Taste and smell dysfunction in patients more than two years after start of immune checkpoint inhibitor therapy

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Coordinating investigator/project leader	Dr. J.J. de Haan Department of Medical Oncology University Medical Center Groningen Hanzeplein 1, 9713 GZ Groningen Phone: +31 50 361 28 21 Email: j.j.de.haan@umcg.nl
Principal investigator(s) (in Dutch: hoofdonderzoeker/ uitvoerder)	Dr. J.J. de Haan Department of Medical Oncology University Medical Center Groningen Hanzeplein 1, 9713 GZ Groningen Phone: +31 50 361 28 21 Email: j.j.de.haan@umcg.nl
Co-investigators	Department of Medical Oncology Dr. Janine Nuver Prof. dr. Anna K.L. Reyners Department of Oral and Maxillofacial Surgery Dr. Harriët Jager-Wittenaar

Sponsor (in Dutch: verrichter/opdrachtgever)	University Medical Center Groningen Hanzeplein 1 PO Box 30.001 9700 RB Groningen
Subsidising party	Not applicable
Independent expert (s)	Dr. J.H. Maduro Radiotherapy University Medical Center Groningen Hanzeplein 1, 9713 GZ Groningen Phone: +31 50 361 61 61 (49375) Email: j.h.maduro@umcg.nl
Laboratory sites	Not applicable
Pharmacy	Not applicable

PROTOCOL SIGNATURE SHEET

Name	Signature	Date
Head of Department: Prof. dr. J.A. Gietema, MD PhD Department of Medical Oncology		
Principal Investigator: Dr. J.J. de Haan, MD PhD Department of Medical Oncology		

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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

ABR	**General Assessment and Registration form (ABR form), the application form that is required for submission to the accredited Ethics Committee; in Dutch: Algemeen Beoordelings- en Registratieformulier (ABR-formulier)**
AE	**Adverse Event**
AR	**Adverse Reaction**
CSQ	**ChemoSensory Questionnaire**
CiTAS	**Chemotherapy-induced Taste Alteration Scale**
CTLA-4	**Cytotoxic T-lymphocyte antigen-4**
CV	**Curriculum Vitae**
GCP	**Good Clinical Practice**
GDPR	**General Data Protection Regulation; in Dutch: Algemene Verordening Gegevensbescherming (AVG)**
IC	**Informed Consent**
ICIs	**Immune checkpoint inhibitors**
METC	**Medical research ethics committee (MREC); in Dutch: medisch-ethische toetsingscommissie (METC)**
NSCLC	**Non-small cell lung cancer**
PD-1	**Programmed death 1**
PDL-1	**PD ligand 1**
QoL	**Quality of life**
RCC	**Renal cell carcinoma**
RODI	**Regional Oral Dryness Inventory**
(S)AE	**(Serious) Adverse Event**
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**
UAVG	**Dutch Act on Implementation of the General Data Protection Regulation; in Dutch: Uitvoeringswet AVG**
WMO	**Medical Research Involving Human Subjects Act; in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen**
XI	**Xerostomia Inventory**

SUMMARY

Rationale: Immune checkpoint inhibitors (ICIs) are widely used as treatment for multiple cancer types and the number of patients with long-term disease control after ICIs is increasing. However, the use of ICIs is associated with adverse events (AEs) which can have a negative impact on quality of life (QoL). These AEs include oral manifestations, like alterations in taste and smell, xerostomia, and oral mucosal disorders, and could lead to unwanted weight loss. However, the characteristics of taste and smell dysfunction and xerostomia after treatment with ICIs are unknown. More insight in this phenomenon should be gained to make health care professionals aware of this problem to help patients cope with these AEs.

Objective: To determine the prevalence of taste and smell dysfunction in patients more than two years after start of ICI therapy - compared with a control group of caregivers. Secondary objective: to assess the association between taste and smell dysfunction, and saliva secretion rate, saliva composition (pH, electrolyte and protein composition) and subjective feeling of a dry mouth (xerostomia) in patients more than two years after start of ICI therapy - compared with a control group of caregivers.

