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eHealth intervention to manage symptoms for patients with cancer on immunotherapy (SOFIA): a study protocol for a randomised controlled external pilot trial

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ABSTRACT

Introduction Immune checkpoint therapy (ICT) is associated with a distinct pattern of immune-related adverse events (irAEs) caused by inadvertently redirecting immune responses to healthy tissues. IrAEs can occur at any time; however, in most cases, they arise during the first 14 weeks of the beginning of immune checkpoint blockade. In many cases, immunotherapy must be discontinued due to irAEs. Early detection of irAEs triggers the temporary withholding of ICT or initiation of short-term immunosuppressive treatment, is crucial in preventing further aggravation of irAEs and enables safe re-exposure to ICT. This prospective study aims to evaluate the feasibility of an eHealth intervention for patients under immunotherapy (managing **s**ymptoms **of i**mmunother**a**py, SOFIA). The SOFIA-App consists of two components: SOFIA-Monitoring, a tool to rate patient-reported outcomes (PROs) including irAEs, and SOFIA-Coaching, which provides important information about cancer-specific and immunotherapy-specific topics and the counselling services of the National Centre for Tumour Diseases (NCT) Heidelberg.

Methods and analysis We outlined a patient-level two-arm randomised controlled pilot trial of the intervention (SOFIA) versus no-SOFIA for patients with cancer beginning an immunotherapy, aged ≥18 years, recruited from the NCT, Heidelberg. Feasibility outcomes include: recruitment rate; drop-out rate; reasons for refusal and drop-out; willingness to be randomised, utilisation rate of SOFIA-Monitoring and utilisation time of SOFIA-Coaching, physicians utilisation rate of the PROs; feasibility of the proposed outcome measures and optimal sample size estimation. The clinical outcomes are measures of quality of life, psychosocial symptoms, self-efficacy, physician-patient communication and medical process data, which are assessed at the beginning of the intervention, postintervention and at 6-month follow-up.

Ethics and dissemination This trial protocol was approved by the Ethical Committee of Heidelberg University, Germany (Reference, S-581/2018).

Trial registration number We registered the study in the German Clinical Trial Register (Reference: DRKS00021064).

Strengths and limitations of this study

► This pilot study is the first randomised controlled trial that investigates the feasibility and acceptance of a two-component eHealth intervention (managing **s**ymptoms **of i**mmunother**a**py, SOFIA) in patients with cancer under immunotherapy versus no-SOFIA.

► Our biopsychosocial intervention includes a twice a week assessment of patient-reported immune-related adverse events and depicts a new paradigm to support clinical management of immune checkpoint therapy for patients with cancer.

► The regular assessment of patient-reported outcomes is of high clinical relevance and may lead to less interruptions and terminations of immunotherapies.

► The generalisability to other settings is limited because this is a single-centre study.

► Since this is a feasibility study, no statements can be made about effectiveness.

Findings will be disseminated broadly via peer-reviewed empirical journals, articles and conference presentations.

INTRODUCTION

Cancer and its subsequent treatment affect an individual's functioning and their quality of life (QoL). Patients with cancer are confronted with both physical and psychosocial consequences and side effects of therapy.[1] Immunotherapy with monoclonal antibodies targeting immune checkpoints is a new treatment option in several tumour diseases and is generally safe; however, it is accompanied by a new spectrum of immune-related adverse events (irAEs) caused by redirection of immune responses against healthy tissues.[2] Early detection and management of irAEs is crucial to prevent aggravation, prevent

immunosuppressive treatment by withholding treatment temporarily and enable immunotherapy re-exposure.

Systematic reviews show the positive effects of eHealth interventions for patients with cancer in reducing psychological and physiological problems (eg, depression, cancer-related fatigue, distress, nutrition problems, pain)[3][4] and improving health-related QoL (HRQoL).[5] Interventions with combined services (eg, educational and electronic patient-reported outcome (PRO) services) are more effective and strengthen cancer patient empowerment.[6][7] Depending on the included services, eHealth interventions can assess repeatedly mental and physical symptoms and can provide a low-threshold supportive intervention that address patients' needs.[6] Additionally, they facilitate diagnostics and treatment by adaptive screening, monitoring and feedback of symptoms and providing supportive interventions.

