

ANZ1301 DOMINO Study Final Report

**Supporting shared decision-making for women offered neoadjuvant
systemic therapy for operable breast cancer**

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Contents

| | |
|--|----|
| Executive Summary..... | 3 |
| Lay summary | 4 |
| Background to this study | 5 |
| Methods..... | 6 |
| Results..... | 8 |
| Interpretation | 11 |
| Translation to policy and practice..... | 14 |
| Future directions..... | 14 |
| Publications, presentations, awards, publicity arising from this work..... | 15 |
| Peer reviewed publications..... | 15 |
| Conference presentations..... | 15 |
| Awards | 16 |
| Publicity..... | 16 |
| Other outputs | 16 |
| Budget reconciliation | 17 |
| Conclusion..... | 18 |
| Acknowledgements..... | 19 |
| Appendix A..... | 20 |
| References | 21 |

Executive Summary

This is the final report on the ANZ1301 DOMINO study that was funded by the HCF Research Foundation and Breast Cancer Trials Ltd. (formerly known as Australia and New Zealand Breast Cancer Trials Group). The study aimed to develop a decision aid to support greater involvement of women in the very complex decision about treatment with pre-operative (neoadjuvant) systemic therapy for operable breast cancer.

First, an evidence-based decision aid was developed via a rigorous process that included relevant stakeholders, using an iterative review process. This resulted in a document including an overview of treatment options, pros and cons of those options, text and graphical representations of outcome probabilities, a values clarification exercise and references to reliable further information. The final document was professionally published as a portable document file (.pdf) for ease of distribution and access.

Second, the decision aid was incorporated into a prospective, multicenter, single-arm clinical study. The study completed its target recruitment, with 59 participants enrolled from four sites in NSW and Victoria, and 51 participants completed the second assessment. All primary study outcomes were achieved, demonstrating that the decision aid was acceptable to patients and clinicians, and was feasible to use in clinical practice. Eighty-two percent of participants would recommend the decision aid to others in their situation; 89% of investigators would continue to use it in routine practice; and 77% of eligible patients enrolled in the study and accessed the decision aid. Secondary outcomes measure results were also positive, consistent with improvements in patient decision making. These outcomes include:

- Significant decreases in decisional conflict, to a level consistent with patients following through with their decision.
- Good agreement between desired and actual treatment received, indicating that patients were able to receive the treatment that they preferred.
- Significant reductions in anxiety and distress over time compared with baseline.
- Low levels of regret, and high levels of satisfaction with the decision about neoadjuvant systemic therapy.
- Good knowledge about neoadjuvant therapy after use of the decision aid.
- High patient feedback scores.

Interviews with patients confirmed the above findings, noting that the decision aid: was helpful for decision making; was feasible to use; improved their knowledge and understanding; was customized and reliable information; and facilitated shared decision-making.

Investigator feedback surveys supported use of the decision aid in routine clinical practice. Most felt that it could be integrated into their clinical workflow, and that it did not require extra time in the clinical consultation, nor did they perceive any patient difficulties with the decision aid.

This study has resulted in the development of a tool to support shared decision-making in the increasing population of women who are considering neoadjuvant systemic therapy for operable breast cancer. It is now available for patient care, and is being used around Australia. Collaborations are underway to disseminate this decision aid internationally.

Lay summary

More and more women with early stage breast cancer (that has not spread beyond the breast and nearby lymph nodes) are being offered chemotherapy and/or hormone-blocking therapy *before* surgery (neoadjuvant therapy). Women who have been offered neoadjuvant say that they would like to be more involved in decisions about their care, however were not as involved as they would have liked. Reasons include a lack of available information, a feeling that the decision needed to be made urgently, the fact that the decision involves a complex interplay of factors, and fear of a less commonly used treatment. However, international research and guidelines show that patient-centred care and shared decision-making are key aspects of high quality health care. This means that these women are missing out on an important aspect of their care.

In response to this identified patient need, we produced a document called a decision aid, which is an accepted way to help patients be more involved in decisions about their health care. Substantial research in the past has shown that decision aids help patients achieve better healthcare outcomes. There was previously no decision aid available for women considering neoadjuvant therapy. The decision aid contains evidence-based information about the pros and cons of having neoadjuvant therapy versus surgery first, information about possible outcomes of one decision or the other, and a worksheet to help clarify which option fits best with an individual's values and preferences.

We then conducted a study in which we gave the decision aid to women who were making the decision about whether to have neoadjuvant therapy. We gave them questionnaires before and after they used the decision aid, between chemotherapy and surgery, and 12 months after enrolling in the study. Women who participated in the study had increased confidence in their decision, greater involvement in the decision, and decreases in both distress and anxiety. Of the women who participated in the study, 80% women read the decision aid and found it useful. The doctors that gave it to their patients to comment on whether it was useful, and 89% said that they would keep using it after the study had ended.

This research has resulted in a resource that is now available to support women who are faced with very difficult decisions at a particularly stressful and vulnerable time of their lives. This resource is being distributed widely, free of charge, to help women with breast cancer receive health care that is most suitable and in line with their values and preferences.