Study design: Observational cross-sectional study.

Study population: Patients (aged ≥18 years) with melanoma, non-small cell lung cancer (NSCLC) or urogenital cancers who have started treatment with an ICI (CTLA-4 inhibitor, PD-(L)1 inhibitor, or both) ≥2 years ago, and their caregivers.

Main study parameters/endpoints: Taste and smell dysfunction, measured using taste strips and Sniffin' Sticks. Secondary parameters are salivary flow rate, salivary pH. proteins and electrolytes, xerostomia and perceived taste and smell dysfunction.

Nature and extent of the burden and risks associated with participation, benefit and group relatedness: Participation in the study will include one study visit of approximately 1,5 hour. If possible, the study visit will be combined with a regular follow-up visit. In this study, no invasive procedures will be performed. The results of the full study group will be used to guide future interventions and support for cancer patients treated with ICIs.

1. INTRODUCTION AND RATIONALE

Immune checkpoint inhibitors (ICIs) are widely used as treatment for multiple cancer types, including renal cell carcinoma (RCC), melanoma and non-small cell lung cancer (NSCLC)(1). It is estimated that 44% of the patients with cancer may derive benefit from ICIs and 13% would have a response to the ICIs(2). ICIs block the immune inhibitory signals of the tumour, so T cells can target cancer cells and exert an anti-tumour effect(3). Effective specific targets of ICIs are the immune-regulatory checkpoints cytotoxic T-lymphocyte antigen-4 (CTLA-4), Programmed death 1 (PD-1) and PD ligand 1 (PD-L1)(4).

The use of ICIs is associated with adverse events (AEs), mostly due to immune system activation. The AEs have various characteristics: they can be mild or life-threatening, can have a short or long onset and can develop in different organ systems(5). The most common affected systems are the gastrointestinal tract, skin, endocrine glands, and liver(6).

Oral manifestations have also been described(7,8). Xerostomia (the feeling of a dry mouth) was reported in 69% of patients with cancer using ICIs, oral mucosal disorders in 33%, and dysgeusia (altered taste) in 24%(9). However, these previous studies did not report whether these patients were surveyed for these oral side effects or the numbers were based on problems spontaneously reported by patients. Oral side effects are often neglected by both patients and health care professionals, and therefore are easily underreported if not structurally surveyed among patients(10).

Due to long-term survival, patients have to cope with continuing side-effects for a longer period of time(11). Chronic AEs have been found in more than 40% of the patients, mostly endocrinopathies and rheumatological toxicities(12).

Also changes in taste and smell have been found in long-term responders using ICIs. A patient with remaining taste changes three years after immunotherapy discontinuation has been described by our group(13). Furthermore, a study which investigated the initiation of oral AEs in patients using ICIs found that these AEs mostly develop in the first 100 days, but can also develop after two years(9). However, these oral AEs were mentioned spontaneously and an objective determination of taste and smell dysfunction and their prevalence after treatment with ICIs is still lacking.

As mentioned previously, a phenomenon that has been found in patients treated with ICIs is xerostomia. Possibly due to T cell-meditated inflammation, the salivary gland is affected(14). It has been hypothesized that oral dryness could be a chronic AE of ICI treatment: the salivary gland can be irreversibly damaged, which would lead to diminished saliva production and secretion(12). The reduced saliva secretion (hyposalivation) is often associated with the subjective feeling of a dry mouth (xerostomia). Oral dryness can contribute to taste disturbances, as saliva dissolves foods and makes it possible that taste molecules bind to gustatory receptor cells. Furthermore, hyposalivation is a risk factor for oral diseases, including dental caries.

Saliva consists of multiple electrolytes and proteins. The electrolytes include sodium, potassium, chloride, magnesium, calcium, bicarbonate and phosphate(15). The proteins in saliva have many biological activities, including antibacterial and antifungal activity, food digestion and promoting wound healing. Therefore alterations in salivary electrolytes and proteins can lead to oral diseases and taste problems, as they make the dissolving of food and

thereby taste possible(16). The ion concentration and pH of the saliva will mostly be altered if the salivary flow rate is low(16). It could therefore be possible that the electrolyte composition of saliva is altered in patients with cancer treated with ICIs suffering from hyposalivation. However, electrolyte and protein analysis of saliva has not been performed in patients treated with ICIs.

