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ORIGINAL ARTICLE

Electronic health intervention to manage symptoms of immunotherapy in patients with cancer (SOFIA): Results from a randomized controlled pilot trial

Christina Sauer PhD[1,2] | Stefanie Zschäbitz MD[3] | Jürgen Krauss MD[3,4] | Thomas Walle MD[3,5,6] | Georg Martin Haag MD[3,7] | Dirk Jäger MD[3,7] | Kiriaki Hiller MD[3] | Till Johannes Bugaj MD[1,2] | Hans-Christoph Friederich MD[1] | Imad Maatouk MD[1,8]

[1]Department of General Internal Medicine and Psychosomatics, University Hospital Heidelberg, Heidelberg, Germany

[2]National Center for Tumor Diseases (NCT), University Hospital Heidelberg, Heidelberg, Germany

[3]Department of Medical Oncology, National Center for Tumor Diseases (NCT), University Hospital Heidelberg, Heidelberg, Germany

[4]Vanudis GmbH, Heidelberg, Germany

[5]Clinical Cooperation Unit Virotherapy, German Cancer Research Center (DKFZ), Heidelberg, Germany

[6]German Cancer Consortium (DKTK), Heidelberg, Germany

[7]Clinical Cooperation Unit Applied Tumor-Immunity, German Cancer Research Center (DKFZ), Heidelberg, Germany

[8]Section of Psychosomatic Medicine, Psychotherapy and Psycho-Oncology, Department of Internal Medicine II, Julius-Maximilian University Würzburg, Würzburg, Germany

Correspondence

Christina Sauer, Department of General Internal Medicine and Psychosomatics, University Hospital Heidelberg, Im Neuenheimer Feld 410, D-69120 Heidelberg, Germany.
Email: christina.sauer@med.uni-heidelberg.de

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National Center for Tumor Diseases Heidelberg

Abstract

Background: For patients receiving immune checkpoint inhibitors, early detection of immune-related adverse events (irAEs) is critical for one's safety. To this end, a smartphone app (SOFIA) was developed that featured the assessment of electronic patient-reported outcomes (ePROs) focusing on irAEs as well as a set of comprehensive supportive information. Its feasibility and preliminary efficacy were evaluated in a randomized controlled trial (RCT).

Methods: Patients who received immune checkpoint inhibition therapy were randomly assigned to an intervention group (IG) or a control group (CG; care as usual). During the 12-week intervention period, IG patients used SOFIA to report twice weekly ePROs and receive cancer- and immunotherapy-relevant contents. Before a patient's next clinical visit, the physician in charge was given the ePRO reports. The primary objective was to test the feasibility of SOFIA. Furthermore, the preliminary efficacy of SOFIA for health-related quality of life (HRQOL), psychosocial outcomes, and medical data was examined. Clinical outcomes were assessed at baseline (T0), post-intervention (T1), and a 3-month follow-up (T2).

Results: Seventy-one patients were randomized to the IG (n = 34) or the CG (n = 37). SOFIA showed high feasibility and acceptance. At T1, patients in the IG reported significantly better HRQOL and role functioning and less depression, distress, and appetite loss. No significant differences were revealed regarding medical data, the utilization of supportive care services, or survival.

Conclusions: SOFIA showed high feasibility and acceptance and improved HRQOL and psychosocial outcomes. These results suggest further evaluation of efficacy in a large-scale confirmatory multicenter RCT.

KEYWORDS
cancer, electronic health (eHealth), electronic patient-reported outcomes (ePROs), immunotherapy, mobile health (mHealth), psycho-oncology

INTRODUCTION

For patients with cancer, the introduction of immunotherapy in the form of immune checkpoint inhibition (ICI) was a breakthrough in the treatment armamentarium. Although the overall survival of patients with advanced metastatic cancer diseases of various entities was improved,[1,2] ICI also enabled new therapeutic indications in earlier stages of cancer disease.[3] To date, several checkpoint inhibitors against programmed cell death protein 1 (PD-1), programmed cell death 1 ligand 1 (PD-L1), and cytotoxic T lymphocyte–associated protein 4 (CTLA-4) are available for the treatment of different cancer entities,[4] both as monotherapies as well as in combination with cytotoxic chemotherapy or targeted therapies.[5]

A pattern of treatment-related adverse reactions, called immune-related adverse events (irAEs), occurs regularly when ICI is applied. With anti–CTLA-4 monotherapy, the incidence of any grade of irAE is 72%, with anti–PD-1/anti–PD-L1 it is 66%.[6] The most common irAEs are dermatological and gastrointestinal toxicities, endocrinopathies, and pneumonitis.[7] However, irAEs can affect any organ system. In order to prevent a further aggravation of irAEs, these toxicities require prompt diagnosis and specific management, including immunosuppression with steroids or other immunosuppressive agents. For the successful management of irAEs, regular monitoring, early recognition, prompt initiation of immunosuppressive therapy, and interdisciplinary collaboration to manage these irAEs are considered crucial.[7,8]

