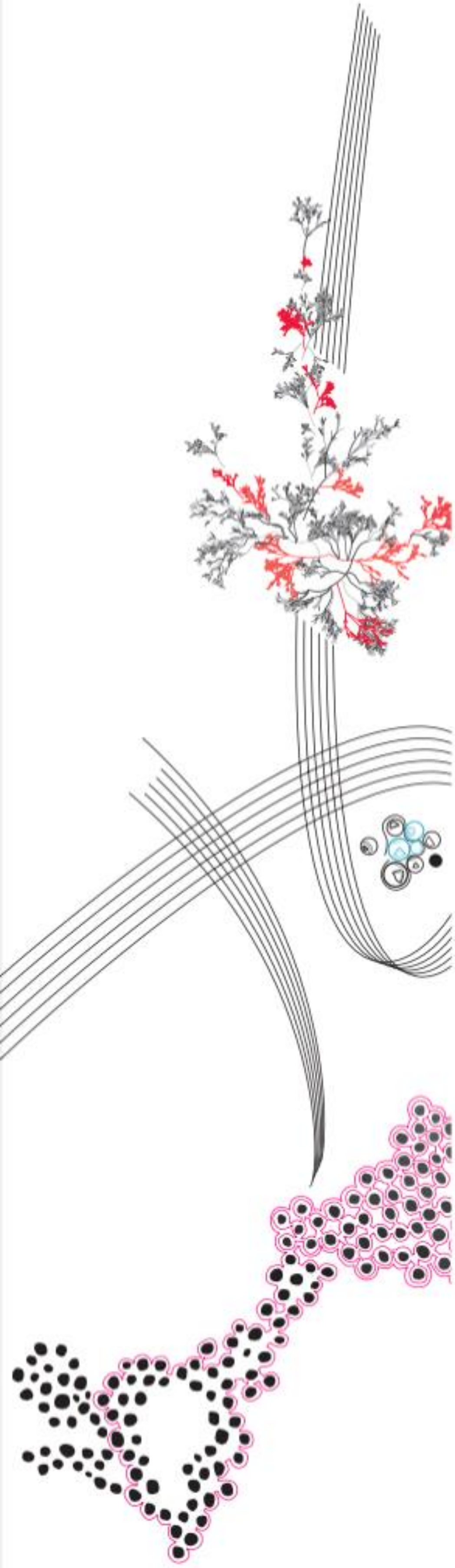
MSc Health Sciences
Master Thesis



CABRIO-study: Workup to Chemotherapy in neoAdjuvant Breast cancer treatment Researched by Interview Outcomes

Experiences of breast cancer patients in the neoadjuvant trajectory

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June, 2023

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Abstract

Background: The “workup to Chemotherapy in neo-Adjuvant Breast cancer treatment Researched by Interview Outcomes” or CABRIO study, investigates the experiences of women with breast cancer in the neoadjuvant chemotherapy (NAC) trajectory. In the Netherlands the quality of healthcare is tightly regulated, encouraging the minimization of lead time for NAC treatment initiation. The complexity of the NAC trajectory, the limited lead time and the emotional burden faced by the patients demand a closer examination of their experiences.

Methods: The CABRIO study is a single-center descriptive study with two components. Firstly, the experiences of patients were assessed using a mixed method questionnaire. The questions revolve around the completeness of information received about diagnosis, treatment, and risks, as well as shared decision-making, the time required to make a decision, and workup to NAC. Secondly, the clinical pathways were mapped out by conducting retrospective clinical record review. Patients were recruited by the nurse specialist during a visit at the outpatient clinic all documents were collected by the nurse specialist during the first NAC treatment.

Results: Fifteen women participated in the study. The overall satisfaction with the care received was high. However, 4/15 patients were not satisfied with the information received about treatment options and their involvement in making treatment decisions. Three participants desired more time for treatment decisions. The opinions about an earlier start of treatment varied. Demographic variables and duration of intervals between events in the NAC trajectory, had no significant influence on satisfaction. The analysis of the clinical pathways revealed much variation in interval duration, order and frequency of occurrence of events; resulting in opportunities for optimization.

Conclusions: This preliminary study provides initial insights into the experiences of women and operational aspects of the NAC trajectory. The majority of patients are satisfied with the care they received and the clinical pathway of NAC patients exhibits considerable variation in order, frequency and duration of events and intervals.

Introduction

Breast cancer is the most prevalent cancer worldwide, with a prevalence of 320000 patients in the Netherlands (1)(2). The measured incidence of breast cancer in the Netherlands has been increasing over the past decades and is currently stagnating at around 15800 new cases in 2021 and 2022 (3). The Netherlands has a national screening program in which women between 50 and 74 are invited for a mammography every two years (4).

Primary treatment of early stage breast cancer is surgery. Depending on tumor characteristics adjuvant therapy(-ies), such as chemotherapy, can be applied. The goal of chemotherapy is to prevent and/-or treat (lymph node) metastasis, to prevent recurrence and therefore improve overall survival (5). Neoadjuvant chemotherapy (NAC) can be part of a breast cancer treatment plan and is defined as conducting chemotherapy before surgery. There two main advantages compared to adjuvant chemotherapy that account for the wide use of NAC (6). Firstly, NAC often results in shrinkage of tumors, which leads to less invasive surgeries and more breast conserving surgeries. Secondly, it is possible to monitor the in vivo sensitivity of the tumor to chemotherapy, giving more clarity on the prognosis of a patient and is therefore an indicator for personalized medicine (6). This information is for example useful for patients with triple negative breast cancer or HER2 positive breast cancer. For these patients it is possible to have NAC as primary treatment and in case there is no complete pathological response to treat them additionally with adjuvant chemotherapy (7) (8). The indication for (neo)-adjuvant chemotherapy is based on; the clinical TNM classification, grade, and the HER2, PR and ER receptor status of the tumor (9). In 2020, 3058 patients received neoadjuvant chemotherapy as primary treatment for newly diagnosed breast cancer, which amounts to 26.1% of the newly diagnosed breast cancer patients; other neoadjuvant (combination) therapies have been excluded in these numbers (10).

In the Netherlands there are several institutions and foundations that regulate and control the quality of healthcare. The use of NAC is regarded as good quality of care for daily practice by the "*foundation for interdisciplinary knowledge-sharing and development of oncological care*" (SONCOS) (11). This foundation releases a yearly report composed by medical professional associations with conditions for daily practice (12). In the year 2014 the condition "there is a clinical pathway for neoadjuvant chemotherapy", for breast cancer care was added (11).

NABON Breast cancer audit (NBCA), one of the focus groups of the "National Breast Cancer Working Group Netherlands" (NABON), defines a set of quality indicator that all breast cancer hospitals are obligated to deliver. For this hospitals send in data either gathered by the Netherlands Cancer Registry (NCR), which is hosted by the Netherlands Comprehensive Cancer Organization (IKNL), or register the data themselves. The audit results are published for transparency about the quality of care (8). One of the indicators for 2023 is the "median lead time in days between date of the biopsy on which the diagnosis invasive breast cancer was given and start of primary treatment", this lead time is also called time to treatment (TTT) (13). Sub indicator 7b is similar but specifically contains the lead time for patients in the NAC trajectory (14). It is stated as rationale that a short lead time is associated with less stress and tension for the patients and a possible better oncological outcome. A longer lead time might induce a higher chance of recurrence (15).

Another institution that supervises the quality, safety and accessibility of healthcare is the Dutch Health Inspectorate (IGJ) (16). Annually the IGJ creates a set of improvement goals and quality indicators for medical specialist care (17). According to the standards of 2019 the maximum lead time between the biopsy on which the pathological diagnosis was performed and start of treatment is 5 weeks (18). Currently, this quality indicator is inactive and not demanded by the IGJ (17).

Before a patient receives NAC there are sometimes multiple consultations and additional imaging tests needed. The clinical pathway of breast cancer patients working up to NAC is complex and has a tight schedule (19). Additional examinations may include: MRI (with additional (multiple) biopsy(-ies)), PET-CT, CT-thorax/abdomen, skeletal scintigraphy and DNA testing. These examinations can be needed for a more accurate diagnosis and/or as a reference image(s) for monitoring of the disease (20). Before start of NAC, a patient might need consultations with the following specialists: a clinical geneticist in case of suspicion of hereditary predisposition, a gynecologist in case of a desire to have children, a medical oncologist and nurse specialist for the chemotherapeutic treatment plan, a plastic surgeon for breast reconstruction and a radiation oncologist for radiotherapy. The appointments and additional examinations make the demanded 5 weeks challenging (19).

Alongside the tight diagnostic schedule, the diagnosis breast cancer has large impact on patients. It can lead to many emotional reactions in women, such as, despair, chaos, anxiety, uncertainty, and hopelessness (21)(22). According to La Court et al., the psychological distress experienced by newly diagnosed breast cancer patients peaks before the start of NAC and decreases after the start of treatment (23).

Considering the limited lead time accepted by various institutions, the tight schedule with examinations and consultations before start of NAC, and the psychological load of diagnosis and treatment decisions for patients, it is important and relevant to see what the experiences of patients in the NAC trajectory are. Therefore, the study aims to describe the experiences and wishes of women in the neoadjuvant trajectory. Additionally, the clinical pathway of each individual patient will be mapped out. The combination of the experiences and clinical pathways will lead to the identification of optimization possibilities for the NAC trajectory.

Methods

The “workup to Chemotherapy in neo-Adjuvant Breast cancer treatment Researched by Interview Outcomes” (CABRIO) study is a single-center descriptive study composed of two distinct components. The first component is to describe the experiences of women in their workup to NAC. For this component a questionnaire containing 13 questions using a Likert scale of agreement and an additional remarks field for each question was developed by the breast cancer treatment team of Dutch hospital Medisch Spectrum Twente (MST) (see Appendix 2A). The questions concern the completeness of information given by the treatment team about diagnosis, treatment, and risks. Other questions aim at the process of shared decision-making, the satisfaction with the time between examinations and results, the time between examinations and start of NAC and the time to choose a treatment. Additionally, demographic information was gathered including the highest level of education completed, living conditions and employment status. Supplementary patient characteristics such as age and tumor characteristics were obtained by reviewing records.

In the second component the clinical pathway of each individual patient was mapped out. This was done using retrospective clinical record review, collecting events for each individual patient such as; consultation dates, examination dates, dates of test results and tumor characteristics (see data dictionary, Appendix 3). The events were stored in an electronic data capture system (CastorEDC), where they were combined with questionnaire responses. MST uses Chipsoft HiX 6.3 as an electronic health record (EHR). The researcher and author of the article performed the data collection and digitalization of the questionnaire. A graphical overview of the methods is found in Figure 1.

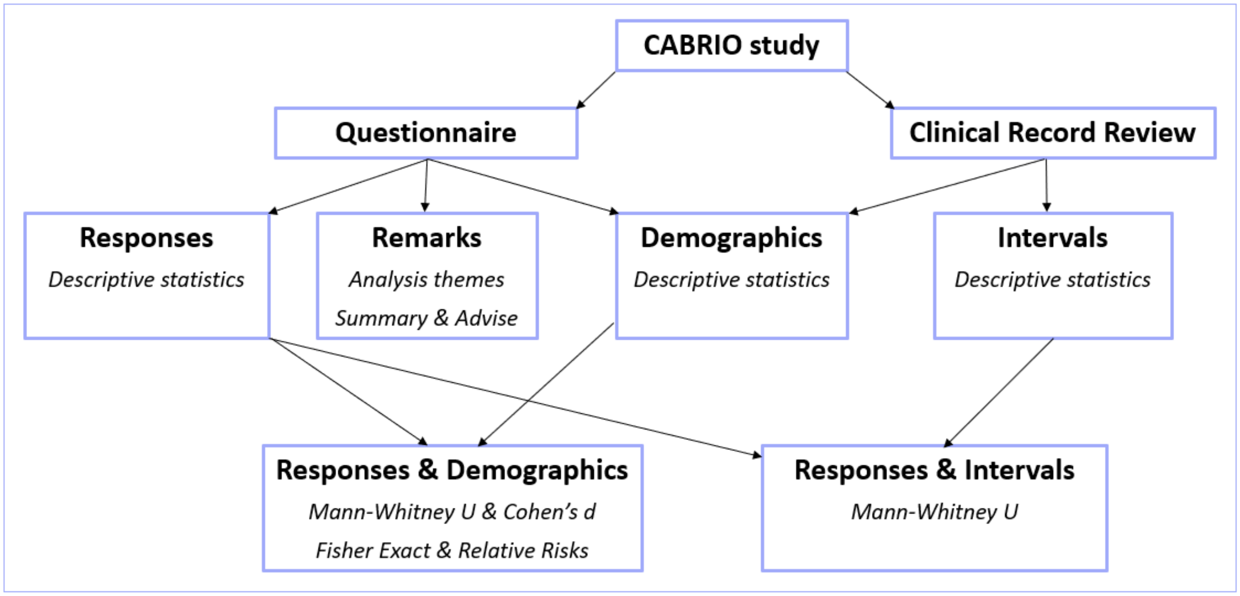


Figure 1: Overview of data processing of the CABRIO study.

Inclusion an exclusion criteria

The study started in January 2023 and will continue till January 2024, therefore this article contains the preliminary results of the CABRIO study. The study population consists of women between 18 and 70 years old that were diagnosed with breast cancer and were eligible for NAC. Men with breast cancer were excluded from the study. A lack of proficiency of the Dutch language excluded patients from participating in the CABRIO study.

Participant enrollment protocol

Patients were recruited by the nurse specialist during a visit at the outpatient clinic. They were informed about the CABRIO study and were given the patient information document, informed consent form and the questionnaire. If patients wanted to participate they brought the filled in documents to their first NAC treatment, where the documents were collected by the nurse specialist.

Statistical analysis

The CABRIO study is a single-center study and is therefore bound to a limited sample size of patients that meet the inclusion criteria. The aim is to include 75 patients before January 2024.

After confirming skewness of responses with visual assessment, the data from the questionnaire was summarized with; the median, first and third quartile. The results per question were visualized with bar plots. To assess the potential influence of the demographic variables on the questionnaire responses various statistical tests were performed as appropriate. The Likert scale was recoded to fit the statistical tests, responses 1,2,3 (completely disagree, disagree and neutral/no opinion) were seen as dissatisfied and responses 4,5 (agree and completely agree) were seen as satisfied. To compare satisfied with dissatisfied patients, the Mann-Whitney-U test was used for the variable age and the Fisher Exact test for the following variables: paid work/other work, high/low education, partner/no partner, living with/without children, grade of cancer and HER2 status (positive/negative). In addition to the Fisher exact test the relative risks for these variables were calculated.

For the second research question, intervals were measured between various collected events. For each interval the mean, standard deviation, median, first quartile and third quartile were determined, as appropriate. After determining the intervals, the questionnaire was compared to the intervals. For the influence of the duration of intervals on the satisfaction (satisfied/dissatisfied), Mann-Whitney-U tests were conducted for Q6-Q11. To visualize the pathway of a patient using intervals, the 12 most common examinations and consultations were represented with pictograms and placed on a timeline for each individual patient. Additionally, the pathways of all patients were merged into one pathway based on the medians of the intervals.

Lastly the remarks for each question were analyzed by summarizing and identifying recurring themes. Advise for the treatment team was derived from these remarks.

The data analysis and statistical computations were performed using the programming language R version 4.2.3 (for an example see Appendix 5).

Ethical consideration The study is not subject to medical research with Human Subjects Act and thus not bound by the Dutch law “Wet Medisch-wetenschappelijk Onderzoek” (WMO). The CABRIO study (K22-37) was submitted to the research bureau of MST and approved by the board of directors. The Dutch laws “Algemene Verodening Gegevensbescherming” (AVG), and “Wet Geneeskundige Behandelovereenkomst” (WGBO) and good clinical practice are practiced in the CABRIO study.