Background to this study

Traditionally, women with early stage breast cancer had the tumour surgically removed, followed by systemic therapy (chemo- and/or endocrine therapy) as indicated¹. Recently, an increasing proportion of these women are being offered, and prescribed, neoadjuvant systemic therapy for operable breast cancer, comprising 18% of stage 2 and 42% of stage 3 patients in the USA². Recent Australian data are not readily available, however international and Australian guidelines recommend consideration of neoadjuvant therapy for larger, or more proliferative early stage breast cancer^{1, 3-5}. Over 16,000 Australians are expected to be diagnosed with breast cancer in 2017, of whom 90% are diagnosed at an early stage^{6, 7}.

Advantages of neoadjuvant therapy include downstaging from mastectomy to lumpectomy and downstaging the axilla^{8, 9}; better oncologic clearance allowing for consideration of immediate breast reconstruction in women still requiring mastectomy; improved prognostication based on response¹⁰; time to plan surgery¹¹; and participation in a neoadjuvant or post-neoadjuvant clinical trial¹². Disadvantages for some patients include fear of progression on chemotherapy¹³, the psychological impact of leaving a tumour in place rather than immediate surgical removal, and the psychological impact of an adverse prognosis if the tumour does not respond to chemotherapy. Importantly, disease-free and overall survival outcomes are equivalent, whether neoadjuvant therapy or surgery is the first treatment modality for operable disease¹⁴.

Previous work done by our group has demonstrated that women who were offered neoadjuvant therapy were not as involved in the decision, or as informed, as they would have liked, and that they would value a tool to support their involvement in the decision¹⁵. Patient centred care is acknowledged as a key component of high quality health care^{16, 17}. The process of shared decision making supports patient centred care by actively involving the patient along with their healthcare provider(s) to choose the best option for that individual¹⁸. One strategy to implement shared decision-making is the patient decision aid, which is an evidence-based, structured tool to support deliberation between patients, clinicians and others when there is more than one health care option^{19, 20}.

Involving patients in the decision about neoadjuvant therapy can be challenging due to the complexity and perceived urgency of the decision. Therefore, we aimed to develop a patient decision aid based on international guidelines²¹, and then evaluate that decision aid in a prospective longitudinal study²².

Methods

Design, patients and setting

This was a prospective, single arm, multicentre, longitudinal study. This study received approval from a recognized ethics committee, and all participants provided informed consent prior to any study processes. Participants were Australian women aged 18 or over with a diagnosis of operable invasive breast cancer, and were candidates for neoadjuvant therapy of 3 months or longer. Exclusion criteria were: insufficient English language to complete study questionnaires; inflammatory, metastatic or inoperable breast cancer; or inability to access the internet and email to complete study requirements.

A decision aid was developed for this study, based on a literature review, patient interviews¹⁵, a clinician survey²³, and the International Patient Decision Aid Standards (IPDAS) Collaboration guidelines¹⁹. A stakeholder group reviewed the decision aid, including medical oncologists, surgeons, a psychologist, breast care nurse, consumers and a breast cancer advocacy group representative. The resulting decision aid is a 26-page booklet available online or in print. It contains a description of the options of adjuvant and neoadjuvant therapy, with advantages and disadvantages, outcome probabilities (pathological complete response, downstaging, progression on neoadjuvant therapy), graphical and pictorial information, and a values clarification exercise. It is designed for flexibility of use, whether to be read cover-to-cover, or only sections of interest. The Flesch-Kincaid reading level is year 10, despite consumer input and substantial effort to simplify the language. A full copy of the decision aid is available via the link in appendix A²⁴.

Participants were recruited by their breast surgeon or medical oncologist, completed a baseline questionnaire, then accessed the decision aid for on-screen or hard copy review (Figure 1, study schema). The decision aid was intended to be given to patients by their surgeon at the time of referral to a medical oncologist, for review prior to that appointment. After the follow-up visit where a decision was made about having neoadjuvant therapy, or surgery first, they received a follow-up questionnaire (assessment 2). Assessment 3 was between completion of systemic therapy and before surgery (or after surgery and before chemotherapy if surgery was first), and the final questionnaire (assessment 4) 12 months after registration. All questionnaires were completed online.

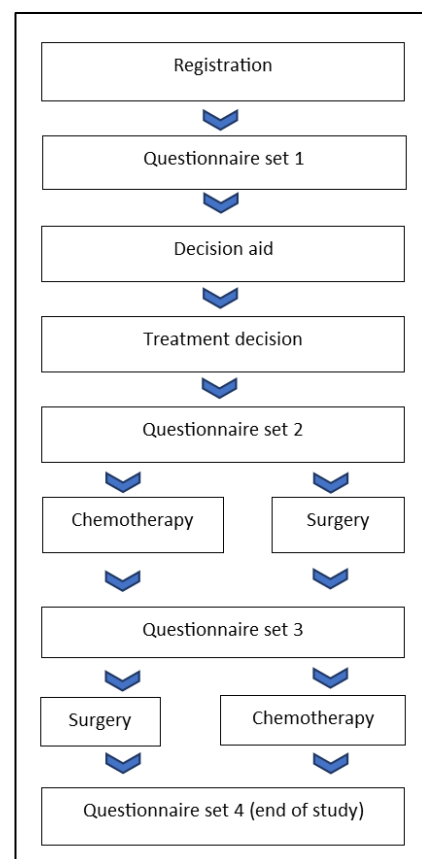


Figure 1. Study schema

Outcomes

Co-primary outcomes comprised feasibility of decision aid use, and acceptability to patients and clinicians. Feasibility was defined as the percentage of eligible patients who accessed the decision aid after being offered participation in the study, which we hypothesized would be greater than

50%. Patient acceptability was defined as the percentage of participants who would recommend the decision aid to others in their situation, hypothesized to be greater than 50%. Investigator acceptability was defined as the percentage of investigators who would use the decision aid in routine practice, hypothesized to be greater than 50%. Acceptability and feasibility margins were prospectively defined based on the estimated proportion of patients and investigators required to warrant routine implementation of the decision aid.

