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The Effects of Communication on Clinical Cancer Patients' Chemotherapy Outcomes Over Time: A Randomized Proof-of-Principle Study

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Research Master Thesis *Clinical and Health Psychology*

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Abstract

Relevance: Efficacy of doctor empathy and placebo education on treatment outcomes of people with cancer has been established across experimental and randomized-controlled trials (RCT).

Objective: i) to test whether distinct effects of clinician empathy and placebo information can also improve psychological and side effect outcomes of clinical advanced breast cancer patients undergoing chemotherapy and ii) to explore whether potential positive effects are persistent over treatment time.

Methods: In this 2x2 proof-of-principle study, before treatment start, a total of 23 Dutch, chemotherapy-naïve, female breast cancer patients undergoing chemotherapy were randomized (1:1:1:1) to short information videos on chemotherapy side effects. The four videos varied on levels of empathy (+ / -) and placebo information (+ / -). During treatment, participants' psychological (primary outcomes: anxiety, distress) and side effect outcomes were assessed by self-report questionnaires at 7-days, 21-days, and 52-days after treatment start.

Results: Repeated linear mixed model analyses indicated that empathy generally did not affect the level of anxiety ($p = .440$) or distress ($p = .056$). Empathy increased overall intensity ($\beta = 0.76$, 95% CI [.07; 1.44], $p = .032$) and number of side effects ($\beta = 0.78$, 95% CI [.11; 1.45], $p = .025$). Placebo information did not seem to influence intensity ($p = .269$) or number of side effects ($p = .975$). Only anxiety levels were indicated to increase over time ($p = .008$), both at 21-days ($\beta = 0.86$, 95% CI [.25; 1.47]) and 52-days ($\beta = 1.18$, 95% CI [.38; 1.98]) post-treatment start.

Conclusions: In clinical settings, advanced breast cancer patients may not profit from empathy or placebo information. Repeating the study with a larger sample is recommended to gain clarity on communication effects. The information videos may benefit training of clinical staff and treatment consultations.

Trial registration: at ClinicalTrials.gov [Identifier: NCT05390723].

Keywords: Clinician Empathy, Placebo, Informed Consent, Breast Cancer, Chemotherapy

Lay summary

Cancer patients' negative chemotherapy outcomes (e.g., anxiety or additional side effects) which are not caused by the chemotherapy itself are called nocebo effects. For nocebo effects to occur, the context in which chemotherapy is given (e.g., negative expectations, doctor-patient interactions) plays an important role. Communication in consultations, such as empathetic physicians or informing cancer patients about nocebo effects has been indicated to reduce negative treatment outcomes. This study investigated whether distinct effects of doctor empathy and nocebo information can generally improve chemotherapy outcomes of advanced breast cancer patients if tested in a real-life hospital setting and whether these effects last throughout treatment.

All 23 Dutch female breast cancer patients watched a short information video on common side effects of chemotherapy before treatment start. These four videos differed on whether they had reassuring empathetic statements and information on nocebo effects. During chemotherapy (after 7-, 21-, and 52-days), participants filled in questionnaires reporting their level of anxiety and distress as well as the number and intensity of their side effects.

In this study, empathy did not lower anxiety or distress levels and increased the number and intensity of side effects. Informing participants about nocebo effects also had no effect on how many or how intensely they experienced side effects. Over treatment time, results hinted that empathy may make the participants' anxiety worse.

To conclude, neither communication method improved advanced cancer patients' outcomes of undergoing chemotherapy in a hospital and instead may even have worsened some. The study needs to be repeated with more clinical, advanced cancer patients to obtain clearer conclusions. The short videos used could still be a first example of how treatment information processes may be altered in a cost- and time-effective way.

The Effects of Communication on Clinical Cancer Patients' Chemotherapy Outcomes Over Time

When undergoing chemotherapy, many cancer patients fear the adverse side effects associated with treatment (e.g., nausea, diarrhea, hair loss) (Beaver et al., 2016; Nies et al., 2018). When these side effects are non-medical and adverse, they are called nocebo-effects, harming the treatment experience of patients. These effects may leave patients more distressed and are considered a reason to stop treatment prematurely (von Blanckenburg et al., 2013; Myers et al. 1987). Potential factors influencing the occurrence of nocebo effects are contextual factors such as i) patients' negative expectations (Colloca & Miller, 2011; Faasse & Petrie, 2013), and ii) the clinician-patient relationship (e.g., degree of empathy) (Blasini et al., 2018; Colloca & Grillon, 2014; Pan et al., 2019). Hence, to diminish negative patient outcomes in the form of nocebo effects these contextual factors may be altered.

Therefore, emphasis on how physicians communicate with their patients is needed (Colloca & Finnis, 2012). One promising way is to be warm and empathetic during consultations. A broad range of randomized controlled and experimental trials have demonstrated that empathetic doctor-patient interactions can improve various psychological (e.g., psychological well-being) (Van Osch et al. 2017; Van Vliet et al. 2013) and physical (e.g., side effects, wound healing, pain) treatment outcomes (Michnevich et al. 2022; Pereira et al. 2016). This was indicated across various patient groups (e.g., with cancer or pain) and not only observed in the short-term (Kaptchuk et al., 2008; Van Osch et al., 2017; Van Vliet et al., 2013) but also long-term (Cánovas et al., 2018; Yang et al., 2018; Pereira et al. 2016). Another option to improve treatment outcomes could be to inform patients about the mechanisms underlying nocebo effects (Faasse et al., 2019; Michnevich et al., 2022; Pan et al., 2019). Recent evidence of an RCT and of a proof-of-concept study has indicated that such nocebo education can have beneficial effects on headache or gastrointestinal cancer patients' experience of side effects when evaluated shortly after obtaining the information (Pan et al. 2019) and over a longer time span (Michnevich et al. 2022).

Despite the largely positive findings of both communication strategies in the short-term, little is known about distinct and lasting treatment effects of empathy and nocebo information in clinical settings, especially within an advanced breast cancer patient population. A recent clinical RCT by Michnevich and colleagues (2022) also investigated the effects of long empathetically delivered nocebo information sessions on the side effects of gastrointestinal cancer patients. While results suggested that patients reported a significant reduction of side effects 12-weeks after the start of chemotherapy, empathy may have affected outcomes. Therefore, each communications strategy's unique contribution remains unclear. Similarly, the experimental video-vignette study by Meijers and colleagues (2022) investigated both combined and distinct effects of short, nocebo education and empathy video clips. In this study, findings suggested that informing analogue patients (cancer patients /- survivors and healthy women) about nocebo effects had no significant effect on side-effect

expectations. Only in combination with empathy patients' belief in the coping ability of parts of side effects were improved. Clinician empathy significantly enhanced patients' short-term trust, satisfaction, self-efficacy and even lowered part of the expected side effects. While distinct effects were considered, effects were neither evaluated in a clinical setting nor over treatment time.

Considering the above-mentioned gaps in the literature the aim of the current study was to i) evaluate whether distinct effects of clinician empathy and placebo information generally improve psychological- (anxiety and distress) and side effect (number and intensity) chemotherapy outcomes of clinical breast cancer patients. Moreover, it was aimed to ii) explore whether potential positive effects persist at later stages of treatment. Participants will be exposed to short informative videos on common side effects of chemotherapy. The effects of this will be measured using online questionnaires. Clarifying individual contributions of clinician empathy and placebo information may benefit the design of feasible future clinical treatment interventions aimed at improving the overall treatment experience of breast cancer patients. Moreover, the exploration of the long-term effectiveness of these effects can provide insight on the overall usefulness of using short video clips in clinical settings (in breast cancer patients), with it being more valuable if patients can profit from lasting improvements in treatment outcomes (Clarke et al., 2019).

Against this background, the following effects were hypothesized:

H1 & H2: A main effect of empathy on anxiety (i) and distress (ii), such that both anxiety and distress would be lower in participants who had viewed informative videos with additional empathy than in patients who did not see videos with additional empathy (Van Dulmen et al., 2004; Van Osch et al. 2017; Weiss et al. 2017).

H3 & H4: A main effect of empathy on both (iii) side effect intensity and (iv) number, such that participants who have viewed videos with additional empathy would have lower intensity and number of side effects compared to when they did not (Michnevich et al., 2022; Meijers et al., 2022).

H5 & H6: A main effect of placebo information on both side effect intensity (v) and side effect number (vi) such that it would be lower for participants who had received additional placebo effect information than for participants without this additional information (Faasse et al., 2019; Michnevich et al., Pan et al., 2019).

Lastly, as previous research provided hints at potential interaction effects, it was explored how the above-mentioned effects of clinician empathy/placebo information on psychological (Pereira et al. 2016; Yang et al., 2018) and side effect outcomes (Cánovas et al., 2018; Michnevich et al. 2022) potentially differed as a function of treatment time.

Methods

Design and development of information videos

This study is a 2x2 randomized controlled, clinical proof-of-principle study. Participants viewed short, randomly assigned informative video clips. All information videos showed a nurse specialist (of the research team) providing a standard explanation of the specific form of chemotherapy administered and commonly associated side effects. Videos differed in the level of reassurance or support during the treatment (+ / - empathy) and whether an explanation of the nocebo effect and its influence on side effects was given (+ / - nocebo information) (Table 1). The scripts were based on a previous study within this project (Meijer et al. 2022). With the help of researchers, oncologists and patient representatives, the video scripts were created, and pilot tested beforehand (Table 2) (entire script in Appendix A, pilot in Appendix B). This study is the final project of a larger research project called ‘Decreasing the Burden of Knowledge by Improving Communication with Seriously Ill Breast Cancer Patients’, which was funded by the Dutch Cancer Society (KWF).

Table 1.

All Four Possible Groups (Depending on Level of Empathy and Nocebo Information).

	No Nocebo Information	Additional Nocebo Information
No Empathy	Video 1 (Standard Information)	Video 3 (Nocebo Information only)
Additional Empathy	Video 2 (Empathy only)	Video 4 (Both combined)

Note. Based on Meijers et al. (2022), self-adapted.

Table 2.

Empathy and Nocebo Information Additions to Standard Video Script.

Additional Empathy ^a	Additional Nocebo information
<p>“Be assured that we will keep a close eye on you and will support and guide you throughout the chemotherapy process. And by ‘we’ I of course mean not only myself, but also the entire team of doctors, nurse specialists, and nurses.”</p> <p>“And please do know, whether it’s better or worse than anticipated, that you are not alone. Our whole team will support you as well as we possibly can.”</p> <p>“And once again, if you encounter any questions in the course of your chemotherapy, we are always here for you.”</p>	<p>“What not everyone knows is that side effects are not only caused by the medication itself. If people expect that they will experience a side-effect, or previously experienced a bothersome side-effect or are afraid of this, this can make side-effects worse. Scientific research has proven this. It is thus not odd at all that this happens. An example is that you for example, might get a headache as soon as you read the information leaflet about certain medication. And that does not make the headache any less real or any less bad. Negative experiences, expectations, and anxieties can worsen bodily reactions and side effects, such as headaches. If you know this, this might help to make sure you suffer less from these side effects in the future. Or that you can cope better with them. Maybe this is because you succeed in paying less attention towards those side effects or because you are less anxious if they occur.”</p>

^a Additional empathetic statements were given at three points during the video (the nocebo information was only given once). The entire script is in Appendix A. Based on Meijer et al. (2022), self-adapted.

Ethics

Ethical approval was exempted by the participating hospital [2022-03-25 METC22.0182] and obtained by the Ethical Committee of Leiden University [2022-06-02-L.M. van Vliet-V1-4056]. The study followed the guidelines of the Declaration of Helsinki, and all participants gave informed consent before the start of the study. The study was registered at ClinicalTrials.gov [Identifier: NCT05390723].

