COMPRehensive assessment of prevalence, risk factors and mechanisms of impaired medical and psychosocial health outcomes among Adolescents and Young Adults with cancer: the prospective observational COMPRAYA cohort study

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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

AE	Adverse Event
AVG/GDPR	General Data Protection Regulation; in Dutch: Algemene Verordening Gegevensbescherming (AVG)
AYA	Adolescent and Young Adult
BIPQ	Brief Illness Perception Questionnaire
BMI	Body Mass Index
BRP	Personal Records Database; in Dutch: Basisregistratie Persoonsgegevens
BRS	Brief Resilience Scale
CAM	Complementary and Alternative Medicine
CBC	Complete Blood Count
CBS	Statistics Netherlands; in Dutch: Centraal bureau voor de statistiek
CERQ	Cognitive Emotion Regulation Questionnaire
DT	Distress Thermometer
eCRF	Electronic Case Report Form
EORTC	European Organisation for Research and Treatment of Cancer
EQ-5D-5L	five-level EuroQol five-dimensional questionnaire
EU	European Union
HADS	Hospital Anxiety and Depression Scale
HRQoL	Health-Related Quality of Life
IC	Informed Consent
ICQ	Illness Cognition Questionnaire
LMR	Hospital discharge register; in Dutch LMR: Landelijke Medische Registratie
METC	Medical research ethics committee; in Dutch: Medisch-Ethische Toetsings Commissie (METC)
NCR	Netherlands Cancer Registry; in Dutch: Nederlandse Kanker Registratie
NEVO	Dutch Nutrients Database
NPR	Netherlands Perinatal Registry
PALGA	National pathology database
PAQ	Patient Autonomy Questionnaire
PHARMO database network	population-based network of electronic healthcare databases and combines data from different primary and secondary healthcare settings in the Netherlands.
PROFILES	Patient Reported Outcomes Following Initial treatment and Long term Evaluation of Survivorship

(S)AE	(Serious) Adverse Event
SOP	Standard Operating Procedure
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.
SQUASH	Short Questionnaire to Assess Health-Enhancing Physical Activity
SUSAR	Suspected Unexpected Serious Adverse Reaction
WMO	Medical Research Involving Human Subjects Act; in Dutch: Wet Medisch-Wetenschappelijk Onderzoek met Mensen

SUMMARY

Rationale: Childhood cancer survivorship attracts attention globally, because successes in treatment have led to increasing number of survivors who reach adulthood, in which survivorship issues affecting health-related quality of life (HRQoL) become prominent. Most paediatric patients are treated intensively with irradiation and/or chemotherapy, which put them at risk for early and/or late adverse medical and psychosocial events. In contrast, much less is known about adolescent and young adult (AYA) cancer patients, diagnosed between 18-39 years, who, with an 80% chance to survive, also have a long life ahead. AYA cancer patients, much more than children, suffer from delay in diagnosis, lack of centralization of care, age-adjusted expertise, and AYA follow-up care. AYAs typically present with a rare tumour: either with a paediatric malignancy (e.g. acute lymphoblastic leukaemia, paediatric brain tumours), a more typical tumour of AYA age (e.g. Hodgkin's disease, germ cell cancer, melanoma, thyroid cancer) or with an adult tumour at unusual young age (e.g. gastrointestinal, lung, breast carcinomas). Next to these differences in epidemiology, the tumour biology, developmental challenges (e.g. forming relationships, becoming financially independent, having children) and treatment regimens differ between AYAs and children, and therefore findings derived from childhood cancer survivors cannot be extrapolated to AYAs. Furthermore, novel treatments with targeted agents or immunotherapy are more likely to be administrated to AYAs compared to children. Finally, a rare group of incurable AYA cancer patients will survive for many years, for whom health outcome and supportive care intervention data are lacking.

Globally, so far, the identification of AYA cancer patient subgroups that might be more susceptible to poor health outcomes has not been systematically addressed. The role of sociodemographic and treatment-associated risks, external exposures (e.g. lifestyle) and host factors (e.g. genetic, biological, physiological); or combinations of influences for impaired (age-specific) health outcomes, remains largely unknown. Understanding who is at risk and why will support the development of evidence-based AYA prevention, treatment and supportive care programs and guidelines, in co-creation with AYA cancer patients.

Objective: To examine the prevalence, risk factors and mechanisms of impaired health outcomes (short- and long-term medical and psychosocial effects and late effects) over time among a population-based sample of AYA cancer patients.

Study design: Prospective, observational cohort study

Study population: All AYAs diagnosed (18-39 years at primary diagnosis) with cancer (any type) within the first 3 months after diagnosis (eligibility window of 1 month to ensure all eligible AYA cancer patients can be included) in one of the participating centres (or treated in one of these centres) in The Netherlands.

Main study parameters/endpoints: The main outcomes are medical (e.g. second tumour; survival; fertility) and psychosocial (e.g. distress) health outcomes. Other study parameters (covariates/moderators/mediators) are characteristics of the individual (e.g. age, sex, cultural background, partner status, educational level, occupation, tumour type, disease stage, body composition, comorbid conditions, coping style), characteristics of the environment (e.g. cancer treatment, lifestyle), and genetic and biological factors (e.g. family history of cancer, stress and inflammation markers (e.g. cortisol, IL-6), microbiome).

Nature and extent of the burden and risks associated with participation, benefit and group relatedness: On an individual level, patients who participate are asked to complete questionnaires on an annual basis for at least 10 years. All sample collections will take place at three time points: 0-3 months after diagnosis (baseline), 2 and 5 years; except blood for DNA analyses which will only take place at baseline. The collection of blood, hair and faeces at three occasions is minimally invasive and the risks of blood draws, hair and fecal sampling are negligible. All safety measures and procedures will be performed according to local guidelines. Patients will not experience direct benefit from participation in the COMPRAYA study.

By participating, patients will contribute to a better insight in the prevalence of impaired medical and psychosocial (age-specific) health outcomes in AYA and evidence on factors associated with these health outcomes. This will lead to better and more personalized cancer care and supportive care tools for future AYA cancer patients.

1. INTRODUCTION AND RATIONALE

Adolescents and young adults (AYA) are recognized as a distinct population within the oncology community due to the unique challenges they encounter including recognition, diagnosis, treatment and monitoring of their disease[1-3]. The US National Cancer Institute proposed defining AYA as those aged 15-39 years at diagnosis[2], however also concluded that this age range should be flexibly applied, depending on health care delivery system[4]. In The Netherlands, there is a clear distinction between centralized pediatric oncology (0-18 years), and adult oncology. Patients diagnosed with cancer between 18 and 39 years old are often called the "lost tribe" as they are too old to profit from the integrated pediatric care and, subsequently, are treated in the adult health care system in many different hospitals throughout the country.