Results

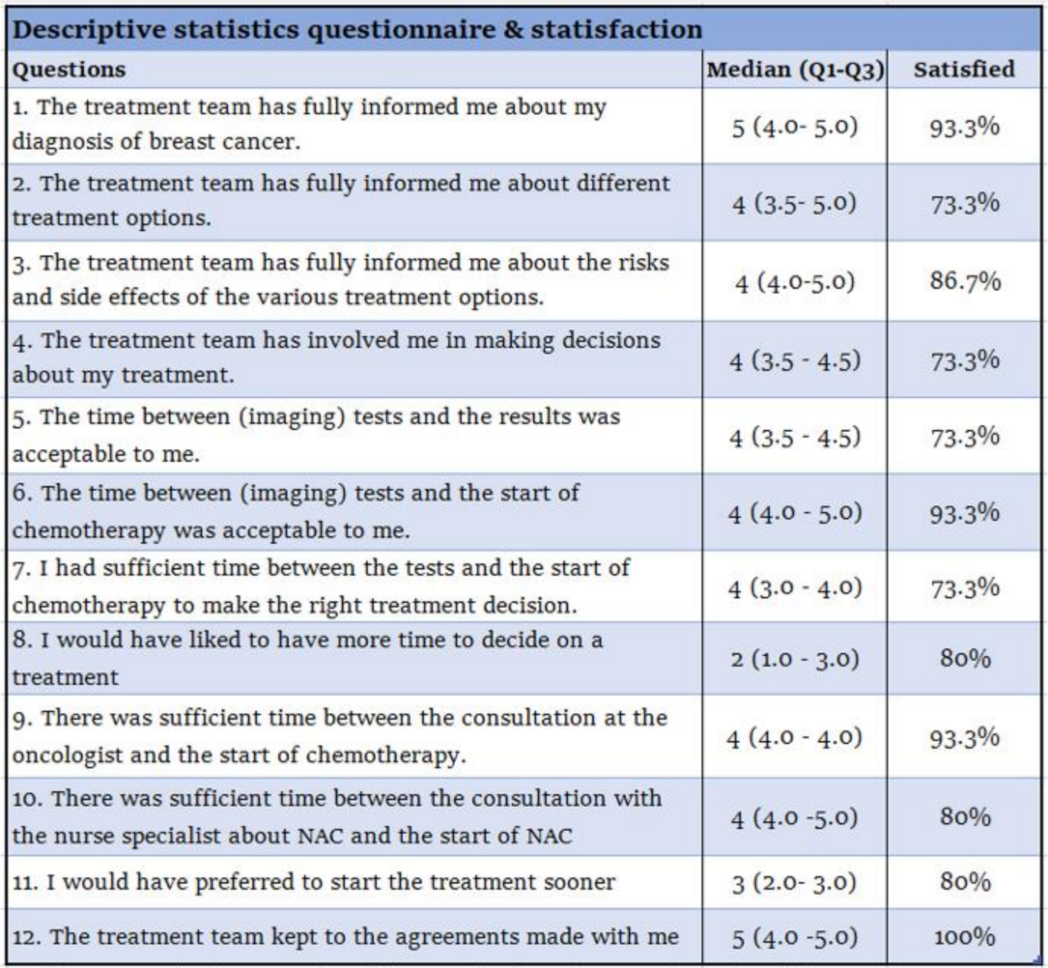
A total of 17 women were invited to participate and 15 women participated (88%). The age, highest level of education, living conditions, employment status and tumor characteristics of the participants can be found in Table 1.

Demographic variables and tumor characteristics				
Age	40% ≤ 40 years	20% 41-50 years	27% 51-60 years	13% >60 years
Employment status	80% paid work	13% retired	7% unable to work	
Living condition	47% with partner & kids	33% with partner	20% living alone	
Highest level of education	33% LBO & MVO	20% MBO	7% HAVO	40% HBO/ university
ER status	40% negative	60% positive		
PR status	33% negative	67% positive		
HER2 status	53% negative	47% positive		
Tumor grade	33% grade 2	67% grade 3		
Tumor type	13% lobulair	80% ductal	7% other	
Location of tumor	73% right side	20% left side	7% both sides	
Tumor stage	6.67% stage I	66,7% stage II	20% stage III	6,67% stage IV

Table 1: Demographic variables and tumor characteristics retrieved from questionnaires and records. N=15. Translations to English: LBO (low vocational education), MVO (secondary education), MBO (secondary vocational education), HAVO (senior general secondary education), HBO (university of applied sciences).

Questionnaire Responses:
The overall results of the CABRIO questionnaire show that for each question at least 2/3 of the women were satisfied with the received care. For all the 12 questions, the median value was a “agree” or “completely agree”, with two exceptions for question 8 (preferring more time for decisions) there the median was “disagree” and for question 11 (starting treatment sooner) the median was “neutral/no opinion” (Table 2 and Appendix Figures S1A-S1L). For Q8 and Q11 disagreeing means being satisfied with the status quo.

Out of the 15 patients, 4 individuals were not satisfied with the completeness of information they received concerning their treatment options (Q2) and 4 out of 15 patients were not satisfied with their involvement in the treatment decision (Q4) (Appendix Figures S1B & S1D). In the remarks field patients mainly stated that there was only one option and it did not feel like they had a choice. Two-thirds of the patients agreed that there was sufficient time to make the right treatment decisions, leaving 5 patients dissatisfied (Appendix Figure S1G). One-fifth of the patients preferred more time to decide on a treatment (Appendix Figure S1H). The responses to question 11 were varied; 3 patients agreed to preferring sooner treatment, 7 of the patients were neutral or had no opinion about starting treatment sooner and 5 patients disagreed to preferring sooner treatment (Appendix Figure S1K).



Descriptive statistics questionnaire & statisfaction		
Questions	**Median (Q1-Q3)**	**Satisfied**
1. The treatment team has fully informed me about my diagnosis of breast cancer.	5 (4.0- 5.0)	93.3%
2. The treatment team has fully informed me about different treatment options.	4 (3.5- 5.0)	73.3%
3. The treatment team has fully informed me about the risks and side effects of the various treatment options.	4 (4.0-5.0)	86.7%
4. The treatment team has involved me in making decisions about my treatment.	4 (3.5 - 4.5)	73.3%
5. The time between (imaging) tests and the results was acceptable to me.	4 (3.5 - 4.5)	73.3%
6. The time between (imaging) tests and the start of chemotherapy was acceptable to me.	4 (4.0 - 5.0)	93.3%
7. I had sufficient time between the tests and the start of chemotherapy to make the right treatment decision.	4 (3.0 - 4.0)	73.3%
8. I would have liked to have more time to decide on a treatment	2 (1.0 - 3.0)	80%
9. There was sufficient time between the consultation at the oncologist and the start of chemotherapy.	4 (4.0 - 4.0)	93.3%
10. There was sufficient time between the consultation with the nurse specialist about NAC and the start of NAC	4 (4.0 -5.0)	80%
11. I would have preferred to start the treatment sooner	3 (2.0- 3.0)	80%
12. The treatment team kept to the agreements made with me	5 (4.0 -5.0)	100%

Table 2: Descriptive statistics of the results from the questionnaire of the CABRIO study. Columns contain the median with first quartile and third quartile and the percentage of satisfied participants. For questions 8 & 11 satisfied means "disagree" and thus satisfied with the current situation. NAC = Neoadjuvant chemotherapy. N=15

The influence of demographic variables on the satisfaction of the participants

None of the demographic variables had a statistically significant influence on the responses to each question (Appendix Tables S1-S7). However, for age the Cohen's d for Q2 "I was fully informed about treatment options" is 0.62 (dissatisfied mean age: 41.5, satisfied mean age: 49.7) and for Q8 "I would have preferred more time to decide" the Cohen's d is 0.67 (dissatisfied mean age 54.7 and satisfied mean age: 42.2) which might indicate that age is of influence for the responses to Q2 and Q8 (Appendix Table S1).

Highly educated patients had a 3-fold higher relative risk of preferring more time for treatment decisions compared to less educated patients (Appendix Table S2). Less educated patients were 2.63 times more likely to report having sufficient time for the right treatment decision compared to highly educated patients. They were also approximately 2 times more likely to be satisfied with their involvement in decision-making and the waiting time for test results compared to highly educated patients. Additionally, all 3 patients who preferred to start treatment sooner were less educated (Appendix Table S2). Patients with paid work were 2.25 times as likely to be satisfied with the time they receive for the treatment decisions than patients that are retired or unable to work (Appendix Table S3). Patients without paid work were 8.33 times more likely to prefer more time for their treatment decision compared to patients with paid work (Appendix Table S3). Patients living with a partner were 2.25 times as likely to be satisfied with the time they receive for the treatment decisions than patients living alone (Appendix Table S4). Also, patients that live without a partner were 8.33 times more likely to prefer more time for their treatment decisions than patients living with a partner (Appendix Table S4). In Appendix Table S5, S6 and S7 the influence of living with children, HER2 status and tumor grade on satisfaction are depicted.

Descriptive Analysis of Clinical Path Intervals

The descriptive data from the 30 intervals of the clinical path can be found in Appendix Table S8. As can be seen in Figure 2, the median time to treatment was 31 days, 3 out of 15 patients started treatment later than 5 weeks. The median for the referral from the general practitioner (GP) to the first consultation at the Breast Cancer Centre was also 4 days. 25% of the patients had biopsy results within 3 days, 50% within 4 days and 25% in 5 days or longer. The median time between the initial consultation and the final treatment plan was 21 days. The interval between the biopsy result and the MRI had a median of 7 days. There is a median of 11 days between the referral to the oncologist and the visit.

To visualize the intervals (Appendix Table S8) the 12 most common consultations and examinations have been mapped out on timeline for each individual patient. As can be seen in Appendix Figure S2A-C, there are many differences between the pathway of individual patients. The number of examinations and consultations differs, the interval between them and the order of events can vary. The fifteen pathways were merged in Figure 2 using the date of biopsy as a reference for each event (Appendix Table S9).

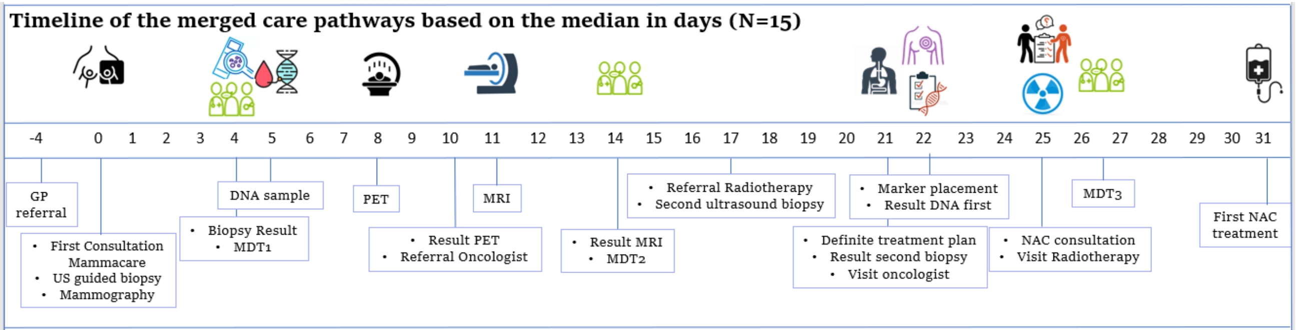
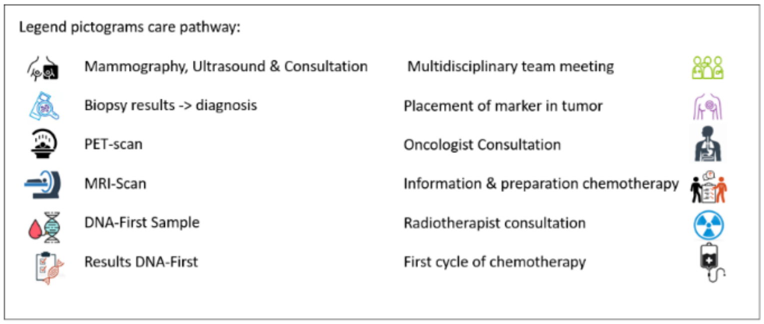


Figure 2: individual pathways of all 15 participants merged into one pathway, above the timeline the same pictograms can be found as in figure 19abc, for the legend see figure 18. Below the timeline pictograms are in text plus extra events that were not in the legend. The merging was done based on table 10. Definitions: GP general physician, US ultrasound, MDT multidisciplinary team meeting, NAC neoadjuvant chemotherapy.



Influence of interval duration on satisfaction

The responses to the questionnaire were combined with the intervals for questions 6-11 (Appendix Figures S3-S8). None of the interval durations had a significant impact on the satisfaction of the patients, p-values can be found in Appendix Table S10. Appendix Figure S3 shows that the only patient that was not satisfied with the time between examinations and test and the chemotherapy, had an interval of 19 days, while the satisfied group had a median of 8 days. Patients that wanted to start treatment sooner had an interval (visit oncologist to start of NAC treatment) with a median of 13 days and patients that were satisfied had a median of 10 days (Appendix Figure S4).

Patient experiences: insights from qualitative remarks

Written remarks were optional in the questionnaire, resulting in a total of 47 written remarks, with a maximum of 7 remarks per question. A recurring theme in the remarks from questions 1-4 was: trusting the professionals to have informed them completely about the diagnosis, risks and treatment options. Another theme is that many participants feel like they do not have a choice and that there are no other options available for them: "*I have heard one option, I don't know if there are other options. I trust that this is the best one*" (response to question 2).

As seen in Appendix Figure S1E not every woman was content with the time between imaging tests and the results. In the remarks there are 3 reported reasons: rescheduling of appointment due to late biopsy results, a failed PET-scan and a late cancellation of appointment. For question 7 & 8 about the treatment decision: the recurring theme is that there is only one option for treatment and therefore not much time needed to decide: "*I did not feel like there was anything left to decide*" (response to question 7).

For question 11 "I would have preferred to start the treatment sooner" there were 6 remarks. Three women wrote down that they would have wanted to start sooner, but that they understand this was not possible due to the necessary examinations and consultations (see Appendix 4). One women commented that the work-up to NAC and the diagnostic period was not very structured.

Lastly, the "other remarks" contain many compliments and appreciation for the empathy and care provided by the breast cancer treatment team of MST. "*In my opinion all the departments are working together well, this gives me confidence in my treatment*". Three patients have responded with ways to improve the care: according to one of them an efficient diagnostic plan would be beneficial. Another patient verifies that some consultations could have been planned earlier on. Additionally, one patient reported feeling unprepared to undergo examinations such as the MRI and would have liked to be informed more about the procedure. In Appendix 4 all original remarks and summarized remarks can be found.

Discussion & Conclusion

Combined conclusions of results

The women in the NAC trajectory are mostly satisfied with care they receive. The experiences and preferences vary between the participants but are not significantly related to demographic variables or duration of intervals. Resulting from the merged clinical pathway some intervals with a long duration are identified, this gives rise to optimization possibilities for the NAC trajectory. Furthermore, patients have ideas about optimizations possibilities as well. Whether these possibilities are desirable for all patients is yet to be determined.

To start off, 4 out of 15 patients were not satisfied with the completeness of information about their treatment options. When combining this outcome with the remarks it seems as though this is related to the patients thinking there only is one option and their complete trust in healthcare professionals. Likewise, A European study found that patients reported "dissatisfaction with their involvement in treatment and health care decisions and the amount of information received" (24). Another study confirms that the needs and opinions of patients about diagnosis and treatment options differ per individual (25). In Australia and New Zealand oncologists tended to be dominant in the decisions for NAC instead of letting the patients make the decision (26).

Five patients did not agree that there was sufficient time for a treatment decision and 3 patients preferred more time. Similarly, a study reports that women felt that the decision for NAC had to be made quickly and that they felt rushed in their decision. Because of this rush they reported that they were not able to comprehend and weigh the information in order to make an informed treatment decision (27). The time for a treatment decision is indirectly determined by organizations as, SONCOS, NBCA and IGJ as they emphasize the importance of a short lead time for the start of NAC. However, evidence indicates that it takes a time to treatment of 61 days before the interval has a negative impact on survival (28). A different study revealed that extending time to NAC with a few weeks will not likely have impact on survival. This study only included HER2 positive and or triple negative breast cancer patients (N=12806) (29).

