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A cluster-randomised, controlled proof-of-concept study to explore the feasibility and effect of a patient-directed intervention on quality of life in patients with advanced soft tissue sarcoma

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ABSTRACT

Introduction Even with evolving and expanding therapeutical options for the treatment of advanced sarcomas over recent years, the balance between efficacy and toxicity still remains a major concern. Moreover, the symptom burden in patients with sarcoma remains high compared with other malignant diseases. It is, therefore, crucial to assess treatment effectiveness not only in terms of disease-related outcomes (eg, overall survival) but also from an individual and patient-centred perspective using the assessment of patient-reported outcomes (PROs). By focusing on PROs as a primary study endpoint, we aim to address key issues for patients with advanced soft tissue sarcoma (STS) undergoing palliative treatment.

Methods and analysis The protocol of the YonLife study describes a multicentre, cluster-randomised, controlled, open-label proof-of-concept study conducted in patients with advanced or metastatic STS treated with trabectedin in seven German hospitals. The primary objective of the study is to exploratively compare overall quality of life between the patients receiving a multidimensional intervention based on individual PROs and those receiving usual supportive treatment. This complex intervention consists of the (1) electronic assessment of PRO, (2) creation of a case vignette based on PRO and clinical data and (3) treatment suggestions based on the discussion of these vignettes in a regularly meeting expert panel. Additionally, the YonLife trial assesses the applicability of a tablet-based assessment of PROs. Patients' and physicians' acceptance and challenges concerning the implementation process will be evaluated.

Ethics and dissemination The YonLife trial has been approved by the Ethics Committee of the University Hospital Dresden as well as by the relevant institutions of each participating centre before patient enrolment. The findings will be reported via relevant peer-reviewed journals as well as through presentation at international conferences.

Trial registration number NCT02204111, pre-results.

Strengths and limitations of this study

- The YonLife trial will describe the experiences of the implementation of mobile electronic PRO assessment in a multicentre setting. The results from the YonLife trial will surely represent a valuable addition to the very scarce data about several patient-reported outcomes (PROs) regarding quality of life and symptom burden in patients with sarcomas who receive palliative treatments.
- The YonLife trial applies a complex treatment and will contribute to the knowledge that can help to shape its implementation and feasibility in clinical routine.
- No effect sizes of such an intervention are previously published, so our sample size calculation was based on comparable, yet not identical effect sizes. The YonLife trial is an important prerequisite for researchers in conducting adequate sample size estimation for future randomised trials.
- Methodological limitations apply such as the fact that there is no PRO measure available that is specific, disjunctive and exhaustive for symptoms experienced by patients with advanced soft tissue sarcoma. Furthermore, information about digital literacy of patients was not obtained and ability to handle a tablet was not set as a mandatory inclusion criterion.
- PRO and clinical data are assessed throughout the whole course of the study. Treatment proposals of the expert panel are only based on those measures obtained in visit 1, which might limit the impact of the treatment proposals as PROs could be changing rapidly.

INTRODUCTION

Although the clinical effectiveness of treatments in advanced soft tissue sarcoma (STS) has improved in the past few years, the corresponding toxicity and the varying degrees

of long-lasting and cumulative treatment side effects in many patients contribute to the overall limited advantages. Current treatment options for patients with STS are frequently guided by safety considerations and convenience. Therefore, it is important to assess the treatment effectiveness both in terms of objective outcomes (eg, progression-free survival or overall survival) and in terms of subjective patient-reported outcomes (PROs). A widely used definition describes PROs as 'any report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else'.[1]

Measuring PROs contributes to a better understanding of patients' disease burden and can serve as a prerequisite for a tailored supportive treatment approach. PRO domains most often measured include quality of life (QoL) as well as illness-related symptoms, such as psychological distress, pain or nutritional status. QoL is a multidimensional construct that encompasses emotional, social, functional and physical status.[2] Furthermore, it is a key issue to assess psychological distress since the prevalence of any psychological disorder among patients with cancer is high.[3]

Since real-time data and information provide advantages in clinical research and routine clinical treatment, incorporating PROs should also be beneficial for healthcare services.[4 5] Therefore, a growing and significant drive to incorporate PROs into routine healthcare services and scientific research develops.[6] These advantages include a higher sensitivity of symptom identification asking patients instead of solely relying on clinical impression as patients and healthcare professionals often differ in reporting symptoms.[7 8] Overall, physicians identify more health problems when routinely assessing PROs in addition to the information acquired from objective patient health records.[9] Notably, PROs contribute to increase the predictive accuracy of prognosis of overall survival, in addition to the sociodemographic and clinical details.[10 11] Physicians are also able to efficiently discuss a larger number of chronic symptoms without overburdening the patient–physician communication[12] with an improved quality of care.[13 14]

However, recently there has been emerging data that PRO assessment has an impact on clinical outcomes,[5] and several barriers that can decrease the beneficial impact of PRO assessment need to be considered. Solely, PRO assessment might not be beneficial for clinical outcomes and needs to be accompanied by additional interventions like nurse-led patient education or self-care support.[15–17] Only if relevant PRO domains are identified and redundant data being avoided[18] can clinical impact be increased.