Increasing incidence and limited progress in survival

Although cancer is a disease primarily affecting older adults, around 3800 AYAs are diagnosed with cancer in The Netherlands every year, which is around 5% of all invasive cancer diagnoses[5]. Over the last decades, the incidence of cancer among AYAs has slightly increased[6]. AYAs typically present with a rare tumor or a common tumor at an unusual age: either with a pediatric malignancy (e.g. acute lymphoblastic leukemia, pediatric brain tumors), a tumor of AYA age (e.g. Hodgkin's disease, germ cell cancer, melanoma, thyroid cancer) or, with an adult tumor (e.g. gastrointestinal, lung, breast carcinomas)[7]. Although five-year relative cancer survival for AYAs (~80%) has improved over time[3,8], progress made in survival of specific tumors lags behind that of children and older adults[9,10]. Potential reasons for the lack of progress in survival are insufficient awareness of cancer risk and symptoms among young patients and healthcare professionals resulting in diagnostic delays[11,12]; unique and incompletely understood tumor biology (cancers that are histologically indistinguishable across the age spectrum may be characterized by particular biological features in the AYA population)[7,13,14]; distinct age-related physiology, pharmacology and genomic properties with respect to cancer susceptibility and treatment[7]; unequal access to and low participation rates in clinical trials[1] and lack of age-adjusted treatments[15] and age-specific care ("I am treated like my 74-year-old grandma")[16].

AYA cancer experience

Adolescence, emerging and young adulthood are complex phases of life due to the many physical, emotional, cognitive and social transitions[17]. Important developmental tasks need to be achieved, such as forming one's own identity and a healthy body image, establishing autonomy, responsibility and independence, finishing education and starting a career, getting a relationship and having children[17]. A cancer diagnosis challenges AYAs' abilities to achieve these developmental milestones[18,19]. Emerging investigations demonstrate an extensive age-specific burden of cancer[20], for example, changes in physical appearance resulting from treatment (e.g. weight changes or hair loss) can negatively impact body image (looking different from peers) and interfere with self-esteem (avoiding social contacts) and identity development[17,21,22]. AYA cancer patients frequently report concerns regarding sexuality and

fertility issues[23-25] and often experience a diminished feeling of autonomy as they are forced to become dependent on parents or partner[26]. Furthermore, cancer treatment and late effects can interfere with completing education and getting a job, and thus contributing to increased risk for financial burden[27]. Although AYA cancer patients may face challenges similar to those of older and younger patients, including short-term (e.g. hair loss,[28] pain[29]) and long-term effects of cancer treatment (e.g. distress[30], fatigue[31] and cognitive problems[32]), and late effects (cardiovascular problems[33], second tumors[6,34-37]), the consequences are different in this phase of life. The way in which AYA cancer patients adjust to their cancer experience might have life-long implications for the quality of their survival[38-41].

Shortcomings in current research

With an 80% chance to survive, AYA cancer patients have a large proportion of their expected lifespan remaining. (Inter)nationally, large cohort studies exist that address many relevant long-term cancer-related health issues, but all from the perspective of tumor histology, rather than an AYA age-specific perspective. Given the age-related differences in tumor epidemiology, biology, developmental challenges and access to care, findings derived from childhood or older cancer cohorts cannot be extrapolated to AYAs. Globally, so far, the identification of AYA cancer patient subgroups that might be more susceptible to poor (age-specific) health outcomes has not been addressed in a systematic and coordinated way. The role of sociodemographic and treatment-associated risks, external exposures (e.g. lifestyle) and host factors (e.g. genetic, biological, physiological); or combinations of influences for impaired (age-specific) health outcomes, remains largely unknown. Understanding *who* is at risk and *why* will support the development of evidence-based AYA prevention, treatment and supportive care programs and guidelines.

Conceptual model to understand mechanisms of impaired health outcomes

The revised Wilson & Cleary conceptual model of patient outcomes (Figure 1)[42-44] was used for the selection of appropriate measurement parameters. The authors of the model present it as taxonomy of patient health outcomes that are linked with *characteristics of the individual, characteristics of the environment* and *biological and physiological* variables.

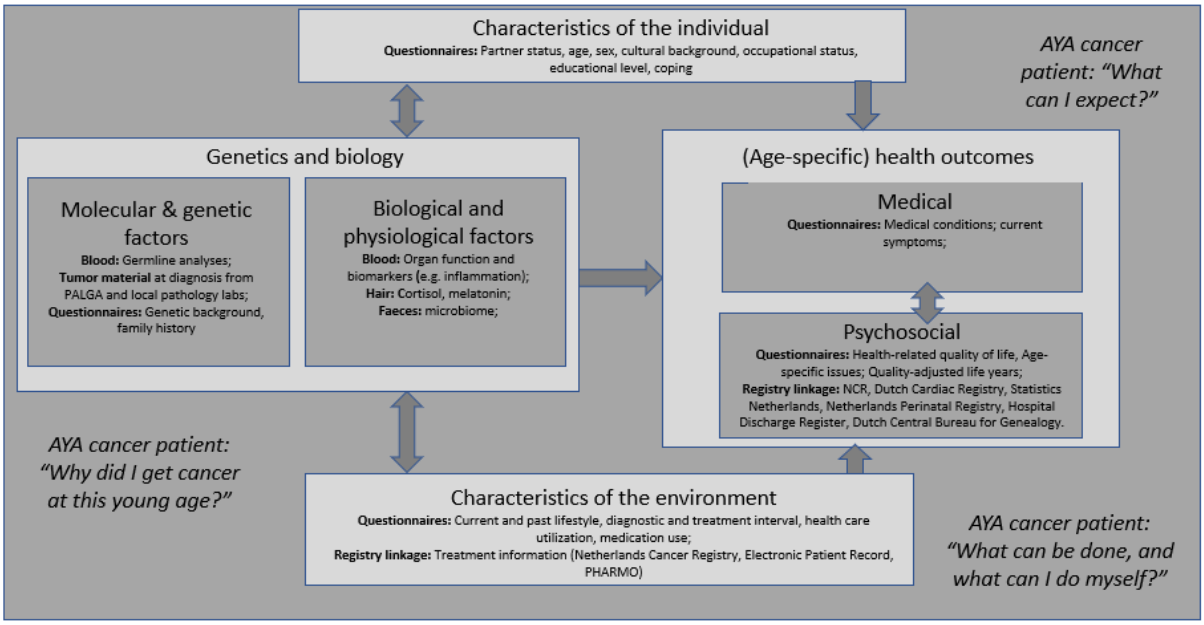

Figure 1. Revised Wilson & Cleary (1995) Model. Adapted from Wilson, I.B., & Cleary, P.D (1995). Linking Clinical Variables with Health-Related Quality of Life: A Conceptual Model of Patient Outcomes. JAMA. 273, 59–65 (Ferrans, C. E., et al. (2005). Conceptual model of health-related quality of life. J Nurs Scholarsh. 37, 336–342.)

