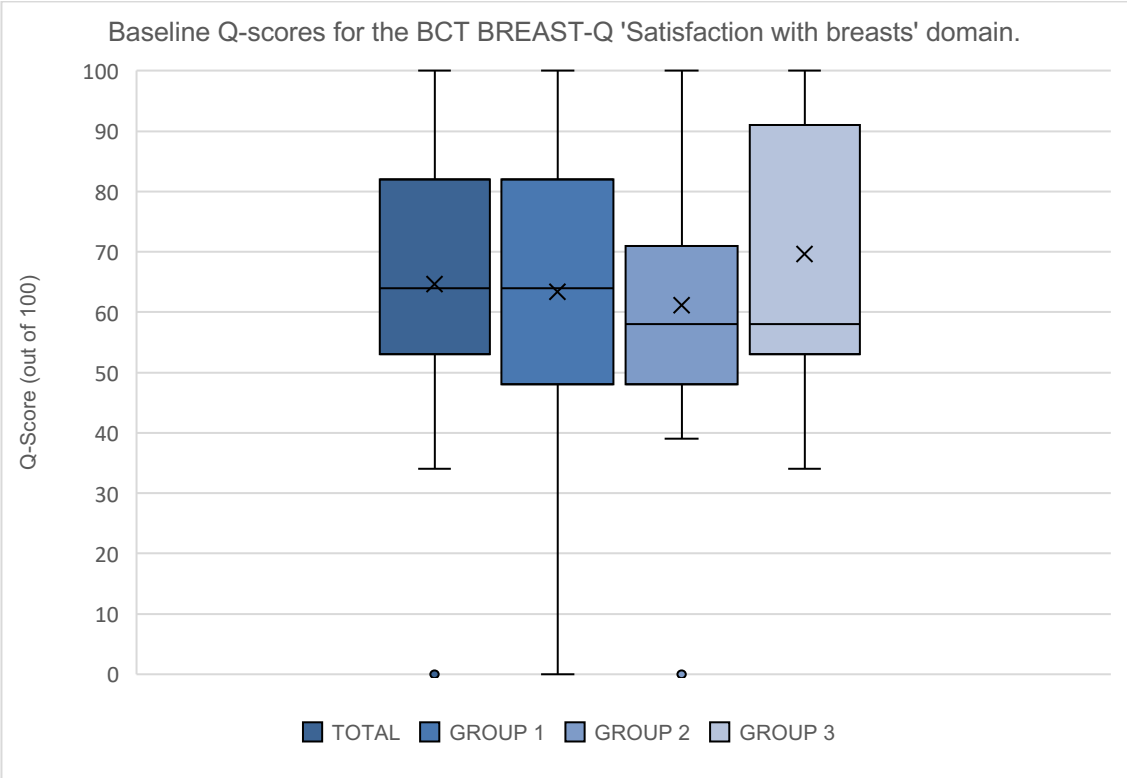

Figure 33 Box and whisker plot for the baseline pre-operative BCT BREAST-Q demonstrating the Q-scores (out of 100) for the 'satisfaction with breasts' domain for the total study population and each of the randomisation groups for comparison

Satisfaction with Breasts Median (IQR)	Total study population	Group 1	Group 2	Group 3
Baseline (n=117)	64(53-82)	64(48-82)	58(48-71)	58(53-87)
3-6 Months (n=71)	74(57-85)	61(57-85)	76(56-85)	77(57-85)
12 Months (n=50)	71(57-199(	66(54-83)	80(60-91)	71(59-100)
Psychosocial wellbeing Median (IQR)	**Total study population**	**Group 1**	**Group 2**	**Group 3**
Baseline (n=117)	69(58-83)	69(55-83)	66(58-77)	77(60-87)
3-6 Months (n=71)	68(55-82)	63(57-82)	73(56-82)	66(52-76)
12 Months (n=50)	79(59-92)	73(61-96)	68(56-87)	87(76-100)
Sexual wellbeing Median (IQR)	**Total study population**	**Group 1**	**Group 2**	**Group 3**
Baseline (n=117)	59(46-70)	59(48-69)	62(46-72)	48(41-67)
3-6 Months (n=71)	48(0-57)	43(0-51)	47(0-59)	49(0-58)
12 Months (n=50)	54(29-64)	57(52-69)	58(36-64)	57(49-66)

Table 15 Q-Scores for BCT BREAST-Q module at baseline, 3 and 12 months post-BCT. Group 1; control, group 2; 2D images, group3; 3D simulation. IQR; inter-quartile range

'Satisfaction with breasts' appears to improve over time for all three randomisation groups (Table 15, Figure 34, Figure 35, Figure 36). Completion of follow-up will clarify any between-group differences i.e. does the preparation method influence 'satisfaction with breasts'. Psychosocial wellbeing appears to worsen at 3 months and recover at 12 months post-BCT superseding the baseline value. Sexual wellbeing declines in all three groups up to 12 months compared to baseline. The complete 5-year follow-up will be useful in order to describe longitudinal trends in PROMs to help manage expectations of patients and potentially introduce treatment strategies to aid recovery at critical time-points.

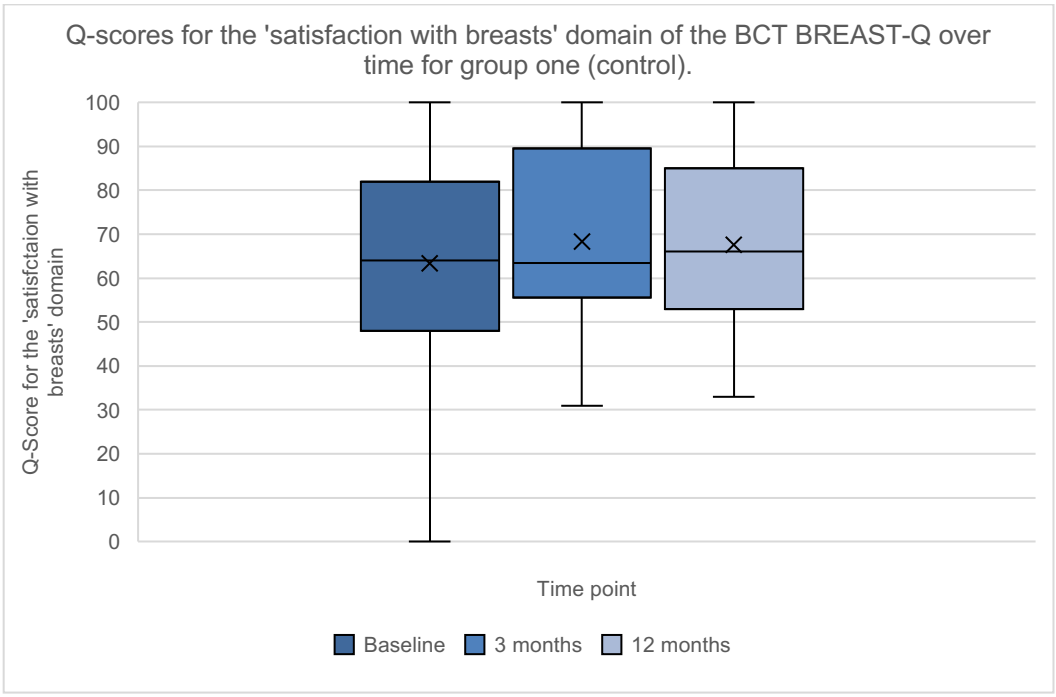

Figure 34 Box and whisker plot for the 'satisfaction with breasts' domain from the BCT BREAST-Q demonstrating the Q-scores (out of 100) for the control group (group 1) at baseline, 3 and 12 months post BCT. x represents the mean

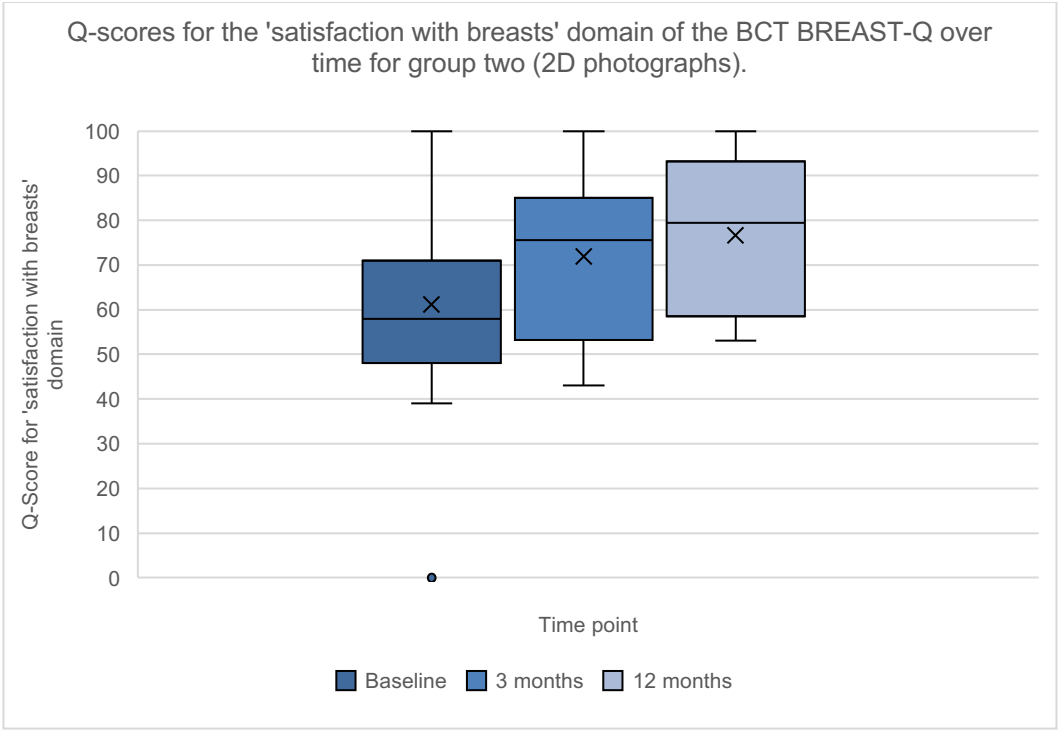

Figure 35 Box and whisker plot for the 'satisfaction with breasts' domain from the BCT BREAST-Q demonstrating the Q-scores (out of 100) for the 2D photograph group (group 2) at baseline, 3 and 12 months post BCT. x represents the mean

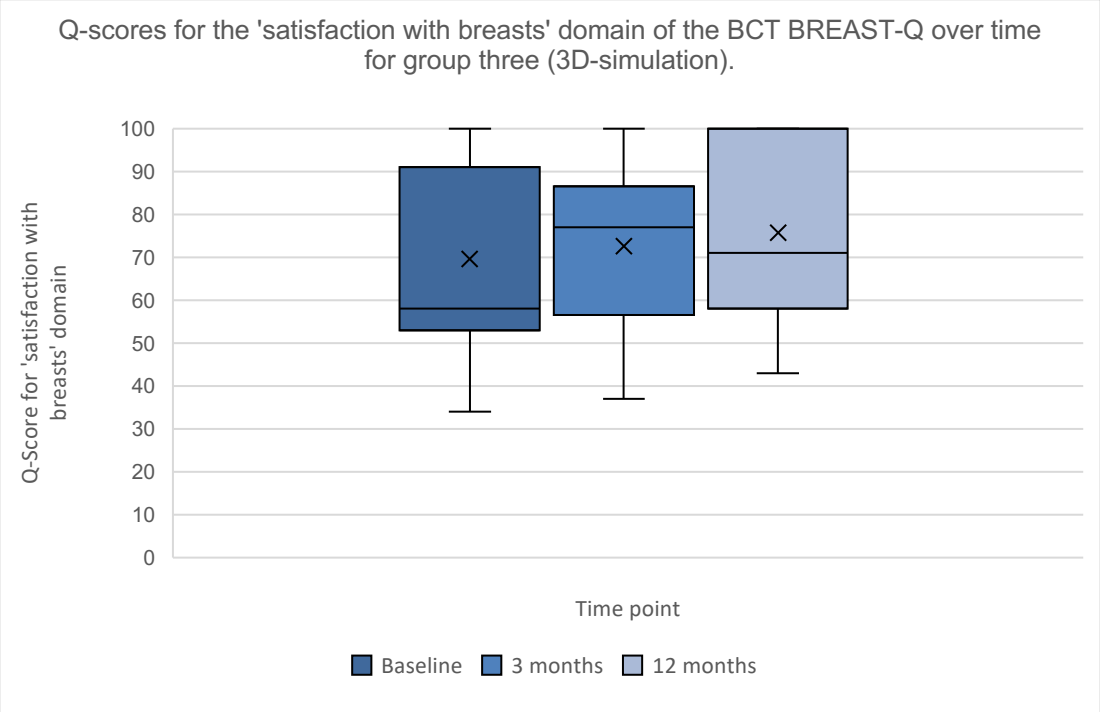

Figure 36 Box and whisker plot for the 'satisfaction with breasts' domain from the BCT BREAST-Q demonstrating the Q-scores (out of 100) for the 3D simulation group (group 3) at baseline, 3 and 12 months post BCT. x represents the mean.

The change in Q-score from baseline for each of the three groups can be observed in Table 16.

	Group 1	Group2	Group3
Satisfaction with breasts Mean (sd)			
3 months - baseline	5.7 (27.15)	8.9 (15.11)	3.2(20.50)
12 months - baseline	7.13 (22.71)	13.83 (15.98)	7.94 (26.08)
Psychosocial wellbeing Mean (sd)			
3 months - baseline	-6.65 (28.7)	1.29 (22.64)	-13.39 (30.32)
12 months - baseline	8.27 (19.15)	3.17 (18.42)	4.35 (19.15)
Sexual wellbeing Mean (sd)			
3 months - baseline	-32.9 (38.21)	-16.28 (38.67)	-13.92 (41.62)
12 months - baseline	-5.5 (36.9)	-17.87 (26.91)	-18.38 (35.36)

Table 16 Change in the Q-scores for the BCT BREAST-Q from baseline to 3 months and from baseline to 12 months for the three randomisation groups. sd; standard deviation

3.5 Discussion

This is the first randomised controlled trial investigating the impact of 3D simulation of appearance on women's pre-operative understanding of aesthetic outcome. It showed that participants who viewed a real-time 3D simulation of their own likely appearance based on an average outcome after BCT reported significantly better preparedness for their aesthetic outcome than the other two groups.

3.5.1 Interpretation

The primary endpoint was reported in the pre-operative period so although it reflects the usefulness of simulation as a visual aid to discussing complex ideas in a simple fashion, it does not reflect how closely the simulation represented reality or indeed how well it prepared participants for their *actual* post-operative outcome.

The strengths of the study included the simplicity of the simulation method providing a quick way to simulate aesthetic outcome in the absence of complicated calculations which could be completed as part of a clinical consultation. The basic simulation enabled participants to view an average outcome from BCT on their own breast and provides proof of principle that viewing simulation was superior to current standards of care prior to investing time and money in development of a bespoke simulation.

In order to provide an average result and avoid an overly optimistic or pessimistic example, the simulation was based upon a BCT population who had scored 2 or 3 out of 4 (Harvard cosmesis scale) for aesthetic outcome. The simulation group was compared to relevant alternatives including a verbal description (control group) and the viewing of 2D- photographs matched for age, BMI, tumour location, and breast volume (which is standard of care for breast reconstruction counselling).

A potential area of bias is that further time spent with a clinician is an intervention in itself, so the number of investigators was kept low (2), every woman had a 3D-SI at baseline so experienced the technology and a standardised "patter"

was used for every participant regardless of group to explain the common aesthetic changes observed from BCT prior to receiving their allocated preparation method. The investigators were blinded to the randomisation group during outcome analysis. The elements that could not be controlled for were the blinding of the investigator or patient during the consultation, the psychological influence of 'getting to see' their simulation, or the previous discussion into expected aesthetic outcome between the participant and their surgeon in the clinical environment.

The simple simulation method may also be viewed as a weakness of the study. Although for the majority of women the simulation would have been close to the actual outcome, for a proportion it would have demonstrated either an overly optimistic or overly pessimistic representation of their aesthetic outcome which may influence the secondary endpoints of the study including PROMs. The development of a bespoke simulation may be required to better represent aesthetic outcome allowing the surgeon to take individual technical and patient factors into account.

3.5.1.1 Objective measures of simulation accuracy

Objective measurement of simulation accuracy has not previously been reported in the literature for BCT. Preliminary results comparing 3- and 12-month images with the simulated images were acceptable given the study brief to provide a simulation of an average outcome from BCT to establish proof of principle of simulation as a communication tool rather than to provide a bespoke individualised simulation for implementation as a decision-making aid.

The most striking differences between the simulation and reality were the range of volume measures observed. The reasons for this are likely to be multifactorial. The range of oncoplastic procedures performed will influence the resection volumes and although this was stratified during the randomisation process to ensure the primary endpoint was not biased by operation type, the objective evaluation of the simulation accuracy is all inclusive. The average excision weight for this study population was 70g compared to 30g in the population used to develop the simulation, likely to represent the higher

proportion of oncoplastic procedures (30% compared to 9%). The accuracy of the software for changes over time i.e. the influence of body position, weight gain and phase of the menstrual cycle is also not accounted for in the analysis.

The poor correlation observed between the simulated image and reality at 3 and 12 months for measures such as IMF height difference, nipple height difference and medial to medial mammary fold distance in addition to flaws in the simulation method, may be secondary to the small magnitude of change observed for these measures between time-points or variability in the placement of landmarks at breast folds i.e. the IMF is marked where the lower breast border meets the chest wall, not at the actual IMF for ptotic breasts as this can't be visualise on the 3D-SI in standing.

Further understanding of the range of 'between breast objective measures' compared to the perception of asymmetry (patient or expert) may be helpful in establishing the clinical significance for the use of objective measures not just for quantifying an acceptable range of accuracy for simulation models, but also for establishing objective scores for aesthetic outcome that may be more comparable with subjective opinion, be that patient or expert. Kasielska-Trojan et al report that patients can detect asymmetry of nipple position when a greater than two centimetre difference is present and 40-50cm^3 for volume differences.[128] The mean differences between the 3D simulation and reality at 3 and 12 months are small, however, the limits of agreement are not, suggesting that for some women a noticeable difference between simulation and reality will have been present, which is not unexpected given the simulation method.

The simulation was based on measures from women who had undergone BCT between 2010 and 2016 since which time we have observed an increased frequency in the use of oncoplastic techniques for breast conservation, improved radiotherapy techniques (including omission in a very low risk subgroup) and changes in the management of the axilla, all of which may influence aesthetic outcome. We included participants who were to undergo oncoplastic tissue rearrangement as long as there was no intention of contralateral adjustment, but a proportion did. Women who have undergone symmetrisation no longer reflect the population on which the simulation was based and the simulation

inaccuracies reflect that. Some measures i.e. nipple height and nipple position are maintained in reality more so than the simulation cohort suggest the oncoplastic techniques are reducing the aesthetic differences between breasts i.e. are effective.

Women with a Harvard score of two or three were used to base the simulation method, in order to provide an *average* outcome from BCT. Care was taken so as not to provide an overly optimistic or pessimistic simulation, either of which may affect psychological recovery in the post-surgical period. Existing natural asymmetry was also not accounted for in the method given the post-operative nature of the retrospective 3D-SIs.

3.5.1.2 Patient-reported outcome measures

Available post-BCT results for 'satisfaction with breasts' and 'psychosocial wellbeing' at one year (71 and 79 respectively) are in line with published results from two large cohorts of 200 and 300 women respectively who report mean satisfaction with breasts of 68 and 66 respectively and mean psychological wellbeing of 82 in both studies.[35, 41]

The general trends in the data available for participants at baseline compared to 3 and 12 months post-BCT would suggest an overall improvement in satisfaction with breasts and psychosocial wellbeing over time (with a dip in psychosocial wellbeing at 3 months post-BCT). Sexual wellbeing is observed to decline over time compared to baseline up to 12 months.

With the follow-up data available thus far, no between-group differences were observed between the randomised groups at 3 and 12 months post BCT. Follow-up is ongoing and the numbers completing the sexual wellbeing domain are particularly small so must be interpreted with caution.

The baseline breast-Q results for this study reflect a newly diagnosed population and may not represent a pre-morbid patient opinion. This has clinical relevance when assessing the change in scores from pre-to-post-BCT which may not reflect a participant's transition back to pre-morbid baseline rather their baseline

having just received a diagnosis of cancer. Between-group difference will still be relevant in addition to changes over time.

3.5.2 Generalisability

Follow-up is ongoing for the second and third VAS designed to capture participant opinion on whether the preparation method matched their reality. Thus far, no significant differences have been found between groups. The median reported scores were high, 90 and 84 for VAS 2 and 3 respectively suggesting women were highly satisfied with their recollection of all three preparation methods compared with reality. This method of reporting is subjective, vulnerable to recall bias and can also be influenced by participant experience in the post-surgical period.

Between-group differences for VAS 2 and 3 will be available for analysis in October 2020 when the final patient reaches one-year follow-up. This will be of value in determining any between-group differences for satisfaction with the different preparation methods versus reality. In addition, qualitative interviews with representative samples from each group may provide a little more explanation of their responses which could help to compare group experiences. It will never be possible to ascertain whether one patient may have preferred a different preparation method as the opinion will always be retrospective and they can only ever experience one journey. But it may be useful to ascertain whether patients from group one or two would have liked to view their simulation and similarly whether participants in group 3 still value the simulation experience a year down the line.

An additional test of simulation accuracy could be to hold a panel assessment (including patients, lay people, and experts) of the 3D simulated images in parallel with the actual results to help to define an acceptable level of accuracy. However, the limitations of panel evaluation are well recognised. At study completion (i.e. 5 years) all study participants could be shown their simulations and asked to score it compared to their actual outcome (with the relevant ethical approval). Panel assessment was used to evaluate the accuracy of simulation for implant augmentation in a study by Vorstenbosch et al, which highlighted

baseline breast type as an influencing factor for simulation success.[108] This may be relevant with Mirror software™ as it was difficult and sometimes not possible for the software to perform simulation in women with large breast, high BMI, or grade 3 ptosis. Clinically this may be relevant to patient selection for simulation until a workaround with the software can be written or bespoke simulation becomes normality.

The simulation population could also provide an opportunity to test the objective outcome tool developed in Chapter 2 in a prospective cohort and to observe how the objective score changes over time. This may be clinically relevant to provide information about the relevance of the timepoint at which aesthetic outcome is measured.

Study completion will also enable the evaluation of longitudinal PROMs in comparison to baseline values. Exploration into any between-group differences may provide a link between pre-operative preparation method and long-term satisfaction and/or psychological wellbeing which may give weight to a particular method. If a trend in PROMs over-time is seen, it may provide evidence not just to inform and manage patient expectation but also to suggest time-points where additional support or intervention may be relevant within survivorship programmes.

With longitudinal BREAST-Q follow-up, the influence of several factors that may affect PROMs can be evaluated over time including surgical (type of surgery to the breast, axilla, and complications), adjuvant treatment (especially radiotherapy versus none), prognostic information (grade, size, nodal involvement, hormone receptor status) and baseline patient information (BMI).

With the completion of follow-up, differences in all three data collection methods (VAS, objective measures, BREAST-Q) between participants who underwent standard wide local excision, oncoplastic procedures, or delayed symmetrisation may provide clinically relevant information.

The manufacture of VECTRA, Canfield Scientific (New Jersey) describe two different methods for measuring the change in surface asymmetry over time i.e. two methods to align multiple 3D-SIs captured at different time-points using

surface landmarks or surface area as reference points. Work is underway in our group to validate the methods. Ethical approval is in place to apply this method to the images from the simulation study to evaluate how symmetry changes over time to five years. Understanding how the natural breast changes in relation to the treated breast could provide clinically relevant information with regard to the timing of symmetrisation enabling the rationalisation of resource by performing the surgery at the optimal time point and potentially reducing the need for further revision (this may be more relevant in reconstructive surgery). This also has relevance to the timing of outcome evaluation.

3.5.3 Overall evidence

The simulation software available using pre-defined algorithms to model outcome from breast surgery are based upon aesthetic surgery i.e. implant augmentation, lipofilling, and mastopexy. To our knowledge, there is no software currently available to model breast reconstruction or BCT using 3D-SI. Some groups have looked at complex modelling of the outcome of BCT using biomechanics and wound healing models based on MRI imaging, but these methods involve complex mathematics, are time consuming, expensive, and not yet at a stage to be used in a clinical setting.[115-117]

There is clinical interest in expansion of simulation for the complex oncoplastic breast conservation and breast reconstruction population with the development of bespoke simulation as a tool for shared decision-making i.e. therapeutic mammoplasty with or without symmetrisation versus unilateral mastectomy and reconstruction or between different types of reconstruction. Additionally, in the initial phase, simulation may be used as an adjunct to the viewing of 2D photographs in order to give a range of outcomes for patients to avoid setting expectations too high in the initial phases of development. Knoops et al have developed a machine learning based method using a non-ionising 3D surface imaging (3DMD) to simulate post-operative appearance for cranio-facial surgery with the intended application of more precise surgical planning and outcome evaluation.[129] The use of artificial intelligence may be the most accurate, reliable and efficient way to develop simulation for breast reconstruction, although a

large image library would be required in order to capture the diversity of UK practice.

3.6 Conclusion

The concept of simulation as an aid to discussing complex ideas simply, with the ability to cross language and literacy barriers and reduce the difference between patient perception (how they interpret an explanation) and expectation (their visualisation of their anticipated result) during a pre-operative consultation is sound. It is superior to standard care and viewing 2D photographs in the preparation of patients for BCT.

The utility of simulation for BCT in routine clinical practice is ill-defined. Currently it is a 'nice to have' option to aid consultation into likely aesthetic outcome, however, the accuracy of the software to simulate outcome will become clear upon longer term follow-up of the study. This will guide additional application of simulation in both operative planning i.e. symmetrising surgery, and shared decision making between surgeon and patient. With completion of follow-up, the long-term influence of simulating outcome on patients' satisfaction with breasts and quality of life may provide additional rationale for the routine use of simulation in a patient centric survivorship capacity.

In order to translate simulation from research into clinical practice, a portable and cheaper device that can be used in the clinic room to simulate and record post-operative results is necessary. The development of these devices is well underway, though evaluation of accuracy lags behind knowledge with VECTRA.

3.7 Acknowledgements

I would like to formally acknowledge the contributions of the participants, Miss Carol Pitches and medical photographer Dennis Underwood to this study.

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The views expressed are those of the authors and not necessarily those of the NIHR or the Department of Health and Social Care.

The protocol was reviewed and passed by London-Riverside NRES committee Ref 17/LO/0399. The study is registered on a publicly accessible database, clinicaltrial.gov, [NCT03250260].

Informed consent was obtained from all individual participants included in the study.

Chapter 4 Reducing the burden of research: The development and pilot of a novel online recruitment, consent, and data collection tool for use in a large-scale multi-centre study in a breast reconstruction population.

RMH R&D Reference	CCR4770
IRAS	224146
REC Reference	17/LO/0763
Clinical Trials.gov ID	NCT03203252
Funding	Grant from the Association of Breast Surgery.

4.1 Introduction

Online research is common place in epidemiological studies,[130] and has reported advantages of being cost effective,[131] accessing hard to reach populations,[132] and providing a sensitive space in which participants are more likely to give a candid response to questions of a sensitive nature.[133] Ninety percent of households have internet access with 89% of adults in the UK using the internet at least weekly which has risen from 51% in 2006. The over-65 age group has seen the biggest growth in internet use since 2008. 87% of households with at least one adult over the age of 65 had internet access in 2018.[134]

Breast reconstruction is a diverse and rapidly evolving field in the UK.[135] As discussed in Chapter 1, aesthetic outcome from breast cancer surgery is important and has well-documented influence on long-term psychosocial wellbeing and for this reason is a major patient centred survivorship focus.[4-10, 19] The acceptance of its importance is reflected in the 2002 NICE guidelines, that all women undergoing mastectomy in the UK should be offered reconstruction.[12]

As mentioned in previous chapters there is no gold standard to measure aesthetic outcome. Panel assessment, with its well-described limitations is the most widely adopted. While the Harvard scale is the most widely used BCT, there are multiple panel scales for breast reconstruction referenced in the literature, all of which share common deficiencies including lack of responsiveness, repeatability, and interpretability.[31,29] This creates an additional layer of complexity when comparing and interpreting results.

