The evaluation of health-related quality of life issues experienced by patients with desmoid-type fibromatosis

QUALIFIED study

Version 1.1
November 26, 2019

PROTOCOL TITLE 'The evaluation of health-related quality of life issues experienced by patients with desmoid-type fibromatosis'

Protocol ID	
Short title	**QUALIFIED study**
EudraCT number	***Not applicable***
Version	**1.1**
Date	**November 26, 2019**
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Laboratory sites	Not applicable

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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

AE	**Adverse Event**
CRF	**Case Report Form**
DSMB	**Data Safety Monitoring Board**
DTF	**Desmoid-type fibromatosis**
EORTC	**European Organisation for Research and Treatment of Cancer**
EORTC QLQ-C30	**European Organisation for Research and Treatment of Cancer, Quality of Life Questionnaire-Core-30**
EQ-5D-5L	**EuroQoL 5 dimensions, 5 levels**
EudraCT	**European drug regulatory affairs Clinical Trials**
FAP	**Familial Adenomatous Polyposis**
GCP	**Good Clinical Practice**
GDPR	**General Data Protection Regulation; in Dutch: Algemene Verordening Gegevensbescherming (AVG)**
HRQoL	**Health-related quality of life**
IC	**Informed Consent**
IQR	**Interquartile range**
METC	**Medical research ethics committee (MREC); in Dutch: medisch-ethische toetsingscommissie (METC)**
MC	**Medical Center**
PROFILES	**Patient Reported Outcomes Following Initial treatment and Long term Evaluation of Survivorship**
QoL	**Quality of Life**
(S)AE	**(Serious) Adverse Event**
SD	**Standard Deviation**
Sponsor	**The sponsor is the party that commissions the organisation or performance of the research, for example a pharmaceutical company, academic hospital, scientific organisation or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidising party.**
SUSAR	**Suspected Unexpected Serious Adverse Reaction**
VAS	**Visual Analogue Scale**
WGBO	**Dutch Medical Treatment Contracts Act; in Dutch: Wet op de Geneeskundige Behandelingsovereenkomst**
WMO	**Medical Research Involving Human Subjects Act; in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen**

SUMMARY

Rationale: Desmoid-type fibromatosis (DTF) is a rare, histologically benign soft tissue tumour. Although incapable of metastasizing, the clinical course is unpredictable and can be aggressive because of local invasive growth. Many invasive treatments (i.e. surgery, chemotherapy, radiotherapy) may be considered in patients with symptomatic disease but unfortunately, these 'traditional' treatment options do not guarantee tumour reduction and/or clinical response [1]. Local recurrence after surgery remains high [2,3]. Active surveillance is now recommended as a first line management for most patients with DTF [1,4]. Therefore, DTF has obtained a more 'chronic' status and its impact on patients should be evaluated accordingly.

Health-related quality of life (HRQoL) provides information beyond traditional measures of efficacy in oncology such as overall survival, and is increasingly used as an endpoint in clinical trials [5,6]. Based on previous studies we concluded that there is currently no HRQoL measure suitable for DTF patients. Additionally, we concluded that few is known about the quality of life of patients living with this rare disease. The previous studies led to the development of a DTF-specific HRQoL questionnaire named the 'DTF-QoL' [7].

By obtaining data from a relatively large group of patients with this rare disease, we will be able to evaluate the prevalence of HRQoL problems in adult DTF patients. The hypothesis is that patients with DTF have issues on several HRQoL domains including physical, social and emotional well-being. This study aims to evaluate HRQoL issues experienced by DTF patients.

Objective:
The primary objective is to evaluate HRQoL problems in adult DTF patients.

The secondary objectives are:
1. To compare the level of HRQoL of DTF patients to the general population.
2. To identify patient subgroups who are at risk for developing certain HRQoL problems,
3. To evaluate patient preferences regarding their health care needs for DTF.

Study design: Multicentre, cross-sectional, observational, cohort study.

Study population:
All patients, aged 18 years and above with a histopathological proven DTF and sufficient Dutch language skills who have received their last check-up at a medical oncologist or surgical oncologist specialized in DTF, in the hospital within the last five years (between October 2014 and October 2019).

Intervention (if applicable): Eligible patients will be asked to fill out a set of questionnaires consisting of 173 questions in total. Patients will only have to fill out these questionnaires once.

Main study parameters/endpoints:
To evaluate HRQoL problems in adult DTF patients, regardless of their disease stage or treatment course, using the DTF-QoL, the EORTC QLQ-C30, and the EQ-5D-5L questionnaires.

Secondary objectives:
a) Comparison of EORTC QLQ-C30 scores (describing symptoms, single items, functioning and global health) between DTF patients and the general population (age- and sex-matched).
b) Identification of DTF patients who are at risk for impaired HRQoL (risk factors).
c) Evaluating patient preferences for the health care for DTF.