Participants and power

Participants were eligible if they were: a) breast cancer patients from the participating hospital, b) female c) ≥ 18 years of age d) chemotherapy naïve e) and treated with AC (Adriamycin Cyclophosphamide) curative neo-adjuvant chemotherapy (in 4 cycles). This type of treatment is commonly administered before the main treatment and aims to reduce the tumor in size (Andrade et al. 2013). To increase recruitment rates, the inclusion criteria were amended throughout the course of the study to also include patients who had previously undergone radiotherapy or breast-saving surgery. Lastly, for filling in the questionnaires online, patients needed to be f) capable (concerning their cognitive abilities), have g) internet access and h) have a sufficient understanding of the Dutch language.

In total, this project aimed to include $n = 40$ participants to obtain at least 80 % power to detect the largest difference between groups for two main and interaction effects at $p < .05$ and an effect size of $d = 0.28$. This calculation was justified by the previous project within this larger research project as well as with the design being a proof-of-principle study (Meijers et al., 2022).

Recruitment and procedures

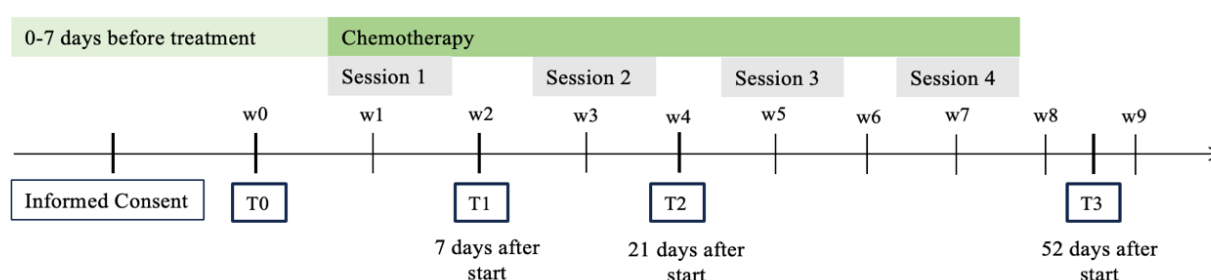
Eligible female breast cancer patients from the Antoni van Leeuwenhoek Hospital in Amsterdam were informed during their chemotherapy consultations. After the start of the study, this was amended so that nurses from the research team could also inform eligible patients with a call. If interested, patients were given a patient information folder (PIF) with a QR code so they could provide informed consent (IC) online. Moreover, to facilitate participation, providing the IC online was later amended with an additional option to combine giving IC and filling in T0 together with a researcher before their first chemotherapy session at the hospital. If IC was given online and the start of treatment was in the next seven days, researchers manually sent an online link to the first questionnaire (T0) by e-mail. In many instances, IC was given shortly before treatment began. Therefore, to prevent exclusion due to sending out T0 too late, this process was later amended and links to the first questionnaire were sent out automatically (via Qualtrics) if the start was within seven days. If the start was later, questionnaire links were still sent out manually. To be included in the study, participants initially needed to complete T0 before the day of their first chemotherapy session. This deadline was later pushed back to before the start of the chemotherapy (on the same

day) to further reduce exclusion. If questionnaires were not completed before the day of the first chemotherapy session, patients received reminders from the research team (by phone or e-mail).

For the first questionnaire (= T0) (see Fig. 1) participants were asked to provide demographic information, watch the randomly assigned video, and fill in information about their expectations concerning outcomes on psychological states and side effects of the treatment. The Qualtrics randomizer allocated participants in a ratio of 1:1:1:1 to the four videos. This ensured that participants and researchers were blind to the assigned video. One researcher of the team who handled dropouts, ensuring equal randomization, was not blind. Seven days after the first chemotherapy session, the next questionnaire (= T1) was sent out and participants had three days to complete it. For all questionnaires after treatment start, participants were asked to indicate psychological and side effect states. The following day, participants received a reminder call and email the day after if not reached by phone. On weekends participants only received a reminder mail and no calls, to avoid disturbing them. The same procedure was repeated for the next questionnaire (= T2), sent out 14 days after the treatment started (Fig. 1). After their third chemotherapy session, no questionnaire was sent. Lastly, after the fourth chemotherapy session participants received the final questionnaire 52-days after treatment start (= T3) (Fig. 1). The send-out of this questionnaire was amended from 14- to 10-days after the last chemotherapy session, to prevent an overlap with a subsequent treatment. This way participants did not need to fill it in on the day of their next chemotherapy session. As usual, participants had three days to complete it. Once the last questionnaire was completed, participants received a debriefing letter with information about the study specifics and their assigned condition. If dropped out before completing the study, participants received the debriefing letter then instead.

Figure 1.

Timeline of the study.



Note. *w = week, T0 pre (before video) /T0 post (after video) were assessed pre-chemotherapy. Based on von Blanckenburg et al. (2013), self-adjusted.

Materials

The timeline of events is presented in Figure 1. To ensure feasibility for clinical patients while undergoing treatment the questionnaires (Appendix C) were developed with patient representatives.

Pre-intervention (before chemotherapy 1 (= T0 pre))

Background characteristics. This included patients' level of education, marital status, living situation, migrant background and prior radiotherapy or breast-saving operations.

State anxiety (main outcome). State anxiety was assessed with the 10-item shortened version of the State-Trait Anxiety Inventory (De Vries et al., 2013). Participants were asked to indicate for 10 different feelings (e.g., I am worried) how often this applies to them (Numerical Rating Scale (NRS), ranging from 1 (not at all) to 4 (very much), (total possible range: 10 – 40). The scale has been translated to Dutch and this subscale was found to have high test-retest reliability (.87 - .96), good internal consistency as well as validity (0.91 – 0.96) (van der Ploeg, 1980).

Distress (main outcome). Participants' distress during and after treatment was assessed with the Distress Thermometer (DT) of the Emotion Thermometer tool (Mitchell et al. 2010), (ranging from 0 (no distress) to 10 (extreme distress). The overall tool has been found to have excellent reliability (.91), which also includes the DT subscale (.89) as well as modest values for the validation of the DT alone (sensitivity of 74 % and specificity of 76.9%; Mitchell et al. 2010).

Post-intervention (after chemotherapy 1,2,4 (= T1, T2, T3))

Psychological Outcomes (primary outcomes).

State Anxiety. Participants' level of anxiety (STAI-state) (see above) (De Vries et al. 2013).

Distress. Participants' level of distress (DT) (see above) (Mitchell et al., 2010).

Physical Outcomes (secondary outcomes).

Side effects (experienced). Entails a list of ten of the most experienced side effects (in Appendix C) of patients undergoing this type of chemotherapy. Side effects were selected based on the advice of clinical experts of the participating hospital. The side effects were evaluated in terms of:

- a) **Intensity:** the seriousness of experienced side effects (0-10 NRS, 'not present at all' to 'very intense', and 'not applicable' (NA) option (scored 0). Scores were added and divided by the total number of symptoms to calculate means (total possible range: 0 – 10). (Taken from the General Assessment of Side Effects scale (GASE; Von Blanckenburg et al. 2013) and adapted from Michnevich et al. (2022)).
- b) **Number:** the number of side effects experienced. Calculated by adding the number of patients' currently present symptoms at a given measurement point (total possible range: 0 – 10) (based on a modified GASE by Michnevich et al., 2022).

Statistical analyses

First, to portray potential differences in participants' background characteristics between conditions a one-way ANOVA and χ^2 tests were performed. Given the lack of power, no additional covariates were included in the main analyses. Pre-analysis, it was checked whether all assumptions

of linear models were met. The decision was made to not impute data for missing values and not correct for multiple testing, as the study was underpowered. Next, repeated linear mixed models analyses were performed in which the main effects of empathy, placebo information and their interaction over time were examined. *Time* was added to both main effect models to facilitate understanding of the later introduced interaction effects. An autoregressive covariance structure was chosen for all four outcomes. Model fit was estimated with Maximum Likelihood (ML) since the normal distribution of the sample did not require any correction. The three assessment occasions (T1, T2, T3) (level 2) were nested within the participants (level 1) and two models were created per outcome variable. Model 1 investigated the main effects of empathy and placebo information to answer the first aim. The second aim was answered with Model 2, which explored the interaction effects of empathy*time and placebo information*time.

For the primary outcome measures, in the simple model (model 1) on state anxiety and distress, the fixed effects of empathy, time and the random intercept were added. In the complex models (model 2), the same fixed and random effects were kept, plus the interaction term of empathy*time was added. For the secondary outcomes measures (intensity and number of side effects), in the simple model (model 1) the fixed effect of placebo information, empathy and time as well as a random intercept were added. The complex model (model 2) was extended with the interactions of empathy*time and placebo*time. Due to non-convergence, the random intercept was removed from the complex model for side effect intensity. The model fit between simple and complex models was assessed by comparing their information criteria AIC/BIC, with lower values indicating a better fit. All effects were standardized, and analyses were conducted using SPSS Version 28.0 at a significance level of $p < 0.05$.