The diagnostic period of the CABRIO study was 8 days, a median of 4 days referral from GP and a median of 4 days waiting on biopsy results. According to SONCOS maximum waiting time between referral of the GP should be 1 week (30). The maximum waiting time between the first consultation and diagnosis should be 3 weeks (30). A diagnostic interval for breast cancer in Canada was measured with a median of 41 days (31). An America study using information from 53758 patients found medians of 23.3 days for mammogram to biopsy, while in MST these often occur on the same day.

Results from NBCA indicator "median lead time in days between date of the biopsy on which diagnosis invasive breast cancer was given and NAC" show that median lead time was 27 days (15-34) in 2019 (N=3058)(10)(32). The interval duration at MST is higher with a median of 31 days (N=15). A explanation can be the difference in sample size or due to organizational aspects of the trajectory.

The merged clinical pathway is a visual representation of the NAC trajectory specific to MST. The results were discussed with two nurse specialists and the identified optimizable intervals are: the interval of the referral to the oncologist and the consultation at the oncologist (median of 11 days) and the interval from the result of the biopsy to the MRI (7 days). Another crucial point in improving patient flow in the NAC trajectory is to have dedicated planners that oversee the consequences of the way they schedule.

Some patients made suggestions for optimization possibilities. One of the ideas is to make a checklist for patients concerning the complete trajectory so patients have an overview. Another suggestion was scheduling appointments in advance as soon as it is known that the appointment is necessary.

Strengths & limitations

The CABRIO study uses a questionnaire with quantitative and qualitative characteristics and clinical record review. This results in a comprehensive understanding of the experiences of patients as well as understanding of the operational aspects of medical practice. This dual approach of combining patient satisfaction and process evaluation is rare in the medical field (33). An advantage of this combination is that through the analysis of the individual and combined clinical pathways it becomes clear whether the satisfaction of patients is objective or subjective. Furthermore, the events result in objective evidence of intervals with a long duration, this evidence can be useful in improvement projects.

Another strong point of the CABRIO study is that the researcher observed almost all examinations and consultations of the neoadjuvant trajectory firsthand. Additionally, the researcher interacted with patients and spoke with more than 20 breast cancer care professionals over the course of five weeks. This allowed the researcher to understand the context, processes and dynamics, adding to the credibility and validity of the research findings and is therefore recommended for all future researchers of the CABRIO study.

As expected, the preliminary results of the CABRIO study were not significant. The sample size of 15 patients was not enough for significant results. However, the response rate of 88% is promising for the continuation of the study. Furthermore, the group of participants is diverse including patients with underlying diseases, patients that started their treatment in other hospitals and patients that went to another clinic for fertility treatment. With a small study size these individuals can distort the results of the study. Additionally, some of the demographics are not independent, having children living at home is age-related, as is the employment status and the age of a person. The interrelationships between demographic variables can potentially lead to confounding. When including more patients the results will stabilize and are expected to become significant.

Questionnaires have a few downsides. Firstly, although there was an option for writing remarks down, the maximum number of remarks was 33% for a question. This poses the problem that it is not known why a participant agrees or disagrees and to what extent they agree. If a patient agrees with “I would have preferred to start treatment sooner” it is not known why or how many days sooner is the patient's preference. Another point is that the interpretation of the questions might be different than the intent (34). For example, question 6 “the time between tests and the start of chemo was acceptable” it is not specified which tests and if it is the first or last test of all tests.

Due to the sole involvement of one researcher, it is important to note that there is a possibility of mistakes and inadvertent errors that may have occurred during the reviewing of records, digitalization of questionnaires and the programming part of the data analysis. To minimize inconsistencies for the following researcher protocols of data collection, including double checks, have been created and in cases of doubt a second opinion is available. In addition to this the programming scripts have been made sustainable for the future and the new data can therefore be analyzed using the same R scripts.

Conclusion

The CABRIO study gives insight into the experiences and wishes of women in the neoadjuvant trajectory. The women are mostly satisfied with the care they receive, although improvements for information about treatment options and more involvement in treatment decisions might be desirable depending on the patient. Because the needs of patients vary for the time needed for a treatment decision and the opinion differs on starting treatment sooner, it is yet to be determined if accelerating the clinical pathway is desirable. Whether the quality indicator of a limited lead time constructed by the NBCA and IGJ contribute to good care from the patients perspective is a subject of debate. Considering the difference in median lead time till NAC in the Netherlands 27 days, and 31 days in MST the NAC trajectory can be optimized. Intervals that can possibly contribute to optimization are; the time from biopsy result to MRI and the time between referral to the oncologist and consultation at the oncologist. However, since the results are preliminary, it is advised to draw definite conclusions after including the final number of patients. Further research is needed to find the optimal balance between the patient experiences and satisfaction, the regulations for good quality breast cancer care and the possibilities and limits of optimizing the patient pathway.

Further Research

The CABRIO study continues to January 2024, for the next researcher the following additions can be made. More events from the clinical records can be added to the data base (see Appendix 3). In the current data set there is a column with additional examination containing: 3 electrocardiograms (ECG’s), 3 referrals to the gynecologist, 3 cardiologic MRI’s and 4 ejection fraction examinations. The intervals for the events are not registered and this is necessary for the identification of optimization possibilities. Also, the dates of referral (for MRI and PET scans) might be interesting to add to the CABRIO study and can also be collected for the current participants. Furthermore, to finalize the pathway of each patient it is possible to include all consultations in the database (33). To visualize patient pathways the use of a SANKEY plot is recommended (35).

As stated in the discussion, it is often unknown what is the underlying reason for an answer of the questionnaire is. If the reasoning of patients is understood better the feedback can be used to improve care. A few options are interviewing (some participants), calling current participants for elaboration of their answers, filling in the questionnaire together with new participants and asking follow-up questions directly. Further, in the digital version of the questionnaire it is possible to make fields obligatory, so the remarks will not remain optional.

Since the questionnaire of the CABRIO study is digitalized and officially not WMO bound, it is easy to spread it and collect answers from patients. Therefore, it might be interesting to extent the research to the Santeon Hospital group (a group of 7 Dutch hospitals of which MST is a part), this leads to a larger sample size and give more insight into the experiences of women who undergo the neoadjuvant trajectory (36). It is also possible to see variation in how women experience the care in different hospitals. This creates an opportunity for benchmarking and the identification of best practices (37). Ultimately achieving the goal of the Santeon group: optimal collaboration and optimal patient satisfaction.

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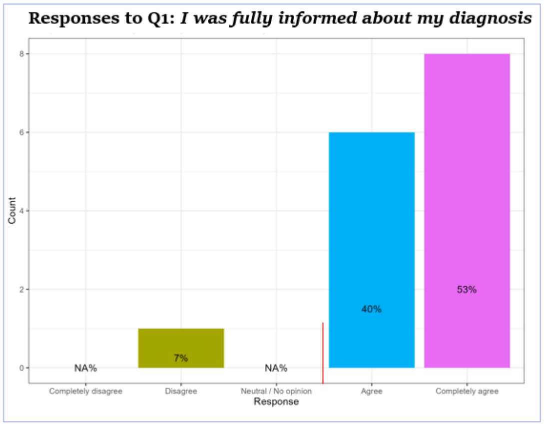
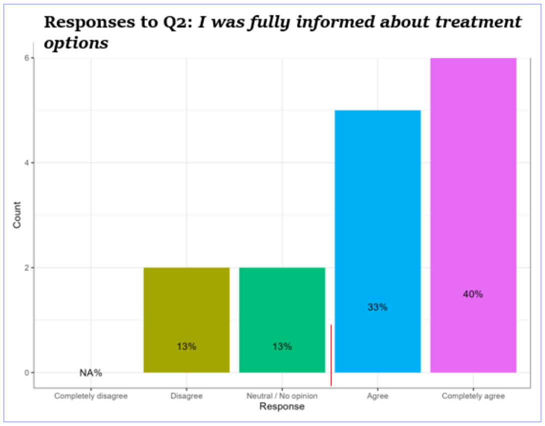
Appendices

Appendix 1: Tables and Figures



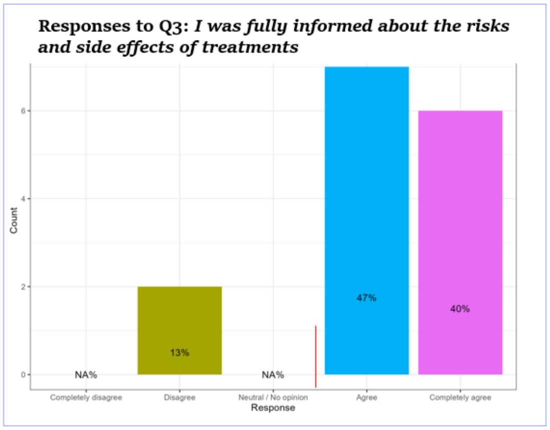
Responses to Q1: ***I was fully informed about my diagnosis***

Figure S1A: Responses to question 3 of the CABRIO study questionnaire. The red line represents the recoding left side of the line dissatisfied, right side of the red line satisfied



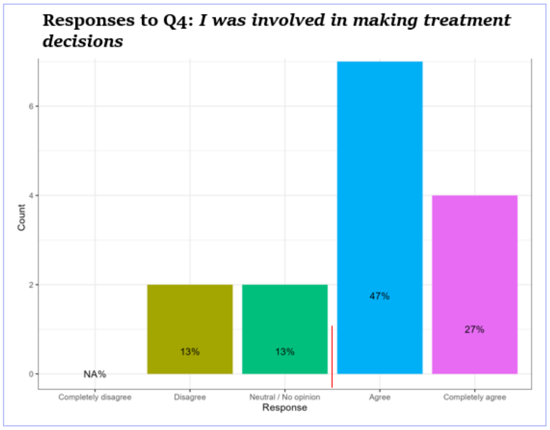
Responses to Q2: ***I was fully informed about treatment options***

Figure S1B: Responses to question 2 of the CABRIO study questionnaire. The red line represents the recoding left side of the line dissatisfied, right side of the red line satisfied.



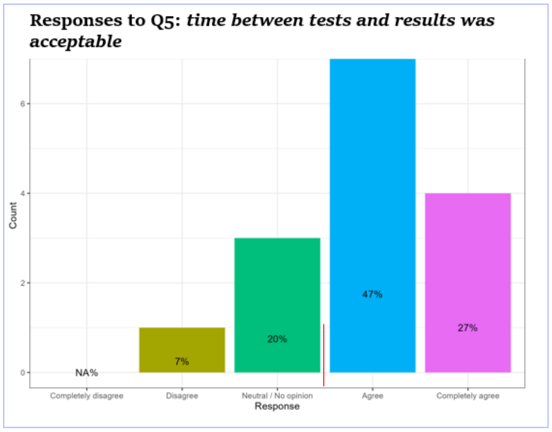
Responses to Q3: ***I was fully informed about the risks and side effects of treatments***

Figure S1C: Responses to question 3 of the CABRIO study questionnaire. The red line represents the recoding left side of the line dissatisfied, right side of the red line satisfied



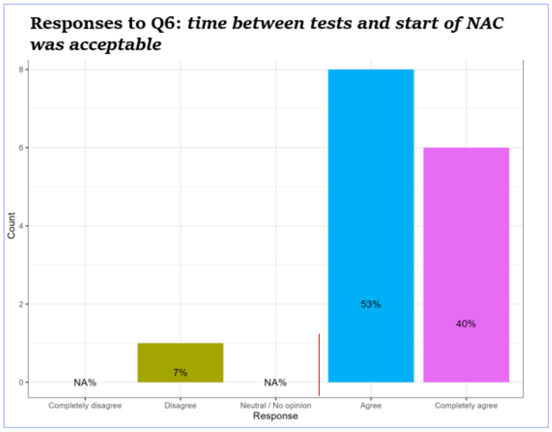
Responses to Q4: ***I was involved in making treatment decisions***

Figure S1D: Responses to question 4 of the CABRIO study questionnaire. The red line represents the recoding left of the line dissatisfied, right of the red line satisfied.



Responses to Q5: ***time between tests and results was acceptable***

Figure S1E: Responses to question 5 of the CABRIO study questionnaire. The red line represents the recoding left side of the line dissatisfied, right side of the red line satisfied



Responses to Q6: ***time between tests and start of NAC was acceptable***

Figure S1F: Responses to question 6 of the CABRIO study questionnaire. The red line represents the recoding left side of the line dissatisfied, right side of the red line satisfied

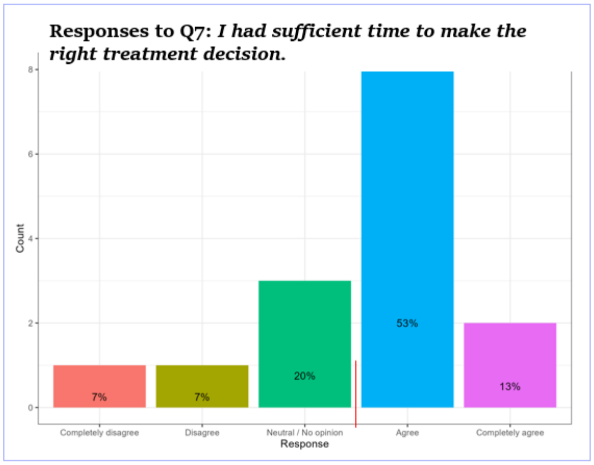

Responses to Q7: ***I had sufficient time to make the right treatment decision.***

Figure S1G: Responses to question 7 of the CABRIO study questionnaire. The red line represents the recoding left side of the line dissatisfied, right side of the red line satisfied.

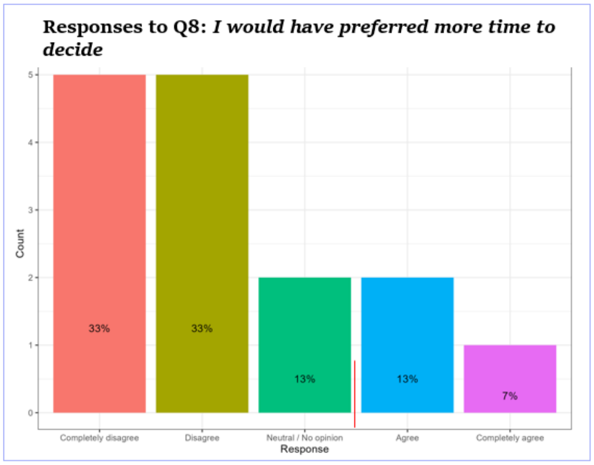

Responses to Q8: ***I would have preferred more time to decide***

Figure S1H: Responses to question 8 of the CABRIO study questionnaire. The red line represents the recoding left side of the line dissatisfied, right side of the red line satisfied.