The routine application of PROs in cancer care is a promising approach, indicating increased discussion of PROs during consultations, improved symptom control, increased supportive care and patient satisfaction.[8] Studies including advanced patients with cancer treated with chemotherapy show that the regular measurement and feedback of PROs improve the overall survival[9–11] and HRQoL.[9][10] The possible mechanisms of these results include the following aspects[12]: The proactive monitoring prompts clinicians to intervene early, before symptoms worsen and cause serious complications that might lead to therapy interruption or discontinuation; and symptom control enables patients to stay more functional and improves control of side effects, enabling more intensive and longer duration of cancer treatment.

To date, a small number of studies investigated the feasibility and effects of PRO assessment on patients under immunotherapy. A prospective one-arm study with advanced patients with cancer under immune checkpoint inhibition (ICI) therapy indicate good feasibility and adherence of electronic PROs (ePROs).[13] Pretreatment PROs show a prognostic value of overall and progression-free survival in patients with advanced lung-cell cancer treated with ICIs.[14] A case study[15] revealed that weekly self-scored symptoms via a web-mediated symptom monitoring helps to distinguish pseudo-progression from true progression during immunotherapy for lung cancer. A mixed-method study investigated the experiences of melanoma patients and clinicians with an eHealth intervention in monitoring side effects during immunotherapy.[16] Results showed high satisfaction and acceptance of the tool among patients and clinicians, and in patients, the weekly rating of PROs led to increased symptom awareness and the feeling of contribution.[16] Another pilot study with patients with metastatic non-small cell lung cancer indicate user satisfaction and acceptance of a stand-alone ePRO tool, but also the importance of the integration of such a tool in the clinical data flow.[17]

Consequently, we have developed a therapy-accompanying eHealth intervention–managing symptoms of immunotherapy (SOFIA)—for patients with cancer on immunotherapy with ICIs in an interdisciplinary setting including medical oncologists and psycho-oncologists. SOFIA is a smartphone application (app) that is technically realised in scientific cooperation with Fosanis (Berlin, Germany).

SOFIA consists of the following two components: (1) SOFIA-Monitoring is an online tool for patients to rate PROs between visits. Before the next scheduled visit, PROs are presented for the oncologists in the in-house documentation system for the most recent assessments, and longitudinally to allow assessment of change over time. PROs are, therefore, well integrated in the clinical routine. Additionally, we assess psychological symptoms and offer psycho-oncological services if a threshold is exceeded.

(2) SOFIA-Coaching provides important information about cancer-specific and immunotherapy-specific topics and the counselling services of National Centre for Tumour Diseases (NCT) Heidelberg.

The following features characterise SOFIA: it provides personalised support for patients with cancer on immunotherapy, includes multiple entities, aligns with a biopsychosocial background and improves the treatment team collaboration.

We aim to assess the feasibility of the procedures associated with a full-scale trial of SOFIA (eg, recruitment rates, willingness of randomisation and retention, effect sizes), and the feasibility and acceptance of the intervention itself (eg, adherence, use rates). The trial will indicate the acceptability and feasibility of this interdisciplinary intervention on patients and clinicians in the clinical routine.

Our clinical outcomes are HRQoL, psychological measures, medical outcomes (ie, interruptions and discontinuation, emergency visits, survival) and the utilisation of counselling services.

METHODS AND ANALYSIS
Study design
The design is a prospective single-centre parallel-arm randomised controlled trial (RCT) of SOFIA versus no-SOFIA. The intervention period lasts 3 months, as in most cases, irAEs occur in the first 14 weeks after immune checkpoint therapy initiation.[18] All participants will be assessed three times—at baseline (T0), postintervention (T2, 3 months after T0) and 6-month follow-up (T3). Participants of the intervention group will additionally be assessed with an interim survey (T1) 4 weeks after starting the intervention. The four measurement points involve face-to-face assessments including the full battery of primary and secondary outcomes and medical data, described below. See figure 1 for a data flow chart.

