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The effect of clinician-expressed empathy and nocebo-alleviating information on breast-cancer-patients' anxiety and side effects during active chemotherapy: A clinical feasibility study

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ABSTRACT

Objective: We set up a pilot-study to investigate main and interaction effects of nocebo-alleviating information and clinician-expressed empathy delivered via a standardized information-video on breast cancer patients' psychological and side effect outcomes during chemotherapy. Additionally, we aimed to reflect on the feasibility of the intervention (acceptability, practicality and integration) to inform future – follow-up – studies.
Methods: Using a clinical proof-of-principle randomized controlled trial, female breast cancer patients undergoing chemotherapy viewed one of four videos, varying in the level of nocebo-alleviating information(+/−) and clinician-expressed empathy(+/−). Due to the small sample size ($n = 27$), descriptive and recruitment data were utilized to evaluate effects and reflect on feasibility.
Results: The interventions appeared to yield limited effects on our small sample. Feasibility reflections mainly focused on the practical level, such as the use of more generalizable videos and optimizing the flow.
Conclusion: The study showed limited effects of the video intervention. It revealed recruitment challenges, while acceptability was high after inclusion. Moving forward, face-to-face clinician-patient interactions remain important, while cautiously exploring the potential benefits of modern technological advancements, ensuring thorough testing of their effects before implementation.
Innovation: This study marks an innovative approach in utilizing digital interventions to enhance cancer patient outcomes within clinical settings.

1. Introduction

There is a wide range of side effects commonly experienced by breast cancer patients undergoing chemotherapy [1-3] that not only impact patients' quality of life [4,5], but can lead to treatment discontinuation [6]. While chemotherapy's side effects are of course induced by pharmacological components of the treatment, they can also be caused or exacerbated by psychological mechanisms [7,8]. When side effects, such as headaches, fatigue, or nausea, are caused or exacerbated by such psychological mechanisms - like expectations, anxiety, or previous experiences - they are called nocebo-effects [7-10].

Ongoing research to alleviate nocebo-effects has been focusing on the effect of clinician-patient communication strategies such as educating patients about nocebo-effects (i.e., nocebo-alleviating information interventions) and the use of clinician-expressed empathy [11,12]. Nocebo-alleviating information interventions have been shown to reduce potential misattribution of side effects, increase patients' coping ability and perceived control, while decreasing expected as well as experienced side effects [7,13,14]. In a recent experimental video-vignette study, however, we did not find that nocebo-alleviating information improved participants' (i.e. analogue patients') side effect expectations nor psychological distress in the setting of advanced breast cancer chemotherapy. Nonetheless, coping expectations concerning specific side effects improved when nocebo-alleviating information was

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combined with clinician-expressed empathy [15]. Moreover, the beneficial effects of clinician-expressed empathy have been demonstrated [16-18]. It can decrease patients' level of anxiety and distress, while improving satisfaction, overall psychological health, and information recall [16,17,19,20]. In our aforementioned experimental study, clinician-expressed empathy decreased psychological distress as well as expected occurrence and intensity of side effects, and it increased feelings of self-efficacy [15].

The question remains what the distinct and combined effects of nocebo-alleviating information and clinician-expressed empathy are over time and in clinical settings opposed to an experimental setting. Michnevich and colleagues examined long-term (12 weeks) effects of nocebo education sessions (20–30 min), in the setting of advanced cancer chemotherapy, which were delivered in an empathetic manner by a psychologist. Although findings indicated a significant long-term decrease of nonspecific (i.e. nocebo) side effects, this does not clarify individual effects of both intervention elements, nor effects on psychological outcomes [11]. Moreover, as nocebo education sessions of this length may not always be feasible in the fast-paced clinical setting, possible shorter and easily accessible innovative interventions should be examined such as the use of standardized information-videos.

We therefore set up a pilot-study to investigate the main and interaction effects of nocebo-alleviating information and clinician-expressed empathy delivered via a standardized information-video on breast cancer patients' psychological and side effect outcomes during chemotherapy. Next to presenting the results, we also aimed to reflect on the feasibility of the intervention (acceptability, practicality and integration) to inform future – follow-up – studies.

Our study contributed to the broader conversation on “Brilliant Failures” by revealing the complexity of translating promising interventions into real-world settings.

2. Methods

2.1. Design

A 2 × 2 pilot clinical randomized controlled trial was conducted using four standardized pre-chemotherapy information videos. The narrative videos portrayed a nurse-practitioner informing patients about possible side effects of curative, neoadjuvant Adriamycine Cyclofosfamide (AC) chemotherapy and were developed based on previous literature (e.g. [15]) and in collaboration with clinical experts. Based on our preceding experimental study [15], the level of nocebo-alleviating information (explaining the psychological mechanisms behind side-effects [15,21]) and clinician-expressed empathy (reassurance about non-abandonment [15,22]) varied (absent – versus present +) between videos (see Table 1). Other content was held constant. Scripts were piloted by 6 researchers, clinical experts, and patient representatives to ensure comprehensibility (M = 8.5 on a 0–10 scale) and manipulation success (nocebo-alleviating information: M = 6.5, clinician-expressed empathy: M = 8.33 on a 0–10 scale). Final scripts were created and shot in collaboration with the production agency (see Appendix A for the final script).