Alterations in taste and smell, xerostomia, and oral mucosal disorders can have impact on quality of life (QoL) and could lead to unwanted weight loss(17,18). Moreover, distribution of household roles and social functioning have also been found to be associated with taste and smell dysfunction(19,20). More insight in the prevalence and impact of taste and smell alterations, and xerostomia should be gained to make health care professionals aware of this problem and to help patients cope with these AEs.

A cohort with melanoma, NSCLC and urogenital cancer patients treated with ICIs and their caregivers has already been built up. In this cohort, we will determine the prevalence and characteristics of taste and smell dysfunction of patients surviving more than two years after starting immune checkpoint inhibitor therapy. Furthermore, the association of taste and smell dysfunction to pH, saliva secretion rate, saliva composition and xerostomia will be assessed.

2. OBJECTIVES

Primary Objective:

- To determine the prevalence of taste and smell dysfunction in patients more than two years after start of ICI therapy - compared with a control group of caregivers.

Secondary Objective(s):

- To assess the association between taste and smell dysfunction, and saliva secretion rate, saliva composition (pH, electrolyte and protein composition) and subjective feeling of a dry mouth (xerostomia) in patients more than two years after start of ICI therapy - compared with a control group of caregivers.
- To assess the impact of taste and smell dysfunction in patients more than two years after start of ICI therapy.

3. STUDY DESIGN

In this cross-sectional study, patients with melanoma, NSCLC or urogenital cancer ≥ 2 years following ICI therapy and their caregivers will be included. We will include patients who have previously participated in the study “Quality of life, cognitive function, and physical fitness of patients surviving more than 2 years after immune checkpoint inhibitor therapy” (METc 2018/158, clinicaltrials.gov NCT03946007) and additional patients who are under control at the departments of Medical Oncology and Pulmonary Disease and did not participate in this previous studyA patient cohort of 70-120 patients and 70-120 of their caregivers has already been built and patients who have given permission to be approached for future research again will be invited for our study.

Patients can be approached in two ways: 1) Patients will be asked during an outpatient clinic appointment by their clinical doctor if they can be approached afterwards by the investigator. When permission is given, the investigator will explain the study design and give the patient and the caregiver both a letter. These letters explains the study design and includes an informed consent form, 2) Patients who do not have an outpatient clinic appointment in the near future will be sent the letter with the study design and the informed consent form. In this letter, we will also ask each participant to invite their caregiver to participate in this study. For this, a separate letter directed at the caregiver will be sent to the participant. Patients and caregivers are asked to contact the investigator team if they are willing to participate. If the patient consents, a single appointment will be made during a regular follow-up visit to the outpatient clinic. If the caregiver consents too, we will make an appointment with both participants at the same time, if possible. Patients can participate alone if the caregiver is not willing to participate, and vice versa.

During this visit, if patients and caregivers have no questions regarding the study or the study information that was sent, they are first asked to sign the informed consent. Next, saliva will be collected, and taste, smell and dry mouth will be subjectively and objectively be measured. Afterwards, characteristics will be taken from the patients’ electronic file, including age, gender, medical history and medication use. As the caregivers do not have a medical file, they are asked for these characteristics.

4. STUDY POPULATION

4.1 Population (base)

The participants in this study will be derived from an existing cohort of 70-120 patients who have undergone ICI treatment and have not received other systemic treatment (METc 2018/158, clinicaltrials.gov NCT03946007). These patients have been previously included in a cross-sectional study in which health-related quality of life, neurocognitive function, endocrine function, cardiovascular risk, physical fitness, mood disorders, sexual problems, and work participation were investigated. Patients have survived two years or more after the first cycle of an immune checkpoint inhibitor for melanoma, NSCLC, or urogenital cancer. Furthermore, the quality of life of the caregivers of these patients was studied.