Participants and recruitment
The proposed feasibility study will seek to enrol 70 patients with cancer aged 18 years and above who are treated with immune checkpoint blockade at NCT Heidelberg. Participants will be randomly divided into two groups:
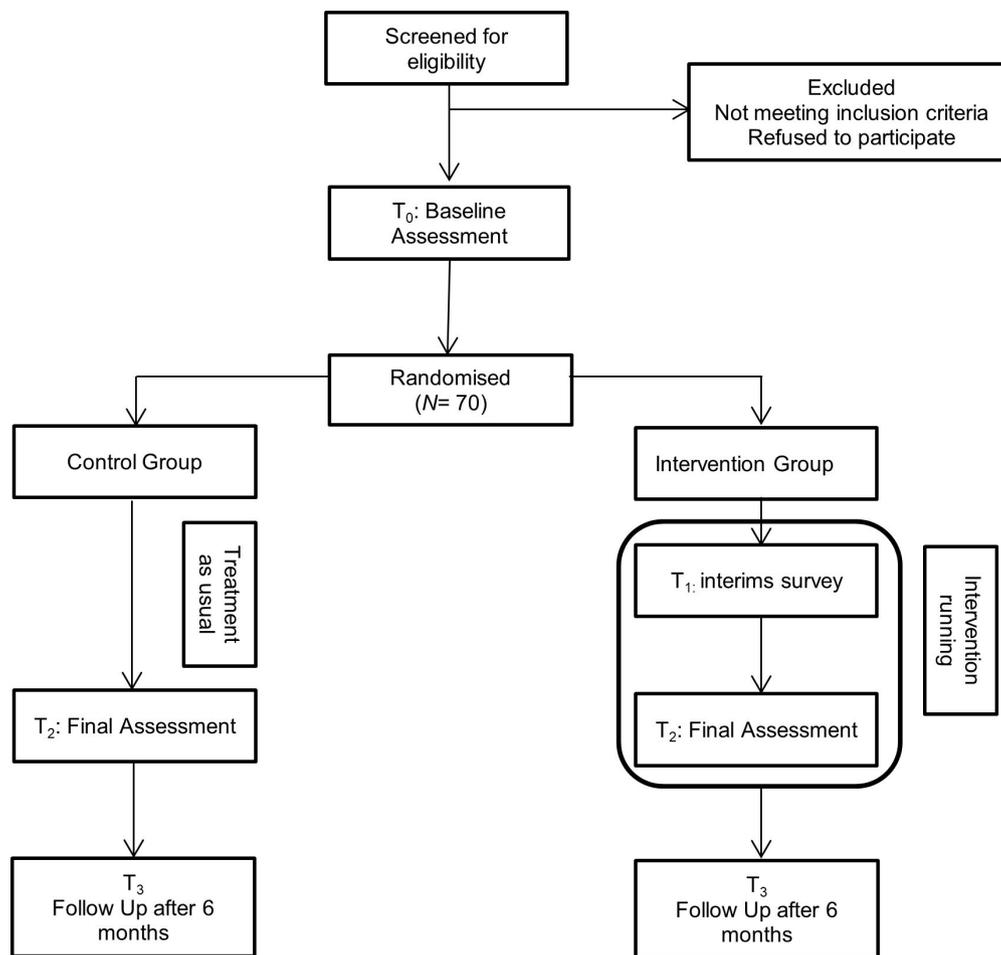
Figure 1 Participants data flow chart.

SOFIA and no-SOFIA. The inclusion criteria are patients on immunotherapy (monotherapy, combined immunotherapy, immunotherapy combined with chemotherapy or tyrosine kinase inhibitor) at the clinic of medical oncology at NCT Heidelberg, inclusion at time around the first dose of treatment, Eastern Cooperative Oncology Group (ECOG) performance status of 0–1, predicted life expectancy >3 months, own an internet-capable end device on which SOFIA can be processed (eg, smartphone), German native speaker or has knowledge of the German language and written informed consent (see online supplemental file A). Conversely, the exclusion criteria are participation in an interventional clinical trial, ECOG score >1, limited legal capacity or impairment thereof, cognitive or physical impairments that make it difficult to process online modules (eg, impaired vision) and serious psychiatric or mental illness.

Patients will be recruited through clinicians of the department of medical oncology, through our team and through flyers and posters. Suitable participants are invited to the baseline assessment session (T0) following initial eligibility screening via telephone. At the beginning of the session, the study will be explained to all participants, and written informed consent will be obtained. Additionally, we will assess screening data and potential exclusion criteria in all patients.

Patient and public involvement

Participants are not involved in the design and conduct of the research, and writing of the manuscript. Participants' feedback at T1 and T2 will be used to improve the SOFIA-app for future research.

Participant allocation

We will classify participants by ECOG score (0 vs 1), and following the baseline assessment (T0), eligible participants will be randomised via a certified online randomisation tool (https://www.randomizer.at). We employ permuted block randomisation with equal block sizes and stratify for ECOG. We used a fixed block size to guarantee equal block sizes for each stratum. The block size is unknown to the investigators. Participants will be notified regarding their group allocation via telephone.