2.2. Ethical approval

The participating hospital exempted the study from official approval [2022-03-25 METC22.0182] but provided IRB approval [2022-06-03 IRBd22–103]. Ethical approval was also obtained by Leiden University, Institute of Psychology [2022-06-02-L.M. van Vliet-V1–4056]. The study was pre-registered at ClinicalTrials.gov [Identifier: NCT05390723]. All participants provided written (online) informed consent.

Table 1.
Overview of the content of the four different videos.

Video 1: Nocebo-alleviating information - / Clinician-expressed Empathy -	Video 2: Nocebo-alleviating information - / Clinician-expressed Empathy +
Video 3: Nocebo-alleviating information + / Clinician-expressed Empathy -	Video 4: Nocebo-alleviating information + / Clinician-expressed Empathy +

2.3. Participants and sample size

Participants were eligible if they were adult (>18 years) females diagnosed with breast cancer and scheduled for their first chemotherapy (four sessions of curative, neoadjuvant AC chemotherapy), had sufficient Dutch understanding (as our participant information – e.g. questionnaires, videos – were only available in Dutch), had cognitive capacity (to complete the online questionnaires - according to the subjective assessment of the recruiting clinicians), and internet access. To increase recruitment rates, eligibility criteria were widened to patients who had undergone a pre-chemo breast-saving operation and radiotherapy. In accordance with our previous experimental study, anxiety was chosen as a main outcome [15]. Power calculations were based on a previous study [23]. The initially planned sample size was 40 to achieve 80 % power for detecting the largest difference between groups for two main and interaction effects at $p < .05$ and delta of 0.28.

2.4. Recruitment and procedures

Participants were included in the period of June 2022 to August 2023 at a specialized cancer hospital in the Netherlands. Eligible patients were informed by the clinical staff at the participating hospital during a pre-treatment consultation. If interested, they received a Patient Information Letter (PIF), including a link and QR code to the online version of the PIF and the informed consent (IC) form. Interested patients who did not complete their IC two days prior to the start of their first chemotherapy were reminded (via phone/email) by the clinical research team. To increase recruitment rates, several amendments were made: i) the clinical research team (ES, MvdS) could inform patients via phone about the study; ii) participants could provide preliminary verbal consent during a reminder call and be met by the research team pre-chemotherapy session 1 to sign the IC form and complete the pre-chemotherapy questionnaire at the hospital.

One week until one day before their first chemotherapy, participants received an email including a link to the pre-chemotherapy questionnaire consisting of the first questionnaire (T0-pre), a video (assigned equally and randomly), and another questionnaire (T0-post). Seven days post-chemo session 1 (T1) and 2 (T2), and fourteen (later amended to ten) days post-chemo session 4 (T3) participants received the subsequent questionnaires which needed to be completed within three days. One reminder (via phone or email) was sent. Post final questionnaire (or post- dropout) participants were debriefed about the study aims and the manipulated communication. For the procedure see Fig. 1. Withdrawal of the study was possible at any time given during the study.

The research team was blind to the condition participants were assigned to. Again, to improve recruitment rates, we amended the protocol to i) automatically re-direct participants to the pre-chemotherapy questionnaire after IC was signed if their first chemo session was in the following seven days, ii) allow participants to complete the first questionnaire until before their first chemotherapy, and iii) send out the last questionnaire ten days after the fourth chemotherapy session, to avoid an overlap with follow-up treatments.

2.5. Measures

Questionnaires were created with input from 2 patient representatives.

2.5.1. Background (T0-pre video)

Socio-demographics and previous cancer-related treatments were

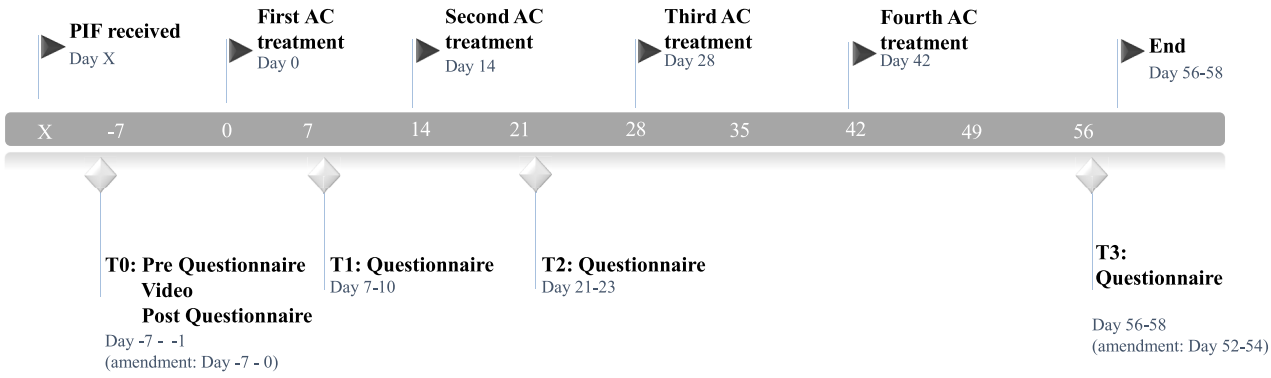

Fig. 1. Standard Timeline of the Study per Participant.
The standard timeline per participant in this study, consisting of the AC treatments (Adriamycine Cyclofosfamide chemotherapy) and the 4 rounds of questionnaires. In case of insufficient blood tests of the patient or other complaints, the chemotherapy could be delayed. Questionnaires and further treatment were then adjusted accordingly.

assessed using self-created questions [15].

