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Pilot Testing of a Nurse-led basic Symptom Self-Management Support for Patients Receiving First-line Systemic Outpatient Anticancer Treatment: A Cluster-randomised Study (Symptom Navi Pilot Study)

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Précis:

The Symptom Navi Programme was appreciated by patients and accepted by health care professionals, yet pilot testing did not show an effect on symptom interference with daily function.

Abstract

Background: The Symptom Navi Program (SNP) is a nurse-led intervention supporting basic symptom self-management for patients with any cancer diagnosis. The SNP has been accepted by patients and health care professionals alike.

Objective: To pilot the SNP and evaluate patient-reported symptom outcomes, nursing support for symptom management, and patient safety.

Interventions / Methods: Using a cluster-randomized design, we randomized centers to the intervention (SNP) or control group (usual care). Adult patients starting first-line systemic cancer treatment were included. The primary outcome was the change in symptom interference with daily functions (SIDF) from treatment onset to 16 weeks. Secondary outcomes included changes in symptom severity, symptom burden, self-efficacy, and perceived symptom management support and patient safety. We employed linear and logistic mixed-effect models to pilot-test differences in mean changes between groups. The trial was registered with ClinicalTrials.gov (NCT03649984).

Results: Changes in SIDF did not differ (mean difference at 16 weeks: -0.50; 95% CI: -1.38 to 0.38; p-value: 0.25) between SNP (3 centers, 49 patients) and control (5 centers, 85 patients) as for all other outcomes. No adverse events were reported.

Conclusions: Our preliminary findings did not indicate an effect of the SNP on patient-reported symptom outcomes, self-efficacy, or symptom management support. Inadequate power and SNP components (e.g. insufficient training, low number of follow-up consultations) may have attributed to the lack of an observed effect.

Implications for practice: The SNP training content and intervention procedures merit reconsideration.

Introduction

Patients diagnosed with cancer need relevant information, emotional support, clear communication, and symptom management support to better cope with their disease, treatment side-effects and how disease/treatment interferes with daily life [1]. A shift to outpatient cancer treatments requires patients to self-manage symptoms when symptom severity increases between treatments [2]. Consequently, patients treated in outpatient settings need symptom self-management support at the onset of treatment [3,4].

Self-management support (SMS) is based on a collaborative partnership between caregivers and patients and comprises tools and techniques to facilitate daily duties and patient self-management of cancer-related challenges [5]. Over the past several decades, SMS has been employed for chronic conditions such as diabetes, arthritis, chronic heart and lung disease, and human immunodeficiency virus infection [6]. SMS expands traditional patient education approaches and aims to facilitate behavior change by using different approaches (e.g. care planning, motivational interviewing, health coaching) [6]. Most SMS research has focused on chronic conditions and findings indicate SMS should be an integral part of high quality care because of improved clinical outcomes and potentially reduced costs [6,7]. Patients diagnosed with cancer differ from patients with other chronic conditions. Cancer patients experience intensive treatment phases with close surveillance by the treatment team, alternating with remission phases. During remission, contact with health care professionals typically decreases yet self-management challenges often increase.

In the context of cancer care, a growing body of research indicates that SMS can reduce physical symptoms (e.g. pain, fatigue, nausea), negative psychosocial consequences (e.g. not returning to work), and can improve general quality of life [8]. However, systematic

reviews have shown components of SMS interventions are heterogeneous with variable magnitudes of effect on outcomes [9,10]. Therefore, it remains unclear which components of SMS interventions are crucial for obtaining optimal patient outcomes for cancer symptom self-management.

Fostering patient self-efficacy is an essential aim of SMS interventions [6,7]. Self-efficacy is the subjective perception that one can achieve a desired behavior or task, even if it is challenging [11]. Facilitating self-efficacy has been an integral part of SMS interventions contributing to better outcomes in several studies [12-14]. Higher perceived self-efficacy is associated with lower symptom prevalence and distress, better quality of life, and may predict physical well-being [15]. Fostering self-efficacy in patients undergoing cancer treatment is challenging because individuals have to manage a variety of co-occurring symptoms and cumulative toxicity over the treatment trajectory [16].

Nurses are in close contact with patients and monitor symptoms earlier and more frequently than other health care professionals [17]. Nevertheless, SMS is not integrated in the standard care provided by oncology nurses in many outpatient settings [18] - even though nurses are well suited to implement SMS [19]. To date, most research on SMS in cancer care has focused on symptom outcomes [9,20]. The process of implementing self-management interventions into clinical routines has rarely been investigated [21].

To address the lack of standardized approaches to nurse-led SMS in Switzerland, we began developing the Symptom Navi Program (SNP) in 2011 by collaborating with health care professionals and patients diagnosed with cancer [22]. The SNP complements usual nursing care and consists of written information leaflets called Symptom Navi Flyers (SN-Flyers), nurse-led semi-structured

consultations using the SN-Flyers, and a training manual to standardize SNP implementation [23]. Best practices recommend testing feasibility and effectiveness of complex interventions, like the SNP, prior to widespread implementation [24].

We conducted a multi-method pilot study (Symptom Navi Pilot Study) to evaluate the implementation process (the study protocol has been previously published [23]). The primary objective of the present study was to explore the impact of the SNP on patient symptom interference with daily function (SIDF) compared with usual care. Secondary objectives were to: investigate the impact of the SNP on patient symptom severity/burden and perceived self-efficacy, explore patient evaluation of nursing symptom management support, and report patient safety.

Study Theoretical Framework

The Theory of Symptom Self-Management (TSSM) [13] was the guiding framework for evaluating the impact of the SNP on patient-reported outcomes. The TSSM emphasizes that patient self-management behavior depends on multiple connected dimensions. The TSSM posits that symptom severity influences patient symptom self-management behavior and perceived self-efficacy for self-management behavior. In parallel, perceived self-efficacy influences self-management behavior. Ultimately, the patient's personal and social health context as well as applied self-management behavior affects functional status (Figure).

Methods

We conducted a cluster-randomized pilot study with two parallel arms. Findings are reported using the extended CONSORT guideline for cluster-randomized trials [25]. Centers interested in implementing the SNP were considered as clusters to prevent cross-contamination between the intervention and the control groups [26]. The SNP pilot test was intended to evaluate the implementation process based on the RE-AIM (Reach Effectiveness – Adoption Implementation Maintenance) framework [27] and to estimate effect sizes and intra-cluster correlation to calculate sample and cluster sizes for a full powered study [26,28]. The Symptom Navi Pilot Study is registered with ClinicalTrials.gov (*NCT03649984).* No methodological changes were made to the study protocol.

Setting and Sample

Cancer outpatient centers in the German speaking part of Switzerland administering systemic anti-cancer therapies and interested in implementing the SNP were eligible to participate in the pilot study. We included employed, graduated nurses with at least one-year experience in oncology nursing and an unlimited employment contract who were administering systemic anticancer treatments at the centers. Eligible participants were adult patients (≥ 18 years) newly diagnosed with any type of cancer within 15 weeks prior to providing informed consent. The period of 15 weeks allowed including patients who had surgery first and started adjuvant systemic treatment thereafter. We excluded patients who could not read or speak German sufficiently, those with a cancer recurrence, or individuals who were exclusively treated with surgical or radiation therapy and those being followed by a palliative care team or participating in another psychosocial study.

Study procedures

Each participating center had a dedicated nurse and/or oncologist responsible for recruiting and screening eligible patients. Nurses approached eligible patients and invited them to participate. After providing written informed consent, patients completed a baseline assessment.

Usual nursing care for supporting symptom management included oral and written information on expected side-effects of treatment. When initiating a new therapy, nurses asked patients about their symptom experience and provided relevant information during a scheduled treatment visit. The use of standardized, validated assessment tools are rarely compulsory in Swiss cancer outpatient settings. Some centers had implemented additional nurse-led consultations to provide the information typically shared at the onset of cancer treatment. As part of usual care, patients also had access to information brochures from the Swiss Cancer League and/or leaflets developed by the treatment centers based on pharmaceutical drug information.

Intervention: Symptom Navi Program

The SNP consists of three components: i) the SN-Flyers (16 symptom-specific and 6 complementary flyers), ii) nurse-led, semi-structured consultations using the SN-Flyers, and iii) a training manual to standardize SNP implementation. SN-Flyers include information on symptoms at three color-coded levels (mild, moderate, and severe) and provide evidence-based recommendations for self-managing symptoms at each level. Color codes (green = mild, yellow = moderate, and red = severe) and emoticons (smiling, concerned, and sad face) are used to support the patient in determining symptom severity. When symptoms become severe (i.e. red/sad

face), patients are instructed to contact the care team. To individualize care, nurses engage the patient in conversation and prioritize the most relevant and important information flyers. The conversational nature of the interaction is intended to help mitigate information overload and facilitate patient collaboration.

Consultations are structured according to six key elements: 1) preparing the consultation, 2) evaluating patient willingness and motivation for the consultation, 3) providing information based on patient need and/or expected treatment side-effects, 4) addressing symptom self-management, 5) facilitating symptom self-management, and 6) documenting the consultation. Before the first consultation, nurses selected the SN-Flyers corresponding to the most common side-effects and symptoms of the therapy regimen for each patient individually. During consultation, patients were invited to express their need for other SN-Flyers and received an overview of all symptoms and problems addressed in the SN-Flyers. Further SN-Flyers were added during follow-up consultations based on patient symptom experiences. Nurse-led, semi-structured consultations were based on self-management education principles [29,30] and included motivational interviewing techniques. Motivational interviewing is an evidence-based, client-centered conversation method used to strengthen client motivation and facilitate behavior change based on individual goals and action plans [31]. Prior to starting patient recruitment, we trained all the nurses to standardize the semi-structured consultations at the intervention sites.