Given the increasing use of technology in oncology and busy time schedules, healthcare research should address how to incorporate electronic PRO assessment into this workflow in a time-saving manner. More studies dealing with challenges associated with incorporating electronic assessments of PROs and tablet PCs have been conducted. These studies demonstrate that patients report a higher acceptance for answering questionnaires on a tablet PC rather than in paper form,[4 19] as well as an improvement in QoL and satisfaction.[20] Ultimately, electronic assessment has proven to be a useful tool for collecting and monitoring symptoms[21] and helping to establish a more trustful relationship between healthcare provider and patient.[22]

Especially in patients with STS, knowledge and data about PROs are very scarce. The burden of disease is high, and even in cases with a prolonged progression-free survival as a result of chemotherapy, QoL tends to decrease over time.[23] A systematic review reported that 30% of patients with STS experienced severe stress and depression, and the authors highly recommended further research on the reduction of psychological distress in this group of patients.[24] One of the few recent studies reported clinically relevant Hospital Anxiety and Depression Scale (HADS) depression scores ranging from 6.6% to 19.4% and HADS anxiety scores between 21.3% and 29.3% in patients treated for sarcoma.[25] Other data indicate that 2 years after finishing cancer therapy, roughly 50% of all patients with sarcoma were diagnosed with a psychological disease according to the Diagnostic and Statistical Manual of Mental Disorders III.[26] Symptoms such as pain, dyspnoea and fatigue are frequent and contribute to an adverse global health status as compared with other malignant diseases, especially in patients with advanced disease.[27] Moreover, these most disabling symptoms often remain undertreated in patients with metastatic disease and referral to early palliative care is recommended due to the high symptom burden.[28] Considerations about the time of initiating specialised palliative care interventions are crucial since the time between stopping active treatment until death is usually very short.

As QoL is a multidimensional construct, different interventions for its improvement that have been investigated vary in their concrete design and characteristics. More elaborate interventions such as the one designed by Klinkhammer-Schalke and colleagues[29] encompassing recommendation of a multiprofessional expert team have proven to benefit women with breast cancer.[30] Their intervention encompasses the exploration of impaired QoL dimensions, which was transformed into a report that was given to five experts. These independently formulated recommendations and consensus were derived in weekly meetings. Consensus was sent to the coordinator in the respective centre. Significantly less patients in the intervention group (56%) than in the control group (71%; $p<0.05$) experienced impairment of any one of their QoL dimensions 6 months after surgical treatment. This marks a 21% relative risk reduction of experiencing QoL impairments. Patients seem to especially differ in their global quality of life, emotional functioning and fatigue. Unfortunately, such an intervention has not yet been designed or tested for patients with STS. Therefore, the proof of concept for such a complex intervention remains to be investigated. Furthermore, no effect size of such a

complex intervention is available in patients with soft tissue sarcoma. This would be required to calculate sample size whenever aiming to conduct randomised controlled trials for proving effects of such a complex intervention. With this in mind, a clinical trial assessing the value and efficacy of such a tailored, patient-directed intervention regarding QoL and exploring effect sizes on various different PRO was designed. This trial entitled 'Patient Directed Intervention to Improve the Quality of Life for Patients With Soft Tissue Sarcoma' (YonLife) includes a complex intervention schedule that uses electronically assessed PROs and expert panel derived treatment recommendations to improve the QoL of patients with STS. In this multicentre, cluster-randomised, controlled, open-label proof-of-concept study, the feasibility of such a patient-directed intervention and the electronic assessment will be field tested and the respective effect size will be explored.

METHODS AND ANALYSIS

Study objectives

The primary objective of the YonLife trial is to exploratively compare the overall QoL between patients with STS receiving a multidimensional intervention, which has been compiled by an expert panel on the basis of patients' individual PROs, and those patients receiving usual supportive treatment.

Furthermore, there are two general secondary objectives in the study. The first secondary objective is to test the applicability of the study design and procedures. The second one is to explore effect sizes of such a complex intervention in patients with sarcoma in order to allow for sample size estimation in further research.

Patient population

Male and female subjects suffering from STS and under palliative treatment with trabectedin are to be screened for participation in the YonLife trial according to the following inclusion and exclusion criteria.

Subjects must fulfil all of the following criteria to be eligible for inclusion in the study:

- Diagnosis of advanced or metastatic histologically proven STS.
- Treatment with trabectedin in an in-label prescription.
- Age ≥18 years at the first visit.
- Patients with a life expectancy of at least 6 months.
- The informed consent form must be signed before any study specific tests or procedures are done.
- Confirmation of the subject's health insurance coverage prior to the first visit.
- Ability to understand and follow study-related instructions.