2.5.2. Psychological outcomes

i) *State Anxiety (T0-pre,T0-post,T1,T2,T3)*: assessed with the shortened 10-item (1–4 scale) *STAI-state* (main outcome) (possible range: 10–40) [24].
ii) *Distress (T0-pre,T0-post,T1,T2,T3)*: assessed with the Distress *Thermometer* (0–10 Numerical Rating Scale (NRS) 'no distress'-'extreme distress') [25].
iii) *Self-efficacy (T0-post,T1,T2,T3)*: Participants' belief in their ability to deal with the future was assessed using a self-created 0–10 NRS ('very little'-'very great') [22].
iv) *Satisfaction (T0-post)* with the communication of the nurse in the video was assessed using a self-created 0–10 NRS, ('not satisfied at all'-'extremely satisfied') [16,19].
v) *Trust (T0-post)* in the medical team was assessed using a self-created 0–10 NRS ('no trust at all'-'full trust').

2.5.3. Side effect outcomes

Side Effects: For 10 pre-defined side effects (determined in collaboration with the involved clinical team; fever, hair loss, nausea, dry mouth, sleep problems, loss of interest, irritability, fatigue, memory loss, concentration problems) we assessed:

i) *Probability (T0-post)*: participants' expected probability of the occurrence of side effects with a self-created 0–10 NRS 'not probable at all'-'very probable', adapted from [14,26]. For our analyses, we calculated the mean of the probability (possible range: 0–10) across all side effects.
ii) *Intensity (T0-post,T1,T2,T3)*: participants' expected (T0-post) and experienced (T1,T2,T3) intensity (seriousness) of side effects using a modified version of the *GASE* [27], based on [11] with a 0–10 NRS 'not at all intense/not applicable'-'very intense'. For our analyses, we calculated the mean of the intensity (possible range: 0–10) across all side effects.
iii) *Number (T1,T2,T3)*: the total number of experienced side effects was calculated by adding all present side effects (intensity>0) (possible range: 0–10).
iv) *Coping (T0-post,T1,T2,T3)*: participants' expected (T0-post) and experienced (T1,T2,T3) coping ability with side effects using a modified version of the *GASE* [27], based on [11] with a 0–10 NRS 'not handling at all'-'handling very well'. We calculated the mean of the coping ability (possible range: 0–10) across all side effects. To not artificially lower this mean if a side effect was not present at all, i.e., no coping ability needed, we added a 'not applicable'-option (−1), excluding this side effect from the calculation.

2.6. Feasibility

Due to difficulties of recruiting the initially planned number of participants ($n = 40$), we decided to stop recruitment after 15 months and post-hoc reflect as a research team on three feasibility-aspects (derived from guidance proposed by Bowen et al. [28], CONSORT [29] and Orsmond & Cohn [30]): i) *Acceptability*: participation willingness and completion rates, ii) *Practicality*: reflections on aspects of the study we amended to ensure the project could be implemented; as well as possible suggestions to optimize the successful implementation of future studies; iii) *Integration*: reflections on integration of our study into the existing hospital setting, and possible suggestions to optimize integration in hospital/healthcare settings in future studies.

2.7. Analysis

First, background characteristics were described per condition. Second, participants' psychological outcomes and side effect outcomes were described at the different timepoints, split up by nocebo-alleviating information (present versus absent) and clinician-expressed empathy (present versus absent). We initially aimed to conduct stepwise linear mixed model analyses (timepoints nested in participants; time, nocebo-alleviating information and clinician-expressed empathy as fixed effects; random intercept, but no random slope) to test main and interaction effects of nocebo-alleviating information and clinician-expressed empathy on all outcome measures at all different timepoints. However, due to the limited numbers of recruited participants, we decided to only describe our descriptive data at the different timepoints split up by nocebo-alleviating information and clinician-expressed empathy. All analyses were carried out in SPSS Version 29.0.