The nurse training was based on the Capability Opportunity Motivational – Behavior (COM-B) model [32] and was standardized in the SNP training manual. The COM-B model emphasizes that changes in nurse practice behavior depend on knowledge and skills (capabilities), analytical decisions (motivation), and center-specific factors enabling the behavior (opportunities). Two research team

members (MB and SKS), who are experts in SMS and familiar with the SNP, provided two training courses of four and two hours, respectively. Nurses were not trained to conduct a standardized assessment of symptom severity because we considered the SNP as a basic intervention to introduce SMS in the Swiss context of oncology nursing, where systematic symptom assessment is yet to be introduced and thus may pose a barrier to behavior change. Results of the training evaluation including nurses' confidence to apply the intervention have been published elsewhere [22].

Nurses provided a first consultation shortly before (or during) the patient's first anticancer treatment at the center and asked patients about previous experiences with health care providers and availability of family caregiving support. During a subsequent treatment visit, nurses provided a follow-up consultation to support individualized patient self-management behaviors. Nurses queried patients about their symptoms and self-management strategies employed by patients. Nurses helped foster patient self-efficacy by guiding patients in setting attainable goals and identifying concrete actions to achieve individualized goals. We recommended nurses use symptom assessment tools to evaluate symptom intensity and facilitate the discussion of self-management behaviors. Intervention fidelity was monitored by nurses' self-reports assessed by an electronic questionnaire to be completed after every SNP intervention including assessment of applied time for semi-structured consultations. Additionally, we observed two follow-up consultations at each SNP center.

Outcomes

Medical records and study-specific questionnaires were used to collect patient information and characteristics of participating centers. For each patient, we assessed mother-tongue (i.e. native language), housing situation, educational attainment, and medical data related to cancer diagnosis, existing co-morbidities, treatment information, and functional status based on the Karnofsky Index [33]. For cluster characteristics, we included center-specific information (e.g. number of full-time equivalent health professionals) and nurse education and training.

The primary outcome was mean change in symptom interference with daily function (SIDF) from baseline to 16-weeks. Secondary outcomes included symptom severity, symptom burden, self-efficacy and quality of nursing care (Table).

Symptom severity, symptom burden and SIDF were assessed using the German version of the MD Anderson Symptom Inventory (MDASI) [34]. The MDASI has 19 items using 11-point Likert scales. Higher ratings indicate increased symptom severity, burden, and interference with daily function. Symptom burden is the sum of symptom severity scores and SIDF scores (0 to 20) with higher ratings indicating greater symptom burden [35]. To assess self-efficacy, we used the German version of the Self-efficacy for Chronic Disease 6 item Scale (SES6G) [36]. The SES6G questionnaire uses 10-point Likert scales with higher ratings indicating higher perceived self-efficacy (i.e. greater confidence in self-managing symptoms). To assess perceived nursing support for symptom management, we translated (into German) and culturally adapted five items from the Patient-Reported Chemotherapy Indicators for Symptoms and Experience (PR-CISE) questionnaire [19]. Details on scoring and psychometric properties of the outcome measures are described in the

study protocol [23]. For the analyses, we dichotomized the PR-CISE outcomes (yes or somewhat = yes, vs. no) because very few patients answered "no". We considered mood a potentially confounding variable and assessed it using the Mood Linear Analogue Self-Assessment Scale (Mood LASA Scale) [37]. To evaluate safety, we used standardized Serious Adverse Event (SAE) reporting and specific questions for nurses on observed 'critical' behavior of patients as well as any signs and problems that might indicate an adverse event. For example, delayed contact with the care team, despite occurrence of a severe symptom (e.g. fever with neutropenia, or exacerbated diarrhea) was considered a critical behavior. Nurses answered safety questions via online survey following each semi-structured patient consultation.

Data Collection

Patients completed the baseline assessment (T_0) at the treatment center and all three follow-up assessments were completed at home (T_1= 1-3 weeks, T_2= 4-6 weeks, T_3= 16 weeks [± one week] after baseline assessment). Nurses provided patients with questionnaires and pre-stamped, addressed envelopes to return the questionnaires to an investigator (MB) who was responsible for data entry.

Randomization

Randomization occurred at the level of participating cancer outpatient centers (i.e. clusters). Patients were recruited consecutively and assigned to the intervention (SNP) or control based on their treatment center. We planned a 1:1 randomization ratio and stratified randomization based on *a priori* assessment of recruitment potential at each center (i.e. fast or slow). Centers with ≤ 150 estimated

patients meeting inclusion criteria per year were considered “slow” recruiters. For each stratum, we generated blocks of two - due to the small number of clusters in the pilot study. Stratification procedures were not applied at the individual patient level.

Allocation concealment of the cancer centers to intervention or control group was ensured by a clinical trial unit (CTU) that generated the random allocation sequence to assign centers to the respective cluster (SNP vs. control). The local principal investigator (responsible oncologist) obtained informed consent from the center prior to randomization. Due to intervention characteristics, blinding procedures were not applicable.

Statistical methods

We hypothesized the SNP intervention would reduce patient symptom interference with daily function. A formal sample size calculation was not performed. For pilot studies sample size calculations are imprecise and uncertain due to the lack of data about expected effect sizes [28]. Based on the estimated number of patients meeting the inclusion criteria at the respective centers, we considered it feasible for each center to recruit 10 to 20 patients. Therefore, we planned for a target sample size of approximately 140 patients with approximately 70 patients in the SNP and control groups respectively. Assuming an intra-class correlation of 0.05 and a type I error rate of 5%, 9 clusters with 15 patients (i.e. n= 135 patients) would us allow to detect effect sizes of 0.5, 0.75, and 1.0 with a power of 60%, 91%, and 99%, respectively [23].

Wilcoxon-Mann-Whitney tests and Fisher’s exact tests were used to compare continuous and categorical patient baseline characteristics as appropriate. We employed intention-to-treat approach for primary analysis (i.e. all patients at randomized clusters

were included in the analyses). For secondary analyses, we used the per-protocol set (PPS) and complete cases (i.e. only patients with complete follow-up data).

Continuous outcomes were analysed by using linear mixed-effects regression models including all measurement time points (i.e. T_1 = 1-3 weeks, T_2 = 4-6 weeks, or T_3 = 16 weeks). We used baseline measurement (BL), treatment group (SNP vs control), time point, interaction of treatment group and time point, and stratification factor (recruitment potential) as fixed covariates. To account for correlations within center and patients, we added a random intercept for center and a random intercept and slope for patient (nested within center). The models were fitted with restricted maximum likelihood (REML) and we used the Satterthwaite approximation for degrees of freedom. We calculated a joint *p*-value over all time points and treatment effects (as mean difference with 95% confidence interval [CI]) at each time point.

We analyzed binary outcomes using logistic mixed-effects regression models (i.e. generalized linear mixed-effects models with binomial distribution and logit link). We used treatment group, time point, interaction of group and time point, and stratification factor used in randomization as fixed effects, as well as random intercepts for center and patient (nested within center). We calculated a joint p-value over all time points and treatment effects (as odds ratio with 95% CI) at each time point. We used mixed-effects models to account for missing follow-up data. Fewer than 10% of patients were excluded from the analysis due to missing baseline data or completely missing follow-up data.

We performed three pre-specified sensitivity analyses: adjustment for potential confounders; separate analysis of time point T_3, and analysis of averaged data at the cluster level. To adjust for potential confounders, we included mood and all baseline outcomes with imbalance between treatment groups ($p<0.1$) as covariates in the mixed model. We omitted therapy scheme, combined chemo-radiotherapy and mental health diagnosis because of very few cases in the sample. Further, we dichotomized the Karnofsky Index to either normal (100% = levels 80 and above) or not normal Karnofsky Index (levels lower than 80). The separate analysis at T_3 was done with a simplified linear or logistic mixed model (for continuous and binary outcomes, respectively) with treatment group and stratification factor as fixed covariates and cluster as random intercept. Cluster means were compared between groups using a linear or logistic regression with treatment group and stratification variable as covariates.

Pre-specified subgroup analyses for symptom interference were performed with daily function at T_3 by recruitment potential (fast vs. slow recruiters), combined chemo-radiotherapy and number of applied anticancer treatments (≤ 25 vs. > 25 therapies per day) at the center. Subgroups were analyzed using linear mixed-effects models with treatment group, subgroup and their interaction as fixed, and cluster as a random effect. We calculated *p*-values for interaction based on likelihood ratio tests and treatment effects for the individual subgroups from the interaction models using contrasts. We also calculated intra-class correlation coefficient (ICC) for all outcomes at every time point - or overall using the linear mixed-effect models specified above.

We considered nurse education level for oncology nursing (higher education level vs. university level) could be a confounding variable. We conducted *post-hoc* analysis that included center-specific nursing education level in the mixed model. Analyses were performed using STATA version 15.1 and R version 3.5.3 (2019-03-11).

Results

Sixteen centers were assessed for eligibility between May and November 2017. Five centers were not interested in the SNP pilot study. One center already used the SN-Flyers, and one center did not have enough resources to implement the SNP (Figure 2). Of the nine participating clusters (i.e. centers), we randomly allocated four clusters to SNP and five clusters to control. One SNP center withdrew consent before recruiting a patient because of a significant decrease in the number of first-line cancer treatments. Patient recruitment started in October 2017 and ended in January 2019. Overall, 20% of screened patients (n=33) were either excluded from the study or did not consent (n=20 SNP patients [29%], n=9 control patients [13%]). In one of the SNP clusters, recruitment was slow and fewer patients were recruited than expected. To reduce a potential imbalance in patient recruitment between groups, we stopped recruiting patients at slow recruiting control clusters. In total, 49 patients were allocated to SNP and 85 patients to the control group.

Baseline Characteristics

The outpatient cancer centers reflected the Swiss context with a mix of small regional and large, urban, tertiary cancer centers. Two of the four SNP centers were breast cancer centers. All other centers included patients with different cancer diagnoses. Approximately half of the nurses employed in the cancer centers had received formal education in oncology nursing (Table 2).

At baseline, patient characteristics at center level differed significantly in age, gender, living with family members needing care, cancer diagnosis, and treatment scheme (intravenous and oral). More patients in the control group were receiving oral anticancer treatments, had reduced functional status and were diagnosed with cancers other than breast cancer. There were no significant differences between SNP and control groups regarding mother-tongue, housing situation, education level, or co-morbidities (Table 3).