An objective method to evaluate aesthetic outcome is required for communication and comparison of techniques and benchmarking of performance, with the intention to report upon and raise standards in reconstructive surgery and to inform best practice. 3D-SI offers a potential solution given its ability to demonstrate projection, shape and contour, and to quantify surface and volume symmetry in addition to linear measures.

I have described how 3D-SI has been used to create an objective aesthetic outcome tool for BCT in Chapter 2. Evaluating reconstructive surgery is arguably more challenging than for BCT where the overarching goal is to maintain or achieve symmetry. In reconstructive surgery there is a broader spectrum of operative choices tailored to the patient and surgeon's pre-operative agreed agenda, and consequently broader aesthetic ambitions perhaps reflected in the heterogeneity of scales used to evaluation outcome.[29]

In order to develop an objective outcome tool for use within the reconstruction population, a multi-centre study is required to capture a library of 3D-SIs large enough to be representative of the diversity in practice across the UK. Participation in research is beneficial for both the participants and healthcare providers but can prove demanding at participant, clinician and trust level – particularly for larger scale trials.

The following chapter discusses the development and testing of a novel online research methodology designed to improve accessibility to research and reduce the burden on both participants and investigators. The intention is to include centres with less research support to capture representative data from the UK population rather than major research centres alone. The online platform was

designed to be scalable for the proposed multi-centre trial. This chapter reports upon the feasibility, acceptability, and accuracy of the novel online recruitment and data collection platform.

4.2 Hypothesis and specific aims

4.2.1 Hypothesis

Research involving 3D-SI and PROMs is amenable to novel online research methods for recruitment and participant-reported data collection to facilitate accessible research.

4.2.2 Aims

1. To develop an online research platform for use in a multi-centre study.
2. To assess the acceptability, feasibility, and accuracy of a novel online research methodology within a pilot study for an implant reconstruction population.
3. To report upon the reliability of 3D-SI measures using VECTRA XT® in an implant reconstruction population.

4.2.3 Objectives

1. Assess recruitment rate to a study of this design.
2. Understand discontinuation rates and time taken to complete the online process.
3. Describe the accuracy of participant-reported clinical information compared with electronic patient records.
4. Evaluate inter- and intra- observer variability for linear measures derived from 3D-SIs for an implant-based reconstruction population.
5. Appraise the feasibility of online PROMs in the form of the BREAST-Q post-operative reconstruction module.

4.3 Method

4.3.1 Study design

The pilot study protocol was reviewed and passed by the London-Surrey Research Ethics Committee (17/LO/0763). The study is available at clinical trials.gov (NCT03203252).

Women over the age of 18 who underwent mastectomy and implant-based breast reconstruction between 2012-17 at the Royal Marsden Sutton were eligible. Potential participants were identified through operation records and their eligibility cross-checked with electronic patient records. The potential participants were invited in reverse chronological order of operation date (most to least recent). The letter contained a unique study ID, a participant information sheet and the URL to a bespoke study website (Appendix 7 and 8).

4.3.1.1 Inclusion criteria:

- Female
- Aged over 18 years
- Implant-based reconstruction 1-5 years before study entry (including unilateral or bilateral, immediate or delayed, nipple-sparing or nipple-sacrificing, risk-reducing or therapeutic)
- Participants who have had revision surgery for symmetry or capsular contracture can be included

4.3.1.2 Exclusion criteria:

- <1 year or over 5 years from surgery
- Implant loss to a flat chest
- Implant loss secondary to infection or extrusion
- Local or distant recurrence
- Ipsilateral autologous component to the reconstruction
- Salvage implant reconstruction
- Lacks capacity

4.3.2 Online Process

Potential participants accessed the website using the URL in the letter of invitation. A standard participant information page was signposted as a minimum and in addition, links to other pages and/or websites if further information was desired. In this way, the website provided a platform for interactive participant information i.e. a choice as to how much or how little information to access before deciding whether to participate. A 'contact us' link provided direct contact with the study team.

Recruitment rate was defined as the number of participants completing the online process and attending for 3D-SI as a proportion of those sent a letter of invitation.

4.3.2.1 Consent

Written informed consent is only legally required for C-TIMP studies and this study was, in many ways, closer to health-services research than drug trials, hence online consent was considered appropriate and acceptable. If the patient opted to participate in the study, they were instructed to follow the consent link, at which point a check screen was shown with two options:

a) I have enough information and I would like to consent to the study

b) I would like further information which is not available on the website

If the participant selected option '1' they were directed to the consent form. If option '2' was selected they were directed to the 'contact us' section of the website (Figure 37). The online consent process required the potential participant to read each section and tick yes or no to each statement if they agreed or disagreed (Figure 38). A confirmation of consent page followed with information on study withdrawal and privacy (Figure 39). The time and date of consent was recorded automatically. The participant could download and/or print the consent form for their records.

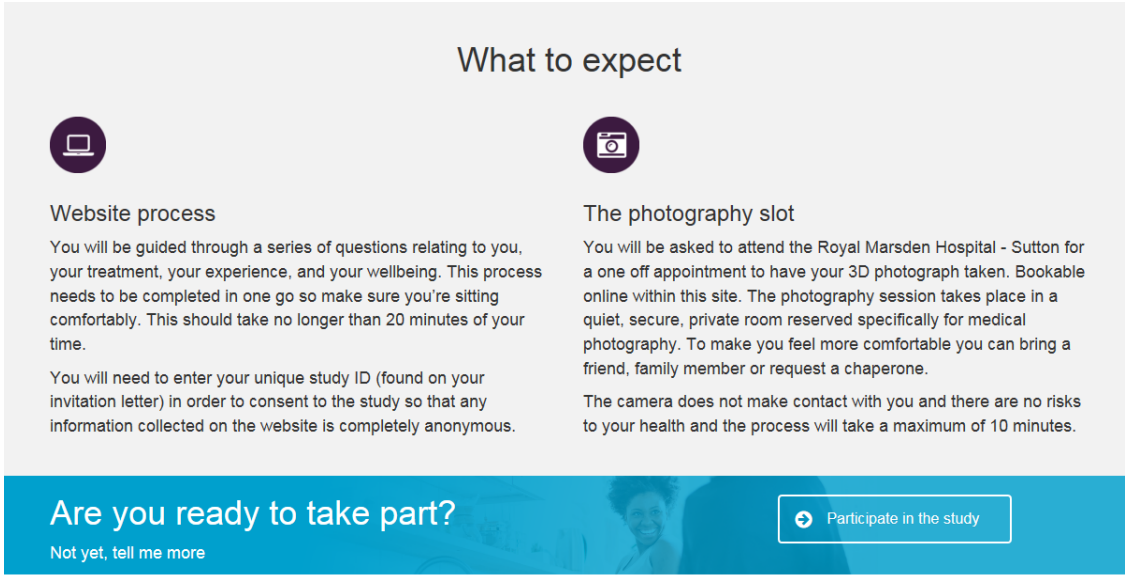

Figure 37 Website image; information checkpoint to ensure the participant has satisfied their questions prior to consenting to participate

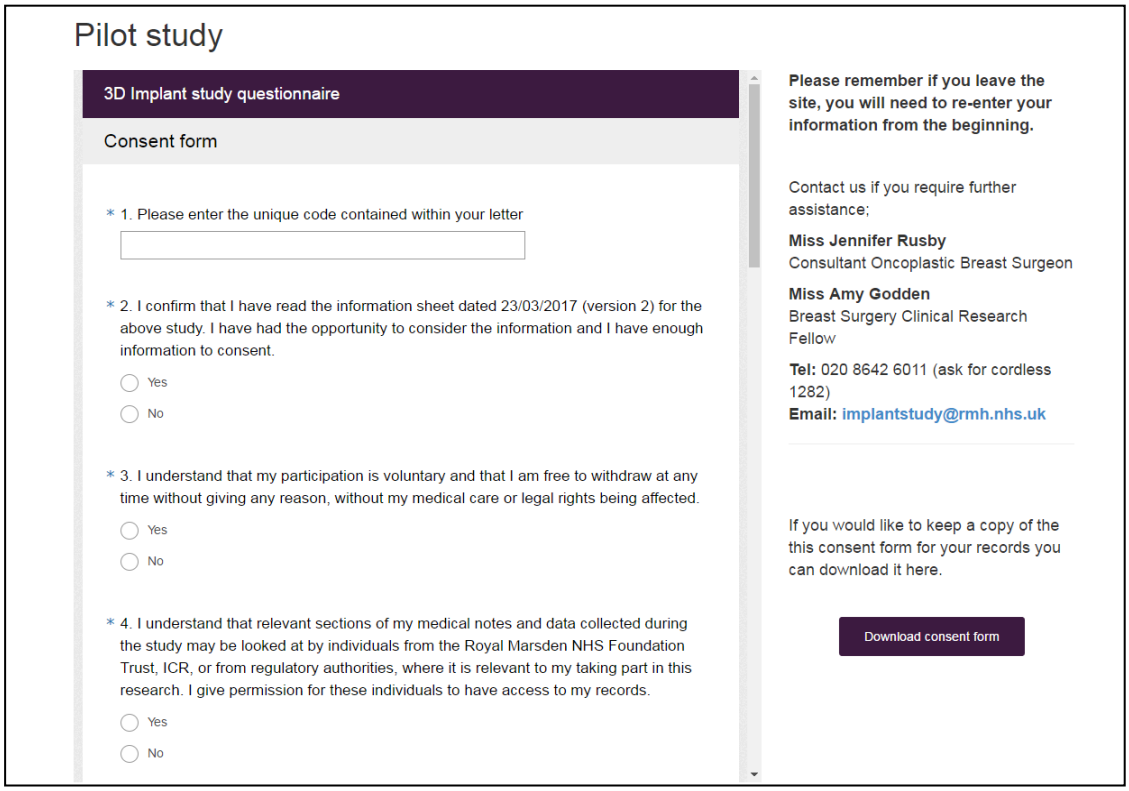

Figure 38 Website image; electronic consent form with Yes/No tick box to encourage the participant to read each statement

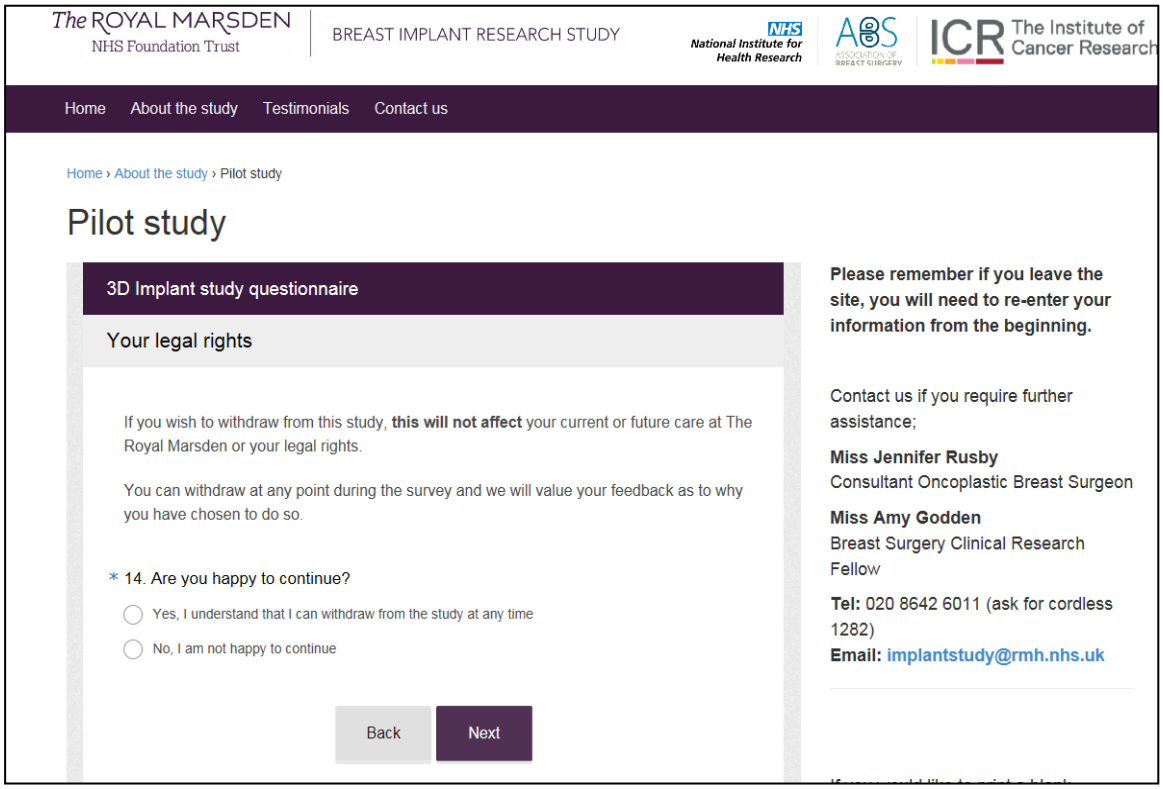

Figure 39 Website image; withdrawal and privacy wording to provide reassurance of this process for potential participants

4.3.2.2 Data entry

Once consent was completed, participants proceeded to the data collection pages including demographics, clinical data, and the BREAST-Q reconstruction module (Appendix 2). At the end of the data collection process they were directed to a live online calendar to book their photography appointment. Following this, they could choose whether to fill out a real-time user evaluation survey (Figure 40). Discontinuation rate was assessed at each stage of the process to help understand acceptability to participants and to provide feedback on website design and content i.e. a common cause for discontinuation. Time taken to complete the process was recorded as a measure of burden on participants.

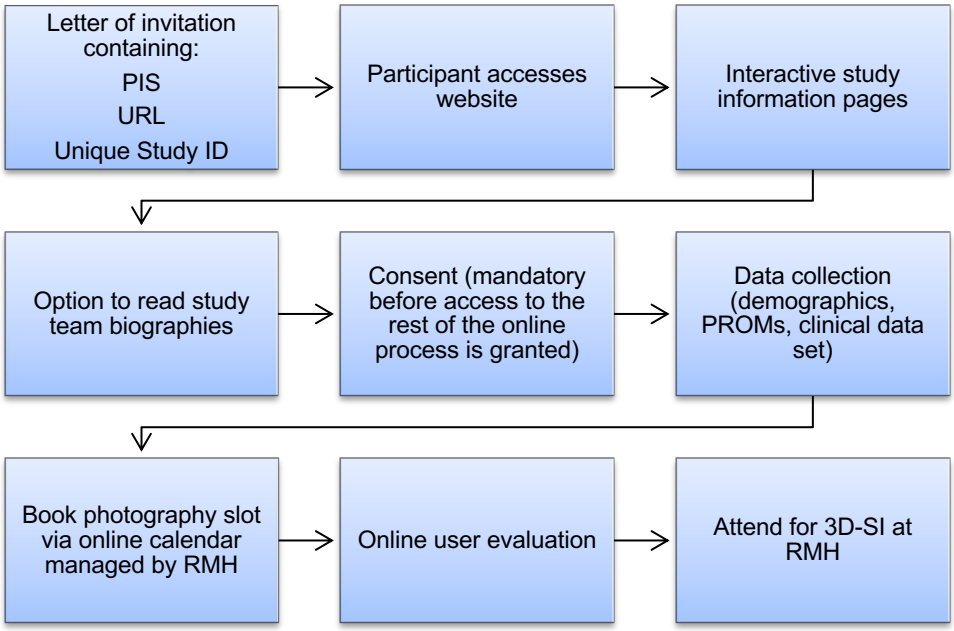

Figure 40 Participant pathway. PIS; participant information sheet, PROMS; patient reported outcome measures, RMH; Royal Marsden Hospital, 3D-SI; 3-dimensional surface image

4.3.3 Data collection

The online data collection was by study ID alone and included demographics, clinical data (Figure 41), Patient Reported Outcome Measures (PROMs) in the form of the BREAST-Q post-operative reconstruction module, and a real-time process evaluation survey. The data collection pages were not accessible until the consent process had been completed in its entirety. Participants visited the Royal Marsden once for a 3D-SI which was booked via the online platform. Similarly, the online calendar was not accessible until the consent process and data collection pages were complete to facilitate complete data sets and to ensure consent for photography had been established.

Demographics
Age
Height
Weight
Ethnicity
Smoking status
Clinical Data Set
Breast surgery including; indication, type and timing of reconstruction and laterality of cancer (if applicable)
Surgery to the axilla
Symmetrising surgery
Surgery to the nipple-areola complex
Chemotherapy timings (if applicable)
Radiotherapy timings (if applicable)

Figure 41 Demographics and clinical data collected online as part of the pilot study

Participant reported data (demographics and clinical data) were compared with electronic records to establish accuracy. A predefined threshold of 95% agreement was set for binary variables i.e. correct or incorrect. For continuous variables individual thresholds were set, height within 5cm, and weight within 5kg.

Relevant domains from the BREAST-Q post-operative reconstruction module (Appendix 2 questions 1-6 and 10), and the radiotherapy domain from the post-operative BCT module (Appendix 1 question 2) were embedded into a Survey Monkey site within the study website. The BREAST-Q results, survey completion rate and ease of analysis were reported on.

4.3.4 Image capture

3D-SIs were captured using Vectra XT ® (Canfield, USA). Women were photographed using a standardised protocol hands on hips in standing, elbows positioned behind the mid-axillary line (to capture the lateral breast), at the end inspiratory pause of quiet breathing. Participants were aligned to the predefined

grid visible on the preview screen prior to image capture. The images omitted the face, were stored under the unique study ID, and were not linked to electronic patient records.

4.3.5 Image analysis

Independent observers (blinded to surgeon, participant identity and clinical data) measured each image using Mirror ® software (Figure 42). One observer had extensive experience with Mirror ® software and the other had not used it before. Breasts were analysed separately for measures that are taken independently of the other side i.e. N-SN, N-IMF, N-Midline, and lateral-to-medial mammary fold (L-MMF) distances (breast width). For the comparative measures, both breasts were analysed together i.e. volume asymmetry, surface asymmetry, difference in projection, difference in nipple height. The observers accessed the images independently hence were blinded to each other's measurements.

Measure	Unit
Independent measures (per breast)	
Nipple to sternal notch (N-SN)	cm
Nipple to infra-mammary fold (N-IMF)	cm
Breast base width (lateral to medial mammary fold [L-MMF])	cm
Nipple to midline (NM)	cm
Single and comparative measures (between breasts)	
Medial to medial mammary fold (i.e. cleavage width [m-mmf])	cm
Projection difference	cm
Nipple height difference	cm
IMF height difference	cm
Nipple to nipple distance (NN)	cm

Figure 42 Measures taken from 3D-SIs by two independent observers to establish inter- and intra- rater variability in an implant reconstruction population

Inter- and intra-observer reliability were analysed for linear mammometrics. Volume and symmetry methods were not assessed as these have been validated previously.[76]

4.3.6 Statistics

4.3.6.1 Sample size

This was a feasibility study, so no formal power calculation was necessary. An estimated sample size of 50 participants was based on the need to gauge uptake and acceptability of the study design. A recruitment rate of 50% was predicted from previous research and set as the target for the pilot. Letters of invitation were sent to 100 patients on this premise.

An amendment to the recruitment process was granted by REC and HRA when the recruitment rate did not meet the target. A telephone call to the potential participants that had not engaged with the first letter of invitation (i.e. not consented and not declined to participate) in order to endorse the study, answer any questions, and provide assistance to the potential participants was permitted. The impact on recruitment rate was reported.

4.3.6.2 Statistical analysis plan

SPSS version 24 was used. Continuous data were summarised as the mean and standard deviation or median and inter-quartile range. Categorical data were expressed as number and percentage. Intra-observer agreement was reported using the mean of the standard deviation. Inter-observer agreement was reported using the Intra-class Correlation Coefficient (ICC). ICC of less than 0.40 was considered poor, between 0.40 and 0.59 fair, between 0.60 and 0.74 good and between 0.75 and 1.00 excellent.[136] Bland-Altman Plots were used to illustrate mean difference and limits of agreement.

4.3.7 Website creation

Together with a patient representative and a website design team (Fluent Interaction), a bespoke study website was created in a one-day 'hackathon'. The website contained a branded home page (Figure 43), with photographs of the study team and access to team biographies (Figure 44) both designed to endorse the study and provide an element of familiarity and relatedness to potential participants, supporting participation. Testimonials from participants of previous studies were included to illustrate the benefits of research on a participant level, with the intention of strengthening a connection to the study to encourage participation. The website was constructed to enable simple adaptation for use by multiple sites in a multi-centre study.

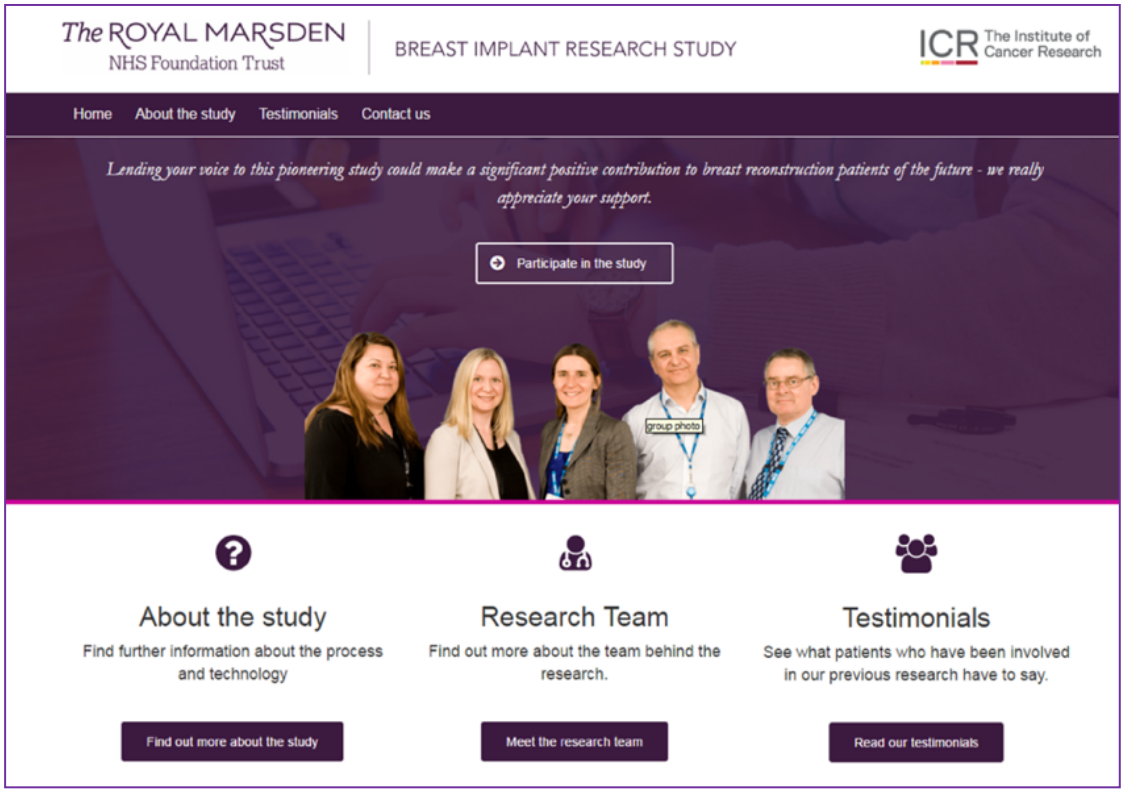

Figure 43 Website Image; home page from the pilot study website designed with RMH branding to endorse the study and make it relatable to potential participants

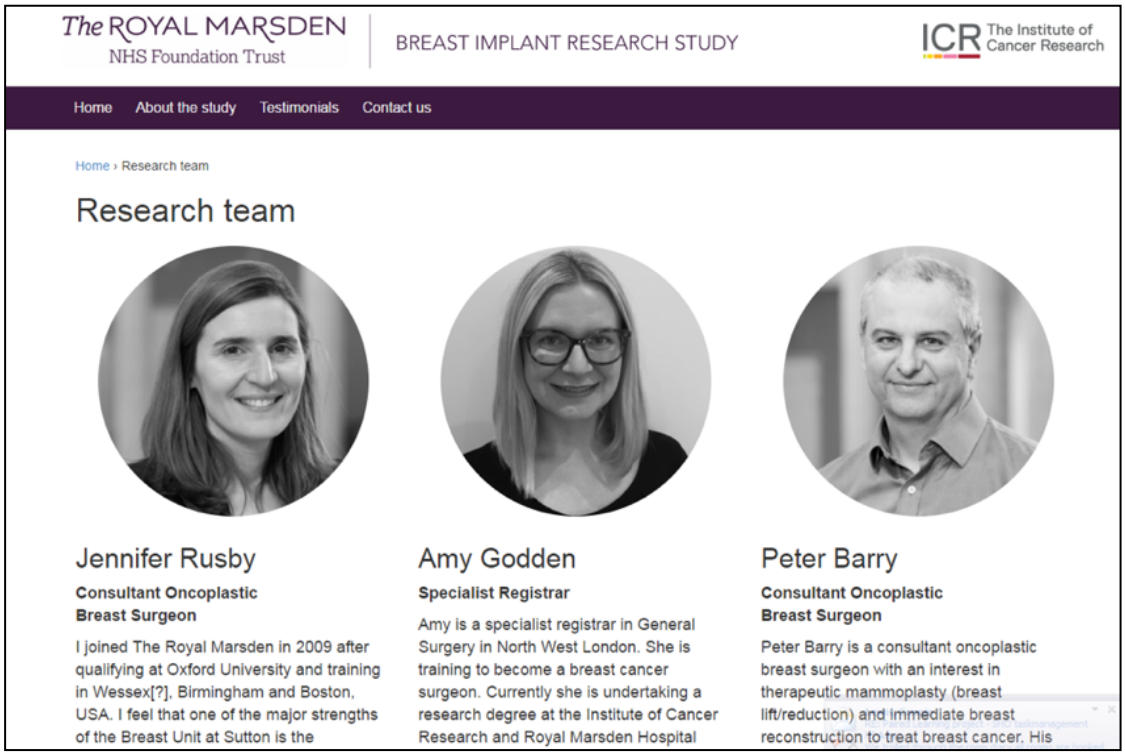

Figure 44 Study team biography page designed to endorse the study and add a human element to the study process making it relatable to participants

4.4 Patient and public involvement

I worked closely with a patient representative, Carol Pitches, who advised at each stage of the study design process. Her professional background is in leadership and development coaching ranging from individual clients to global companies. She volunteered her time to help develop this study and edited the website content, combining her professional knowledge with her experience as a patient.

The proposal was presented to members of the Royal Marsden Patient and Carer Research Panel for review. The study design was discussed with women who have participated in other 3D-SI studies at the Marsden at a PPI event held in January 2017. Representative comments included:

1. A web-based storage is more secure than emailing images
2. Most of us are happy to use internet banking

3. Concerns about limiting to internet-savvy women are outweighed by the reduction in hospital visits and the extension of the research over a wider geographical area.
4. Overwhelming support for the rationale of making research easy and accessible for all women, with only a few who are either not internet savvy or are wary of online access to banking etc.
5. Recognition of the benefits of a single visit to the study centre to participate, citing multiple additional visits as a disincentive to participation.

Results

The demographics and clinical data for the pilot, amendment, and total study population are illustrated in (Table 17). The median time from surgery to study participation was 29 months (IQR 14-41). The average age was 52 ranging from 28 to 77 year suggesting online research is not exclusively for the younger generations. The most common operation was a unilateral mastectomy (43%), with the majority having immediate definitive fixed volume implant reconstruction (68%).