Nature and extent of the burden and risks associated with participation, benefit and group relatedness:
The total number of questions is 173.

Completing all the questionnaires will take about 30-60 minutes. Our experience of high response in previous large-scale cancer survivorship studies using the PROFILES (Patient Reported Outcomes Following Initial treatment and Long term Evaluation of Survivorship) registry indicates that this number of questionnaires and its content is feasible and well accepted by patients. However some patients might find this burdensome. Risks are considered to be negligible and the burden is considered to be minimal. Because patients will complete these questionnaire in their own time, they will have the time and space to think about HRQoL issues which are important to them.

1. INTRODUCTION AND RATIONALE

Desmoid-type fibromatosis (DTF) is a benign soft tissue tumour which can cause significant morbidity by local aggressive growth behaviour [8]. Due to its local aggressive behaviour, and its known tendency of local recurrence after initial surgical resection, it is categorized as a borderline tumour in clinical guidelines [8].This tumour is rare with an estimated incidence of 5 patients per million persons per year in the Dutch population [9]. The biological behaviour is variable with phases of progressive growth, growth stabilization and even regression of the tumour without any treatment [10]. Most patients are females, aged between 20 and 40 years at primary diagnosis [9].

Sporadic DTF arises in musculoaponeurotic structures with the most common sites being the abdominal wall and the extremities [11]. Symptoms vary, depending on tumour site, size and infiltration of adjacent structures, resulting in pain and/or functional impairment. DTF does not metastasize, and rarely has fatal outcomes. Surgical resection, radiotherapy, non-cytotoxic and cytotoxic systemic therapies may be considered in patients with symptomatic disease but unfortunately, these 'traditional' treatment options do not guarantee tumour reduction and/or clinical response [1]. Local recurrence after surgery remains high [2,3], leading to a reduction in surgical treatments for DTF over recent decades [9,11]. Additionally, 'active' forms of treatment can be debilitating, causing greater morbidity than the tumour itself. For these reasons, active surveillance is now recommended as a first line management for most patients with DTF [1,4]. Therefore, DTF has obtained a 'chronic' status and its impact on patients should be evaluated accordingly.

Health-related quality of life (HRQoL) provides information beyond traditional measures of efficacy in oncology such as overall survival, and is increasingly used as an endpoint in clinical trials [5,6]. We previously performed a systematic literature review to evaluate which HRQoL-measures were used in research to assess HRQoL in DTF [12]. Studies used generic HRQoL-measures (e.g. the cancer specific core questionnaire from European Organisation for Research and Treatment of Cancer; the EORTC quality of life core questionnaire (EORTC QLQ-C30)), which may not consider disease-specific issues in DTF patients. Also, site-specific tools (e.g. Toronto Extremity Salvage Score), were used, which may not be relevant to certain groups (e.g. those with an abdominal wall, or head and neck tumours).

At present, there is no validated DTF-specific HRQoL-tool. In order to gain greater insight into the issues that patients with DTF experience in their daily lives, and to evaluate their experiences with the current health care and supportive system for DTF, we previously organised focus groups and semi-structured interviews, in the United Kingdom and in the Netherlands [7,12]. These studies identified issues covering various domains including; the diagnostic pathway, the treatment pathway, daily limitations (e.g. physical and psychological symptoms), and experiences with the current health care system. Additionally, issues were ranked according to their relevance by patients and health care providers (Timbergen et al., 2019, submitted). A DTF-specific HRQoL tool, named the DTF-QoL, was developed based on the results of these studies.

With the current study we would like to assess the HRQoL problems experienced by DTF patients. The DTF-specific tool, the (DTF-QoL), combined with additional HRQoL-tools will be used to gain more insight into the problems that DTF patients face on a daily basis. This study functions as an exploratory study which may generate new hypotheses for future studies.

2. OBJECTIVES

Primary objective: To evaluate HRQoL problems in adult DTF patients, regardless of their disease stage or treatment course, using the DTF-QoL, the EORTC QLQ-C30, and the EQ-5D-5L questionnaires.

Secondary objectives:
1. To compare the level of HRQoL of DTF patients to that of the general population (age- and sex-matched), using the EORTC QLQ-C30 (version 3.0).
2. To identify DTF patients who are at risk for late effects and/or impaired HRQoL (risk factors), using the baseline questionnaire, the DTF-QoL (version 1.0), the EORTC QLQ-C30 (version 3.0), and the EQ-5D-5L (version 1.0).
3. To evaluate patient preferences regarding their health care for DTF, using the healthcare utility and decision making questionnaires (both version 1.0).