The main research questions addressed in this study are:

(1) Who is at risk for impaired medical and psychosocial health outcomes? What is the role of characteristics of the individual (e.g. age, sex, cultural background, partner status, educational level, tumor type, disease stage, comorbid conditions, coping style), characteristics of the environment (e.g. cancer treatment, lifestyle), and genetic and biological factors (e.g. family history, genetic profile, body composition, inflammation markers, organ functions, metabolic syndrome, microbiome) on (age-specific) medical and psychosocial health outcomes?

A more specific example for a medical health outcome of interest for AYA with cancer: What is the effect of characteristics of the individual (age, sex, ethnicity, tumor type, disease stage, medical conditions, distress, coping style), characteristics of the environment (type of systemic or local treatment and dose and related adverse events, medication use, lifestyle factors including physical activity, smoking, alcohol consumption and dietary intake) and genetic (family history cardiovascular disease, genetic disposition), biological (IL6 and other inflammation markers in blood, cortisol levels hair, gut microbiome) and physiological factors (body composition, organ functions) on later cardiovasculair outcomes?

A more specific example for a psychosocial health outcome of interest for AYA with cancer: What is the role of characteristics of the individual (sex, ethnicity, partner status, having children, educational level, breadwinner status, illness perceptions, coping style, resilience, autonomy, spirituality, tumor type, disease stage), characteristics of the environment (type of treatment, lifestyle), biological factors (inflammation markers in blood, cortisol and melatonin levels in hair) on AYA impact of cancer?

(2) What is the prevalence of impaired (age-specific) medical (e.g. second tumor) and psychosocial (e.g. distress) health outcomes among AYA cancer patients at each point in time?

(3) What is the course of (age-specific) medical and psychosocial health outcomes among AYA cancer patients over time?

(4) Why is a person at risk? What are the (underlying) mechanisms of impaired health outcomes?

2. OBJECTIVES

Primary Objective:
- To identify individual, environmental, biological and psychological characteristics of AYA cancer patients who are at high risk for impaired medical and psychosocial health outcomes. In other words: To develop a prediction model for impaired medical and psychosocial health outcomes (at baseline, 2-, 5- and 10-year follow-up).

Secondary Objective(s):
-To assess the prevalence of impaired (age-specific) medical (e.g. second tumour) and psychosocial (e.g. social isolation) health outcomes at each time point (at baseline, 2-, 5- and 10-year follow-up).

Exploratory Objective(s):
-To analyse the course of medical and psychosocial health outcomes over time (all timepoints needed)
-To analyse mediating mechanisms associated with impaired health outcomes in AYA cancer patients (at baseline, 2-, 5- and 10-year follow-up).

Other Objective(s):
-To form a prospective observational cohort of patients diagnosed with cancer at AYA age, and follow them over time until death.

3. STUDY DESIGN

We will conduct a nationwide, multicenter, prospective, population-based, observational cohort study. All AYA cancer patients (aged 18-39 years at primary cancer diagnosis), diagnosed or treated in one of the participating hospitals, within the first 3 months post diagnosis, and alive at study invitation, are eligible to participate.

List with participating hospitals that gave consent:
Netherlands Cancer Institute– Antoni van Leeuwenhoek Hospital (NKI-AvL)
Radboud university medical center (Radboudumc)
University Medical Center Groningen (UMCG)
University Medical Center Leiden (LUMC)
Erasmus Medical Center (ErasmusMC)
Maastricht Medical Center (MUMC+)
University Medical Center Utrecht (UMCU)
Amsterdam MC – location AMC
Amsterdam MC – location VUMC

4. STUDY POPULATION

4.1 Population (base)

All AYA cancer patients, diagnosed at age 18-39 years in one of the participating hospitals, receive an invite within the first 3 months after diagnosis (eligibility window of 1 month to ensure all eligible AYA cancer patients can be included) and will be asked to complete the COMPRAYA questionnaires on an annual basis up to 10 years after diagnosis (again with a window of 2 months before and after). Collection of clinical data and samples (e.g. faeces, hair and blood) will be done at baseline, 2, and 5 years after diagnosis. Questionnaire data collection is guaranteed by the PROFILES registry and patients will give informed consent for linkage with registry data, which makes long-term follow-up possible.

4.2 Inclusion criteria

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

- Pathological confirmed cancer diagnosis;
- Age 18 – 39 years at time of first cancer diagnosis;
- Able to understand the informed consent form;
- Provide written informed consent.

4.3 Exclusion criteria

- Mentally incompetent patients based on the opinion of treating physician .
- Inability to understand the Dutch language
- Life expectancy less than 6 months based on the opinion of treating physician .

4.4 Sample size calculation

Recruitment will take place over a 4.5-year period. With an incidence of 3800 new AYA cancer diagnoses/year, 1-year survival of 93%, nationwide coverage of 60% by participating hospitals, response rate of 40%, we aim to recruit 4000 AYA cancer patients in this period.

The sample size needed for regression analyses for our primary aim is based on the rule of thumb of Green [book discovering statistics using SAS, Andy Field, 2010, page 197]. There are two rules, one for the minimum number for optimal fit of the model and one to test the individual predictors. Minimum number for optimal fit: 50+8k (k=number of predictors). If we assume 25 predictors (characteristics of the individual (e.g. age, sex, cultural background, partner status, educational level, tumor type, disease stage, comorbid conditions), characteristics of the environment (e.g. cancer treatment, lifestyle, and genetic and biological factors) in the model, then we need 50+200=250 patients. Minimum number for individual predictors is 104+k=129. To be able to do subgroup analyses among patients we also need sufficient power in subgroups.

The secondary endpoint will be describing the proportion of patients with an impaired score for each health outcome at each time point.

No formal sample size calculation is conducted for the exploratory objectives. This project is designed to continuously include new AYA cancer patients (depending on funding) and will provide an on-going source of patient data to answer secondary research questions.