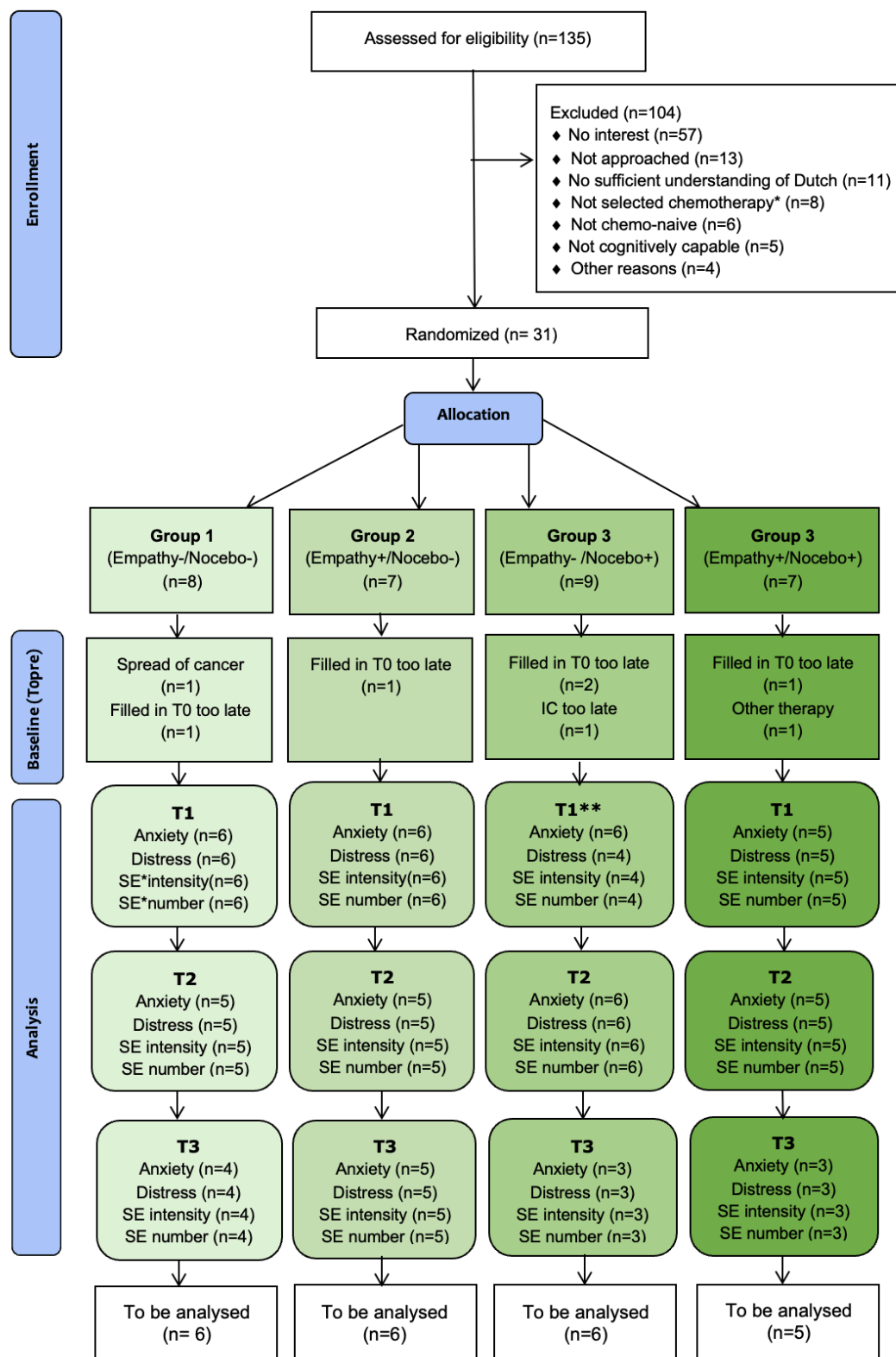
Results

Sample

Considering time restrictions, the decision was made to cut off the sample 6 weeks before the end of data collection (on 15th of June 2023). To this date, a total of $n=135$ patients were assessed concerning their eligibility for the study (Fig. 2). More than 104 participants were excluded beforehand, which is explained in more detail in Fig. 2. For the cut-off a sample size of $n = 23$ participants was reached. If they completed the first assessment point after the start of chemotherapy (T1), participants were included in the analyses. On average, participants were 47.9 years ($SD = 11.75$), primarily Dutch (73.9 %), had a high SES (high education, paid occupation, living situation; approximately 77 %) and most of them were naïve of prior treatment (87.5%). A summary of the background characteristics per group can be found in Table 3.

Figure 2.

CONSORT Diagram of Participant flow and randomization per group.



Note. *SE = Side effect; Table adapted from the Netherlands Healthcare Institute (2022); Data collection: 02.06.2022 to 15.06.2023. Reasons for the dropout between timepoints are i) due to stopping recruitment early ii) initial overlap of T3 with next treatment (see recruitment) or unknown reasons (** participants not filling in a (part of a) questionnaire).

Table 3.

Summary of Background Variables of all participants (divided by group).

Variables	Total N = 23	F (df); (p)	Group 1	Group 2	Group 3	Group 4
			(Empathy-/ Nocebo-) N = 6	(Empathy+/ Nocebo-) N = 6	(Empathy-/ Nocebo+) N = 6	(Empathy+/ Nocebo+) N = 5
	Mean (SD)		Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Age	47.90 (11.75)	F (3) = 1.65; p = 0.38	56.14 (9.41)	46.53 (14.98)	42.09 (11.49)	46.61 (6.82)
	N (%)	χ^2 (df) =; (p)	N (%)	N (%)	N (%)	N (%)
Marital status		χ^2 (3) = 7.10; p = 0.07				
Not Married	7 (30.4%)		0 (0%)	1 (16.7%)	4 (66.7%)	2 (40.0%)
Married	16 (69.6%)		6 (100.0%)	5 (83.3%)	2 (33.3%)	3 (60.0%)
Living Situation		χ^2 (3) = 2.35; p = 0.50				
Alone	4 (17.4%)		0 (0%)	1 (16.7%)	2 (33.3%)	1 (20.0%)
With Someone	19 (82.6%)		6 (100%)	5 (83.3%)	4 (66.7%)	4 (80.0%)
Occupation		χ^2 (3) = 3.21; p = 0.36				
Unemployed	5 (21.7%)		2 (33.3%)	1 (16.7%)	0 (0%)	2 (40.0%)
Paid Employment	18 (78.3%)		4 (66.7%)	5 (83.3%)	6 (100%)	3 (60.0%)
Prior Treatment**		χ^2 (3) = 3.05; p = 0.38				
No treatment	14 (87.5%)		5 (100%)	3 (75.0%)	2 (66.7%)	4 (100.0%)
Earlier treatment	2 (12.5%)		0 (0%)	1 (25.0%)	1 (33.3%)	0 (0%)
Migrant Background		(Fisher Exact) p = 0.77				
Native Dutch	17 (73.9%)		5 (83.3%)	4 (66.7%)	5 (83.3%)	3 (60.0%)
Western	2 (8.7%)		0 (0%)	0 (0%)	1 (16.7%)	1 (20.0%)
Non-Western	4 (17.4%)		1 (16.7%)	2 (33.3%)	0 (0%)	1 (20.0%)
Highest Education*		(Fisher Exact) p = 0.94				
Intermediate	6 (26.1%)		2 (33.3%)	1 (16.7%)	2 (33%)	1 (20.0%)
High	16 (69.6%)		4 (66.6%)	5 (83.3%)	3 (50%)	4 (80.0%)
Other	1 (4.3%)		0 (0%)	0 (0%)	1 (16.7%)	0 (0%)

Note. *Intermediate level refers to secondary school + vocational education, high to higher vocational education or a university degree. **Refers to prior lumpectomy or radio therapy.

Primary outcomes

Main effects of empathy (simple model)

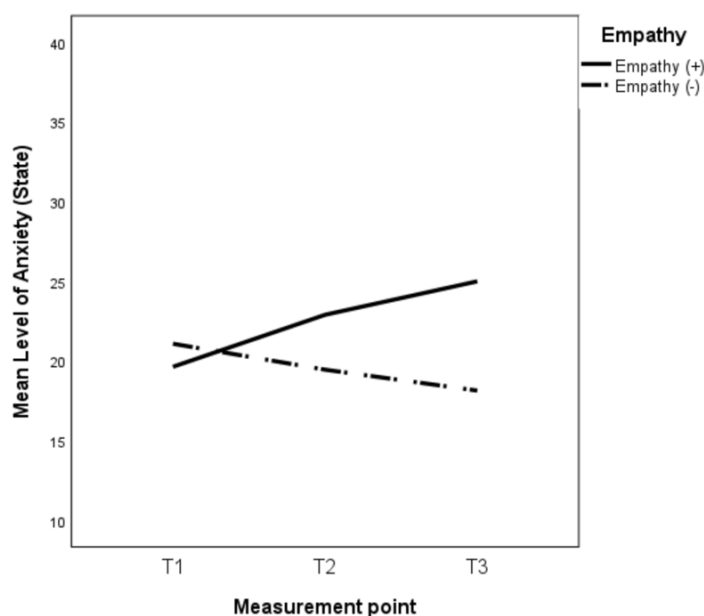
The assumptions for model 1 (linearity, homoscedasticity, normality of residuals) for both outcomes of anxiety and distress were met. Results of the linear mixed model analysis for model 1 of psychological outcomes indicate that there was no significant main effect of empathy on anxiety ($F(1, 22.44) = .62, p = .440$). This finding suggests that providing participants with additional empathetic statements or not, did not influence their general level of anxiety during treatment (see Table 4). For the outcome of distress, findings did not indicate a significant main effect of empathy either ($F(1, 19.89) = 4.11, p = .056$) suggesting that when participants viewed videos with additional empathetic statements this did not change their level of distress undergoing chemotherapy compared to when participants did not watch the empathetic video.

Interaction effects of empathy and time (complex model)

Running a linear mixed model analysis for model 2, the interaction effect of empathy*time on anxiety was explored. Assumptions for model 2 (linearity, homoscedasticity, normality of residuals) of both anxiety and distress were tested pre-analysis and were indicated to be met. Results demonstrated a statistically significant difference ($F(2, 21.03) = 6.06, p = .008$), indicating that participants' level of anxiety when watching videos with additional empathy, may differ as a function of time (Figure 3). Both during T2 ($\beta = 0.86; 95\% \text{ CI } [.25; 1.47]$) and T3 ($\beta = 1.18; 95\% \text{ CI } [.38; 1.98]$) (see Table 4) anxiety seemed to be higher than in participants who received no empathetic messages. This is in accordance with the raw means (Table 5), indicating a steady increase of anxiety. Effects on anxiety levels are estimated to be strong (see β -values), however, the wide CI suggest a degree of uncertainty, with effect sizes potentially varying. However, considering that there were only small differences (below 2 points) in the information criteria from the complex model (with interaction effects) ($BIC = 167.17$) to the simple model (main effects only) ($BIC = 169.13$), the simpler model was preferred and chosen as a final model to prevent overfitting (see above). For model 2 testing interaction effect of empathy*time on level of distress, no statistically significant difference was found ($F(2, 23.45) = .60, p = .558$). Therefore, for participants who received additional empathy, their level of distress did not seem to differ depending on time (Table 4).

Figure 3.

Interaction effect of empathy over time on level of anxiety.



Note. Explorative analysis. Although results were significant, given the model fit and lack of power this finding needs to be carefully interpreted.

Table 4.

Parameter estimates for main and interaction (exploratory) effects of psychological (anxiety and distress) and side effect (intensity and number) outcomes.

Model 1 – main effects empathy + placebo	Anxiety (state)			Distress			Side effect intensity			Side effect number		
	B	95% CI	P	B	95% CI	P	B	95% CI	P	B	95% CI	P
Empathy	.28	-.46 1.01	.440	.65	-.02 1.35	.056	.76	.07 1.44	.032*	.78	.11 1.45	.025*
Nocebo***	-	-	-	-	-	-	.38	-.31 1.06	.269	.01	-.66 .68	.975
T2	.18	-.15 .51	.277	.38	-.03 .78	.070	.47	.14 .82	.004**	.54	.21 .87	.002**
T3	.31	-.17 .79	.201	.37	-.15 .88	.153	.48	.16 .78	.010*	.58	.15 1.02	.011*
Model 2 – main effects empathy + placebo and interactions with time (exploratory)	Anxiety (state)			Distress			Side effect intensity****			Side effect number		
	B	95 % CI	P	B	95% CI	P	B	95% CI	P	B	95% CI	P
Empathy	-.28	-1.05 .50	.473	.42	-.38 1.22	.299	.50	-.23 1.23	.172	.81	.06 1.56	.034*
Nocebo	-	-	-	-	-	-	.30	-.44 1.03	.413	-.32	-1.07 .43	.398
T2	-.24	-.66 .19	.262	.17	-.42 .75	.564	.28	-.21 .76	.251	.15	-.36 .66	.554
T3	-.31	-.88 .27	.274	.13	-.61 .88	.718	-.07	-.74 .60	.833	.57	-.10 1.23	.089
Empathy*T2	.86	.25 1.47	.007**	.40	-.42 1.21	.326	.27	-.30 .83	.345	.29	-.29 .87	.319
Empathy*T3	1.18	.38 1.98	.006**	.44	-.58 1.46	.381	.60	-.19 1.39	.133	-.42	-1.20 .35	.270
Nocebo *T2	-	-	-	-	-	-	.08	-.48 .65	.765	.52	-.06 1.11	.079
Nocebo *T3	-	-	-	-	-	-	.41	-.39 1.20	.311	.63	-.16 1.41	.111

Note. The interaction effects were purely explorative and need to be carefully interpreted. Significance is marked in bold letters. B = standardized beta *p < 0.05, ** p < 0.01. - = effect not tested for this outcome. *** nocebo = nocebo information. **** interaction model for side effect intensity does not include a random intercept due to nonconvergence of model.