Patient reported outcome questionnaires were completed by participants at each time point, which have been described in detail previously²². Measures were: Decisional Conflict Scale²⁵; Information and Involvement Preferences²⁶; Control Preferences scale²⁷; 6-item State-Trait Anxiety Inventory²⁸; Distress Thermometer²⁹; Fear of Cancer Progression³⁰; Fear of Cancer Recurrence Inventory³¹; custom knowledge questionnaire; Decision Regret³²; Satisfaction with Decision³³; and decision aid feedback³⁴. Investigators were also asked to complete a feedback questionnaire.

Analysis

Recruitment of 50 participants was planned, so that a primary outcome score of 67% or more would provide 80% power with a one-sided alpha of 5% to reject a true rate of 50% or less. To provide sufficient numbers for secondary outcome analysis, recruitment was planned to continue until 50 participants had completed assessment 2. We summarize demographic, tumour and treatment data by mean and standard deviation for continuous data, and by number and frequency for categorical data. Primary outcomes are analysed using tests of proportions and presented with 95% confidence intervals (CI). Those who did not complete assessment 2 were assumed to have not read the decision aid. Differences in decisional conflict subscale and information and involvement preferences (detail) were assessed using paired t-tests. Change in information and involvement preference (information type) from baseline was tested using McNemar's test. Linear mixed models were used to examine changes in distress and anxiety with fixed effects for final treatment choice and time (modelled as a categorical variable) and a subject level random intercept term. Fear of progression, fear of cancer recurrence, and decisional regret are reported using summary statistics and paired t-tests. Agreement in decision control and treatment choice (preferred vs achieved at assessment 2) is presented using Kappa, with scores defined as: <0, poor; 0-0.2, slight; .021-0.4, fair; 0.41-0.6, moderate; 0.61-0.8, substantial; and 0.81-0.99, almost perfect³⁵. Change in decisional control is presented using Bowkers test, collapsing categories into shared (collaborative, guided by either patient, doctor, or both equally) vs not shared (only patient or doctor makes the final decision). An exploratory analysis of outcomes at assessment 2 was conducted according to whether the participant had read the decision aid or not. A p-value of less than 0.05 was considered significant for all analyses. Analyses were computed using STATA/IC version 13.1 (StataCorp, College Station, TX).

Results

Between June 2015 and September 2016, 77 eligible women were offered participation and consented to demographic details being recorded. Fifty-nine completed the online consent, first questionnaire and accessed the decision aid (table 1).

| Variable | | N=59 |
|---------------------------|------------------|-----------|
| Age, years [mean (SD)] | | 52 (8.9) |
| Marital status [n (%)] | Married/De facto | 48 (81.4) |
| | Single | 11 (18.6) |
| Highest education level | Postgraduate | 17 (28.8) |
| | Undergraduate | 13 (22.0) |
| | Vocational | 13 (22.0) |
| | High school | 15 (25.4) |
| | Missing | 1 (1.7) |
| Private health insurance | Yes | 51 (86.4) |
| | No | 8 (13.6) |
| Health Professional | Yes | 10 (17.0) |
| | No | 49 (83.0) |
| English as first language | Yes | 56 (94.9) |
| | No | 3 (5.1) |

Table 1. Participant characteristics

Feasibility and acceptability of the decision aid

The decision aid was feasible, with 59 of 77 eligible patients accessing the decision aid (76.6%, 95% CI 67.2-86.1, $P < 0.0001$). Of those 59 participants, 47 read all or part of the decision aid (79.7%, 95% CI 69.4-89.9, $p < 0.0001$). There were no significant differences in baseline demographics or outcome measure scores between those who read the decision aid and those who did not. The decision aid was acceptable to 41 of 51 participants who completed assessment 2, who would recommend the decision aid to others in their situation (82.4%, 95% CI 69.5-91.3, $p < 0.0001$), and 18% (9/51) were neutral. The decision aid was acceptable to 16 of 18 site investigators (88.9%, 95% CI 74.4-103.4, $p < 0.001$) for routine use.

Patient-reported outcomes

Overall 51/59 (86.4%) chose neoadjuvant therapy. Agreement was good between desired (post-decision aid) and actual treatment (kappa 0.6, 95% CI 0.290-0.911). At baseline, 18 participants were unsure about whether to proceed with neoadjuvant therapy or surgery as their first treatment, six of whom proceeded with surgery and 12 received neoadjuvant therapy. Decisional conflict decreased in total and in all subscales (informed, values clarity, support, uncertain, effective) after use of the decision aid in combination with clinical consultation (all p -values < 0.002 , figure 2). The post-decision aid score was less than 25 in all except the 'uncertain' subscale. Patient reported outcome measure scores are presented in table 3.