Subjects are to be excluded from the study if they display any of the following criteria:

- Eastern Cooperative Oncology Group (ECOG) performance status >2.
- Estimated life expectancy of less than 6 months.
- Patients with STS not receiving trabectedin.
- Contraindications according to the local summary of product characteristics of trabectedin.
- Subject is in custody by order of an authority or a court of law.
- Exclusion periods from other studies or simultaneous participation in other clinical studies.
- Previous assignment to treatment during this study.
- Close affiliation with the investigator (eg, a close relative) or persons working at the study site.
- Subject is an employee of GWT-TUD or Pharma Mar.
- Criteria that in the opinion of the investigator preclude participation for scientific reasons, for reasons of compliance or for reasons of the subject's safety.

We refrain from testing for digital literacy prior to study conduction and excluding patients with low technical skills due to ethical concerns. Nevertheless, gathering information on patients' experience with information technology could impact on study outcomes.[5] In case patients need support when handling the tablet, it will be provided by study staff.

The protocol is conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines.[31] The YonLife trial was approved by the Ethics Committee of the University Hospital Carl Gustav Carus in Dresden on 16 June 2014 (EK241062014). Moreover, all participating centres have obtained the approval of the local ethics committee before patient enrolment. All patients will have to provide written informed consent before inclusion in the study. Informed consent is obtained by an authorised study nurse or principal investigator of the respective centre.

Design overview and intervention

The YonLife trial is conducted as a cluster-randomised, controlled, open-label, proof-of-concept study. This article refers to the current version of protocol 4.0 as from 18 December 2016. The trial is performed at six German hospitals that are randomised 1:1 in an intervention group and a control group. An additional reference centre is located in Dresden. All seven participating hospitals are tertiary referral centres with a university affiliation and are members of the German Interdisciplinary Sarcoma Group. They all provide care according to national and international sarcoma care guidelines.[32 33] The expected number of patients fulfilling inclusion criteria is expected to range from 10 to 50 with a median of 20 patients.

Randomisation was carried out using computerised routine by a staff member not actively involved in this trial. As being a non-blinded, cluster-randomised trial, centres were informed during initiation whether they are in the intervention or control cluster. The Dresden centre is treated as being in the intervention group, but data derived from this centre will be evaluated separately. The aim here is to identify possible problems in implementing the multimodal intervention and prevent