Intra-class correlation coefficient

Overall, intra-class correlation coefficients (ICC) were very close to zero in most situations - indicating that observations within centers were not correlated (Tables 4 and 5).

Effect on symptom outcomes and perceived self-efficacy

Descriptive plots of the outcomes are shown in Figures 3 and 4. The primary analysis (SNP: n=42, control: n=81), showed no significant effect on any of the assessed patient-reported symptom outcomes (Table 6). Similarly, no effect on self-efficacy was observed at any time point (Table 6). The SNP had no effect on SIDF over all time points (joint p=0.59) and the SNP had no effect at 16 weeks after baseline (mean difference: -0.50 (95% CI -1.38 to 0.38, p=0.25). These findings suggest that SNP interventions were not superior to usual care regarding the primary outcome.

Patients in both groups reported mild symptom severity and burden scores (Table 6). Mean symptom severity and burden scores increased from T_1 to T_3, while mean self-efficacy scores decreased during this period. These observations indicate that patients dealt with increased and/or more severe symptoms at T_3, and concurrently, they felt less confident in managing their symptoms. However,

SNP patients rated their self-efficacy slightly higher compared to controls (mean difference at 16 weeks -0.14 (95% CI: -0.79 to 1.07), joint *p*=0.46 over all time points, Table 6).

The per-protocol and complete case analyses confirmed results from the main analysis. Controlling for potential confounding variables (age, gender, living with persons who need care, education, type of cancer [breast, lung, others], functional status, and mood) had small effects. However, the mean difference for SIDF was somewhat increased in controls (- 0.83, 95% CI:-1.62 to -0.04, *p*=0.040 at 16 weeks, Table 7). A simplified analysis limited to the final follow-up visit (T_3) showed a mean difference in SIDF of -0.68 (95% CI: 1.76 to -0.40, *p*= 0.17) (Table 8). Comparing cluster means confirmed the SNP had no significant effect on any patient-reported outcome (Table 9).

Nurse support for symptom management

Primary analysis showed no significant change in perceived nurse support for symptom management for any of the PR-CISE items (Table 10). For three PR-CISE items, the SNP group had a favorable trend from T_1 to T_3 compared to controls. The proportion of patients reporting that nurses were aware of their symptom severity decreased from 94% to 86% in controls. In contrast, the SNP group exhibited increased rates at T_3 – approximating the results from T_1 (OR =1.39, 95% CI: 0.21 to 9.27 at 16 weeks, joint *p*=.77). The proportion of SNP patients reporting they received useful information for managing their symptoms increased from 79% to 85% between T_1 and T_3. Among controls, the proportion decreased from 92% to 84%. Approximately one-third of the patients in both groups were not confident managing their symptoms (Table 10).

Per-protocol analysis, complete case analyses, and adjustment for potential confounders (same variables used as for preliminary effectiveness analysis) confirmed results of the primary analysis on symptom management support (data not shown). Similarly, analysis restricted to T_3 only and comparing cluster-averaged data supported the primary analysis (data not shown).

Subgroup and *post-hoc* analysis

Analysis of pre-defined subgroups (i.e. recruitment potential, combined chemo-radiotherapy, number of applied tumor therapies at the centers) did not reveal any differences in SNP effect on symptom interference at T_3 (16 weeks) (Figure 5). Including nurse education level in the mixed-effect models had no influence on any patient-reported outcomes. In summary, none of the additional analyses changed findings from the primary analysis (i.e. no significant difference between the SNP and control groups).

Patient safety

No adverse events were reported at any center randomized to SNP. Nurses did not report any critical patient behaviors or signs of adverse events while using the SN-Flyers. Based on Swiss ethics committee guidance, we did not assess patient safety outcomes in the control group.

Nurses fidelity

Overall, 92% of all defined core components were applied during semi-structured consultations (95% CI: 87% to 95%). On average, nurses applied 45.2 ±26.3 minutes (range 20 to 60 minutes) for initial consultations and 24.3 ±13.9 minutes (range 15 to 30 minutes/patient) for follow-up consultations. Considering additional time for preparation and documentation, initial consultations

required 90.9 ±31.9 minutes (range 70 to 120 minutes) on average, and follow-up consultations 34.4 ±18.3 minutes (range 20 to 45 minutes).

Observations revealed that nurses frequently addressed self-monitoring and self-management of symptoms during consultations. Other self-management education components such as tailoring the intervention to individual needs, or coaching patients in goal setting, action planning, problem solving and decision making were rarely included.

Discussion

In this cluster-randomized pilot study, we evaluated whether the SNP could support patient symptom self-management. Despite promising descriptive results on acceptability and satisfaction with the SNP, we did not find an effect of the SNP on patient outcomes. No effect was observed on the primary outcome (SIDF) nor for secondary outcomes (symptom severity, burden, self-efficacy and perceived nursing support for symptom management. The SNP did not lead to any reported adverse events or delayed contact with health care providers based on adverse event and nurses' reporting.

On average, patients in both groups reported only slightly increased symptom severity and symptom burden over 16 weeks. This observation is in contrast to a survey reporting substantial numbers of patients with moderate or severe symptom severity over the trajectory of their treatment [19]. Patients with rather mild and less burdensome symptoms may have a greater capacity and motivation to manage symptoms on their own. Therefore, some patients in the SNP intervention may not have used the SN-Flyers and may have not needed extra SMS from health care providers [38] – yet we did not evaluate this element in our pilot study. Notably, standardized

symptom assessments are not commonly employed in Swiss cancer centers. Thus, a limitation of this study is that nurses did not conduct standardized symptom assessments to tailor the SMS intervention. Using structured approaches to symptom assessment to inform tailoring warrants further development. Symptom severity and burden scores varied largely in both groups of our study, emphasizing the need for a tailored, stepwise approach to care providing patients with personalized SMS. The increase in symptom severity and burden over treatment trajectory is well known [16] and evidence suggests SMS and self-efficacy support is crucial for improving symptom outcomes and functional status [2,12,13,39]. Self-efficacy can fluctuate and supporting patients to foster self-efficacy can improve patient emotional and functional well-being [40]. However, symptom severity affects patient self-efficacy [13,15,41] which may explain the decrease in perceived self-efficacy in both groups that was concurrent with increasing symptom severity and burden scores. We designed two semi-structured consultations for the SNP. As a basic SMS intervention, this might not have been sufficient to support self-efficacy. Indeed, approximately one-third of all patients in our study reported not feeling confident in managing their symptoms.

We asked nurses to deliver a complex self-management intervention using motivational interviewing (MI) techniques to support self-efficacy and facilitate behavior change. Such an approach is an advanced, sophisticated, patient-centered behavior change intervention that should be supervised [42]. Feasibility results might indicate that the level of complexity required for the SNP may have been too ambitious for nursing practice in chemotherapy units. As an alternative to MI, brief primary care approach termed the “5 A’s” (assess, advise, agree, assist, arrange) [43] could be a feasible option. Future developments of the SNP could include intensifying self-efficacy

support by adding more follow-up consultations, and/or emphasizing dedicated approaches to foster self-efficacy during the consultations.

To our knowledge, few studies have investigated SMS interventions for patients with cancer at the onset of anticancer treatment. A sequential pre-post study tested a SMS intervention (CHEMO-SUPPORT) provided by trained nurses (two days training) for patients with different cancer diagnoses during ambulatory chemotherapy. Patients reported less symptom distress and severity, and improved self-efficacy after CHEMO-SUPPORT was introduced [18]. The intervention included two tailored coaching sessions (in person and phone call) based on tailored symptom monitoring and patient diaries. Interventions were complemented with a brochure and an online (or on-call) nursing service to answer patient questions. Additional coaching sessions to support symptom management were provided on request. In the present study, graduate nurses were trained to use the SNP (6-hour training) to provide semi-structured consultations with SN-Flyers. In contrast to the CHEMO-SUPPORT intervention, symptom assessment was used in our study to assess outcomes - but was not included in semi-structured consultations. The SNP aims to provide *basic* SMS. Therefore, every patient in our study received basic intervention regardless of symptom severity and interference with daily function. Tailoring SMS to the cancer therapy, and not specifically to individual needs, does not fully align with recommended best practices for tailored SMS approaches [9,20,44]. Accordingly, this warrants consideration for further developing the SNP and SMS programs in general.

Face-to-face SMS interventions provided by trained health care professionals (like in the SNP pilot study) require personal and institutional resources. Electronic tools can facilitate symptom monitoring and outcome reporting for health care providers and

sometimes for patients [38,45,46]. While electronic and online tools are easily accessible and facilitate symptom monitoring, they are dependent on the patient engagement and tool use. A recent study identified predictive factors for using an electronic toolkit for cancer survivors. Higher symptom burden and better cognitive functions at the onset of the intervention and the increasing of symptom severity over time were associated with continued toolkit use [38]. Using the electronic tool alone neither improved symptom outcomes [38] nor self-management behavior [47]. Adding in-person symptom management education by trained nurses was associated with reduced fatigue and improved sleep [45].

Controlling for nurse education level in our post-hoc analysis did not identify any effect on patient-reported outcomes. Therefore, we conclude that implementing the SNP does not require specialized nurses *per se*. However, including symptom monitoring in the SNP could facilitate follow-up of patients with greater symptom intensity/burden who probably need SMS thereby potentially increasing the impact of the SNP. A possibility for adapting the SNP is to make SN-Flyers accessible online. However, whether or not results from studies using electronic tools are transferable to the SNP will need further investigation.

Limitations

Our pilot study results should be interpreted with caution. A study design limitation is that cluster randomization was exclusively stratified on recruitment potential. As a result, the two breast cancer centers were randomized to the intervention group leading to more female patients receiving the intervention. On the other hand, none of the controlled confounding variables affected study results.

Nevertheless, for a full-powered randomized study, stratification criteria on cluster level should be extended to mitigate differences between groups.