For symptom monitoring and the early detection of irAEs, the assessment of electronic patient-reported outcomes (ePROs) might be a promising approach.[9] The regular use of ePROs in patients with advanced cancer treated with chemotherapy improved the overall survival and health-related quality of life (HRQOL).[10–12] In patients with lung cancer receiving palliative antineoplastic treatment, ePROs provided relevant prognostic measures for survival and progression.[13] So far, relatively few randomized controlled trials (RCTs) have assessed ePROs and HRQOL in patients receiving immune checkpoint inhibitors. A recent review indicated that currently used instruments lack sufficient precision to capture important symptomatology unique to immune checkpoint inhibitors, which highlights a need for specific PROs for patients undergoing immunotherapy.[14]

Digital interventions, including electronic health (eHealth) interventions (i.e., health services that are delivered via the use of information technology, including the internet, digital gaming, and virtual reality) and mobile health (mHealth) interventions (i.e., health services that are delivered via mobile or wireless applications) aim to improve patients' access to care, quality, safety, and cost-effectiveness.[15] Systematic reviews and meta-analyses show that eHealth interventions improve the HRQOL, distress, fatigue, self-efficacy, and patient–provider communication in patients with cancer and survivors.[16–18] However, no eHealth or mHealth intervention that includes information and targets the specific needs of patients undergoing immunotherapy exists so far, except for the studies assessing ePROs mentioned above.

Therefore, we developed an eHealth/mHealth intervention for patients receiving ICI—managing symptoms of immunotherapy (SOFIA)—that combines the assessment of ePROs and provides information.[19] Because of studies showing the need for the prompt detection of symptoms that could be caused by irAEs, patients were asked to rate ePROs focusing on irAEs twice a week in the SOFIA app.

The aim of this RCT was to investigate the feasibility and acceptability (recruitment rates, adherence, and usage rates) and preliminary efficacy of SOFIA regarding HRQOL (primary outcome), psychosocial symptoms, and medical data in routine clinical care.

MATERIALS AND METHODS

Trial design and participants

This prospective monocenter, two-arm, randomized, controlled feasibility trial included patients with any cancer entity starting ICI at the National Center for Tumor Diseases (NCT), Heidelberg, Germany. The trial protocol was approved by the Ethical Committee of Heidelberg University (reference S-581/2018); the study protocol has been previously published.[19] Before recruiting, we registered the study in the German Clinical Trial Register (reference DRKS00021064).

Patients with any cancer entity or at any stage who started immunotherapy with an immune checkpoint inhibitor (PD-1/PD-L1 monotherapy, dual therapy with CTLA-4 and PD-1 inhibitors, or an immune checkpoint inhibitor combined with chemotherapy or tyrosine kinase inhibitor) in the outpatient clinic of NCT Heidelberg, were aged ≥18 years, had an Eastern Cooperative Oncology Group (ECOG) score of 0 or 1, and had a predicted life expectancy of >3 months were eligible. (The outpatient clinic of NCT Heidelberg does not treat patients with hematologic cancer because there is a special clinic for these cancers at University Hospital Heidelberg.) In addition, eligible patients had access to an internet-connected device on which SOFIA could be processed (e.g., smartphone), commanded sufficient knowledge of German, and agreed to provide written informed consent. Conversely, exclusion criteria included the

eventual participation in another interventional clinical trial, an ECOG score >1, a limited legal capacity or impairment thereof, cognitive or physical impairments that made it difficult to process online modules (e.g., impaired vision), and serious psychiatric or mental illness.

Study procedures

Patients who started an ICI-based therapy at the Department of Medical Oncology, NCT Heidelberg, were contacted by the study team and informed about the study. Upon positive interest, they were supplied with further information. After signing the informed consent, the study team conducted a short interview to assess medical and sociodemographic data, expectations, and concerns about the study. After the interview, patients received the first questionnaire (baseline assessment; T0) by email. After T0, we randomized the patients via a certified online randomization tool (https://www.randomizer.at). Here, we used permuted block randomization with equal block sizes and stratified for ECOG (0 or 1). We then notified participants regarding their group allocation via telephone. Group assignment did not affect the planned treatment intervals (typically every 3 weeks) of the enrolled patients. After the 3-month intervention phase, patients completed the post-intervention questionnaires (T1). After a further 3 months, the follow-up questionnaires were assessed.

Care as usual

Patients of the control group (CG; no SOFIA) received standard care; namely they were informed about the therapy, received an emergency telephone number in case of severe symptoms and side effects, received their medical therapy, and could use all regular counseling services of the NCT (e.g., psycho-oncology, nutritional advice, and social services) in case of subjective (i.e., wish for support) or objective needs (i.e., a need concluded from the psychosocial screening procedure).

Intervention

The smartphone app SOFIA consists of the following two components.

SOFIA monitoring: Assessment of ePROs

SOFIA monitoring consists of 11 physical and up to nine mental ePROs. Participants had to rate the ePROs twice a week and received short reminders via email for the assessment. The 11 physical symptoms were chosen on the basis of European Society for Medical Oncology (ESMO) guidelines[20] by a team of highly experienced medical oncologists, and included weakness, diarrhea, melaena, dry cough, shortness of breath, reduced urinary output, joint pain, muscle pain, skin toxicity, fever, and yellow coloring of the skin (see also Supplement A).

SOFIA coaching

Contents provided important cancer-specific information about mental health, immunotherapy, nutrition, sports, and social law as well as contact information of the counseling services of NCT Heidelberg (for a detailed description of the included modules, see Supplement B).