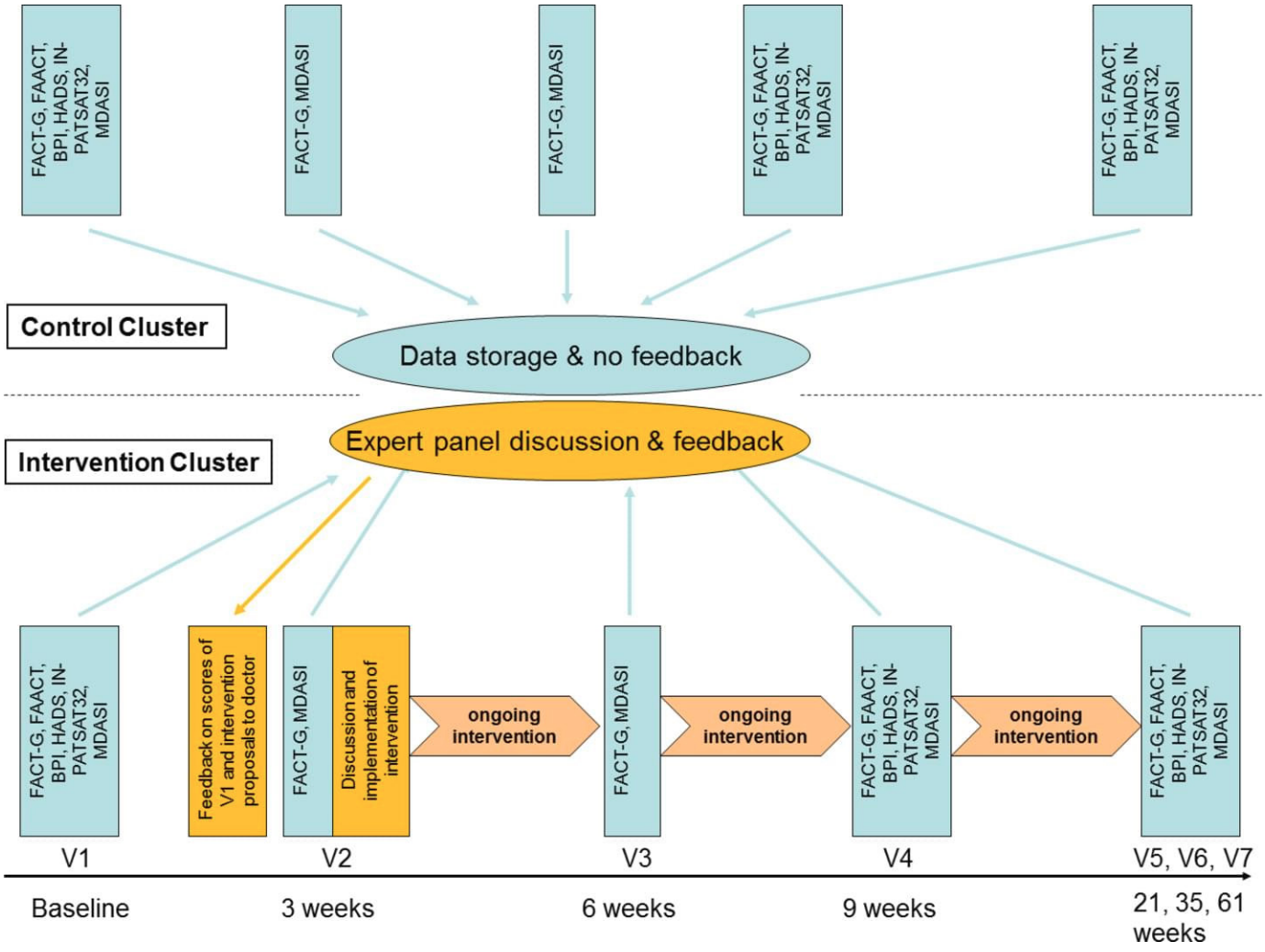


Figure 1 Study flowchart.

BPI: brief pain inventory; FAACT: Functional Assessment of Anorexia/Cachexia Therapy; FACT-G: Functional Assessment for Cancer Therapy - General; HADS: Hospital Anxiety and Depression Scale; IN-PATSAT32: Cancer in-patient satisfaction with care measure; MDASI: M. D. Anderson Symptom Inventory

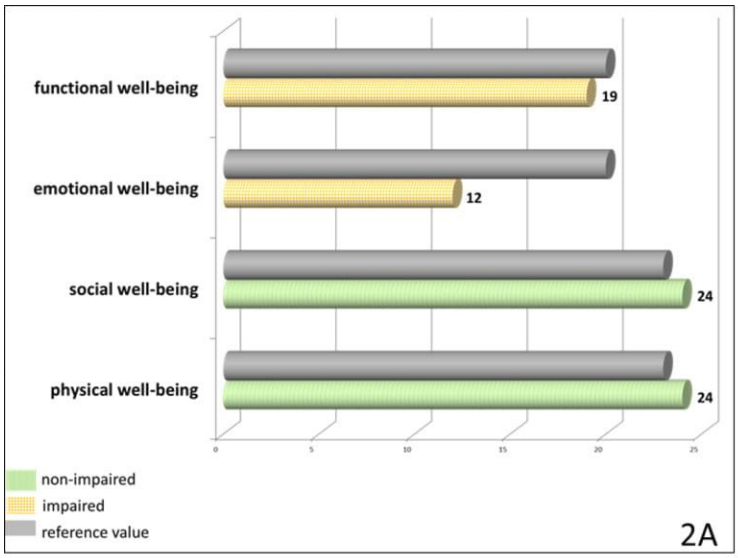
observer bias of professionals acting as both treating physician and member of the expert panel. Data are obtained prospectively at four intervals of 3 weeks each (visit 1 to 4); follow-up is conducted at 21, 35 and 61 weeks (visit 5 to 7) after baseline. Thus, the total duration of the study is 61 weeks per subject. Recruitment will be ongoing for 2 years with a follow-up for another 12 months.

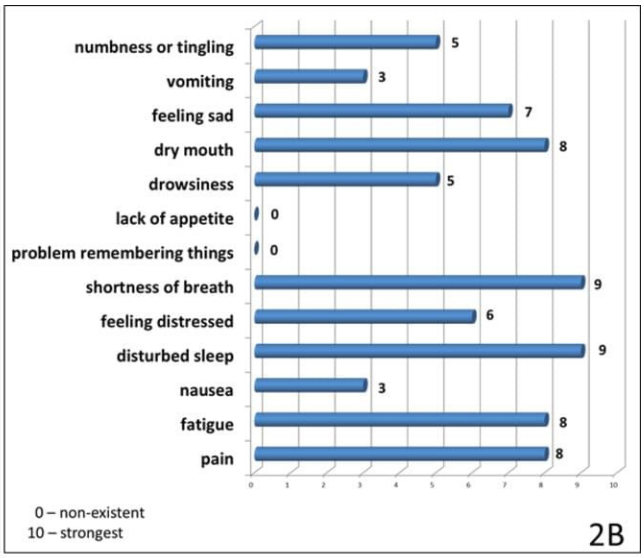
A multidimensional intervention is applied for patients in the intervention group. This complex intervention consists of the (1) electronic assessment of PRO, (2) the creation of a case vignette based on PRO and clinical data, (3) treatment suggestions based on the discussion of these vignettes in a regularly meeting expert panel and (4) provision of these suggestions as well as graphical representation of obtained PRO to the treating physicians in the interventional centres.