Secondary outcomes

Main effects of empathy and placebo information (simple model)

Assumption checks for model 1 on linearity, homoscedasticity, and normality of residuals for both side effect intensity and number, yielded no apparent violations, suggesting assumptions to be met. The linear mixed model analysis for model 1 of side effect outcomes suggested a significant main effect of empathy on side effect intensity ($F(1, 21.73) = 5.29, p = .032$). However, the effect found was the opposite of the hypothesized direction. Findings indicated that participants who received empathy experienced more intense side effects ($\beta = 0.76, 95\% \text{ CI } [-.31; 1.06]$) (see Table 4) compared to the participants who did not (Table 5). A significant main effect of empathy ($F(1, 20.63) = 5.84, p = .025$), was also found for the number of side effects. As for side effect intensity, findings indicated the contrary to the initially hypothesized effects, suggesting that when participants were assigned to videos with empathetic messages, it increased their number of side effects ($\beta = 0.78, 95\% \text{ CI } [.11; 1.45]$) (Table 4 and 5). The strength of the effect of empathy on both side effect outcomes is estimated to be strong (see β). However, considering the wide confidence intervals, effect sizes may be smaller or larger.

No statistically significant difference was found for placebo information on side effect intensity ($F(1, 21.88) = 1.29, p = .269$), which suggests that providing participants with additional placebo information had no significant influence on how intense they indicated their side effects to be. Additional placebo information was also indicated to have no statistically significant effect on the total number of side effects experienced by participants ($F(1, 20.82) = .00, p = .975$). This implies that there is no difference in terms of perceived intensity or amount of side effects between participants who were informed about placebo effects and participants who were not.

Interaction effects of empathy and time and placebo information and time (complex model)

Assumption checks for model 2 of side effect intensity and number indicated no violations on linearity, homoscedasticity, or normality of residuals, demonstrating assumptions to be met. Running a linear mixed model analysis for model 2 testing the interaction effects for side effect intensity, yielded no significant result for either empathy*time ($F(2, 33.46) = 1.17, p = .321$) or placebo*time ($F(2, 33.38) = .60, p = .555$) (Table 4). The same applied to the results of the analysis of model 2 for side effect number, as no statistically significant difference was found for the interaction of empathy*time ($F(2, 22.26) = 2.37, p = .117$) and placebo*time ($F(2, 22.23) = 2.02, p = .156$) (Table 4). This suggested that neither empathy or placebo information differed concerning its effect on intensity or number of side effects as a function of time.

Table 5.*Raw uncontrolled means of each outcome per timepoint.*

	T	Empathy Without (+)		With (+)		Nocebo Information Without (-)		With (+)	
		Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N
Anxiety (state) Range: (10 to 40)	T1	21.08 (5.02)	12	19.64 (6.04)	11	20.50 (5.76)	12	20.27 (5.37)	11
	T2	19.45 (3.88)	11	22.90 (5.47)	10	20.90 (5.04)	10	21.27 (5.02)	11
	T3	18.14 (2.12)	7	25.00 (5.83)	8	23.56 (5.73)	9	19.17 (4.67)	6
Distress Range: (0 to 10)	T1	5.00 (2.45)	10	5.91 (2.84)	11	5.25 (2.77)	12	5.78 (2.59)	9
	T2	5.18 (2.64)	11	7.40 (2.27)	10	6.00 (2.26)	10	6.45 (3.08)	11
	T3	5.00 (1.83)	7	7.63 (1.41)	8	6.33 (2.60)	9	6.50 (1.05)	6
Side effect intensity Range: (0 to 10)	T1	2.60 (1.75)	10	3.51 (1.97)	11	2.81 (1.66)	12	3.43 (2.19)	9
	T2	3.02 (1.63)	11	4.65 (1.44)	10	3.37 (1.47)	10	4.18 (1.91)	11
	T3	2.04 (.65)	7	4.74 (1.64)	8	3.07 (1.36)	9	4.10 (2.45)	6
Side effect number Range: (0 to 10)	T1	5.20 (2.49)	10	6.64 (2.29)	11	6.00 (2.37)	12	5.89 (2.67)	9
	T2	5.45 (2.38)	11	8.40 (1.35)	10	6.60 (2.72)	10	7.09 (2.26)	11
	T3	5.57 (2.07)	7	7.25 (1.28)	8	6.22 (1.99)	9	6.83 (1.72)	6

Note. Mean item scores at a given measurement point and with information on number of participants (n) are presented in this table.

Discussion

The present proof-of-principle study aimed to investigate whether distinct effects of clinician empathy and nocebo information can generally improve the psychological and side effects outcomes of advanced breast cancer patients when undergoing AC neoadjuvant chemotherapy in a clinical setting. Second, it was explored how persistent these effects are over treatment time. Results did not provide support for a positive effect of empathy, as participants' level of anxiety or distress did not decrease generally and not at later stages of chemotherapy. On the contrary, empathy seemed to elevate participants' anxiety levels both 21- and 52-days after treatment start. Similarly, empathy was suggested to increase the overall intensity and number of side effects experienced, but not over the treatment time. Lastly, nocebo information has neither influenced the overall intensity or quantity of side effects nor at later points during treatment.

As opposed to most of the literature (e.g., Hoffstädt et al. 2020; Van Osch et al. 2017; Van Vliet et al. 2013) in this study empathy generally did not reduce either anxiety or distress. Both the chosen patient group as well as the treatment setting might have influenced how empathy was received. In a systematic review on clinical empathy, only a few of the randomized-controlled studies with anxiety- or distress-reducing effects were conducted with cancer patients (Howick et al., 2018). Although a recent clinical observational study found anxiety-reducing effects of empathy in advanced breast cancer patients, no chemotherapy had been administered (Hoffstädt et al., 2020). On top of that, not only do previous studies suggest that breast cancer patients have a higher anxiety prevalence (41 %) compared to other patient groups (e.g., ovarian cancer (approximately 27 %) (Hashemi et al. 2020), but these patients' anxiety levels also seem to be even higher during chemotherapy (Charalambous et al. 2017; Lim et al. 2011). Hence, empathy effects were perhaps not strong enough to counter the anxiety-provoking situation of receiving chemotherapy in this already more anxious patient group. Given that only few studies demonstrated positive long-term effects of empathy on anxiety (or distress) in clinical treatment cancer settings (e.g., Zachariae et al. 2003; Pereira et al. 2016) as well as being opposed to a suggested general decrease of anxiety over treatment time (Mendes et al., 2005 as cited in Pereira et al. 2016) no logical theoretical explanation can be given why in this study empathy increased anxiety at later points in time (Schneider et al. 2016). Therefore, issues with statistical power need to be highlighted which have likely affected both the lack of and negative empathy effects. This may even be more problematic if considering that the above-mentioned systematic review (Howick et al., 2018) indicated that empathy only tended to decrease anxiety (and pain) of various patient groups slightly, making it plausible to be harder to detect in such a small sample.

In contrast to previous studies (Meijers et al., 2022; Michnevich et al. 2022; Pan et al. 2019), informing about nocebo effects generally did not change the intensity or number of side effects in this study, even at later stages of treatment. Hypothetically, the absence of effects could be rooted in the variability of breast cancer patients' side effect information preference, as was shown in the

qualitative study by Van Vliet and colleagues (2021). Based on the findings of a recently published multicenter survey and an experimental online study informing patients about nocebo effects, differences may persist even after knowing about nocebo effects' adversity. After learning about nocebo effects, teenage patients preferred more information, while adult patients preferred to know less about side effects (of antidepressants) (de Bruijn et al. 2023; Nestoriuc et al. 2021). Therefore, it may be possible that participants' individual preferences on side effect information may have cancelled nocebo information effects on experienced side effects. Another perspective may be that without delivering nocebo information empathetically, the effects were not strong enough to reduce participants' side effects. Support for this assumption is provided by the earlier discussed experimental study of Meijers and colleagues (2022) which only found coping ability for side-effects to be improved when nocebo information was combined with empathy. Similarly, although the findings of Michnevich and colleagues (2022) suggested reduced long-term reported side effects of gastrointestinal cancer, this effect may have not been seen without empathy. In turn, this study's finding that distinct effects of empathy generally increased the number and intensity of side effects is even more surprising given the above-mentioned considerations. While to our knowledge, no clinical studies exist that specifically suggest distinct positive effects of physician empathy on treatment side effects, various studies suggest benefits on other physical treatment outcomes (e.g., pain, diabetic outcomes) (Hojat et al. 2011; Kaptchuk et al. 2008; Pereira et al, 2016). Consequently, the answer to the nocebo effect null and negative empathy findings on participant's side effects may likely also be rooted in problems with statistical power.

This study came with several limitations. First, due to the slowness of recruitment, the already small sample further shrunk, leading to low statistical power making findings imprecise. Not only does this limit finding existing true effects, but it also heightens the chances of falsely finding untrue significant results (Tsang et al. 2009). Dealing with a small sample further negatively affected decisions concerning analyses, as no baseline or other control variables were added to models, no outliers were excluded, missing values were not imputed and corrections for multiple testing were not applied. Without being able to include baseline assessments it cannot be excluded that pre-existing differences of participants confound manipulation effects (Nunes et al. 2011; Twisk et al. 2018). This specifically applies to baseline distress levels which may determine the effectiveness of a psychological intervention (Schneider et al., 2010). Additionally, considering that time points were not equally spaced, this may have negatively affected the models' validity due to various reasons (e.g., not fulfilling model assumptions, difficulty of estimating covariance structures) (Nunez-Anton & Woodworth, 1994). Lastly, one must note that the external validity of the study may be restricted due to the homogenous nature of the sample, being predominately white, highly educated, and Dutch-speaking as well as limiting recruitment to one hospital site.

Various aspects need to be further researched to increase understanding and draw more thorough conclusions. First, as also noted by experts in the field (Evers et al. 2021), it could be

important to investigate the influence of patients' information preference on the reception of nocebo information messages. For example, patients with a low need compared to a high need for information on side effects may profit differently from nocebo information presented in this way. Gaining an understanding of potential moderating forces could help tailor treatment information more effectively. Lastly, considering that both recently published cancer studies on empathetically delivered nocebo information showed an effect on expectations or experiences of side effects, future studies should investigate whether nocebo information interventions only improve cancer patients' side effects if administered in an empathetic manner. Lastly, and most importantly, this small-scale proof-of-principle study needs to be replicated with a much larger, varied sample to estimate the general effectiveness of empathy and nocebo information in a clinical advanced breast cancer sample undergoing chemotherapy and the durability of these effects.

While the findings of this study did not show beneficial effects of either empathy or nocebo information, it still has important implications for clinical care. Although it is broadly recognized that empathy should be incorporated in consultations (Evers et al., 2021; Howick et al. 2018), cost-effectiveness is a common concern (Howick et al., 2020). This could be facilitated by using short treatment information video clips. By providing empathy and meeting patients' information needs, clinicians may be able to build stronger relationships with their patients and provide cancer patients with support to go through the burdensome experience of chemotherapy. Moreover, the produced chemotherapy information videos could easily be taken to train clinical staff on methods how to integrate nocebo information and reassuring statements in standard care with the possibility to adapt it to other patient groups and treatment forms (Pereira et al., 2016; Zhang et al., 2023). In turn, this may facilitate job procedures not only benefiting the clinical staff themselves but the overall treatment experience of advanced breast cancer patients by strengthening trust in providers as well as overall satisfaction.