Both components (SOFIA monitoring and coaching) are described in detail in Supplements A and B and in the study protocol.[19] SOFIA was integrated into Mika, an app-based digital therapeutic for patients with cancer developed by Fosanis GmbH.[21] Mika is compatible with both Android and IOS smartphones (see Supplement B for further details).

Intervention group (IG) patients were introduced to SOFIA via a standardized telephone session conducted by a study assistant (mostly conducted during the COVID-19 pandemic). Participants were then issued an invitation code for the SOFIA app and had the opportunity to ask further questions. As written in the informed consent, we emphasized that reports of ePROs and mental symptoms were *not* immediately forwarded but that their physician collected the data before their next consultation (see Figure 1). We highlighted this to clarify that patients must consult the clinic on their own if severe side effects and symptoms were to occur.

Outcomes

Feasibility outcomes

The primary outcomes of this pilot trial were the feasibility and acceptance of SOFIA in routine clinical care. Feasibility in this trial was defined as feasibility with the available technical and personal resources, integration into routine clinical care, utilization and facilitation of SOFIA monitoring and coaching, as well as adherence.[19] Feasibility outcomes included recruitment rate, refusal and dropout rates, reasons for refusal and dropout, willingness to be randomized, utilization rate of SOFIA monitoring and coaching, feasibility and acceptability of the proposed outcome measures and sample size estimation, and utilization and benefits for the physician.

To measure the usefulness and acceptability of the ePRO assessment, we used the translated version of the adapted Patient Feedback Form,[22] which is an established instrument to assess patient satisfaction with ePROs. Furthermore, we developed an evaluation questionnaire for IG physicians to evaluate their utility of ePROs (see Table 1). The data were assessed via online questionnaires (https://www.soscisurvey.de/).[23]

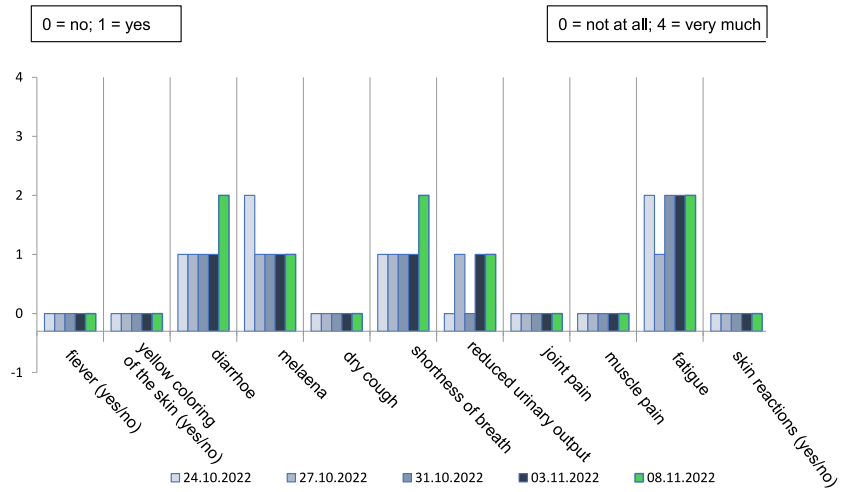

FIGURE 1 Graph showing the progression of electronic patient-reported outcomes over the past 3 weeks.

TABLE 1 Results of physicians' evaluation (assessed at post-intervention).

Physician's evaluation form	No.	Always, No. (%)	Often, No. (%)	Seldom, No, (%)	Never, No. (%)
Used graph of SOFIA monitoring for patients' care	43	3 (7.0)	12 (27.9)	19 (44.2)	9 (20.9)
SOFIA monitoring was useful/helpful for patients' treatment[a]	34	10 (29.4)	10 (29.4)	13 (38.2)	1 (2.9)
		Very, No. (%)	**Moderate, No. (%)**	**A little, No. (%)**	**Not at all, No. (%)**
SOFIA monitoring was useful for					
Detection of side effects	34	10 (29.4)	15 (44.1)	8 (23.5)	1 (2.9)
Preparation of the physician's consultation	34	11 (32.4)	12 (35.3)	9 (26.5)	2 (5.9)
Better understanding of the patient	33	5 (15.2)	12 (36.4)	15 (45.5)	1 (3.0)
Facilitating communication about symptoms with the patient	34	7 (20.6)	14 (41.2)	12 (35.2)	1 (2.9)
Preventing and averting treatment disruptions and termination	33	1 (3.0)	11 (33.3)	17 (51.5)	4 (12.1)

Note: Always indicates at every physician's consultation; never indicates at no physician's consultation.

[a]Nine further physicians reported that they never used SOFIA monitoring (electronic patient-reported outcome assessment).

Clinical outcomes (preliminary efficacy)

All clinical outcomes were assessed via self-report questionnaires at baseline (T0), post-intervention (T1), and a 3-month follow-up (T2).

Primary outcome

The primary clinical outcome was the two-item global health/QoL scale (How would you rate your overall quality of life during the past week?/How would you rate your overall health during the past week?) of the valid and reliable European Organization of Research and Treatment of Cancer Quality of Life of Cancer Patients questionnaire (EORTC QLQ-C30), version 3.[24]

Secondary outcomes

Self-reported symptoms of depression were assessed with the Patient Health Questionnaire 9 (PHQ-9; depression module),[25] a widely used screening tool in several clinical and oncological settings. The questionnaire evaluates the presence of nine depression symptoms contained in the *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition). The PHQ-9 shows good reliability, validity, and sensitivity of change.[26]

Anxiety levels were measured via German General Anxiety Disorder Scale 7,[25] another reliable PHQ module for measuring general anxiety symptoms that shows good factorial and construct validity.[27]

The National Comprehensive Cancer Network distress thermometer (DT)[28] was used to assess patients' distress on an 11-point numerical scale with end points of "no distress" or "extreme distress." The short, standardized DT has been proven highly sensitive when evaluated against established criteria.