	Pilot n = 34	**Amendment n = 10**	**Total Population n = 44**
	n (%)	n (%)	n (%)
Age			
Mean (range) years	51 (28-69)	54 (40- 77)	52 (28-77)
Height			
Mean (standard deviation) metres	1.64 (0.08)	1.61 (0.06)	1.63 (0.08)
Weight			
Mean (standard deviation) kilograms	67.1 (9.7)	67.4(7.2)	67.1 (9.1)
Indication for Initial Surgery			
Unilateral mastectomy and implant reconstruction for cancer	15	4	19 (43)
Bilateral mastectomy and implant reconstruction one for cancer and one for symmetry/risk reduction	11	1	12 (27)
Bilateral risk reducing mastectomy	5	3	8 (18)

Bilateral mastectomy and implant reconstruction for bilateral cancer	3	2	5 (11)
Timing of reconstructive surgery			
Mastectomy and immediate definitive implant reconstruction	24	6	30 (68)
Mastectomy, expander and delayed definitive implant	10	4	14 (32)
Date of most recent operation			
2012	3	0	3 (7)
2013	4	3	7 (16)
2014	5	0	5 (11)
2015	9	3	12 (27)
2016	12	4	16 (36)
2017	1	0	1 (2)
Symmetrisation surgery			
Bilateral mastectomy at first surgery	18	6	24(55)
Contra-lateral reduction	1	2	4 (9)
Symmetrising mastectomy and reconstruction of a different type	1	0	1 (2)
None	14	2	15 (34)
Nipple surgery			
Nipple sparing mastectomy	18	6	24 (55)
Nipple removed and not reconstructed	12	3	15 (34)
Nipple removed and reconstructed	4	1	5 (11)
Chemotherapy			
Adjuvant chemotherapy	10	2	12 (27)
Neoadjuvant chemotherapy	9	2	11 (25)
Cancer, but chemotherapy not indicated	10	3	13 (30)
No radiotherapy: risk reducing surgery	5	3	8 (18)
Radiotherapy			
Post mastectomy radiotherapy to reconstruction	12	4	16 (36)
Adjuvant following previous BCS	2	0	2 (5)
Cancer, but radiotherapy not indicated	15	3	18 (41)
No radiotherapy: risk reducing surgery	5	3	8 (18)

Axillary surgery			
SLNB	18	4	22 (50)
ALNC	8	1	9 (20)
Unilateral SLNB and contralateral ALNC	1	1	2 (5)
None (risk reducing)	5	3	8 (18)
None (patient choice)	2	1	3 (7)

Table 17 Demographics and clinical data for the pilot, amendment, and total study populations. SLNB; sentinel lymph node biopsy, ALNC; axillary lymph node clearance, BCS; Breast conserving surgery.

100 potential participants were invited by letter, 38 started the online process and 36 consented to the study. Two potential participants actively declined by email, and 60 did not respond. 30 (79% of those that started) completed the online process and attended for 3D-SI (Figure 45). The recruitment rate for letter-only invitation was therefore 30%.

The amendment, permitting a follow-up telephone call to potential participants who had not previously engaged, was applicable to 62 women (36 had previously consented and 2 had declined to participate). 53(85%) remained eligible (4 had undergone autologous reconstruction since the pilot study, 1 had metastatic disease and 4 had moved out of area). Eligible women were contacted by telephone. 36 (68%) participants were contactable, and 17(32%) were not contactable on two separate occasions. All of the women successfully contacted expressed interest in participation. 24 (67%) did not engage further, 12 (33%) started the online process and 10(28%) completed recruitment i.e. online data entry and 3D-SI. With telephone endorsement the recruitment rate was 19% (10 out of 53). Put simply with telephone endorsement a further 10 participants were recruited to the study that otherwise did not engage, thus improving the overall recruitment rate from 30 to 40% (Figure 45).

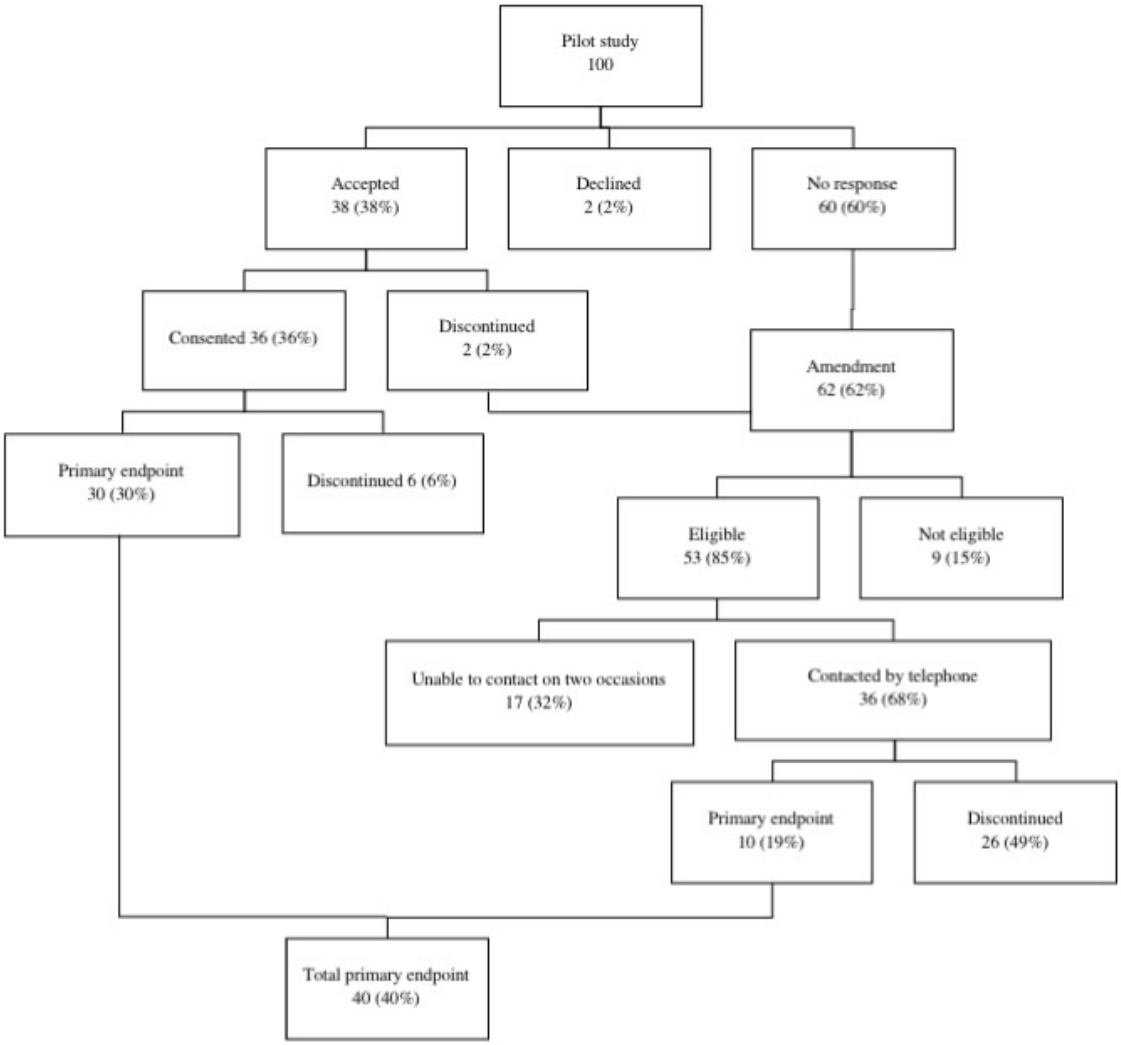

Figure 45 Recruitment rate for the total study population separating the pilot from the amendment populations

The participants from the first cohort will henceforth be referred to as the ‘pilot cohort’ and the women from the second cohort, the ‘amendment cohort’, taken together they are referred to as the ‘total study population’.

4.4.1 Discontinuation rate

The discontinuation rates for the total study population and the separate cohorts are illustrated in Figure 46. 50 out of the 100 women invited started the online process. 40 (80%) of those that started the online process attended for 3D-SI (primary endpoint). The majority of discontinuations occurred between consenting and entering demographics (3, 6%), and between completing the BREAST-Q and booking an appointment for 3D-SI using the online calendar (3, 6%).

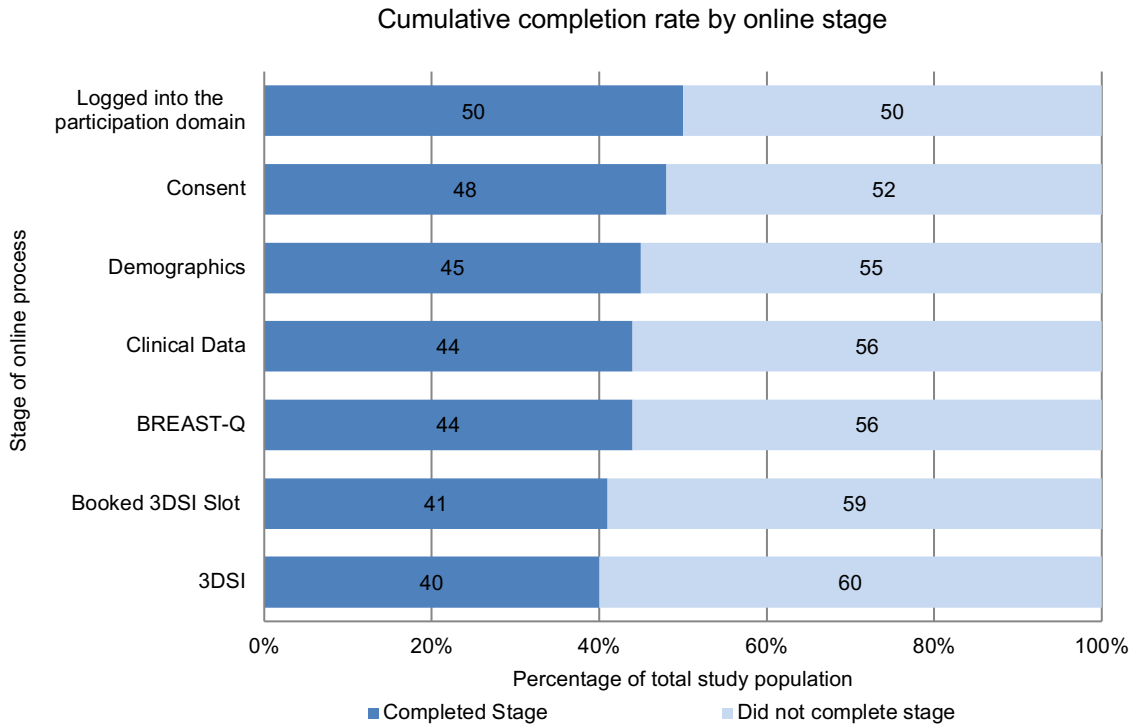

Figure 46 Cumulative completion rate by online stage

4.4.2 Time taken to complete the online process

The median time taken from starting the consent process to completing the BREAST-Q was 23 minutes (IQR 14-28 minutes) for the total study population.

4.4.3 Accuracy of participant reported clinical data

Participant-reported clinical data met the predefined criteria for acceptable accuracy of 95% concordance with medical records in 12 of the 13 domains for the total study population (Figure 47). The domain 'date of reconstruction' did not meet the predefined threshold of 95% (91%). Height was reported to within 5cm in 96% of cases, with a median error of 1cm (IQR 0 – 2cm) for the total study population. Of the 28 women in the pilot cohort who had their weight measured at the time of photography, 27 (97%) were accurate to within 5kg with a median error of 2kg (IQR 1-2kg). Weight at the time of photography was not measured for the amendment cohort.

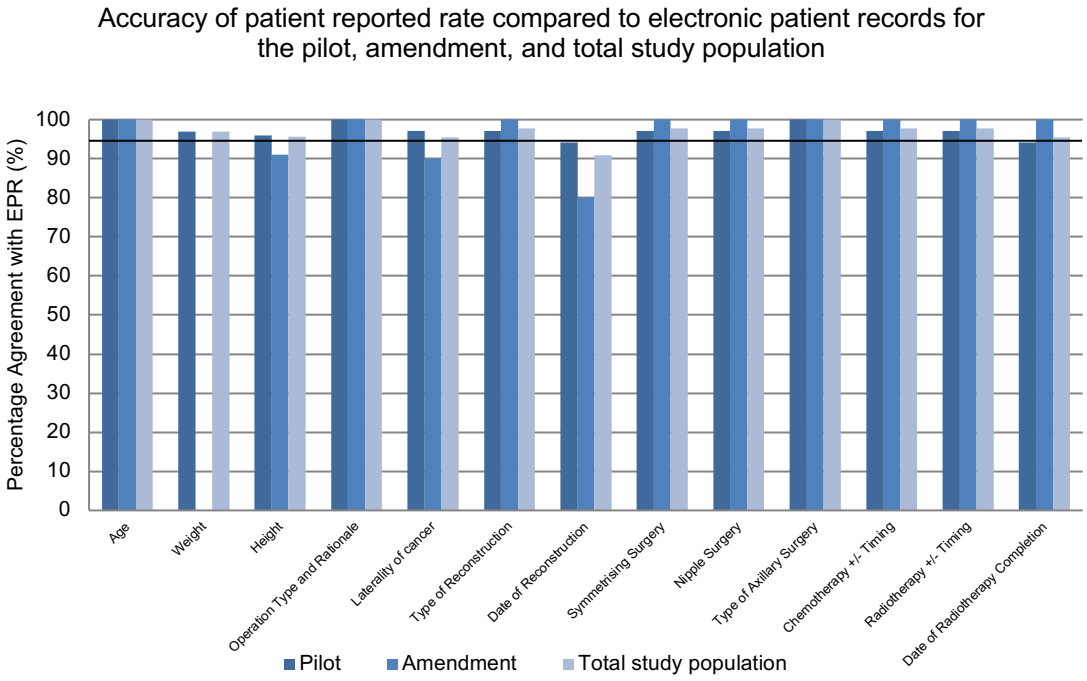

Figure 47 Participant reported clinical data compared to electronic patient records (EPR) for accuracy. A predefined threshold of 95% concordance was set (horizontal bar)

4.4.4 Online patient-reported outcome measures

All participants (44) who started the online BREAST-Q completed it, demonstrating acceptability (Figure 46). The median Q-score for 'satisfaction with breasts' and 'sexual well-being' were appreciably lower than the other

domains, 54.5 (IQR 47.5 – 65.5) and 50.5 (34-57.75) respectively (Figure 48). The sample size was small so the results may not be generalisable.

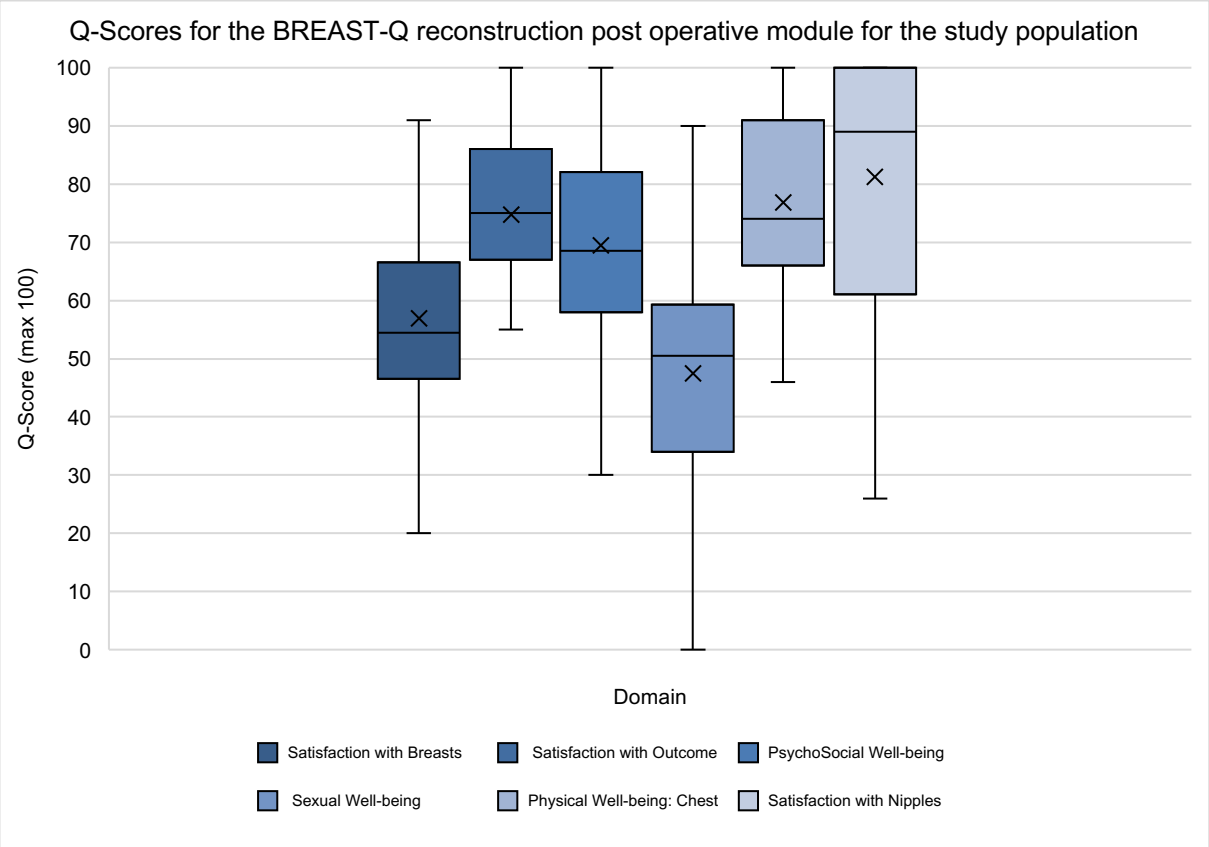

Figure 48 BREAST-Q analysis for the post-operative reconstruction module for the total study population. Q-score out of 100 where 100 is best. X represents the mean

4.4.5 Real-time user evaluation

The real-time user evaluation was completed by 19 participants in the pilot cohort and 11 from the amendment cohort. All participants said the website was easy to navigate and 93% found the questions clear and easy to understand. 12 participants made suggestions for additional areas pertaining to aesthetics and wellbeing for inclusion in the main study which included satisfaction with the contralateral symmetrisation, satisfaction with prosthetic nipples, implant versus native breast (specifically temperature, how they move, and how they feel to touch), availability of pre-operative information on aesthetic outcome, and changes over time (Table 18). Comments from the free text boxes highlighted elements to guide refinement of the website for the main study.

Question	Summary	Total Population (30)
Thinking about the website, was there any information missing?	Responded	24
	Skipped	6
	No	17
	Length of time for photography slot	1
	Not enough space to document previous cancer treatment	2
	Animation not covered	1
	Could not find PIS	1
	No option for no SLNB in cancer treatment section	1
	Freeze panes for questionnaires	1
Was it easy to Navigate the Website?	Responded	30
	Skipped	0
	Yes	30
	No	0
Thinking about the survey, were the questions clear and easy to understand?	Responded	29
	Skipped	1
	Yes	27
	No	2
Which of the following would you prefer for a study like this?	Responded	30
	Skipped	0
	Completely anonymous survey that you have to complete in one sitting	16
	Some identifiable information to be stored so you can save progress and continue another time	13
	Other	1
Can you tell us what worked well for you?	Responded	23
	Skipped	7
	Non-specific positive comment	3
	Liked multiple choice/tick box answers	4
	Easy and patient friendly	11

	Liked free text box to clarify	2
	Could fill out at home	1
	Liked online calendar	1
	Liked weight and height converter	1
Can you make any suggestions for improvement?	Responded	19
	Skipped	11
	Asking to include further areas of cancer care in questionnaire	1
	Option to enter further details regarding surgical treatment – especially previous cancer surgery	4
	Save Progress	1
	Couldn't find PIS	1
	No	9
	Freeze panes for survey	2
	Option for 'no axillary surgery' in the cancer group too	1
	Review calendar	12
Finally, about you: is there anything about your appearance and wellbeing that is important to you and not covered in the survey	Responded	21
	No	9
	Satisfaction with symmetrising surgery	1
	Pre-op information on aesthetic outcome	1
	Shared experiences from other women pre-op	1
	Satisfaction with prosthetic nipples	1
	Animation	1
	Implant reconstruction versus native breast	2
	How clothes fit	1
	Cording	1
	Shoulder issues	1
	Changes over time – how the natural aging process of the native breast worsens asymmetry	2

Table 18 Summary of results from the real-time user evaluation survey

Cross checking the real-time user evaluation with the participant reported clinical data drew attention to important areas for consideration when modifying the questionnaire for the main study. For example, there was no option to say that sentinel lymph node biopsy was declined in the presence of a cancer, so participants chose a 'best fit' option, not because they were unclear of their situation, but due to limitations in the format of the questionnaire.

4.4.6 Intra- and inter-observer variability for objective measures

Intra-observer agreement

The mean standard deviation for observer one ranged from 0.07cm for projection, to 0.32cm for Nipple-Sternal Notch distance. For observer two it ranged from 0.05cm for projection to 0.32cm for medial to medial breast border (Table 19).

Objective measure	Mean SD observer one	Mean SD observer two
Nipple to sternal-notch (cm)	0.32	0.31
Nipple to infra-mammary fold (cm)	0.18	0.26
Lateral to medial-mammary fold (cm)	0.28	0.22
Nipple to midline (cm)	0.15	0.14
Medial to medial-mammary fold (cm)	0.23	0.32
Projection difference (cm)	0.07	0.05
Nipple height difference (cm)	0.14	0.20
Infra-mammary fold height difference (cm)	0.12	0.15
Nipple to nipple distance (cm)	0.14	0.12

Table 19 Mean standard deviation (SD) for observer one and observer two for measures taken from 3D-SI in an implant reconstruction population

Inter-observer agreement

As illustrated in Table 20, the ICC for seven of the 3D-SI measures demonstrate excellent reliability (ICC >0.9). nipple to IMF distance and nipple-height difference have good reliability (ICC 0.899, and 0.892 respectively). There is significant agreement between observer one and two for all measures ($p < 0.005$). All show excellent internal consistency (Cronbach's alpha of >0.9). Bland Altman plots illustrate the mean differences between observer one and two were close to zero and with narrow limits of agreement (Table 21).

3D-SI measure	ICC	Significance	Cronbach's alpha
Nipple to sternal-notch	0.997	<0.005	0.989
Nipple to infra-mammary fold	0.899	<0.005	0.947
Breast base width i.e. Lateral to medial-mammary fold	0.944	<0.005	0.971
Nipple to midline	0.926	<0.005	0.998
Medial to medial-mammary fold distance	0.974	<0.005	0.988
Projection difference	0.951	<0.005	0.975
Nipple height difference	0.892	<0.005	0.95
Infra-mammary fold height difference	0.96	<0.005	0.979
Nipple to nipple distance	0.997	<0.005	0.998

Table 20 Inter-rater agreement for 3D-SI derived objective measures between observer one and two. (ICC intra-class correlation coefficient)

3D-SI measure	Mean difference between observer 1 and 2 (cm)	Upper limit of agreement (cm)	Lower limit of agreement (cm)
Nipple to sternal-notch	-0.2	1.1	-1.5
Nipple to infra-mammary fold	0.3	1.5	-1
Breast base width i.e. Lateral to medial-mammary fold	-0.5	0.8	-1.8
Nipple to midline	0.0	1.1	-1.1
Medial to medial-mammary fold distance	-0.4	0.7	-1.5
Projection difference	0	0.6	-0.6
Nipple height difference	0	1.2	-1.2
Infra-mammary fold height difference	-0.1	0.9	-1.2
Nipple to nipple distance	0.0	0.4	-0.3

Table 21 Summary of the mean difference and limits of agreement between observer one and two for linear measures taken from 3D-SI of participants in an implant reconstruction population

4.5 Discussion

This pilot study has demonstrated feasibility of the online platform, acceptability to participants and accuracy of participant reported data in an implant-based reconstruction sample population. UK breast reconstruction practice is variable between surgeons and centres. In order to create an objective aesthetic evaluation tool, a large population from different centres is required to reflect this diversity. A scalable method of online recruitment and data collection to facilitate an inclusive large multi-centre study has been described.

The population within this pilot was from a single specialist cancer centre and may not be generalisable to the rest of the UK population. The breast cancer patients at the Royal Marsden in Sutton, Surrey are predominantly drawn from the local area, both screening and symptomatic presentations, rather than transferring care from a wider geography and are therefore more generalisable than other parts of our organisation's practice. The rate of participation demonstrated is sufficient to support the view that a highly scalable online platform will recruit many participants when offered through multiple research centres, without requiring significant research staff input from those centres. The

reported accuracy of data collection for the 40% of women invited that completed the online component may also be exposed to non-responder bias and that must be taken into account.

The recruitment rate was based on previous studies using 3D-SI technology conducted at our organisation, however, there were numerous differences in study design which may suggest the initial target of 50% recruitment was too optimistic. Differences included the addition of an online component, the removal of a study endorsement telephone call, no face-to-face contact with a member of the study team, an additional trip to the hospital (previously studies worked on the surveillance mammograph schedule, so participant were already at the hospital), and a different demographic of participant. The recruitment rate with and without telephone endorsement was 40% and 30% respectively which is in line with other letter only invitation studies in the breast cancer population (PROCAS 20%).[137] Ashley et al report a response rate of 55% for online PROMs for patients with potentially curable breast, colorectal and prostate cancer. A varied approach was utilised and considerably more participated when approached face-to-face (61%) compared to telephone (48%) or letter(41%).[138] A meta-analysis by Cook et al report an average recruitment rate of 39% for 68 internet base surveys in 49 studies.[139] Harris et al report a response rate of 18% and a completion rate of 5% for the CUPID study (Contraceptive Use, Pregnancy Intention, and Decisions) consisting of online consent and a survey, using a mailed invitation, stratified sampling technique and incentivised participation.[140]

One-to-one contact time with a member of the research team to endorse the study is reported to be the most effective way to enhance understanding and optimise recruitment.[141, 142] The burden placed on clinical or research teams to provide this contact time may preclude participation from units with little or no research support. Several elements of the online method described in this study have been designed to overcome this lack of ‘face-time’ including study team biographies, photographs of the research team, patient testimonials, and an easily accessible ‘contact us’ link. A further consideration to augment the recruitment process could be the inclusion of short video with the primary investigator embedded within the website.

There has been ongoing concern with internet mediated research of non-response bias i.e. is the data collected representative of the population or is the sample skewed by the method of collection. Several studies have been reassuring in this domain including a study by Harris et al who recruited 3795 women in Australia aged 18-23 to an internet based research project on contraceptive use and pregnancy and found the population to be broadly representative of the general population aside from an over representation of tertiary educated women (88% versus 72%).[143] Hatch et al compared results from an internet- based survey to well-known statistics for perinatal health (i.e. low birth weight and smoking status) across six domains, and found similar results in a cohort of women at reproductive age.[144] The comparison is with paper questionnaires, which are heralded as the gold standard, however, are not perfect and are also open to non-response bias.

Participant reported clinical information was demonstrated to be accurate in 12 out of 13 domains to a minimum standard of 95% concordance with electronic records in this pilot study. Closer analysis of the errors in data reporting, together with cross checking the answers to the real-time user survey, data was more often than not incomplete (missing multiple operations or historical reconstructions) rather than inaccurate, and this was due to the terminology or options available in the multiple-choice answers. This is rectifiable by clarifying the vocabulary and adding further options or free text boxes where required. The accuracy of patient reported data is promising for use in similar trials in the future which could dramatically reduce the burden on investigators. The data collected within this trial was simple, but prospective patient-reported data collection could be used in future studies to enable more complex data entry in real-time, but would require further validation. The reported accuracy is in line with a large study by Andreeva et al who investigated the internal validity of demographic data entered online for their study of over 84,000 participants and reported 94% consistency with database records.[145]

While providing low burden, accessible research, the online design may exclude less internet savvy women. The 3D-SI patient steering group at the Royal

Marsden were consulted both during the protocol development and following the pilot study completion and concluded that the potential selection bias of more internet savvy women was acceptable given the ability for improved accessibility to potential participants from less research supported centres or who find hospital visits difficult and the advantage of providing the ability to take part in research in a more comfortable environment, especially when answering questions of a more sensitive nature. Indeed 8% (3) participants chose the 'not applicable' option for the sexual wellbeing domain in this study compared to 18% for the simulation study, Chapter 3. This observation is concordant with the literature which reports less non-response,[146-148] and an increase in disclosure of sensitive information in web-based surveys.[133]

It has been reported that participants of online research often do not read the consent form prior to consenting.[149-152] The consent form used in this study was designed in line with the British Psychological Society Ethics Guideline for Internet-Mediated Research to optimise the chance of participants reading it thoroughly.[153] The consent form was simply laid out, tick boxes were used next to each statement of consent to encourage the participants to address each point, a check point was built into the system to ascertain whether the potential participant had enough information to consent and if not, there were links to more information or an opportunity to make contact with the study team, the withdrawal policy was clearly defined prior to completion of the consent process, and finally, the data collection pages were not accessible unless the consent form had been completed in its entirety.