The complete study comprises a total of three study periods: (1) screening, (2) intervention phase and (3) follow-up. A summary of the study design is depicted in figure 1.

The screening period starts with the subject's signature of the informed consent form and ends with the eligibility for the intervention phase.

The intervention phase starts with the consecutive inclusion of eligible patients to the intervention and control group and ends after visit 4. Patients from the participating centres are included consecutively and complete standardised PRO measures (ie, FACT-G, MDASI) during visit 1 on a tablet PC. An individual ranking (priority list) is conducted by the patients grading impaired dimensions of the FACT-G and the five symptoms ranked worst in the MDASI according to their own perceived need for intervention. Clinical data such as disease stage, tumour, node, metastases classification, previous treatments, medication, comorbidities, sociodemographics (eg, about housing, financial difficulties) are derived by a study nurse from the patient's file and provided in an electronic case report form. These information were based





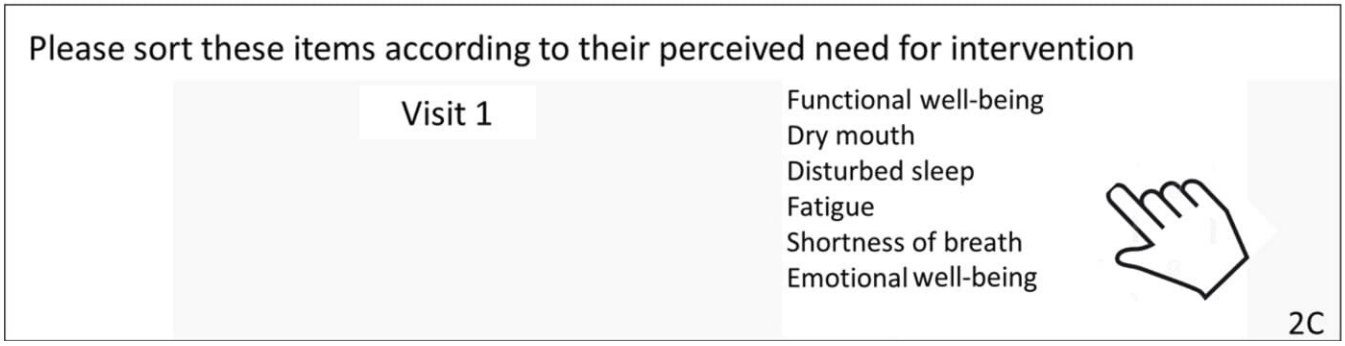


Figure 2 (A–C) Excerpt from case vignette for expert panel.

on panel members' interviews on which information they might need in order to overcome the obstacle of not encountering the patient in person. Patient's individual scores, his/her ranking and clinical data are compiled by the trial coordinator into a case vignette (figure 2A–C) and sent to the experts prior to their meetings. Whenever patients were included, expert panel meetings are held on a regular basis, at least 2 weeks after visit 1 of that particular patient in order to provide treatment suggestions prior to visit 2. The expert panel consists of representatives from different professions, including internal medicine, palliative care medicine, psychology and nursing, social care workers and a representative of a patient advocacy group. Treatment proposals that are provided to the centres are obtained as described in the following: experts receive case vignettes prior to the meeting. Each expert can suggest treatment proposals and send them to the trial coordinator in case he/she cannot participate in the meeting. Patient's impaired dimensions are then presented at the meeting and further treatment proposals might be discussed. The multiprofessional team consents on a proposal for supportive intervention. Proposals are then sent to the treating physician in the respective intervention centre prior to the scheduled visit 2 of the patient. During visit 2, the treating physician has the opportunity to discuss the expert proposal with the patient and to decide on these suggestions.

Treatment proposals can encompass suggestions from surgery, internal medicine, radiotherapy, pain therapy, palliative care, psycho-oncology, nursing, social work, physical therapy and patient advocacy. The electronic case report form lists on which of these areas suggestions are made by the expert circle, which are regarded as beneficial by the treating physician and which were effectively conducted by the patient. Patients treated in hospitals of the control group are asked to fill in the questionnaires at all visits, but their treating physicians do not receive treatment proposals from the expert panel.

The primary study endpoint of the trial will be analysed at the end of the interventional phase (visit 4). Analyses of long-term effects will include data from time points visit 1 as well as visit 4 to visit 7.