In the physician–patient interaction questionnaire (FAPI),[29] the quality of physician–patient communication is measured via 14 items. It is an efficient measuring instrument with good reliability and validity.[29]

We assessed self-efficacy with the German version of the Cancer Behavior Inventory–Brief Version.[30,31] It records the coping

self-efficacy expectations of patients with cancer and measures independence (maintaining independence), participation (taking part in treatment decisions), stress management (assessing one's own ability to cope with stress), and affect management.

Patient treatment satisfaction was assessed with one item (How satisfied are you overall with the medical treatment so far? Rating: 1, not at all; 5, very much).

Exploratory outcomes

The subscales of the EORTC QLQ-C30 that multidimensionally assess the HRQOL of patients with cancer were analyzed as exploratory outcomes.[32,33] In addition, we collected medical data (e.g., frequency of phone contacts to the clinic, emergency visits, intensity of side effects, immunotherapy-related inpatient visits, survival, interruption and termination of therapy, and death) and the utilization of NCT counseling services (psycho-oncology, nutrition, and social services) from the patients' medical record. The intensity of side effects was measured by the Common Terminology Criteria for Adverse Events (CTCAE) and then classified by an experienced medical oncologist (K.H.) and a doctoral student. All variables were investigated for the intervention period (T0–T1) and the follow-up period (T1–T2).

Analyses

We analyzed descriptive statistics, clinical characteristics, and outcome measures to compare the IG and the CG, as well as the results of the patients' and physicians' evaluations of SOFIA. Mixed analyses of variance (ANOVAs) were used to exploratively compare longitudinal changes in primary and secondary outcomes in the IC and CG between T0, T1, and T2. ANOVAs included main effects for group (IG vs. CG), measurement point (time), and their two-way interaction (group*time). Because of multiple testing, we evaluated the significance of p values of mixed ANOVAs with the Benjamini–Hochberg procedure.[34] All analyses were performed according to the intention-to-treat principle. A p value of <.05 was considered significant for all analyses. Partial eta-square (η_p^2) and Cramer V (for χ^2 tests) were used to estimate the effect size and clinical significance. $\eta_p^2 = .01$ can be considered as a small effect, $\eta_p^2 = .06$ as a medium effect, and $\eta_p^2 = .14$ as a large effect.[35] Cramer $V = .1$ can be considered as a small effect, Cramer $V = .3$ as a medium effect, and Cramer $V = .5$ as a large effect.[35] We used IBM Statistical Package for the Social Sciences (SPSS), version 27,[36] for descriptive and inferential analyses.

Microsoft Excel was used to calculate retention rates, adherence of ePROs, and use of SOFIA. Adherence with ePRO assessment was checked by calculating the proportion of the number of required prompts against the number of actual prompts used during the intervention period. The frequency of use was defined on the basis of the number of sessions with a duration longer than 10 s. The time gap between two sessions should be a minimum of 5 min.

Sample size

According to the simulation approach of sample size requirement in external pilot trials with continuous outcome variables,[37] a total of 70 patients ($n = 35$ per group) was needed for the estimation of key parameters for the main trial.

RESULTS

Baseline characteristics

Between October 2020 and August 2022, $n = 241$ patients started immunotherapy at the Department of Medical Oncology at NCT Heidelberg. Of these, $n = 170$ patients were excluded: $n = 90$ (53%) because of the exclusion criteria, $n = 50$ (30%) declined to participate, and $n = 30$ (17%) were neither reached nor could participate because of other reasons (e.g., the patient did not receive immunotherapy after all or died). The remaining $n = 71$ (29.5%; 58.7% of eligible and available patients) were enrolled and randomly assigned to the IG ($n = 34$) or the CG ($n = 37$) (see Figure 2).

Baseline characteristics were balanced between the IG and CG. See Table 2 for patient characteristics.

Feasibility

SOFIA showed high feasibility and acceptance in patients in the IG. No patient refused participation because of randomization. Only two patients (6%) dropped out during the intervention phase (see Figure 2 for detailed reasons), and two patients died (6%). Twenty-nine patients finished the intervention phase and conducted a post-assessment, which showed a high retention rate of 85%.

Adherence of ePRO

During the 12-week intervention period, patients' ratings of ePROs equated to 91% (range, 46%–100%) within the twice weekly required assessment points. The mean number of required ePRO assessment points was 26.31 (SD, 1.80), and the mean number of reported ePRO assessment points was 24.00 (SD, 4.34).

Satisfaction with ePRO assessment

At post-assessment, 95.5% of patients ($n = 21$) found the amount of time needed to complete ePROs just right, and 4.5% found it to be too short ($n = 1$); 90.9% of patients in the IG perceived the frequency of the PRO assessment just right, 4.5% found it to be too often, and 4.5% found it to be too infrequent. The full set of results of patients' evaluations of ePROs can be found in Table 3.