5. TREATMENT OF SUBJECTS

Not applicable

5.1 Investigational product/treatment

Not applicable

5.2 Use of co-intervention (if applicable)

Not applicable

5.3 Escape medication (if applicable)

Not applicable

6. INVESTIGATIONAL PRODUCT

Not applicable

6.1 Name and description of investigational product(s)

Not applicable

6.2 Summary of findings from non-clinical studies

Not applicable

6.3 Summary of findings from clinical studies
Not applicable

6.4 Summary of known and potential risks and benefits
Not applicable

6.5 Description and justification of route of administration and dosage
Not applicable

6.6 Dosages, dosage modifications and method of administration
Not applicable

6.7 Preparation and labelling of Investigational Medicinal Product
Not applicable

6.8 Drug accountability
Not applicable

7. NON-INVESTIGATIONAL PRODUCT
Not applicable

7.1 Name and description of non-investigational product(s)
Not applicable

7.2 Summary of findings from non-clinical studies
Not applicable

7.3 Summary of findings from clinical studies
Not applicable

7.4 Summary of known and potential risks and benefits
Not applicable

7.5 Description and justification of route of administration and dosage
Not applicable

7.6 Dosages, dosage modifications and method of administration
Not applicable

7.7 Preparation and labelling of Non Investigational Medicinal Product
Not applicable

7.8 Drug accountability
Not applicable

8. METHODS

8.1 Study parameters/endpoints

Medical health outcomes & psychosocial health outcomes

Other study parameters / predictors (if applicable)

*Characteristics of the individual (*Sociodemographic characteristics, disease characteristics, psychosocial characteristics)

Characteristics of the environment (Treatment characteristics, Lifestyle)

Genetic and biological factors (Genetics, Biology, Physiological characteristics)

8.2 Randomisation, blinding and treatment allocation

Not applicable

8.3 Study procedures

8.3.1 Invitation and informed consent

Every 2 weeks, the local COMPRAYA research nurse will receive a list, derived from the NCR, of AYAs diagnosed with cancer approximately 0-3 months ago. A 1-month eligibility window for baseline recruitment ensures all eligible AYA can be included.

The local COMPRAYA research nurse will receive patients' hospital number, if known, otherwise name and date of birth derived from the NCR. The local COMPRAYA research nurse, in consultation with the treating physicians, will check the patient selection on eligibility criteria and invite eligible patients for the study, on behalf of their treating physician. The local COMPRAYA research nurse, in consultation with the treating physicians, will also check the completeness of the NCR selection, missing patients meeting the inclusion criteria will also be invited on behalf of their treating physician. AYA cancer patients will receive an invitation package by mail consisting of a letter, patient information and informed consent. The local COMPRAYA research nurse will contact the patients one week after sending the invitation package to give more information if necessary, check whether they want to participate and schedule an appointment at the outpatient clinic (preferably simultaneously with other routine appointments). A unique personal study number will be assigned to each AYA participant.
Participants will receive an information letter how to fill in a questionnaire via PROFILES (Patient Reported Outcomes Following Initial treatment and Long term Evaluation of Survivorship). This includes a link to a secure website (www.profielstudie.nl), a login name, and a password. If the patient prefers written rather than digital communication, paper questionnaires can be completed and returned to the researcher using a return envelope. All procedures will be in line with the Dutch/European privacy legislation (AVG/GDPR).

Once the AYA cancer patient has consented to participate and accomplished all the planned assessments at baseline, we follow them prospectively by annually sending a selection of questionnaires (table 1). Biological samples will be collected at baseline, 2 and 5 years after diagnosis (germline specimens only at baseline) and thereafter when additional funding is in place).

8.3.2 Measures

Table 1 describes the schedule of assessments

Medical and psychosocial health outcomes (questionnaires, registries)

-AYA Impact of cancer

To identify the positive and negative psychosocial impact of cancer, participants will complete a modified version of the 18-item Life Impact Checklist [45,46] at each time point. Nine of the 18 items are from the original checklist that was used in a study of breast cancer patients [46], and nine items related to other life domains (body image, future goal setting, plans for education and work) will be included that have been identified as important to AYA cancer patients [47,48]. On a five-point Likert scale, patients specify whether cancer had a negative, positive or no impact on 18 life domains (1—very negative impact; 2—somewhat negative impact; 3—no impact; 4—somewhat positive impact; 5—very positive impact). A participant will be deemed to perceive 'a negative impact' on a life domain if their response was 1 or 2 to that item in the questionnaire, while a response of 4 or 5 indicates 'a positive impact' on that life domain.

-Health-related quality of life

The EORTC QLQ-C30 is a 30-item HRQoL questionnaire consisting 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 (dyspnea, loss of appetite, sleep disturbance, constipation and diarrhea) and perceived financial impact of the disease[49]. After linear transformation, all scales and single item measures range in score from 0-100. A higher score on the functional scales and global QoL means better functioning and HRQoL, whereas a higher score on the symptom scales means more complaints [50]. To determine cut-off for impaired HRQoL, the thresholds for clinical importance of Giesinger et al will be used [51].The EQ-5D-5L is a descriptive system for the measurement of health. It measures HRQoL on five dimensions of health: mobility, self-care, usual activities, pain-discomfort, and anxiety/depression [52]. Dutch cut-off scores are used to determine impaired health outcomes [53]. Both questionnaires will be part of the questionnaire package at each time point.

-Psychological distress

Psychological distress will be assessed at each time point with the Hospital Anxiety and Depression Scale (HADS), with seven items each for assessing symptoms of anxiety and depression [54]. All items will be scored on a 0- to 3-point scale, with higher scores indicating more symptoms. A score on the subscale of ≥8 indicates a substantial level of psychological distress [54-56].

-Medical history/conditions will be assessed by the COMPRAYA research nurse at the time of the clinic visit with a short version of the questionnaire used in the St. Jude Childhood Cancer Survivorship study (e.g. hearing/ vision/ speech, urinary, hormonal, heart and circulatory, respiratory, digestive, brain and nervous system, child births and malignancies). An impaired medical health outcome is defined as having the medical condition at time of assessment. At baseline medical history is assessed by the COMPRAYA research nurse, at 2, 5 and 10-year follow-up all changing medical conditions will be registered via the patient-reported questionnaire.

-*Linkage* will be done with the NCR (second malignancies), PHARMO Database Network, BRP (Survival status), Dutch Cardiac Registry (cardiac interventions, hospitalizations), Statistics Netherlands (CBS) (cause-of-death, work-related outcomes including individual income, type of occupation, number of working hours, number of contracts, receipt of disability benefits, unemployment benefits and welfare), Netherlands Perinatal Registry (NPR) (pregnancy and children), Hospital Discharge Register (LMR) (hospitalizations and referrals) and Dutch Central Bureau for Genealogy (mortality).