3. Results

3.1. Participants

Of the 150 patients who were screened, almost a third ($n = 48$) did not meet our inclusion criteria (See Fig. 2). Patients were not eligible for the following reasons: not scheduled for curative treatment ($n = 7$); insufficient Dutch ($n = 13$); not cognitively able to participate ($n = 5$); not interested ($n = 9$); not chemo-naïve ($n = 8$); not approached (n = 5); various reasons (n = 1). Of the 102 eligible participants, 35 provided IC and were randomized. Ultimately, 27 of the 35 participants who provided IC were included as they at least filled out T0-post until and including the state anxiety measure in time. The resulting sample of 27

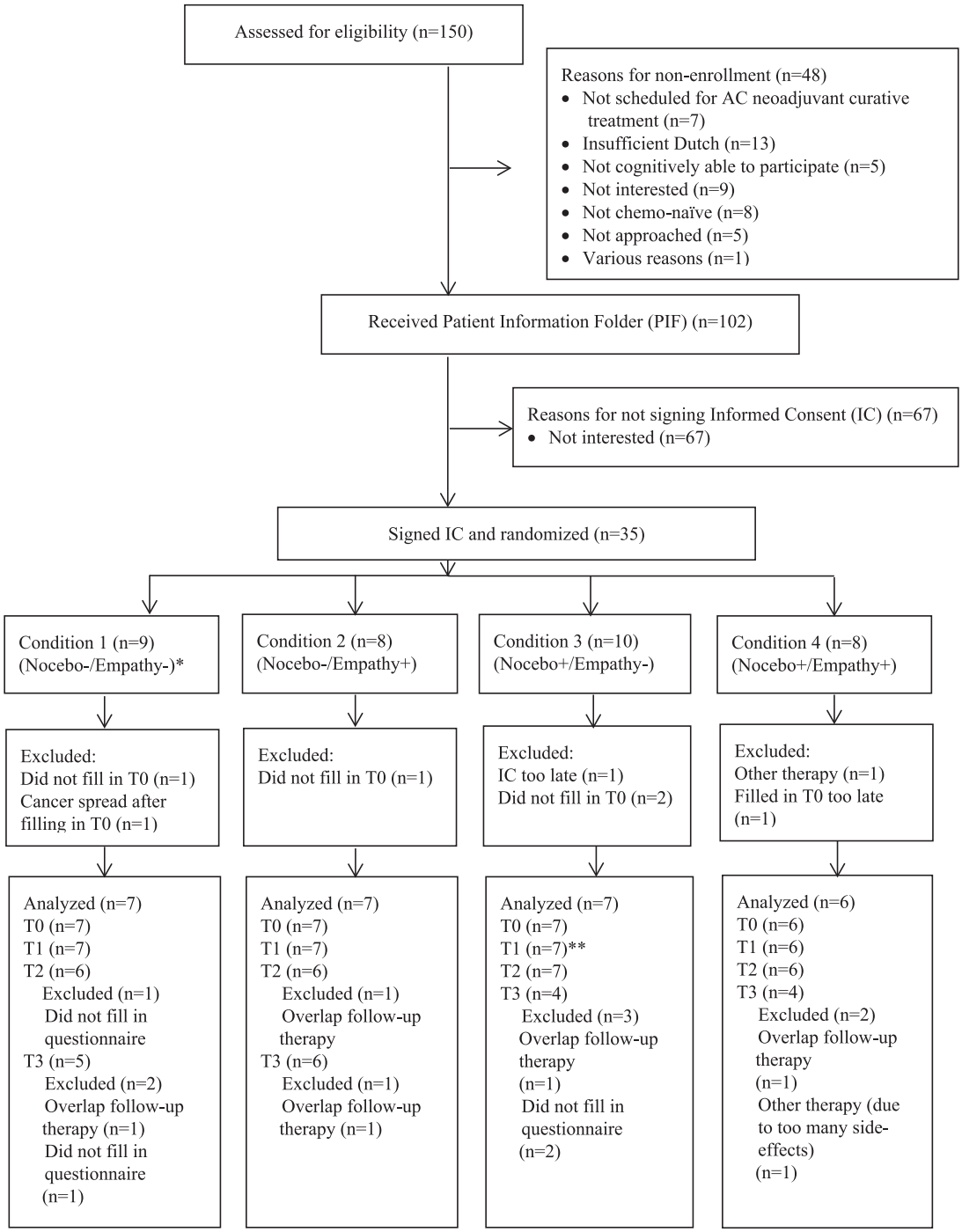

Fig. 2. Participant Flow by the Four Conditions.
Participant flow per condition from screening to distributing patient information folders (PIF), giving informed consent (IC) and finally presenting the final analyzed participants with information on exclusion. *Note.* *Nocebo = nocebo-alleviating information; empathy = clinician-expressed empathy; ** = participants only filled in part of the whole questionnaire (n = 2).

participants was mostly middle-aged (M = 48.42, SD = 11.49) and highly educated (63 %). All demographic information is displayed in Table 2.

3.2. *Psychological and side effect outcomes of nocebo-alleviating information and clinician-expressed empathy at the different timepoints*

Overall, we observed very mixed patterns in the raw descriptive data (See Table 3). For both the psychological as well as the side-effect outcome measures assessed at multiple timepoints we neither observed a clear pattern in the total scores, nor in the raw data split up by nocebo-alleviating information and clinician-expressed empathy. For the psychological outcome measures satisfaction and trust that were only assessed at T0-post, we observed the unexpected trend that adding nocebo-alleviating information (satisfaction: M = 8.92 versus M = 9.29; trust: M = 9.15 versus M = 9.29) or clinician-expressed empathy (satisfaction: M = 8.85 versus M = 9.36; trust: M = 9.00 versus M = 9.43) seemed to lead to worse scores than not adding them. Regarding the side-effect outcomes, these strongly mixed results seem to suggest that providing participants with additional nocebo-alleviating

Table 2.
Socio-demographics and previous cancer-related treatments (at T0-pre) per condition.