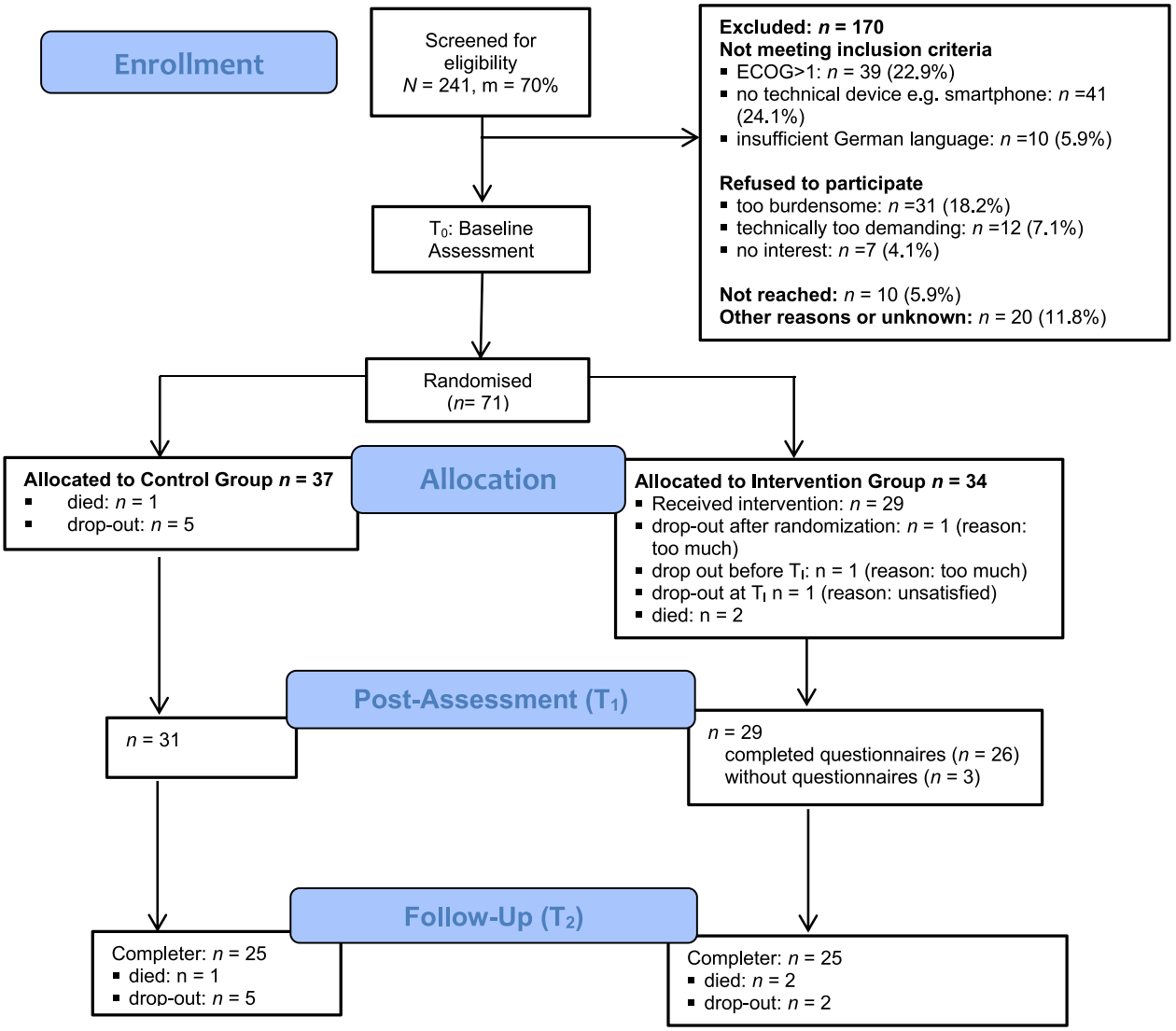

FIGURE 2 Flow diagram for the study. ECOG indicates Eastern Cooperative Oncology Group; m, male; T1, post-intervention assessment; T2, 3-month follow-up; T_I , interim survey (only in the intervention group; data are not reported).

Physicians' evaluation of ePROs

We contacted $n = 104$ physicians who treated IG patients during the intervention period and received feedback from $n = 45$ physicians (board-certified, $n = 6$; residents, $n = 35$; no indication of the level of training, $n = 4$). Results show that more than 50% of physicians evaluated SOFIA monitoring as useful and saw benefits for treatment (see Table 1). However, 65.1% of physicians never or seldom used SOFIA in routine clinical care.

Use of SOFIA coaching

Of the $n = 29$ patients who received the intervention and did not drop out from T0 to T1, 26 patients (90%) used SOFIA coaching. The median number of sessions was 5.5 during the 12-week intervention period (interquartile range [IQR], 4–11.5). Thirteen patients (50%) continued to use SOFIA coaching in the follow-up period (median number of sessions, 0.5; IQR, 0–1.75).

Preliminary efficacy of SOFIA

Table 4 shows between-group differences concerning the primary and the secondary outcome measures. From T0 to T1, the course of HRQOL, depression, and distress significantly differed between the groups (see group*time interactions) with medium effects. IG patients showed significantly better HRQOL ($p = .013$) as well as less depression ($p = .006$) and distress ($p = .006$) at T1 compared with patients of the CG. No differences were revealed regarding anxiety,

TABLE 2 Patient characteristics.