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3. STUDY DESIGN

Multicentre, cross-sectional, observational, cohort study.

4. STUDY POPULATION

4.1 Population (base)

Patients, aged ≥18 years, diagnosed with a histopathological proven DTF, regardless of disease stage and received treatment(s) who have received their last check-up of their DTF in one of the participating hospitals the hospital between October 2014 and October 2019.

4.2 Inclusion criteria

In order to be eligible to participate in this study, a subject must meet all of the following criteria:

- Patients, aged ≥18 years
- Patients with histopathological proven DTF, regardless of disease stage or treatment.
- Patients diagnosed between January 1990 and October 2019, with a visit to the hospital for their DTF (between October 2014 and October 2019)
- Patients with sufficient Dutch language skills
- Patients competent to complete a questionnaire
- Patients with a written informed consent

4.3 Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:

- Patients diagnosed with familial adenomatous polyposis (FAP)

4.4 Sample size calculation

The incidence of DTF is 5.4 patients per million per year [9]. However, a sample size calculation is challenging due to rarity of the disease and lack of published data regarding this subject. In our previous study, the response rate of the Dutch patients was 41.5%. The Erasmus MC pathology database from 1990 until 2019 contains roughly 250 patients. Since we are a tertiary academic centre, about one third of these patients are pathology consultations from other centres. A small fraction of the remaining patients will be excluded because they are younger than 18 years old (about 5%) and because their desmoid tumour is part of the genetic syndrome Familial Adenomatous Polyposis (FAP) (about 5%). Because of the high incidence of malignant colorectal tumours in FAP patients, these patients might experience different HRQoL problems compared to patients with “sporadic” DTF. Currently, there are about 80 patients who are under follow-up at our institution. With the participation of two other centres with similar patient numbers we hope to approach a total of 250 patients. Based on the previous response rate we expect to obtain data from 100 DTF patients.

5. TREATMENT OF SUBJECTS

Not applicable, as this study does not involve an investigational product.

5.1 Investigational product/treatment
Not applicable, as this study does not involve an investigational product.

5.2 Use of co-intervention (if applicable)
Not applicable, as this study does not involve an investigational product.

5.3 Escape medication (if applicable)
Not applicable, as this study does not involve an investigational product.

6. INVESTIGATIONAL PRODUCT
Not applicable, as this study does not involve an investigational product.

6.1 Name and description of investigational product(s)
Not applicable, as this study does not involve an investigational product.

6.2 Summary of findings from non-clinical studies
Not applicable, as this study does not involve an investigational product.

6.3 Summary of findings from clinical studies
Not applicable, as this study does not involve an investigational product.

6.4 Summary of known and potential risks and benefits
Not applicable, as this study does not involve an investigational product.

6.5 Description and justification of route of administration and dosage
Not applicable, as this study does not involve an investigational product.

6.6 Dosages, dosage modifications and method of administration
Not applicable, as this study does not involve an investigational product.

6.7 Preparation and labelling of Investigational Medicinal Product
Not applicable, as this study does not involve an investigational product.

6.8 Drug accountability
Not applicable, as this study does not involve an investigational product.

7. NON-INVESTIGATIONAL PRODUCT
Not applicable, as this study does not involve a non-investigational product.

7.1 Name and description of non-investigational product(s)
Not applicable, as this study does not involve a non-investigational product

7.2 Summary of findings from non-clinical studies
Not applicable, as this study does not involve a non-investigational product

7.3 Summary of findings from clinical studies
Not applicable, as this study does not involve a non-investigational product

7.4 Summary of known and potential risks and benefits
Not applicable, as this study does not involve a non-investigational product

7.5 Description and justification of route of administration and dosage
Not applicable, as this study does not involve a non-investigational product

7.6 Dosages, dosage modifications and method of administration
Not applicable, as this study does not involve a non-investigational product

7.7 Preparation and labelling of Non Investigational Medicinal Product
Not applicable, as this study does not involve a non-investigational product

7.8 Drug accountability
Not applicable, as this study does not involve a non-investigational product

8. METHODS

8.1 Study parameters/endpoints

8.1.1 Main study parameter/endpoint

The EORTC QLQ-C30 (version 3.0) questionnaire, the DTF-QoL questionnaire, and the EQ-5D-5L questionnaire will be used. More information about these questionnaires can be found in Appendix 1.

The mean score or median score per scale of the EORTC QLQ-C30 questionnaire (symptom scales, single item scales, global health scale, and functioning scales) will be calculated with the standard deviation (SD) or interquartile range (IQR). Additionally, a summary score will be calculated based on all scales except financial difficulties and the global quality of life score, to reflect overall quality of life.

A mean score per item with an SD or a median score with a IQR will be calculated for the DTF-QoL questionnaire.