		Nocebo-alleviating Information – Clinician-expressed Empathy –	Nocebo-alleviating Information – Clinician-expressed Empathy +	Nocebo-alleviating Information + Clinician-expressed Empathy –	Nocebo-alleviating Information + Clinician-expressed Empathy +
	N = 27	n = 7	n = 7	n = 7	*n* = 6
	Mean (SD)	Mean(SD)	Mean(SD)	Mean(SD)	Mean(SD)
Age	48.42 (11.49)	56.22(8.59)	48.90(15.05)	42.89(10.70)	45.23(6.98)
	n(%)	**n(%)**	**n(%)**	**n(%)**	**n(%)**
Highest Education [a]					
Low	–	–	–	–	–
Intermediate	10(37.0)	3(42.9)	2(28.6)	3(42.9)	2(33.3)
High	17(63.0)	4(57.1)	5(71.4)	4(57.1)	4(66.7)
Occupation					
Paid employment	22(81.5)	5(71.4)	6(85.7)	7(100)	4(66.7)
Unemployed [b]	5(18.5)	2(28.6)	1(14.3)	–	2(33.3)
Living situation					
Alone	4(14.8)	–	1(14.3)	2(28.6)	1(16.7)
Together	23(85.2)	7(100)	6(85.7)	5(71.4)	5(83.3)
Ethnicity					
Native Dutch	21(77.8)	6(85.7)	5(71.4)	6(85.7)	4(66.7)
Western Immigrant	2(7.4)	-	-	1(14.3)	1(16.7)
Non-Western Immigrant	4(14.8)	1(14.3)	2(28.6)	-	1(16.7)
Pre-chemotherapy treatments [c]					
Yes	3(11.1)	1(14.3)	1(14.3)	1(14.3)	-
No	17(63.0)	5(71.4)	4(57.1)	3(42.9)	5(83.3)
Not assessed [d]	7(25.9)	1(14.3)	2(28.6)	3(42.9)	1(16.7)

Note. [a] Low (< secondary school); intermediate (secondary school & vocational education); high (higher vocational education or University). [b] Including being a student, retired, disabled/on sick leave, or a housewife. [c] Pre-chemotherapy breast-saving operation and radiotherapy. [d] This measure was added after the study commenced.

information or clinician-expressed empathy had no clear direction of influence on patients' side-effects over time.

3.3. Innovation: feasibility of the study

3.3.1. Acceptability

In total 102 patients matched the inclusion criteria during the time of recruitment, from which 35 provided informed consent and where randomized and 27 completed at least everything until and including the state anxiety measure at T0-post. The 67 who did not sign IC were not interested in participating. Although 67 patients who would have been eligible for inclusion ended up not signing IC, once participants gave IC ($n = 35$), only few dropped out or did not complete questionnaires. Reasons for dropout between provision of IC and filling in the first questionnaire T0 ($n = 8$) were the following: cancer spread ($n = 1$); filled out T0 too late (n = 1); did not fill in T0 ($n = 4$), providing IC after the first chemo session (n = 1), started another treatment (n = 1). Of the 27 participants who completed the first questionnaires, 25 completed T2 and 19 completed T3. In total, there were 10 questionnaires missing at T2 and T3 together. From the 10 missing questionnaires, 5 were not completed due to an overlap with a follow-up chemotherapy, 1 due to a participant changing to another chemotherapy, while for 4 no reason was known. This illustrates that while recruitment of participants was difficult, the acceptability of the study procedures – and especially completing questionnaires over time – was acceptable.

3.3.2. Practicality

We assessed practical problems during the project, which we tried to adjust and/or might be adjusted in follow-up studies.

Firstly, inclusion was low, but retention high. So, we implemented several amendments to increase the inclusion: i) the clinical research team (ES, MvdS) could inform patients via telephone about the study; ii) eligibility criteria were widened to patients who had undergone pre-chemo breast-saving operations and radiotherapy, leading to 3 more included participants; iii) participants could provide preliminary verbal consent, and were then met at the hospital by the research team pre-chemotherapy to sign the IC form and complete the pre-chemotherapy questionnaire, leading to 0 more included participants; iv) participants were allowed to complete the first questionnaire until before their first chemotherapy, leading to 7 more included participants. Future studies might use i) an opt-out procedure; ii) recruit patients in the hospital before chemo-start when they wait (which can also increase inclusion of people with low health literacy).

Secondly, our videos included specific information about curative, neoadjuvant AC chemotherapy in chemo-naïve breast cancer patients at the participating hospital. This limited the possibility to broaden our inclusion criteria. Future studies could try to make the videos more general in terms of hospital and populations. We believe this is achievable, as the nocebo-alleviating information and clinician-expressed empathy are relevant to various patient groups.

Thirdly, one of our inclusion criteria was that patients should have sufficient command of Dutch. Thirteen participants were excluded because of insufficient Dutch language knowledge/skill. Therefore, future studies could offer the video and questionnaires in English or other languages or it may be considered to conduct questionnaires face-to-face with the assistance of a translator.