A study by Perrault et al concluded that participants preferred concise online consent forms with the option of reading further information.[149] In addition they conclude that the majority of participants did not choose to find out more information, raising the question of whether the consent was indeed informed. To promote the importance of informed consent, the first statement on the consent form used in this study was to confirm the participant had read the patient information sheet (this was sent with the letter of invitation and also available online). This was designed to ensure each participant had the baseline knowledge required to give informed consent. They could then choose whether

or not to read further information. This is a low-risk, online study, so although there is no way to prove the consent was fully informed (short of testing the participants knowledge prior to consenting) the process was deemed acceptable but may not be appropriate for higher risk trials.

The median 'satisfaction with breast' Q-score was 55 (max 100) using the BREAST-Q post-operative reconstruction module. This is from a heterogenous group i.e. immediate and delayed-immediate, with or without radiotherapy so drawing accurate comparison to reports from the literature is difficult. The National Mastectomy and Reconstruction Audit reported that 59% of women with immediate reconstruction (implant and autologous) were satisfied with how they looked in the mirror unclothed.[19] A study by Pusic et al published in 2017 of over 1,000 women following mastectomy and breast reconstruction reported a mean 'satisfaction with breasts' score of 64 (out of 100) at one-year follow up for implant-based reconstruction. The majority of women in Pusic's cohort (92%) had a two-stage approach to reconstruction with tissue expander compared to 32% in this study and the follow up period was shorter (12 versus 29 months). With this caveat, the study population does not appear to be skewed towards participants who are either overly dissatisfied or overly satisfied compared to other populations studied.

Demographics, clinical data, and the BREAST-Q results were downloaded from the website in Excel format for analysis. This was advantageous over paper case report forms by reducing transcription error, improving time-efficiency, and enabling simple central analysis of results. A similar approach will further reduce burden placed on participating centres for the main study. The format of the data downloaded from the website was easy to analyse and will remain so for large scale analysis. The BREAST-Q results required conversion from words to numbers for use within the Q-score software which may be cumbersome when upscaled. Consultation with Fluent Interaction web designers has helpfully identified a way to overcome this for the main study.

Some control of participant activity is lost with online research.[153] The data collection pages were designed, where possible, to be multiple choice questions, with each question requiring an answer or at least a "not applicable" box to be

ticked. This was to facilitate ease of data analysis, reduce misinterpretation of prose during data analysis, bridge literacy/language gaps (medical versus lay), and to ensure complete data sets.

Feedback on the website design from patient representatives endorsed the use of RMH and NHS branding to engender trust. This is in line with NHS England's NHS identity research published in 2016 stating the NHS logo is associated with trust, respect, service quality, expertise and accountability to the public.[154] This will be carried forward to the main study where each participating centre will have a branded subdomain of the website under the umbrella of the NHS and Royal Marsden.

4.6 Conclusion

The development of a bespoke online research platform has been described. The population from this small single centre pilot has demonstrated feasibility, accuracy and acceptability to participants of the online platform. It has been designed to be scalable for use in a multi-centre study, and carried low burden for investigators. The research method has been designed to enable data collection from a broader, more representative sample of the population. Further validation at a different centre may be appropriate prior to use in a large scale multicentre study.

4.7 Acknowledgements

I would like to formally acknowledge the contributions of the participants, Miss Carol Pitches and medical photographer Dennis Underwood to this study.

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The Website was created by Fluent Interaction, specialists in digital insight and innovation focussing on naturalistic user research, evidence-based design, and measurable business objectives.

The protocol was reviewed and passed by London-Riverside NRES committee Ref 17/LO/0763. The study is registered on a publicly accessible database, clinicaltrial.gov, NCT03203252.

Informed consent was obtained from all individual participants included in the study.

Chapter 5 A scoring system for 3D surface images of breast reconstruction developed using the Delphi consensus process.

RMH R&D Reference	CCR4770
IRAS	224146
REC Reference	17/LO/0763
Clinical Trials.gov ID	NCT03203252
Funding	Grant from the Association of Breast Surgery.

5.1 Introduction

Patient reported outcome measures (PROMs) are an important reflection of aesthetic satisfaction, however, they do not correlate well with professional evaluation of aesthetics,[19,31, 35, 36] frequently reporting more favourable outcomes.[15, 37, 38] Qualitative interviews with patients who had undergone breast reconstruction shed some light on factors contributing to patients' decision making. How a patient feels about their reconstruction and how they feel they are perceived by others', the relationship with their surgeon or other practitioners, clinical outcome (i.e. complications) and how they viewed reconstruction as part of their cancer journey were described.[33]

A positive patient *experience* may translate into a favourable opinion of *aesthetic outcome* as measured by PROMs when a professional judgement may suggest the contrary, thus, PROMs may not be responsive enough to build clinical evidence and develop best practice.

An objective tool for the evaluation of aesthetic outcome from BCT has been described in Chapter 2. The future vision is to develop an objective evaluation tool for the reconstruction population. There are a number of challenges prior to embarking on such a project. The aesthetic goals from breast reconstruction

are broader and arguably more challenging to evaluate (as discussed in Chapter 3), surgical practice is diverse and evolving rapidly within the UK,[135] and there are numerous panel scales in the literature which share common deficiencies with no consensus on which one to use.[18, 31,29]

In order to communicate and compare results, benchmark performance and inform best practice an objective method of aesthetic evaluation is required. With well-described failings of current aesthetic measures,[18, 29] a contemporary panel aesthetic scoring system is required to assess which 3D-SI measures can be used to define an objective aesthetic evaluation model. In this study a Delphi consensus process was used to develop an aesthetic scoring system for the panel assessment of 3D-SIs of women who have undergone breast reconstruction.[155]

5.2 Hypothesis and specific aims

5.2.1 Hypothesis

A Delphi process can be used to reach consensus to define an expert aesthetic scoring system for use in panel assessment of 3D-SIs of women who have undergone breast reconstruction.

5.2.2 Aims

1. Derive a contemporary panel assessment scale for use in a reconstruction population.
2. Test the reliability of the Delphi derived panel scale.

5.2.3 Objectives

1. Identify key items for evaluation in a reconstruction specific panel scale using a Delphi consensus process.
2. Report upon inter-panellist and intra-panel reliability of the Delphi derived panel scale.
3. Evaluate the correlation between the Delphi derived panel evaluation and Patient Reported Outcome Measures.

5.3 Methodology

This study was part of a pilot study reviewed by the London-Surrey Research Ethics Committee (17/LO/0763) in preparation for a large multi-centre trial, available at clinicaltrials.gov (NCT03203252).

5.3.1 Delphi consensus process

A literature review and consultation with experts in the field shaped the online questionnaire for use in the Delphi consensus process. The purpose was to identify key aesthetic criteria used by clinicians when evaluating aesthetic outcomes. Some of these items would be selected by the Delphi process into a panel scoring scale for the evaluation of breast reconstruction using 3D-SI. The questionnaire was circulated to oncoplastic and plastic surgeons via iBRA-net (a community of research active breast/plastic surgeons) and the UK Association of Breast Surgery (ABS). Participants were required to rate each item on their perception of its importance for inclusion in an expert panel assessment for breast reconstruction, from 1 (extremely important) to 9 (unimportant).

The Delphi process consisted of two iterative rounds of voting with predefined exclusion criteria (Figure 49) followed by two consensus discussions, and a final round using binary “in” or “out” voting. Participants must complete prior rounds in order to participate in subsequent rounds. The rationale for hosting two consensus discussions was pragmatic, to enable maximum participation. One was held in Birmingham at the iBRA-net meeting (October 2018) and the other in London at the Royal Marsden cross-site oncoplastic research meeting (November 2018). Only votes from members who had participated in rounds one and two contributed to the final round, although others contributed to the discussion.

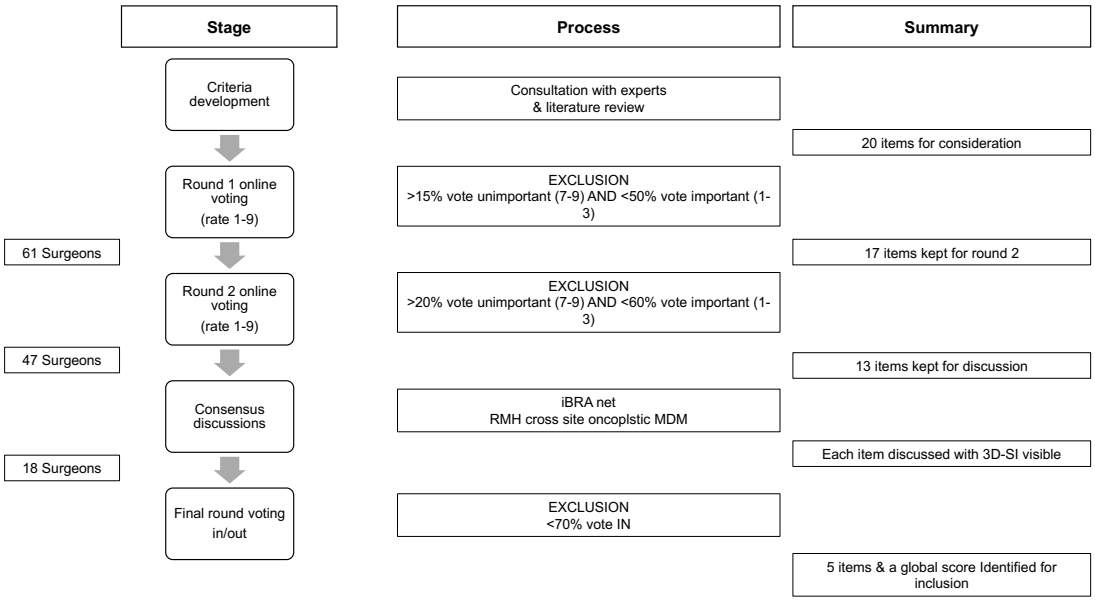

Figure 49 Delphi consensus process to establish an expert panel assessment for reconstructive breast surgery

Additional questions posed within the questionnaire that were not part of the Delphi process pertained to the participant (profession, grade, experience [years in post], gender) and the proposed panel methodology (number of panellists, number of points on the Likert scale).

The validity, inter-panellist reliability and intra-panel reliability of the scoring system was tested by a multi-disciplinary panel with representation from two centres in London with high rates of autologous and implant reconstruction (Imperial College Healthcare NHS Trust and The Royal Marsden NHS Foundation Trust). The panel comprised of three oncoplastic breast surgeons, three clinical oncologists, and three plastic surgeons. The panellists were all consultants with at least 5 years', experience. The panellists were blinded to patient, surgeon and clinical oncologist identity, and to the treatment received.

5.3.2 Three-dimensional surface images

3D-SIs were captured using Vectra XT® (Canfield, USA). Women were positioned with their hands on their hips and their elbows behind the mid-axillary line to optimise visualisation of the lateral aspect of the breast. The images were taken at the end inspiratory pause during quiet breathing. Images for the adjuvant radiotherapy cohort were collected as part of a previous study [NCT03072316],[31] and the images for the neoadjuvant radiotherapy group were from the aesthetic subgroup of the Primary Radiotherapy And Diep flap study (PRADA) [NCT02771938].

5.3.3 Evaluation of the aesthetic scoring system

3D-SIs of 55 women who had undergone mastectomy (unilateral or bilateral) and immediate autologous breast reconstruction with adjuvant or neoadjuvant radiotherapy were viewed in a standardised animation (7 views in sequence). AP, oblique (left and right), lateral (left and right), cranial, and caudal views were presented (Figure 50). 10 3D-SIs were selected at random and repeated within the panel assessment to allow assessment of intra-panel reliability. No discussion was permitted during the panel assessment. The panel was not shown example images to benchmark standards. Panellists were given written definitions for the Likert scales in order to standardise the scoring.

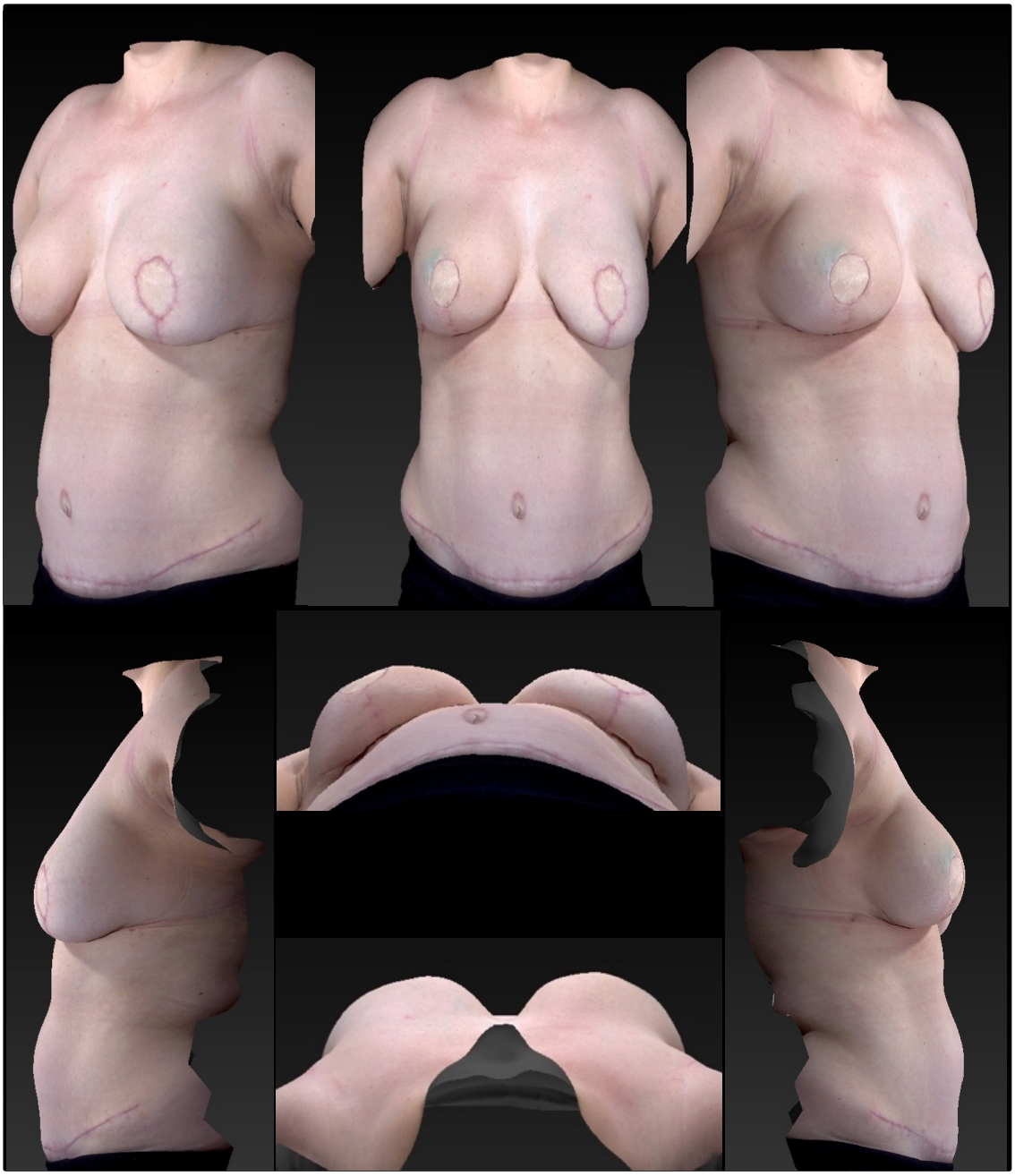

Figure 50 Standardised views of 3D-SIs viewed by the panel including antero-posterior (AP), oblique (left and right), lateral (left and right), cranial, and caudal. Each image was viewed individually in sequence

5.3.4 Statistical analysis

IBM SPSS 23 was used. Delphi results were represented with descriptive statistics.

Intra-panel reliability was reported using weighted kappa ($w\kappa$) for the 10 repeated images. A $w\kappa$ of 0 was considered to indicate poor agreement, 0.01–0.20 slight agreement, 0.21–0.40 fair agreement, 0.41–0.60 moderate agreement, 0.61-0.80 substantial agreement, 0.81-0.99 very good and 1.00 perfect agreement.

Inter-panellist agreement was measured using the intra-class correlation coefficient (ICC). ICC of less than 0.40 was considered poor, between 0.40 and 0.59 fair, between 0.60 and 0.74 good, and between 0.75 and 1.00 excellent.[136] Internal consistency was evaluated using Cronbach's alpha (α). An α value of $\geq$0.9 translates to excellent internal consistency, $\geq$0.8 to <0.9 good, $\geq$0.7 to <0.8 acceptable, $\geq$ 0.6 to <0.7 questionable, $\geq$0.5 to <0.6 poor, and <0.5 unacceptable.[156] When calculating the ICC (single measures), each score for each view is regarded as separate, hence there are 20 measures (10 images seen twice) and any intra-panellist disagreement will impact this score. For the ICC (average measures) the average score for the two viewings is taken for each panellist and these are compared. There are therefore 10 scores for comparison and the impact of any intra-panellist disagreement is mitigated.

Using Spearman's correlation coefficient (r), the correlation between each item (shape, symmetry, volume, position of breast mound, nipple position) with the global score was used to test the validity of the method. For interpretation, r of $\geq$0.9 to 1.0 very high positive correlation, $\geq$0.7 to 0.9 high positive, $\geq$0.5 to 0.7 moderate positive , $\geq$0.3 to 0.5 low positive, 0.3 to -0.3 negligible correlation.[157] Equivalent negative values represent an inverse correlation. Spearman's correlation coefficient was also used to assess the correlation between the global score and PROMs (BREAST-Q satisfaction with breasts Q-score 0-100, where 100 is the best score).[39, 40]

5.4 Results

61 surgeons (88% consultants) completed round one, 49 round two, and 18 were involved in final round voting. Oncoplastic and plastic surgeons were represented (75% and 25% respectively). 46 were consultant oncoplastic surgeons (1 retired), 11 consultant plastic surgeons, and 4 were trainees. 19 (31%) had spent <3 years in their current post, 12 (20%) 3-5 years, 11 (18%) 6-10 years, 19 (31%) >10 years. 28 (46%) were male, 30 (49%) female, 1 (2%) transgender, and 2 (3%) preferred not to say.

Round one voting reduced the number of items included in the questionnaire from 20 to 17 (Figure 51, Figure 52), and round two from 17 to 13 (Figure 53, Figure 54) and the final round established 5 items (surface symmetry, volume, shape, position of breast mound, nipple position) in addition to a global score for the Delphi-derived panel evaluation (Figure 55). The Delphi process is summarised in Table 22. The majority voted for a 5-point Likert scale, and 3-5 panellists to comprise the panel.

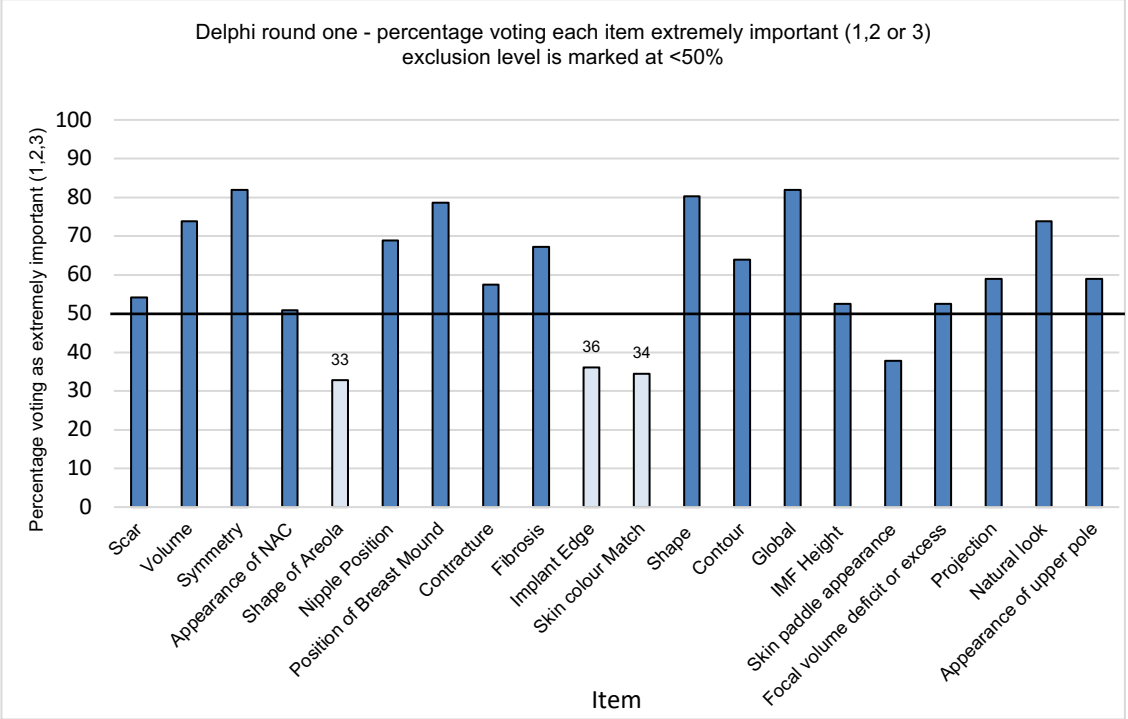

Figure 51 Round one of the Delphi process. Percentage voting the item as extremely important (1,2 or 3). To be excluded, <50% must vote an item important AND >15% must vote it unimportant (score 7,8 or 9). If either >50% vote it important OR <15% vote it unimportant, the item proceeds to the next round. Excluded items shown in pale blue

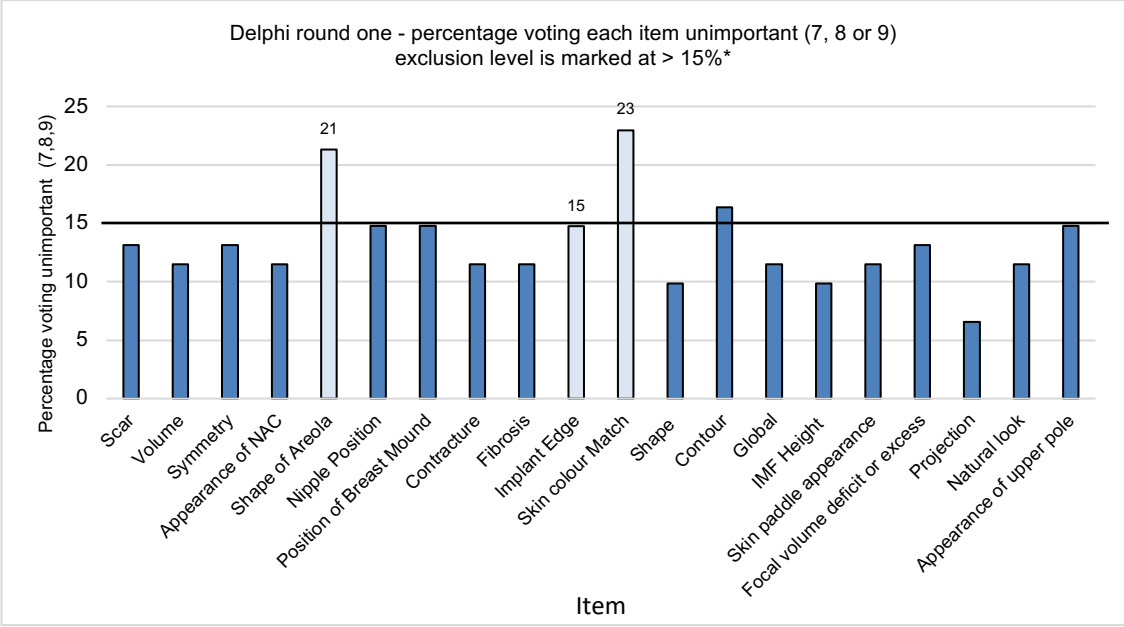

Figure 52 Round one of the Delphi process. Percentage voting the item as unimportant (7,8 or 9). To be excluded, <50% must vote an item important (score 1, 2 or 3) AND >15% must vote it unimportant. If either >50% vote it important OR <15% vote it unimportant, the item proceeds to the next round. Excluded items shown in pale blue

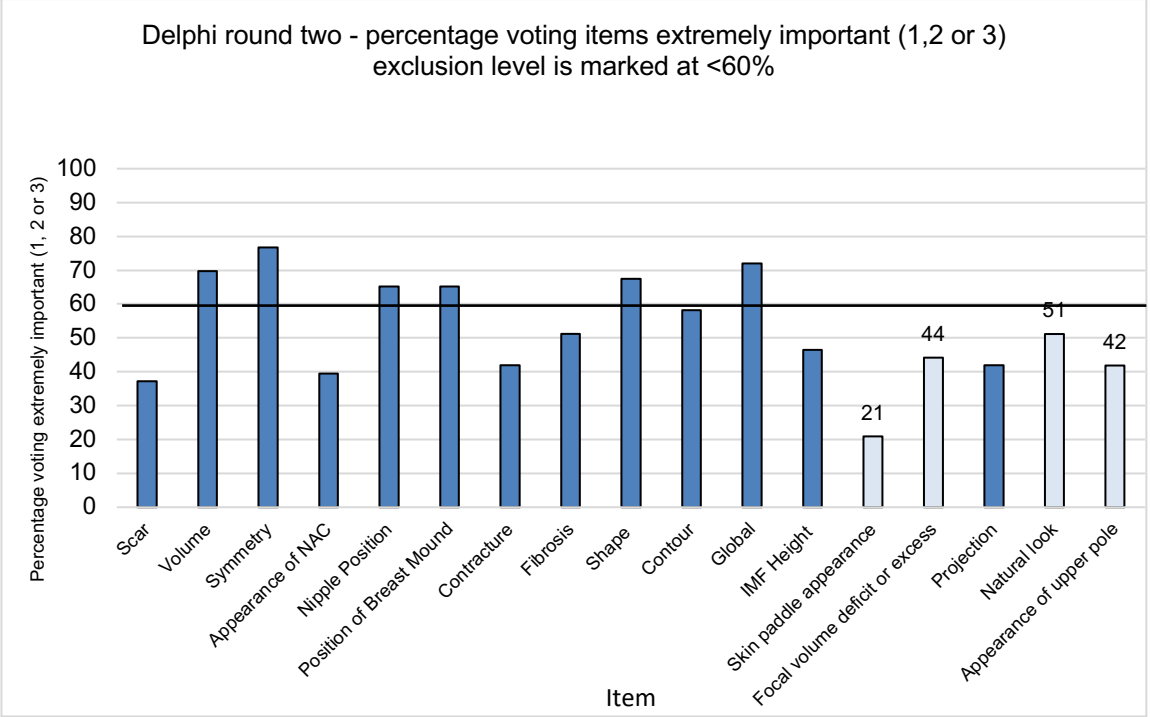

Figure 53 Round two of the Delphi process. Percentage voting the subscale as extremely important (1,2 or 3). To be excluded, <60% must vote an item important AND >20% must vote it unimportant (score 7,8 or 9). If either >60% vote it important OR <20% vote it unimportant, the item proceeds to the next round. Excluded items shown in pale blue