As one cluster withdrew, the statistical power was compromised by an unequal number of clusters in the intervention and control groups [48]. The decision to include nine centers was a feasibility decision based on the number of centers that expressed interest in the pilot study. We cannot exclude that the sample was too small to detect significant differences between the SNP and control groups - assuming a modest intervention effect [49]. Further, we cannot rule-out that insufficient power limited our ability to detect significant results [50]. The intervention effect depends on successful SNP implementation as well as nursing behavior change to provide SMS and adopt a coaching role. Information on nurses' fidelity was evaluated based on self-reports being susceptible for reporting bias. Only six expert observations could be integrated in this study, limiting their reliability. We assume that nurses in both groups were similarly motivated to support patients. Therefore, SMS elements may have already been integrated in usual care in the control group. Small between group differences in the intervention may have diluted the effect size in this pilot study.

Generalizability for pilot study results is limited [28]. Because we did not show a superior effect for the SNP, sample and cluster size calculations are not yet possible. A randomized study would require considerably more participating centers and patients to achieve sufficient power [48]. Further, eligibility of centers should be based on the volume of anticancer treatments and workforce resources rather than on estimated recruitment potential.

Conclusions

We believe the SNP is a promising, nurse-led intervention that is feasible and accepted by patients and nurses alike [22]. However, two semi-structured consultations with SN-Flyers may not be sufficient to improve symptom interference with daily function, perceived self-efficacy or perceived nurse support for symptom management over 16 weeks after initiating first-line cancer treatment. Our pilot study results do not provide an empirical basis for introducing a basic SMS intervention for all patients at the onset of anticancer treatment. Thus, a tailored approach may be warranted, as a "one-size-fits-all" approach appears insufficient to meet all patient needs. Clinicians and patients gave the SNP high acceptability/approval ratings. However, it seems plausible that the SNP could be improved. For example, systematic symptom assessments during semi-structured consultations could be used to tailor the SMS intervention and better meet individual patient needs. Further, patient symptom severity and perceived self-efficacy could be used to guide follow-up consultations. Regardless of future SNP modifications, stakeholder involvement will be critical to help facilitate nursing behavior change in implementing the SNP and coaching patient self-management. It is possible that tailoring and refining the SNP could help change usual care practices. Moreover, such alterations could increase the likelihood of the SNP improving patient-reported outcomes. Further investigation is needed to evaluate the effect of modified SNP content (e.g. adding systematic symptom assessments, stronger focus on building self-efficacy) and dosing adjustments (e.g. tailored follow-up consultations for patients with low self-efficacy scores and/or high SMS need) on patient-reported outcomes.

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Legends of tables and figures

Table Assessed Outcomes and Covariates

Abbreviations: BL, Baseline; LASA, Linear Analogue Self-Assessment; MDASI, MD Anderson Symptom Inventory; N, number; PR-CISE, Patient-Reported Chemotherapy Indicators for Symptoms and Experience; SES6G, Self-efficacy for Chronic Disease 6 item Scale; t1, 1-3 weeks (between second and third treatment application); t2, 4-6 weeks (between third and fourth treatment application); t3, 16 weeks (± one week).

Figure Theoretical Framework for Pilot Study and Semi-Structured Consultations

Abbreviations: MDASI, MD Anderson Symptom Inventory; PR-CISE, Patient-reported Chemotherapy Indicators for Symptoms and Experience; SES6G, Self-efficacy for Chronic Disease 6 item Scale; SN-Flyers, Symptom Navi Flyers; SNP, Symptom Navi Programme;

Symptom specific SN-Flyers: Alopecia, Anxiety, Breathlessness, Diarrhoea, Emesis and nausea, Fatigue, Increased susceptibility: infections and bleeding, Irradiated skin, Loss of appetite, Inflamed oral mucosa, Obstipation, Pain, Peripheral neuropathy, Sexuality, Skin alteration: feet and hand, and Skin alterations related to target therapies.

General SN-Flyers: information how to use the flyers, complementary information on pain management and on Oxaliplatin, useful addresses for support at home, and a list of all available flyers.

Figure 2. Cluster and Patient Flow

One cluster withdrew the consent before recruiting any patients.

Table 2. Cluster Baseline Characteristics

Abbreviations: FTE, Full Time Equivalent; BScN, Bachelor Science in Nursing; lq, lower quartile; MScN, Master Science in Nursing; sd, standard deviation; SNP, Symptom Navi Programme; uq, upper quartile;

Legend: [a] Numbers do not sum up as several entries are possible; [b] level I = education at non-university level; [c] level II = education at university level

Table 3. Patient Baseline Characteristics

Legend: [a] Missing for one patient in control group, [b] Missing for two patients in control group, Other cancer diagnosis summarise prostate, colorectal, head and neck, pancreatic, hematologic, ovarial, and other cancers.

Table 4. Intra-class Correlation Coefficient (ICC) for Continuous Efficacy Outcomes at Every Visit and Overall

Calculated from linear mixed-effects regression models. The adjusted ICC is based on models with group and stratum (and visits for the overall estimate) as fixed effects and centre (and patient for the overall estimate) as random effect. The crude ICC is based on models with random effects only. N: number of clusters; n: number of observations; n.e. not estimable.

Table 5. Intra-class Correlation Coefficient (ICC) for Binary Efficacy Outcomes (PR-CISE items) at Every Visit and Overall

Calculated from logistic mixed-effects regression models. The adjusted ICC is based on models with group and stratum (and visits for the overall estimate) as fixed effects and centre (and patient for the overall estimate) as random effect. The crude ICC is based on models with random effects only. N: number of clusters; n: number of observations; n.e. not estimable.

Figure 3. Descriptive Boxplots for Continuous Efficacy Outcomes Based on MDASI and SES6G Questionnaires at Each Visit

Figure 4. Descriptive Bar Charts for Patients' Perceived Nursing Support for Symptom Management Based on PR-CISE Items

Table 6. Mean Difference of Symptom Interference, Severity, Burden and Self-Efficacy (MDASI and SES6G Items)

Legend: Primary analysis based on the full analysis set. Mean in each group and mean difference between groups (SNP vs control) with 95% confidence intervals (CI) were derived from a linear mixed model. N refers to the number of non-missing observations.

Table 7. Sensitivity Analysis of Continuous Efficacy Outcomes Adjusted for Potential Confounders Based on the FAS at Each Time Point

A positive mean difference indicates an improvement in the Symptom Navi group (SNP).

Table 8. Sensitivity Analysis of Continuous Efficacy Outcomes Using Only the last Follow-up Visit (T_3,16 Weeks)

A positive mean difference indicates an improvement in the Symptom Navi group (SNP).

Symptom interference and symptom severity scores 0 – 10 (higher ratings indicating higher symptom interference and higher symptom severity); symptom burden scores 0 – 20 (higher ratings indicating higher symptom burden); self-efficacy sores 1 – 10 (higher ratings

indicating higher/better self-efficacy); CI = confidence interval; N refers to non-missing observations. N refers to non-missing observations. Mean in each group and mean difference between groups with 95% CI were derived from a simplified linear mixed-effects regression model with treatment group and stratification factor as fixed covariates and cluster as random intercept.

Table 9. Sensitivity Analysis of Continuous Efficacy Outcomes Based on the Comparison of Cluster Means of the Change Score from Baseline to T_3 (16 Weeks).

The effects are presented as mean difference or Mann-Whitney statistic (the probability that a random patient in the Symptom Navi group (SNP) has better outcome than a random patient from the Control group) with 95% confidence intervals (CI). A positive mean difference and a Mann-Whitney statistic larger than 0.5 indicates an improvement in SNP. N refers to the number of clusters.

†Mean (sd), mean difference (95% CI) and p-value from linear regression adjusted for stratum used in randomisation.

*Median (lower, upper quartile), Mann-Whitney statistic (95% CI) and p-value from van Elteren test with stratum used in randomisation.

Table 10. Odds Ratio for Symptom Management Support (PR-CISE Items)

Primary analysis based on the full analysis set. Odds ratios of SNP vs control with 95% confidence intervals (CI) were derived from a generalised linear mixed model. N refers to the number of non-missing observations, n to the number of patients answering with yes.

Figure 5. Forest Plot for Subgroup Analysis of the Primary Outcome for Binary Subgroups

A positive mean difference indicates an improvement in the Symptom Navi group (SNP).

Means in each group and mean differences between groups (SNP vs Control) with 95% confidence intervals (CI) were derived from linear mixed-effects regression models with the subgroup and its interaction with treatment group as covariates. Only the last follow-up (T_3, 16 weeks) was taken into account. The p-values for interaction were derived from likelihood ratio test of models with and without interaction. The treatment effect was not estimable (n.e.) in patients with combined chemo-radiotherapy. N refers to the number of non-missing observations.

Table Assessed Outcomes and Covariates

Level	Instruments (N items)	Assessed	Outcomes
Cluster / center	Cluster characteristics (6)	T_0	Specialised cancer center, nurses' formation, number of employed nurses and oncologists at each intervention center, average number of delivered anti-cancer treatments per day, number of treated patients at the center per year, information leaflets usually delivered to patients
Individual / patient	Patient's characteristics (9)	T_0	Age, gender, diagnosis, co-morbidities, pharmaceutical information of treatment, and Karnofsky index, mother tongue, housing context, highest education degree
Individual / patient	Primary outcome: MDASI (6)	T_0, T_1, T_2, T_3	6 items on symptom interference for daily functions (general activity, mood, work, relations with others, walking, enjoyment of life)
Individual / patient	Secondary outcomes: MDASI (13)	T_0, T_1, T_2, T_3	Symptom severity: pain, fatigue, nausea, disturbed sleep, distress, shortness of breath, difficulty remembering, poor appetite, drowsiness, dry mouth, sadness, vomiting, numbness or tingling
Individual / patient	PR-CISE (5)	T_0, T_1, T_2, T_3	Nurse support for symptom management, patient-reported: - Nurses ask about your symptoms - Nurses are aware of your symptoms' severity - Nurses provide useful information to manage symptoms - Nurses provide practical advice to manage symptoms - Are you confident to manage the symptoms you are experiencing?
Individual / patient	SES6G (6)	T_0, T_1, T_2, T_3	Self-efficacy for: - Managing fatigue, - Managing physical discomfort, - Managing emotional distress, - Keeping symptoms from interfering with things they want to do, - Managing health conditions without doctors help, - Generally feeling confident to find alternative approaches than just taking medications to relieve a symptom.
Individual / patient	Further covariate: Mood LASA scale (1)	T_0, T_1, T_2, T_3	How do you rate your mood during the last two weeks?
Individual / patient	Safety (2)	At any time occurring and regularly at T_0, T_1, T_2, T_3	Reporting on serious adverse events related to SNP Narrative reporting by nurses (online)

Abbreviations: BL, Baseline; LASA, Linear Analogue Self-Assessment; MDASI, MD Anderson Symptom Inventory; N, number; PR-CISE, Patient-Reported Chemotherapy Indicators for Symptoms and Experience; SES6G, Self-efficacy for Chronic Disease 6 item Scale; T_1, 1-3 weeks (between second and third treatment application); T_2, 4-6 weeks (between third and fourth treatment application); T_3, 16 weeks (± one week).