Characteristics of the individual and environment

Sociodemographic data including age, gender, marital status, children, education, and breadwinner status (sole/shared) will be obtained via the COMPRAYA research nurse at baseline and all changes at follow-up will be registered via the patient-reported questionnaire. Clinical information including cancer site, size, stage, grade, pathological stage, month/year of diagnosis, received (and future) treatment(s), i.e., surgery, radiation, chemotherapy, immunotherapy, targeted treatment, hormonal therapy or combination, medication, recurrence(s) of the disease and comorbidity will be obtained from the medical records, the Netherlands Cancer Registration (NCR), and/or via self-report. The data will be registered in the eCRF.

All adverse events occurring after treatment and the intensity of these adverse events will be graded according to the NCI Common Toxicity Criteria (NCICTCAE, Version 4.03, final 7 April 2009; see http://evs.nci.nih.gov/ftp1/CTCAE/About.html

Data on drug use will be obtained from the PHARMO database, which was previously successfully done for other PROFILES studies. The drug dispensing database of PHARMO contains complete longitudinal information on the dispensed drug, prescriber, date and amount of dispensing, prescribed dose regimens and thus on duration of drug use obtained from community pharmacies[47].

Questions on diagnostic and treatment interval [48, 49] will be registered by the COMPRAYA research nurse at baseline. Questions on clinical trial participation, use of over the counter medication and complementary and alternative medicine (CAM) will be registered by the COMPRAYA research nurse at baseline and added to the questionnaire package at all follow-ups.

-**Psychosocial characteristics** (questionnaire)

Coping style

At baseline, 2- 5- and 10-year follow-up, coping *w*ill be assessed with the Cognitive Emotion Regulation Questionnaire (CERQ) [57]. The CERQ is a multidimensional questionnaire constructed in order to identify the cognitive coping strategies someone uses after having experienced negative events or situations. Contrary to other coping questionnaires that do not explicitly differentiate between an individual's thoughts and his or her actual actions, the present questionnaire refers exclusively to an individual's thoughts after having experienced a negative event. Patients will complete this questionnaire at baseline, 2-, 5,- 10 year follow-up.

Resilience

At baseline, 2- 5- and 10-year follow-up, resilience will be assessed by the brief resilience scale (BRS) [58]. Resilience is a skill which helps people to recover from a life event. People with high (perceived) resilience have the ability to move on faster after a setback. The BRS is a 6-item scale with a 5 point Likert-scale. Patients will complete this questionnaire at baseline, 2-, 5,- 10 year follow-up.

Illness perceptions

At baseline, 2- 5- and 10-year follow-up, illness perceptions will be assessed using the Brief Illness Perception Questionnaire (B-IPQ), a nine-item instrument used to assess cognitive and emotional representations of the illness [59]. The B-IPQ uses a single-item scale approach to assess perceptions on a continuous linear 0-10 point scale. Five of the items assess cognitive illness representations: 1. How much does your illness affect your life (consequences); 2. How long do you think your illness will continue (timeline); 3. How much control do you feel you have over your illness (personal control); 4. How much do you think your treatment can help your illness (treatment control); 5. How much do you experience symptoms from your illness (identity). Two items assess emotional representations: 6. How concerned are you about your illness (concern) and 7. How much does your illness affect you emotionally (emotional representation). One item assesses illness comprehensibility:

8. How well do you understand your illness (coherence). Answer scales of three items (personal control, treatment control and coherence) were reversed for statistical analyses to get the same response direction as the other five items. A higher score means worse illness perception.

Autonomy

At each time point, the short (4-item) version of the Patient Autonomy Questionnaire (PAQ) will be added to the questionnaire package to assess autonomy problems [60].

Spirituality

At baseline, 2- 5- and 10-year follow-up, the 6-item SPIRIT questionnaire will be used to measure spirituality in 5 dimensions: experiential, cognitive, coping, moral and social [61].

-**Lifestyle and other environmental exposures** (questionnaire)

We will use questions previously used in American National Institute of Health studies on life-time smoking history and current smoking status, lifetime alcohol consumption history and current alcohol consumption, history of and current recreational drug use, history of previous illnesses, disorders, lifetime physical activity history, past and present sunbathing behavior. The Short Questionnaire to Asses Health enhancing physical activity (SQUASH) will be used to assess physical activity [62]. The COMPRAYA research nurse will register the answers of the patients at baseline, patients will complete questionnaires on current lifestyle behavior at each time point by themselves.

Food intake will be assessed by asking patients to register all foods and drinks they had taken during the day using the 'Eetmeter' from the Dutch 'Voedingscentrum'. Participants will be asked to complete the Eetmeter at baseline, 1-, 2-, 5-, and 10 year follow-up for three consecutive days (including one day in the weekend). The Eetmeter is connected to the Dutch Nutrients Database (NEVO) so the quantity of macro- and micronutrients will be calculated immediately. Patients participating in the study will receive a link to create an account for the Eetmeter. When patients have registered their food intake, results will be sent to the secure environment of PROFILES. Patients will get access to their results if they indicate they would like to receive these.

-Costs related to productivity and medical consumption
We will use the Productivity Cost Questionnaire (iPCQ) to evaluate the impact of disease on the productivity of a person and the Medical Consumption Questionnaire (iMCQ) gaining more insight in the frequently occurring contacts with health care providers[63]. The combination of these two questionnaires will be used for the measurement of costs. Answers on the questionnares will be registered by the COMPRAYA research nurse on baseline and the questionnaires will be completed by patients themselves at each follow-up assessment.

PROductivity and DISease Questionnaire (PRODISQ) will be used to assess all relevant aspects of the relationship between health and productivity including absence from work, compensation mechanisms that may reduce productivity loss, reduced productivity at work (efficiency losses) and productivity costs at the level of organizations[64]. Answers on the questionnares will be registered by the COMPRAYA research nurse on baseline and the questionnaires will be completed by patients themselves at each follow-up assessment.

Genetics and biology

-**Genetic background and family history**
For synoptic reporting of the occurrence of cancer in first and second degree relatives, the standard list of the Radboudumc outpatient hereditary cancer clinic will be used and added to the baseline COMPRAYA research nurse questionnaire.

-**Special phenotypic features** of the patient (questionnaire):
As genetic cancer predisposition may also be associated with other phenotypic features a questionnaire is made to synoptically report features, e.g. head circumference, skin lesions, cleft lip, an aberrant number of fingers or toes, number of miscarriages. This specific questionnaire will also be added to the baseline COMPRAYA research nurse questionnaire.