Characteristic	IG (n = 34)	CG (n = 37)	p
Age, mean (SD), years	59.79 (11.68)	61.65 (8.58)	.45
Time since diagnosis, mean (SD), months	26.32 (40.64)	38.41 (45.54)	.24
Male sex, No. (%)	20 (58.8)	28 (75.7)	.13
Tumor entity, No. (%)			.56
Urological	13 (38.2)	16 (43.2)	
Gastrointestinal	9 (26.5)	9 (24.3)	
Hepatobiliary	5 (14.7)	5 (13.5)	
Head and neck	1 (2.9)	3 (8.1)	
Bronchial	1 (2.9)	3 (8.1)	
Gynecological	3 (8.8)	0	
Squamous cell	2 (5.9)	1 (2.7)	
Metastasis (yes), No. (%)	31 (94.1)	32 (86.5)	.20
Palliative treatment, No. (%)	34 (100)	36 (97.3)	1.00
ECOG score, No. (%)			1.00
0	15 (44.1)	17 (45.9)	
1	19 (55.9)	20 (54.1)	
Immunotherapy sequence, No. (%)			.54
ICI (monotherapy)	11 (32.4)	10 (27.0)	
ICI ICI	6 (17.6)	4 (10.8)	
ICI TKI	10 (29.4)	14 (37.8)	
ICI chemotherapy	7 (20.6)	9 (24.3)	
Previous cancer treatments (yes)	29 (85.3)	34 (91.9)	.47
Previous treatments, No. (%)			.30
Radiation	2 (6.9)	2 (5.9)	
Surgery	6 (20.7)	4 (10.8)	
Chemotherapy	3 (10.3)	3 (8.8)	
Immunotherapy	1 (3.4)	—	
More than one previous cancer treatment	17 (56.6)	25 (73.5)	
Psychiatric side diagnosis, No. (%)	1 (2.9)	3 (8.1)	.60

Abbreviations: CG, control group; ECOG, Eastern Cooperative Oncology Group; ICI, immune checkpoint inhibition; IG, intervention group; TKI, tyrosine kinase inhibitor.

physician–patient communication, overall treatment satisfaction, and self-efficacy from T0 to T1. We exploratively investigated the effects on the subscales of the EORTC, and found significantly better role functioning (p = .047) as well as less fatigue (p = .038) and appetite loss (p = .040) in the IG compared to the CG (see Supplement C).

We found no group*time interaction when investigating differences from T0 to T2. Results of mixed ANOVA (including T0, T1, and T2) are depicted in Supplement D.

Medical data

Furthermore, we detected no statistically significant differences with regard to survival, rate and severity of irAEs, treatment-related variables, inpatient visits, steroid initiation, or the utilization of supportive care services during the intervention or follow-up period (see Supplement E). However, we identified a trend toward more emergency room visits in the CG (n = 11) compared with the IG (n = 4) during the intervention period (p = .09). The utilization of

TABLE 3 Patients' evaluation of ePRO assessment (SOFIA monitoring) at post-intervention.

Item	Strongly agree, No. (%)	Agree, No. (%)	Do not agree, No. (%)	Do not agree at all, No. (%)
SOFIA monitoring was easy to complete	15 (68.2)	7 (31.8)	0 (0)	0 (0)
It was helpful for me to complete SOFIA monitoring	11 (50.0)	8 (36.4)	3 (13.6)	0 (0)
SOFIA monitoring was easy to understand	16 (72.7)	5 (22.7)	1 (4.5)	0 (0)
SOFIA monitoring helped me to remember side effects or symptoms during the physician consultation	11 (50.0)	7 (31.8)	3 (13.6)	1 (4.5)
SOFIA monitoring improved conversations between me and my physician	5 (22.7)	8 (30.8)	8 (30.8)	1 (4.5)
The physician used the information from SOFIA monitoring for my treatment	3 (13.6)	7 (31.8)	10 (45.5)	2 (9.1)
SOFIA monitoring improved the quality of my treatment	4 (18.2)	6 (27.3)	11 (50.0)	1 (4.5)
SOFIA monitoring improved the communication with my physician	2 (9.1)	9 (40.9)	10 (45.5)	1 (4.5)
SOFIA monitoring gave me more control over the treatment	3 (13.6)	9 (40.9)	9 (40.9)	1 (4.5)
I would recommend SOFIA monitoring to other patients	11 (50.0)	10 (45.5)	1 (4.5)	0 (0)
I would like to use SOFIA monitoring further	7 (31.8)	9 (40.9)	6 (27.3)	0 (0)

Note: $N = 22$ (four missing data).

Abbreviation: ePRO, electronic patient-reported outcome.

psycho-oncological services was marginally higher in the IG ($n = 3$) than in the CG ($n = 0$) in the follow-up period ($p = .08$).

DISCUSSION

An app for patients receiving immunotherapy with immune checkpoint inhibitors including symptom monitoring with immune-related ePROs as well as information about self-management showed good feasibility and acceptability among patients in routine clinical care. Preliminary efficacy showed positive effects on HRQOL, depression, distress, fatigue, role functioning, and appetite loss in IG patients post-intervention.