Table 2. Cluster Baseline Characteristics

Participating Clusters	SNP (N=3)	Control (N=5)
Outpatient Cancer Center: n (%)[a]		
Independent oncological ambulatory	1 (33%)	2 (40%)
Ambulatory from a hospital network	0 (0%)	2 (40%)
Ambulatory from a cantonal hospital	1 (33%)	2 (40%)
Ambulatory from a tertiary hospital	1 (33%)	0 (0%)
Certificated oncological center	3 (100%)	3 (60%)
Engaged Workforce: Median of total FTE [lq, uq]		
Oncologists	7.4 [2.0, 14.4]	4.6 [2.2, 7.4]
Nurses	3.1 [2.2, 7.1]	6.1 [2.6, 10.8]
Number Anticancer Treatments per Day		
Mean (sd)	26 (16)	22 (14)
Median [lq, uq]	22 [12, 44]	26 [9, 32]
Nurses Education: n/total (%)		
Graduated (higher education)	8/18 (44%)	27/54 (50%)
Graduated (BScN)	0/18 (0%)	1/54 (1.9%)
Graduated (MScN)	1/18 (5.6%)	1/54 (1.9%)
Education in oncology nursing, level I[b]	4/18 (22%)	20/54 (37%)
Education in oncology nursing, level II[c]	5/18 (28%)	5/54 (9.3%)

Abbreviations: FTE, Full Time Equivalent; BScN, Bachelor Science in Nursing; lq, lower quartile; MScN, Master Science in Nursing; sd, standard deviation; SNP, Symptom Navi Programme; uq, upper quartile;
Legend: [a] Numbers do not sum up as several entries are possible; [b] level I = education at non-university level; [c] level II = education at university level

Table 3. Patient Baseline Characteristics

	SNP (N=49)	Control (N=85)	P-Value
age: mean (sd)	59 (12)	66 (12)	.001
Women: n (%)	35 (71%)	44 (52%)	.030
Mother tongue[a]: n (%)			.37
German	46 (94%)	72 (85%)	
French	1 (2.0%)	1 (1.2%)	
Romansh	1 (2.0%)	3 (3.5%)	
Others	1 (2.0%)	8 (9.4%)	
Housing context[a]: n (%)			.43
Living alone	7 (14%)	15 (18%)	
Living with partner or spouse	42 (86%)	66 (78%)	
Other	0 (0%)	3 (3.5%)	
Caring for children or family members [b]: n (%)	14 (29%)	10 (12%)	.019
Highest education degree[a]: n (%)			.05
Compulsory school education (8 years)	5 (10%)	7 (8.2%)	
Completed vocational training	21 (43%)	55 (65%)	
Higher professional degree	19 (39%)	16 (19%)	
University degree	4 (8.2%)	6 (7.1%)	
Cancer diagnosis: n (%)			.013
Breast cancer	25 (51%)	24 (28%)	
Lung cancer	8 (16%)	12 (14%)	
Other	16 (33%)	49 (58%)	
Therapy scheme: n (%)			
intravenous	48 (98%)	68 (80%)	.003
subcutaneous	1 (2.0%)	6 (7.1%)	.42
oral	1 (2.0%)	19 (22%)	< .001
Co-Morbidities: n (%)			
Diabetes	6 (12%)	9 (11%)	.78
COPD	2 (4.1%)	6 (7.1%)	.71
Heart failure	1 (2.0%)	5 (5.9%)	.41
Mental diseases	0 (0%)	6 (7.1%)	.09
Dementia	1 (2%)	1 (1.2%)	1.0
Others	5 (10%)	17 (20%)	.16
Functional status based on Karnofsky Index: n (%)			.020
- unable to carry on normal activity or less (≤ 70%)	5 (10%)	13 (15.4%)	
- normal functionality with effort (80%)	8 (16%)	11 (13%)	
- minimal disease symptoms (90%)	9 (18%)	35 (41%)	
- normal condition, no manifest disease (100%)	27 (55%)	26 (31%)	

Legend: [a] Missing for one patient in control group, [b] Missing for two patients in control group, Other cancer diagnosis summarise prostate, colorectal, head and neck, pancreatic, hematologic, ovarial, and other cancers.

Table 4. Intra-class Correlation Coefficient (ICC) for Continuous Efficacy Outcomes at Every Visit and Overall

	N	n	Adjusted ICC (95% CI)	Crude ICC (95% CI)
Mean symptom interference				
T_1 (1-3 weeks)	8	118	0.0 (n.e.)	0.03 (0.00 to 0.54)
T_2 (4-6 weeks)	8	108	0.001 (0.00 to 0.96)	0.00 (0.00 to 1.00)
T_3 (16 weeks)	8	106	0.00 (n.e.)	0.00 (n.e.)
Overall	8	332	0.00 (n.e.)	0.02 (0.00 to 0.52)
Mean symptom severity				
T_1 (1-3 weeks)	8	117	0.00 (n.e.)	0.02 (0.00 to 0.84)
T_2 (4-6 weeks)	8	109	0.03 (0.00 to 0.63)	0.03 (0.00 to 0.48)
T_3 (16 weeks)	8	105	0.00 (n.e.)	0.00 (n.e.)
Overall	8	331	0.00 (n.e.)	0.02 (0.00 to 0.71)
Mean symptom burden				
T_1 (1-3 weeks)	8	117	0.00 (n.e.)	0.06 (0.00 to 0.41)
T_2 (4-6 weeks)	8	108	0.03 (0.00 to 0.77)	0.02 (0.00 to 0.84)
T_3 (16 weeks)	8	105	0.00 (n.e.)	0.00 (n.e.)
Overall	8	330	0.00 (n.e.)	0.03 (0.00 to 0.45)
Mean self-efficacy				
T_1 (1-3 weeks)	8	118	0.01 (0.00 to 1.00)	0.01 (0.00 to 1.00)
T_2 (4-6 weeks)	8	108	0.00 (n.e.)	0.01 (0.00 to 1.00)
T_3 (16 weeks)	8	104	0.00 (n.e.)	0.00 (n.e.)
Overall	8	330	0.00 (n.e.)	0.00 (n.e.)

Calculated from linear mixed-effects regression models. The adjusted ICC is based on models with group and stratum (and visits for the overall estimate) as fixed effects and centre (and patient for the overall estimate) as random effect. The crude ICC is based on models with random effects only. N: number of clusters; n: number of observations; n.e. not estimable.

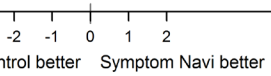
Table 5. Intra-class Correlation Coefficient (ICC) for Binary Efficacy Outcomes (PR-CISE items) at Every Visit and Overall

	N	n	Adjusted ICC (95% CI)	Crude ICC (95% CI)
Nurses ask about symptoms				
T_1 (1-3 weeks)	8	116	0.00 (n.e.)	0.00 (n.e.)
T_2 (4-6 weeks)	8	108	0.10 (0.00 to 0.78)	0.14 (0.00 to 0.72)
T_3 (16 weeks)	8	104	0.00 (n.e.)	0.02 (0.00 to 1.00))
Overall	8	328	0.04 (0.00 to 0.67)	0.07 (0.01 to 0.48)
Nurses are aware of symptom severity				
T_1 (1-3 weeks)	8	115	0.00 (n.e.)	0.00 (n.e.)
T_2 (4-6 weeks)	8	109	0.00 (n.e.)	0.00 (n.e.)
T_3 (16 weeks)	8	104	0.00 (n.e.)	0.00 (n.e.)
Overall	8	327	0.00 (n.e.)	0.00 (n.e.)
Nurses provide useful information to manage symptoms				
T_1 (1-3 weeks)	8	117	0.00 (n.e.)	0.18 (0.02 to 0.73)
T_2 (4-6 weeks)	8	108	0.07 (0.00 to 0.86)	0.17 (0.01 to 0.75)
T_3 (16 weeks)	8	103	0.00 (n.e.)	0.00 (n.e.)
Overall	8	328	0.02 (0.00 to 0.90)	0.08 (0.01 to 0.52)
Nurses provide practical advice to manage symptoms				
T_1 (1-3 weeks)	8	117	0.00 (n.e.)	0.14 (0.01 to 0.70)
T_2 (4-6 weeks)	8	108	0.00 (n.e.)	0.00 (n.e.)
T_3 (16 weeks)	8	102	0.00 (n.e.)	0.00 (n.e.)
Overall	8	327	0.00 (n.e.)	0.00 (n.e.)
Are you confident to manage symptoms				
T_1 (1-3 weeks)	8	117	0.00 (n.e.)	0.00 (n.e.)
T_2 (4-6 weeks)	8	108	0.00 (n.e.)	0.00 (n.e.)
T_3 (16 weeks)	8	103	0.05 (0.00 to 0.51)	0.06 (0.00 to 0.47)
Overall	8	328	0.00 (n.e.)	0.00 (0.00 to 1.00)

Calculated from logistic mixed-effects regression models. The adjusted ICC is based on models with group and stratum (and visits for the overall estimate) as fixed effects and centre (and patient for the overall estimate) as random effect. The crude ICC is based on models with random effects only. N: number of clusters; n: number of observations; n.e. not estimable.