-**Tumor material** (PALGA linkage):
Patients are asked to provide consent for use of tumor and normal material, and data that is already registered in the nationwide PALGA system. In addition, participants are asked to provide consent for the use of tissue material of recurrences or new malignancies, and data concerning these new events.

-Blood (hospital visit):
At baseline, at 2 years and at 5 years, blood of AYA cancer patients will be collected during a (regular follow-up) visit after an overnight fasting by venipuncture at one of the participating hospitals using a standard protocol (accompied with a standard questionnaire).

To minimize possible differences in the processing of the samples for analysis, the blood will be processed according to the COMPRAYA SOPs and temporarily stored in the participating hospitals. On a regular basis, the blood will be collected from the hospitals and, analyzed and stored in line with our research questions at the Netherlands Cancer Institute.
Study blood collection serves two purposes:

1) Germline DNA for research on cancer susceptibility genes, SNP-array, methylation profile and telomere length
2) Biomarkers of impaired health outcomes (metabolic syndrome; markers of inflammation, fertility hormones; methylation profile; markers of the Senescence-associated secretory phenotype (SASP); biochemical markers for cardiovascular damage; telomere length assessed in white blood cell DNA as a measure of accelerated ageing)

For these purposes, we will collect the following blood samples:
Standard blood set:
EDTA 1x 10 ml tube
Li-Heparine 1x 10 ml tube
SST-tube (with gel) (8.5 ml)
Cell-free DNA 2x 10 ml Streck tube (only baseline):
EDTA for DNA 1x 10 ml
Plasma samples will be processed within 4 hours of collection and stored at –80°C until further analyses.

Assessments for standard follow-up care will also be used (i.e. CBC, cardiovascular risk profile; renal and liver functions, glucose, lipids, urine albumin/creatinine).

-**Faeces**:
At baseline, at 2 years and at 5 years, AYA cancer patients from 3 participating sites (AvL; UMC Groningen; Radboudumc) will be asked to collect faeces samples at home the day before, or the day of assessment/blood collection (accompied with a standard questionnaire). The samples can be sent by mail at room temperature to the NKI-AvL where it will be aliquoted and stored at -80° until DNA extraction. These samples will be used to evaluate exploratory biomarkers (microbiome), which may be predictive for impaired medical health outcome endpoints.

-**Hair**:
Cortisol measurement in hair is a relatively new method that allows for assessments of *chronic* stress over time. Levels of melatonin can be detected in blood and saliva, but, similar to cortisol, melatonin is also stored in the hair, allowing for stable assessments of melatonin production over extended periods of time. Melatonin can act as an indicator for prolonged sleep disruption[65].

At baseline, at 2 years and at 5 years, hair sampling will be done by the trained COMPRAYA research nurse in the hospital. For hair sample collection for follow-up, participants will be asked to self-collect their hair samples according to the accompanying instruction and complete the accompied questionnare, and return by postal mail.
All hair samples will be sent to the Netherlands Cancer Institute and stored in a dark place at room temperature until analysis. At the end of the study, the hair samples will be sent in packages of multiple samples by postal mail to *Erasmus Medical Center, department of Clinical Chemistry*. Mean cortisol and melatonin concentrations will be assessed per 1 cm hair segment.

-**Physiological characteristics** (hospital):
Physical examination during a hospital visit will include: Standardized resting blood pressure and heart rate, body composition (BMI (height, weight, waist-, hip-, and calf circumference), bioimpedance, grip strength.

Bioimpedence
Whole-body single frequency (SF) (50 kHz) BIA measurements were performed according to Standard Operating Procedures by trained personnel, using Bodystat 500 (Bodystat Ltd., Isle of Man, British Islands). Patients laid in supine position on the examination table, and had their right hand and foot cleaned with alcohol. For each patient two new electrodes were placed on the right hand, and two new electrodes on the right foot. Raw BIA data (impedance, resistance, reactance, and phase angle) were registered in electronic medical records. Estimates of FFM (in kg, %, and kg/m2), and FM (in kg, %, and kg/m2) were obtained, using the Kyle equation.

Percentile estimates for the fat free mass index (FFMI) (kg/m2), and fat mass index (FMI) (kg/m2), based on Schutz, were used to compare anthropometric outcomes of patients to healthy people of similar age, and gender in clinical practice.

Grip strength
All handgrip tests were executed with the dominant hand using the Jamar system, consisting in an adjustable handgrip handle (standard JD configuration) equipped with in-build compression load cell (capacity=0-90kg, accuracy=<1% of rated load) and connected via a strain gauge amplifier to a computer. This device allows continuous monitoring and recording of the force exerted on the handgrip handle. All data were sampled at 100Hz (low pass filtered, 10Hz) and stored on a computer for further analysis. The system was calibrated prior to the start and checked during the study by applying a 20 kg load to the Jamar handle. Before each assessment session a zero-calibration was performed in order to adjust for environmental conditions (ambient temperature). In order to avoid in-between assessment zero-calibrations, the handgrip handle will be calibrated in position 2 (middle grip position) and maintained in that position for all patients. Patients will be asked to squeeze the handle as hard as possible for 3 times with 30 seconds interval. Afterwards, subjects were instructed to maintain this maximal pressure as long as possible. The time (in seconds) during which GS

dropped to 50% of its maximum was recorded as FR (time to fatigue) and the maximal grip strength value reached during the test as grip strength max.

Table 1: Schedule of assessments

	Screening/ baseline	**Follow-up** 1 year	**Follow-up** 2 year	**Follow-up** 3,4,6,7,8,9 year	**Follow-up** 5 year	**Follow-up** 10 year
		(profiles only)		(profiles only)		
Informed consent	X					
Background characteristics[1]	X	x	x	x	x	x
Clinical characteristics	X		X		X	X
Genetic background and Family history / Special phenotypic features	X					
Lifestyle and other environmental exposures[2]	X		x		x	x
Medical history/conditions	X		x		x	x
Physical examination/ vital parameters[3]	X		X		X	
Blood sample + standard questionnaire	X		X		X	
Faeces sample + standard questioannaire[4]	X		X		X	
Hair sample + standard questionnaire	X		X		X	
Questionnaires						
Impact cancer[5]	X	X	X	X	X	X
Health-related quality of life[6]	X	X	X	X	X	X
Psychological distress[7]	X	X	X	X	X	X
Psychosocial characteristics[8]	X		X	X	X	X
Costs related to productivity and medical consumption[9]	X	X	X	X	X	X
Food intake diaries/Eetmeter	X	X	X		X	X
Survival	----------→					