Fourthly, during the project we found out that when patients received the T3 questionnaire (14 days after their last chemo) some of them had already started with a new and other type of chemo that day. We therefore adjusted the timepoint of T3 from 14 to 10 days after the last chemo. We had chosen 14 days to measure potential long-term effects of the videos, however, upon consultation with the clinical team we decided that 10 days would also be feasible. There was also a few participant who completed the questionnaire not within our exact time frame (e.g. as their chemotherapy dates changed). Future studies should ensure that timepoints clash with other treatments, and questionnaires

Table 3.
Raw uncontrolled means (standard deviations) of each outcome at the different timepoints.

		Total		Nocebo-alleviating Information				Clinician-expressed Empathy			
				Without –		With +		Without –		With +	
	Timepoint	Mean(SD)	n	Mean(SD)	n	Mean(SD)	n	Mean(SD)	n	Mean (SD)	n
Psychological Outcomes											
State Anxiety	T0-pre	22.96(7.39)	27	22.50(8.38)	14	23.46(6.45)	13	25.57(7.23)	14	20.15(6.72)	13
Range(10–40)	T0-post	21.41(6.57)	27	21.07(7.92)	14	21.77(5.02)	13	23.57(5.60)	14	19.08(6.93)	13
	T1	20.52(5.69)	27	21.36(5.89)	14	19.62(5.55)	13	21.71(5.20)	14	19.23(6.11)	13
	T2	21.08(5.16)	25	21.42(5.18)	12	20.77(5.34)	13	20.54(4.54)	13	21.67(5.91)	12
	T3	21.32(6.66)	19	24.36(5.87)	11	17.13(5.49)	8	19.11(5.88)	9	23.30(6.98)	10
Distress	T0-pre	6.00(2.94)	27	5.36(3.39)	14	6.69(2.29)	13	6.50(2.88)	14	5.46(3.02)	13
Range(0–10)	T0-post	5.93(2.87)	27	5.64(3.32)	14	6.23(2.39)	13	6.36(3.00)	14	5.46(2.76)	13
	T1	5.20(2.74)	25	5.07(2.84)	14	5.36(2.73)	11	5.25(2.30)	12	5.15(3.18)	13
	T2	5.96(2.67)	25	5.83(2.08)	12	6.08(3.20)	13	5.31(2.46)	13	6.67(2.81)	12
	T3	6.11(2.23)	19	6.45(2.34)	11	5.62(2.13)	8	5.22(1.72)	9	6.90(2.42)	10
Self-efficacy	T0-post	7.70(1.61)	27	7.64(1.74)	14	7.77(1.54)	13	7.50(1.87)	14	7.92(1.32)	13
Range(0–10)	T1	7.88(1.69)	25	7.86(1.66)	14	7.91(1.81)	11	7.92(1.44)	12	7.85(1.95)	13
	T2	8.32(1.63)	25	7.92(1.88)	12	8.69(1.32)	13	8.46(1.39)	13	8.17(1.90)	12
	T3	7.84(1.61)	19	7.18(1.17)	11	8.75(1.75)	8	8.11(1.45)	9	7.60(1.78)	10
Satisfaction	T0-post	9.11(1.19)	27	9.29(0.91)	14	8.92(1.44)	13	9.36(0.93)	14	8.85(1.41)	13
Range(0–10)											
Trust	T0-post	9.22(0.93)	27	9.29(0.83)	14	9.15(1.07)	13	9.43(0.94)	14	9.00(0.91)	13
Range(0–10)											
Physical Outcomes											
Probability	T0-post	5.36(1.74)	27	5.79(1.33)	14	4.89(2.04)	13	5.30(1.79)	14	5.42(1.75)	13
Range(0–10)											
Intensity	T0-post (expected)	4.86(1.81)	27	5.03(1.48)	14	4.67(2.16)	13	4.84(1.70)	14	4.88(1.99)	13
Range(0–10)	T1	2.89(1.83)	25	2.71(1.61)	14	3.12(2.14)	11	2.67(1.59)	12	3.09(2.06)	13
	T2	3.67(1.66)	25	3.36(1.46)	12	3.96(1.83)	13	3.16(1.56)	13	4.23(1.64)	12
	T3	3.55(1.85)	19	3.39(1.64)	11	3.76(2.22)	8	2.76(1.68)	9	4.27(1.78)	10
Number	T1	5.64(2.46)	25	5.79(2.26)	14	5.45(2.81)	11	5.25(2.26)	12	6.00(2.68)	13
Range(0–10)	T2	6.88(2.26)	25	6.67(2.50)	12	7.08(2.10)	13	5.85(2.38)	13	8.00(1.54)	12
	T3	6.68(1.83)	19	6.45(1.97)	11	7.00(1.69)	8	6.33(2.35)	9	7.00(1.25)	10
Coping	T0-post (expected)	6.09(1.90)	27	5.86(1.59)	14	6.33(2.24)	13	6.11(1.76)	14	6.06(2.12)	13
Range(0–10)	T1	6.41(2.21)	25	6.78(2.08)	14	5.95(2.39)	11	6.22(2.03)	12	6.60(2.44)	13
	T2	3.83(2.24)	25	3.76(2.45)	12	3.90(2.12)	13	3.30(2.18)	13	4.41(2.24)	12
	T3	6.49(2.17)	19	6.74(2.07)	11	6.14(2.41)	8	5.94(1.96)	9	6.98(2.34)	10

are always sent out within the right – adjusted - timeline.