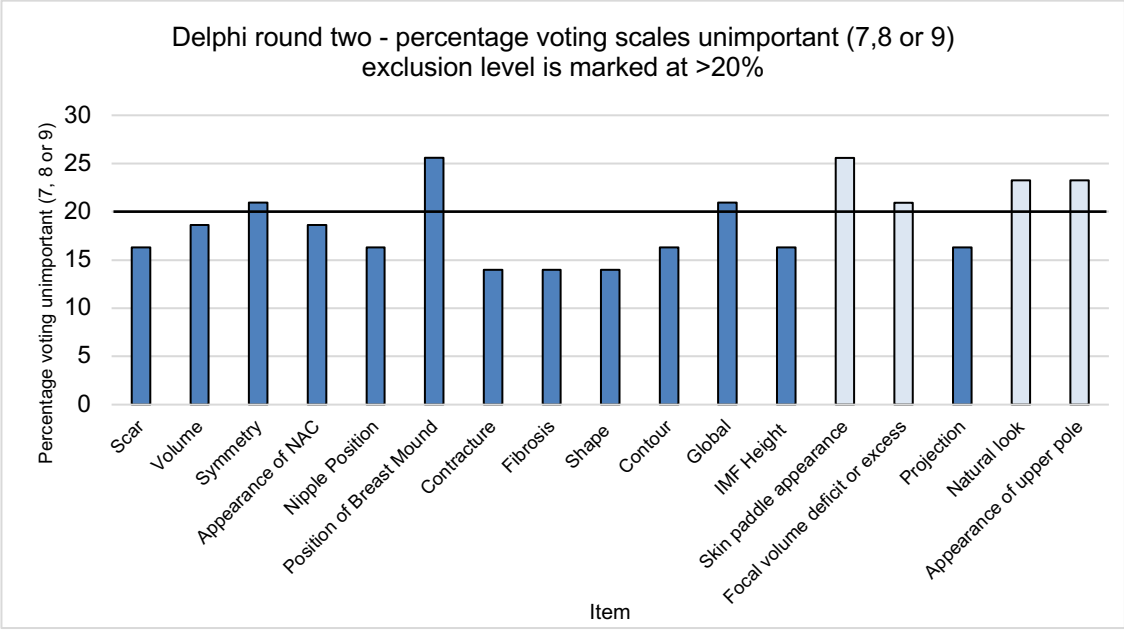

Figure 54 Round two of the Delphi process. Percentage voting the subscale as unimportant (7,8 or 9). To be excluded, <60% must vote an item important (score 1, 2 or 3) AND >20% must vote it unimportant. If either >60% vote it important OR <20% vote it unimportant, the item proceeds to the next round. Excluded items shown in pale blue

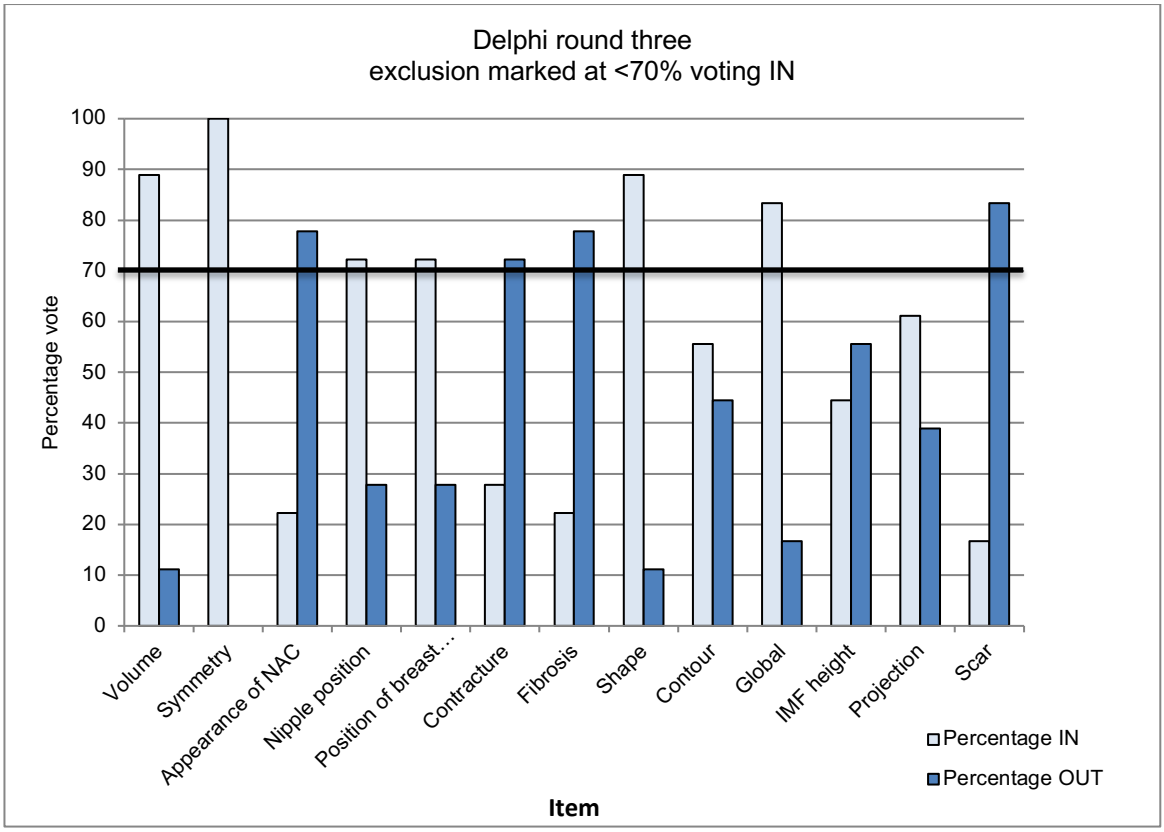

Figure 55 Final round of the Delphi process. Binary in/out voting. A threshold of 70% was set for inclusion of the item.

The detailed descriptions of scores for each item used in the panel evaluation are given in (Table 23). The rationale was not only to guide the panelists, but also to aid in the future interpretation of the result, making the process more clinically relevant.

	Round 1 (n=61)				Round 2 (n=47)				Round 3 (n=18)	
Item	Voted Important 1-3 (%)	Voted Unimportant 7-9 (%)	Progress to next round >50% vote important or < 15% vote unimportant		Voted Important 1-3 (%)	Voted Unimportant 7-9 (%)	Progress to next round >60% vote important or < 20% vote unimportant		Votes to retain criteria (%)	Item retained (>70% voted 'in')
Symmetry	82	13	Yes		77	21	Yes		100	Yes
Global	82	11	Yes		72	21	Yes		83	Yes
Shape	80	10	Yes		66	15	Yes		89	Yes
Position of breast mound	79	15	Yes		64	26	Yes		72	Yes
Volume	74	11	Yes		68	19	Yes		89	Yes
Natural look	74	11	Yes		49	23	No		-	-
Nipple position	69	15	Yes		64	17	Yes		72	Yes
Fibrosis	67	11	Yes		51	15	Yes		22	No
Contour	64	16	Yes		55	17	Yes		55	No
Projection	59	7	Yes		40	15	Yes		61	No
Appearance of upper pole	59	15	Yes		40	23	No		-	-
Contracture	57	11	Yes		43	13	Yes		28	No
Scar	54	13	Yes		37	17	Yes		17	No
IMF height	52	10	Yes		47	17	Yes		44	No
Focal volume deficit or excess	52	13	Yes		45	19	No		-	-
Appearance of NAC	51	11	Yes		38	17	Yes		22	No
Skin paddle appearance	38	11	Yes		23	23	No		-	-
Implant edge	36	15	No		-	-	-		-	-
Skin colour match	34	23	No		-	-	-		-	-
Shape of areola	33	21	No		-	-	-		-	-

Table 22 Progression of items through the Delphi rounds with percentage voting important (1-3) and unimportant (7-9) in rounds 1 and 2 and percentage voting to keep or exclude each item in round 3. The parameters for retaining items are listed.

		Excellent (5)	Good (4)	Moderate (3)	Poor (2)	Very Poor (1)
Shape	The global shape of the reconstructed breast/s	Shape symmetry out of bra achieved	Shape of operated breast is pleasing but ***not symmetrical***	Moderate difference in shape but does ***not*** detract from overall aesthetic result	Moderate focal deficits ***detracting*** from overall aesthetic result	Large focal deficits ***distorting contour*** significantly detracts from overall aesthetic result
Volume	Overall volume symmetry between breasts	Equal volume between breasts	Minor difference in Volume	Moderate difference in volume but does ***not*** detract from overall aesthetic result	Volume difference impacts overall aesthetic result	Major volume mismatch significantly detracts from overall aesthetic result
Nipple Position	Nipple position in relation to the ipsilateral breast	Excellent symmetry between sides and nipple in an ideal position on reconstructed breast mound	Minor adjustments required to achieve excellence in nipple position	Noticeably suboptimal but does ***not*** influence overall aesthetic results	Nipple position slightly impacts overall aesthetic result	Nipple position significantly detracts from overall aesthetic result
Projection	Patient view of symmetry	Projection is **equal**	Minor differences in projection	Noticeable difference but ***not*** detracting from overall aesthetic result	Slightly impacts overall aesthetic result	Significantly detracts from overall aesthetic result
Position of Breast Mound	In relation to chest wall and other breast	Equal to the other side ***and*** in an optimal position on chest wall	Minor asymmetry of position ***or*** symmetrical but suboptimal position	Asymmetry of position ***or*** symmetrical but suboptimal position ***not*** detracting from overall aesthetic result	Slightly impacts overall aesthetic result	Significantly detracts from overall aesthetic result
Symmetry	Comparison between breasts	Out of bra symmetry achieved	Mild asymmetry	Moderate asymmetry but does ***not*** detract from overall aesthetic result	Moderate asymmetry detracting from overall aesthetic result	Significant asymmetry detracting from overall aesthetic result
Global	Taking into consideration subscale evaluation what is your overall impression of the quality of the reconstruction	Excellent	Good	Moderate	Poor	Very Poor

Table 23 Likert scale description used for reference during the panel assessment

5.4.1 Reliability of the panel methodology

5.4.1.1 Inter-panellist reliability

The ICC could not be calculated for nipple position because there were too few cases i.e. the majority of women in the images had not had NAC conservation or reconstruction. The ICC for the individual items was fair (range 0.4-0.5) and was good (0.6) for the global score (Table 24). Cronbach's alpha was good to excellent.

Item	Cronbach's alpha.	ICC (single measures)	Significance	ICC (average measures)	Significance
Position of breast mound	0.931	0.51	<0.01	0.903	<0.01
Symmetry	0.918	0.511	<0.01	0.904	<0.01
Volume	0.892	0.432	<0.01	0.872	<0.01
Shape	0.906	0.466	<0.01	0.887	<0.01
Global	0.938	0.564	<0.01	0.921	<0.01

Table 24 Inter-panellist agreement and internal consistency of the panel methodology per item. ICC; intra-class correlation coefficient.

5.4.1.2 Intra-panel reliability

Intra-panel reliability for 10 repeated images showed moderate to substantial agreement between the mean panel score for the two occasions when the images were shown (range $w\kappa$0.4-0.7). Shape and symmetry demonstrating the strongest agreement (Table 25).

Item	Weighted kappa
Position of breast mound	0.4
Symmetry	0.7
Volume	0.4
Shape	0.7
Global	0.5

Table 25 Intra-panel agreement using weighted kappa for each item for the 10 repeated images. The mean panel score was used for evaluation

5.4.1.3 Validity

Each item (shape, symmetry, volume, position of breast-mound, nipple position) independently showed a high or very high positive correlation with the global score (range r = 0.88-0.92).

5.4.2 Correlation between panel evaluation and patient reported outcome measures

There was a statistically significant moderate strength positive correlation between the mean global panel score and the 'satisfaction with breasts' domain of the BREAST-Q post-operative reconstruction module (r = 0.5 p<0.01) as illustrated in Figure 56.

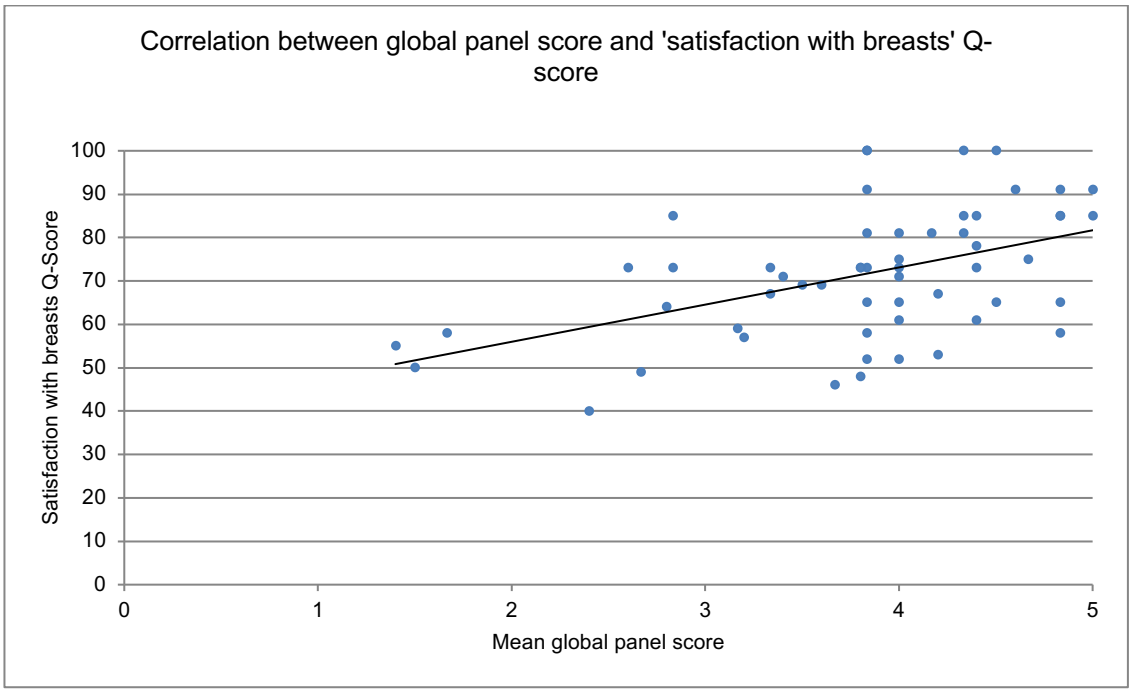

Figure 56 Scatter plot to demonstrate the correlation between mean global panel score and the 'satisfaction with breasts' Q-score of the BREAST-Q post-operative reconstruction module (r=0.5). A Q-Score of 100 and panel score of 5 is best

5.5 Discussion

The rationale for the development of this scale is primarily as the gold standard against which an objective measure of aesthetic outcome for breast reconstruction can be developed using measures derived from 3D-SI in a future multicentre study. 3D-SI may provide a highly reliable and robust way to communicate aesthetic outcome to enable comparison of results, benchmarking, and development of best practice guidelines, but a robust gold standard is required, against which to test these measurements.

This chapter describes the successful development of a reliable, contemporary scale for evaluating breast aesthetic outcomes as captured on 3D-SI. The scale is designed specifically for breast reconstruction and was developed through a Delphi consensus process using expert oncoplastic and plastic breast surgeons. The strengths include the robust development of the scoring criteria using the Delphi process incorporating a literature review with opinion from experts representing different centres across the UK. The scale was developed specifically for breast reconstruction and has been tested by a multi-disciplinary panel. Careful consideration of the written descriptors for each individual item enabled panellists to have a clear understanding of what each score represented clinically. This is also important when interpreting scores to ensure a qualitative meaning can be gleaned from a quantitative score.

A systematic review by Maas et al employed the modified Medical Outcomes Trust (MOT) criteria to evaluate the professional aesthetic assessment scales referenced in the literature.[12] The MOT criteria evaluate each scale based on a predefined scoring system encompassing 7 domains including development of the framework, reliability, validity, responsiveness, interpretability, burden (for professional and patient), and correlation to PROMs. The maximum score is 7. The highest scoring aesthetic evaluation scale (4.5 out of 7) was the ten-point Visser scale which includes 5 subscales (volume, symmetry, scar, nipple-areola complex, shape) and a global ten-point (Likert) scale. The Vrieling's scale which incorporates 6 subscales (scar, size, shape, nipple position, shape of areola, skin colour) and a global four-point Likert scale from 0, excellent to 3, poor, was the most commonly referenced in the literature and scored 3 out of 7.[12] The

Delphi derived panel scale scored 5. Thus, until the 3D-SI objective scoring system is available, this Delph-derived scale provides a robust alternative.

As with all panel assessments, some logistical constraints remain. The strict non-discussion policy during panel assessment was designed to mimic conditions of a 'virtual panel' i.e. independently viewing and scoring of images from a remote location, which would surmount the majority of logistical challenges associated with traditional panel assessment and potentially reduce the burden for panellists (travel, inconvenience). Discussion permits a level of benchmarking between panellists, as hearing the opinions of others may lead to re-evaluation of an individual's scoring. If this variation was significant it would be reflected in the inter-panellist variability i.e. it would be worse with no discussion.

There is a wide range of inter-panellist variability reported in the literature, often using different statistical tests, rendering comparison challenging. Vrieling et al report moderate inter-rater reliability (κ0.55) for their scale,[30] and the linear numeric analogue scale (the second highest scoring scale in the Maas review) reports inter-rater agreement of 0.23-0.38. The Delphi derived panel scale is most closely related to the 10-point Visser scale, first described in 2010 to score aesthetic outcome of tertiary free flap breast reconstruction following failed implant based reconstruction.[158] No description of how it was developed was made. The scale consists of 5 subscales (volume, symmetry, shape, nipple areolar complex and scars) scored on a 5-point Likert scale, and an overall global scale out of 10. The scale varies from the Delphi derived score in that scar evaluation is replaced by position of breast mound and the global scale is scored out of 10.

Inter-rater variability using the Visser scale for a similar cohort of patients scored in our unit was "moderate" ($w\kappa$0.4) for the global score and ranged from $w\kappa$0.2 – 0.36 for the subscales.[14] The inter-rater reliability for the method developed in this paper ranged from an ICC of 0.4-0.5 for the subscales and 0.6 for the global score, in line with the best scoring other scales suggesting remote panel assessment is a feasible alternative.

The Inter-panellist variability for the Delphi derived scale (ICC single measures) was highest for the global scale (ICC 0.56) and lowest for volume (ICC 0.43). The reported ICC for the Visser scale in a study by Dikmans et al ranged from 0.56 for shape to 0.82 for the nipple areola complex. Volume, scars, symmetry and the global scale reported ICCs of 0.61, 0.62, 0.64 and 0.74 respectively.[43] The images used for Dikmans' study were two dimensional and the participants were risk reducing mastectomy with implant-based reconstruction, therefore a more homogenous cohort i.e. all bilateral and no radiotherapy. The panel for Dikmans et al was different to the panel used for the Delphi derived scale in that it included five plastic surgeons and three mammography nurses, and the scores were reported separately (plastic surgeon's scores are reported here as the closest match to the panel utilised to test the Delphi derived scale).

The validity of the Delphi derived scale (Spearman's correlation (r) for the individual items with the global score) ranged from 0.88 to 0.92. The reported validity of the Visser scale in the study by Dikmans et al ranged from 0.58 for the global scale to 0.86 for shape (symmetry r=0.8, volume r=0.73 nipple r=0.61). They also included patient reported scores using the Visser scale which reported inferior correlation of subscales with the global scale (ICC range 0.35 – 0.66).

Intra-panel agreement for the Delphi derived scale was better for shape and symmetry ($w\kappa$0.7) compared to position of breast mound, volume and the global scale ($w\kappa$ 0.4, 0.4 and 0.5 respectively). The explanation for this may lie in the broader interpretation of the terms and influence of personal opinion i.e. the ideal breast mound position as judged by one expert may vary from another whether the breasts are symmetrical is less open to interpretation. Volume symmetry is slightly harder to judge than surface symmetry as a difference in volume distribution can skew opinion i.e. a ptotic breast with an empty upper pole may appear to be less voluminous than a breast of the same volume with fullness in the upper pole following a reconstruction so called "in-bra volume symmetry'. Intra-panel agreement is not reported in the literature for the Visser scale, so direct comparison can't be drawn.

The number of experienced surgeons participating in the Delphi consensus was good, however, the inclusion of clinical oncologists could have broadened the

experience and provided additional elements for consideration. The concept was to design a panel to represent expert opinion on aesthetic outcome, hence the intentional exclusion of patient representation. Patient reported evaluation of aesthetics is consistently discordant with expert opinion hence the need to separate the two.[34, 158,43, 159]

Comparison between PROMs and expert panel evaluation is reported in the literature but it is difficult to draw reliable conclusions due to the different scales and methods of comparisons used. Ramon et al report moderate correlation between the ten-point Visser scale with PROMs (r=0.48)[160] which is comparable to the results observed here (r=0.5). The PROMs were in the form of a study specific questionnaire rather than the validated and widely used BREAST-Q which was used for this study. A low correlation between patient satisfaction (study specific questionnaire) and surgeons aesthetic evaluation (r=0.4) was reported using the Spearman-Baker capsular contracture scale.[160] Thompson et al also report low correlation between PROMS (study specific questionnaire) and panel score (r=0.36).[161] They used a 5 point Likert scale to score 5 subscales (symmetry, shape, size, skin colour, scars) and a global scale. Schuster et al report good correlation with PROMs using the Vrielings scale.[162] Nicholson et al report a low correlation between the Linear measures analogue scale (8 subscales and 1 global scale on a VAS from 0-100) and patient reported aesthetic evaluation using the same scale (r=0.47).[163] Cohen et al report a weak correlation between patient and expert reported aesthetic outcome using their scale which employed 5 subscales and a global scale (r=0.36-0.53).[164]

As discussed within Chapter 1, PROMs are consistently reported to be discordant from expert opinion, [31, 34-36] often reported more favourably. [15, 37, 38] PROMs are influenced by many factors including emotional factors (how the patient feels others view her reconstruction, how she feels about her reconstruction, relationship with the clinical team),[33] operative factors (type of axillary surgery, complications, position along the reconstructive pathway),[33, 35] mechanical features of the reconstruction (movement, rigidity) and sensory features (pain, hypersensitivity, numbness).[43] The discordance between expert and patient opinion and the multiple influencing factors for PROMs makes the

robustness of PROMs as a measure of the technical success of aesthetic outcome questionable and gives weight to the development of an objective tool to be used alongside PROMs.

The Delphi-derived panel evaluation described here appears to be at least as good as other scales referenced in the literature and has been developed specifically to provide an expert evaluation of aesthetic outcome after breast reconstruction. The methodological flaws of panel assessment remain, giving weight to the importance of the development of an objective way to report upon aesthetic outcomes.

5.6 Conclusion

This study has successfully harnessed expert opinion to develop a scale for the expert evaluation of breast reconstruction for use as a gold standard against which to test an objective scale using measures from 3D-SI.

5.7 Acknowledgements

I would like to formally acknowledge the contributions of the participants, Miss Rachel O'Connell and medical photographer Dennis Underwood to this study.

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The protocol was reviewed and passed by London-Riverside NRES committee Ref 17/LO/0763. The study is registered on a publicly accessible database, clinicaltrial.gov, NCT03203252.

Informed consent was obtained from all individual participants included in the study.

Chapter 6 Primary Radiotherapy And Deep Inferior Epigastric artery Perforator (DIEP) flAp study (PRADA): Aesthetic outcome and patient satisfaction at one year.

RMH R&D Reference	CCR4328
REC Reference	17/LO/1071
Clinical Trials.gov ID	NCT02771938

6.1 Introduction

Postmastectomy radiotherapy (PMRT) remains a hot topic in the context of breast reconstruction and one which consensus has not been reached. The literature on PMRT and breast reconstruction is heterogenous in type and timing of reconstruction, radiotherapy regime, follow-up period, satisfaction scales, primary endpoints, definition of complications, systemic therapy regime, and the use of targeted therapies. This renders comparison challenging.

PMRT is offered to women with high risk of locoregional recurrence. The benefits include improved locoregional control and disease free and overall survival in a subset of women with node positive tumours of intermediate to high grade.[165] One advantage of giving radiotherapy *after* surgery is the certainty of histopathology results to indicate treatment, but with increasing use of neoadjuvant systemic therapy the relevance of this is becomes less clear. Potential disadvantages include surgical complications causing delays to adjuvant treatment and deleterious effects of radiotherapy on the reconstructed breast leading to many women being advised against immediate reconstruction.

It is generally accepted that immediate reconstruction is preferable over delayed reconstruction due to superior aesthetic outcome and in addition, low emotional wellbeing, poor body image and social distress while awaiting delayed reconstruction.[4, 166-171] Autologous breast reconstruction is reported to be, on balance, more favourable than implant-based reconstruction in the context of post-mastectomy radiotherapy given its lower rate of complications and reconstruction failure,[172-175] acceptable flap survival rates,[176, 177] and

cosmesis.[174, 176] The reported deleterious effects of radiotherapy on autologous reconstruction are flap volume reduction (12.3% versus 2.6%)[178] and higher rates of fat necrosis,[179, 180] flap contracture,[181] and breast symptoms.[182] Some women do not suffer these and others do to a significant extent, the unpredictability leads to caution among surgeons. Two thirds of complications occur within the first year following radiotherapy and 80% within two years.[183, 184]

Neoadjuvant radiotherapy (NART) in breast cancer surgery is not a new concept. Ten years ago, Monrigal et al published results on NART and latissimus dorsi reconstruction reporting the alteration in sequence did not influence morbidity, disease free or overall survival.[185] NART is consistently reported to be both oncologically and surgically safe,[185-190] however, the literature is largely based on case series with heterogenous methods and limited follow-up with the absence of randomised controlled trials.

Aesthetic outcome after NART and reconstruction is reported to be good to excellent in the majority of studies.[187, 188, 190, 191] There is heterogeneity between methods, scales, and follow-up limiting comparison between or meta-analysis of results.

By irradiating the breast prior to mastectomy and reconstruction, the autologous flap itself is spared radiotherapy, potentially reducing fibrosis and fat necrosis. Other potential benefits of NART include reduced time to completion of treatment,[192] improved access to immediate breast reconstruction[192, 193] and the ability to assess tumour response which may prove to be a surrogate endpoint for local control, potentially improving the efficiency of knowledge-generating research and offering the opportunity for radiobiological studies.[193]

The reported negative implications of PMRT for implant based reconstruction include an increased incidence of overall complications,[194] reconstruction failure,[195, 196] unexpected re-operation rate,[197] capsular contracture,[196, 198, 199] and inferior patient-reported satisfaction with symmetry.[200]

The PRADA study [NCT02771938] is a prospective cohort study to assess the surgical safety and feasibility of NART in women undergoing neoadjuvant

chemotherapy and Deep Inferior Epigastric artery Perforator (DIEP) flap reconstruction who would be recommended PMRT. The primary endpoint was presence of an open breast wound at 4 weeks post-surgery. Secondary endpoints included aesthetic evaluation and patient satisfaction which are reported within this chapter.

6.2 Hypothesis and specific aims

6.2.1 Hypothesis

3D-SI and patient reported outcome measures can be used to compare aesthetic outcome between Deep Inferior Epigastric Perforator (DIEP) flap reconstruction with neoadjuvant radiotherapy (NART) and DIEP flap reconstruction with post-mastectomy radiotherapy (PMRT).

6.2.2 Aims

1. Describe aesthetic outcome in the form of PROMs and panel evaluation for the aesthetic subgroup from the PRADA study.
2. Compare aesthetic outcome between the PRADA aesthetic sub-group and a historic cohort (DIEP and PMRT).

6.2.3 Objectives

1. Perform panel evaluation for the PRADA aesthetic subgroup using the Delphi derived panel method (Chapter 4) for 3- and 12- month post-operative 3D-SI.
2. Report PROMs in the form of the BREAST-Q reconstructive module from pre-operative, to 3 and 12 months post-operatively for the PRADA aesthetic sub-group.
3. Compare outcome (measured by panel evaluation and PROMs) between the PRADA aesthetic sub-group and a historic cohort (DIEP and post mastectomy radiotherapy)

6.3 Methodology

6.3.1 Study design

The PRADA study recruited at two major London centres (3 geographical sites). An aesthetic subgroup was selected because they had surgery at a site with 3-Dimensional Surface Imaging (3D-SI) capability or were willing to travel there. These participants underwent 3D-SI and completed the BREAST-Q reconstruction questionnaire at baseline, 3 and 12 months post-operatively.