To conclude, neither clinician empathy nor nocebo information positively affected the sampled patients' treatment outcomes, not generally nor over time. While some results hinted at a potential negative impact of empathy, no strong conclusions should be drawn considering the lack of power in this study. With that being said, without repeating the study with a larger sample, the validity of the found effects cannot be entirely disregarded either.

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Appendix A.**Complete Translated Video Script (including Empathy / Nocebo Information Manipulations).**

English version (text)	Camera perspective
<p>Not long ago you spoke with the nurse specialist and received information about the AC-chemotherapy, which you will start shortly.</p> <p>This information video is an addition to that conversation.</p>	<p>Patient + partner arrive at AVL, talking to each other, both looking rather anxious.</p> <p>Enter through the revolving door</p> <p>Voice of nurse specialist (Elise Sluiter) starts. Nurse specialist is shown standing on the balcony on the first floor, looking out over the hall. Nurse specialist 's name (Elise Sluiter) and her position (nurse specialist (trainee)) are shown beside her.</p> <p>Patient + partner arrive at the polyclinic</p>
<p>AC chemotherapy consists of two medications: Adriamycin and cyclophosphamide. The chemotherapy will be administered every two weeks.</p> <p>Before the chemotherapy session, the patient has a blood test.</p> <p>After that, they go to the doctor or nurse specialist.</p> <p>The decision about whether to proceed with the chemo session depends on the results of the blood tests and any complaints the patient may be experiencing.</p> <p>The patient goes to the day unit where she will receive the chemotherapy via a drip.</p> <p>The day after the chemotherapy, you will receive an injection at home.</p> <p>For that, we will organize a visit from the community nurse.</p>	<p>Standup nurse specialist walking along the corridor in the U-building</p> <p>Shot of a screen, where the patient clicks on "blood test"</p> <p>Patient walking to the blood test department</p> <p>Interview-style nurse specialist in U-building corridor</p> <p>Entering the outpatient clinic/day unit. One other patient is lying in one of the beds. (one shot from in front of the patient and one from behind)</p> <p>Interview-style nurse specialist in in U-building corridor</p> <p>Close-up shot of nurse (saying he will attach the drip now)</p> <p>Close-up of patient's face (looks tense)</p> <p>Close-up clicking/starting the drip</p> <p>Shot of patient's face and drip machine</p> <p>Standing interview shot of nurse specialist (U-building)</p> <p>At the patient's home, sitting down at the table, together with the community nurse</p> <p>Close-up shot of the community nurse's face</p> <p>Interview-style nurse specialist U-building corridor</p>

<p>The patient can pick up the medication for the injection on the day of the chemotherapy, at the onco-pharmacy.</p> <p>This medication stimulates the bone marrow to produce white blood cells, which are important for the immune system.</p>	<p>Close-up shot of patient's face. Talking to the nurse, looking a little anxious/tense</p> <p>Close-up shot of community nurse's face</p> <p>Shot of conversation between the patient and the community nurse</p>
<p>Empathy manipulation</p> <p>Be assured that we will keep a close eye on you, and will support and guide you throughout the chemotherapy process. And by 'we' I of course mean not only myself, but also the entire team of doctors, nurse specialists, and nurses.</p>	<p>Close-up shot of nurse specialist's face, in a waiting area in the U-building. In the background, we see a decorative ball depicting hands and a heart.</p>
<p>AC chemotherapy has side effects. These sometimes occur, but not always. It differs per person.</p> <p>Most side effects are temporary, and the degree to which they occur has no implications for the results of the treatment.</p> <p>The most common side effects are:</p> <ul style="list-style-type: none"> ○ Nausea and vomiting <p>This can be caused by irritation of the lining of the stomach.</p>	<p>The patient and her partner get to the waiting room and sit down. They talk together; close-up of each face.</p> <p>Walking stand up nurse specialist walking in the corridor of U-building</p> <p>Another nurse specialist (Mirte) walks into the waiting room and calls the patient</p> <p>Interview-style shot of first nurse specialist in U-building corridor.</p> <p>Second nurse specialist, the patient, and her partner sit down in one of the rooms in the polyclinic.</p> <p>Close-up of partner's face (looking at the patient)</p> <p>Close-up of patient's face (listening to the nurse specialist)</p> <p>Close-up of second nurse specialist 's face</p> <p>In the frame, a text box appears showing the words "Nausea and vomiting"</p> <p>Standing interview with first nurse specialist in U-building corridor</p> <p>Close-up face second nurse specialist (still in the room in the polyclinic)</p>

<p>To support you, you will receive anti-nausea medication.</p> <ul style="list-style-type: none"> ○ Impact on bone marrow function <p>The chemotherapy impacts bone marrow function.</p> <p>This will mean you produce fewer new blood cells, which can lead to anemia and a higher chance of infections and hemorrhaging,</p> <p>such as a nosebleed that will not stop.</p> <ul style="list-style-type: none"> ○ Hair loss <p>This chemotherapy has a very high risk of causing hair loss.</p> <p>You could consider using scalp cooling to prevent hair loss, or consider getting a wig, hat, or scarf.</p> <ul style="list-style-type: none"> ○ Menstrual irregularities 	<p>Shot of the faces of the patient and her partner (in conversation with the nurse specialist)</p> <p>Scene shot of the room in the polyclinic, with in the background the nurse specialist, in conversation with the patient and her partner</p> <p>In the frame, the text on the bar changes to “Impact on bone marrow function”</p> <p>Interview-style shot of first nurse specialist in U-building corridor</p> <p>Patient half lying/sitting in bed at the outpatient clinic/day unit, with drip in her arm</p> <p>Close-up shot of the tube from the drip on her arm</p> <p>First nurse specialist sits down next to the patient in bed. Another patient is lying in a bed next to her.</p> <p>Close-up of the patient’s face, talking</p> <p>Close-up of first nurse specialist’s face (looks empathic)</p> <p>In the frame the text on the bar changes to “Hair loss”</p> <p>Standing interview of nurse specialist in U-building corridor</p> <p>Moving shot in the patient’s living room. The patient and her partner are sitting on the couch. The patient is looking through a magazine; her partner is looking at his phone.</p> <p>Shot of the faces of both the patient and her partner</p> <p>Close-up of patient leafing through the magazine, zooming in on an article about hair and short hair styles</p> <p>Shot of the patient sitting on the couch, looking through the magazine</p> <p>In the frame the text on the bar changes to “Menstrual irregularities”</p> <p>Interview-style shot of nurse specialist in U-building corridor</p> <p>Patient and partner sitting on the couch, partner shows patient something on his phone</p> <p>Close-up of phone showing text about chemotherapy</p> <p>Shot of the patient’s face, with part of her partner’s face in the foreground</p>
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<p>You may have menstrual irregularities. This can vary from “skipping a period” to your menstrual cycle stopping completely.</p> <p>You may also experience menopause symptoms such as hot flushes.</p> <p>After the chemotherapy, your period may come back.</p> <ul style="list-style-type: none"> ○ Irritation of the oral mucosa <p>Irritation of mucous membranes in the mouth can also occur.</p> <p>You might experience complaints such as a dry mouth, thicker saliva, or mouth ulcers. Good oral hygiene is important.</p> <ul style="list-style-type: none"> ○ Possible side effects of Neulasta injection <p>You may also experience side effects from the injection you receive the day after your chemotherapy. This might include flu-like symptoms that last for a few days, aching joints, headaches, or nausea.</p> <p>You can use paracetamol for these.</p>	<p>In the frame, the text on the bar changes to “Irritation of the oral mucosa”</p> <p>Interview-style shot of nurse specialist in U-building corridor</p> <p>Shot of the patient sitting on a chair, reaching for a cup and drinking</p> <p>Close-up shot of the patient drinking</p> <p>Close-up of the cup in her hand</p> <p>In the frame the text on the bar changes to “Side effects of Neulasta injection”</p> <p>Interview-style shot of nurse specialist in U-building corridor</p> <p>Patient and partner sitting on the couch</p> <p>Close-up of patient’s face, reading</p> <p>Close-up of partner’s face, on his phone</p> <p>Patient and partner sitting next to each other on the couch</p>
<p>Nocebo-effect manipulation</p> <p>What not everyone knows is that side effects are not only caused by the medication itself.</p> <p>If people expect that they will experience a side-effect, or previously experienced a bothersome side-effect or are afraid of this, this can make side-effects worse. Scientific research has proven this. It is thus not odd at all that this happens.</p> <p>An example is that you for example, might get a headache as soon as you read the information leaflet</p>	<p>Patient outside, walking beside the water</p> <p>Nurse specialist walks slowly towards the camera in a corridor in the hospital</p> <p>Shot outside of a bridge, with a cyclist cycling over it</p> <p>Shot of the patient sitting by the water (camera goes slowly up from her hand on her knee, up to her face)</p> <p>Shot of reflections on the water</p>

<p>about certain medication. And that does not make the headache any less real or any less bad.</p> <p>Negative experiences, expectations, and anxieties can worsen bodily reactions and side effects, such as headaches. If you know this, this might help to make sure you suffer less from these side effects in the future. Or that you can cope better with them. Maybe this is because you succeed in paying less attention towards those side effects or because you are less anxious if they occur.</p>	<p>Shot of an empty little boat at the side of the water, trees on the riverbank</p> <p>Shot of patient's face, with the water in the background. Focus slowly moves from the background to the patient's face</p> <p>Boat at the side of the water</p> <p>Close-up of patient's face</p> <p>Shot from behind the patient, sitting by the water</p> <p>Wide shot, patient sitting by the water</p>
<p>Empathy Manipulation</p> <p>And please do know, whether it's better or worse than anticipated, that you are not alone. Our whole team will support you as well as we possibly can'</p>	<p>Close-up nurse specialist, waiting area U-building</p> <p>Patient walks away from the water</p>
<p>If you do experience side effects, there are certain cases when you need to call your doctor or nurse specialist. Even if in the evening, or the weekend, or in the middle of the night.</p> <p>If you experience</p> <ul style="list-style-type: none"> - Nausea or vomiting that persists even after you take medication - Spontaneous bruising - Frequent nosebleeds that are difficult to stop - A temperature above 38.5 C <p>If you have any other questions about the treatment and/or side effects, you can contact us during office hours to arrange a telephone appointment with your doctor or nurse specialist.</p>	<p>Standup Interview shot of nurse specialist on the first floor balcony</p> <p>Close-up shot of switchboard operator (with headset)</p> <p>The frame turns slightly white, background photo of switchboard operator stops, text appears (successively)</p> <ul style="list-style-type: none"> - Persistent nausea or vomiting - Spontaneous bruising - Frequent nosebleeds - Temperature above 38.5 C - <p>Shot of a different part of the patient's living room (two chairs beside a little table). Patient sitting on the chair with her phone and an information leaflet in her hand.</p> <p>Patient types on her phone, puts down the information leaflet, and calls</p>
<p>The phone number you can use to contact us 24/7 is 020 – 512 9111. Our switchboard operators will connect you through to the right department.</p>	<p>Standing interview with nurse specialist, first-floor balcony</p> <p>Phone number appears on the screen</p> <p>3 close-up shots of three different switchboard operators, wearing a headset and sitting at their computer</p>
<p>Empathy manipulation</p> <p>And once again, if you encounter any questions in the course of your chemotherapy, we are always here for you.</p>	<p>Interview style shot of nurse specialist on the first-floor balcony</p>

Appendix B.

Pilot Procedure WP4 (17.12.2022)

We will pilot the videos in two different phases. This procedure is based on a previous study (Meijers et al, submitted).