Fifthly, during the study it often occurred that patients filled in IC the night before their chemo or on the same day, leaving very little to no time for the research team to still send out the pre-chemo questionnaire and for them to fill it out on time. We, therefore, made a change in the online platform so that patients were automatically re-directed to the T0-questionnaire after they signed IC. We would encourage future studies to immediately implement this strategy. As most patients completed IC on their phone, this led to people watching the interventions on their phone. Future studies could look into which device participants tend to use for participating in the study and whether this influences the effects of the intervention.

3.3.3. Integration

The video was not integrated in the standard hospital care. However, the use of standardized videos, e.g., as a link within pre-chemotherapy information, seems feasible (also in future studies).

4. Discussion and conclusion

4.1. Discussion

This pilot-study aimed to investigate the main and interaction effects of nocebo-alleviating information and clinician-expressed empathy delivered via a standardized information-video on breast cancer patients' psychological and side effect outcomes during chemotherapy. Moreover, we aimed to reflect on the feasibility of the intervention (acceptability, practicality, and integration) to inform future – follow-up – studies. While we did not succeed in including our aimed sample, the available data did not suggest that either the nocebo- or empathy-interventions successfully improved patient outcomes. Reflections on the feasibility were presented mainly on the practical levels, such as the use of more generalizable videos.

While we do not want to put too much emphasis on our quantitative results, given our limited sample size, our results seem to indicate that the benefits for using communication-manipulated information-videos to improve patient outcomes while undergoing chemotherapy might be limited. That being said, perceived satisfaction with the communication in the video and trust in the medical team was high ($>M = 8$) across all conditions, raising the suggestion that the use of standardized videos might be perceived as useful in itself in order to prepare patients before the start of a treatment. It is important that more studies – including a diverse set of psychological and side-effect outcomes over time - are being conducted using standardized videos before final conclusions can be drawn on their specific use, specifically including also a non-video (control) condition. While we might not be aware of all currently running studies in this area, a published protocol indicates that in the US a study is being conducted aiming to test the effect of standardized pre-consultation videos in oncology with or without added clinician-expressed empathy on patients' outcomes such as anxiety [31].

4.2. Innovation

Our study marks an innovative approach of testing digital (video) interventions in the clinical setting. However, it is important not to overlook the current technological advancements in e-health, which extend beyond standardized videos and a focus on manipulating individual communication to improve patient outcomes. The literature suggests that e-health interventions, such as electronic health records and application on mobile devices (e.g. computer, phones), can support

clinician-patient communication, enhanced symptom assessment, and improved patient engagement of cancer patients [32], and tech-supported communication, such as patient portals, applications and web-based communication improves patient's life satisfaction and emotion management [33]. In an increasingly digital world, eHealth interventions present opportunities to improve communication and understanding within cancer care as well as increase accessibility, scalability, and implementation of the care [32,33]. It should be noted, however, that these studies also highlight the use of technology as additional interventions next to in-person interactions with patients. The newest and most prominent example of current developments in communication strategies is the use of Artificial Intelligence (AI) generated applications, such as ChatGPT. In a groundbreaking study by Ayers et al. [34], ChatGPT outperformed clinician responses in terms of empathy to patient-queries on public social media forums. There is, of course, a distinction between employing interactive AI responses personalized for individuals and relying on a standardized, one-size-fits-all manipulated video. This contrast highlights the potential for continued technological advancements to facilitate digital communication elements, such as clinician-expressed empathy, in more personalized and interactive ways.

Future studies could benefit from the valuable insights from our research findings. Specifically, for future studies intending to utilize standardized information videos with manipulated communication, we advise colleagues to create easy-to-adapt videos suitable for diverse settings and patients. Such videos should include brief, jargon-free sentences to also reach the large group of patients with low health literacy [35] – e.g. in Europe is estimated that up to 48 % of the population has low health literacy [36]. Moreover, to also reach patients with low digital literacy it would be useful to offer viewing the video at the hospital.

Ideally, videos should be offered in several languages to also reach patients from non-dominant languages due to the importance of high quality interpretation for patient communication and understanding and the limited availability of interpreters [37-39]. For this, animation videos which have voice-overs from different languages could be used, while their might even be promise in AI-applications such as “Elai” [40] which can dub videos, while making it look like the individual speaks the language. However, it's crucial to consider potential variations in communication customs and experiences between cultures, as studies have revealed cultural differences in communication and empathy experiences and preferences [41-43]. For example, we found that participants from minority groups were most satisfied after viewing a video with clinician-expressed empathy [41] while it is known that cultures differ in the level of preferred explicit or implicit communication styles [44]. This again highlights the complexity of interactions between clinicians and patients and despite all these technological advances, the importance of personal attention and face-to-face interaction in health care in general [45] and among breast cancer [46] care should not be forgotten.