Table 6. Mean Difference of Symptom Interference, Severity, Burden and Self-Efficacy (MDASI and SES6G Items)

	Symptom Navi (SNP)		Control		Mean difference (95% CI)	P-value	Joint
	N	mean (95% CI)	N	mean (95% CI)			p-value
Mean symptom interference	42		81				.59
t1 (1-3 weeks)		2.77 (2.24 to 3.30)		2.37 (2.01 to 2.74)	-0.40 (-1.17 to 0.37)	.26	
t2 (4-6 weeks)		2.74 (2.14 to 3.35)		2.34 (1.93 to 2.75)	-0.40 (-1.21 to 0.41)	.30	
t3 (16 weeks)		3.26 (2.60 to 3.92)		2.76 (2.29 to 3.23)	-0.50 (-1.38 to 0.38)	.25	
Mean symptom severity	42		81				.65
t1 (1-3 weeks)		2.37 (1.96 to 2.78)		2.07 (1.78 to 2.36)	-0.30 (-0.90 to 0.30)	.28	
t2 (4-6 weeks)		2.43 (1.96 to 2.90)		2.15 (1.83 to 2.46)	-0.28 (-0.91 to 0.35)	.35	
t3 (16 weeks)		2.76 (2.24 to 3.27)		2.61 (2.24 to 2.97)	-0.15 (-0.83 to 0.53)	.65	
Mean symptom burden	42		81				.58
t1 (1-3 weeks)		5.11 (4.26 to 5.95)		4.40 (3.81 to 4.99)	-0.71 (-1.95 to 0.54)	.22	
t2 (4-6 weeks)		5.17 (4.19 to 6.14)		4.50 (3.84 to 5.16)	-0.67 (-1.99 to 0.64)	.29	
t3 (16 weeks)		5.90 (4.81 to 6.99)		5.37 (4.60 to 6.14)	-0.53 (-1.97 to 0.90)	.45	
Mean self-efficacy	41		81				.46
t1 (1-3 weeks)		7.66 (7.01 to 8.31)		7.27 (6.83 to 7.71)	0.39 (-0.48 to 1.27)	.35	
t2 (4-6 weeks)		7.69 (6.99 to 8.39)		7.03 (6.58 to 7.49)	0.66 (-0.26 to 1.57)	.15	
t3 (16 weeks)		7.01 (6.31 to 7.72)		6.87 (6.39 to 7.36)	0.14 (-0.79 to 1.07)	.75	



Legend: Primary analysis based on the full analysis set. Mean in each group and mean difference between groups (SNP vs control) with 95% confidence intervals (CI) were derived from a linear mixed model. N refers to the number of non-missing observations.

Table 7. Sensitivity Analysis of Continuous Efficacy Outcomes Adjusted for Potential Confounders Based on the FAS at Each Time Point

A positive mean difference indicates an improvement in the Symptom Navi group (SNP).

	SNP		Control			
	N	Mean (95% CI)	N	Mean (95% CI)	Mean difference (95% CI)	P-value	Joint p-value
Mean symptom interference	42		80				.19
T_1 (1-3 weeks)		2.84 (2.36 to 3.32)		2.36 (2.03 to 2.68)	-0.48 (-1.22 to 0.26)	.17	
T_2 (4-6 weeks)		2.94 (2.41 to 3.47)		2.29 (1.94 to 2.65)	-0.65 (-1.40 to 0.11)	.09	
T_3 (16 weeks)		3.45 (2.89 to 4.02)		2.62 (2.23 to 3.02)	-0.83 (-1.62 to -0.04)	.040	
Mean symptom severity	42		80				.76
T_1 (1-3 weeks)		2.31 (1.95 to 2.68)		2.09 (1.85 to 2.34)	-0.22 (-0.80 to 0.36)	.38	
T_2 (4-6 weeks)		2.45 (2.03 to 2.88)		2.19 (1.90 to 2.47)	-0.27 (-0.87 to 0.33)	.35	
T_3 (16 weeks)		2.80 (2.31 to 3.29)		2.56 (2.22 to 2.90)	-0.23 (-0.89 to 0.42)	.46	
Mean symptom burden	42		80				.35
T_1 (1-3 weeks)		5.13 (4.40 to 5.86)		4.40 (3.91 to 4.90)	-0.72 (-1.88 to 0.44)	.18	
T_2 (4-6 weeks)		5.39 (4.54 to 6.23)		4.47 (3.91 to 5.03)	-0.92 (-2.11 to 0.28)	.12	
T_3 (16 weeks)		6.18 (5.23 to 7.14)		5.19 (4.53 to 5.85)	-0.99 (-2.29 to 0.31)	.12	
Mean self-efficacy	41		80				.43
T_1 (1-3 weeks)		7.48 (6.82 to 8.15)		7.42 (6.97 to 7.87)	0.06 (-0.89 to 1.01)	.89	
T_2 (4-6 weeks)		7.44 (6.74 to 8.15)		7.25 (6.79 to 7.71)	0.19 (-0.77 to 1.15)	.67	
T_3 (16 weeks)		6.65 (5.94 to 7.36)		7.18 (6.70 to 7.66)	-0.53 (-1.50 to 0.44)	.26	

Symptom interference and symptom severity scores 0 – 10 (higher ratings indicating higher symptom interference and higher symptom severity); symptom burden scores 0 – 20 (higher ratings indicating higher symptom burden); self-efficacy sores 1 – 10 (higher ratings indicating higher/better self-efficacy); CI = confidence interval; N refers to non-missing observations. Means in each group and mean differences between groups with 95% CI were derived from linear mixed-effects regression models.

Table 8. Sensitivity Analysis of Continuous Efficacy Outcomes Using Only the Last Follow-up Visit (T_3,16 Weeks)

A positive mean difference indicates an improvement in the Symptom Navi group (SNP).

	SNP		Control		Mean difference	P-value
	N	mean (95% CI)	N	mean (95% CI)	(95% CI)	
Mean symptom interference	36	3.33 (2.64 to 4.01)	70	2.65 (2.16 to 3.13)	-0.68 (-1.76 to 0.40)	.17
Mean symptom severity	35	2.65 (2.11 to 3.20)	70	2.60 (2.22 to 2.99)	-0.05 (-0.90 to 0.79)	.89
Mean symptom burden	35	5.81 (4.68 to 6.95)	70	5.28 (4.48 to 6.07)	-0.54 (-2.30 to 1.23)	.48
Mean self-efficacy	34	7.16 (6.42 to 7.90)	70	6.80 (6.30 to 7.31)	0.35 (-0.76 to 1.47)	.47

Symptom interference and symptom severity scores 0 – 10 (higher ratings indicating higher symptom interference and higher symptom severity); symptom burden scores 0 – 20 (higher ratings indicating higher symptom burden); self-efficacy sores 1 – 10 (higher ratings indicating higher/better self-efficacy); CI = confidence interval; N refers to non-missing observations. N refers to non-missing observations. Mean in each group and mean difference between groups with 95% CI were derived from a simplified linear mixed-effects regression model with treatment group and stratification factor as fixed covariates and cluster as random intercept.

Table 9. Sensitivity Analysis of Continuous Efficacy Outcomes Based on the Comparison of Cluster Means of the Change Score from Baseline to T_3 (16 Weeks).

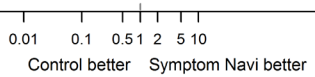
The effects are presented as mean difference or Mann-Whitney statistic (the probability that a random patient in the Symptom Navi group (SNP) has better outcome than a random patient from the Control group) with 95% confidence intervals (CI). A positive mean difference and a Mann-Whitney statistic larger than 0.5 indicates an improvement in SNP. N refers to the number of clusters.

	SNP (N=3)	Control (N=5)	Effect measures (95%CI)	P-value
Change of mean symptom interference				
Parametric†	1.21 (0.67)	0.91 (1.04)	-0.26 (-2.04 to 1.53)	.73
Non-parametric*	1.45 [0.45, 1.73]	0.97 [0.95, 1.59]	0.47 (0.16 to 0.80)	.81
Change of mean symptom severity				
Parametric†	0.94 (0.37)	0.99 (0.59)	0.07 (-0.94 to 1.09)	.86
Non-parametric*	0.81 [0.66, 1.36]	1.15 [0.97, 1.34]	0.60 (0.24 to 0.88)	.48
Change of mean symptom burden				
Parametric†	2.00 (1.00)	1.90 (1.59)	-0.04 (-2.79 to 2.71)	.97
Non-parametric*	1.80 [1.11, 3.08]	2.47 [1.92, 2.74]	0.60 (0.24 to 0.88)	.48
Change of mean self-efficacy				
Parametric†	-0.05 (0.28)	-0.76 (1.00)	0.70 (-1.01 to 2.42)	.34
Non-parametric*	-0.18 [-0.24, 0.27]	-1.10 [-1.32, 0.20]	0.67 (0.28 to 0.91)	.35

†Mean (sd), mean difference (95% CI) and p-value from linear regression adjusted for stratum used in randomisation.
*Median (lower, upper quartile), Mann-Whitney statistic (95% CI) and p-value from van Elteren test with stratum used in randomisation.