The outcomes of the EQ-5D-5L will be reported as frequency (proportion) of reported problems for each level and for each dimension

8.1.2 Secondary study parameters/endpoints

Patients with DTF will be matched to the general Dutch population using age and sex. The data from the general population in the Netherlands was obtained from the EORTC [13]. The median or mean values for each scale (symptom scales, single items scales, global health scale, and functioning scales) of the EORTC QLQ-C30 (version 3.0) from DTF patients will be compared to the median or mean scores per scale of the general population.

Subgroups will be created based on the information of the baseline questionnaire and will encompass: sex (male, female), age groups (categorized based by the median age and/or quartiles), primary treatment type (surgical resection, systemic treatment, radiotherapy, local treatment (e.g. cryoablation), ethnicity, educational level, relationship status, job demands, comorbidities, tumour location, and tumour recurrences.

Mean or median scores of each scale (EORTC QLQ-C30, version 3.0), items (DTF-QoL, version 1,0) or frequency scores (EQ-5D-5L, version 1,0) will be calculated for each relevant subgroup. More information about these questionnaires can be found in Appendix 1.

The outcomes of the health care utilization and the decision making questionnaires will be descriptive and reported in numbers and corresponding frequencies per answer option. More information about these questionnaires can be found in Appendix 1.

8.1.3 Other study parameters

The following variables will be collected from the medical records:

- Date of first histological diagnosis
- Details about treatment
    - Treatment start date
    - Type of treatments, including medication doses
    - Radiation dose

  - Date of surgery
  - Sequence of treatments
- Response to treatment
  - Progression, stable disease, regression based on imaging
  - Tumour sizes on imaging (magnetic resonance imaging, computed tomography or ultrasound)
  - Recurrence (based on imaging), recurrence based on pathology
  - Date of recurrence
  - Treatment type of recurrent tumour, date of treatment of recurrence

8.2 Randomisation, blinding and treatment allocation

Not applicable, as this study is no intervention study.

8.3 Study procedures

Selected patients will receive an invitation package by mail from their (former) treating health care professional (surgical oncologist, or medical oncologist). Data collection is done via PROFILES. Chapter 12 describes the use of PROFILES in more detail.

Patients are asked to complete the following questionnaires once. More information about these questionnaires can be found in Appendix 1.
Questionnaire A: Baseline questionnaire, version 1.0 (21 questions
Questionnaire B: Health care utilization, version 1.0 (7 questions)
Questionnaire C: Decision-making, version 1.0 (6 questions)
Questionnaire D: EORTC QLQ-C30, version 3.0 (30 questions)
Questionnaire E: DTF-QoL, version 1.0 (102 questions)
Questionnaire F: EQ-5D-5L, version 1.0 (7 questions)

Clinical characteristics (8.1.3) will be collected from the medical records.

Patients are assured that non-participation has no consequences for their treatment or follow-up care. If the patient does not have access to internet, or prefers written rather than digital communication, (s)he will receive a paper version of the questionnaire package. The informed consent form and questionnaires are then sent by post.

The questionnaire will be available at www.profielstudie.nl for a total of three months. Patients only have to fill out the questionnaire once but are able to stop at any given time point and are able to continue the questionnaire at any given time point. In case only a part of the questionnaire is filled out, the patient will receive a reminder (via PROFILES) to fill out the remaining questionnaire. Patients will receive a reminder 4 weeks after the first invitation.

Patients will be made aware of the fact that additional data will be obtained from their electronic patients files in the patient information file and will sign informed consent for this on the informed consent form.

8.4 Withdrawal of individual subjects

Subjects can leave the study at any time for any reason if they wish to do so without any consequences.

8.4.1 Specific criteria for withdrawal (if applicable)

Not applicable, as this is not an interventional study

8.5 Replacement of individual subjects after withdrawal
Not applicable, as this is not an interventional study.

8.6 Follow-up of subjects withdrawn from treatment
Not applicable, as this is not an interventional study.

8.7 Premature termination of the study
Not applicable, as this is not an interventional study.

9. SAFETY REPORTING
As this is not an interventional study and patients are not subjected to treatment in this study, this does not apply.

9.1 Temporary halt for reasons of subject safety
As patients are not subjected to treatment in this study, this does not apply.

9.2 AEs, SAEs and SUSARs

9.2.1 Adverse events (AEs)
As patients are not subjected to treatment in this study, this does not apply.

9.2.2 Serious adverse events (SAEs)
As patients are not subjected to treatment in this study, this does not apply.

9.2.3 Suspected unexpected serious adverse reactions (SUSARs)
As patients are not subjected to treatment in this study and the study does not involve an investigational medicinal product, this does not apply.