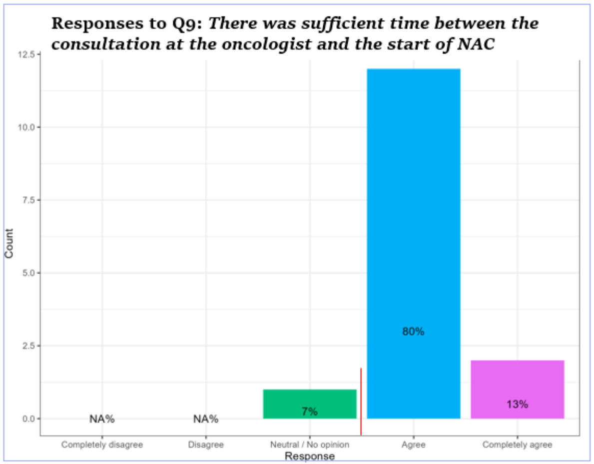

Responses to Q9: ***There was sufficient time between the consultation at the oncologist and the start of NAC***

Figure S1I: Responses to question 9 of the CABRIO study questionnaire. The red line represents the recoding left side of the line dissatisfied, right side of the red line satisfied

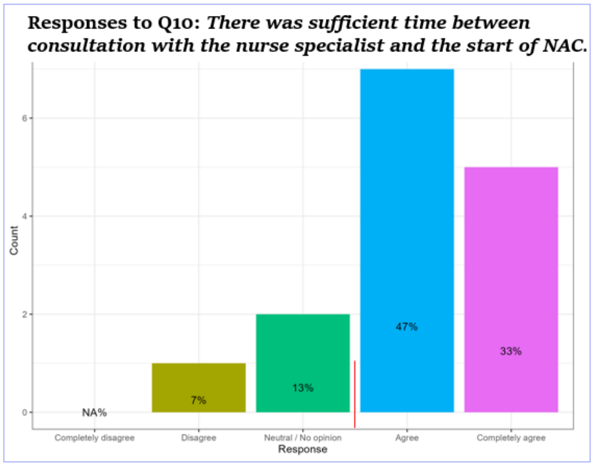

Responses to Q10: ***There was sufficient time between consultation with the nurse specialist and the start of NAC.***

Figure S1J: Responses to question 10 of the CABRIO study questionnaire. The red line represents the recoding left side of the line dissatisfied, right side of the red line satisfied

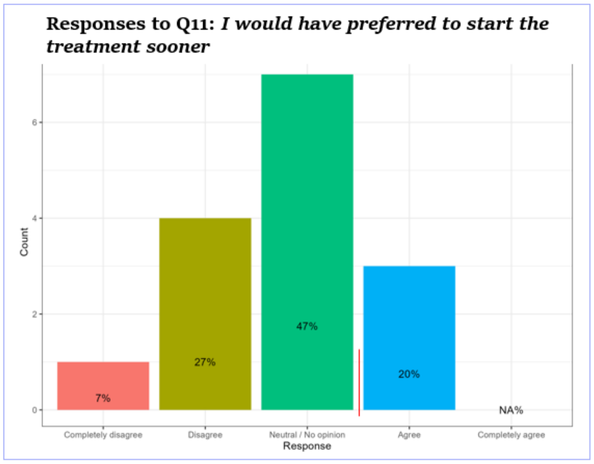

Responses to Q11: ***I would have preferred to start the treatment sooner***

Figure S1k: Responses to question 11 of the CABRIO study questionnaire. The red line represents the recoding left side of the line dissatisfied, right side of the red line satisfied.

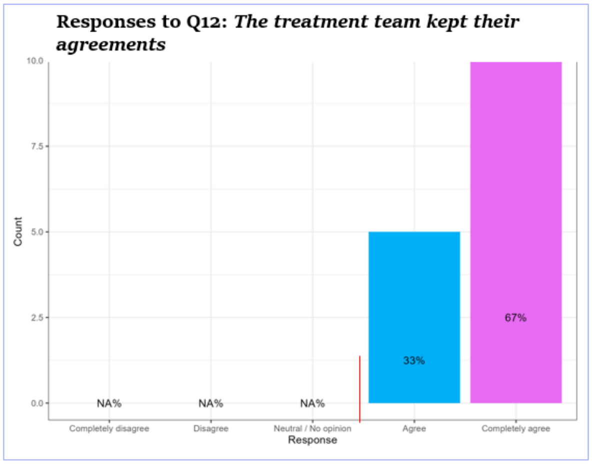
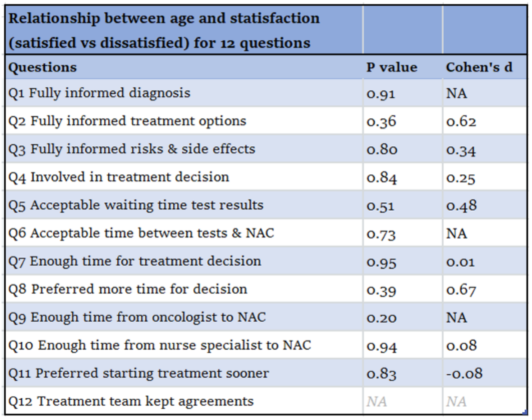
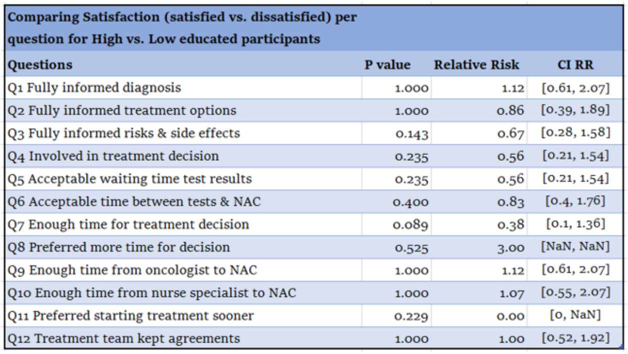

Responses to Q12: ***The treatment team kept their agreements***

Figure S1L: Responses to question 12 of the CABRIO study questionnaire. The red line represents the recoding left side of the line dissatisfied, right side of the red line satisfied



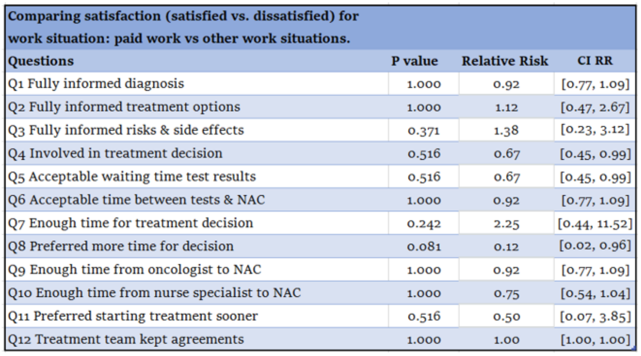
Relationship between age and statisfaction (satisfied vs dissatisfied) for 12 questions		
Questions	**P value**	**Cohen's d**
Q1 Fully informed diagnosis	0.91	NA
Q2 Fully informed treatment options	0.36	0.62
Q3 Fully informed risks & side effects	0.80	0.34
Q4 Involved in treatment decision	0.84	0.25
Q5 Acceptable waiting time test results	0.51	0.48
Q6 Acceptable time between tests & NAC	0.73	NA
Q7 Enough time for treatment decision	0.95	0.01
Q8 Preferred more time for decision	0.39	0.67
Q9 Enough time from oncologist to NAC	0.20	NA
Q10 Enough time from nurse specialist to NAC	0.94	0.08
Q11 Preferred starting treatment sooner	0.83	-0.08
Q12 Treatment team kept agreements	NA	NA

Table S1: Relationship between age and satisfaction concerning 12 questions. Negative Cohen's d: the mean age of the dissatisfied group is lower than the mean age of the satisfied group. NA not available Cohen's d: only one or none of the participants are dissatisfied (93,3% satisfaction or higher), not enough data to calculate Cohen's d . Definitions: NAC, Neoadjuvant chemotherapy. N=15



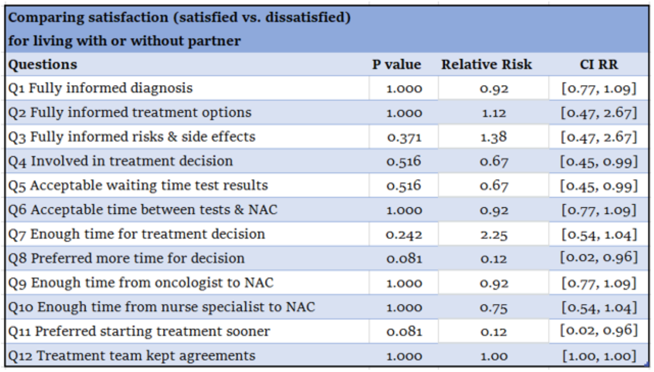
Comparing Satisfaction (satisfied vs. dissatisfied) per question for High vs. Low educated participants			
Questions	**P value**	**Relative Risk**	**CI RR**
Q1 Fully informed diagnosis	1.000	1.12	[0.61, 2.07]
Q2 Fully informed treatment options	1.000	0.86	[0.39, 1.89]
Q3 Fully informed risks & side effects	0.143	0.67	[0.28, 1.58]
Q4 Involved in treatment decision	0.235	0.56	[0.21, 1.54]
Q5 Acceptable waiting time test results	0.235	0.56	[0.21, 1.54]
Q6 Acceptable time between tests & NAC	0.400	0.83	[0.4, 1.76]
Q7 Enough time for treatment decision	0.089	0.38	[0.1, 1.36]
Q8 Preferred more time for decision	0.525	3.00	[NaN, NaN]
Q9 Enough time from oncologist to NAC	1.000	1.12	[0.61, 2.07]
Q10 Enough time from nurse specialist to NAC	1.000	1.07	[0.55, 2.07]
Q11 Preferred starting treatment sooner	0.229	0.00	[0, NaN]
Q12 Treatment team kept agreements	1.000	1.00	[0.52, 1.92]

Table S2: Comparing satisfaction on highest level of education completed. High education is HBO or university other is low educated. Relative risk >1 means high educated patients are more satisfied. P values of 1, relative risks of 0, upper or lower bound confidence interval NaN: means one of the quadrants of the contingency table is empty. Definitions: NAC Neoadjuvant chemotherapy, CI confidence interval, RR relative Risk. N=15



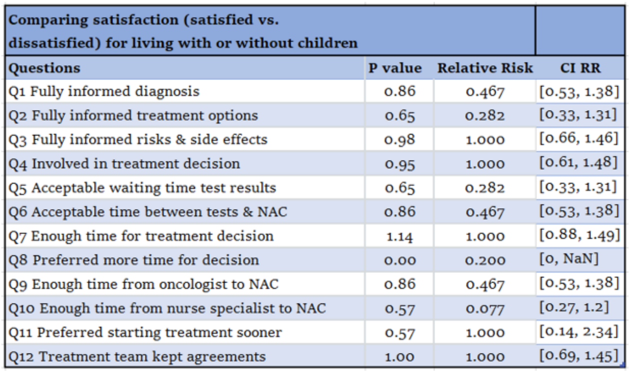
Comparing satisfaction (satisfied vs. dissatisfied) for work situation: paid work vs other work situations.			
Questions	**P value**	**Relative Risk**	**CI RR**
Q1 Fully informed diagnosis	1.000	0.92	[0.77, 1.09]
Q2 Fully informed treatment options	1.000	1.12	[0.47, 2.67]
Q3 Fully informed risks & side effects	0.371	1.38	[0.23, 3.12]
Q4 Involved in treatment decision	0.516	0.67	[0.45, 0.99]
Q5 Acceptable waiting time test results	0.516	0.67	[0.45, 0.99]
Q6 Acceptable time between tests & NAC	1.000	0.92	[0.77, 1.09]
Q7 Enough time for treatment decision	0.242	2.25	[0.44, 11.52]
Q8 Preferred more time for decision	0.081	0.12	[0.02, 0.96]
Q9 Enough time from oncologist to NAC	1.000	0.92	[0.77, 1.09]
Q10 Enough time from nurse specialist to NAC	1.000	0.75	[0.54, 1.04]
Q11 Preferred starting treatment sooner	0.516	0.50	[0.07, 3.85]
Q12 Treatment team kept agreements	1.000	1.00	[1.00, 1.00]

Table S3: Comparing satisfaction to work situations of participants paid work vs other (retirement or unable to work). Relative risk > 1 means patients with paid work are more satisfied. P values of 1, relative risks of 0, upper or lower bound confidence interval NaN: means one of the quadrants of the contingency table is empty. Definitions: NAC Neoadjuvant chemotherapy, CI confidence interval, RR relative Risk. N=15



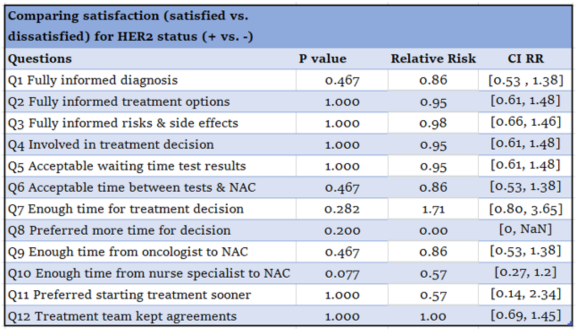
Comparing satisfaction (satisfied vs. dissatisfied) for living with or without partner			
Questions	**P value**	**Relative Risk**	**CI RR**
Q1 Fully informed diagnosis	1.000	0.92	[0.77, 1.09]
Q2 Fully informed treatment options	1.000	1.12	[0.47, 2.67]
Q3 Fully informed risks & side effects	0.371	1.38	[0.47, 2.67]
Q4 Involved in treatment decision	0.516	0.67	[0.45, 0.99]
Q5 Acceptable waiting time test results	0.516	0.67	[0.45, 0.99]
Q6 Acceptable time between tests & NAC	1.000	0.92	[0.77, 1.09]
Q7 Enough time for treatment decision	0.242	2.25	[0.54, 1.04]
Q8 Preferred more time for decision	0.081	0.12	[0.02, 0.96]
Q9 Enough time from oncologist to NAC	1.000	0.92	[0.77, 1.09]
Q10 Enough time from nurse specialist to NAC	1.000	0.75	[0.54, 1.04]
Q11 Preferred starting treatment sooner	0.081	0.12	[0.02, 0.96]
Q12 Treatment team kept agreements	1.000	1.00	[1.00, 1.00]

Table S4: Comparing satisfaction on living with or without a partner. Relative risk >1 means patients living with a partner are more satisfied. P values of 1, relative risks of 0, upper or lower bound confidence interval NaN: means one of the quadrants of the contingency table is empty. Definitions: NAC Neoadjuvant chemotherapy, CI confidence interval, RR relative Risk. N=15



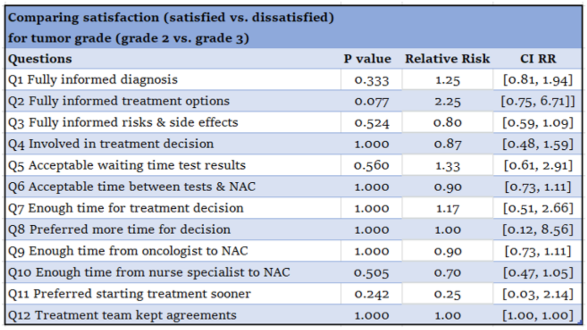
Comparing satisfaction (satisfied vs. dissatisfied) for living with or without children			
Questions	**P value**	**Relative Risk**	**CI RR**
Q1 Fully informed diagnosis	0.86	0.467	[0.53, 1.38]
Q2 Fully informed treatment options	0.65	0.282	[0.33, 1.31]
Q3 Fully informed risks & side effects	0.98	1.000	[0.66, 1.46]
Q4 Involved in treatment decision	0.95	1.000	[0.61, 1.48]
Q5 Acceptable waiting time test results	0.65	0.282	[0.33, 1.31]
Q6 Acceptable time between tests & NAC	0.86	0.467	[0.53, 1.38]
Q7 Enough time for treatment decision	1.14	1.000	[0.88, 1.49]
Q8 Preferred more time for decision	0.00	0.200	[0, NaN]
Q9 Enough time from oncologist to NAC	0.86	0.467	[0.53, 1.38]
Q10 Enough time from nurse specialist to NAC	0.57	0.077	[0.27, 1.2]
Q11 Preferred starting treatment sooner	0.57	1.000	[0.14, 2.34]
Q12 Treatment team kept agreements	1.00	1.000	[0.69, 1.45]

Table S5: Comparing satisfaction on living with or without children. Relative risk >1 means patients living with children are more satisfied. P values of 1, relative risks of 0, upper or lower bound confidence interval NaN: means one of the quadrants of the contingency table is empty. Definitions: NAC Neoadjuvant chemotherapy, CI confidence interval, RR relative Risk. N=15