Assessment of PRO and safety variables

Patients' responses to questionnaires used in this study are assessed directly via tablet PC (ie, iPads), and scores are calculated using a tablet-based application for clinical research (ESPRIO; Seracom, Germany). Obtained scores can be compared with each other to pre-set norm data or reference values. Data are automatically transferred to a secure server as soon as a connection is available for the tablets. Data entry is synchronised every 30 seconds and stored on a secure server. Details on data transfer, storage and server security as well as different user profiles and

data protection are provided in the ESPRIO data and security guidelines.

The primary outcome of the YonLife trial is the FACT-G total score indicating overall QoL. The FACT-G[34] is a well-established and widely used questionnaire for the assessment of QoL in patients with cancer. This questionnaire assesses the overall QoL as a total sum score and as four subdimensions: physical, emotional, functional and social well-being. It has been tested extensively,[34–36] normative data for patients with cancer are available[37] and minimal clinical important difference as well as effect sizes are published.[38 39] The secondary outcomes include FACT-G dimensions as described above except the total score. They range from 0 to 28 (except emotional well-being, which ranges from 0 to 24) with higher scores indicating higher well-being. Total score ranges from 0 to 108.

Psychological distress is measured by the Hospital Anxiety and Depression Scale (HADS).[40 41] HADS remains one of the most common instruments to assess distress in patients with cancer. It consists of two scales, anxiety and depression, both ranging from 0 to 21 with higher scores indicating worse psychological status. A total score ranging from 0 to 42 can be summed up. Furthermore, HADS identifies clinically relevant cases of anxiety and depression using pre-determined cut-off scores. Another secondary outcome includes the proportion of patients classified as 'cases' by a cut-off equalling or exceeding the threshold of 5 on the depression subscale, the threshold of 7 on the anxiety scale and the threshold of 13 on total score.[42]

The Functional Assessment of Anorexia/Cachexia Therapy (FAACT) questionnaire measures both the impact of cachexia and anorexia on patients' QoL and patients' overall QoL.[43] In this case, secondary outcomes include the means of the anorexia/cachexia scale, which ranges from 0 to 48 with higher values indicating higher well-being, and the aggregated trial outcome index calculated from the physical and functional well-being and the anorexia/cachexia scale. It ranges from 0 to 104 with higher values indicating a better response to medical intervention.

The Brief Pain Inventory (BPI) determines the intensity of pain and pain-related interference.[44] This is a short, self-administered test and validated measure of pain. Secondary outcomes are the means of the four (intensity at the moment, at the worst, in average, at least) intensity scales (ranging from 0 to 10 with higher scores indicating higher pain intensity) and the interference scale (ranging from 0 to 10 with higher scores indicating higher interference with daily living).

The M.D. Anderson Symptom Inventory (MDASI)[45] measures the severity of 13 cancer-related symptoms and their impact on six dimensions of daily life during the last 24 hours. It is a well-established instrument used in patients with cancer. The secondary outcomes are the answers on each of the 13 symptoms as well as the mean score of the six interference items. Answers range from 0 to 10 with higher scores indicating more intense symptoms and more interference with daily living.

The EORTC Cancer in-patient satisfaction with care questionnaire (EORTC IN-PATSAT32)[46] assesses dimensions such as patients' satisfaction with the quality of doctors' and nurses' care as well as further aspects of clinical care. The secondary outcomes are the means of these dimensions, linearly transferred to scores from 0 to 100 with higher scores indicating higher satisfaction with the different care aspects.

To test the feasibility, doctors' and patients' opinions about the electronic assessment and the multimodal intervention, qualitative, semistructured interviews during site visits and self-developed questionnaires based on the Goal Attainment Scaling Technic (GAS) were used.[47 48] To develop a GAS questionnaire concerning the feasibility aspects of this intervention, relevant aims of the intervention were identified. These are transferred into questions that are usually answered on a scale ranging from '−2' (illustrating non-achievement), '0' (achieving goal) towards '+2' (exceeding goal). Patients in the intervention group receive 13 of these questions, persons in the control group answer 10 and physicians 9 items. A sample question for patients was 'How difficult was it to handle the iPad?' with answers ranging from '−2' (very difficult), to '0' (not difficult) towards +2 (very uncomplicated). This intervention is regarded as being feasible when 20% or less of all questions are answered less than '0'. Progression-free survival and the overall survival will be assessed during follow-up.

No specific safety parameters are analysed in the YonLife trial. Questioning for adverse events is performed at each visit. A reporting system has been established to report any occurrence of serious adverse drug reactions that are suspected of being related to the background medication Yondelis. Monitoring will be conducted at least twice in every site. Possibility of remote monitoring is obtained via computerised data storage.

Statistical evaluation and sample size calculation

The trial is designed as a cluster-randomised study that aims at estimating the efficacy of an additional multidimensional intervention compared with a single standard care in patients with STS. The usability of the study design will be pilot tested in this trial; therefore, no attrition rates are currently known. Response and dropout rates will be assessed and reported. For the analysis, patients not fulfilling the selection criteria of the trial (non-eligible) will be excluded from the statistical analysis. Only casuistic reports will be provided for this group. All other patients will primarily be evaluated in an intent-to-treat analysis (full analysis set).