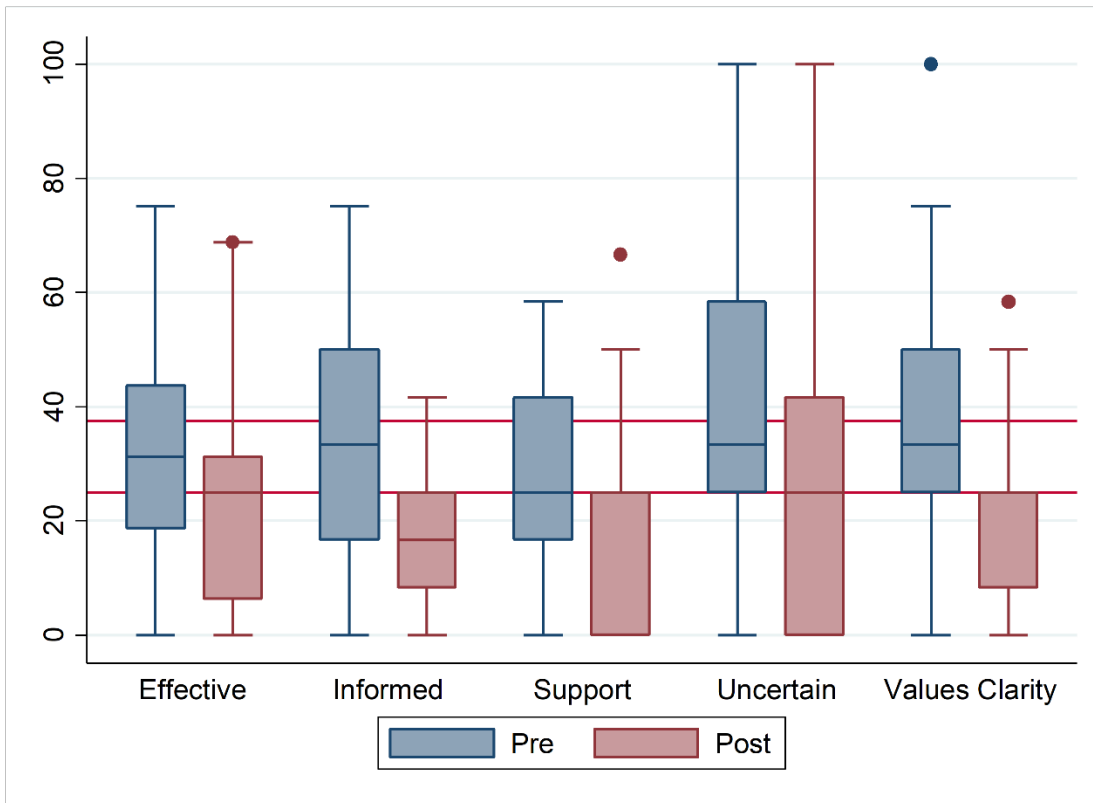


Figure 2. Decisional Conflict scores before and after decision aid

There were no differences in baseline demographics or assessment 1 outcome scores between those who read the decision aid and those who did not. At assessment 2, those who read the decision aid had no difference in decisional conflict, anxiety, distress, or decision control preferences. Those who read the decision aid had a higher mean knowledge score.

Most patients preferred, and achieved, a shared approach in their decision about neoadjuvant therapy (Table 2). Eighty-six percent of patients (44/51) achieved at least as much decisional control as they desired. No significant changes were observed between pre-decision aid preferred decisional control, and actual perceived decisional control ($p=0.50$). Fair agreement was observed between preferred and achieved decisional control at assessment 2 (Kappa 0.32, 95% CI 0.16-0.49). Fear of cancer progression scores were low in 76.5% of participants, moderate in 19.6% and severe in 3.9% at assessment 2. At assessment 3, scores were low in 88.2% and moderate in the remainder.

| Measure | Assessment 1 (n=59) | Assessment 2 (n=51) | Assessment 3 (n=51) | Assessment 4 (n=29) ¹ | P-value |
|--------------------------------------|---------------------|---------------------|---------------------|----------------------------------|---------------------|
| Total decisional conflict (mean) | 33.4/100 (SD 19.3) | 21.0 (SD 14.1) | - | - | <0.001 ² |
| Information detail preference (mean) | 8.5/10 (SD 2.16) | 8.6/10 (SD 2.02) | - | - | 0.73 ² |
| Information type | | | | | 0.69 ³ |
| All information, good and bad | 76.3% | 72.6% | - | - | |