9.3 Annual safety report
As patients are not subjected to treatment in this study and the study does not involve an investigational medicinal product, this does not apply.

9.4 Follow-up of adverse events
As patients are not subjected to treatment in this study and the study does not involve an investigational medicinal product, this does not apply.

9.5 [Data Safety Monitoring Board (DSMB) / Safety Committee]
As patients are not subjected to treatment in this study and the study does not involve an investigational nor a non-investigational medicinal product, this does not apply. No DSMB will be installed for this study. No safety measures are involved since there are no risks involved in administering questionnaires to the patients.

10. STATISTICAL ANALYSIS
Rstudio (RStudio, version 1.0.153, Boston, MA, USA) and SPSS Statistics (version 24, IBM, Armonk, New York, USA) will be used for the statistical analysis.

The following questionnaires are descriptive outcomes and will be expressed as numbers and corresponding percentages:

Questionnaire A: Baseline questionnaire, version 1.0
Questionnaire B: Health care utilization, version 1.0
Questionnaire C: Decision-making, version 1.0
Questionnaire E: DTF-QoL, version 1.0

More information about these questionnaires can be found in Appendix 1.

10.1 Primary study parameter(s)

The scores for each item of the DTF-QoL will be calculated using a Likert scale from 1-4. The scores of each item will be calculated as mean ± SD, or as median (IQR). These scores (median or mean) will be reported per item.

The scores of the EORTC-QLQ30 (version .3.0) will be calculated using a Likert scale from 1-4. The scoring manual of the EORTC will be followed. After linear transformation, all scales and single item measures range in score from 0-100[14]. Scores for each scale will be reported as mean (SD), or as median (IQR).The EORTC QLQ-C30 summary score will be calculated using the mean scores of the function scales and the reversed mean scores of the symptom scales and represented as the mean of the combined 13 QLQ-C30 scale scores (financial impact and global health status excluded) [15,16].

Each of the five dimensions of the EQ-5D-5L (version 1.0) can be divided into five levels of perceived problem (1-5). Health states can be converted into single index values. The outcomes will be reported as frequency (proportion) of reported problems for each level and for each dimension. The Visual Analogue Scale (VAS) data will be presented as a mean value (SD). In case of skewed data, median values and IQR will be used.

10.2 Secondary study parameter(s)

Using the baseline values (reported in the baseline questionnaire) for age and sex, patients will be matched, using a 1:10 nearest-neighbour match method, with the general population[13] based on age, and sex using Rstudio (RStudio, version 1.0.153, Boston, MA, package MatchIt).

Differences in scores (of the EORTC QLQ-C30 scales between groups will be tested for their significance using the Mann-Whitney U test or the t-test, depending on the distribution. SPSS Statistics (IBM, Armonk, New York, USA, version 24) will be used for these tests. A two-sided $p<0.05$ will be considered statistically significant.

The outcomes of the health care utilization and the decision making questionnaire will be reported in numbers and corresponding percentages per answer option.

10.3 Other study parameters

Information extracted from medical files will be used as follows:

- Date of first histological diagnosis: this variable will be used to calculate age at diagnosis using date of birth and date of first histological diagnosis,
- Details about treatment
    - Treatment start date: this variable will be used to calculate age at the start of treatment using date of birth and the date of the start of the treatment. Additionally this variable can be used to calculate the time between the diagnosis and the start of treatment.
    - Type of treatments, including medication doses: this variable will be used as numbers with corresponding percentages
    - Radiation dose: this variable will be used in case a patient received surgery. This variable will be used descriptively
    - Date of surgery: this variable will be used to calculate the age at the time of surgery. Additionally this variable can be used to calculate the time between the diagnosis or the first treatment and surgery.
    - Sequence of treatments will be used descriptive
- Response to treatment

- Progression, stable disease, regression based on imaging: these variables will be used in a descriptive manner
- Tumour sizes on imaging (magnetic resonance imaging, computed tomography or ultrasound): these variables will be used to calculate mean size with standard deviation or median with interquartile range. Additionally this variable can be used to evaluate treatment outcome.

10.4 Interim analysis (if applicable)

Not applicable, no interim analysis will be done.

11. ETHICAL CONSIDERATIONS

11.1 Regulation statement

The study will be conducted according to the principles of the Declaration of Helsinki (64th World Medical Association General Assembly, Fortaleza, Brazil, October 2013). This study has been exempted by the medical research ethics committee (MREC); in Dutch: Medisch Ethische Toetsings Commissie (METC). Following review of the protocol, the MREC concluded that this study is not subject to the Medical Research Involving Human Subjects Act (WMO). They concluded that the study is a medical/scientific research, but no patients are subjected to procedures or are required to follow rules of behaviour. The study will be conducted according to the rules of the Dutch Medical Treatment Contracts Act (WGBO) and the Dutch General Data Protection Regulation (AVG) and in accordance with the Code of Conduct for Health Research (in Dutch: Gedragscode Gezondheidsonderzoek).