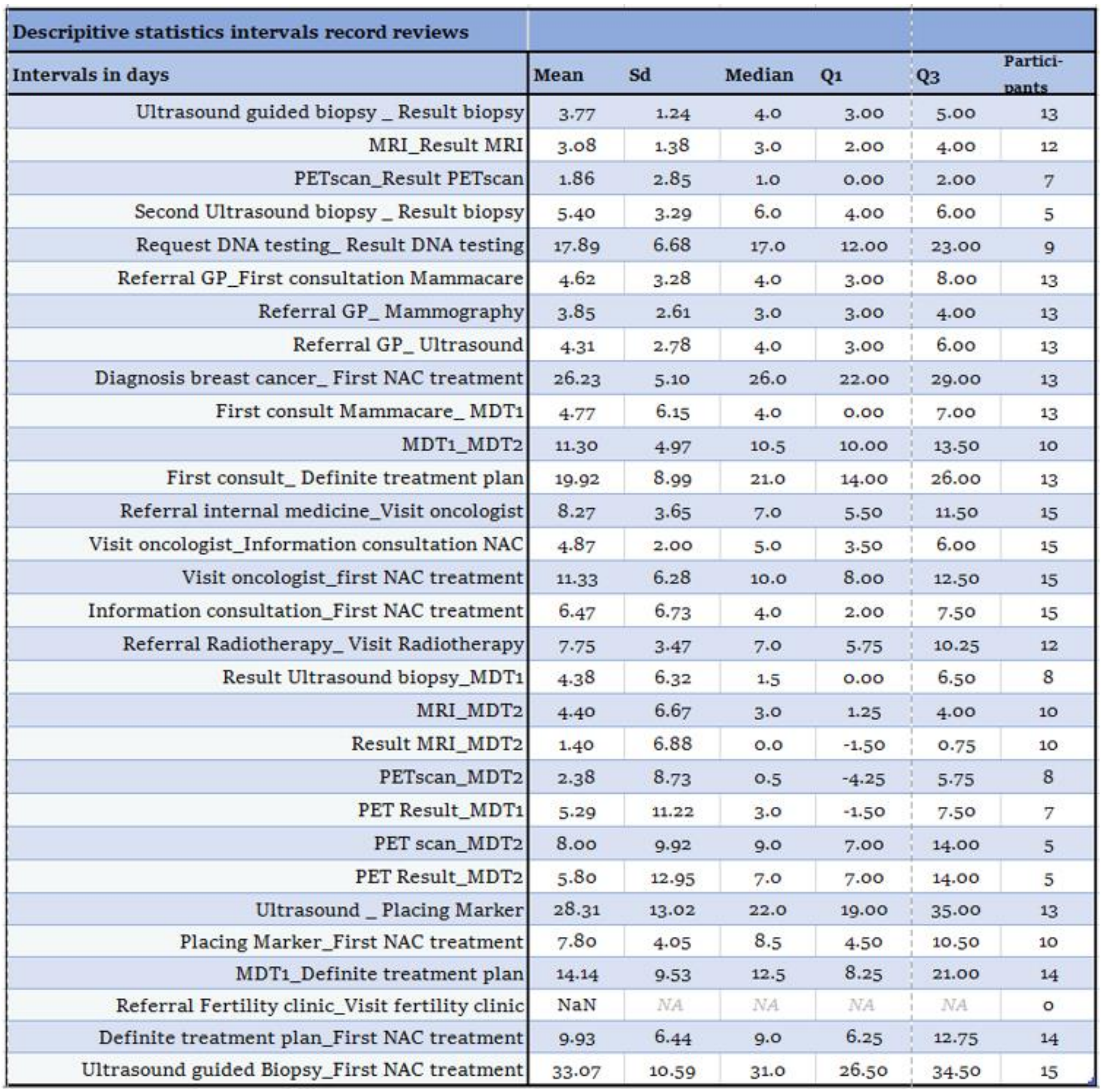
Comparing satisfaction (satisfied vs. dissatisfied) for HER2 status (+ vs. -)			
Questions	**P value**	**Relative Risk**	**CI RR**
Q1 Fully informed diagnosis	0.467	0.86	[0.53 , 1.38]
Q2 Fully informed treatment options	1.000	0.95	[0.61, 1.48]
Q3 Fully informed risks & side effects	1.000	0.98	[0.66, 1.46]
Q4 Involved in treatment decision	1.000	0.95	[0.61, 1.48]
Q5 Acceptable waiting time test results	1.000	0.95	[0.61, 1.48]
Q6 Acceptable time between tests & NAC	0.467	0.86	[0.53, 1.38]
Q7 Enough time for treatment decision	0.282	1.71	[0.80, 3.65]
Q8 Preferred more time for decision	0.200	0.00	[0, NaN]
Q9 Enough time from oncologist to NAC	0.467	0.86	[0.53, 1.38]
Q10 Enough time from nurse specialist to NAC	0.077	0.57	[0.27, 1.2]
Q11 Preferred starting treatment sooner	1.000	0.57	[0.14, 2.34]
Q12 Treatment team kept agreements	1.000	1.00	[0.69, 1.45]

Table S6: Comparing satisfaction for having a positive vs. a negative HER2 status. Relative risk >1 means patients with a positive HER2 status are more satisfied. P values of 1, relative risks of 0, upper or lower bound confidence interval NaN: means one of the quadrants of the contingency table is empty. Definitions: NAC Neoadjuvant chemotherapy, CI confidence interval, RR relative Risk. N=15



Comparing satisfaction (satisfied vs. dissatisfied) for tumor grade (grade 2 vs. grade 3)			
Questions	**P value**	**Relative Risk**	**CI RR**
Q1 Fully informed diagnosis	0.333	1.25	[0.81, 1.94]
Q2 Fully informed treatment options	0.077	2.25	[0.75, 6.71]]
Q3 Fully informed risks & side effects	0.524	0.80	[0.59, 1.09]
Q4 Involved in treatment decision	1.000	0.87	[0.48, 1.59]
Q5 Acceptable waiting time test results	0.560	1.33	[0.61, 2.91]
Q6 Acceptable time between tests & NAC	1.000	0.90	[0.73, 1.11]
Q7 Enough time for treatment decision	1.000	1.17	[0.51, 2.66]
Q8 Preferred more time for decision	1.000	1.00	[0.12, 8.56]
Q9 Enough time from oncologist to NAC	1.000	0.90	[0.73, 1.11]
Q10 Enough time from nurse specialist to NAC	0.505	0.70	[0.47, 1.05]
Q11 Preferred starting treatment sooner	0.242	0.25	[0.03, 2.14]
Q12 Treatment team kept agreements	1.000	1.00	[1.00, 1.00]

Table S7: Comparing satisfaction for having a grade 2 vs grade 3 tumor. Relative risk >1 means patients with a grade 3 tumor are more satisfied. P values of 1, relative risks of 0, upper or lower bound confidence interval NaN: means one of the quadrants of the contingency table is empty. Definitions: NAC Neoadjuvant chemotherapy, CI confidence interval, RR relative Risk. N=15

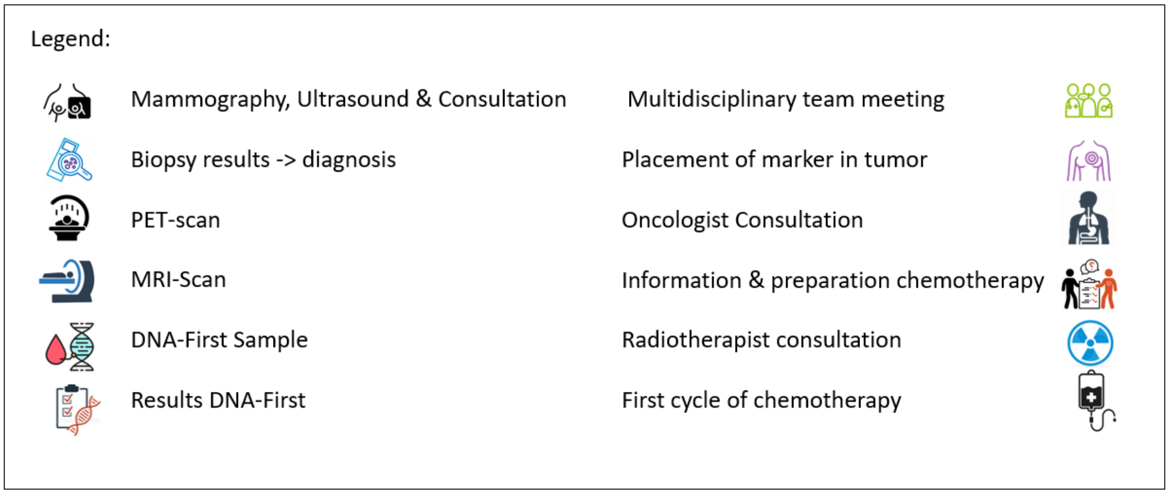


Descripitive statistics intervals record reviews						
Intervals in days	**Mean**	**Sd**	**Median**	**Q1**	**Q3**	**Partici-pants**
Ultrasound guided biopsy _ Result biopsy	3.77	1.24	4.0	3.00	5.00	13
MRI_Result MRI	3.08	1.38	3.0	2.00	4.00	12
PETscan_Result PETscan	1.86	2.85	1.0	0.00	2.00	7
Second Ultrasound biopsy _ Result biopsy	5.40	3.29	6.0	4.00	6.00	5
Request DNA testing_ Result DNA testing	17.89	6.68	17.0	12.00	23.00	9
Referral GP_First consultation Mammacare	4.62	3.28	4.0	3.00	8.00	13
Referral GP_ Mammography	3.85	2.61	3.0	3.00	4.00	13
Referral GP_ Ultrasound	4.31	2.78	4.0	3.00	6.00	13
Diagnosis breast cancer_ First NAC treatment	26.23	5.10	26.0	22.00	29.00	13
First consult Mammacare_ MDT1	4.77	6.15	4.0	0.00	7.00	13
MDT1_MDT2	11.30	4.97	10.5	10.00	13.50	10
First consult_ Definite treatment plan	19.92	8.99	21.0	14.00	26.00	13
Referral internal medicine_Visit oncologist	8.27	3.65	7.0	5.50	11.50	15
Visit oncologist_Information consultation NAC	4.87	2.00	5.0	3.50	6.00	15
Visit oncologist_first NAC treatment	11.33	6.28	10.0	8.00	12.50	15
Information consultation_First NAC treatment	6.47	6.73	4.0	2.00	7.50	15
Referral Radiotherapy_ Visit Radiotherapy	7.75	3.47	7.0	5.75	10.25	12
Result Ultrasound biopsy_MDT1	4.38	6.32	1.5	0.00	6.50	8
MRI_MDT2	4.40	6.67	3.0	1.25	4.00	10
Result MRI_MDT2	1.40	6.88	0.0	-1.50	0.75	10
PETscan_MDT2	2.38	8.73	0.5	-4.25	5.75	8
PET Result_MDT1	5.29	11.22	3.0	-1.50	7.50	7
PET scan_MDT2	8.00	9.92	9.0	7.00	14.00	5
PET Result_MDT2	5.80	12.95	7.0	7.00	14.00	5
Ultrasound _ Placing Marker	28.31	13.02	22.0	19.00	35.00	13
Placing Marker_First NAC treatment	7.80	4.05	8.5	4.50	10.50	10
MDT1_Definite treatment plan	14.14	9.53	12.5	8.25	21.00	14
Referral Fertility clinic_Visit fertility clinic	NaN	NA	NA	NA	NA	0
Definite treatment plan_First NAC treatment	9.93	6.44	9.0	6.25	12.75	14
Ultrasound guided Biopsy_First NAC treatment	33.07	10.59	31.0	26.50	34.50	15

Table S8: Descriptive statistics of intervals between events: mean, standard deviation, median, first quartile, third quartile and the number of participants. The intervals are written down as “event1_event2”. NA means that the event did not occur for any of the patients. Negative numbers means that event 2 happened before event 1. Definitions: NAC Neoadjuvant chemotherapy, MDT multi disciplinary team meeting, GP general practitioner.

Intervals Ultrasound (US) Biopsy as Reference						
Intervals	**Mean**	**Sd**	**Median**	**Q1**	**Q3**	**Participants**
US Biopsy_ Results Biopsy	3.77	1.24	4.0	3.00	5.00	13
US Biopsy_ MDT1	5.08	5.81	4.0	0.00	7.00	13
US Biopsy _ MRI	11.25	4.77	11.0	7.75	15.00	12
US Biopsy _MRI result	14.33	5.12	14.0	10.75	17.75	12
US Biopsy _ PET	10.29	4.92	8.0	7.50	11.00	7
US Biopsy _ PET result	12.14	7.36	10.0	8.00	12.00	7
US Biopsy _ MDT2	14.50	5.80	14.0	11.25	16.50	10
US Biopsy _ MDT3	29.75	9.22	26.5	23.75	32.50	4
US Biopsy _ Definite treatment plan	20.23	8.78	21.0	14.00	25.00	13
US Biopsy _ Referral Oncologist	11.46	4.48	10.0	10.00	14.00	13
US Biopsy _ Visit Oncologist	20.38	5.38	21.0	15.00	25.00	13
US Biopsy _ (Information) Consultation NAC	25.00	5.35	25.0	21.00	29.00	13
US Biopsy _ Referral Radiotherapy	17.91	8.40	17.0	12.50	22.00	11
US Biopsy _ Visit Radiotherapy	25.91	8.85	25.0	19.50	32.00	11
US Biopsy _ Marker placement	25.67	9.28	22.0	19.00	31.25	12
US Biopsy _ First NAC treatment	30.00	5.12	31.0	25.00	34.00	13
US Biopsy _ DNA sample	8.89	6.41	5.0	5.00	10.00	9
US Biopsy _ Result DNA first	26.78	8.79	22.0	22.00	28.00	9
US Biopsy_ Second US Biopsy	17.67	5.28	17.0	14.25	21.25	6
US Biopsy _ Result Second US Biopsy	21.60	7.20	21.0	15.00	25.00	5
US Biopsy _ GPreferral	-4.31	2.78	-4.0	-6.00	-3.00	13

Table S9: Descriptive statistics of intervals between events with US biopsy as reference group: mean, standard deviation, median, first quartile, third quartile and the number of participants. The intervals are written down as "event1_event2". Negative numbers mean that event 2 happened before event 1. Definitions: US ultrasound, NAC Neoadjuvant chemotherapy, MDT multi disciplinary team meeting and GP general physician.



Legend:

Mammography, Ultrasound & Consultation	Multidisciplinary team meeting
Biopsy results -> diagnosis	Placement of marker in tumor
PET-scan	Oncologist Consultation
MRI-Scan	Information & preparation chemotherapy
DNA-First Sample	Radiotherapist consultation
Results DNA-First	First cycle of chemotherapy

Figure S2A: participants 10-15 of the study and their individual pathways portrayed with pictograms.

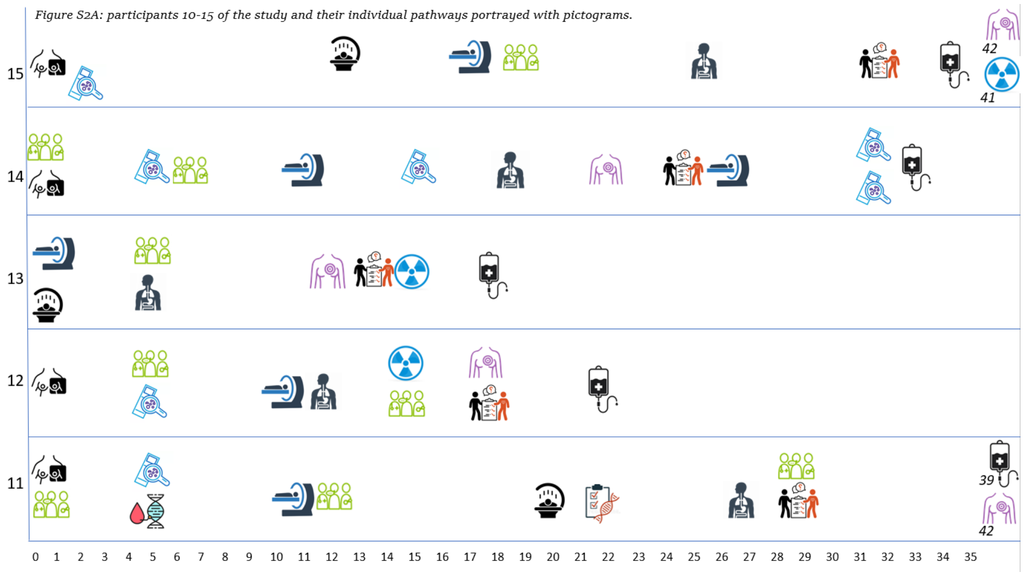


Figure S2B: participants 5-10 of the study and their individual pathways portrayed with pictograms.