No-SOFIA

Patients of the control group (no-SOFIA) receive standard care, that is, they get their medical therapy and—if required—all regular counselling services of the NCT (psycho-oncology, nutritional advice, social service, movement und sports therapy). These services are available for all patients of the NCT with subjective (counselling request) or objective demand (identified by standard screening for need for psychological support). (As a

standard operating procedure, all patients are screened for psychological distress by a study nurse at the beginning of the medical therapy at the NCT Heidelberg. This screening is independent of the study, that is, participants of the SOFIA and no-SOFIA group are screened with the standard screening. Our study team do not know the screening data and the study inclusion is independent of the screening results.)

Intervention

At the beginning of the intervention, we introduce patients of the intervention group with SOFIA and explain the components in a face-to-face appointment. Participants will receive their invitation code for the SOFIA app and will be encouraged to ask further questions. As written in the informed consent, we emphasise that reports of PROs and mental symptoms are not immediately forwarded, but that their doctor will collect the data before their next consultation. We highlight this to clarify that patients must consult the clinic on their own if side effects and symptoms occur.

SOFIA-Monitoring

SOFIA-Monitoring consists of 11 physical and up to 9 mental PROs. The 11 physical symptoms were chosen based on European Society of Medical Oncology (ESMO) Guidelines[2] by a team of highly experienced medical oncologists. Some PROs (eg, weakness, diarrhoea, melaena, dry cough, shortness of breath, reduced urinary excretion, joint pain, muscle pain) are rated between 0 (not at all) and 4 (very much) while others (skin toxicity, fever, yellow colouring of the skin) are rated yes/no. In case of fever or yellow colouring of the skin or a rating ≥3, patients will receive a pop-up message with the text 'In the case of (…), it is strongly recommended to present to a clinic', along with the contact information of our clinic and emergency room and schedule during weekdays and weekends and at night. In case of skin toxicities, patients have to complete two additional questions to specify their symptoms (skin rash or reddening, itching). The PRO results will be forwarded to the responsible physician before the next scheduled visit.

Additionally, we assess mental symptoms (ie, psychological distress, depression, anxiety and fatigue) with up to nine items. The German version of the National Comprehensive Cancer Network (NCCN) distress thermometer (DT)[19] is used to assess the patients' distress on an 11-point numerical scale with endpoints of 'no distress' or 'extreme distress'. If patients rate their distress ≥5, we assess depression and anxiety symptoms using the Patient Health Questionnaire-4 (PHQ-4),[20] the ultrabrief screening tool of the PHQ, German version (PHQ-D). Two items each ask for depression and anxiety symptoms experienced over the last 24 hours (We adapted the original PHQ-4 version that asked for anxiety and depression over the last 2 weeks due to clinical reasons and the twice-a-week assessment). A score >3 in each scale indicates depression and anxiety disorder. Moreover, cancer-related

fatigue is assessed via two items: 'Has your physical fitness decreased in the last few days?' (not at all, light, clearly, extreme) and 'Do you feel exhausted or suffer from persistent tiredness?' (yes or no). If yes, the participants rate the intensity of their physical and mental exhaustion on an 11-point numerical scale with endpoints of 'not at all' or 'extreme'.

For these items, participants get no recommendations via the app. During the interims survey and the post-treatment interview, we show the participants a process diagram presenting the different psychological symptoms; if required, we recommend them to contact our psycho-oncological service.

Participants have to rate the PROs twice a week and they will receive short reminders for the assessment.

SOFIA-Coaching

SOFIA-Coaching is a modular intervention, comprising 24 independent modules. We provide modules that we have developed together with the counselling services (ie, nutrition, physical activity, psycho-oncological service, social service) and oncologists of the NCT, which were partially piloted in a previous study[21] and represent frequent topics and questions of patients with cancer. The NCT counselling services developed the contents of the modules. Most of the modules are written; however, a video clip with an expert interview and podcasts with mindfulness and relaxing exercises are available. Patients of the intervention group have access to the modules and can use them as often as they like during the intervention period. The topics of these modules include immunotherapy and its side effects, psycho-oncological counselling, sport undergoing immunotherapy, nutrition under immunotherapy, social law issues and respective contact information. Additionally, modules created by Fosanis provide further information on various cancer-specific and immunotherapy-specific topics. Further information regarding the modules can be found in online supplemental file B.