Feasibility

The first aim of this study was to investigate the feasibility of SOFIA integrated into routine clinical care. The recruitment rate of 30% is similar to or higher than in other studies investigating eHealth interventions in patients with advanced cancer or survivors assessing ePROs[38,39] but lower than in studies not including ePROs.[40] The main reason to reject participation in our study was the perception of it being too burdensome (approximately 18%). Mindful of the fact that potential participants suffered from an advanced form of cancer, the actual participation rate observed in this study can be considered very good.

Overall, the acceptance for SOFIA was high, which is first observed by the high satisfaction and adherence to the ePRO assessment. Such a finding is in line with previous studies showing similar satisfaction with ePRO assessments in patients with different cancer entities[41] or patients with advanced cancer,[42] as well as similar adherence rates.[43] Compared to other studies assessing ePROs once a week[10,43,44] or less frequently[42,45] the adherence found in our study was higher, which indicates excellent feasibility of a twice weekly ePRO assessment for close monitoring in patients undergoing ICI. Over 80% of patients in the IG reported that ePROs helped them to remember side effects or symptoms during the physicians' consultation, which indicates a significant patient benefit from ePROs. Acceptance for SOFIA was secondarily shown by the use of SOFIA coaching. The median number of logins was higher than in a study with an eHealth intervention for patients with cancer undergoing palliative care,[40] which indicates a clear acceptability of our self-management modules.

Over 50% of physicians who responded to the physicians' questionnaire evaluated ePROs as useful and saw large benefits for the management of treatment with ICI (e.g., for the preparation of the physician's consultation or the detection of side effects), which is in line with previous studies.[42] However, nearly two thirds of physicians never or seldom used the ePROs in routine clinical care. Low usage and integration rates were also shown in previous studies (e.g., 44). Thus, it is important to approach clinicians' barriers and facilitate the use and integration of ePROs in routine clinical care. Because we integrated the graph with the course of ePROs into the clinical documentation system, the integration of ePRO data was not time consuming—a concern clinicians reported in a study investigating the experiences of clinicians using ePROs in patients with melanoma undergoing immunotherapy.[41] Other studies revealed that health care providers show concerns regarding an increase in workload and workflow, the formation of additional needs, and data overload.[42,46] In line with other studies,[42] the results indicate that ePRO assessment did not increase phone calls to the clinic (there was even a

TABLE 4 Results of mixed ANOVAs.

	Baseline		Post-intervention (T1)	Group*time (T0–T1)		Follow-up (T2)		Group*time (T0–T2)	
	No. (T0–T1)	M (SD)	M (SD)	*p*	η_p^2	No. (T0–T2)	M (SD)	*p*	η_p^2
Primary outcome									
EORTC HRQOL									
IG	23	53.26 (24.58)	61.59 (19.58)	.013	.122	23	60.51 (19.50)	.762	.002
CG	27	50.93 (23.38)	44.75 (22.78)			23	52.90 (26.19)		
Secondary outcomes									
Depression									
IG	26	15.50 (4.36)	15.31 (4.33)	.006	.128	24	14.96 (3.95)	.250	.028
CG	31	16.26 (4.59)	19.31 (6.15)			25	16.40 (4.86)		
Anxiety									
IG	26	10.96 (2.92)	11.27 (3.14)	.228	.026	24	10.21 (3.20)	.113	.053
CG	31	12.13 (4.60)	13.42 (5.25)			25	11.76 (3.85)		
Distress									
IG	26	4.23 (2.03)	3.69 (2.24)	.006	.127	25	3.72 (2.05)	.823	.001
CG	31	4.87 (2.94)	5.90 (2.50)			25	4.76 (2.95)		
Self-efficacy									
IG	24	77.00 (16.18)	76.79 (18.88)	.096	.052	23	76.39 (19.43)	.962	.000
CG	30	81.33 (16.75)	74.53 (20.70)			24	80.38 (20.72)		
Physician–patient communication									
IG	22	3.81 (0.95)	3.54 (1.25)	.271	.026	23	3.34 (1.20)	.459	.013
CG	27	3.75 (0.90)	3.13 (1.05)			23	3.52 (1.14)		
Treatment satisfaction									
IG	22	8.95 (1.68)	8.23 (2.11)	.850	.001	23	9.35 (1.79)	.829	.001
CG	27	8.70 (1.36)	7.89 (1.65)			23	9.26 (1.80)		

Note: Significance of *p*-values was evaluated according to the Benjamini–Hochberg procedure. HRQOL was assessed with the EORTC QLQ-C30 (range, 0–100). Depression was assessed with Patient Health Questionnaire 9 (depression module; range, 0–27). Anxiety was assessed with General Anxiety Disorder Scale 7 (range, 0–27). Distress was assessed with the National Comprehensive Cancer Network distress thermometer (range, 0–10). Self-efficacy was assessed with the Cancer Behavior Inventory–Brief Version (range, 14–126). Physician–patient communication was assessed with the physician–patient interaction questionnaire (FAPI; range, 1–5). The treatment satisfaction scale ranged from 0 to 10.