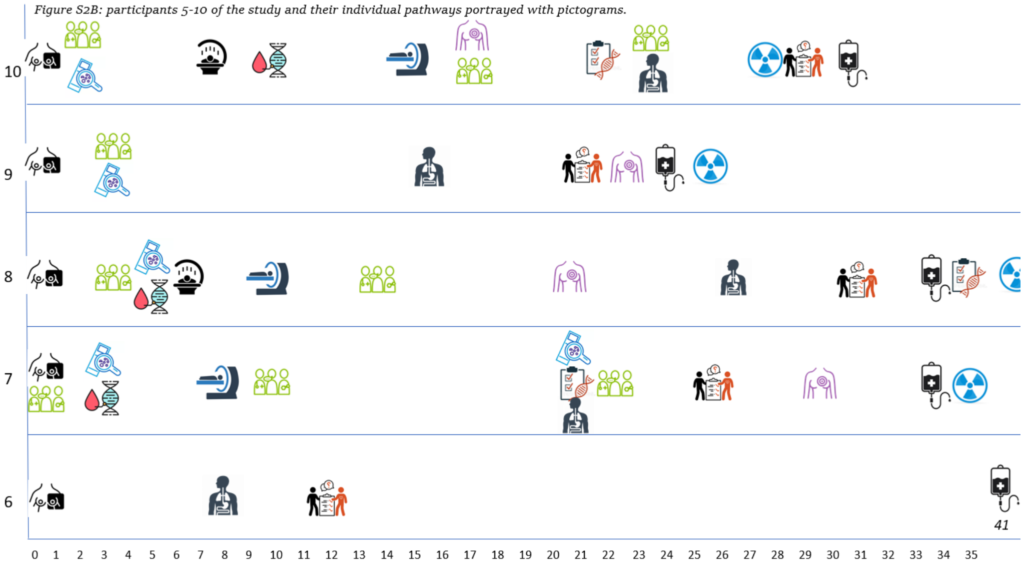
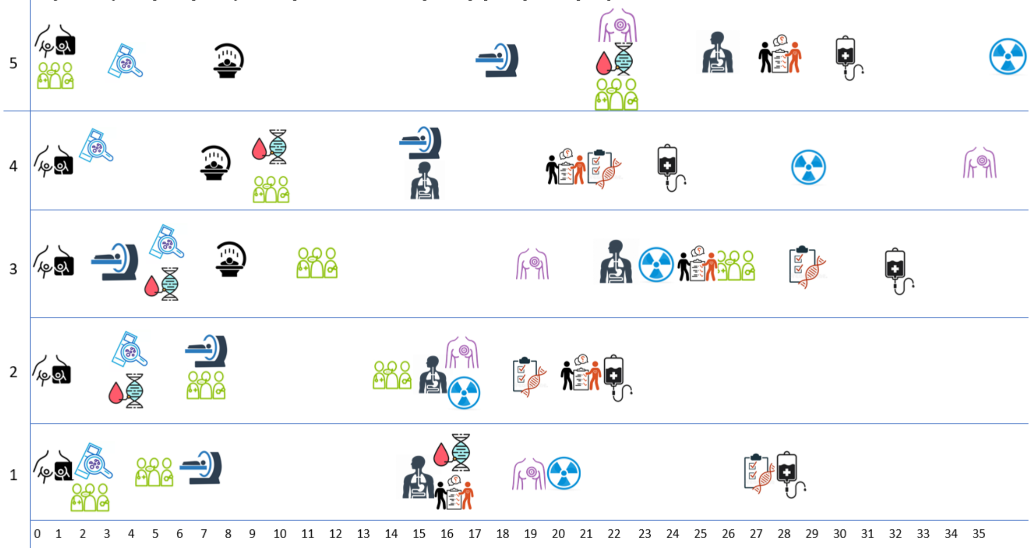


Figure S2C: first 5 participants of the study and their individual pathways portrayed with pictograms.



Comparing intervals in days to statisfaction (satisfied vs. dissatisfied)	
Questions	**P value**
Q6 Acceptable time between tests & NAC	0.320
Q7 Enough time for treatment decision	0.267
Q8 Preferred more time for decision	0.843
Q9 Enough time from oncologist to NAC	0.244
Q10 Enough time from nurse specialist to NAC	0.604
Q11 Preferred starting treatment sooner	0.424

Table S10: association of the questions 6-11 to the HIX interval. The responses to Q6 were compared to the interval definite treatment plan _ first NAC treatment. The responses to Q7 were compared to "visit oncologist_first NAC treatment". The responses of Q8 were compared to result "Ultrasound guided biopsy_ first NAC treatment". The responses to Q9 were compared to "information consultation_ first NAC treatment", responses Q10 to visit "oncologist_first NAC treatment". The responses to question 11 was compared to interval "visit oncologist_ first NAC treatment". Definition: NAC Neoadjuvant chemotherapy. N=15

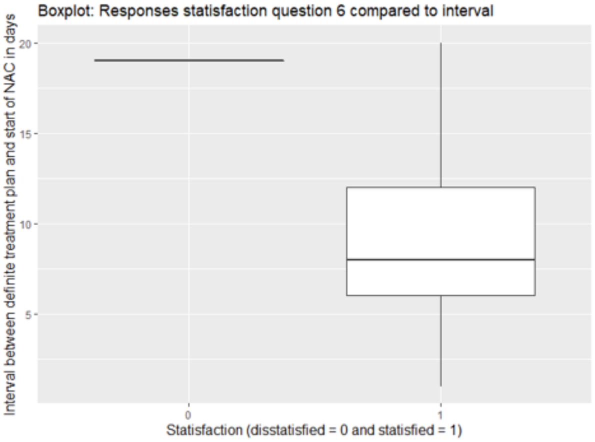


Figure S3: Responses to question 6 compared to the interval "definite treatment plan _ first NAC treatment". Satisfaction response: is either 0 (disstatisfied) or 1 (satisfied). Definition: NAC Neoadjuvant chemotherapy. N=15

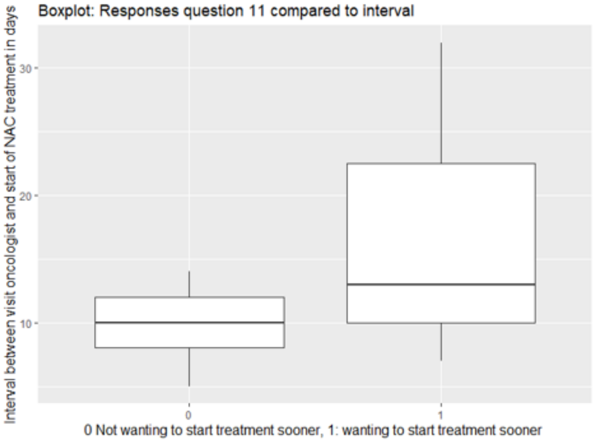


Figure S4: Responses to question 11 compared to the interval to "visit oncologist_ first NAC treatment". Satisfaction response: is either 0 (disstatisfied) or 1 (satisfied). Definition: NAC Neoadjuvant chemotherapy. N=15

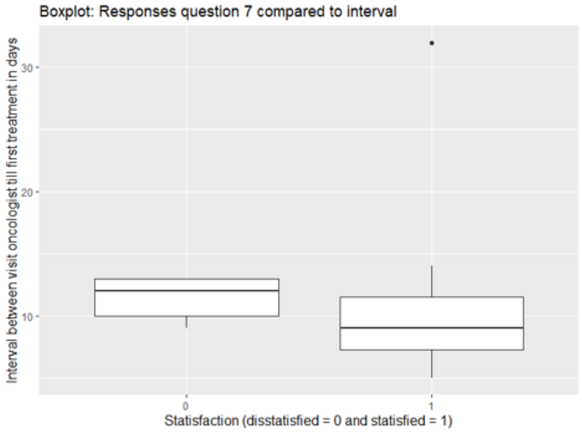


Figure S5: Responses to question 7 compared to the interval “visit oncologist_first NAC treatment”. Satisfaction response: is either 0 (disstatisfied) or 1 (satisfied). Definition: NAC Neoadjuvant chemotherapy. N=15

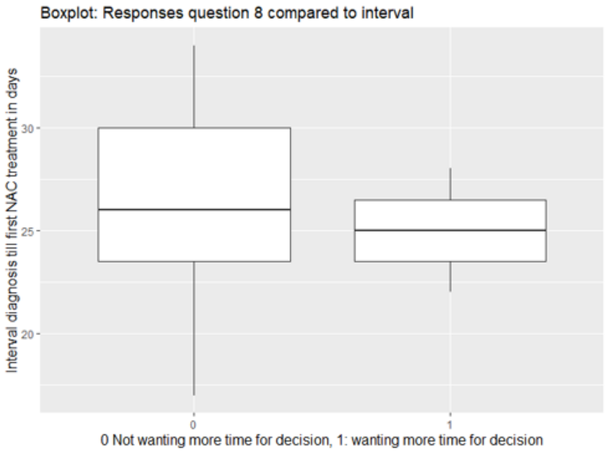


Figure S6: Responses to question 8 compared to the interval “Ultrasound guided biopsy_ first NAC treatment”. Satisfaction response: is either 0 (disstatisfied) or 1 (satisfied) Definition: NAC Neoadjuvant chemotherapy. N=15

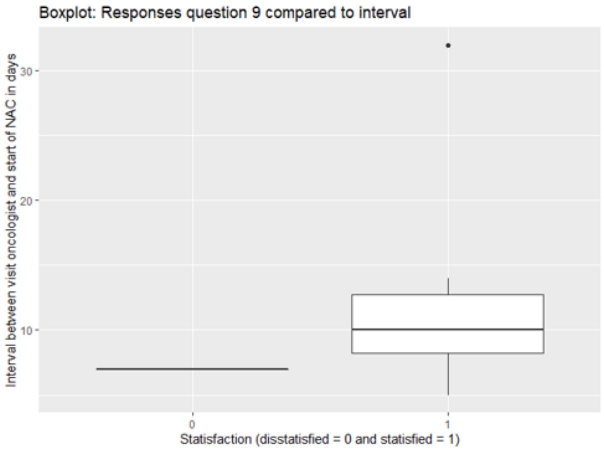


Figure S7: Responses to question 9 compared to the interval to “information consultation_ first NAC treatment”. Satisfaction response: is either 0 (disstatisfied) or 1 (satisfied). Definition: NAC Neoadjuvant chemotherapy N=15

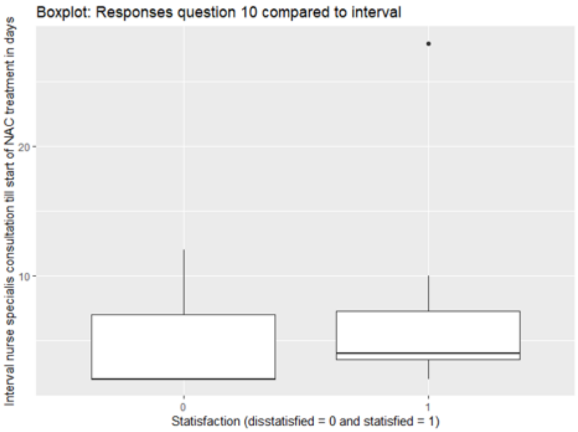


Figure S8: Responses to question 10 compared to the interval “oncologist_first NAC treatment”. Satisfaction response: is either 0 (disstatisfied) or 1 (satisfied). Definition: NAC Neoadjuvant chemotherapy. N=15

Appendix 2: Questionnaire (Dutch)

CABRIO studie

Onderzoek naar de wensen en ervaringen van de borstkankerpatiënte in het neo-adjuvante traject

Mammacare

De vragenlijst: Bij de diagnose borstkanker, komt er veel op u af. Ook u is dat overkomen. Na de vele onderzoeken, en vaak ook vervolgonderzoeken, volgen verschillende keuzeopties. De tijd tussen diagnose en start behandeling is niet alleen spannend maar vaak ook complex. Wat is er mogelijk? Wat kan ik aan? Wat wil ik? Enz.

In de praktijk streven wij er naar om maximaal 5 weken na het vaststellen van de diagnose te starten met de behandeling. Dit betekent dat een patiënt veel beslissingen moet nemen in een korte periode.

Als Centrum voor Mammacare zijn wij benieuwd naar uw ervaringen in de afgelopen weken. Met deze vragenlijst willen wij u vragen uw ervaringen in de afgelopen weken met ons te delen. Wij willen de zorg graag zo goed mogelijk toespitsen op uw wensen. Daarvoor hebben wij uw hulp nodig. Het invullen van de vragenlijst duurt ongeveer 10 minuten. Uw medewerking wordt zeer op prijs gesteld.

U kunt de vragen beantwoorden door het getal te omcirkelen dat het meest op u van toepassing is.

1=Helemaal mee oneens

2=Mee oneens

3=Neutraal / Geen mening

4=Mee eens

5=Helemaal mee eens.

Vragen over de behandelperiode

	Helemaal mee oneens	Mee oneens	Neutraal / Geen mening	Mee eens	Helemaal mee eens
1. Het behandelteam heeft mij volledig geïnformeerd over mijn diagnose borstkanker.	1	2	3	4	5

Indien oneens: welke informatie heeft u gemist?

2. Het behandelteam heeft mij volledig geïnformeerd over de verschillende behandelingsmogelijkheden.	1	2	3	4	5

Indien oneens: welke informatie heeft u gemist?

3. Het behandelteam heeft mij volledig geïnformeerd over risico’s en bijwerkingen van de diverse behandelingen.	1	2	3	4	5

Indien oneens: welke informatie heeft u gemist?

4. Het behandelteam heeft mij betrokken bij het nemen van beslissingen omtrent mijn behandelingen.	1	2	3	4	5

Indien oneens: Bij welke beslissing is er onvoldoende naar u geluisterd?

5. De tijd die tussen de onderzoeken en de uitslag van de onderzoeken zat, vond ik acceptabel.	1	2	3	4	5

Indien oneens: Op welke uitslag hebt u lang moeten wachten?

6. De tijd die tussen de onderzoeken en start chemotherapie zat, vond ik acceptabel.	1	2	3	4	5

Opmerkingen:

7. Ik heb voldoende tijd gehad tussen de onderzoeken en start chemotherapie om een juiste behandelkeuze te maken.	1	2	3	4	5

Opmerkingen:

8. Ik had graag meer tijd willen krijgen om te beslissen.	1	2	3	4	5

Opmerkingen:

9. Er zat voldoende tijd tussen het bezoek aan de internist-oncoloog en de start chemotherapie.	1	2	3	4	5

Opmerkingen:

10. Er zat voldoende tijd tussen de voorlichting door de verpleegkundig specialist / oncologie verpleegkundige over de chemotherapie en de start van de chemotherapie	1	2	3	4	5

Opmerkingen:

11. Ik had graag sneller willen starten met de behandeling.	1	2	3	4	5

Opmerkingen:

12. Het behandelteam hield zich aan de met mij gemaakte afspraken.	1	2	3	4	5

Opmerkingen:

De onderstaande vraag alleen beantwoorden indien u ten tijde van de diagnostiek een actieve kinderwens had.	Helemaal mee oneens	Mee oneens	Neutraal / Geen mening	Mee eens	Helemaal mee eens
13. Ik heb voldoende tijd gehad om na te denken over mijn actieve kinderwens.	1	2	3	4	5

Opmerkingen:

Algemene vragen

Hieronder willen wij u vragen nog een aantal algemene vragen te beantwoorden:

1. Wat is uw hoogst afgeronde (school)opleiding? (1 vakje aankruisen)
   - ☐ Basisschool
   - ☐ Lager Voortgezet Onderwijs (LAVO, VGLO)
   - ☐ Lager Beroepsonderwijs (LHNO, Huishoudschool, LTS, LDS)
   - ☐ Middelbaar Voortgezet Onderwijs (VMBO, MAVO, MMO, MULO)
   - ☐ Middelbaar Beroepsonderwijs (MEAO, MTS, MDGO)
   - ☐ Hoger Algemeen Voortgezet Onderwijs (HAVO)
   - ☐ Voorbereidend Wetenschappelijk Onderwijs (VWO, HBS, Atheneum, Gymnasium)
   - ☐ Hoger Beroepsonderwijs (HBO, HTS, HEAO)
   - ☐ Universiteit

2. Hoe is uw woonsituatie? (een vakje aankruisen)
   - ☐ Ik woon alleen
   - ☐ Ik woon alleen met een kind(eren)
   - ☐ Ik woon met een partner
   - ☐ Ik woon met een partner en kinderen

☐ Ik woon met mijn ouders
☐ Ik woon in een woongroep
☐ Anders namelijk:……………………………………………..