Preparations: The scripts were created in collaboration with the research team (clinicians, researchers, nurses).

Validation 1: Written scripts

1. Experts

The written scripts will be send to different experts: researchers, patients, oncologists, nurses, patient representative

Now: 2 researchers, 1 patient, 1 oncologist, 1 nurse, 1 patient representative

2. Questions (based on WP3)

- Realism (not at all, partially, very realistic)
- Internal validity: manipulations (1-10 scale)
- Other comments

Script 1 = Nocebo information + / Empathy +

Script 2 = Nocebo information - / Empathy +

Script 3 = Nocebo information + / Empathy -

Script 4 = Nocebo information - / Empathy -

Validation 2: Videotaped scripts

1. Experts

The videotaped scripts will be send again to the same group of experts

Now: 2 researchers, 1 patient, 1 oncologist, 1 nurse, 1 patient representative

2. Questions (Based on WP3)

Comments on:

- Internal validity 1-10 scale
 - Realism (not at all, partially, very realistic)
-

Appendix C.

Complete Questionnaires T0 – T3 (in Dutch)

Questionnaire T0 Pre Video (in Dutch (Original Version))

Achtergrondinformatie

1. Wat is uw geboortedatum?

Vul deze cijfermatig in: dd/mm/jjjj (voorbeeld: 8 januari 1980 = 08/01/1980).

2. Wat is uw hoogst voltooide opleiding? (Een opleiding afgerond met diploma of voldoende getuigschrift)

- Geen opleiding (lager onderwijs: niet afgemaakt) (1)
- Lager onderwijs (basisschool, speciaal basisonderwijs) (2)
- Lager of voorbereidend beroepsonderwijs (zoals LTS, LEAO, LHNO, VMBO) (3)
- Middelbaar algemeen voortgezet onderwijs (zoals MAVO, (M)ULO, MBO-kort, VMBO-t) (4)
- Middelbaar beroepsonderwijs en beroepsbegeleidend onderwijs (zoals MBO-lang, MTS, MEAO, BOL, BBL, INAS) (5)
- Hoger algemeen en voorbereidend wetenschappelijk onderwijs (zoals HAVO, VWO, Atheneum, Gymnasium, HBS, MMS) (6)
- Hoger beroepsonderwijs (zoals HBO, HTS, HEAO, HBO-V, kandidaats wetenschappelijk onderwijs) (7)
- Wetenschappelijk onderwijs (universiteit) (8)
- Anders, namelijk... (9) __

3. Wat is op dit moment uw huidige burgerlijke staat?

- Alleenstaand (1)
- Gehuwd (2)
- Samenwonend (3)
- LAT relatie (vaste relatie, niet samenwonend) (4)
- Gescheiden/uit elkaar (5)
- Weduwe/partner overleden (6)

4. Met wie woont u momenteel samen?

- Alleen (1)
- Partner (2)
- Kinderen onder de 18 (3)
- Kinderen boven de 18 (4)
- Ouders (5)
- Anders (6)

5. Wat is het geboorteland van uzelf?

- Nederland (1)
 - Duitsland (10)
 - België (12)
 - Frankrijk (13)
 - Indonesië/voormalig Nederlands-Indië (2)
 - Suriname (3)
 - Marokko (4)
 - Turkije (5)
 - Voormalig Nederlandse Antillen en Aruba (7)
 - Ander land binnen Europa, namelijk... (9)
-
- Ander land buiten Europa, namelijk... (11)
-

6. Wat is het geboorteland van uw vader?

- Nederland (1)
- Duitsland (10)

- België (13)
 - Frankrijk (14)
 - Indonesië/voormalig Nederlands-Indië (2)
 - Suriname (3)
 - Marokko (4)
 - Turkije (5)
 - Voormalig Nederlandse Antillen en Aruba (6)
 - Ander land binnen Europa, namelijk... (9)
-
- Ander land buiten Europa, namelijk... (11)

7. Wat is het geboorteland van uw moeder?

- Nederland (1)
 - Duitsland (10)
 - België (12)
 - Frankrijk (13)
 - Indonesië/voormalig Nederlands-Indië (2)
 - Suriname (3)
 - Marokko (4)
 - Turkije (5)
 - Voormalig Nederlandse Antillen en Aruba (7)
 - Ander land binnen Europa, namelijk... (9)
-
- Ander land buiten Europa, namelijk... (11)
-

8. Welke omschrijving is op dit moment het meest op u van toepassing? Ik ben/heb:

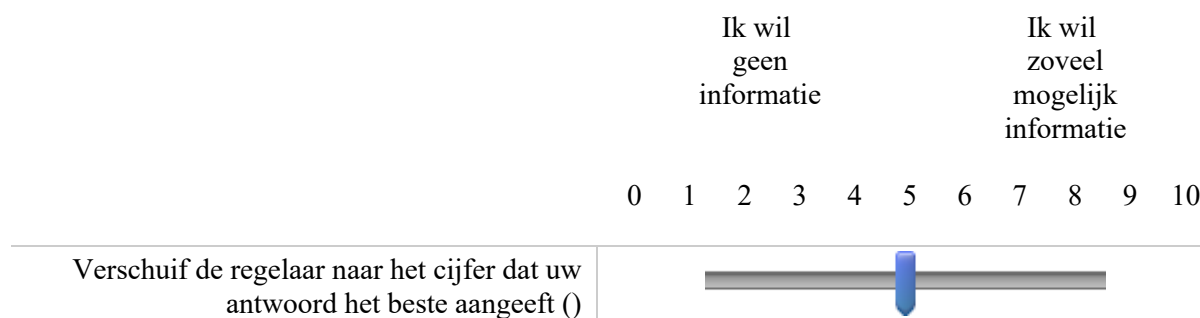
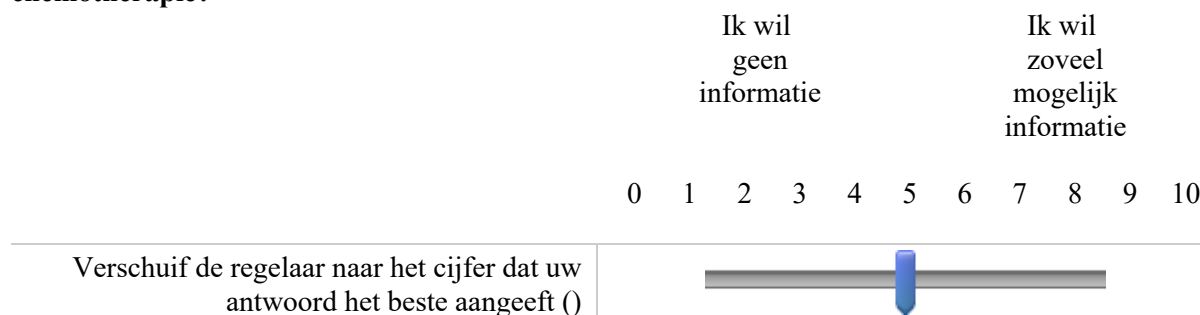
- Schoolgaand/studerend (1)
- Betaald werk (2)
- Werkloos/werkzoekend (geregistreerd bij het arbeidsbureau) (3)
- Arbeidsongeschikt/WIA (WAO) (4)
- Geen betaald werk (5)
- Pensioen (AOW, VUT, enz.) (6)
- Anders, namelijk... (7) _____

9. Heeft u voor deze chemotherapie een borstsparende operatie en radiotherapie gehad?

- Ja (1)
- Nee (2)

Coping - Informatie behoefte

De volgende 2 vragen gaan over uw behoefte aan informatie over de chemotherapie.

10. In hoeverre wilt u informatie ontvangen over de chemotherapie?**11. In hoeverre wilt u informatie ontvangen over mogelijke bijwerkingen van de chemotherapie?**

Gevoelens - Angst

12. Hieronder vindt u een aantal uitspraken, die door mensen gebruikt worden om zichzelf te beschrijven. Lees iedere uitspraak door en vink het bolletje aan rechts van die uitspraak om daarmee aan te geven hoe u zich in het algemeen voelt.

	Bijna nooit (1)	Soms (3)	Vaak (4)	Bijna altijd (5)
1. Ik voel me prettig (1)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
2. Ik voel me nerveus en onrustig (2)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
3. Ik voel me tevreden (3)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
4. Ik kan een tegenslag maar heel moeilijk verwerken (4)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
5. Ik voel me vrijwel in alles tekortschieten (5)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
6. Ik voel me uitgerust (6)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
7. Ik voel me rustig en beheerst (7)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
8. Ik voel dat de moeilijkheden zich opstapelen zodat ik er niet meer tegenop kan (8)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
9. Ik pieker te veel over dingen die niet zo belangrijk zijn (9)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
10. Ik ben gelukkig (10)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
11. Ik word geplaagd door storende gedachten (11)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
12. Ik heb gebrek aan	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

zelfvertrouwen (12)				
13.Ik voel me veilig (13)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
14.Ik voel me op mijn gemak (14)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
15.Ik ben gelijkmatig van stemming (15)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
16.Ik ben tevreden (16)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
17.Er zijn gedachten die ik heel moeilijk los kan laten (17)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
18.Ik neem teleurstellingen zo zwaar op dat ik ze niet van me af kan zetten (18)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
19.Ik ben een rustig iemand (19)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
20.Ik raak gespannen en in beroering als ik denk aan mijn zorgen van de laatste tijd (20)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

Gevoelens - Angst**13. Kunt u aangeven hoe u zich op dit moment voelt?**

	Geheel niet (1)	Een beetje (3)	Tamelijk veel (4)	Zeer veel (5)
1. Ik voel me kalm (1)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
2. Ik ben gespannen (2)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
3. Ik voel me op mijn gemak (3)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
4. Ik pieker over nare dingen die kunnen gebeuren (4)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
5. Ik voel me aangenaam (5)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
6. Ik voel me nerveus (6)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
7. Ik ben ontspannen (7)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
8. Ik voel me tevreden (8)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
9. Ik maak me zorgen (9)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
10. Ik voel me prettig (10)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

Gevoelens - Angst**14. Hoe gespannen voelt u zich op dit moment?**

	Helemaal niet	Heel erg
	0 10 20 30 40 50 60 70 80 90 100	
Verschuif de regelaar naar de plaats die uw antwoord het beste aangeeft ()		

Emotionale Thermometer

15. Kunt u bij de thermometer de regelaar naar het cijfer (0-10) verschuiven dat het best weergeeft hoeveel emotionele last u heeft ervaren in de afgelopen week, inclusief vandaag?