| Measure | Assessment 1 (n=59) | Assessment 2 (n=51) | Assessment 3 (n=51) | Assessment 4 (n=29) ¹ | P-value |
|--|---------------------|---------------------|---------------------|----------------------------------|---------------------|
| Additional information only if it is good news | 5.1% | 3.9% | - | - | |
| Only information needed to care for myself | 18.6% | 23.5% | - | - | |
| Anxiety | 55.4/100 (SD 15.0) | 49.4 (SD 14.1) | 40.1 (SD 13.0) | 36.1 (SD 12.2) | <0.001 ⁴ |
| Distress (mean) | 5.9/10 (SD 2.9) | 5.0/10 (SD 2.5) | 3.2/10 (SD 2.5) | 2.2/10 (SD 2.5) | <0.02 ⁴ |
| Fear of cancer progression | | 33.4/60 (SD 7.2) | 29.9/60 (SD 7.2) | - | <0.001 ² |
| Fear of cancer recurrence | - | - | 58.9/168 (SD 25.0) | 57.5/168 (SD 22.9) | 0.359 ⁵ |
| Satisfaction with decision (mean) | - | - | 25.5/30 (SD 3.6) | - | 0.005 ⁶ |
| Decision Regret | - | - | 16.4/100 (SD 20.0) | 10.0/100 (SD 15.4) | 0.0176 ⁵ |
| Knowledge (mean) | - | 76% (SD 12.5) | - | - | <0.001 ⁵ |
| Feedback (mean) | - | 74% (SD 8.4) | - | - | <0.001 ⁵ |

Table 3. Patient reported outcome scores. SD, standard deviation; CI, confidence interval. ¹At the data cut-off, 20 patients had yet to complete their 4th questionnaire; ²Paired t-test; ³McNemar's test; ⁴Linear mixed model; ⁵P-value comparison with pre-specified hypothesis.

| Level of control | Survey 1 – preferred (n=59) | % | Survey 2 – preferred (n=51) | % | Survey 2 – actual (n=51) | % |
|--|-----------------------------|------|-----------------------------|------|--------------------------|------|
| Doctor makes final decision | 7 | 11.9 | 5 | 9.8 | 6 | 11.8 |
| Doctor makes final decision, seriously considering my opinion | 9 | 15.3 | 11 | 21.6 | 6 | 11.8 |
| Shared | 28 | 47.5 | 26 | 51.0 | 18 | 35.3 |
| I make final decision, seriously considering my doctor's opinion | 15 | 25.4 | 8 | 15.7 | 19 | 37.3 |
| Patient makes final decision | 0 | - | 1 | 2.0 | 2 | 3.9 |

Table 2. Control preferences scale.

Investigator-reported outcomes

Eighteen of 24 (75%) participating investigators (7/11 medical oncologists and 11/13 surgeons) completed the investigator questionnaire. Sixteen (88.9%) indicated that they would use the decision aid in routine practice. Sixteen also indicated that the decision appeared easier, or no more difficult for patients compared with previous patients who had not used the decision aid. Fourteen felt that the decision aid did not change patients' decision about neoadjuvant therapy, and the remaining four investigators felt that the decision aid increased the likelihood of a patient choosing

neoadjuvant therapy. Twelve noted no change in consultation time, and the remaining six noted a mean increase of 7.5 minutes.

Cost implications

A health economic scale, the EQ-5D-5L, was used in this study at all time points. However, based on statistical advice from a health economist when developing the study protocol, this can only be used to provide a general understanding of the cost implications of neoadjuvant therapy. Therefore, a formal cost effectiveness analysis was not performed. Further work will be done in 2018 to better understand the societal and cost implications of neoadjuvant therapy.

Health service delivery

The decision aid was able to be implemented into routine care pathways. Patients who are referred to a medical oncologist typically have several days to a week or more to wait for an appointment, and that time can be used to inform themselves about their options. The decision aid did not require significant additional resources above and beyond the traditional neoadjuvant pathway. The availability of a nurse liaison was one aspect of care that was an important part of the smooth delivery of neoadjuvant therapy. Sites with prompt referral pathways and multidisciplinary teams appeared to deliver neoadjuvant therapy, including the decision aid, most effectively. Health services, with clinical motivation, were able to adapt to an increase in neoadjuvant therapy.

Interpretation

This study fills a gap in the breast cancer decision literature by producing a neoadjuvant decision aid that had not previously been available¹⁵. The study demonstrates that a decision aid in this setting is acceptable to a majority of patients and clinicians, and could feasibly be used within routine clinical workflow. Decision-related patient reported outcome scores improved in the post-decision aid assessments. These findings are consistent with literature showing that systematically developed DAs designed for patient use in healthcare decision-making effectively improve decision-related outcomes for a range of general medical treatment decisions³⁶, and for breast cancer³⁷.

Previous work has indicated that patients benefit from being at least as involved as they wish to be³⁸. The decision about neoadjuvant therapy is complex due to the need to consider the implications of a range of individual treatment decisions, in the context of distress from a recent diagnosis of breast cancer. Patients in the present study engaged in decision-making despite this inherent complexity. Using the decision aid did not appear to increase patient anxiety, and, with an additional consultation, appeared to resolve decisional uncertainty.

A decision aid should be implementable in routine practice, to realize the benefits seen in the study. Whilst the hypothesized threshold values for feasibility and acceptability were based on estimated likelihood of routine uptake, lower (or higher) thresholds might be appropriate depending on individual clinician and patient factors. A minority of patients in this study were neutral in their recommendation for the decision aid to others in their situation and only one indicated that she would recommend against it. Most read part or all of the decision aid, once they had accessed it.