3. Hoe is uw werksituatie: (1 vakje aankruisen)
   ☐ Betaald werk
   ☐ Vrijwilligerswerk
   ☐ Werkzoekende
   ☐ Arbeidsongeschikt
   ☐ Gepensioneerd
   ☐ Studente
   ☐ Anders, namelijk:……………………………………………..

Opmerkingen:

Appendix 2: Questionnaire Translation (English)

1. **The treatment team has fully informed me about my diagnosis of breast cancer.**
   Remarks:

2. **The treatment team has fully informed me about different treatment options.**
   Remarks:

3. **The treatment team has fully informed me about the risks and side effects of the various treatment options.**
   Remarks:

4. **The treatment team has involved me in making decisions about my treatment.**
   Remarks:

5. **The time between (imaging) tests and the results was acceptable to me.**
   Remarks:

6. **The time between (imaging) tests and the start of chemotherapy was acceptable to me.**
   Remarks:

7. **I had sufficient time between the tests and the start of chemotherapy to make the right treatment decision.**
   Remarks:

8. **I would have liked to have more time to decide on a treatment**
   Remarks:

9. **There was sufficient time between the consultation at the oncologist and the start of chemotherapy.**
   Remarks:

10. **There was sufficient time between the consultation with the nurse specialist about chemotherapy and the start of the chemotherapy.**
    Remarks:

11. **I would have preferred to start the treatment sooner**
    Remarks:

12. **The treatment team kept to the agreements made with me**
    Remarks:

13. **I had sufficient time to think about my desire to have children**

    Remarks:

General questions

1. **What is your highest completed level of education?**

Options: Primary education, lower secondary education, low vocational education, secondary education, secondary vocational education, senior general secondary education, university of applied sciences and university.

2. **What is your living situation?**

Options: Living alone, living alone with children, living with a partner, living with a partner and children, living with parents, living in a living community or different.

3. **What is your employment status?**

Options: paid work, volunteering, job seeker, unable to work, retired, student or different.

Remaining remarks: do you have remaining remarks about the period between your diagnosis and the start of the chemotherapy?

Appendix 3 Data Dictionary (Dutch)

1 Studienummer patiënt
2 Geboortedatum
3 Leeftijd bij diagnose
4 Datum verwijzing mammapoli
5 Datum eerste consult
6 Datum mammografie
7 Datum echo
8 Datum echogeleid biopt
9 Datum MDO 1
10 Datum uitslag biopt
11 Datum MDO 2
12 Datum MDO 3
13 Datum stereotactisch biopt
14 Datum uitslag stereotactisch biopt
15 Datum MRI
16 Datum uitslag MRI
17 Datum MRI geleid biopt
18 Datum tweede echogeleid biopt
19 Datum PET scan
20 Datum uitslag PET scan
21 Datum CT scan
22 Datum uitslag CT scan
23 Datum MRI lever
24 Datum uitslag MRI lever
25 Datum lever biopt
26 Datum uitslag lever biopt
27 Datum MRI wervelkolom
28 Datum uitslag MRI wervelkolom
29 Datum biopt wervel
30 Datum uitslag biopt wervel
31 Datum Botscan
32 Datum uitslag botscan
33 Datum botbiopt
34 Datum uitslag botbiopt
35 Datum inbrengen marker mamma
36 Datum inbrengen marker axilla
37 cTNM
38 Datum definitief behandelplan chirurg/VS
39 Datum verwijzing internist oncoloog
40 Datum eerste bezoek internist oncoloog
41 Datum voorlichting gesprek chemotherapie
42 Datum aanmelding radiotherapeut
43 Datum eerste bezoek radiotherapeut
44 Datum aanmelding fertiliteitskliniek
45 Datum bezoek fertiliteitskliniek

46 Datum afname DNA first
47 Datum binnenkomst uitslag DNA first
48 Uitkomst DNA first
49 Overige onderzoeken
50 ER status
51 PR status
52 HER2 status
53 Zijde mammacarcinoom
54 Tumortype lobulair/ductaal/anders
55 Graad tumor
56 Wat ging er mis bij biopten? Indien deze herhaald werden
57 Datum oogsten eitjes bij fertiliteit kliniek
58 Datum eerste chemokuur
59 Datum verwijzing plastisch chirurg
60 Datum eerste bezoek plastisch chirurg
61 Datum tweede stereotactisch biopt
62 Datum uitslag tweede stereotactisch biopt
63 Datum tweede MRI geleid biopt
64 Datum uitslag tweede MRI geleid biopt

Appendix 4: Remarks Questionnaire CABRIO study

1. **The treatment team has fully informed me about my diagnosis of breast cancer**

Nr of remarks	5
Remarks in writing (Dutch)	1. Heb niet echt wat gemist, maar dat de "bron" niet echt duidelijk is gevonden is lastig soms. Geeft toch een stukje angst en zoek dan naar geruststelling. Dat het vaker voorkomt en behandelbaar is. (2) 2. Dat denk ik. (5) 3. Ik ga er vanuit dat alles is verteld, de herneu2 informatie kwam volgens mij wel wat laat. (4) 4. Ik heb op 04-04-2023 pas alle scans gezien, informatie ontvangen en een update gekregen over de erfelijkheid, terwijl ik 7/4 al de eerste chemo ontvang. Hierdoor was het niet/nauwelijks mogelijk om een second opinion aan te vragen en was het mij niet duidelijk hoe groot de kans op terugkeer was. (Bij erfelijke borstkanker loop je groter risico op uitzaaiingen bij de eierstokken). (4) 5. Ik heb twijfels over mijn diagnose omdat men mij in een ander ziekenhuis een verkeerde diagnose gegeven heeft. (4)
Summary remarks	1. Missing source of information 2. Looking for more comfort 3. Trusting that professional has fully informed them 4. Not fully informed, late results, no time for second opinion 5. Doubts because of wrong diagnosis (other hospital)
Improvement of care	

2. **The treatment team has fully informed me about different treatment options**

Nr of remarks	5

Remarks in writing	1. Mogelijkheden niet echt over gehad. Ze vertelden over hoe het zou gaan. Wat de behandel manier is. Ik ga ervan uit dat zij het weten.(3) 2. Ik heb 1 optie gehoord, weet ook niet of er meer mogelijkheden zijn. Ik ga er vanuit dat dit het beste is. (3) 3. De informatie die gegeven werd was erg warrig en soms ook erg onduidelijk- dit lag ook aan het feit dat ik een bindweefselziekte heb , maar wanneer ik los van de bindweefsel ziekte om feitelijke statistieken vroeg bleef men er summier. Hierdoor is het voor mij erg moeilijk om gedegen afwegingen te maken en/of een risicoschatting te maken waarvoor ik bij bijvoorbeeld levenskwaliteit op ga offeren voor levensjaren. Als ik bijvoorbeeld me neuropathie en oedeem moet leren leven in ruil voor een kankervrij worden het een overmate levensverwachting, teloor ik toch echt voor fysiek ongemak in ruil voor meer tijd. (2) 4. Ik had niet echt het idee dat er echt iets te kiezen viel. (2) 5. Mogelijkheden zijn besproken, ik voel dat ik wel echt behandeld moet worden. (4)
Summary remarks	1. Only one option, trusting the professional to know best (2x) 2. Information was unclear and chaotic due to another illness. This makes decisions concerning quality of life difficult. 3. There was not really a choice to be made
Improvement of care	

3. **The treatment team has fully informed me about the risks and side effects of the various treatment options**

Nr of remarks	3
Remarks in writing	1. Ik ga er vanuit dat alles is verteld. (4) 2. Er werden wel risico's en bijwerkingen genoemd, maar er is geen onderzoek/literatuur voorhanden over EDS en kanker. Alhoewel ik een milde vorm van EDS heb, werd er soms extreem voorzichtig gedaan met het doen van uitspraken. Verder heb ik het idee dat het hele process een soort van trial & error gaat worden waarbij er weer momenten zijn waarop gekeken wordt of de behandeling zinvol is gebleken. Dit maakt me wel redelijk onzeker. (2) 3. Ik heb niet alles opgenomen en zeker ook niet alle informatie kunnen onthouden, de periode van diagnose is erg intensief. (4)
Summary remarks	1. Trusting the professional to have fully informed them

	2. No information available for comorbidity. 3. Extremely careful with predictions/chances about treatment 4. Information overload, so not remembering everything 5. Diagnostic period is very intensive
Improvement of care	

4. **The treatment team has involved me in making decisions about my treatment**

Nr of remarks	3
Remarks in writing	1. Zie vraag 2. Ik vertrouw erop dat de beste behandelingen zijn gekozen. (4) 2. Even twijfelachtig tussen 4&5 omdat ik graag wil dat beide borsten worden afgezet. Dit heb ik in 2020 bij het verwijderen van mijn protheses aan dokter Rakhorst al gevraagd. Daar is toen niet naar geluisterd en nu heb ik borstkanker met uitzaaiingen. Al vanaf mijn 12e loop ik al bij artsen voor mijn borsten. op mijn 15e heb ik protheses gekregen omdat dit mooier zou zijn. Op mijn 16e zijn de implantaten geplaatst. En sindsdien heb ik alleen pijn & ellende door mijn borsten gehad. Ik ben er klaar mee en wil ze niet meer.(4) 3. Ik had niet het idee dat er echt iets te kiezen viel. (2)
Summary remarks	1. Trusting the professional to make the right decision for them 2. Was not heard in the past and now experiences the consequences
Improvement of care	

5. **The time between (imaging) tests and the results was acceptable to me.**

Nr of remarks	3
Remarks in writing	1. Uitslag biopt duurde mij iets te lang waarschijnlijk ook doordat de afspraak verplaatst was. (4) 2. De uitslag van de biopten was vertraagd, kan gebeuren maar we waren al op weg naar de afspraak toen er gebeld werd afgebeld/verplaatst. (3) 3. Al met al duurde de onzekerheuid lang doordat de PET-scan “mislukt” was. (3)
Summary remarks	1. The biopsy results took a long time, and the appointment was rescheduled. 2. Late cancellation of appointment 3. Long period of uncertainty due to failed PET-scan
Improvement of care	

6. **The time between (imaging) tests and the start of chemotherapy was acceptable to me.**

Nr of remarks	2
Remarks in writing	1. Ik vond het best lang duren, voor mijn gevoel. Maar er moest ook veel gebeuren. Als ik daar naar kijk had het niet veel sneller gekund. (4) 2. De onderzoeken voor bijv het hart hadden eigenlijk eerder ingepland moeten worden evenals de terugkoppeling met de vaatchirurg over een PICC lijn of Port a Cath- men wist bij de intake al van mijn EDS en ik heb dit zelf uit moeten zoeken. (4)
Summary remarks	1. It took a lot of time but there was probably no way to do it faster 2. Examinations and tests could have been planned earlier 3. Communication between departments could have been better, about port a Cath
Improvement of care	

7. **I had sufficient time between the tests and the start of chemotherapy to make the right treatment decision.**

Nr of remarks	5
Remarks in writing	1. De keus was gemaakt en ik ga ervoor. (4) 2. Ik heb maar 1 keuze gehoord, ik ga ervan uit dat dat ook het beste is. 3. Geen second opinion aan kunnen vragen. Geen port a cath kunnen plaatsen alvorens chemo- onderzoeken waren rommelig ingepland/ checklist en casemanagement ontbrak. (1) 4. Ik had niet het idee dat er echt iets te kiezen viel. (2) 5. Diep van binnen twijfel ik nog over de behandelkeuze. Ik had het liefst langer gewacht maar dat voelt niet als een optie omdat de tumor groeit. (3)
Summary remarks	1. There was only one option 3x 2. No time for second opinion 3. Doubts about choice of treatment 4. Wanting to wait longer but fearing negative impact on disease
Improvement of care	1. Advise to make a checklist for each patient

8. **I would have liked to have more time to decide on a treatment**

Nr of remarks	4
Remarks in writing	1. Eigenlijk hoefde ik nergens over te beslissen. (1)

	2. Snel beginnen lijkt mij juist goed. (2) 3. Met name had ik graag een checklist willen krijgen waar ik aan moest denken, wat ik moest voorbereiden en zoo. Nu heb ik alles via vrienden en het internet moeten halen (zelfs over de port a cath en PICClijn). (1) 4. Ik had het liever willen uitstellen maar dit voelde niet als een optie omdat de tumor blijft groeien. (5)
Summary remarks	1. There was not really a decision to make. 2. A fast start is beneficiary according to me 3. Postphoning has a negative impact on disease
Improvement of care	1. I would have liked a checklist with everything I needed to prepare for this

9. **There was sufficient time between the consultation at the oncologist and the start of chemotherapy.**

Nr of remarks	1.
Remarks in writing	1. Wel genoeg tijd, maar door extra onderzoeken praktisch dagelijks in het ziekenhuis. (3)
Summary remarks	1. There was enough time but many hospital visits
Improvement of care	

10. **There was sufficient time between the consultation with the nurse specialist with detailed information about chemotherapy and the start of the chemotherapy.**

Nr of remarks	1
Remarks in writing	1. Er zat maar 1 dag tussen. Dit was voor mij echter voldoende want ik wist dat komen zou en graag z.s.m. (4)
Summary remarks	1. I knew it was needed, so I was prepared
Improvement of care	

11. **I would have preferred to start the treatment sooner**

Nr of remarks	6
Remarks in writing	1. Ik had best sneller willen starten, maar zie ook zeker in dat dat lastig was met mijn diagnose en onderzoeken. Dus als ik erop "terugkijk" is het goed zo! Er is veel aan gedaan om z.s.m. onderzoeken te doen. Top. (4) 2. Kon niet sneller, wel gewild. (4) 3. Ik wil natuurlijk zsm starten, maar het is ook goed dat alles eerst goed is onderzocht. (3) 4. Ik had graag gestructureerder een plan van aanpak voor de onderzoeken en de voorbereidingsfase gehad. Daarnaast had ik graag gehad dat de PICClijn & Port a Cath gezien mijn EDS en het behandelplan proactief alvorens de chemo van start ging was aangeboden/ kon worden geplaatst. (3)

	5. Ik voel dat de grootte van de tumor toeneemt, daarom zie ik het belang van een snelle behandeling in. (4) 6.Ik vond het erg fijn nog even met mijn gezin op vakantie te kunnen gaan en dat dit gesteund werd vanuit het ziekenhuis. (1)
Summary remarks	1. Wanted to start as soon as possible (3x) 2. A more structured plan for the examinations and preparationphase would be appreciated 3. The tumor is growing, so treatment as soon as possible 4. I felt supported by the hospital to go on a holiday with my family
Improvement of care	Making a structured plan for the preparation phase

12. **The treatment team kept to the agreements made with me**

Nr of remarks	1
Remarks in writing	1. Tot op heden nog weinig met het gehele team te maken gehad. Toch vond ik het in Enschede wat zakelijker/ prettiger verlopen doordat de communicatie eenvoudig en concreet was. Ik heb veel afspraken ad hoc zelf ingepland op basis van uitval. (4)
Summary remarks	1. Not having seen the whole treatment team
Improvement of care	

13. **I had sufficient time to think about my desire to have children**

Nr of remarks	1
Remarks in writing	1. Je moet ook gewoon snel schakelen (5)
Summary remarks	1. You have to switch gears fast
Improvement of care	

14. **Other remarks:**

Nr of remarks	7
Remarks in writing	1. Het onzekere is het zwaarst. mentaal. Dat wachten op bijv. de uitslag van de PET-scan. Zou niet weten hoe het anders moet, maar dat was wel een heftige week. 2. Het duurde vrij lang wanneer er plek was bij de internist. Dr Pleunis werkt volgens een bepaalde methode en de daarbij horende onderzoeken. Van mij had dit voor die tijd al wel ingepland mogen worden even als de afspraak met de verpleegkundig specialist waardoor je de laatste dagen voordat je begint erg druk bent. 3. Ik vind dat ik overal ontzettend goed opgevangen ben. Het traject is erg duidelijk uitgelegd maar wel met een menselijke ondertoon. En dat is ook erg belangrijk in deze al onzekere tijd.