11.2 Recruitment and consent

Patients will be selected (based on their diagnosis) by the responsible treating Surgical Oncology or Medical Oncology Consultant who will check the patient for eligibility criteria from the electronic patient records. The treating healthcare professional or specialist nurse will introduce the study to the patient in the outpatient clinic and provide an invitation package. In case that the patient does not visit the outpatient clinic within two months of the start of the study, the treating healthcare professional or specialist nurse will invite the patient with the invitation package per post. The patients' address data will be checked with the national administration (in Dutch: gemeentelijke basis administratie) to assure its correctness.

The invitation package consists of a letter, a patient information sheet, an informed consent form and a prepaid return envelope. The patient information sheet explains the goals and procedure of the study. It includes a link to a secure website (www.profielstudie.nl), a login name, and a password. If patients have read the information sheet and have no further questions, they can login to the website. Informed consent is obtained both written and online. After providing written and online informed consent, they will be able to complete the questionnaires online.

11.3 Objection by minors or incapacitated subjects (if applicable)

Not applicable. No minors or incapacitated subjects will participate in this study.

11.4 Benefits and risks assessment, group relatedness

The study involves completing questionnaires and therefore risks are considered to be negligible and the burden is considered to be minimal. For the patient there is no direct advantage with participating in this study, as the answers to the questionnaire will not impact their current treatment plan. As the study is used to gain insight into HRQoL problems of DTF patients, it can potentially benefit their health care in the future.

Because patients will complete these questionnaire in their own time, they will have the time and space to think about HRQoL issues which are important to them. It is possible that a patient will become upset when thinking about how their DTF has impact on their HRQoL. Researchers will need to be aware of this and provide support if participants become upset.

11.5 Compensation for injury

As the study is not subjected to the Medical Research Involving Human Subjects Act (WMO), the statutory obligation to provide insurance for subjects participating in medical research (article 7 of the WMO) also does not apply.

11.6 Incentives (if applicable)

There is no compensation offered to participants.

12. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

12.1 Handling and storage of data and documents

Questionnaire administration will be done within the PROFILES registry (Patient Reported Outcomes Following Initial treatment and Long term Evaluation of Survivorship; www.profilesregistry.nl). PROFILES is a data management system set up in 2009 in The Netherlands for the study of the physical and psychosocial impact of cancer and its treatment. PROFILES is currently used in the Erasmus MC for the QUEST study (MEC-2018-1037) and the HOLISTIC study (MEC-2018-1101) investigating HRQoL in sarcoma patients. PROFILES uses an audit trail.

The local research coordinator at each study site will have access to a password protected file which links patients study ID number to their PROFILES online login username.

All answers that are entered by each individual patient are linked to their study ID number and do not contain overt identifiers (i.e. names or date of birth). Only after written informed consent from the patient, answers can be collected and linked to data collected from the medical records on case report forms in Open Clinica. All case report forms are completed with the patient's study number and do not contain person-identifiable information such as name or date of birth.

PROFILES

The PROFILES management system is hosted in The Netherlands on multi-processor servers for which infrastructure, configuration, license, security and patching are established in accordance with current norms (Dutch Data Protection Act (in Dutch: 'Algemene Verordening Gegevensbescherming (AVG)). Participants log in with their own user name and password into a PHP web application that communicates with a MySQL database located on a different server. This database server is shielded through a firewall from the internet. Both PHP and MySQL database servers run Linux as Operating System. Participants fill in their questionnaire on a separate server cluster, consisting of Windows 2008 R2 Servers running BlaiseIS questionnaire software (Statistics Netherlands). The answers to the questions are stored on a dedicated data storage server, shielded through firewalls from the internet. All servers are located in a secured room with access only for authorized personnel. The PROFILES infrastructure and software is updated regularly to optimize system operations and security. In addition, PROFILES has been awarded with the international data seal of approval for trusted data repository (http://www.datasealofapproval.org/en/). Questionnaire data will be stored on this secure Dutch system for 15 years.

Questionnaires on paper
Paper copies of the questionnaires will be entered by the research coordinator using the data entry option of PROFILES, after which a control check takes place on the eventually generated dataset. Paper versions of the questionnaires will be stored for 15 years in a according to legal requirements at the study site.

Completion of the study
The questionnaire data will be linked with the case report form (CRF) database (Open Clinica) (containing coded clinical data). Data linkage will be done by an epidemiologist involved in this project. Data linkage will take place using non-identifiable study numbers generated by PROFILES, allowing us to analyse the data pseudonymously.