(0=Helemaal niet, 10=Extreem veel)



- 0 (0)
- 1 (1)
- 2 (2)
- 3 (3)
- 4 (4)
- 5 (5)
- 6 (6)
- 7 (7)
- 8 (8)
- 9 (9)
- 10 (10)

Hier wordt nu een van de vier verschillende video's bekeken:

VIDEO 1 – Geen Empathie, Geen Nocebo Informatie

VIDEO 2 – Met Empathie, Geen Nocebo Informatie

VIDEO 3 – Geen Empathie, Met Nocebo Informatie

VIDEO 4 – Met Empathie, Met Nocebo Informatie

Questionnaire T0 post video (in Dutch (Original Version))

T0_post_stai **Gevoelens – Angst**

1. Kunt u aangeven hoe u zich op dit moment voelt?

	Geheel niet (1)	Een beetje (3)	Tamelijk veel (4)	Zeer veel (5)
1. Ik voel me kalm (1)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
2. Ik ben gespannen (2)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
3. Ik voel me op mijn gemak (3)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
4. Ik pieker over nare dingen die kunnen gebeuren (4)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
5. Ik voel me aangenaam (5)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
6. Ik voel me nerveus (6)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
7. Ik ben ontspannen (7)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
8. Ik voel me tevreden (8)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
9. Ik maak me zorgen (9)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
10. Ik voel me prettig (10)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

Gevoelens - Angst

2. Hoe gespannen voelt u zich op dit moment?

	Helemaal niet	Heel erg
	0 10 20 30 40 50 60 70 80 90 100	
Verschuif de regelaar naar de plaats die uw antwoord het beste aangeeft ()		

Verwachtingen over bijwerkingen

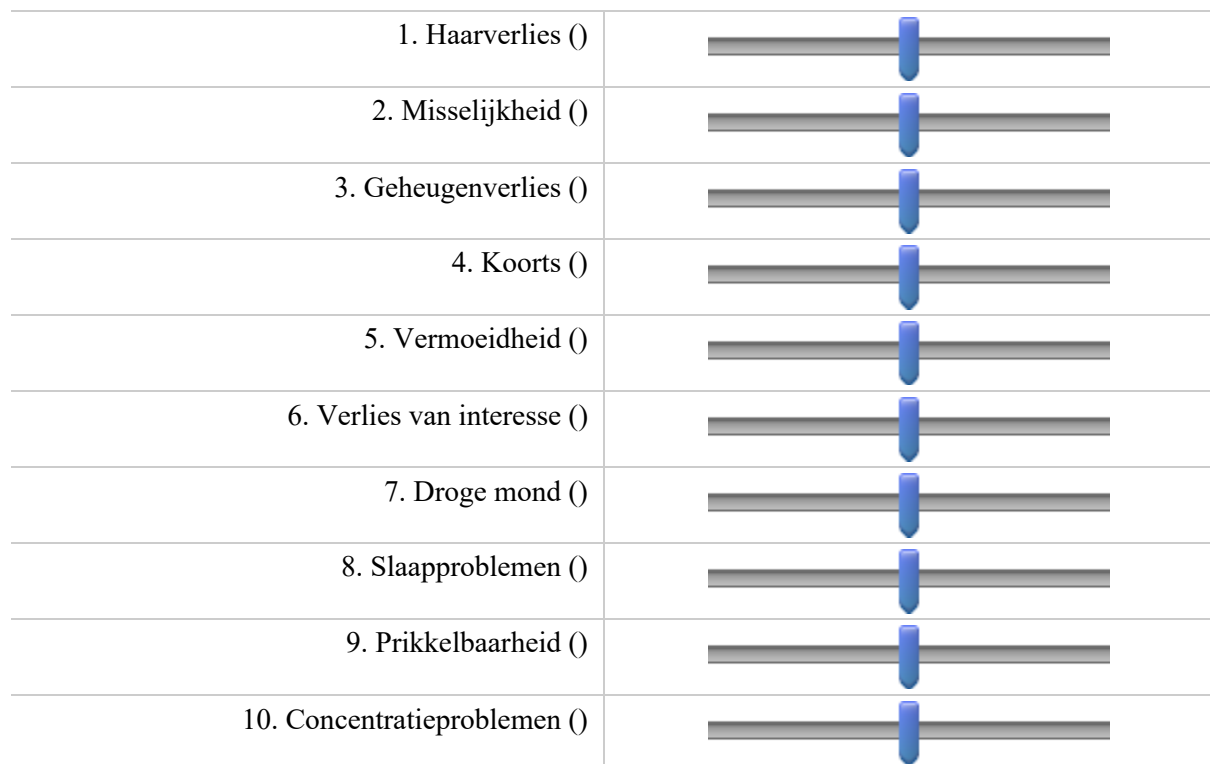
De volgende vragen gaan over bijwerkingen.

3. Hoe waarschijnlijk denkt u dat het is dat de volgende bijwerkingen optreden als u met de chemotherapie start?

(Verschuif de regelaar naar het cijfer dat uw antwoord het beste aangeeft)

0= Helemaal niet
waarschijnlijk10= Heel erg
waarschijnlijk

0 1 2 3 4 5 6 7 8 9 10

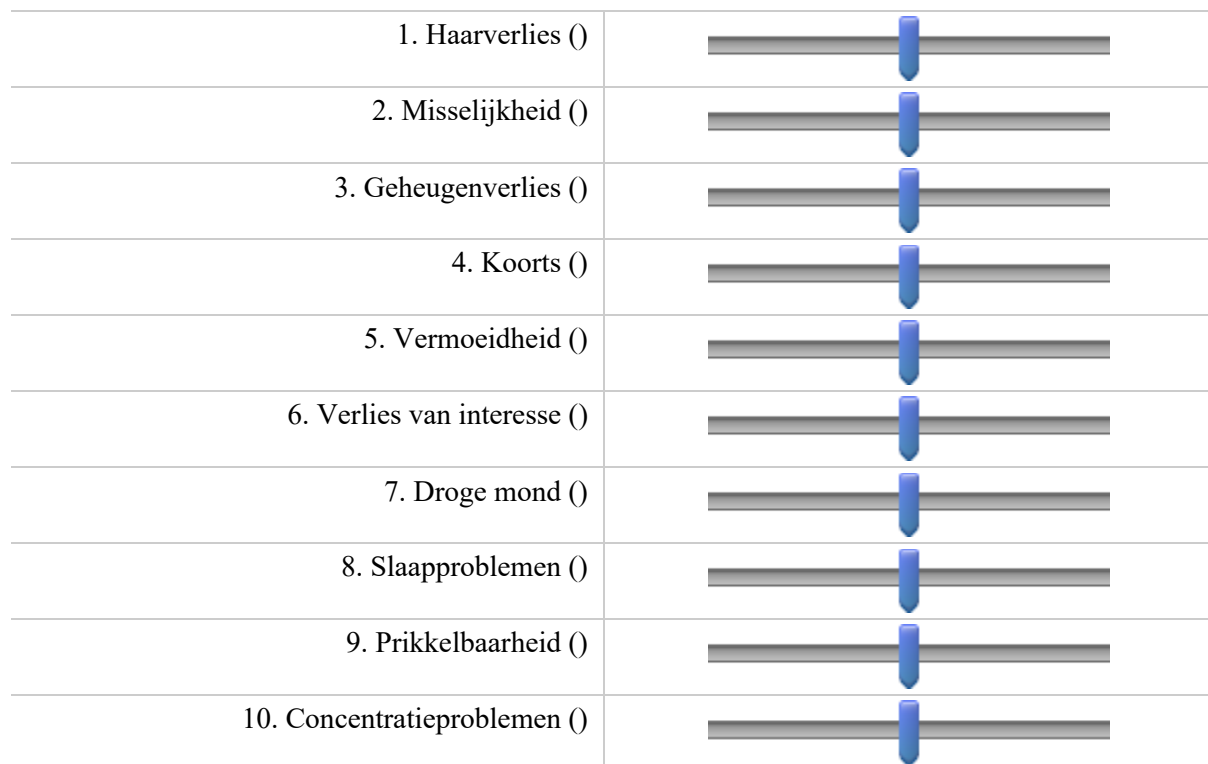


Verwachtingen over bijwerkingen**4. Hoe ernstig denkt u dat de volgende bijwerkingen zijn als u met de chemotherapie start?**

(Verschuif de regelaar naar het cijfer dat uw antwoord het beste aangeeft)

0= Helemaal niet ernstig 10= Heel erg ernstig

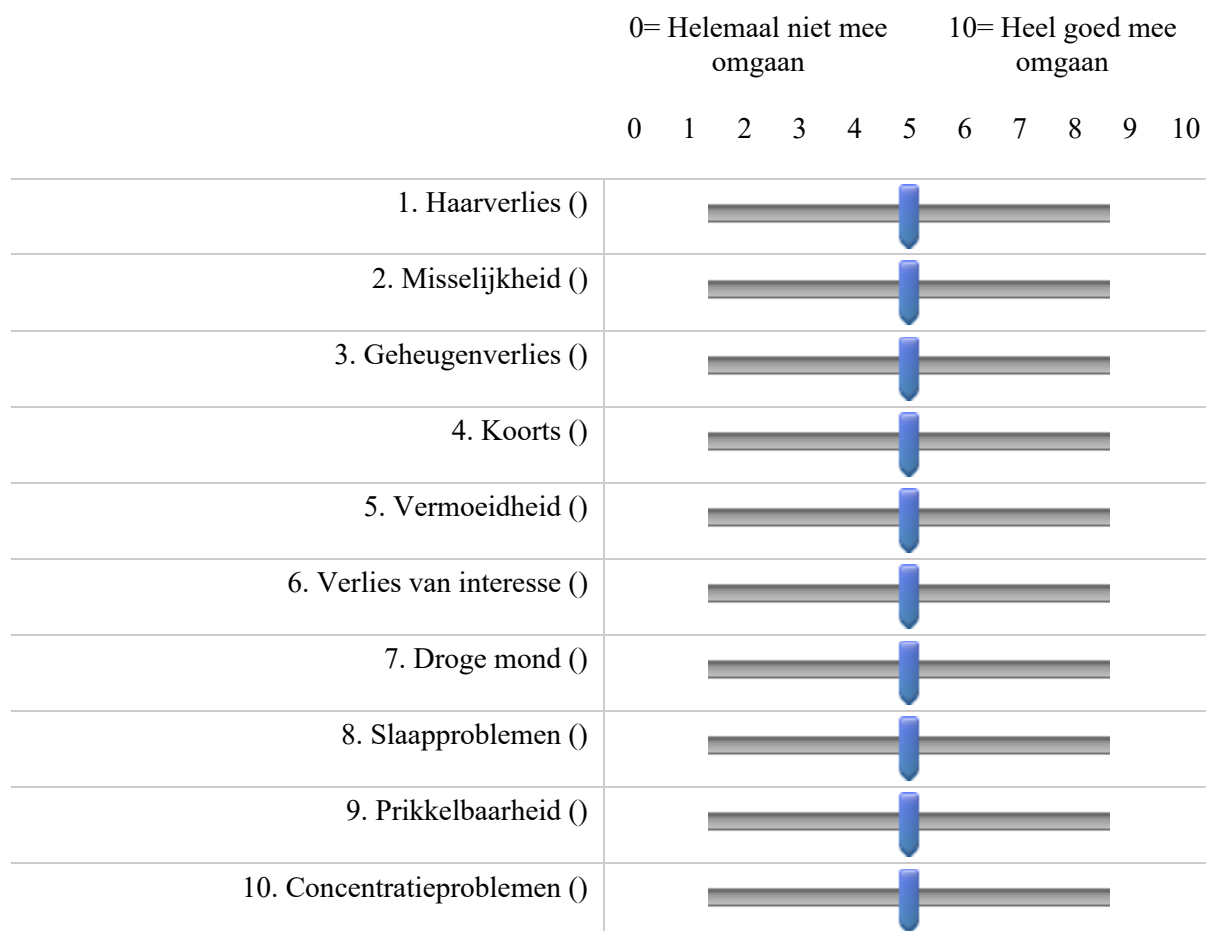
0 1 2 3 4 5 6 7 8 9 10



Verwachtingen over bijwerkingen

5. In hoeverre denkt u dat u om kunt gaan met de volgende bijwerkingen als deze optreden nadat u met de chemotherapie start (bv door rust te houden of door, indien nodig, contact met zorgverleners te zoeken)?