Analyses of efficacy endpoints will be performed on the per-protocol analysis set, defined as the subset of subjects of the full analysis set who have complete data of primary and secondary target variables at the first (visit 1) and last visit of the intervention phase (visit 4), and who have no major protocol deviations thought to impact on the

efficacy conclusions of the trial. All patients included in the study are generally evaluable for safety and will be included in the safety analysis set.

The primary target variable of this trial is the health-related QoL measured as total score of FACT-G after 9 weeks at the end of the intervention phase (visit 4). The secondary variables are dimensions of health-related QoL (scales of FACT-G), anxiety and depression (HADS), satisfaction with care (IN-PATSAT32), anorexia-related and cachexia-related impact on QoL (FAACT), intensity of pain and pain-related interference (BPI), severity and interference of several cancer-related symptoms (MDASI) and general tumour-specific and sociodemographic parameters.

The sample size calculation for the comparison between the multidimensional treatment and the standard treatment was based on the following assumptions: H_0: FACT-$G_{multi} \leq$ FACT-$G_{standard}$, H_1: FACT-G_{multi} > FACT-$G_{standard}$, type I error α=0.05 (one-sided), power 1−β=0.80 and minimum of expected clinical relevant difference between the groups in FACT-G=15 (medium effect[38]), with an estimated SD of σ=17.0.[37] This calculation ended up with a cluster size of 11 patients per centre. Additionally, a conservative estimate of intracluster correlation coefficient ρ=0.1 and a dropout rate of 15% were included. Rounding up for an equal patient number across all centres, the total sample size was calculated to be n=78 patients ($N_{1/2}$=39 patients of three centres per study group and 13 patients per centre) for a valid number of 66 patients of six centres for the per-protocol analysis. This sample size may also provide enough power for further analyses. We aim to include only centres with an estimated average practice size of 15 patients and more. Additionally, we planned to assign 11 patients at the reference centre in Dresden to receive intervention. Patients in Dresden will be analysed as a separate group and the same descriptive statistics as in both other groups will be calculated for explorative reason providing 'positively biased' results about potential interventional effects. Subjects who prematurely discontinue participation after baseline data have been recorded (visit 1)—or subjects with major protocol violations—may be replaced when the dropout occurs within the intervention period (visit 1 to visit 4) as this is the time frame for the evaluation of the primary outcome. Dropouts during the follow-up period (visit 4 to visit 7) will not be replaced.

Descriptive statistics and predictor analyses are planned. All parameters will be evaluated in a descriptive manner, providing means, medians, ranges, SD, 95% CIs and intracluster correlation coefficients. Data will be analysed on a patient level (unit of inference) with a significance level of 5%. The primary study endpoint will be analysed by one-sided t-test for independent samples with adjustment for the design effect (inflation factor of the cluster design) comparing total scores of FACT-G of both groups at the end of the intervention phase (visit 4) and assuming a benefit for the multidimensional treatment group. Additionally, results on the primary endpoint will be assured by a mixed-model regression with the cluster included as a nested random effect, the group effect and data of baseline (visit 1) and end of the interventional phase (visit 4). The same statistical approach will be used to analyse the metric secondary study endpoints (HADS, FAACT, BPI, MDASI, IN-PATSAT32). One-sided t-tests for independent samples with adjustment for the design effect favouring the multidimensional treatment group at the end of treatment (visit 4) followed by mixed-model regressions or generalised linear mixed models with appropriate link functions will be applied. Adequate covariates (ie, age, gender, ECOG status) may be included prior to the start of statistical analysis to ensure that the modelling is hypothesis led. Analyses of long-term effects will include data from time points visit 1 as well as visit 4 to visit 7 and will be analysed by mixed-model regressions or generalised linear mixed models with appropriate link functions taking account of possible missing data entries without the need for imputation of data. Time-to-event data (progression-free survival, overall survival) will be evaluated as time-to-event outcomes by Kaplan-Meier estimators and log-rank tests in case of proportional hazards. Otherwise, modified Wilcoxon tests will be used.

ETHICS AND DISSEMINATION

This trial was registered under the US National Institutes of Health ClinicalTrials.gov identifier NCT02204111. Currently, it is in a pre-results-state. It is classified as an observational study as the study-specific treatment is not a drug or a medical device and specific treatment options are not mandatory. Therefore, the Medicinal Products Act (Gesetz über den Verkehr mit Arzneimitteln) or Medical Devices Law (Gesetz über Medizinprodukte) were not applicable. It is therefore registered and conducted, and ethical approval was obtained according to federal states Medical Association's professional code (Berufsordnung für Arzte in Sachsen) as an observational study. Ethical approval was obtained at each study centre. Relevant protocol changes will be provided to responsible parties including ethics committees.