In order to retrieve the data, the coordinating investigator at each study site who is authorised to login, can download the data in SPSS or Microsoft excel format. The FileSender server software allows authenticated users to securely send large files to other uses. This application has been developed to the requirements of the higher education and research community and allows end to end encryption. The combined dataset will be stored on computers within the Erasmus MC and will be under appropriate password protection.

Confidentiality and pseudo-anonymity of patients
Confidentiality and pseudo-anonymity of patients will be guaranteed with the assignation of a study number to each patient. Only a delegated research study member from each study team (site) will have access to a record that links the patient study numbers and their PROFILES login details to identifiable information. A study number is auto-generated by the PROFILES system. An example of the study number is: RNEMC0001 (RN[centre][number]).

Clinical data
Clinical data will be collected from the medical files of patients and maintained according to GCP standards and entered into the study password protected database where it will be stored. The patient records will not leave the hospital where the patient is treated. The research data will be stored in a password protected, database and will be handled confidentially. Research data that can be traced to individual persons can only be viewed by the on-site researcher. From a legal point of view; members of the health care inspection and members of the Medical Research Ethics Committee of the participating hospital also have access to this data. Data review may be necessary in order to ensure the reliability and quality of the research. The handling of personal data is in compliance with the Dutch Data Protection Act (in Dutch: ‘Algemene Verordening Gegevensbescherming (AVG)).

Data will be saved and stored for a period of 15 years, conform Erasmus MC’s agreements for studies that are not subject to the Medical Research Involving Human Subjects Act (WMO).

12.2 Monitoring and Quality Assurance
The principal investigator or a project leader, will monitor quality of the data in the database by checking correctness and completeness of data (e.g. the answers from the DTF-QoL and EORTC QLQ-C30 questionnaires) for a random selection of 10% of patients, with a minimum of 10 patients per participating hospital. The data sources are the answers of the questionnaires completed by the patients and stored at the PROFILES server (in Dutch: Profiel).

12.3 Amendments

Amendments are changes made to the research after a favourable opinion by the accredited METC has been given. All amendments will be notified to the METC that gave a favourable opinion.

12.4 Annual progress report

Not applicable, as this study will not be subject to the Medical Research Involving Human Subjects Act (WMO).

12.5 Temporary halt and (prematurely) end of study report

Within one year after the end of the study, the investigator/sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC.

12.6 Public disclosure and publication policy

The results of this cross-sectional study will be reported using the STROBE guidelines [17].
The results of this study will be presented (orally or poster presentations) at conferences and the final results will be published into relevant journals. Patients' anonymity will be ensured throughout every publication.

This study is funded by Stichting Coolsingel (reference number: 566), which will be mentioned during any oral or poster presentations. Additionally they will be mentioned in the acknowledgement section of each published paper.

Patients will be informed about the results of the study in case they specifically asked to be informed.

Agreements on authorship:

The current study is a multicentre study; therefore, any publication based on the results obtained during this study will not be made before the first multicentre presentation. This will be coordinated by the coordinating investigator and/or the epidemiologist.

All authors, mentioned under steering group (intellectual input), who provided significant input to the study and/or publication will receive an authorship position. The principal investigator of each participating centre will receive an authorship position.

Milea J.M. Timbergen, PhD candidate will be first author of the first publication. Olga Husson will be the final author of the first publication. The remaining authorships will be allocated in mutual agreement according to the final contribution to the paper. Additional publications will include persons from the steering group and the PI's from every including centre as authors. The order of authors will be determined in mutual agreement.
This study will be registered at clinicaltrials.gov (https:/clinicaltrials.gov)

13. STRUCTURED RISK ANALYSIS

Not applicable, as this study does not involve an experimental investigational or non-investigational product (see chapters 6 and 7).

13.1 Potential issues of concern

Not applicable, as this study does not involve an experimental investigational or non-investigational product.

a. Level of knowledge about mechanism of action

Not applicable.

b. Previous exposure of human beings with the test product(s) and/or products with a similar biological mechanism

Not applicable.

c. Can the primary or secondary mechanism be induced in animals and/or in *ex-vivo* human cell material?
Not applicable.

d. Selectivity of the mechanism to target tissue in animals and/or human beings
Not applicable.

e. Analysis of potential effect
Not applicable.

f. Pharmacokinetic considerations
Not applicable.

g. Study population
Not applicable.

h. Interaction with other products
Not applicable.

i. Predictability of effect
Not applicable.

j. Can effects be managed?
Not applicable.

13.2 Synthesis

Not applicable since this study does not involve an investigational or non-investigational product.