Stated reasons for not reading the decision aid were that they had already made their decision, or that the decision aid was provided too late in their decision-making process. The non-randomized analysis of outcomes according to whether the participant had read the decision aid or not is exploratory and should be interpreted as such.

Study procedures such as the online delivery and pre-decision aid assessment made access to the decision aid more difficult than it would be in routine practice, where it would be appropriate to hand the patient a paper copy for immediate review. We suspect that others did not access the decision aid because it, and the study, were a burden at a time when they are dealing with the impact of their diagnosis, and planning for treatment. Therefore, patient uptake in this study may underestimate real-world conditions. Broader reach might be gained if the decision aid were distributed by breast care nurses as well as clinicians.

At baseline, mean decisional conflict scores were high, consistent with patients delaying or feeling unsure about decision-making²⁵. Following use of the decision aid and a subsequent clinical consultation, decisional conflict scores were consistent with patients proceeding with implementation of their treatment choice. This correlates with a significant decrease in the proportion of participants who reported being unsure about which treatment they preferred. The relative contributions of clinical consultation vs the decision aid are unable to be enumerated with this single-arm study design. Anxiety scores were consistent with participants being in a stressful situation, and did not decrease to population norms until assessment 4²⁸. Lower anxiety in the neoadjuvant group might be explained by patients' expectations of receiving neoadjuvant therapy if they were offered that treatment. Alternatively, anxious patients might have elected to have surgery first. Lower anxiety might also have been associated with seeing their tumour shrink, and with getting a feared treatment 'over and done with'. A decision to have surgery up front might also have been seen as contradicting the perceived medical recommendation in patients who had been referred for neoadjuvant therapy.

Fear of cancer progression scores were similar to the mean score of 60.6 (SD 24.6) reported by historical breast cancer controls³¹. This suggests that these women were no more worried than the average breast cancer patient about the impact of the cancer getting larger or developing distant metastases whilst on treatment. Mean decision regret at assessment 3 was comparable with historical breast cancer patient data indicating low levels of regret related to the decision about neoadjuvant therapy³². The strength of clinical recommendation for neoadjuvant therapy will depend on the individual patient and tumour characteristics. Clinical equipoise was not expected about whether neoadjuvant therapy or surgery was the best initial approach for individual patients, nor was the decision aid expected to change patients' minds. Results support this, with no significant changes in preferred treatment following use of the decision aid. Only 18 reported being unsure about their preferred treatment schedule pre-decision aid, which may represent clinical influence towards treatment decisions. Six of those 18 chose surgery, while two of the 41 who were sure about their decision at baseline chose surgery. Unsure patients may choose the normative behaviour of surgery first, or the decision aid may influence unsure patients towards surgery. It is possible that the decision aid was not in fact balanced, however, most patients and clinicians perceived the decision aid to be balanced.

This study is limited by its relatively small sample size and single-arm design. A single arm design was felt to provide adequate confidence in the decision aid's safety and acceptability. Positive endpoints allow broad implementation of this decision aid, given the large existing literature on the efficacy of DAs. We cannot derive the relative contribution of the decision aid versus clinical consultations, independent information-seeking, discussion with family and friends, or natural history. The study

population was well educated, which may reduce the generalizability to a less educated group. The decision aid was written at year 10 reading level, higher than the recommended year 8 level, which is a common issue in patient information material³⁹. Strengths include the evidence-based, systematic development process and the use of validated patient reported outcome measures. The decision aid was used successfully in a variety of settings as part of this study, supporting ability to be implemented in routine clinical care.

Future work will focus in decision aid implementation⁴⁰. A minority of investigators reported a small increase in consultation time when they used the decision aid, with no impact on their intention to use the decision aid, suggesting the benefits of the decision aid were considered worth additional consultation time. The document was intended to be reviewed in detail outside of the consultation to reduce impact on consultation time. The decision aid is scalable through electronic distribution. The intervention has been made freely available to encourage sustained uptake.

Translation to policy and practice

This study has provided a new, previously unavailable resource that supports shared decision making and patient centred care for a group of patients who were previously not sufficiently involved in decisions about their care. This work aligns with Australian and international policy that aims to ensure optimal healthcare by placing emphasis on the values and preferences of patients, in the context of best available evidence-based practice^{17, 20, 41}. The resource is now freely available for patients and clinicians to access and download for immediate use.

The ANZ1301 DOMINO study results have been presented at several Australian and international scientific meetings, to a wide range of audiences, including breast surgeons, medical oncologists, radiation oncologists, nurses, allied health, and consumers. National meetings include oral presentations at the Clinical Oncology Society of Australia Annual Meeting; and Medical Oncology Group of Australia Annual Meeting. Results were presented internationally as an oral presentation at the Controversies in Breast Cancer Conference in Tokyo, Japan; and as a poster at the European Society of Medical Oncology Congress in Madrid, Spain.

The manuscript describing the primary results has also been accepted for publication in the international, peer-reviewed Journal of the National Comprehensive Cancer Network (NCCN). This journal has broad reach, and is produced by the NCCN, an alliance of leading United States cancer centres. This Group also produces widely used guidelines and patient support material. During review of the manuscript, the journal suggested that the decision aid could be adapted for the NCCN to distribute.