Data flow

PRO data are shared through an encrypted file sharing software 'Seafile' by Fosanis (encryption with AES 256/CBC). Data are uploaded to a password-protected encrypted storage system. A member of the research team downloads the file, where the file is decrypted on their terminal, once a week. Data on the 11 PROs and 9 mental symptoms are presented in two progress graphs generated with Microsoft Excel (Office 2019), displaying the current intensity of symptoms and their courses. Before the scheduled doctors' consultations on the day of immunotherapy application (normally every 2–4 weeks), we copy the graph with the PROs into the patient's electronic medical record for the doctor to be aware of the symptoms and use it for the consultation.

Measures

The primary aim of this pilot study is to test the feasibility of SOFIA in the clinical routine. Feasibility in our trial

is defined as feasibility with the available technical and personal resources, integration in the clinical routine, utilisation and facilitations of SOFIA-Monitoring and SOFIA-Coaching and adherence. Feasibility outcomes included: recruitment rate; refusal and drop-out rate; reasons for refusal and dropout; willingness to be randomised, utilisation rate of SOFIA-Monitoring and utilisation time of SOFIA-Coaching, feasibility and acceptability of the proposed outcome measures and information required to estimate sample size for a full trial; utilisation and benefits for the physicians. We will use data from the evaluation interviews, online questionnaires (via Soscisurvey. de),[22] user behaviour (duration, frequency) and from the medical records to answer these questions.

Clinical outcomes

HRQoL is assessed with the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30, V.3.[23] This valid and reliable questionnaire[24][25] contains 30 questions and evaluates multidimensionally the HRQoL of oncological patients over 10 subscales. The primary outcome of the full trial will be the two-item global health/QoL scale. Reference data from the general German population exist, to compare the HRQoL of the general population with our study population.[26]

Further outcomes include depressive and anxiety symptoms, psychological distress, physician–patient interaction quality, treatment satisfaction and self-efficacy, which are assessed via self-report questionnaires at T0, T2 and T3. In addition, we collect medical data (eg, number of emergency visits, intensity of side effects, inpatient visits, survival, interruption and termination of the therapy, death) and the utilisation of NCT counselling services from the patients' medical record. The intensity of side effects is measured by the Common Terminology Criteria for Adverse Events classification.

The following questionnaires are used:

Self-reported symptoms of depression are assessed with the PHQ-9, depression module,[27] a widely used screening tool in several clinical settings. The questionnaire evaluates the presence of nine depressive episode symptoms contained in the Diagnostic and Statistical Manual of Mental Disorders, fourth Revision. The PHQ-9 shows good reliability, validity and sensitivity of change.[28][29]

We assess anxiety levels using the German GAD-7,[27] another reliable PHQ module to measure general anxiety symptoms showing good factorial and construct validity.[30]

The NCCN DT[19] is used to assess the patients' distress on an 11-point numerical scale with endpoints of 'no distress' or 'extreme distress'. The short-standardised DT has been proven highly sensitive when evaluated against established criteria.

In the Doctor–Patient Interaction Questionnaire,[31] the quality of doctor–patient communication is measured through 14 items. It is an economic measuring instrument with good reliability and validity.[31]

We assess self-efficacy with the German version of the Cancer Behaviour Inventory-Brief Version.[32][33] 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.

We use the German version of the Supportive Care Needs Survey.[34] It surveys the subjective support needs of patients with cancer in various areas such as healthcare system and information, psychological support needs, physical aspects, medical treatment and sexuality and partnership, and shows excellent psychometric properties.[34]

We assess patient's treatment satisfaction (one item: How satisfied were you overall with the medical treatment so far? (Rating, 1=not at all; 5=very much)) and the physician's evaluation of the treatment of patients in the intervention arm with a self-made evaluation record.

In order to evaluate the utility of SOFIA-Monitoring for the physicians, we developed an evaluation questionnaire for the physicians of our participants (see online supplemental file C). Furthermore, user data (frequency and duration of the utilisation) are assessed.

METHODOLOGICAL ASPECTS

Sample size

According to the approach of Teare et al.[35] for the estimation of sample size in external pilot trials with continuous outcome variables, a total of N=70 cases (n=35 per treatment arm) is needed to test our study aims.

Data collection and confidentiality

Outcome data for all patients will be collected via the online tool SoSci Survey[22] and face-to-face interviews at baseline, post-treatment and 6-month follow-up. Additionally, we will conduct an interim survey (T1) via interview 4 weeks after T0 with the intervention group to ask about the satisfaction and problems with the different components of SOFIA (see online supplemental file D for the interview guide). Participants will be reminded or called if they do not complete the follow-up questionnaire.