1. Age, gender, Ethnicity, postal code, partner status, living situation, education, employment, income, siblings, parenthood
2. Smoking, alcohol, drugs, exercise (SQUASH), nutrition, sun behavior, sedentary behavior, CAM
3. Blood pressure, heart rate, BMI, grip strength, bio-impedance measurement
4. Faeces only collected at AvL, radboudumc and UMCG
5. 18-item Life Impact Checklist
6. EORTC QLQ-C30; EQ5D
7. HADS
8. BIPQ, CERQ, BRS, PAQ, SPIRIT
9. iMCQ, IPCQ, PRODISQ

We are aware that the number of assessments and the length of our questionnaire could be burdensome for patients. Nevertheless, previous PROFILES studies show that patient do not have problems with donating blood or hair samples. With regard to the questionnaires, we will acknowledge the length and advise patients to complete the questionnaire over 2 days if they feel tired or are stretched for time when completing the questionnaire. Patients who fill in the online questionnaire can stop and save their data at each desired moment. When they login again they can continue with the question were they stopped. At baseline, most of the data will be collected by the COMPRAYA research nurse. This personal contact between COMPRAYA research nurse (often also AYA clinical nurse specialist) and AYA cancer patient will hopefully strengthen the relationship and result in lower attrition rates. Furthermore, AYA cancer patients are actively involved as advisors in the COMPRAYA study set-up.

We expect that the baseline assessments will take 60-90 minutes; 2 and 5 year follow-up 60 minutes and all other follow-up assessments 30 minutes.
Although patients will not directly benefit from participation in the COMPRAYA study we will highlight the importance of the study to improve care and outcomes for future AYA cancer patients. In addition, next to the COMPRAYA study, we will create an online “Young and Cancer” Platform together with and for AYAs where age-specific information, support and bespoke interventions will become available for the study participants and all other AYA cancer patients. This online “Young and Cancer” will be strongly linked to the national AYA healthcare network.

8.4 Withdrawal of individual subjects

AYA cancer patients can leave the study at any time for any reason if they wish to do so without any consequences. The investigator can decide to withdraw a subject from the study for urgent medical reasons. Data and already used material will be used until the date of withdrawal.

8.4.1 Specific criteria for withdrawal (if applicable)

Not applicable

8.5 Replacement of individual subjects after withdrawal

Not applicable

8.6 Follow-up of subjects withdrawn from treatment

The investigators will not follow up subjects that withdraw from the study. Subjects can leave the study at any time for any reason if they wish to do so without any consequences.

8.7 Premature termination of the study

This concerns an observational cohort study, with continuous inclusion of new participants and premature termination of the study is not anticipated.

9. SAFETY REPORTING

9.1 Temporary halt for reasons of subject safety

In accordance to section 10, subsection 4, of the WMO, the sponsor will suspend the study if there is sufficient ground that continuation of the study will jeopardise subject health or safety. The sponsor will notify the accredited METC without undue delay of a temporary halt including the reason for such an action. The study will be suspended pending a further positive decision by the accredited METC. The investigator will take care that all subjects are kept informed.

9.2 AEs, SAEs and SUSARs

9.2.1 Adverse events (AEs)

Adverse events are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to the study. All adverse events reported spontaneously by the subject or observed by the investigator or his staff will be recorded.

9.2.2 Serious adverse events (SAEs)

Not applicable

9.2.3 Suspected unexpected serious adverse reactions (SUSARs)

Not applicable

9.3 Annual safety report

The sponsor will submit, once a year throughout the inclusion period, a safety/progress report to the accredited METC

9.4 Follow-up of adverse events

All AEs will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist.
SAEs are not expected in this observational study

10. STATISTICAL ANALYSIS

All statistical analyses will be performed using R software. All statistical tests will be two-sided and differences considered significant if $p<0.05$. Missing items in the questionnaire will be handled as follows. If (an) item(s) from a multi-item scale is/are missing, and at least half of the items from the scale have been answered, then scale scores are calculated ignoring any items with missing values, which is the same as assuming that the missing items have values equal to the average of those items. If less than half of the items from the scale have been answered, then the scale score is set to missing. For single-item measures, score is also set to missing.

10.1 Primary study parameter(s)

Primary research question: Who is at risk for impaired health outcomes? What is the role of characteristics of the individual (e.g. age, sex, cultural background, partner status, educational level, tumor type, disease stage, comorbid conditions), characteristics of the environment (e.g. cancer treatment, lifestyle), and genetic and biological factors (e.g. family history) on (age-specific) medical and psychosocial health outcomes?

In preliminary analysis differences in outcomes between predefined groups (e.g. tumor types, gender) will be examined using chi-square statistics for categorical variables and independent t-tests, ANOVA or their nonparametric equivalences (Mann-Whitney U, Kruskall-Wallis tests) for continuous variables. Clinically meaningful differences will be determined with Norman's 'rule of thumb'[65], or the method of Cocks for the EORTC QLQ-C30[50]. Univariable logistic regression models will be fitted to test the association between potential risk factors (characteristics of the individual, environment and genetic and biological factors) and probability of impairment. The multivariable model will include all variables statistically significant (at $p<0.1$) in univariable analysis. A backward selection method will be used to identify a parsimonious model per outcome. Bonferroni correction (six primairy outcomes (medical conditions, health care consumption, AYA Impact of cancer, health-related quality of life, psychological distress, productivity) will be applied making a p-value of 0.05/6= 0.008 significant.

10.2 Secondary study parameter(s)

What is the prevalence of impaired (age-specific) medical (e.g. second tumor) and psychosocial (e.g. distress) health outcomes among AYA cancer patients at each time point?

Proportion with 85% CI will be used to describe the AYA cancer patient population and prevalence of impaired health outcomes.

10.3 Other study parameters

What is the course of impaired (age-specific) medical and psychosocial health outcomes among AYA cancer patients over time?

We will carry out repeated analyses using linear mixed models, which accounts for the intra-patient dependency of the repeated measures. Missing outcomes will be assumed missing at random (MAR). An advantage of linear mixed models is that all patients can be included in the analyses, regardless of whether they have been missing some follow-up measurements.

Why is a person at risk? What are the (underlying) mechanisms of poor health outcomes (e.g. coping style, genetic makeup, cortisol levels, inflammation)?

This research question is explorative. Moderation (a third variable that affects the strength of the relationship between an outcome and independent variable) will be tested by adding an interaction term to the regression models described above according to the principles of Baron and Kenny[67]. Mediation (another variable explains the relationship between the outcome and the independent variable) will be tested according to the principles of Baron and Kenny and via the Sobel test[68].