6.3.2 Panel evaluation

3D-SIs were subject to panel evaluation using a scale developed through a Delphi consensus process specifically for breast reconstruction as described in Chapter 5. As described previously, nine consultants with at least 5 years-experience in-post comprised the panel; three oncoplastic surgeons, three plastic surgeons, and three radiation oncologists from two London centres with a high volume of autologous breast reconstruction. In an attempt to reduce bias, they reviewed a mixed population of 3D-SIs of PRADA participants and images from a historical cohort of patients who underwent mastectomy and DIEP reconstruction followed by PMRT. The groups were not propensity matched as the follow up period did not overlap. The panellists were blinded to surgeon, radiation oncologist, and patient identity in addition to the treatment received. A standardised sequence of 7 views of each 3D-SI were shown to the panel (right and left lateral and oblique, anteroposterior, cranial, and caudal). The images were viewed in one sitting and there was no time restriction on analysis. Pre-treatment images were not scored. Discussion between panellists about scores was not permitted. The panel was not shown benchmark images.

The BREAST-Q reconstruction module questionnaires were analysed using Q-Score software. The resulting Q-score is from 0-100, with 100 being the best score. The results were compared to those from the historical cohort for reference.

6.3.3 Statistical analysis

IBM SPSS Statistics 24 was used. The mean global panel score from the 9 panellists was used for analysis. Simple descriptive statistics were used, either mean and standard deviation or median and inter-quartile range according to the distribution of the data. The Mann-Whitney U test was used to describe the significance of between-group differences for panel and Q-scores.

6.4 Results

17 participants from the PRADA study participated in aesthetic evaluation. 3D-SI was completed by 15 participants at baseline, 15 (82%) at three-months and 13 (76%) at 12-months follow-up. 14 (82%) participants filled out a baseline BREAST-Q, 13(76%) at 3 months and 12(71%) at 12 months. Completed BREAST-Q questionnaires were available for 27 of the 28 participants in the historical control cohort.

Demographics and clinical data are reported in Table 26. Median follow-up was significantly longer in the historical control cohort compared to the PRADA cohort at 23 (IQR 17-38) and 12 (IQR 12-13) months respectively ($p<0.01$). Operation dates for the historical cohort ranged from October 2009 to September 2014 and for the PRADA cohort from April 2016 to March 2018. The participants in the PRADA cohort were significantly younger than those in the control (49 (range 36-60) and 57 (range 42-72) ($p>0.01$). BMI was similar between cohorts. Median time from radiotherapy to surgery was 25 days (IQR 16-29 days) in the PRADA cohort. Seven women in the PRADA cohort and six in the historical control cohort had symmetrising surgery.

	PRADA cohort n=17	Historic control n=28	Significance
Age mean (range)	49 (36-60)	57 (42-74)	P<0.001
Ethnic origin Caucasian	17	28	-
BMI mean (sd)	27 (21-36)	27 (21-34)	P=0.57
Follow up in months median (IQR)	12 (12-12)	23 (17-38)	P=<0.01
Axillary treatment (%) Surgery SLNB ALND Radiotherapy Axilla SCF IMC	 9 (47) 8 (53) 2 11 1	 9 (32) 19 (68)	 P=0.29 -
Symmetrising surgery (%) Yes Reduction Mastectomy and DIEP	 8(47) 4 4	 6(21) 6 0	P=0.07
Radiotherapy regime (%) 50Gy 25# 40Gy 15# 42.67Gy 16# Performed at a different centre	 0 13 (76) 4 (24) 0	 7 (25) 13 (46) 2 (7) 6 (21)	P=0.09

Table 26 Demographics for the PRADA cohort and the historical control cohort (mastectomy, immediate DIEP and PMRT)

The median global panel score for the PRADA cohort at 3 months was 3.9 (IQR 3.8-4.4) and 4.3 (IQR 3.9 - 4.6) at 12 months, the median score for the historical controls was 3.6 (IQR 2.8-4) as illustrated in Figure 57 . The panel score for the PRADA cohort at 12 months was significantly higher than for the historical control (p = 0.003). Example 3D-SI from both cohorts are illustrated in figure 58.

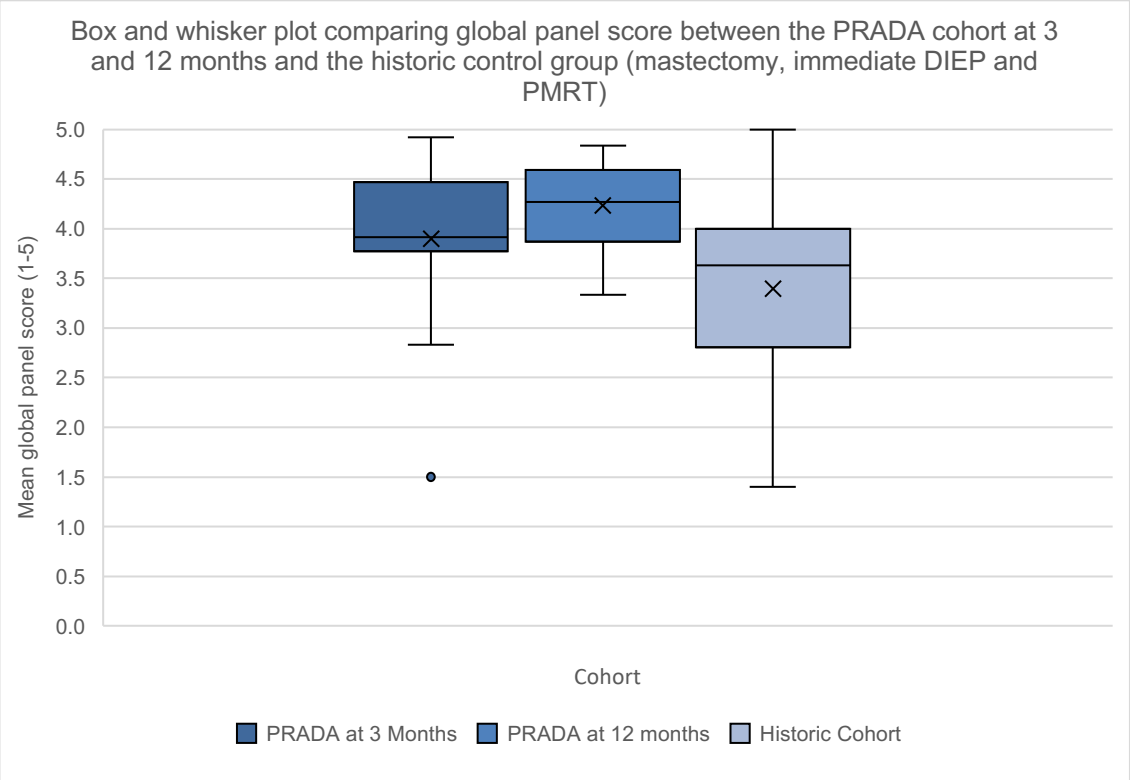

Figure 57 Box and whisker plot comparing mean panel scores for the PRADA group at 3 and 12 months post-surgery and the historic control group (median post-radiotherapy follow up 23 months). DIEP; deep inferior epigastric artery perforator flap, PRADA; primary radiotherapy and DIEP flap reconstruction study, PMRT; post mastectomy radiotherapy

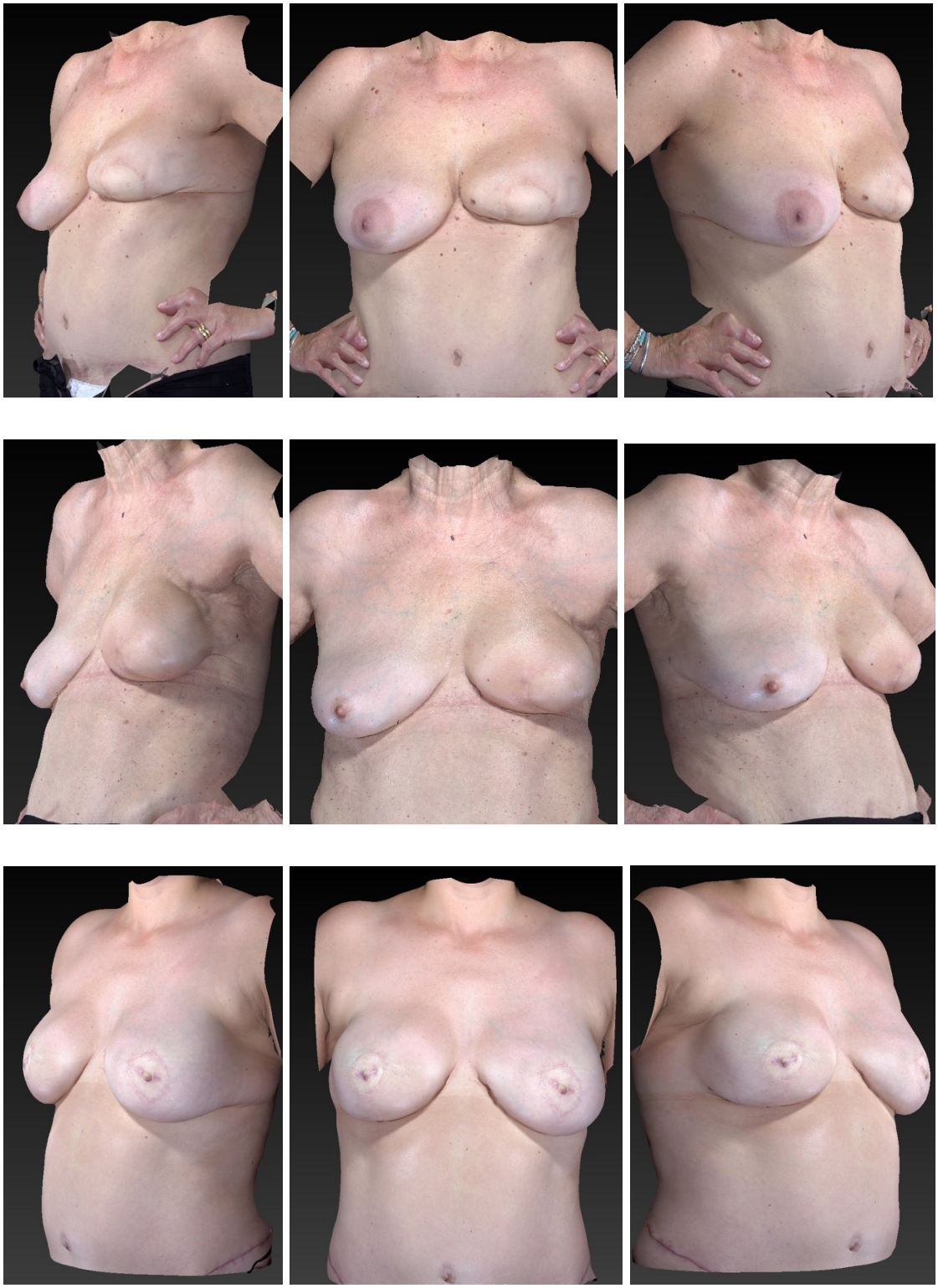

Figure 58 3D-SIs of study participants. From left to right, left oblique view, AP view, right oblique view. Top row historic cohort participant 1; global panel score 1, satisfaction with breasts Q-score 55, middle row historic cohort participant 2; global panel score 3, satisfaction with breasts Q-score 73, bottom row PRADA participant at 12 months; global panel score 4 satisfaction with breasts Q-score 81

The median ‘satisfaction with breasts’ Q-score for the PRADA cohort was 48 (IQR 48-53), 73 (IQR 67-81) and 77 (IQR 72-87) at baseline, 3 and 12 months respectively, and 63 (IQR 54-71) in the historical control cohort (Figure 59). The Q-score for the PRADA cohort at 12 months was significantly higher than for the historical control cohort (p = 0.01). The Q-scores for the other BREAST-Q domains are illustrated in Table 27 for the PRADA cohort at baseline, 3 and 12 months and for the historical controls.

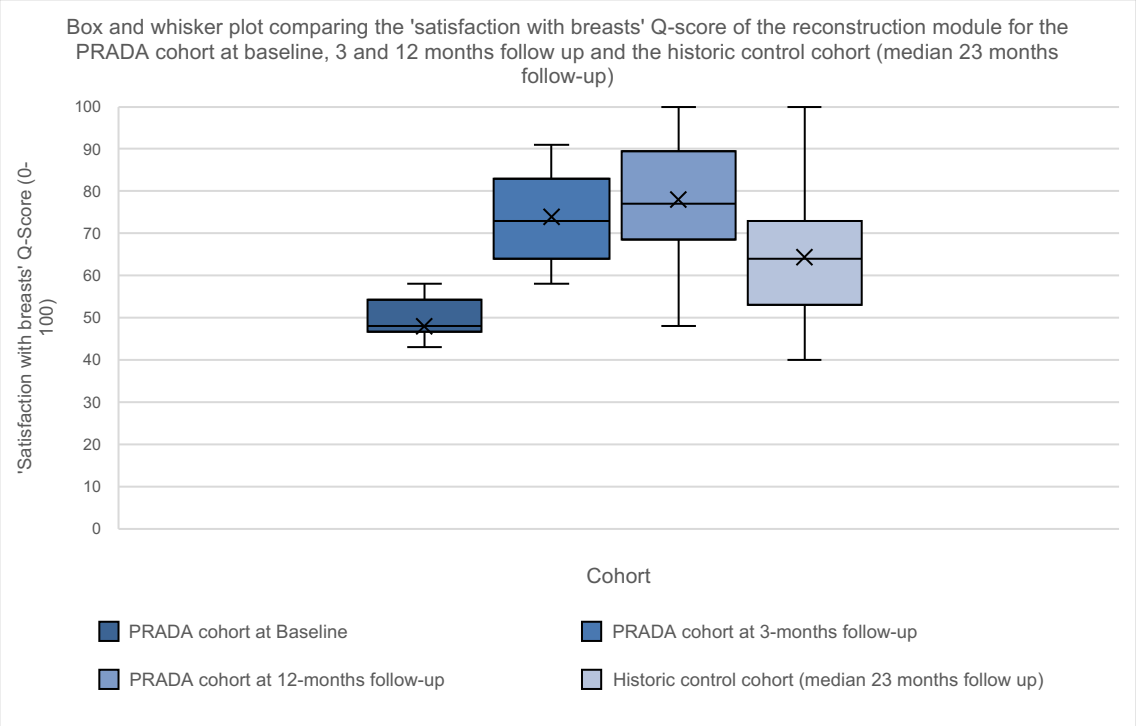

Figure 59 Box and whisker plot comparing the median Q-Score for the BREAST-Q reconstruction module for the PRADA cohort at baseline, 3 and 12 months and the historical control cohort (median follow up 23 months). Q-score of 100 is best

	Satisfaction with breasts	Satisfaction with outcome	Psychosocial wellbeing	Physical wellbeing (chest)	Physical wellbeing (abdomen)	Sexual wellbeing
	Median (IQR)	Median (IQR)	Median (IQR)	Median (IQR)	Median (IQR)	Median (IQR)
PRADA cohort baseline	48 (48-53)	-	60 (53-79)	77 (70-91)	91.5 (83-100)	47.5 (40-60)
PRADA cohort at 3 months	73 (67-81)	100 (75-100)	79 (62-82)	63 (58-78)	70 (67-84)	54 (49-67)
PRADA cohort at 12 months	77 (72-87)	100 (83-100)	76 (62-92)	83 (80-93)	79 (70-100)	57 (42-93)
Historic control	64 (54-71)	75 (67-100)	70 (62-86)	74 (66-85)	89 (75-89)	49 (44-66)

Table 27 Summary of Q-score for the BREAST-Q Reconstruction module for the PRADA cohort at baseline, 3 and 12 months post-surgery and the historical control cohort (median follow up 23 months). Q-score of 100 is best

6.5 Discussion

This is the first prospective study to report on aesthetic outcome after NART and DIEP flap reconstruction. The expert panel gave good aesthetic outcome scores to the PRADA cohort, with an average panel score of 4.3 out of a maximum of 5 points at 12 months follow-up. The scores were higher for the PRADA cohort than for historical controls who underwent DIEP reconstruction followed by PMRT which did reach statistical significance, however, within the context of a feasibility study was not powered to this endpoint. The wider IQR observed in the historical control cohort may reflect the variability of results with PMRT, and potentially indicate more predictable results with neoadjuvant radiotherapy.

There are caveats to the comparison, in that the follow-up period for the historical control cohort is almost double that of the PRADA cohort, therefore the effect of radiotherapy over time may not be fully appreciated. It is reported that two thirds of complications of PMRT occur within the first year and 80% within two years,[183, 201] so although major differences are unlikely to have been missed, longer term follow up is required to examine degradation of aesthetic results over time. There were also differences in radiotherapy dose between groups with a proportion of the historical cohort receiving higher dose which may also act as a confounder for aesthetic results.

Calculations for the minimally important difference for the BREAST-Q reconstruction module is reported as 4 points.[202] Consultation with the PRADA patient steering committee felt 10-points was clinically relevant. A difference of 14 points was observed between groups in the PRADA aesthetic cohort, however, we may not expect to observe such a difference in the follow up study where the groups are matched. A sample size calculation to detect a statistically significant mean±SD ($p<0.05$) difference of 10±20 points on the BREAST-Q satisfaction with breasts domain with 90% power requires a sample of 186 patients. With approximately 15% loss to follow up, a sample size of 220 participants would be required (110 per arm).

92% of patients in the PRADA cohort received a good/excellent panel score (score of 4 or 5). Comparison with other neoadjuvant radiotherapy studies is challenging not only because of methodological differences between the panel evaluation, but also numerous difference between the cohorts including reconstruction type, follow-up period, radiotherapy dose, time from radiotherapy to surgery and previous treatments received.

National trends in breast reconstruction have changed over the past two decades with immediate breast reconstruction increasing in popularity (two-fold between 1996-2012).[203] Implant based breast reconstruction remains the most popular reconstruction method (2015 data), there has been a decline in the popularity of latissimus dorsi based reconstruction and an increase in DIEP flap reconstruction, most notably at specialist and academic centres.[203] At our institution rates of LD-assisted reconstruction fell from 54% (2003–2004) to under 1% of total immediate breast reconstruction (2012-13). Conversely DIEP flap reconstruction rose from 1% to 38% over the same period.[203] A more widespread change in practice may be reflected in the heterogeneity of reconstruction type in the literature.

6.5.1 Panel assessment of aesthetics

In 2010, Giacalone et al reported aesthetic outcome for 18 patients who received neoadjuvant chemoradiotherapy, skin-sparing mastectomy and immediate latissimus dorsi reconstruction and 54 patients who received mastectomy,

adjuvant radiotherapy and delayed reconstruction at mean follow up of 4.7 years. 78% of the NART and immediate reconstruction group were awarded a good or excellent score by physicians versus 87% for the PMRT and delayed reconstruction group.[191] The scale used was the Gerber scale which includes 6 domains each with a maximum of 2-points (volume, shape, symmetry, ipsilateral and contralateral scars, and infra-mammary fold),[204] and two physicians rated the outcome either in person at a follow-up visit or using photographs. Although a few of the domains are similar to those used in the PRADA cohort, the methodology is different on a number of levels (blinding, number of raters, views, 2D versus 3D photography) in addition the comparison is drawn between a group with PMRT and *delayed* reconstruction limiting the reliability of the comparison.

Pazos et al used the same scale to compare NART, mastectomy and immediate reconstruction (n=10) with patients who had mastectomy for failed breast conserving surgery i.e. positive resection margins with no option for further BCS (n=12).[188] The aesthetic outcome was good or excellent in 66% (n=6) of the patient who had not had prior breast conserving treatment and 37% (n=4) in those that had. This study had small numbers and a variety of reconstruction types including implant-based (with ADM, latissimus dorsi, or implant only), DIEP and transverse rectus abdominis myocutaneous flap (TRAM). The median follow up was 30 months (without explicit statement that it was equal for the two groups). The median time from radiotherapy to surgery was 47 days which is longer than for the PRADA cohort (25 days) with a wider range (26 - 162 versus 16 - 28.5 days). The radiotherapy dose was also higher than for PRADA (50.4Gy versus 40Gy).

Ho et al published a retrospective review in 2012 of 30 women who received NART followed by autologous reconstruction and reported 66% good or excellent results.[187] A 4-point scale was used for shape and symmetry (described by Kroll), where 3-points equated to a good score and 4- an excellent score.[205] The senior author of the paper evaluated the outcome leaving the results open to bias. The median follow-up was longer than PRADA (3.5 years), the types of reconstruction used were latissimus dorsi, TRAM, or a combined

method rather than DIEP reconstruction, the median time from radiotherapy to surgery was longer at 6.9 weeks (range 2.7-12.9), and the dose of radiotherapy was higher for most participants, 50Gy for 60% and hypo-fractionated for 40% (2.5Gy per fraction over 3.5 weeks).

6.5.2 Patient-reported outcome measures

The satisfaction with breasts Q-scores for the PRADA population at 12 months follow-up were superior to those for the historical cohort (77 [IQR 72-87] and 63 [IQR 54-71] respectively). The follow-up period may be a confounder as could the higher percentage of women undergoing ALND in the historical cohort versus PRADA, which has been shown to influence patient satisfaction after BCT.[206] Participants in the PRADA cohort may also have a perception that their reconstruction has been 'spared' from radiotherapy which may serve to bias the results. Complications associated with radiotherapy and breast reconstruction in the adjuvant or neoadjuvant setting can develop over a number of years, therefore longer term comparison between groups is required.[207]

Patient reported aesthetic outcome was excellent or good in 89% of participants in the study by Giacalone et al using the Gerber scale.[191] In a retrospective series of 111 patients who received NART with latissimus dorsi reconstruction with or without implants, at a median follow-up of 31months an average patient satisfaction score of 17 out of 20 (85%) was reported.[190] The questionnaire used was not validated so interpretation of results is challenging, but nonetheless encouraging.

Other studies of neoadjuvant radiotherapy and breast reconstruction either do not evaluate aesthetic outcome at all,[185, 186, 208] or do not describe their methods.[189] The literature on aesthetic evaluation of reconstruction followed by PMRT has similar limitations, with heterogenous populations and methods. Inferior outcomes have been reported for reconstructions that receive PMRT compared to un-irradiated reconstructions. [31, 180, 206, 209, 210] In contrast, a number of studies have failed to show a difference in patient reported satisfaction for autologous reconstruction with or without PMRT.[181, 182, 211, 212] Higher patient reported satisfaction following PMRT is described amongst women with

autologous flaps compared to implant based reconstruction.[172] In a systematic review of PMRT, Rochlin et al combined patient reported aesthetic evaluation from three studies concluding that out of 96 patients, 77% rated their results as excellent/good and only 5.2% as poor.[180]

The 'satisfaction with breasts' Q-score for the PRADA population is higher than for reported scores in studies of PMRT. Q-scores for irradiated implant-based reconstruction range from 40 to 58,[213-215] and for irradiated autologous reconstructions from 44 to 66.[181, 206, 211, 215] A study comparing 'satisfaction with breasts' in all types of breast cancer surgery (conservation, mastectomy only, mastectomy and reconstruction (implant and autologous) reported a Q-score of 71 for autologous reconstruction of which only 21% were irradiated.[216] With all of the aforementioned caveats, this may suggest that patients can be just as satisfied with their aesthetic outcome with NART as they are in the absence of radiotherapy taking in to account the small sample size of this feasibility study and the short follow-up.

O'Connell et al report a median BREAST-Q 'satisfaction with breast' Q-score for patients with DIEP reconstruction without radiotherapy of 75 (65–85) at median follow up period of 48.7 months.[31] This is comparable with the 12 month follow-up Q-score for the PRADA cohort (77). Hurley et al report a median 'satisfaction with breasts' Q-score for unirradiated latissimus dorsi reconstruction of 62 and psycho-social well-being Q-score of 77 at a median 3.4 years follow-up.[217] There are of course differences in type of reconstruction and length of follow-up and the numbers are small (n=18). In line with this are results from a study by He et al comparing Q-scores for 'satisfaction with breasts' after autologous reconstruction (TRAM or DIEP) with (n=86) and without (n=246) radiotherapy at >1-year follow-up. At 12 months the scores were 66 and 68 for the irradiated and unirradiated cohorts respectively.[181] Psychosocial wellbeing was reported as 73 and 76 for the irradiated and unirradiated cohorts respectively which is comparable to the PRADA cohort at one year (psychosocial wellbeing Q-score 76). Lagendijk et al report Q-scores for psychological, physical, and sexual well-being for 83 autologous reconstruction (78, 76 and 62 respectively) of which 22% were irradiated, [216] which is similar to the PRADA cohort score for the

respective domains (76, 83, 57). Given that all of the PRADA patients had locally advanced breast cancer and received radiotherapy both of which have a negative impact on patient satisfaction, these early results from the feasibility study are not discouraging. [218] [219-223]

6.6 Conclusion

The PRADA cohort represents the first prospective cohort of neoadjuvant radiotherapy and DIEP flap reconstruction. Aesthetic outcome is reported as good or excellent in 93% of cases using a bespoke panel assessment with robust methodology. Patient satisfaction at one year is encouraging and superior to patients who have had DIEP and PMRT. Heterogeneity in the literature precludes reliable comparison. Nonetheless the PRADA treatment sequencing does not appear to be inferior within the limitations of this feasibility study and warrants further large-scale, multi-centre evaluation.

6.7 Acknowledgements

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The protocol was reviewed and passed by London-Riverside NRES committee Ref 17/LO/1071. The study is registered on a publicly accessible database, clinicaltrial.gov, NCT02771938.

Informed consent was obtained from all individual participants included in the study.

Chapter 7 Discussion

The focus of my thesis was to evaluate the role of 3D Surface Imaging (3D-SI) in the objective evaluation and simulation of aesthetic outcome from breast cancer surgery. Much of the discussion has been included in the relevant chapters for ease of cross-referencing. Here, therefore, I will bring everything together and consider future directions.

Aesthetic Outcome Reporting

Within Chapter 2, I have demonstrated the feasibility of an objective aesthetic outcome tool for Breast Conserving Therapy (BCT) using 6 measures derived from 3D-SI. Based upon the widely accepted Harvard Scale, the tool centres on the primary aesthetic objective of BCT: to achieve or maintain symmetry.

The tool is designed to replace panel evaluation with the advantage of a non-biased evaluation of aesthetic outcome. It is not designed to replace Patient Reported Outcome Measures (PROMs) and should be reported in parallel. Elements of aesthetics such as how the breast moves and feels are currently best reported by the patient, however, the role of tonometry in this capacity could be further explored. Cheaper portable devices and automation of the scoring system will enable its widespread use within the NHS and beyond. Secure cloud-based storage of 3D-SI (available through Canfield and Crisalix) protects patient confidentiality whilst enabling clinicians to build a library of their results, not only for their own education, reflection and improvement, but for collaborative research to compare techniques, benchmark practice and ultimately drive-up standards for patients.

Investigation of the role of 3D-SI in outcome reporting for a reconstruction population is the logical next step. There is no gold standard to measure aesthetic outcome from reconstructive breast surgery and no widely accepted panel scale. The expansion of a 3D aesthetic evaluation tool into the reconstruction population will enable the reliable communication and comparison of results providing a robust way to evaluate existing and new techniques in order to innovate. The largest audits of mastectomy and breast

reconstruction to date are the “National Mastectomy and Breast Reconstruction Audit” and the national “implant Breast Reconstruction Audit” (iBRA) which involved PROMs and surgical complications but no objective outcome measurement. Within the context of ‘no surgical innovation without evaluation’,[45, 224, 225] an objective scoring system would provide a robust communication method for aesthetic outcome, an important factor when considering new techniques and materials. Several studies with which I am currently involved (including Primary Radiotherapy And DIEP flAp reconstruction trial [PRADA]), would benefit from an objective method to evaluate aesthetic outcome in order to provide more robust evidence upon which to base best practice guidance, rather than relying solely upon PROMs and panel assessment.

The challenges (discussed throughout my thesis) with evaluating aesthetic outcome from breast reconstruction, together with the variability in UK practice, means a large multi-centre study involving several hundred women of diverse demographics is required to evaluate whether 3D-SI is a clinically-relevant and reliable method to objectively assess breast reconstruction and overcome the limitations of the current option of panel assessment. The successful pilot study of a low burden online research platform (Chapter 4) and development of the Delphi derived panel scale (Chapter 5), paves the way to develop an objective scoring system for a reconstruction population.