Results of the trial will be provided via relevant peer-reviewed journals and conference presentations. The trial sponsor is GWT-TUD. On completion of the trial and after publication of all planned proceedings, access to full protocol, statistical code and study material can be submitted to the first author.

DISCUSSION

We hypothesise that it is beneficial for the quality of life of patients with sarcoma to receive treatment proposals compiled by an expert panel based on electronically assessed PRO. The YonLife trial aims to gain knowledge about PROs and to pilot test an interventional pathway to support clinicians in the multidimensional treatment of patients with sarcoma. The present protocol employs a real-time electronic assessment application that uses tablet PCs for obtaining data, calculating scores and

automatically transfers the information to a secured database. The effect of such an electronic measurement of PROs between patients receiving standard medical care (PRO assessment without feedback to treatment team) and the intervention group (PRO assessment with feedback to treatment team) will be investigated in this multicentre, cluster-randomised, controlled trial.

Additionally, the system provides the possibility of comparing calculated scores from obtained PROs with each other and pre-set norm data or reference values directly on the tablet PC. In fact, the YonLife trial uses this functionality to present QoL dimensions that are below reference values as well as the five symptoms of the MDASI answered as most disturbing by the patients. As a result, patients are asked to rank these items according to their individual perceived need of intervention. By applying this approach, an objective measure of patients' symptom burden and impaired QoL dimensions as compared with the subjectively most relevant individually perceived symptom interference with daily life are obtained. All of these steps function without any additional data transfer or calculation by, for example, a study nurse or documentarian, thus saving both time and resources.

To our knowledge, this will be the first randomised trial to incorporate this kind of priority list into supportive cancer care. Moreover, in the framework of this trial, it will be field tested whether recommendations by a multiprofessional palliative expert team will be able to support the physician and further improve QoL when receiving palliative chemotherapy. Challenges remain when defining an appropriate set of questionnaires to assess PRO in patients with soft tissue sarcoma. To our knowledge, there is no PRO measure available that is specific, disjunctive and exhaustive for symptoms experienced by patients suffering from advanced soft tissue sarcoma. Therefore, several questionnaires addressing different aspects of PROs are used together with clinical variables to give a broad perspective on the patient's disease and personal status in order to develop individually tailored, patient-directed treatment recommendations. To keep the balance between gaining information and a justifiable number of questions, some questionnaires were kept out of this trial, but may prove beneficial for further research. Another challenging question will be to evaluate whether an expert panel comprising several professions will be able to contribute with additional and valuable information to foster the treating physician. It will be of great interest to determine the compliance and agreement of doctors and patients to such a programme.

Although the complex intervention applied in the YonLife trial was designed with care, areas of uncertainties nevertheless remain. It is still a matter of investigation which clinical data to include in the expert panel's discussion to overcome the obstacle of not encountering the patients in person. Yet, we conducted non-structured interviews with expert panel members about which information might be useful to them to be included for their respective area of expertise, and a Delphi consensus should be conducted to agree on a common set of necessary information. Additionally, the lack of clinical impression of the patient is challenging as well as the modalities of the presentation of the assessed PROs. There is starting awareness on the unresolved question of how to present obtained PROs graphically,[49 50] which is a quite important topic for future research. Consequently, this aspect of the YonLife study retains an explorative character.

There is mixed yet overall positive evidence of the impact of complex interventions on outcomes. This study conducts one-sided tests as the majority of conducted trials applying complex interventions involving PRO assessments, PRO feedback and a PRO-led intervention had a positive impact.[4 5 51 52]

Nevertheless, the results of this study can be used as the groundwork for future directed research. Effect sizes gained in this study will allow for adequate sample size calculations of further trials and studies to investigate the most active component of the complex intervention.

In conclusion, the YonLife trial adds knowledge to the limited data about PROs in patients with advanced STS, which will help to gain deeper insights of patients' perspective on his/her disease as well as to optimise palliative treatment of symptoms and side effects. The implementation of the priority list represents an innovative and unique way of measuring patients' subjectively perceived needs for intervention based on a dynamic list of their most impaired symptoms without the need for intermediate scoring. Additionally, the feasibility and potential benefit of a complex intervention based on the individual PROs and recommendations from an expert panel are explored. Ultimately, the YonLife trial will add knowledge about the feasibility and the challenges of electronic assessment of PROs in the setting of a multicentre, randomised trial.

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Contributors MS and LH conceived the study, designed it and wrote the manuscript. MS is the coordinating investigator of the trial. LH is the trial coordinator and manages the day-to-day running of the trial. SR was involved in the study's design and the manuscript writing. GE and MB were involved in designing the study. All authors read and approved the final draft of the manuscript for submission.

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Ethics approval Initially approved by the Ethics Committee of the University Hospital Carl Gustav Carus in Dresden (EK241062014); moreover, ethical approval was obtained from the local ethics committee of participating centres.

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