	4. Ik heb het idee dat alle afdelingen die betrokken zijn goed samenwerken en dat geeft vertrouwen in de behandeling. 5. Enigzins chaotisch, niet altijd helder en concreet, gene tijd voor second opinion, maar wel fijn dat ik snel geholpen werd gezien de agressie v/d tumor + uitzaaiingen. Denk dat een betere inventarisatie tijdens de intake (er was toen al voor 95% duidelijk dat het kanker met uitzaaiingen in de lymfe was, dus dat er wel hoogst waarschijnlijk chemo zou volgen). Een efficiënter onderzoeksplan waarbij bezoek aan de cardio & vaatchirurg al in week 2/3 hadden kunnen worden ingepland. Had veel stress en onzekerheid gescheeld. 6. Topteam! Fijn dat ik met al mijn onzekerheden terecht kan bij internist /vpk specialist. Juiste voorlichting ook door vpk dagbehandeling/ start kuur. 7. Bij sommige onderzoeken (vooral MRI-scan en hartfilmpje ging de verpleegkundige er vanuit dat ik alles wel wist). Bij de MRI ben ik (voor mijn gevoel) onvoldoende voorbereid op hoe dat onderzoek ging. Ik heb het als een heel naar onderzoek ervaren. Dit had m.i. voorkomen kunnen worden door een betere voorbereiding op hoe het zou gaan.
Summary remarks	1. Waiting for biopsy results is mentally the most difficult period. 2. I had to wait a long time before the oncologist had time. 3. Some consultations such as with the nurse specialist could have been planned earlier on. 4. I was in good hands; the trajectory was clearly explained. 5. There was chaos, no clear explanation and no time for a second opinion. 6. A more efficient diagnostic plan with more anticipation would be beneficiary. 7. I was content that they could help me so fast. 8. I was able to discuss all my doubts with the oncologist and specialist nurse. 9. For some examinations it was expected that I knew how it would go, I would have liked better preparations (for example MRI).
Improvement of care	1.Some consultations such as with the nurse specialist could have been planned earlier on. 2.A more efficient diagnostic plan with more anticipation would be beneficiary 3.Better preparations for examinations (with information etc.)

Appendix 5: partial R-script for intervals and influence of intervals on satisfaction.

```
#Combination HiX & Vragenlijsten

# Load the CSV file into R using the read.csv() function
#CabrioHixNaslagRaw <- read.csv("~/UTwente/HS Master/Master Assignment/Dataverwerking/Data uit Castor
/new 10 participants value/CABRIO_HIX_naslag_export_20230501.csv", header = TRUE, sep = ";",
stringsAsFactors = FALSE)
CabrioHixNaslagRaw <- read.csv("~/UTwente/HS Master/Master Assignment/Datafile/Final export value
/CABRIO_HIX_naslag_export_20230517.csv", header = TRUE, sep = ";", stringsAsFactors = FALSE)
#CabrioVragenlijstRaw <- read.csv("~/UTwente/HS Master/Master Assignment/Datafile
/CABRIO_csv_export_20230331150607/CABRIO_CABRIO_studie_vragenlijst_export_20230331.csv", header = TRUE
, sep = ";", stringsAsFactors = FALSE)
#CabrioVragenlijstRaw <- read.csv("~/UTwente/HS Master/Master Assignment/Dataverwerking/Data uit
Castor/10 participants values/CABRIO_CABRIO_studie_vragenlijst_export_20230501.csv", header = TRUE,
sep = ";", stringsAsFactors = FALSE)
CabrioVragenlijstRaw <- read.csv("~/UTwente/HS Master/Master Assignment/Datafile/Final export value
/CABRIO_CABRIO_studie_vragenlijst_export_20230517.csv", header = TRUE, sep = ";", stringsAsFactors =
FALSE)

#loading packages
library(dplyr)
library(tidyr)
library(lattice)
library(survival)
library(psych)
library(Hmisc)
library(summarytools)
library(ggplot2)
library(DataExplorer)
library(Rserve)
library(tidyverse)
library(openxlsx)
library(lubridate)
library(robustbase)
library(MASS)
library(effsize)

#Creating tables with questions and with variables
QuestionsLikert <-((CabrioVragenlijstRaw[,c("Castor.Participant.ID", "Vraag1volledigeinformatiediag",
"Vraag2volledinginfobehandelingsopties", "Vraag3risicosbehandeling", "Vraag4betrokkenbeslissing",
"Vraag5tijduitslagenvoldoende", "Vraag6tijdonderzoekenchemo", "Vraag7voldoendetijdkeuze",
"Vraag8meertijdbeslissing", "Vraag9tijdinternististartchemo", "Vraag10voldoendetijdvoorlichtingstart",
"Vraag11snellerstarten", "Vraag12afsprakenhouden")]))
```

```
#alleen maar datums in tabel
Dates <- CabrioHixNaslagRaw[,c("Castor.Participant.ID", "Geboortedatum", "Dmammo", "Decho",
"Dechobiopt", "Duitslagechobiopt", "Dstereobiopt", "Duitstereobiopt", "Duitstereobiopt", "DMRI",
"DuitMRI", "DMRIbiopt", "DuitMRIbiopt", "D2MRIbiopt", "D2uitMRIbiopt", "D2echobiopt", "D2uitechobiopt"
, "DPET", "DuitPET", "DCT", "DuitCT", "DMRIlever", "Dleverbiopt", "Duitleverbiopt", "DMRIwervel",
"DuitMRIwervel", "Dbioptwervel", "Duitbioptwervel", "Dbotscan", "Duitbotscan", "Dbotbiopt",
"Duitbotbiopt", "Dmarkermamma", "Dmarkeraxilla", "DafnameDNA", "DuitDNA", "Deitjesfertiliteit",
"D1chemo", "Dverwpoli", "Deersteconsultmamma", "DMDO1", "DMDO2","DMDO3", "Ddefplan", "Dverwinteronco",
"D1bezinteronco", "Dvoorchemo", "Dverwradio", "D1bezradio", "Daanmfertiliteit", "Dbezfertiliteit",
"Dverwplastisch", "D1bezplastisch")]
#Dates <- subset (Dates, select = -Castor.Participant.ID)

# select only the date columns
Dates <- CabrioHixNaslagRaw[,c("Castor.Participant.ID", "Geboortedatum", "Dmammo", "Decho",
"Dechobiopt", "Duitslagechobiopt", "Dstereobiopt", "Duitstereobiopt", "Duitstereobiopt", "DMRI",
"DuitMRI", "DMRIbiopt", "DuitMRIbiopt", "D2MRIbiopt", "D2uitMRIbiopt", "D2echobiopt", "D2uitechobiopt"
, "DPET", "DuitPET", "DCT", "DuitCT", "DMRIlever", "Dleverbiopt", "Duitleverbiopt", "DMRIwervel",
"DuitMRIwervel", "Dbioptwervel", "Duitbioptwervel", "Dbotscan", "Duitbotscan", "Dbotbiopt",
"Duitbotbiopt", "Dmarkermamma", "Dmarkeraxilla", "DafnameDNA", "DuitDNA", "Deitjesfertiliteit",
"D1chemo", "Dverwpoli", "Deersteconsultmamma", "DMDO1", "DMDO2","DMDO3", "Ddefplan", "Dverwinteronco",
"D1bezinteronco", "Dvoorchemo", "Dverwradio", "D1bezradio", "Daanmfertiliteit", "Dbezfertiliteit",
"Dverwplastisch", "D1bezplastisch")]

#right date format using dmy function
for (col in 2:53) {
  Dates[[col]] <- dmy(Dates[[col]])
}

# Time biopsy and results
Dates$Echobiopt_uitslag <- ifelse(is.na(Dates$Dechobiopt) | is.na(Dates$Duitslagechobiopt) |
                                    Dates$Dechobiopt > Dates$Duitslagechobiopt,
                                  NA,
                                  as.numeric(difftime(Dates$Duitslagechobiopt, Dates$Dechobiopt, units
= "days")))

#Dates$Echobiopt_uitslag <- difftime(Dates$Duitslagechobiopt, Dates$Decho, units = "days")

# MRI datum en uitslag
Dates$MRI_uitslag <- ifelse(is.na(Dates$DMRI) | is.na(Dates$DuitMRI) |
                              Dates$DMRI > Dates$DuitMRI,
                            NA,
                            as.numeric(difftime(Dates$DuitMRI, Dates$DMRI, units = "days")))
```

```
#Dates$MRI_uitslag <- difftime(Dates$DuitMRI, Dates$DMRI, units = "days")

#PET scan uitslag PETscan
Dates$PETscan_uitslag <- ifelse(is.na(Dates$DPET) | is.na(Dates$DuitPET) |
                                  Dates$DPET > Dates$DuitPET,
                                NA,
                                as.numeric(difftime(Dates$DuitPET, Dates$DPET, units = "days")))


#Tweede echobiopt en uitslag
# Time biopsy and results
Dates$Tweede_echobiopt_uitslag <- ifelse(is.na(Dates$D2echobiopt) | is.na(Dates$D2uitechobiopt) |
                                           Dates$D2echobiopt > Dates$D2uitechobiopt,
                                         NA,
                                         as.numeric(difftime(Dates$D2uitechobiopt, Dates$D2echobiopt, units =
"days")))

#Afname en uitslag DNA First
Dates$DNA_uitslagDNA <- ifelse(is.na(Dates$DafnameDNA) | is.na(Dates$DuitDNA) |
                                 Dates$DafnameDNA > Dates$DuitDNA,
                               NA,
                               as.numeric(difftime(Dates$DuitDNA, Dates$DafnameDNA, units = "days")))

#Verwijzing huisarts en eerste consult
Dates$Verwijzinghuisarts_eersteconsult <- ifelse(is.na(Dates$Dverwpoli) | is.na(Dates$Deersteconsultmamma) |
                                                   Dates$Dverwpoli > Dates$Deersteconsultmamma,
                                                 NA,
                                                 as.numeric(difftime(Dates$Deersteconsultmamma,
Dates$Dverwpoli, units = "days")))
#Verwijzing en mammo
Dates$Verwijzinghuisarts_mammo <- ifelse(is.na(Dates$Dverwpoli) | is.na(Dates$Dmammo) |
                                           Dates$Dverwpoli > Dates$Dmammo,
                                         NA,
                                         as.numeric(difftime(Dates$Dmammo, Dates$Dverwpoli, units = "days")))
```

```r
#New dataframe with only intervalls
Intervals <- data.frame(Dates[,c(54:83)])

Means <- round(colMeans(Intervals, na.rm = TRUE), digits = 2)
Standarddev <- round(apply(Intervals, 2, sd, na.rm = TRUE), digits = 2)
Median <- round(apply(Intervals, 2, median, na.rm =TRUE), digits =2)
Q1 <- apply(Intervals, 2, quantile, probs = 0.25, na.rm = TRUE)
Q3 <- apply(Intervals, 2, quantile, probs = 0.75, na.rm = TRUE)
IQR <- Q3- Q1
Countparticipants <- apply(!is.na(Intervals), 2, sum)

Statistics <- data.frame(mean = Means, sd= Standarddev, median= Median, Q1= Q1, Q3=Q3, Countparticipants=
Countparticipants )


#Mann Whitney U test:vraag 6
# recoding Likert
# create a function to recode the values
recode_func <- function(x){
  ifelse(x <= 3, 0, 1)
}

# apply the recode function to the columns of QuestionsLikert
QuestionsLikert[,2:13] <- lapply(QuestionsLikert[,2:13], recode_func)

Vraag6vraag <- ((QuestionsLikert[,c("Castor.Participant.ID", "Vraag6tijdonderzoekenchemo")]))
Vraag6interval <-((Dates[,c("Castor.Participant.ID", "defplan_eerstechemo")]))
Vraag6tot <- merge (Vraag6vraag, Vraag6interval, by = "Castor.Participant.ID")

Result_Vraag6 <- wilcox.test(defplan_eerstechemo ~ Vraag6tijdonderzoekenchemo, data = Vraag6tot, exact = FALSE
, conf.int = TRUE)
print(Result_Vraag6)

ggplot(Vraag6tot, aes(x = factor(Vraag6tijdonderzoekenchemo), y = defplan_eerstechemo, group =
Vraag6tijdonderzoekenchemo)) +
  geom_boxplot() +
  labs(title= "Boxplot: Responses question 6 compared to interval",
    x = "Statisfaction (disstatisfied = 0 and statisfied = 1)",
       y = "Interval between definite treatment plan and start of NAC in days")+
  theme(axis.title=element_text(size = 12))
```

```r
Result_Vraag10 <- wilcox.test(voorlichting_eerstechemo ~ Vraag10voldoendetijdvoorlichtingstart, data =
Vraag10tot, exact = FALSE, conf.int = TRUE)
print(Result_Vraag10)

ggplot(Vraag10tot, aes(x = factor(Vraag10voldoendetijdvoorlichtingstart), y = voorlichting_eerstechemo, group
= Vraag10voldoendetijdvoorlichtingstart)) +
  geom_boxplot() +
  labs(title = "Boxplot: Responses question 10 compared to interval",
    x = "Statisfaction (disstatisfied = 0 and statisfied = 1)",
       y = "Interval nurse specialis consultation till start of NAC treatment in days")
theme(axis.title=element_text(size = 12))

#Mann Whitney U test:vraag 11
Vraag11vraag <- ((QuestionsLikert[,c("Castor.Participant.ID", "Vraag11snellerstarten")]))
Vraag11interval <-((Dates[,c("Castor.Participant.ID", "interne_eerstechemo")]))
Vraag11tot <- merge (Vraag11vraag, Vraag11interval, by = "Castor.Participant.ID")

Result_Vraag11 <- wilcox.test(interne_eerstechemo ~ Vraag11snellerstarten, data = Vraag11tot, exact = FALSE,
conf.int = TRUE)
print(Result_Vraag11)

ggplot(Vraag11tot, aes(x = factor(Vraag11snellerstarten), y = interne_eerstechemo, group =
Vraag11snellerstarten)) +
  geom_boxplot() +
  labs(title = "Boxplot: Responses question 11 compared to interval",
    x = "0 Not wanting to start treatment sooner, 1: wanting to start treatment sooner ",
       y = "Interval between visit oncologist and start of NAC treatment in days")+
theme(axis.title=element_text(size = 12))

# Calculate confidence interval
lower_ci <- result$estimate - qnorm(1 - (0.05 / 2)) * result$statistic / sqrt(length(Result_Vraag11$variable1
))
upper_ci <- result$estimate + qnorm(1 - (0.05 / 2)) * result$statistic / sqrt(length(Result_Vraag11$variable1
))

# Create the Mannwhitney dataframe with confidence interval
Mannwhitney <- data.frame(W = result$statistic,
                          P_Value = result$p.value,
                          Lower_CI = lower_ci,
                          Upper_CI = upper_ci)
Mannwhitney <- data.frame(W = Result_Vraag11$statistic, P_Value = Result_Vraag11$p.value)
```