Working in conjunction with iBRA-net I developed a protocol for a large-scale multicentre trial ‘CAMERA’ (Clinician-pAnel or Measured Evaluation of breast Reconstruction Aesthetics) based on the pilot study in chapter 4. The Royal Marsden has agreed to sponsor the study and we await funding and Ethical approval. 10 centres have committed to participate. Artificial intelligence, in the form of neural networks will be used to develop the tool from 3D-SI measures of 600 participants.

Simulation

Simulation of aesthetic outcome from BCT has been shown to improve patients’ confidence going into surgery (Chapter 3), however, investigation into how

simulation prepares patients for their actual outcome and how it translates into satisfaction and psychosocial wellbeing is ongoing.

Simulation can have a two-fold benefit, in addition to managing patients' expectations it can also play a role in operative planning to enable *informed* shared decision-making between the surgical team and the patient. It can be used to demonstrate what is an *achievable* result and illustrate the breadth and limitations of reconstructive surgery. Simulation has the ability to provide a visual experience that crosses language and literacy barriers and can present complex ideas simply, reducing room for misinterpretation of verbal description into an unrealistic expected outcome. Taking this further, it may influence long-term satisfaction and psychosocial wellbeing.

The CAMERA study will provide a large library of 3D-SI from which a simulation model could be developed. Only the unilateral reconstructions could be used as the un-operated side would be required to act as a reference point for the simulation. Ultimately a library of paired pre- and post-operative images will enable the development of the most accurate simulation model, however, this will take a number of years to collate. Future research into the development of simulation could include artificial intelligence in the form of machine learning to predict aesthetic outcome from different types of reconstruction on different baseline breast volumes, shapes, and breast mound positions (i.e. degrees of ptosis).

As mentioned in Chapter 3, the acceptable accuracy of simulation is thus far an under-researched area, however, if based on the current standard of showing women 2D photographs of other women who have had a similar procedure, simulating an average outcome would not be inferior, provided clear expectations are set during the consultation. Simulation could be shown in addition to current standard practice to enable a range of outcomes to be viewed in order that expectations are not set too high or too low for certain procedures.

Future work

Individual women and surgeons differ in their opinions of an ideal breast. The concept of aesthetic evaluation answering the question "did we create the ideal

breast?" is not relevant to reconstructive surgery. More relevant are agreed pre-operative goals and compromises shared by patient and surgeon i.e. volume symmetry in a bra, volume symmetry unclothed, shape symmetry in varying positions. Consultation with experts in the field of reconstructive surgery provided interesting insights into the intricacies of assessing aesthetic outcome including position along the reconstructive pathway and agreed compromise in aesthetics to facilitate patient wishes i.e. single operation or unilateral surgery.

My future vision for aesthetic evaluation includes pre-operative images and an agreed goal set by the surgeon and patient balancing what is desired and what is achievable. This discussion will ideally include simulation of likely appearance, thereby addressing patient expectations, and conversely for the patient to be able to explain her preferences to the surgeon while viewing a simulated image of what the surgeon regards as an achievable outcome. The outcome of the reconstruction would thence be judged according to this i.e. a bespoke scale to answer the question 'did we achieve what we set out to achieve?' not 'did we create the ideal breast?' which is contentious and subjective. There are, however, several steps before we can achieve this goal which is what the CAMERA study sets out to address and towards which, the library of images gathered will undoubtedly contribute.

Conclusion

3D-SI offers advantages over 2D evaluation in that it includes measures such as volume and surface symmetry as well as projection, it does not require a medical photographer, and provides multiple views from a single capture.

In this body of work, I have demonstrated that 3D-SI can be used to objectively evaluate appearance after BCT and could replace panel evaluation. Further validation within a cohort from a different centre or a prospective cohort is required. The objective evaluation of aesthetic outcome, potentially overseen centrally, will enable large scale collaborative research into aesthetic outcome, assessment of surgical innovations and quality assurance in the form of benchmarking practice.

I have illustrated the potential of simulation in clinical practice. It improved patient preparedness for aesthetic outcome following BCT, and the cohort of patients presented in chapter xxx are under ongoing follow-up to investigate the accuracy of the simulated image compared to reality and the influence of seeing their own simulation on satisfaction with the appearance of the breast and the information received in longitudinal PROMs will guide development and future application. The potential for bespoke simulation and extension into simulating outcome after breast reconstruction are both exciting prospects towards shared decision-making and operative planning. Development of cheaper portable devices will aid wider spread use in clinical practice.

The results from the aesthetic evaluation for the PRADA cohort give weight to further evaluation of the proposed pathway in a large RCT which is currently in the final stages of development.

The Delphi-derived panel scale is ready for introduction into clinical practice. The main purpose for which it was developed was for use as a gold standard upon which to base an objective aesthetic tool for the reconstruction population, mirroring and extending the work presented here in objective evaluation of breast-conserving treatment. Furthermore, the online platform has widespread applicability in recruitment of patients to quality of life and survivorship studies,

especially since the COVID pandemic has highlighted the need to offer options that do not require a face-to-face conversation.

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9 Appendices

Breast-Q ™
Breast Conserving Therapy Module (Preoperative) 2.0

After reading each question, please circle the number in the box that best describes your situation. If you are unsure how to answer a question, choose the answer that comes closest to how you feel. Please answer all questions.

1. With your breast area in mind, in the past 2 weeks, how satisfied or dissatisfied have you been with:

	Very Dissatisfied	Somewhat Dissatisfied	Somewhat Satisfied	Very Satisfied
a. How you look in the mirror clothed?	1	2	3	4
b. How comfortably your bras fit?	1	2	3	4
c. Being able to wear clothing that is more fitted?	1	2	3	4
d. How you look in the mirror unclothed?	1	2	3	4

2. With your breast area in mind, in the past 2 weeks, how often have you felt:

	None of the time	A little of the time	Some of the time	Most of the time	All of the time
a. Confident in a social setting?	1	2	3	4	5
b. Emotionally able to do the things that you want to do?	1	2	3	4	5
c. Emotionally healthy?	1	2	3	4	5
d. Of equal worth to other women?	1	2	3	4	5
e. Self-confident?	1	2	3	4	5
f. Feminine in your clothes?	1	2	3	4	5
g. Accepting of your body?	1	2	3	4	5
h. Normal?	1	2	3	4	5
i. Like other women?	1	2	3	4	5
j. Attractive?	1	2	3	4	5

Please check that you have answered all the questions before going on to the next page

Breast-Q ™
Breast Conserving Therapy Module (Preoperative) 2.0

3. In the past 2 weeks, how often have you experienced:

	None of the time	A little of the time	Some of the time	Most of the time	All of the time
a. Neck pain?	1	2	3	4	5
b. Upper back pain?	1	2	3	4	5
c. Shoulder pain?	1	2	3	4	5
d. Arm pain?	1	2	3	4	5
e. Difficulty lifting or moving your arms?	1	2	3	4	5
f. Difficulty sleeping because of discomfort in your breast area?	1	2	3	4	5
g. Tightness in your breast area?	1	2	3	4	5
h. Pulling in your breast area?	1	2	3	4	5
i. Tenderness in your breast area?	1	2	3	4	5
j. Sharp pains in your breast area?	1	2	3	4	5
k. Shooting pains in your breast area?	1	2	3	4	5
l. Aching feeling in your breast area?	1	2	3	4	5

Please check that you have answered all the questions before going on to the next page

Breast-Q™
Breast Conserving Therapy Module (Preoperative) 2.0

4. Thinking of your sexuality, how often do you generally feel:

	None of the time	A little of the time	Some of the time	Most of the time	All of the time	Not Applicable
a. Sexually attractive in your clothes?	1	2	3	4	5	N/A
b. Comfortable/at ease during sexual activity?	1	2	3	4	5	N/A
c. Confident sexually?	1	2	3	4	5	N/A
d. Satisfied with your sex-life?	1	2	3	4	5	N/A
e. Confident sexually about how your breast area looks when unclothed?	1	2	3	4	5	N/A
f. Sexually attractive when unclothed?	1	2	3	4	5	N/A

Please check that you have answered all the questions

Breast-Q ™
Breast Conserving Therapy Module (Postoperative) 2.0

The following questions are about your breasts and your breast cancer treatment (by treatment, we mean lumpectomy with or without radiation). After reading each question, please circle the number in the box that best describes your situation. If you are unsure how to answer a question, choose the answer that comes closest to how you feel. Please answer all questions.

1. With your breasts in mind, in the past 2 weeks, how satisfied or dissatisfied have you been with:

		Very Dissatisfied	Somewhat Dissatisfied	Somewhat Satisfied	Very Satisfied
a.	How you look in the mirror clothed?	1	2	3	4
b.	The shape of your lumpectomy breast when you are wearing a bra?	1	2	3	4
c.	How normal you feel in your clothes?	1	2	3	4
d.	Being able to wear clothing that is more fitted?	1	2	3	4
e.	How your lumpectomy breast sits/hangs?	1	2	3	4
f.	How smoothly shaped your lumpectomy breast looks?	1	2	3	4
g.	The contour (outline) of your lumpectomy breast?	1	2	3	4
h.	How equal in size your breasts are to each other?	1	2	3	4
i.	How normal your lumpectomy breast looks?	1	2	3	4
j.	How much your breasts look the same?	1	2	3	4
k.	How you look in the mirror unclothed?	1	2	3	4

Please check that you have answered all the questions before going on to the next page.

Breast-Q™
Breast Conserving Therapy Module (Postoperative) 2.0

2. With your lumpectomy breast in mind, in the past 2 weeks, how much have you been bothered by:

	I don't have this problem	I have this problem and it bothers me....		
		Not at all	A little	A lot
a. Your radiated breast skin looking different (e.g. too dark or too light)?	☐	1	2	3
b. Your radiated areola looking different (e.g. too dark or too light)?	☐	1	2	3
c. Marks on your breast caused by radiation (e.g. small visible blood vessels)?	☐	1	2	3
d. Your radiated breast skin feeling dry?	☐	1	2	3
e. Your radiated breast skin feeling sore (sensitive) when touched (e.g. changes in water temperature when you bathe/shower)?	☐	1	2	3
f. Your radiated breast skin feeling unnaturally thick (rough, tough) when you touch it?	☐	1	2	3
g. Your radiated breast feeling irritated by clothing that you wear?	☐	1	2	3

3. With your breasts in mind, in the past 2 weeks, how often have you felt:

	None of the time	A little of the time	Some of the time	Most of the time	All of the time
a. Confident in a social setting?	1	2	3	4	5
b. Emotionally able to do the things that you want to do?	1	2	3	4	5
c. Emotionally healthy?	1	2	3	4	5
d. Of equal worth to other women?	1	2	3	4	5
e. Self-confident?	1	2	3	4	5
f. Feminine in your clothes?	1	2	3	4	5
g. Accepting of your body?	1	2	3	4	5
h. Normal?	1	2	3	4	5
i. Like other women?	1	2	3	4	5
j. Attractive?	1	2	3	4	5

Please check that you have answered all the questions before going on to the next page.

Breast-Q ™
Breast Conserving Therapy Module (Postoperative) 2.0

4. Thinking of your sexuality, since your lumpectomy surgery, how often do you generally feel:

	None of the time	A little of the	Some of the time	Most of the time	All of the time	Not Applicable
a. Sexually attractive in your clothes?	1	2	3	4	5	N/A
b. Comfortable (at ease) during sexual activity?	1	2	3	4	5	N/A
c. Confident sexually?	1	2	3	4	5	N/A
d. Satisfied with your sex-life?	1	2	3	4	5	N/A
e. Confident sexually about how your breast(s) look when unclothed?	1	2	3	4	5	N/A
f. Sexually attractive when unclothed?	1	2	3	4	5	N/A
g. That you enjoy your lumpectomy breast being touched?	1	2	3	4	5	N/A
h. That you feel sexual pleasure when your lumpectomy breast is touched?	1	2	3	4	5	N/A

Please check that you have answered all the questions before going on to the next page.

Breast-Q ™
Breast Conserving Therapy Module (Postoperative) 2.0

5. With your breasts in mind, in the past 2 weeks, how often have you experienced:

	None of the time	Some of the time	All of the time
a. Neck pain?	1	2	3
b. Upper back pain?	1	2	3
c. Shoulder pain?	1	2	3
d. Arm pain?	1	2	3
e. Difficulty lifting or moving your arms?	1	2	3
f. Difficulty sleeping because of discomfort in your lumpectomy breast?	1	2	3
g. Tightness in your lumpectomy breast?	1	2	3
h. Pulling in your lumpectomy breast?	1	2	3
i. Tenderness in your lumpectomy breast?	1	2	3
j. Sharp pains in your lumpectomy breast?	1	2	3
k. Shooting pains in your lumpectomy breast?	1	2	3
l. An aching feeling in your lumpectomy breast?	1	2	3
m. Difficulty laying on the side of your lumpectomy breast?	1	2	3
n. Swelling (lymphedema) of the arm on the side that you had your lumpectomy surgery?	1	2	3

Please check that you have answered all the questions before going on to the next page.

Breast-Q™
Breast Conserving Therapy Module (Postoperative) 2.0

6. How satisfied or dissatisfied were you with the information you received from your breast surgeon about:

	Very Dissatisfied	Somewhat Dissatisfied	Somewhat Satisfied	Very Satisfied
a. The possible need for radiation depending on the surgery you have (mastectomy vs lumpectomy)?	1	2	3	4
b. The options you were given regarding types of breast cancer surgery (mastectomy vs lumpectomy)?	1	2	3	4
c. How your survival would be the same with either type of surgery (mastectomy vs lumpectomy)?	1	2	3	4
d. Healing and recovery time?	1	2	3	4
e. What your treatment plan would involve if the cancer is found in your lymph nodes?	1	2	3	4
f. How much pain to expect during recovery?	1	2	3	4
g. Possible complications?	1	2	3	4
h. How the chances that the cancer would come back would be the same with either type of surgery (mastectomy vs lumpectomy)?	1	2	3	4
i. What you could expect your lumpectomy breast to look like after surgery?	1	2	3	4
j. What the lumpectomy scars would look like?	1	2	3	4
k. What size you could expect your breast to be after lumpectomy surgery?	1	2	3	4
l. What shape you could expect your breast to be after lumpectomy surgery?	1	2	3	4

Please check that you have answered all the questions before going on to the next page.

Breast-Q™
Breast Conserving Therapy Module (Postoperative) 2.0

7. These questions ask about your breast surgeon. Did you feel that he/she:

		Definitely Disagree	Somewhat Disagree	Somewhat Agree	Definitely Agree
a.	Was professional?	1	2	3	4
b.	Gave you confidence?	1	2	3	4
c.	Was reassuring?	1	2	3	4
d.	Answered all your questions?	1	2	3	4
e.	Made you feel comfortable?	1	2	3	4
f.	Was thorough?	1	2	3	4
g.	Was easy to talk to?	1	2	3	4
h.	Understood what you wanted?	1	2	3	4
i.	Was sensitive?	1	2	3	4
j.	Made time for your concerns?	1	2	3	4
k.	Was available when you had concerns?	1	2	3	4

Please check that you have answered all the questions before going on to the next page.

Breast-Q ™
Breast Conserving Therapy Module (Postoperative) 2.0

8. These questions ask about members of the medical team other than the surgeon (e.g. nurses and other doctors who looked after you on the day of your lumpectomy surgery). Did you feel that they:

	Definitely Disagree	Somewhat Disagree	Somewhat Agree	Definitely Agree
a. Were professional?	1	2	3	4
b. Treated you with respect?	1	2	3	4
c. Were knowledgeable?	1	2	3	4
d. Were friendly and kind?	1	2	3	4
e. Made you feel comfortable?	1	2	3	4
f. Were thorough?	1	2	3	4
g. Made time for your concerns?	1	2	3	4

9. These questions ask about members of the office staff (e.g. secretaries, office or clinic nurses). Did you feel that they:

	Definitely Disagree	Somewhat Disagree	Somewhat Agree	Definitely Agree
a. Were professional?	1	2	3	4
b. Treated you with respect?	1	2	3	4
c. Were knowledgeable?	1	2	3	4
d. Were friendly and kind?	1	2	3	4
e. Made you feel comfortable?	1	2	3	4
f. Were thorough?	1	2	3	4
g. Made time for your concerns?	1	2	3	4

Please check that you have answered all the questions.

BREAST-Q™
RECONSTRUCTION MODULE (PREOPERATIVE) 1.0

After reading each question, please circle the number in the box that best describes your situation. If you are unsure how to answer a question, choose the answer that comes closest to how you feel. Please answer all questions.

1. With your breasts in mind, or if you have had a mastectomy, with your breast area in mind, in the past 2 weeks, how satisfied or dissatisfied have you been with:

	Very Dissatisfied	Somewhat Dissatisfied	Somewhat Satisfied	Very Satisfied
a. How you look in the mirror clothed?	1	2	3	4
b. How comfortably your bras fit?	1	2	3	4
c. Being able to wear clothing that is more fitted?	1	2	3	4
d. How you look in the mirror unclothed?	1	2	3	4

2. With your breasts in mind, or if you have had a mastectomy, with your breast area in mind, in the past 2 weeks, how often have you felt:

	None of the time	A little of the time	Some of the time	Most of the time	All of the time
a. Confident in a social setting?	1	2	3	4	5
b. Emotionally able to do the things that you want to do?	1	2	3	4	5
c. Emotionally healthy?	1	2	3	4	5
d. Of equal worth to other women?	1	2	3	4	5
e. Self-confident?	1	2	3	4	5
f. Feminine in your clothes?	1	2	3	4	5
g. Accepting of your body?	1	2	3	4	5
h. Normal?	1	2	3	4	5
i. Like other women?	1	2	3	4	5
j. Attractive?	1	2	3	4	5

Please check that you have answered all the questions before going on to the next page

BREAST-Q™
RECONSTRUCTION MODULE (PREOPERATIVE) 1.0

3. In the past 2 weeks, how often have you experienced:

	None of the time	A little of the time	Some of the time	Most of the time	All of the time
a. Neck pain?	1	2	3	4	5
b. Upper back pain?	1	2	3	4	5
c. Shoulder pain?	1	2	3	4	5
d. Arm pain?	1	2	3	4	5
e. Rib pain?	1	2	3	4	5
f. Pain in the muscles of your chest?	1	2	3	4	5
g. Difficulty lifting or moving your arms?	1	2	3	4	5
h. Difficulty sleeping because of discomfort in your breast area?	1	2	3	4	5
i. Tightness in your breast area?	1	2	3	4	5
j. Pulling in your breast area?	1	2	3	4	5
k. Nagging feeling in your breast area?	1	2	3	4	5
l. Tenderness in your breast area?	1	2	3	4	5
m. Sharp pains in your breast area?	1	2	3	4	5
n. Shooting pains in your breast area?	1	2	3	4	5
o. Aching feeling in your breast area?	1	2	3	4	5
p. Throbbing feeling in your breast area?	1	2	3	4	5

Please check that you have answered all the questions before going on to the next page

BREAST-Q™
RECONSTRUCTION MODULE (PREOPERATIVE) 1.0

4. In the past 2 weeks, with your abdomen (tummy area) in mind, how often have you experienced:

	None of the time	A little of the time	Some of the time	Most of the time	All of the time
a. Difficulty sitting up because of abdominal muscle weakness (e.g. getting out of bed)?	1	2	3	4	5
b. Difficulty doing everyday activities because of abdominal muscle weakness (e.g. making your bed)?	1	2	3	4	5
c. Abdominal discomfort?	1	2	3	4	5
d. Abdominal bloating?	1	2	3	4	5
e. Lower back pain?	1	2	3	4	5

5. In the past 2 weeks, how satisfied or dissatisfied have you been with:

	Very Dissatisfied	Somewhat Dissatisfied	Somewhat Satisfied	Very Satisfied
a. How your abdomen looks?	1	2	3	4

6. Thinking of your sexuality, how often do you generally feel:

	None of the time	A little of the time	Some of the time	Most of the time	All of the time	Not Applicable
a. Sexually attractive in your clothes?	1	2	3	4	5	N/A
b. Comfortable/at ease during sexual activity?	1	2	3	4	5	N/A
c. Confident sexually?	1	2	3	4	5	N/A
d. Satisfied with your sex-life?	1	2	3	4	5	N/A
e. Confident sexually about how your breast(s) look when unclothed?	1	2	3	4	5	N/A
f. Sexually attractive when unclothed?	1	2	3	4	5	N/A

Please check that you have answered all the questions

BREAST-Q™
RECONSTRUCTION MODULE (POST OPERATIVE) 2.0

The following questions are about your breasts and breast reconstruction surgery. After reading each question, please circle the number in the box that best describes your situation. If you are unsure how to answer a question, choose the answer that comes closest to how you feel. Please answer all questions.

1. With your breasts in mind, in the past 2 weeks, how satisfied or dissatisfied have you been with:

		Very Dissatisfied	Somewhat Dissatisfied	Somewhat Satisfied	Very Satisfied
a.	How you look in the mirror clothed?	1	2	3	4
b.	The shape of your reconstructed breast(s) when you are wearing a bra?	1	2	3	4
c.	How normal you feel in your clothes?	1	2	3	4
d.	The size of your reconstructed breast(s)?	1	2	3	4
e.	Being able to wear clothing that is more fitted?	1	2	3	4
f.	How your breasts are lined up in relation to each other?	1	2	3	4
g.	How comfortably your bras fit?	1	2	3	4
h.	The softness of your reconstructed breast(s)?	1	2	3	4
i.	How equal in size your breasts are to each other?	1	2	3	4
j.	How natural your reconstructed breast(s) looks?	1	2	3	4
k.	How naturally your reconstructed breast(s) sits/hangs?	1	2	3	4
l.	How your reconstructed breast(s) feels to touch?	1	2	3	4
m.	How much your reconstructed breast(s) feels like a natural part of your body?	1	2	3	4
n.	How closely matched your breasts are to each other?	1	2	3	4
o.	How your reconstructed breast(s) look now compared to before you had any breast surgery?	1	2	3	4
p.	How you look in the mirror unclothed?	1	2	3	4

BREAST-Q™
RECONSTRUCTION MODULE (POST OPERATIVE) 2.0

Please check that you have answered all the questions before going on to the next page

This question is about breast reconstruction using IMPLANTS. If you do not have an implant(s) please skip to question 3. If you do have an implant(s), please answer question 2 below.

2. In the past 2 weeks, how satisfied or dissatisfied have you been with:

	Very Dissatisfied	Somewhat Dissatisfied	Somewhat Satisfied	Very Satisfied
a. The amount of rippling (wrinkling) of your implant(s) that you can see?	1	2	3	4
b. The amount of rippling (wrinkling) of your implant(s) that you can feel?	1	2	3	4

3. We would like to know how you feel about the outcome of your breast reconstruction surgery. Please indicate how much you agree or disagree with each statement:

	Disagree	Somewhat Agree	Definitely Agree
a. Having reconstruction is much better than the alternative of having no breast(s).	1	2	3
b. I would encourage other women in my situation to have breast reconstruction surgery.	1	2	3
c. I would do it again.	1	2	3
d. I have no regrets about having the surgery.	1	2	3
e. Having this surgery changed my life for the better.	1	2	3
f. The outcome perfectly matched my expectations.	1	2	3
g. It turned out exactly as I had planned.	1	2	3

Please check that you have answered all the questions before going on to the next page

BREAST-Q™
RECONSTRUCTION MODULE (POST OPERATIVE) 2.0

4. With your breasts in mind, in the past 2 weeks, how often have you felt:

	None of the time	A little of the time	Some of the time	Most of the time	All of the time
a. Confident in a social setting?	1	2	3	4	5
b. Emotionally able to do the things that you want to do?	1	2	3	4	5
c. Emotionally healthy?	1	2	3	4	5
d. Of equal worth to other women?	1	2	3	4	5
e. Self-confident?	1	2	3	4	5
f. Feminine in your clothes?	1	2	3	4	5
g. Accepting of your body?	1	2	3	4	5
h. Normal?	1	2	3	4	5
i. Like other women?	1	2	3	4	5
j. Attractive?	1	2	3	4	5

5. Thinking of your sexuality, since your breast reconstruction, how often do you generally feel:

	None of the time	A little of the time	Some of the time	Most of the time	All of the time	Not Applicable
a. Sexually attractive in your clothes?	1	2	3	4	5	N/A
b. Comfortable/at ease during sexual activity?	1	2	3	4	5	N/A
c. Confident sexually?	1	2	3	4	5	N/A
d. Satisfied with your sex-life?	1	2	3	4	5	N/A
e. Confident sexually about how your breast(s) look when unclothed?	1	2	3	4	5	N/A
f. Sexually attractive when unclothed?	1	2	3	4	5	N/A

Please check that you have answered all the questions before going on to the next page

BREAST-Q™
RECONSTRUCTION MODULE (POST OPERATIVE) 2.0

6. In the past 2 weeks, how often have you experienced:

	None of the time	A little of the time	Some of the time	Most of the time	All of the time
a. Neck pain?	1	2	3	4	5
b. Upper back pain?	1	2	3	4	5
c. Shoulder pain?	1	2	3	4	5
d. Arm pain?	1	2	3	4	5
e. Rib pain?	1	2	3	4	5
f. Pain in the muscles of your chest?	1	2	3	4	5
g. Difficulty lifting or moving your arms?	1	2	3	4	5
h. Difficulty sleeping because of discomfort in your breast area?	1	2	3	4	5
i. Tightness in your breast area?	1	2	3	4	5
j. Pulling in your breast area?	1	2	3	4	5
k. Nagging feeling in your breast area?	1	2	3	4	5
l. Tenderness in your breast area?	1	2	3	4	5
m. Sharp pains in your breast area?	1	2	3	4	5
n. Shooting pains in your breast area?	1	2	3	4	5
o. Aching feeling in your breast area?	1	2	3	4	5
p. Throbbing feeling in your breast area?	1	2	3	4	5

Please check that you have answered all the questions before going on to the next page

BREAST-Q™
RECONSTRUCTION MODULE (POST OPERATIVE) 2.0

The following questions are about reconstruction using a TRAM or DIEP flap (i.e., reconstruction using skin and fat from you abdomen/tummy area). If you do not have a TRAM or DIEP flap, please skip to question 10. If you do have a TRAM or DIEP flap, please answer the following questions:

7. In the past 2 weeks, with your abdomen (tummy area) in mind, how often have you experienced:

	None of the time	A little of the time	Some of the time	Most of the time	All of the time
a. Difficulty sitting up because of abdominal muscle weakness (e.g. getting out of bed)?	1	2	3	4	5
b. Difficulty doing everyday activities because of abdominal muscle weakness (e.g. making your bed)?	1	2	3	4	5
c. Abdominal discomfort?	1	2	3	4	5
d. Abdominal bloating?	1	2	3	4	5
e. Abdominal bulging?	1	2	3	4	5
f. Tightness in your abdomen?	1	2	3	4	5
g. Pulling in your abdomen?	1	2	3	4	5
h. Lower back pain?	1	2	3	4	5

8. In the past 2 weeks, how satisfied or dissatisfied have you been with:

	Very Dissatisfied	Somewhat Dissatisfied	Somewhat Satisfied	Very Satisfied
a. How your abdomen looks?	1	2	3	4
b. The position of your navel (belly button)?	1	2	3	4
c. How your abdominal scars look?	1	2	3	4

9. In the past 2 weeks, how satisfied or dissatisfied have you been with:

	Very Dissatisfied	Somewhat Dissatisfied	Somewhat Satisfied	Very Satisfied
a. How your abdomen feels now compared to before your surgery?	1	2	3	4
b. How your abdomen looks now compared to before your surgery?	1	2	3	4

Please check that you have answered all the questions before going on to the next page

BREAST-Q™
RECONSTRUCTION MODULE (POST OPERATIVE) 2.0

This question is about NIPPLE reconstruction. If you did not have nipple reconstruction, please skip to question 11. If you did have nipple reconstruction, please answer question 10 below.