To maintain data privacy, all participants will obtain a pseudonym study ID (consisting of letters and numbers) for personally identifying information not to be linked with the assessment. The data, which are transmitted to the study team either within the scope of the study (questionnaires and interview) or online, will be treated in strict confidence and will only be used and tested by study employees and the cooperation partner Fosanis. Patient names and all other confidential information are subject to medical confidentiality and the provisions of the German Federal Data Protection Act (Bundesdatenschutzgesetz). All data (including all personal data) will be stored in German databases of the university medical centre of Heidelberg (UKHD) and of Fosanis. Data files with personally identifying information will be locked with limited access to the immediate researcher team (CS

and SK). The key to identify patients with pseudonyms is separately stored. Only the principal investigators have access to the trial data.

Statistical analysis plan

Analyses of the outcomes will be conducted by the trial statistician, following Consolidated Standards of Reporting Trials extension for pilot and feasibility trials.[36] No interim analyses are planned. All statistical analyses will be conducted with SPSS V.26.

The feasibility outcomes will be reported descriptively and narratively. For the clinical endpoints, only descriptive statistics, means/ standard deviations for continuous outcomes and raw count (%) for categorical outcomes, will be reported.

Repeated measurement analysis of variance will be used to compare groups on clinical outcomes at the three assessment points (eg, changes in HRQoL). The clinical outcomes (primary and secondary outcomes in the future RCT) will be reported as estimates with 95% confidence intervals without p values, because our pilot trial is not powered for testing hypotheses about effectiveness.[36]

Qualitative data will be analysed according to the principles of qualitative content analyses using the MAXQDA software.

Monitoring and data management

The trial will be conducted at the NCT Heidelberg, Germany. The research team will meet once a month to monitor recruitment, deal with any adverse event, and coordinate the different stages of the project. The research team consists of a research clinical psychologist (PhD), a medical doctor and an assistant research psychologist.

Ethics and dissemination

This trial protocol has been approved by the Ethical Committee of Heidelberg University, Germany (Reference, S-581/2018). Findings will be disseminated broadly via peer-reviewed empirical journals, articles and conference presentations.

DISCUSSION

Systematic reviews show positive effects of eHealth interventions for patients with cancer in reducing various physical and psychological symptoms[3 4] and improving HRQoL.[5] Two randomised controlled studies showed that the regular assessment of PROs in metastatic patients with cancer via an online tool lengthened survival, possibly by earlier detection of adverse events or recurrence.[10 11 37] Additionally, a case study[15] showed that weekly self-scored symptoms help discriminate pseudo-progression from true progression during immunotherapy of lung cancer. Among melanoma patients and clinicians, satisfaction with an eHealth intervention to weekly monitor PROs under immunotherapy was high and led to higher symptom awareness and the feeling of contribution among patients.[16] Pilot studies with immunotherapy patients indicate the feasibility and acceptance of PROs in these patients.[13 17]

Further reviews about eHealth intervention for oncology patients show that the combination of different web elements—information, monitoring, feedback and self-management—was more promising than information alone.[7] Interdisciplinary eHealth interventions including enhanced monitoring of patients improve treatment outcomes and self-efficacy.[38]

SOFIA, an eHealth intervention for patients with immunotherapy, combines a monitoring tool for PROs and coaching modules. This randomised controlled pilot trial tests the feasibility and acceptability of SOFIA in routine clinical care.

Strengths and limitations

Our study has several important strengths and will extend the development and research on eHealth interventions in patients with cancer. It is the first pilot RCT that investigates the feasibility and acceptance of a biopsychosocial, two-component eHealth intervention (SOFIA) in patients with cancer under immunotherapy. SOFIA includes a twice a week assessment of patient-reported irAEs and depicts a new paradigm to support clinical management of ICI. As irAEs are common among patients receiving ICI, regular PRO assessment may lead to less interruptions and terminations of immunotherapies. However, since this is a pilot study, no statements about effectiveness can be made. Furthermore, the generalisability to other settings is limited because this is a singe centre study. A future multicentre main RCT is needed to test the effects on HRQoL and other outcome variables.

If SOFIA will show feasibility and acceptance, the results of our pilot trial will inform a research protocol and optimal sample size calculation for a well-powered main study, investigating the effects of such an intervention for HRQoL and other symptoms for patients under immunotherapy.

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