The variables listed in section 8.1.2 will be used for description of the AYA patient group and they will be analyzed as covariates.

10.4 Interim analysis (if applicable)

Not applicable

11. ETHICAL CONSIDERATIONS

11.1 Regulation statement

This study will be conducted according to the principles of the Declaration of Helsinki (64th WMA General Assembly, Fortaleza, Brazil, October 2013) and in accordance with the Medical Research Involving Human Subjects Act (WMO), and this study protocol.

11.2 Recruitment and consent

In consultation with the treating clinician, the local COMPRAYA research nurse fully explains the study to the patient.
During recruitment, a written patient information form giving details of the study will be provided to the patient to read and retain. After the patients have had the time they need to consider the information and have been encouraged to ask questions, they will be asked to give informed consent by signing and dating an informed consent form. All informed consent forms should be countersigned and dated by qualified and trained personnel (local COMPRAYA research nurse/ treating physician).
Written informed consent will be obtained before any study procedures will be performed. Procedures that are part of standard care and not done for study-specific purposes for this study, can occur before informed consent is obtained. The original of the informed consent form will be filed according to local practices in the study file or patient file. A copy will be given to the patient. The patients have the right to withdraw from the study at any time, without giving an explanation and without prejudice to their subsequent care.

The informed consent will consist of different items that are mandatory for inclusion. Schedule of assesments can be found in table 1.

Longitudinal clinical data collection (extraction from medical records and other registries); longitudinal collection of patient-reported outcomes via validated questionnaires (at outpatient clinic and paper or online questionnaires); collection of blood samples for COMPRAYA study purposes or secondary research initiatives; collecting vital parameters (bio-impedence measures and grip strength; usage of tumor and normal tissue stored in the nationwide National Pathology Database (PALGA) system; use of material and data from tumor recurrences or new malignancies.

Faeces and hair samples for COMPRAYA study purposes or secondary research initiatives and hair sample for COMPRAYA study purposes or secondary research initiatives.

Informed consent for invitation to participate in studies aimed at detection of germline cancer-predisposing mutations

11.3 Objection by minors or incapacitated subjects (if applicable)

Not applicable

11.4 Benefits and risks assessment, group relatedness

Patients will not experience direct benefit from participation in the COMPRAYA study. Since this is an observational study, apart from the blood sampling there are no additional risks associated with participation (blood draw will by preference be done during a regular blood draw needed for routine care. The risk of a blood draw is negligible).

By participating, patients will contribute to the evidence on factors associated with medical and psychosocial (age-specific) health outcomes. This may lead to better and a more personalized cancer care for future patients. Clinical parameters will be collected during a COMPRAYA hospital visit and derived from medical charts. Consenting patients will be asked to fill out standard questionnaires (approximately 60-90 minutes for baseline questionnaire together with COMPRAYA research nurse and 30 minutes for each follow-up questionnaire). Blood samples will be drawn during a routine blood sampling or in the context of the COMPRAYA hospital visit to assess clinical and physiological parameters.

11.5 Compensation for injury

The sponsor/investigator has obtained dispensation from the statutory obligation to provide insurance, because participating in the study is with limited risk.

11.6 Incentives (if applicable)

In case the participant travels to the hospital only for COMPRAYA purposes travelcost will be reimbursed.

12. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

12.1 Handling and storage of data and documents

Confidentiality and anonymity of participants will be guaranteed with the assignment of a study number to each participant.

eCRFs are to be completed using Castor. Sites will receive training and help text for appropriate eCRF completion. Data collection and entry into the eCRF is the responsibility of the clinical study staff at the investigational site under supervision of the principle investigator.

Data will be subjected to validation according to the Data Validation and Medical Review Plan.

eCRFs will be submitted electronically to the Sponsor and should be handled in accordance with instructions from the Sponsor.
Prior to database lock, all eCRFs should be completed and electronically signed and dated by the investigator or sub-investigator.
At the end of the study, after 10 years of follow-up, the investigator will receive patient data for his or her site in a readable format on a compact disc that must be kept with the study records. Acknowledgement of receipt of the compact disc is required.

All data will be collected on specially designed data-platforms using only the unique patient identification code to link all data. These data-platforms will be designed by the NKI in collaboration with Health-RI taking all the appropriate GDPR data-protection measures into account. For the logistics of the study the program LDOT may be used, which is a study planning tool that has been developed by the University of Maastricht and has been implemented in the Health-RI infrastructure.

As such, the returned questionnaires, blood, hair and faeces samples have no names attached and will be linked to registry data and eCRFs by study number. Therefore, it will not be possible for the researchers to track participants' names with the study numbers. Returned questionnaires will be stored at a secured location for at least 20 years.

The actual biomaterial samples (blood, hair, and faeces samples) will be labelled using unique codes and will not be traceable to individual patients without the patient identification code lists. The patient material and collected data will be stored for as long as data will be relevant for research purposes. This will be evaluated every 20 years for biomaterials and every 20 years for data. All participants will give separate informed consent to store data and materials for a longer period of time for future research. All records identifying the patients will be kept confidential and will not be made publicly available. Strict measurements will be undertaken to protect confidentiality of the data and registration of the biomaterials. Although the GDPR does not apply for countries outside the EU, the privacy of the patients will be protected in a similar way.

Twenty years after the end of the study the relevance of storage of patient data and materials will be evaluated. If still relevant for this study purposes it will be stored an additional 20 years".

12.2 Monitoring and Quality Assurance

The risk of blood draws, hair and fecal sampling is negligible. Therefore, we qualify the risk of this study as negligible and will not perform official monitoring of the study.

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

The sponsor/investigator will submit a summary of the progress of the study to the accredited METC once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the study, serious adverse events/ serious adverse reactions, other problems, and amendments.

12.5 Temporary halt and (prematurely) end of study report

The investigator/sponsor will notify the accredited METC of the end of the study within a period of 8 weeks. The end of the study is defined as the last patient's last visit.

The sponsor will notify the METC immediately of a temporary halt of the study, including the reason of such an action.

In case the study is ended prematurely, the sponsor will notify the accredited METC within 15 days, including the reasons for the premature termination.

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

All results will be given as feedback to the treating clinicians, patients' representatives, and research society involved in the field of cancer, by means of tumour working groups, symposia, congresses, emailed newsletters, the website of COMPRAYA (www.compraya.nl) and international peer-reviewed publications.

13. STRUCTURED RISK ANALYSIS

Not applicable

13.1 Potential issues of concern

Not applicable

13.2 Synthesis

Not applicable

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