Within Australia, leading breast cancer organisations including Breast Cancer Trials Ltd, Breast Cancer Network Australia, and The McGrath Foundation, have endorsed the decision aid and provide access to it via their websites. Furthermore, the decision aid study results have been presented to Breast Cancer Trials clinician members, representing a multidisciplinary group of breast cancer specialists. The decision aid has been featured in the Breast Surgeons of Australia and New Zealand newsletter, which is sent to the majority of breast specialist surgeons in the region.

In summary, this decision aid has gained broad scientific attend, and has the support of leading clinician and consumer breast cancer organisations. This publicity and support has launched the decision aid into the clinical treatment pathway, and will be important for the ongoing sustainable implementation of the decision aid.

Future directions

The decision aid will be subject of ongoing implementation work. Discussions are underway with colleagues in The United States and Germany to evaluate optimal methods of distributing the decision aid in different settings. We are collaborating with these groups, who are international leaders in neoadjuvant therapy, with anticipated flow-on effects to the broader clinical community. We will apply for the decision aid to be featured on the Ottawa Decision Aid Inventory website, which is the major international decision aid repository. Ongoing local implementation work is also planned.

Publications, presentations, awards, publicity arising from this work

Peer reviewed publications

| | |
|---|--------------------------|
| Zdenkowski N , Butow P, Spillane A, Douglas C, Snook K, Jones, M, Oldmeadow C, Fewster S, Beckmore C, Boyle FM. A single-arm longitudinal study to evaluate a decision aid for women who have been offered neoadjuvant systemic therapy for operable breast cancer (ANZ1301 DOMINO). Journal of the National Comprehensive Cancer Network 2017. [In press] | Accepted 1/9/17 |
| Herrmann A, Boyle FM, Butow P, Hall A, Zdenkowski N . Exploring women's experiences with a decision aid for neoadjuvant systemic therapy for operable breast cancer. Health Science Reports 2017;e23. [Available online 22/8/17] doi: 10.1002/hsr2.13 | Published ahead of print |
| Herrmann A, Hall A, Zdenkowski N . Women's experiences with deciding on neoadjuvant systemic therapy for operable breast cancer: A qualitative study. Asia-Pacific Journal of Oncology Nursing. [Available online 21/11/17] | Published ahead of print |
| Zdenkowski N , Butow P, Hutchings E, Douglas C, Coll JR, Boyle FM. A Decision Aid for Women Considering Neoadjuvant Systemic Therapy for Operable Invasive Breast Cancer: Development and Protocol of a Phase II Evaluation Study (ANZ1301 DOMINO). JMIR Research Protocols 2016;5(2):e88. doi: 10.2196/resprot.5641. | Published |

Conference presentations

| | |
|---|----------|
| Zdenkowski N . Neoadjuvant systemic therapy: Practice, patient and research considerations. Bangladesh Breast Cancer Conference, Dhaka, December 2017. Invited oral presentation. | 1/12/17 |
| Zdenkowski N , Butow P, Boyle FM. Patient reported outcomes according to receipt of neoadjuvant or adjuvant systemic therapy for breast cancer: results of a prospective longitudinal study. Controversies in Breast Cancer Conference, Tokyo, Japan, October 2017. Oral presentation. | 26/9/17 |
| Zdenkowski N , Butow P, Spillane AJ, Douglas C, Beckmore C, Jones M, Boyle FM. Primary results of a study to evaluate a decision aid for women offered neoadjuvant systemic therapy for breast cancer. European Society of Medical Oncology Annual Meeting 2017, Madrid, Spain. Annals of Oncology 2017. | 9/9/17 |
| Zdenkowski N , Butow P, Boyle F. Patient reported outcome results from the ANZ1301 DOMINO neoadjuvant breast cancer decision aid study. Medical Oncology Group of Australia Annual Scientific Meeting 2017, Melbourne. Oral presentation 'Best of the Best Research 2017'. Asia-Pacific Journal of Clinical Oncology 2017;13(S2)50-52. | 3/8/17 |
| Zdenkowski N . Decision aids, patient views and barriers. Clinical Oncology Society of Australia/Australia and New Zealand Breast Cancer Trials Group Annual Scientific Meeting 2016, Gold Coast. Oral presentation. Asia-Pacific Journal of Clinical Oncology 2016;12(Suppl. S12):66-168. | 17/11/16 |
| Zdenkowski N . Development and testing of a decision aid for women contemplating neoadjuvant systemic therapy for operable breast cancer. Clinical Oncology Society of Australia/Australia and New Zealand Breast Cancer Trials Group Annual Scientific Meeting 2016, Gold Coast. Oral presentation. Asia-Pacific Journal of Clinical Oncology 2016;12(Suppl. S12):66-168. | 16/11/16 |

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| Zdenkowski N , Herrmann A, Hall A, Butow P, Boyle FM. Women's experiences with a decision aid for neoadjuvant systemic therapy for operable breast cancer. San Antonio Breast Cancer Symposium, San Antonio, TX, USA. <i>Cancer Research</i> 2016;77. | 9/12/16 |
| Herrmann A, Hall A, Zdenkowski N . Exploring how women make decisions on neoadjuvant systemic therapy (NAST) for operable breast cancer. Breast Cancer in Young Women International Conference, Lugano, Switzerland. <i>Breast</i> 2016;29:S27. | 11/11/16 |