Abbreviations: ANOVA, analysis of variance; CG, control group; EORTC QLQ-C30, European Organization of Research and Treatment of Cancer Quality of Life of Cancer Patients questionnaire; HRQOL, health-related quality of life; IG, intervention group.

trend that the IG showed fewer calls) or the use of health care services, which highlights that ePROs do not lead to an increased workload. It is therefore important to train physicians in the use of PROs (interpreting data in the clinical context and integrating results into patient–physician communication) and underline their benefits.[47] In the beginning and during the recruitment, the study was regularly presented to physicians treating patients at NCT Heidelberg. In a future trial, we recommend the adoption of the integration and use of ePROs during training sessions or via an eLearning tool. It is important to note that despite low physician use of ePROs, we found promising preliminary values, which shows that the implementation of ePROs alone might be helpful for patients.

Preliminary efficacy

IG patients showed significantly better HRQOL as well as less depression and distress after the intervention compared with CG patients. The medium (nearly large) effect sizes indicate a moderate to important clinical significance of our findings. As far as explorative outcomes, we found better role functioning and less fatigue and appetite loss in the IG. It is noteworthy that the CG and IG were comparable in terms of treatment setting and ECOG score. The results of better HRQOL after reporting ePROs are in line with studies with patients with melanoma undergoing ICI[48] or patients with advanced cancer undergoing chemotherapy.[10] However, other

studies found stable HRQOL of patients with urothelial cancer receiving chemo- or immunotherapy.[44] A systematic review revealed heterogeneous effects of eHealth interventions with regard to psychosocial outcomes and HRQOL.[49] Thus, the results indicate that a combined eHealth intervention including ePROs and supportive information might be promising vis-à-vis HRQOL and psychosocial outcomes in patients with cancer undergoing ICI.

No differences regarding anxiety, physician–patient communication, overall treatment satisfaction, and self-efficacy from T0 to T1 or from T0 to T2 were revealed. However, it is important to note that this pilot study was not powered to detect statistical significance, although—despite the limited number of patients—promising results regarding HRQOL, psychological distress, and fatigue were observed. Ultimately, the rich data generated by this study can facilitate the development of a well-founded power analysis for a full RCT.

As far as medical outcomes investigated on an explorative basis, we did not find statistically significant differences between the IC and CG. However, on closer inspection, the findings indicate some tendencies, such as fewer patients in the IG showing therapy-related emergency visits, a conclusion consistent with the result of Basch et al.[11] Furthermore, more patients in the IG used psycho-oncological support during the follow-up period. Considering again that this study was not powered to detect statistical significance, future multicenter RCTs are needed with larger sample sizes to establish both the statistical and clinical significance of SOFIA.

Strengths of this study include its randomized controlled design, biopsychosocial focus, assessment of ePROs focused on immune-related events, and development of a study-specific app. However, this pilot RCT should also be seen in the context of certain limitations. First, this was a single monocenter study in a certified cancer center in Germany, which limits the generalizability of the results. Second, ePROs used in this study were created specifically for this study, which limits the comparability with other studies using validated PROs, such as the PRO-CTCAE.[50] Such studies underline the implementation of disease-specific PROs for different patient groups. However, validated PROs for irAEs do not exist in German. Thus, ePROs were developed by ICI experts on the basis of the ESMO guidelines,[20] which assess relevant domains of irAEs. Third, results of preliminary efficacy are promising, but because this study was not powered to detect statistical significance, the results must be interpreted with caution. Fourth, it is important to note that only 43% of physicians, of whom 80% were residents, responded to the physician questionnaire, which may have biased the results (in the sense that only physicians who found SOFIA useful responded to the questionnaire and only the opinion of residents might be depicted). Furthermore, it is still unclear which content of the app was more helpful for the patients (ePROs or self-management modules). Fifth, the results were not controlled for computer experience in this pilot trial. In a future study with a larger sample size, it will be important to investigate moderators and covariates that might affect the results.

In conclusion, an app for patients undergoing immunotherapy assessing ePROs focusing on immune-related events and providing disease-related information showed high feasibility and acceptance. It also improved HRQOL, depression, and distress. These results matter, while suggesting further evaluation of efficacy via a large-scale confirmatory multicenter RCT.

AUTHOR CONTRIBUTIONS

Christina Sauer: Conceptualization, funding acquisition, writing–original draft, methodology, formal analysis, project administration, and investigation. **Stefanie Zschäbitz:** Conceptualization, resources, and writing–review and editing. **Jürgen Krauss:** Funding acquisition, conceptualization, and writing–review and editing. **Thomas Walle:** Resources, investigation, and writing–review and editing. **Georg Martin Haag:** Conceptualization and writing–review and editing. **Dirk Jäger:** Resources and writing–review and editing. **Kiriaki Hiller:** Investigation. **Till Johannes Bugaj:** Writing–review and editing. **Hans-Christoph Friederich:** Resources and writing–review and editing. **Imad Maatouk:** Conceptualization, methodology, funding acquisition, supervision, and writing–review and editing.

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CONFLICT OF INTEREST STATEMENT

Thomas Walle has received grants from CanVirex; owns stock in Hoffmann-La Roche, AstraZeneca, Merck, Innate Pharma, FibroGen, and Bayer; and has received travel support from Hoffmann-La Roche. Georg Martin Haag has been a consultant for Pierre Fabre Pharmaceuticals, AstraZeneca, Daiichi Sankyo Europe, Novartis, Bristol-Myers Squibb, Merck Sharp and Dohme, and Eli Lilly. The other authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on reasonable request from the corresponding author.

ORCID

Christina Sauer https://orcid.org/0000-0003-3628-9056

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