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Appendix 1. Questionnaires

Baseline questionnaire, version 1.0, October 29 2019, (Dutch)
Self-reported demographic data include age, sex, ethnicity, relationship status, family composition, educational level, employment status, physical and mental demands of current job, comorbidities will be collected using this baseline questionnaire. Additionally, clinical data regarding the DTF will be collected: tumour location, multiple DTF locations, received treatments, current treatment, recurrences. Health literacy will be assessed by one single item question (question 14). The baseline questionnaire (A) will be used to identify relevant subgroups (e.g. sex or age).

Outcomes of this questionnaire will be descriptive and are expressed as numbers with corresponding percentages.

Information regarding the pathology, treatment and outcome will be extracted from the (electronic) medical patient records by the researcher on the case report form (CRF). Details about which information is extracted from the (electronic) medical patient records can be found in paragraph 8.1.3. Patients will be made aware of this in the patient information file and will sign informed consent for this on the informed consent form.

Health care utilization, version 1.0, October 29 2019, (Dutch)
Health care utilization will be assessed by the health care utilization questionnaire. Patients will be asked about the following topics: satisfaction with received care, frequency of visits to the general practitioner / specialist, satisfaction with the follow-up schedule, preferences and needs for receiving care in a DTF expert centre, receiving additional care of support from professionals (medical and non-medical).

Outcomes of this questionnaire will be descriptive and expressed as numbers with corresponding percentages to explore health care utilization.

Decision-making, version 1.0, October 29 2019, (Dutch)
Six questions were designed to obtain information on how patients make medical decisions, what their current role is and what their preferred role, and one question regarding their awareness of their choices, the benefits and risks of certain treatment and whether they received support an advice are designed. Two questions were designed to gain insight into the reasons for choosing an active form of treatment.

Outcomes of this questionnaire will be descriptive and expressed as numbers with corresponding percentages.

EORTC QLQ-C30, version 3.0, (Dutch)
Health-related quality of life will be assessed with the EORTC QLQ-C30, version 3.0. This 30-item HRQoL questionnaire consists of five functional scales (physical, role, cognitive, emotional and social), a global quality of life scale, 3 symptom scales (fatigue, pain, nausea and vomiting) and a number of single items assessing common symptoms (dyspnoea, loss of appetite, sleep disturbance, constipation and diarrhoea) and perceived financial impact of the disease.

For the interpretation of the Global health related quality of life score (EORTC-QLQ-C30), the manuals of the European Organisation for Research and Treatment of Cancer (EORTC) will be used [18]. Each question will be scored: not at all (1), a little (2), quite a bit (3), very much (4). After linear transformation, all scales and single item measures range in score from 0-100. A higher score on the functional scales and global quality of life means better functioning and HRQoL, whereas a higher score on the symptom scales means more complaints [14]. The EORTC QLQ-C30 summary score will be calculated using the mean

scores of the function scales and the reversed mean scores of the symptom scales and represented as the mean of the combined 13 QLQ-C30 scale scores (financial impact and global health status excluded). A higher summary score represented a better outcome [15,16].

DTF-QoL, version 1.0, October 29 2019, (Dutch)

This topic is of particular interest for DTF patients because of the rarity of the disease with an incidence of 5.4 patients per million persons per year [9]. Even doctors sometimes do not know what the best approach for a particular patient is. Therefore we would like to know what the issues are that patients are dealing with in daily life.

We designed a 102-items questionnaire encompassing HRQoL issues that DTF patients might experience. The questions were designed based on the previous studies were the issues were identified and ranked by DTF patients and health care professionals (manuscript submitted to Quality of Life and Health Outcomes) [7,12]. Topics covered regard issues in several domains including: diagnosis, treatment, living with DTF, health care facilities for DTF. These questions have not been validated but serve as patient reported experience measure rather than patient reported outcome measure. The scores will be calculated using a Likert scale from 1-4. The mean scores will be calculated with standard deviation (SD), or median scores with an interquartile range (IQR). De prevalence will be calculated using the percentages of patients reporting this problem compared to the total population.

EQ-5D-5L, version 1.0, September 1, 2014, (Dutch)

The EuroQol five-dimensional questionnaire (EQ-5D-5L) is a descriptive system for the measurement of health. It measures health-related quality of life on five dimensions of health: mobility, self-care, usual activities, pain-discomfort, and anxiety/depression.[19] Additionally two questions aim to rank a patients' health (scale 0-100, with 100 representing a better health).

Each of the five dimension of the EQ-5D-5L can be divided into five levels of perceived problems; no problems (level 1), slight problems (level 2), moderate problems (level 3), severe problems (level 4) and extreme problems (level). Health states can be converted into single index values. The outcomes will be reported as frequency (proportion) of reported problems for each level and for each dimension. EQ- Visual Analogue Scale (VAS) data will be presented as a mean value with standard deviation. In case of skewed data, median values and IQR will be used.