(Verschuif de regelaar naar het cijfer dat uw antwoord het beste aangeeft)

**Houding**

6. Hoe zeker bent u dat u uw chemotherapie (de eerste 4 AC kuren) zult voltooien?



Gevoelens**Tevreden****7. Hoe tevreden bent u over de communicatie van de verpleegkundige in de video?**

Helemaal niet tevreden Zeer tevreden

0 1 2 3 4 5 6 7 8 9 10

Verschuif de regelaar naar het cijfer dat uw antwoord het beste aangeeft ()	
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Toekomst aankunnen**8. In hoeverre geeft de manier waarop de verpleegkundige in de video communiceerde u het gevoel dat u de toekomst aankunt?**

Helemaal niet aan te kunnen Heel erg aan te kunnen

0 1 2 3 4 5 6 7 8 9 10

Verschuif de regelaar naar het cijfer dat uw antwoord het beste aangeeft ()	
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Vertrouwen**9. In hoeverre heeft u vertrouwen in uw medische team (arts en verpleegkundigen) na het zien van de video?**

Helemaal geen vertrouwen Heel veel vertrouwen

0 1 2 3 4 5 6 7 8 9 10

Verschuif de regelaar naar het cijfer dat uw antwoord het beste aangeeft ()	
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Emotionale Thermometer

10. Kunt u bij de thermometer de regelaar naar het cijfer (0-10) verschuiven dat het best weergeeft hoeveel emotionele last u heeft ervaren in de afgelopen week, inclusief vandaag?

(0 = Helemaal niet, 10 = Extreem veel)



- 0 (0)
- 1 (1)
- 2 (2)
- 3 (3)
- 4 (4)
- 5 (5)
- 6 (6)
- 7 (7)
- 8 (8)
- 9 (9)
- 10 (10)

Questionnaires T1 – T3 (in Dutch (Original Version))

Gevoelens - Angst**1. Kunt u aangeven hoe u zich op dit moment voelt?**

	Geheel niet (1)	Een beetje (3)	Tamelijk veel (4)	Zeer veel (5)
1. Ik voel me kalm (1)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
2. Ik ben gespannen (2)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
3. Ik voel me op mijn gemak (3)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
4. Ik pieker over nare dingen die kunnen gebeuren (4)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
5. Ik voel me aangenaam (5)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
6. Ik voel me nerveus (6)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
7. Ik ben ontspannen (7)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
8. Ik voel me tevreden (8)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
9. Ik maak me zorgen (9)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
10. Ik voel me prettig (10)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

2. Hoe gespannen voelt u zich op dit moment?

Helemaal niet

Heel erg

0 10 20 30 40 50 60 70 80 90 100

Verschuif de regelaar naar de plaats die uw antwoord het beste aangeeft ()

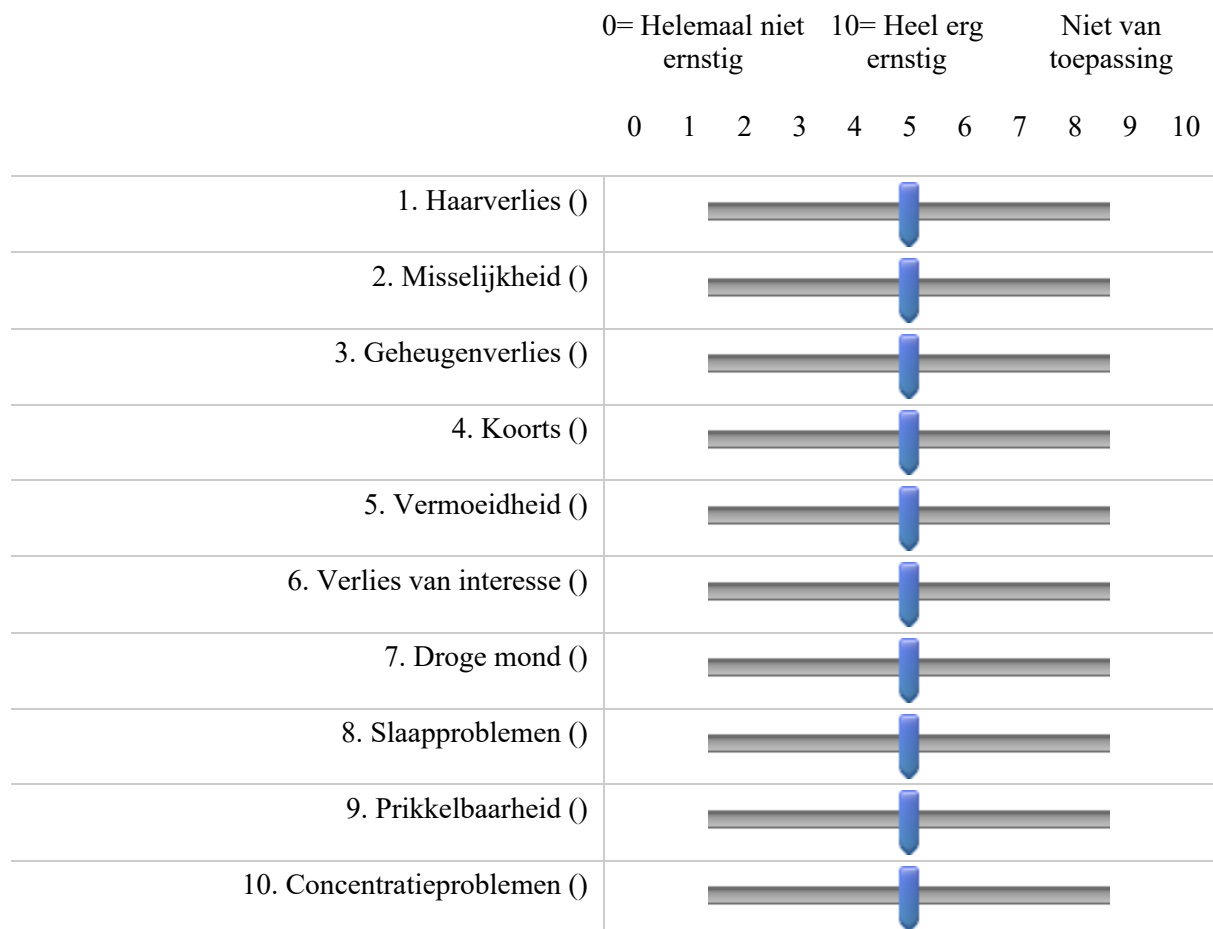


Bijwerkingen

De volgende vragen gaan over bijwerkingen.

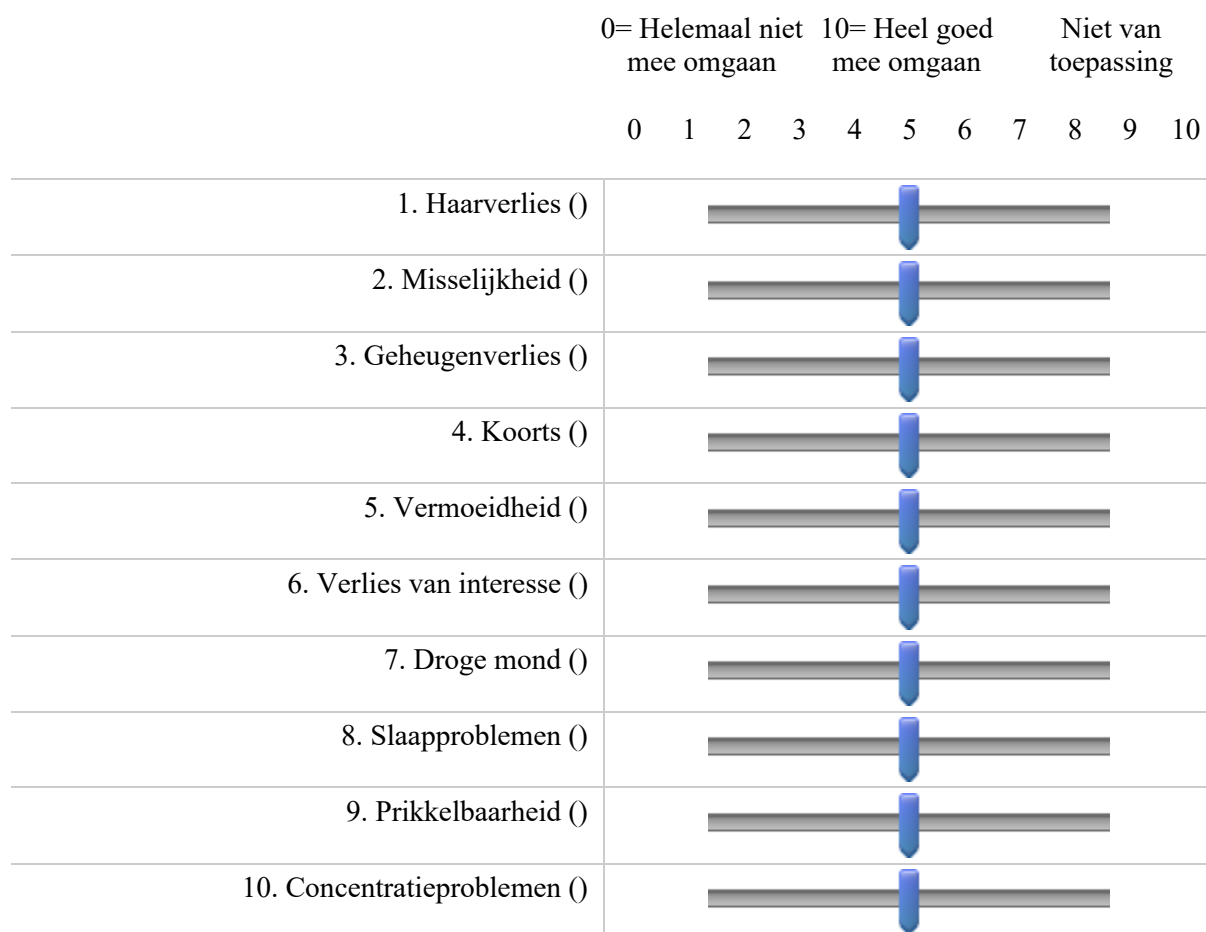
3. Hoe ernstig waren de volgende bijwerkingen in de afgelopen 7 dagen?

Mocht deze bijwerking niet aanwezig zijn geweest, kies dan “Niet van toepassing”. (Verschuif de regelaar naar het cijfer dat uw antwoord het beste aangeeft)



4. In hoeverre kunt u omgaan met de volgende bijwerkingen die zich in de afgelopen 7 dagen voordeden (bv door rust te houden of door, indien nodig, contact met zorgverleners te zoeken)?

Mocht deze bijwerking niet aanwezig zijn geweest, kies dan “Niet van toepassing”.
(Verschuif de regelaar naar het cijfer dat uw antwoord het beste aangeeft)




Houding

5. Hoe zeker bent u dat u uw chemotherapie (de eerste 4 AC kuren) zult voltooien?



Toekomst aankunnen**6. In hoeverre heeft u het gevoel dat u de toekomst aankunt?**

	Helemaal niet aan te kunnen	Heel erg aan te kunnen
	0 1 2 3 4 5	6 7 8 9 10
Verschuif de regelaar naar het cijfer dat uw antwoord het beste aangeeft ()		

Emotionale Thermometer**7. Kunt u bij de thermometer de regelaar naar het cijfer (0-10) verschuiven dat het best weergeeft hoeveel emotionele last u heeft ervaren in de afgelopen week, inclusief vandaag?**

(0 = Helemaal niet, 10 = Extreem veel)



- 0 (0)
- 1 (1)
- 2 (2)
- 3 (3)
- 4 (4)
- 5 (5)
- 6 (6)
- 7 (7)
- 8 (8)
- 9 (9)
- 10 (10)