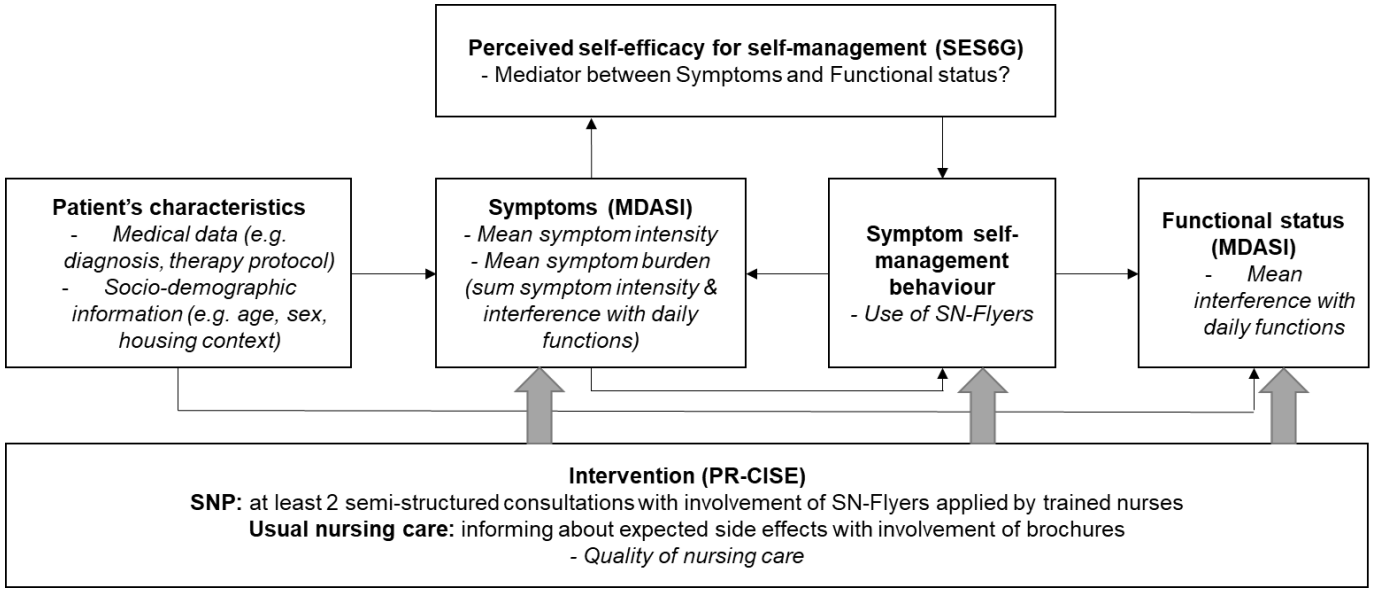
Table 10: Odds Ratio for Symptom Management Support (PR-CISE Items)

	Symptom Navi (SNP)		Control		Odds ratio (95% CI)	P-value	Joint
	N	n/N (%)	N	n/N (%)			p-value
Ask about symptoms	42		81				.95
t1 (1-3 weeks)		33/37 (89%)		74/79 (94%)	0.63 (0.07 to 5.72)	.68	
t2 (4-6 weeks)		25/31 (81%)		69/77 (90%)	0.58 (0.07 to 4.43)	.60	
t3 (16 weeks)		27/34 (79%)		60/70 (86%)	0.63 (0.09 to 4.21)	.63	
Aware of symptom severity	42		81				.77
t1 (1-3 weeks)		32/36 (89%)		74/79 (94%)	0.49 (0.06 to 3.71)	.49	
t2 (4-6 weeks)		25/31 (81%)		68/77 (88%)	0.56 (0.09 to 3.43)	.53	
t3 (16 weeks)		30/34 (88%)		60/70 (86%)	1.39 (0.21 to 9.27)	.74	
Information to manage symptoms	42		81				.17
t1 (1-3 weeks)		30/38 (79%)		73/79 (92%)	0.15 (0.02 to 1.26)	.08	
t2 (4-6 weeks)		24/31 (77%)		70/77 (91%)	0.15 (0.02 to 1.32)	.09	
t3 (16 weeks)		28/33 (85%)		59/70 (84%)	0.85 (0.10 to 7.04)	.88	
Practical advice to manage symptoms	42		81				.11
t1 (1-3 weeks)		28/38 (74%)		72/79 (91%)	0.14 (0.02 to 0.86)	.034	
t2 (4-6 weeks)		25/31 (81%)		69/77 (90%)	0.41 (0.06 to 2.98)	.38	
t3 (16 weeks)		28/33 (85%)		57/69 (83%)	1.48 (0.21 to 10.30)	.69	
Confident managing symptoms	42		81				.73
t1 (1-3 weeks)		25/38 (66%)		58/79 (73%)	0.52 (0.15 to 1.77)	.29	
t2 (4-6 weeks)		23/31 (74%)		61/77 (79%)	0.61 (0.16 to 2.44)	.49	
t3 (16 weeks)		21/33 (64%)		48/70 (69%)	0.69 (0.19 to 2.45)	.56	



Primary analysis based on the full analysis set. Odds ratios of SNP vs control with 95% confidence intervals (CI) were derived from a generalised linear mixed model. N refers to the number of non-missing observations, n to the number of patients answering with yes.

Figure Theoretical Framework for Pilot Study and Semi-Structured Consultations

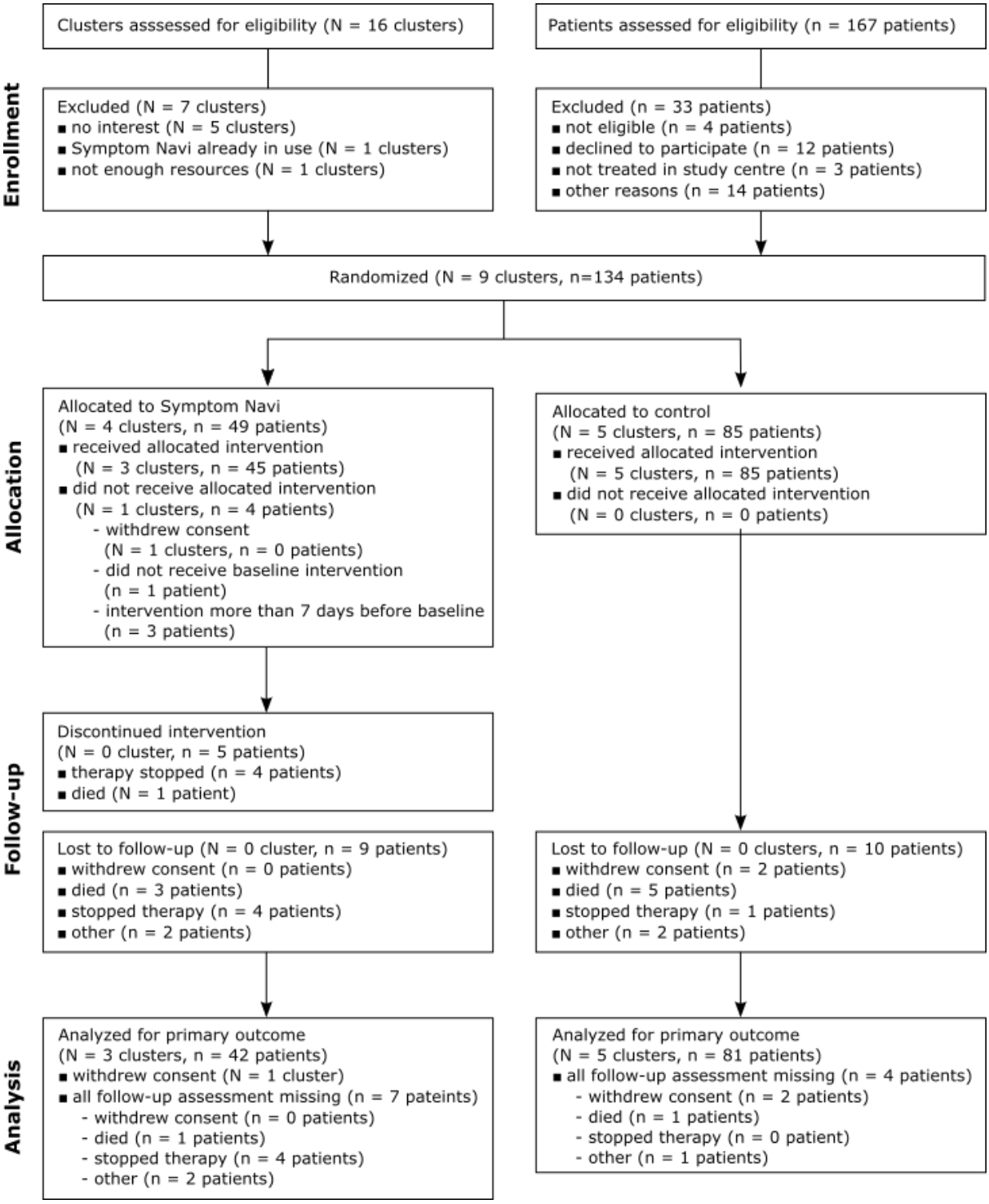


Abbreviations: MDASI, MD Anderson Symptom Inventory; PR-CISE, Patient-reported Chemotherapy Indicators for Symptoms and Experience; SES6G, Self-efficacy for Chronic Disease 6 item Scale; SN-Flyers, Symptom Navi Flyers; SNP, Symptom Navi Programme;

Symptom specific SN-Flyers: Alopecia, Anxiety, Breathlessness, Diarrhoea, Emesis and nausea, Fatigue, Increased susceptibility: infections and bleeding, Irradiated skin, Loss of appetite, Inflamed oral mucosa, Obstipation, Pain, Peripheral neuropathy, Sexuality, Skin alteration: feet and hand, and Skin alterations related to target therapies.

General SN-Flyers: information how to use the flyers, complementary information on pain management and on Oxaliplatin, useful addresses for support at home, and a list of all available flyers.

Figure 2. Cluster and Patient Flow



One cluster withdrew the consent before recruiting any patients.