Awards

| | |
|--|---------|
| Winner, 'Patients as Partners' category. Hunter New England Local Health District Excellence Awards: Supporting Decision-Making for Early Stage Breast Cancer. | 8/8/17 |
| Nominee: Rising Star PhD Award, NSW Premier's Awards for Outstanding Cancer Research. | 3/11/17 |

Publicity

| | |
|--|---------------|
| Calvary Mater Newcastle: Mater Matters article | August 2017 |
| Hunter Lifestyle Magazine article | October 2017 |
| Health Matters Magazine article | November 2017 |

Other outputs

| | |
|---|----------|
| PhD Thesis: Zdenkowski N, Supporting decision-making for women with breast cancer, University of Sydney (Submitted November 2017). <i>The DOMINO study formed a major component of this thesis.</i> | 22/11/17 |
|---|----------|

Note: The HCF Research Foundation has been duly acknowledged in outputs arising from this work.

Budget reconciliation

| | |
|---|---|
| Amount requested: | \$220,654 |
| Amount awarded by HCF Research Foundation: | \$191,936 |
| | (reduced as per HCF Research Foundation, to remove salary and operating overheads, and 10% contingency) |
| Breast Cancer Institute of Australia contribution: | \$61,074 |
| Total cost of project: | \$253,000 |

Budget items (in units of \$1,000):

| | <u>Apr 13 - Mar 14</u> | <u>Apr 14 - Mar 15</u> | <u>Apr 15 - Mar 16</u> | <u>Apr 16 - Mar 17</u> | <u>Apr - Nov 17</u> | <u>TOTAL</u> |
|----------------------------|----------------------------|----------------------------|----------------------------|----------------------------|-------------------------|--------------|
| Income | | | | | | |
| Grants & External Income | 0 | 71 | 101 | 0 | 19 | 191 |
| Total Income | 0 | 71 | 101 | 0 | 19 | 191 |
| Gross Profit | 0 | 71 | 101 | 0 | 19 | 191 |
| Expense | | | | | | |
| Labour | 5 | 84 | 72 | 8 | 1 | 170 |
| Trial Site Funding | 0 | 0 | 16 | 10 | 0 | 26 |
| Computer Expenses | 0 | 20 | 24 | 7 | 0 | 51 |
| Printing & Office Supplies | 0 | 0 | 0 | 1 | 0 | 1 |
| Professional Fees | 0 | 3 | 1 | 0 | 0 | 4 |
| Property Expenses | 0 | 0 | 0 | 0 | 0 | 0 |
| Other Operating Expenses | 0 | 0 | 1 | 0 | 0 | 1 |
| Total Expense | 5 | 107 | 114 | 26 | 1 | 253 |

Comment

The bulk of the study was financed by the HCF Research Foundation grant, with the remainder made up using funds donated to Breast Cancer Trials (formerly the Breast Cancer Institute of Australia) by the community.

The \$33,000 difference between the original grant application and the final expenditure was predominantly IT costs, and salary. The bulk of expenditure was between April 2014 and March 2016, as anticipated in the original 2-year study timeframe. IT costs were higher than anticipated because the study was conducted predominantly online, rather than paper and pen as originally intended. This additional cost in IT set-up and automation offset the labour costs of administering paper and pencil surveys and study procedures at geographically distant sites. Overall this cost represents the increasing complexity of running high quality studies in the current clinical trials environment.

Conclusion

This research has resulted the development of, and evidence supporting, a decision aid for women with operable breast cancer who have been offered neoadjuvant systemic therapy. The study showed that the decision aid was acceptable to clinicians and patients. The decision aid was feasible to integrate into patients' care pathway, ideally after seeing a surgeon and before consultation with a medical oncologist for a final treatment decision. Improvements in decision-related outcomes were seen, without evidence of adverse effects. We have collaborated with major clinical and consumer organisations to integrate the decision aid into routine clinical pathways. Implementation strategies are now being evaluated to further scale up use in routine patient care.

Acknowledgements

We acknowledge and thank the patients who participated in the study, along with their support people, for their time and effort participating in a study at this difficult time of their lives.

A large group of people, including co-investigators on this grant, and a broader advisory group, made substantial contributions to decision aid and study design and conduct. These groups include clinicians, researchers, consumers, and Breast Cancer Network Australia.

Thanks to site investigators and trial coordinators for recruiting patients, collecting and submitting data, and providing feedback on the decision aid.

The HCF Research Foundation and Breast Cancer Trials funded the study. Breast Cancer Trials coordinated the study. Statisticians from Hunter Medical Research Institute and the Psycho-Oncology Cooperative Group provided statistical advice on protocol development and analysis of data. Newton Green Technologies developed the online questionnaire forms and database.

My salary was supported by the Hunter New England Local Health District in the form of a Clinical Research Fellowship. I was housed by the Calvary Mater Newcastle, Breast Cancer Trials Ltd and The Patricia Ritchie Centre for Cancer Care and Research, while conducting this work.

Appendix A

Neoadjuvant decision aid link

This decision aid is freely available on the Breast Cancer Trials website:

<https://www.breastcancertrials.org.au/file/44/Neoadjuvant-Patient-Decision-Aid>

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