10. In the past 2 weeks, how satisfied or dissatisfied are you with:

	Very Dissatisfied	Somewhat Dissatisfied	Somewhat Satisfied	Very Satisfied
a. The shape of your reconstructed nipple(s)?	1	2	3	4
b. How your reconstructed nipple(s) and areola(s) look?	1	2	3	4
c. How natural your reconstructed nipple(s) look?	1	2	3	4
d. The color of your reconstructed nipple/areolar complex?	1	2	3	4
e. The height (projection) of your reconstructed nipple(s)?	1	2	3	4

Please check that you have answered all the questions before going on to the next page

BREAST-Q™
RECONSTRUCTION MODULE (POST OPERATIVE) 2.0

11. How satisfied or dissatisfied were you with the information you received from your plastic surgeon about:

		Very Dissatisfied	Somewhat Dissatisfied	Somewhat Satisfied	Very Satisfied
a.	How the breast reconstruction surgery was to be done?	1	2	3	4
b.	Healing and recovery time?	1	2	3	4
c.	Possible complications?	1	2	3	4
d.	The options you were given regarding types of breast reconstruction?	1	2	3	4
e.	The options you were given regarding timing of your breast reconstruction (i.e. same time as your mastectomy versus later)?	1	2	3	4
f.	The pros and cons of the timing of your breast reconstruction?	1	2	3	4
g.	How long the process of breast reconstruction would take from start to finish?	1	2	3	4
h.	What size you could expect your breasts to be after reconstructive surgery?	1	2	3	4
i.	How much pain to expect during recovery?	1	2	3	4
j.	What you could expect your breasts to look like after surgery?	1	2	3	4
k.	How long after reconstruction surgery it would take to feel like yourself/feel normal again?	1	2	3	4
l.	How the surgery could affect future breast cancer screening (e.g. mammogram, self examinations)?	1	2	3	4
m.	Lack of sensation in your reconstructed breast(s) and nipple(s)?	1	2	3	4
n.	What other women experience with their breast reconstruction surgery?	1	2	3	4
o.	What the scars would look like?	1	2	3	4

BREAST-Q™
RECONSTRUCTION MODULE (POST OPERATIVE) 2.0

Please check that you have answered all the questions before going on to the next page

12. These questions ask about your plastic surgeon. Did you feel that he/she:

	Definitely Disagree	Somewhat Disagree	Somewhat Agree	Definitely Agree
a. Was professional?	1	2	3	4
b. Gave you confidence?	1	2	3	4
c. Involved you in the decision-making process?	1	2	3	4
d. Was reassuring?	1	2	3	4
e. Answered all your questions?	1	2	3	4
f. Made you feel comfortable?	1	2	3	4
g. Was thorough?	1	2	3	4
h. Was easy to talk to?	1	2	3	4
i. Understood what you wanted?	1	2	3	4
j. Was sensitive?	1	2	3	4
k. Made time for your concerns?	1	2	3	4
l. Was available when you had concerns?	1	2	3	4

Please check that you have answered all the questions before going on to the next page

BREAST-Q™
RECONSTRUCTION MODULE (POST OPERATIVE) 2.0

13. These questions ask about members of the medical team other than the surgeon (e.g. nurses and other doctors who looked after you in the hospital when you had your breast reconstruction surgery). Did you feel that they:

	Definitely Disagree	Somewhat Disagree	Somewhat Agree	Definitely Agree
a. Were professional?	1	2	3	4
b. Treated you with respect?	1	2	3	4
c. Were knowledgeable?	1	2	3	4
d. Were friendly and kind?	1	2	3	4
e. Made you feel comfortable?	1	2	3	4
f. Were thorough?	1	2	3	4
g. Made time for your concerns?	1	2	3	4

14. These questions ask about members of the office staff (e.g. secretaries, office or clinic nurses). Did you feel that they:

	Definitely Disagree	Somewhat Disagree	Somewhat Agree	Definitely Agree
a. Were professional?	1	2	3	4
b. Treated you with respect?	1	2	3	4
c. Were knowledgeable?	1	2	3	4
d. Were friendly and kind?	1	2	3	4
e. Made you feel comfortable?	1	2	3	4
f. Were thorough?	1	2	3	4
g. Made time for your concerns?	1	2	3	4

Please check that you have answered all the questions

Patient name

Patient address

Date

Research study of the use of 3D surface imaging in the objective assessment of breast conserving therapy

We are writing to invite you to participate in a study of 3D photography. We are writing to you because you have had an operation for breast cancer at the Royal Marsden Hospital and your surgical consultant has identified you as a potential participant. We are enclosing an information sheet which gives details about the study. Please telephone the numbers given if you have any questions.

We will telephone you in about a week to ask whether you are interested in participating and, if so, to schedule a photography session. We can schedule the photography to take place at the same time as your scheduled yearly mammogram, a clinic appointment or at another time convenient to you.

Thank you for considering this study.

Yours sincerely

Miss Jennifer Rusby
Consultant breast surgeon

Miss Amy Godden
Research Fellow in Breast Surgery

The ROYAL MARSDEN

PATIENT INFORMATION SHEET

The use of 3D photography in the objective assessment of breast conserving therapy

Version 3 08/03/2016

We invite you to take part in our research study

- Before you make your decision, it is important for you to understand why the research is being done and what it will involve.
- Please take time to read the following information carefully.
- You may want to talk to friends and relatives about the study before taking part.
- You are free to decide whether or not to take part in this study.
- If you choose not to take part, this will not affect your treatment and your rights as a patient in any way.
- You may withdraw from the study at any time if you wish and you do not have to give a reason for withdrawing.

What is involved?

- We are investigating the use of 3D surface imaging in the assessment of breast conserving therapy.
- We hope that by understanding the 3D appearance and your feelings about your appearance, and linking these to various features of your cancer, your breast and your treatment, we may be able to improve on the outcome for women with breast cancer in the future.
- With your permission, we will access information about these features from your electronic medical notes.
- During a single visit, we will take 3D photographs of both of your breasts using the VECTRA XT camera. We will not store any personal details such as your name or date of birth and your face will not be visible in the 3D image. Only the study team will have access to the images.
- We will measure your height and weight to calculate your BMI
- You will be asked to complete a questionnaire about your breasts.
- The visit will take between 30 and 60 minutes.
- We will schedule your appointment at a time that suits you, for example when you come for your regular mammogram.
- Miss Jennifer Rusby, consultant breast surgeon, or Miss Amy Godden, research registrar in breast surgery and a member of the Royal Marsden medical photography team will be present during the photography.
- You may bring a friend or partner if you wish.
- If you decide to take part in this study, you will be asked to sign a consent form to say that you agree to participate in the study, and you will be given a copy of the signed consent form.

- All data will be destroyed after 60 months

Why have you been invited?

- We have approached you because you have undergone breast conserving surgery for breast cancer at the Royal Marsden.

What are the possible benefits and advantages of taking part?

- There would be no direct benefit to you in taking part.
- Your help in this research would allow us to obtain data so that we could determine the best way to evaluate and predict the appearance following breast conserving surgery.
- The ultimate aim is to improve the way we assess the cosmetic appearance of the breast after surgery, to understand in more detail what factors affect how patients feel about their breasts after surgery, and what features predict for a good or poor cosmetic outcome.

What are the possible disadvantages and risks of taking part?

- There are no known risks or side-effects of 3D photography as no radiation is involved.
- Your legal rights are not affected by your giving consent to participate and any personal information gained from this study will remain strictly confidential.
- Your photographic images will be kept in a secure database at the Royal Marsden Hospital, but will be identified by a study number only, and not linked to any personal information.
- With your permission, we will inform your GP of your participation in this study.

Who has reviewed this research?

- This research was reviewed by Patient and Carer Research Review Panel at The Royal Marsden.
- This research has also undergone rigorous review by the Committee for Clinical Research at The Royal Marsden and The Institute of Cancer Research and the Riverside Research Ethics Committee.
- Their feedback has been used to improve the design of the study.

How will this research be reported?

- We will be delighted to share your individual results with you.
- The overall results of the study will be reported to colleagues inside and outside of The Royal Marsden and submitted to a medical journal.
- Nobody will be able to identify you from the results.

Who should I contact if I have any questions?

If you have any questions about this study, please contact the doctors who are organising it:

Miss Jennifer Rusby
Consultant Oncoplastic Breast Surgeon

Miss Amy Godden
Breast Surgery Clinical Research Fellow

Patient Advice and Liaison Service 0800 783 7176 or patientcentre@rmh.nhs.uk**Thank you for taking the time to consider this study**

Appendix 5

Measure	Abbreviation	Unit	Definition
Breast base width i.e. lateral to medial mammary fold *Figure 2a*	L-MIMF	cm	The right and left lateral mammary fold landmarks (LMFr or LMF l) are placed where the breast meets the anterior-axillary line (figure 1c&d). The left and right medial mammary fold landmarks (MMFr or MMFl) are placed at the most medial point of the mammary fold (Figure 1a). L-MIMF distance is surrogate for the breast base width
Medial to medial breast border *Figure 2a*	M-MMF	cm	The medial mammary fold landmarks (MMFr or MMFl) are placed at the most medial point of the mammary fold (**Error! Reference source not found.**a). The M-MMF distance is termed M-M breast border
Nipple to Inframammary fold distance *Figure 2a*	N-IMF	cm	The right and left nipple landmarks (Nl or Nr) are positioned on the centre of the nipple (Figure 1a). The right and left inframammary fold landmarks (IMFl or IMF r) are placed at the position where the breast meets the chest wall at its inferior border in line with the nipple (Figure 1b)
Nipple to midline distance *Figure 2a*	NM	cm	The right and left nipple landmark (Nl or Nr) are positioned on the centre of the nipple (Figure 1a). Midline is automatically placed.
Nipple to sternal notch distance *Figure 2a*	N-SN	cm	The right and left nipple landmarks (Nl or Nr) are positioned on the centre of the nipple (Figure 1a). The Sternal Notch (SN) landmark is sited at the superior part of the V skin crease (Figure 1a).
Nipple to nipple distance *Figure 2a*	NN	cm	The right and left nipple landmarks (Nl or Nr) are positioned on the centre of the nipple (Figure 1a)
Difference in nipple height	NH difference	cm	The right and left nipple landmarks (Nl or Nr) are positioned on the centre of the nipple (Figure 1a)

Figure 2b			
Difference in IMF height *Figure 2b*	IMF difference	cm	The right and left infra-mammary fold landmarks (IMFl or IMF r) are placed at the position where the breast meets the chest wall at its inferior border in line with the nipple (Figure 1b)
Difference in projection *Figure 2c*	-	cm	Automatically calculated
Breast volume		cc	As per O'Connell et al 2018[95]
Surface asymmetry	SA	rms	As per O'Connell et al 2018[95]
Non-specific landmarks used as part of other calculation	-		The right and left areolar landmarks (Ar or Al) are placed at the areola border at the 12 o'clock position (Figure 1a). The right and left clavicle landmarks (Cr or Cl) are placed equidistant from the sternal notch at approximately the lateral border of the medial 1/3 of clavicle (Figure 1a)

Appendix 5

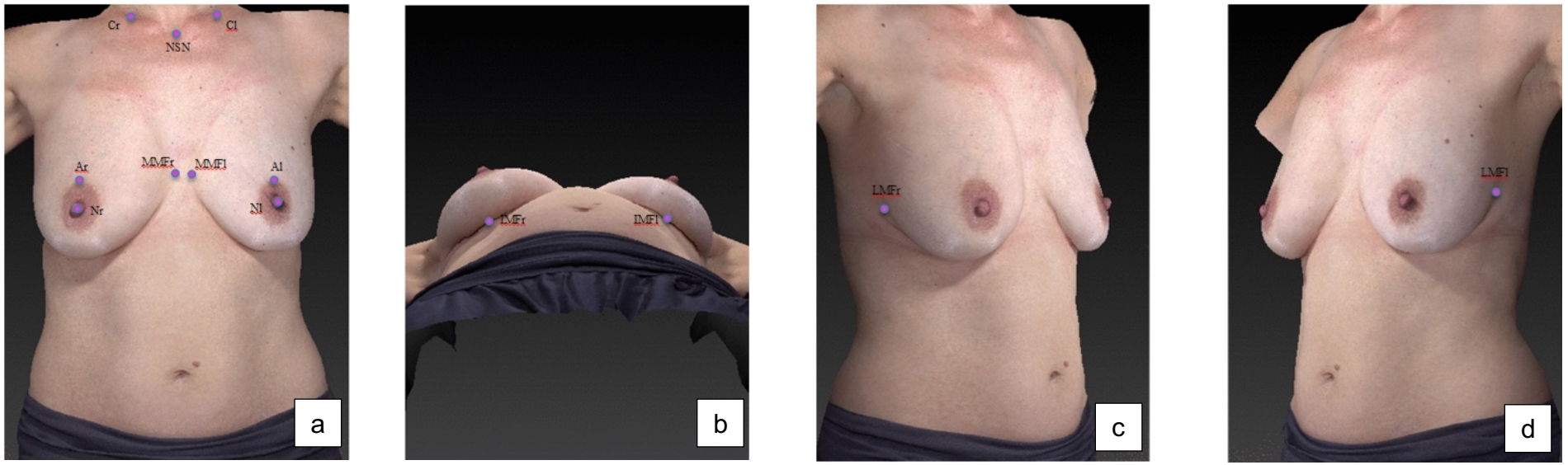

Figure 1Landmark positioning for linear measurements using Mirror software® for 3D-SIs using Vectra XT®. a) Cr; clavicle right, Cl; clavicle left, NSN; nipple sternal notch, MMFr; medial mammary fold right, MMFl; medial mammary fold left, Ar; areola right, Al; Areola left, Nr; nipple right, Nl; nipple left, b) IMFr; inframammary fold right, IMFl; inframammary fold left, c) LMFr; lateral mammary fold right, d) lateral mammary fold left.

Appendix 5

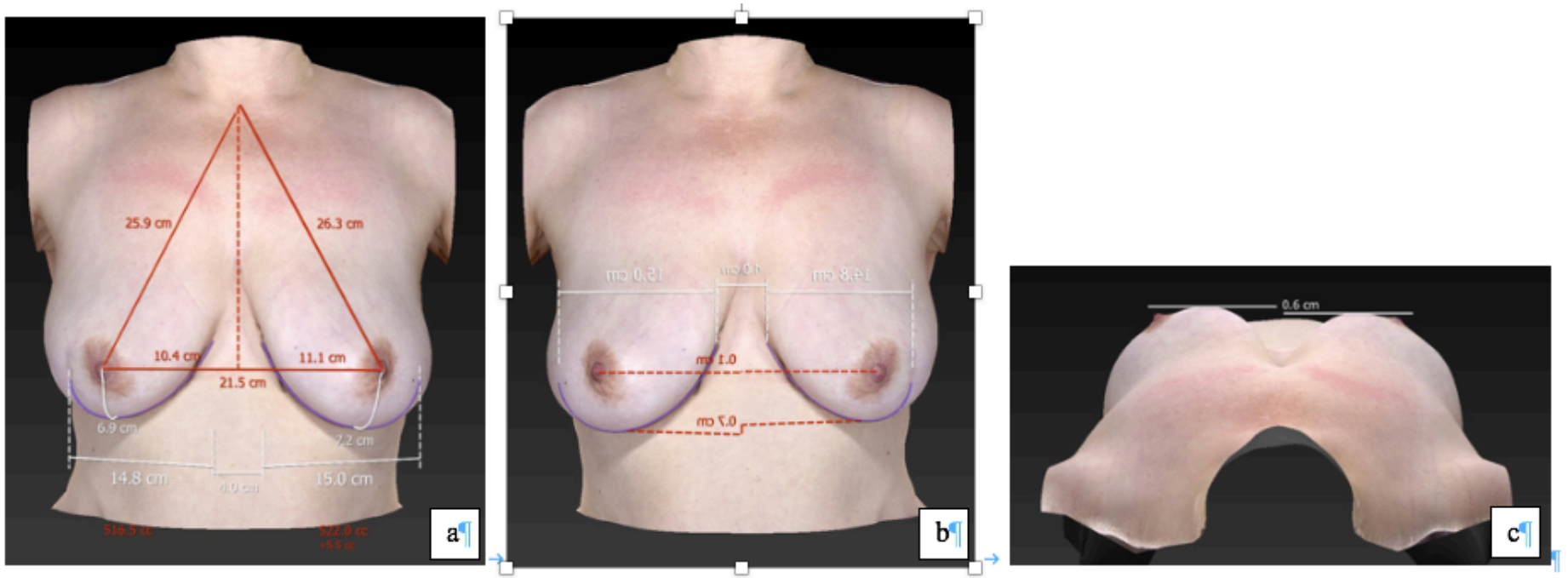

Figure 2 Linear measures derived from 3D-SI taken with Vectra XT® using Mirror Software ® a) N-SN; Nipple to Sternal-Notch, NN; Nipple to Nipple, NM; Nipple to Midline, N-IMF; Nipple to Inframammary fold, M-LMF; Medial to Lateral Mammary Fold, M-MIMF; Medial to Medial Mammary Fold b) M-LMF; Medial to Lateral Mammary Fold, IMF-H; Inframammary Fold Height difference, NH; Nipple Height difference c) Projection difference.

The ROYAL MARSDEN

PATIENT INFORMATION SHEET

Simulating appearance after breast conserving therapy using 3D-surface imaging

We invite you to take part in our research study

- Before you make your decision, it is important for you to understand why the research is being done and what it will involve.
- Please take time to read the following information carefully.
- You may want to talk to friends and relatives about the study before taking part.
- You are free to decide whether or not to take part in this study.
- If you choose not to take part, this will not affect your treatment and your rights as a patient in any way.
- You may withdraw from the study at any time if you wish and you do not have to give a reason for withdrawing.

What is involved?

- We are investigating the use of 3D surface imaging in the simulation of likely appearance after breast conserving therapy (surgery and radiotherapy).
- 3D surface imaging involves 6 mounted digital cameras taking simultaneous photographs which can be merged to give a 3D image. This can be adjusted to simulate the possible appearance after breast conserving therapy. There is no physical contact between you and the camera.
- We are asking women who are going to have breast conserving therapy to have 3D surface imaging so that we can learn how best to prepare women for this type of surgery.
- All women will receive standard care (the conversation that you have had with the breast care nurse). 1/3 (chosen at random by a computer) will be shown a portfolio of 2D photographs of other women that have had a similar operation. 1/3 will be shown a 3D-simulation of how *their own* breasts are likely to look after their operation. 1/3 will receive standard care alone.
- With your permission, we will access information about your cancer and medical history from your electronic medical notes.
- You will be asked to complete a questionnaire about your breasts and your expectations for surgery.
- The initial visit will take approximately 30 minutes.
- After surgery we will ask you to have 3D-surface images taken at 2 weeks, just before radiotherapy, and at 3-6months, and 12 months after your treatment has finished. Then annually for five years. These visits will last approximately 5 minutes.
- We will ask you to complete a questionnaire at 3-6months and 12 months after radiotherapy.
- We will schedule your appointments at times that suit you, for example when you come for anaesthetic pre-operative assessment.
- Miss Jennifer Rusby, consultant breast surgeon, or Miss Amy Godden, research registrar in breast surgery or a member of the Royal Marsden medical photography team will be present during the photography.
- You may bring a friend or partner if you wish.

- If you decide to take part in this study, you will be asked to sign a consent form to say that you agree to participate in the study, and you will be given a copy.

Why have you been invited?

- We have approached you because you are planning to undergo breast conserving surgery for breast cancer at the Royal Marsden Hospital in Sutton.

What are the possible benefits and advantages of taking part?

- There is a possibility that those who are invited to have a further discussion with one of the researchers will feel better prepared for surgery. Everyone will receive the current standard of care.

- Your help in this research would allow us to develop techniques to simulate the likely appearance after breast conserving treatment and to understand whether this helps patients.

What are the possible disadvantages and risks of taking part?

- There are no known risks or side-effects of 3D surface imaging.

- Your legal rights are not affected by your giving consent to participate and any personal information gained from this study will remain strictly confidential.

Data Storage

- Your photographic images will be kept in a secure database at the Royal Marsden Hospital and will be identified by a study number only without any personal information.

- Research data will be destroyed after 5 years.

- Anonymised photographs will not be destroyed.

Who has reviewed this research?

- All research in the NHS is looked at by independent group of people, called a Research Ethics Committee, to protect your interests. This study has been reviewed and given favourable opinion by the Health Research Authority. This study is monitored by and has been adjusted according to feedback from a patient-steering committee.

GDPR

- The Royal Marsden is the sponsor for this study based in the United Kingdom. We will be using information from you and your medical records in order to undertake this study and will act as the data controller for this study. This means that we are responsible for looking after your information and using it properly. The Royal Marsden will keep identifiable information about you for 1 year after the study has finished.

- Your rights to access change or move your information are limited, as we need to manage your information in specific ways in order for the research to be reliable and accurate. If you withdraw from the study, we will keep the information about you that we have already obtained. To safeguard your rights, we will use the minimum personally identifiable information possible.

- You can find out more about how RM uses your information by contacting the Data Protection Officer at RM. Email: dpo@rmh.nhs.uk

- The Royal Marsden will use your name, NHS number and contact details to contact you about the research study, and make sure that relevant information about the study

is recorded for your care, and to oversee the quality of the study. Individuals from the Royal Marsden and regulatory organisations may look at your medical and research records to check the accuracy of the research study. The only people at The Royal Marsden who will have access to information that identifies you will be people who need to contact you or audit the data collection process. The people who analyse the information will not be able to identify you and will not be able to find out your name, NHS number, or contact details.

Who should I contact if I have any questions?

- If you have any questions about this study, please contact the doctors who are organising it:

Miss Jennifer Rusby
Consultant Oncoplastic Breast Surgeon

Miss Amy Godden
Breast Surgery Clinical Research Fellow

020 8642 6011 (ask for cordless 1282)

- If you have any questions about participation in research in general, please contact:

Patient Advice and Liaison Service
0800 783 7176 or patientcentre@rmh.nhs.uk

Thank you for taking the time to consider this study

Appendix 7

Patient name

Patient address

Unique Study ID XXXX

Date

Dear XX

Re: Pilot study towards development of an objective evaluation of outcome after implant-based breast reconstruction, using 3D-surface imaging (3D-SI) and a novel online research tool.

During the time that you spent with us at the Royal Marsden Hospital, you may have been aware of our focussed efforts to research, develop and improve the treatments that we can offer to our patients.

In many areas, the success of our research relies on input from our patient network and our current study is one such project. As you have had an implant-based reconstruction within the last 5 years - one of your surgical consultants has identified you as a potential participant for an exciting new project that we would like to invite you to join and share your valuable opinions.

This study focusses on the use of 3D photography and the commitment we will ask of you is to;

a. Read the accompanying information sheet
b. Visit a fully secure website www.implant-study.co.uk to consent, complete enrolment (this will take around 20 minutes), and book an appointment for 3D photography
c. Attend a single appointment at the hospital for the photography to take place

Please be assured that as you are assigned a unique study ID your identity is treated with total confidentiality.

We very much hope that after reading the enclosed information sheet that you will elect to participate. To ensure that we collect all information in time to launch the main study we would ask that you complete the online recruitment within two weeks of receiving this letter.

You will need the Unique Study ID given at the top of this letter at each stage of the online process. You will be asked for information on your treatment so it may be helpful to collect any hospital letters before you start. When you are booking your appointment for photography, there is a space below to write the date and time. Please keep this letter as a reminder of that, and to show at your appointment to confirm your identity (this will be by study number only).

Thank you for considering this study. We appreciate your time and highly valued input.

www.implant-study.co.uk

Appointment for 3D photography at Royal Marsden Hospital

Date:.....

Time:.....

Please complete the date and time you choose and bring this letter with you when you come!

The ROYAL MARSDEN

PATIENT INFORMATION SHEET

Pilot study to assess novel systems to help conduct a large multi-centre study for the development of an objective outcome measure after implant-based breast reconstruction, using 3D-surface imaging (3D-SI).

We invite you to take part in our research study

- Before you make your decision, it is important for you to understand why the research is being done and what it will involve.
- Please take time to read the following information carefully.
- You may want to talk to friends and relatives about the study before taking part.
- You are free to decide whether or not to take part in this study.
- If you choose not to take part, this will not affect your treatment and your rights as a patient in any way. You may withdraw from the study at any time if you wish and you do not have to give a reason for withdrawing.

Why have you been invited?

- We have approached you because you have had an implant-based reconstruction for one or both of your breasts in the past 1-5 years.

Why is this research needed?

- 3D surface imaging is a novel technology, until now mainly used in cosmetic breast surgery. We believe it has potential to help us improve surgical and radiotherapy treatments for breast cancer and have already studied this in other settings. For more information see our website.
- Next, we want to create an outcome score using 3D-photography for use in research to evaluate new surgical techniques and to drive clinical excellence in implant-based breast reconstruction.
- This is a pilot study testing the planned methods (including a website) before we design a large multi-centre study of over 1000 women who have had implant-based reconstruction.
- If successful, our website will enable women who do not live near a research centre to be involved in research and will enable hospitals without large research capabilities to offer the opportunity to their patients to participate in studies like this.

What is involved?

- We have designed a website to provide you with detailed information and to facilitate consent and data collection. The website is secure, and all of your data entry will be collected under a unique study ID which you will find on the covering letter attached to this information sheet. We would like you to test our website for ease of use from the comfort of your own home. We will improve the website based on your recommendations. Some people may have difficulty using the internet either through lack of access or anxiety about security. If you do not wish to participate for these reasons it would be helpful if you could tell us so.
- If, after reading information about the study, you are willing to participate, you will be asked to re-enter your study number to give your consent to the study. The website will then take you through the following steps:

1. It will ask you to complete a questionnaire covering:
    a. information about you
    b. information about the treatment you have had
    c. BREAST-Q questionnaire which asks about quality of life and satisfaction with your appearance, and
    d. the experience of participating in this research, such as how you found the website and whether you have any suggestions for improvement for our future study.
2. You will then be asked to book a convenient time to come for a single visit to the Royal Marsden to have a 3D-surface image (3D photograph) taken.
3. When you have finished using the website, there will be a short survey to fill out to let us know how the process felt for you and how we can make it better for ladies in the future.
4. When you come for your 3D imaging appointment, we will use the VECTRA, (pictured on the front page of this information leaflet). This is a system of 6 cameras which take pictures simultaneously so that software can build a 3D image of you. We can take measurements which we believe will simplify the evaluation of appearance after breast reconstruction with implants. The image will be taken in our medical photography suite by one of our medical photographers. The equipment does not touch you and there is no radiation involved. Your dignity and privacy are paramount. The photographs do not include your face and will be stored using your study number (without any personal information), on a secure database by Canfield Scientific (the manufacturer of the VECTRA imaging system and experts in images storage with a track record in studies of skin diseases).

- The 3d photographs taken in the pilot study will be used by a panel of experts to devise a manual outcome scoring system for use in the main study.

- From the questionnaires we will be able to assess patient priorities after breast reconstruction and how well ladies' satisfaction with their appearance relates to a panel of clinician and patient representatives' opinion.

- If you were to abandon the online process at any point, we will give you a follow up telephone call to make sure you are not having any technical difficulties or see if we can help you complete the process in any way.
- The Royal Marsden Hospital is responsible for your care during the study period.

What are the possible benefits and advantages of taking part?

- There would be no direct benefit to you in taking part, but you can see a selection of comments on our website from participants in our previous studies about what they have found to be positive about participating in similar studies.

What are the possible disadvantages and risks of taking part?

- There are no known risks or side-effects of 3D surface imaging.
- The study involves a single visit to the hospital.
- Your legal rights are not affected by your giving consent to participate and any personal information gained from this study will remain strictly confidential.

Who has reviewed this research?

- The study has been approved by the Committee for Clinical Research and by the Patient and Carer Research Review Panel at The Royal Marsden. Their feedback has been used to improve the study design. All research in the NHS is looked at by independent group of people, called a Research Ethics Committee, to protect your interests. This study has been reviewed by the Surrey Research Ethics Committee.

How is my Data Stored?

- The data we collect online contains no personally identifiable information, just a secure study ID found on your invitation letter.
- Your images will be stored, anonymously, on a secure central storage system and will only be accessed by members of the study team
- Any personally identifiable data will be destroyed within 12 months of study completion
- All other study information will be destroyed at 5 years. Your photographs will not be destroyed but kept securely.

Who should I contact if I have any questions?

- If you have any questions about this study, please contact the doctors who are organising it:

Miss Jennifer Rusby
Consultant Oncoplastic Breast Surgeon

Miss Amy Godden
Breast Surgery Clinical Research Fellow
020 8642 6011 (ask for cordless 1282)
Email: implantstudy@rmh.nhs.uk