Figure 3. Descriptive Boxplots for Continuous Efficacy Outcomes Based on MDASI and SES6G Questionnaires at Each Visit

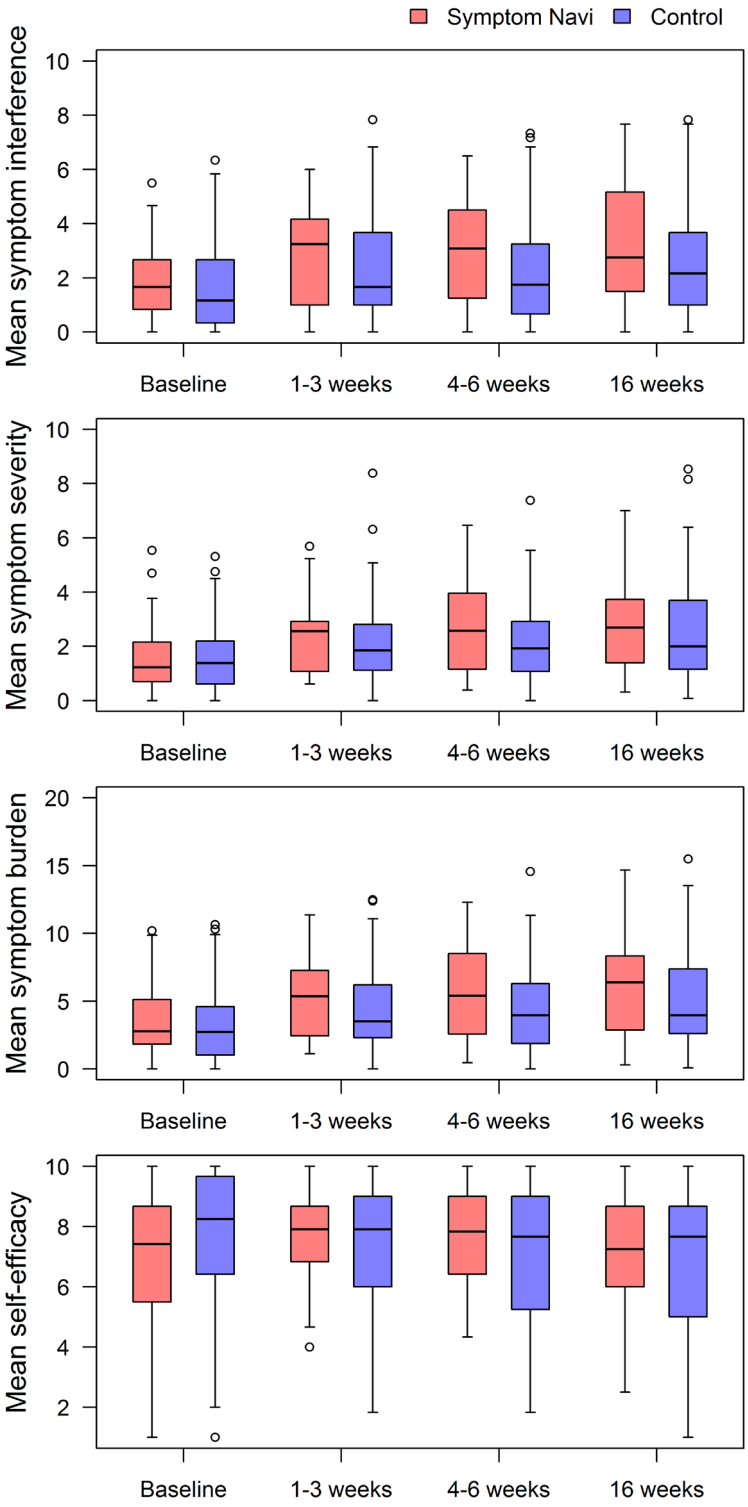


Figure 4. Descriptive Bar Charts for Patients' Perceived Nursing Support for Symptom Management Based on PR-CISE Items

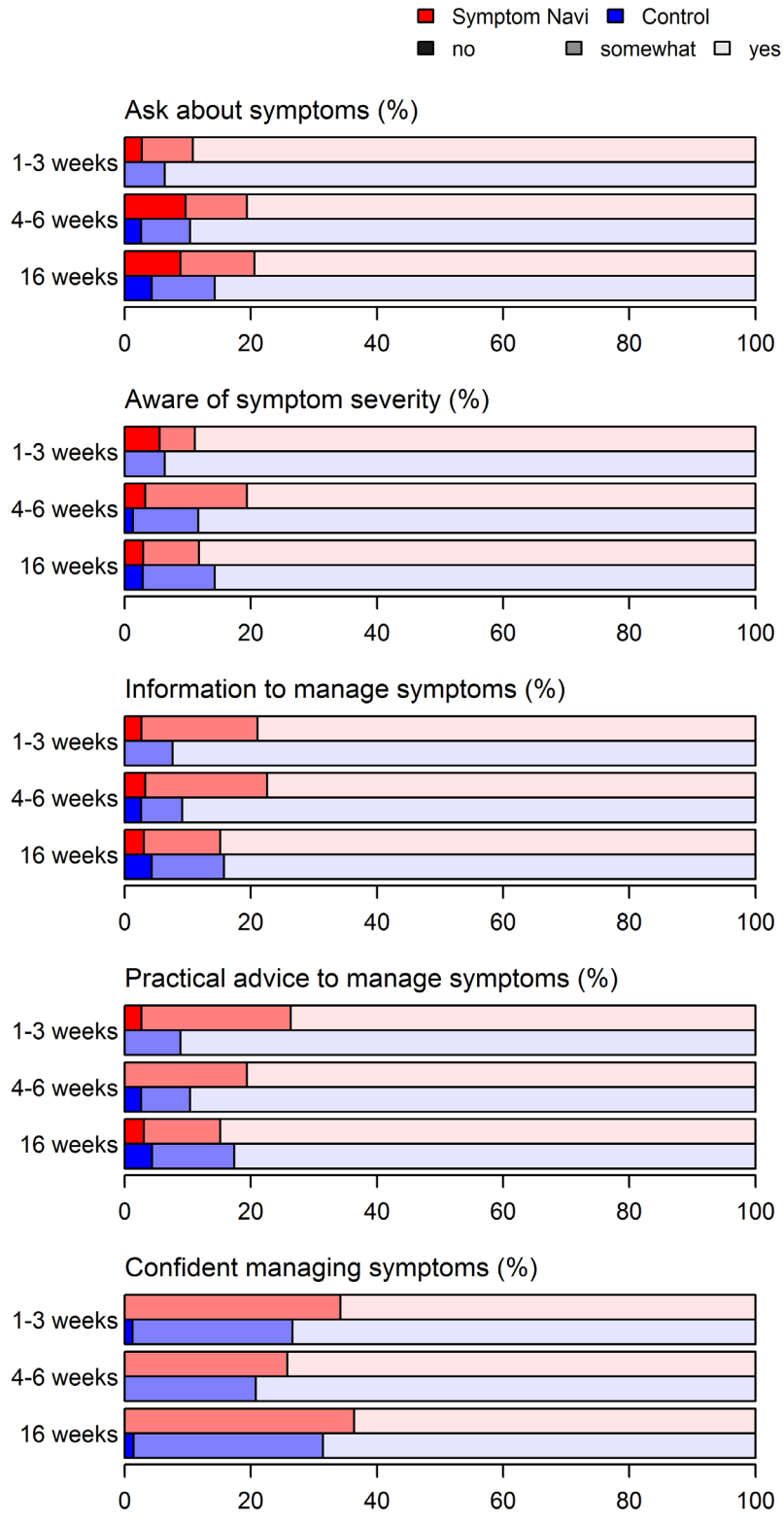
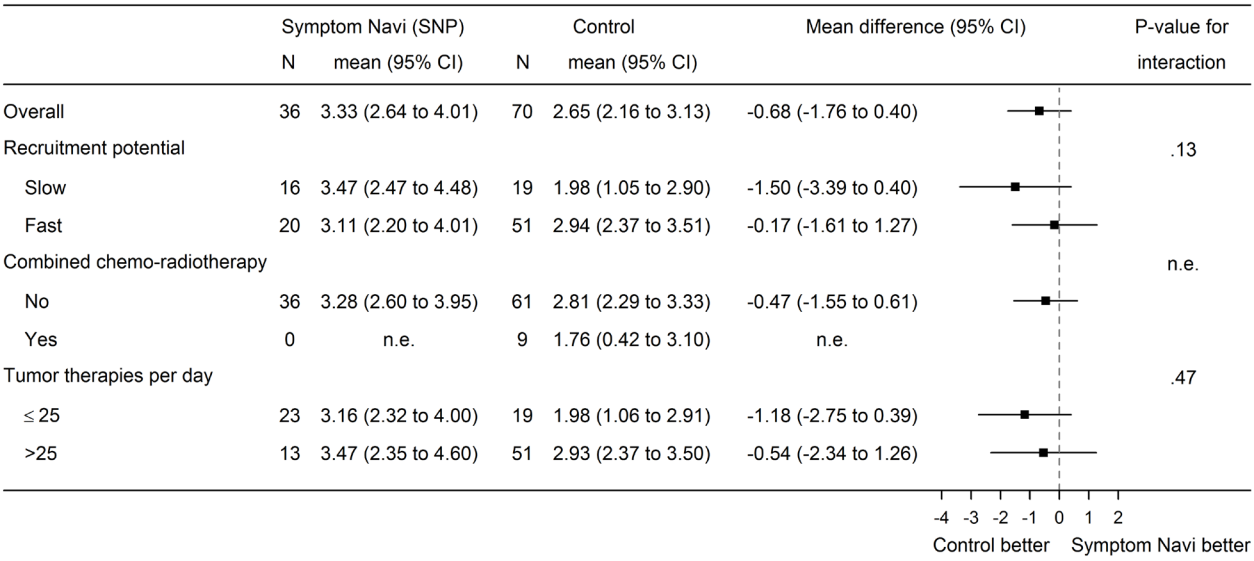


Figure 5. Forest Plot for Subgroup Analysis of the Primary Outcome for Binary Subgroups

A positive mean difference indicates an improvement in the Symptom Navi group (SNP).



Means in each group and mean differences between groups (SNP vs Control) with 95% confidence intervals (CI) were derived from linear mixed-effects regression models with the subgroup and its interaction with treatment group as covariates. Only the last follow-up (T_3, 16 weeks) was taken into account. The p-values for interaction were derived from likelihood ratio test of models with and without interaction. The treatment effect was not estimable (n.e.) in patients with combined chemo-radiotherapy. N refers to the number of non-missing observations.