This study has limitations. Most importantly, due to the small sample size results need to be interpreted with caution. Secondly, given our highly educated, middle-aged sample, the generalizability of results is limited since populations of different cultures and with different ethnical backgrounds might perceive clinician-expressed empathy in different ways [43,47]. Thirdly, we did not control the level of nocebo-alleviating information nor empathy participants received from the clinical staff, influencing outcomes. Fourthly, we did not include patient interview data on the feasibility of the study, which could have yielded additional insights.

4.3. Conclusion

In conclusion, while our study revealed challenges in participant recruitment, it underscores the acceptability of study procedures once participants were engaged. The limited effects of standardized videos in improving patient outcomes during chemotherapy, emphasizes the need for caution as viewing such digital interventions as a singular solution. Moving forward, the face-to-face interaction between the patients and clinical staff remains important, while cautiously exploring the potential benefits of modern technological advancements, ensuring thorough testing of their effects before implementation.

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CRediT authorship contribution statement

Lara C. Gröschel: Writing – original draft, Visualization, Validation, Software, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Fiona T. Brosig:** Writing – original draft, Visualization, Validation, Software, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Marcel Soesan:** Writing – review & editing, Project administration, Methodology, Investigation, Data curation, Conceptualization. **Katherina T. Vourtsis:** Writing – review & editing, Visualization, Validation, Software, Resources, Project administration, Investigation, Formal analysis, Data curation. **Mirte van der Spek:** Writing – review & editing, Project administration, Methodology, Investigation, Data curation, Conceptualization. **Elise Sluiter:** Writing – review & editing, Project administration, Methodology, Investigation, Data curation, Conceptualization. **Liesbeth M. van Vliet:** Writing – original draft, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Data curation.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests.

Liesbeth van Vliet reports financial support was provided by Dutch Cancer Society. Liesbeth van Vliet reports a relationship with Several speaking fees from educational agencies & Bayer that includes: speaking and lecture fees. Liesbeth van Vliet reports a relationship with Dutch Psychosocial Oncology Association that includes: board membership. Liesbeth van Vliet reports a relationship with Various other grants, e.g. ZonMW that includes: funding grants. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Appendix

Appendix A

Video Script (total length 5 min 12 s), English translation.

Nurse: Not long ago you spoke with the nurse specialist and received information about the AC-chemotherapy, which you will start shortly.
This information video is an addition to that conversation.
Nurse: AC chemotherapy consists of two medications: Adriamycin and cyclophosphamide.
The chemotherapy will be administered every two weeks.
Before the chemotherapy session, the patient has a blood test.
After that, they go to the doctor or nurse specialist.
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.
The patient goes to the day unit where she will receive the chemotherapy via a drip.
The day after the chemotherapy, you will receive an injection at home.
For that, we will organize a visit from the community nurse.
The patient can pick up the medication for the injection on the day of the chemotherapy, at the onco-pharmacy.
This medication stimulates the bone marrow to produce white blood cells,
which are important for the immune system.

Clinician-expressed empathy manipulation (19 s, shown only to participants in the empathy conditions)

Nurse: 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.
Nurse: AC chemotherapy has side effects. These sometimes occur, but not always. It differs per person.
Most side effects are temporary, and the degree to which they occur has no implications for the results of the treatment.
The most common side effects are:

o Nausea and vomiting
This can be caused by irritation of the lining of the stomach. To support you, you will receive anti-nausea medication.
o Impact on bone marrow function
The chemotherapy impacts bone marrow function. This will mean you produce fewer new blood cells, which can lead to anemia and a higher chance of infections and hemorrhaging, such as a nosebleed that will not stop.
o Hair loss
This chemotherapy has a very high risk of causing hair loss. You could consider using scalp cooling to prevent hair loss, or consider getting a wig, hat, or scarf.
o Menstrual irregularities
You may have menstrual irregularities. This can vary from "skipping a period" to your menstrual cycle stopping completely. You may also experience menopause symptoms such as hot flushes. After the chemotherapy, your period may come back.
o Irritation of the oral mucosa
Irritation of mucous membranes in the mouth can also occur. You might experience complaints such as a dry mouth, thicker saliva, or mouth ulcers. Good oral hygiene is important.
o Possible side effects of Neulasta injection
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. You can use paracetamol for these.

Nocebo-alleviating information manipulation (55 s, shown only to participants in the nocebo conditions)

Nurse: 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.

Clinician-expressed empathy Manipulation (10 s, shown only to participants in the empathy conditions)

Nurse: 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.
Nurse: 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.
If you experience

- Nausea or vomiting that persists even after you take medication
- Spontaneous bruising
- Frequent nosebleeds that are difficult to stop
- A temperature above 38.5C

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.
Nurse: The phone number you can use to contact us 24/7 is 020–5,129,111. Our switchboard operators will connect you through to the right department.

Clinician-Expressed empathy manipulation (12 s, shown only to participants in the empathy conditions)

Nurse: And once again, if you encounter any questions in the course of your chemotherapy, we are always here for you.

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