The participants of this previously performed study who have given permission to be approached again, will be asked to participate in this study. In addition, to complete the required number of participants, additional patients from the departments of Medical Oncology and Pulmonary Disease, who were not included in the previously mentioned cohort, but who meet the criteria for this study, will be invited to participate in the study. Furthermore, a part of the caregivers of these patients have also been included in this previously mentioned cohort and has given permission to be approached again. The caregivers will act as control group for practical purposes, as they often accompany the patient on the hospital appointments. Furthermore, caregivers tend to have the same basic characteristics as the patients, and therefore, these characteristics will be distributed more equally in both groups. If a patient has a new caregiver, this new caregiver can also be asked to participate in this study instead of the previously included caregiver. Patients can also participate if they don't have a caregiver. The caregivers of the additional patients will also be invited.

4.2 Inclusion criteria

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

1. Patient with melanoma, NSCLC or urogenital cancers ≥ 2 years since treatment with at least one cycle of immune checkpoint inhibitor (CTLA-4 inhibitor, PD-(L)1 inhibitor, or both) within the Department of Medical Oncology or Pulmonary Oncology of the UMCG.
2. Age ≥18 years at time of immune checkpoint inhibitor treatment
3. Understand or abide to the study procedures
4. Have given informed consent

A caregiver must meet all of the following criteria:

1. Age ≥18 years
2. Understand or abide to the study procedures
3. Have given informed consent

The inclusion criteria of the earlier study with this cohort have been adapted to this study.

4.3 Exclusion criteria

A patient or caregiver who meets any of the following criteria will be excluded from participation in this study:

1. As previous or subsequent therapies, only surgery and palliative radiotherapy is allowed (excluding radiotherapy in the head-neck and brain region)
2. Previous treatment in the past ten years for malignancy other than melanoma (excluding non-melanoma skin cancer, cervical intra-epithelial neoplasia or carcinoma in situ of breast) (for patients: other than current malignancy)
3. History of ear-nose-throat disease or auto-immune disorder affecting taste, smell, mouth mucosa, or saliva production (for patients: before start ICI)
4. As previous or subsequent therapies, palliative radiotherapy for bone metastasis in the brain and head-and-neck region

The exclusion criteria of earlier studies with this cohort have been adapted to this study.

4.4 Sample size calculation

It is expected that long-term taste and smell dysfunction are prevalent in 25% of the patients. As described in the introduction, taste changes were found in 24% of patients using immunotherapy(9). In this study, however, it is not reported whether these changes were reported spontaneously or were actively asked. It is therefore possible that the percentage of 24% will be even higher. From earlier studies in patients years after treatment of testis carcinoma or childhood cancer, it is know that about 25% of these (former) patients have long-term taste and smell changes(21,22). Based on this information, the percentage of 25% was determined.
As caregivers with a history of disorders affecting taste and smell will be excluded, it is expected that these dysfunctions are present in 5% of the caregivers. If so, the differences between the patient and control group of caregivers can be assessed in a cohort of in total 49+49=98 patients and caregivers with a 95% confidence level and a power of 80%.

5. TREATMENT OF SUBJECTS

Not applicable

6. INVESTIGATIONAL PRODUCT

Not applicable.

7. INVESTIGATIONAL PRODUCT

Not applicable.

8. METHODS

8.1 Study parameters/endpoints

8.1.1 Main study parameter/endpoint

Taste and smell dysfunction measured using taste strips and Sniffin' Sticks in patients compared to caregivers.

8.1.2 Secondary study parameters/endpoints

- Salivary flow rate
- Salivary pH
- Salivary electrolytes and protein concentrations
- Perceived taste and smell dysfunction
- Perceived xerostomia (XI-scores and RODI-scores)

8.2 Study procedures

Both patients and caregivers are asked not to smoke, brush teeth, eat, or drink anything except water one hour before the tests. Then, unstimulated and chewing-stimulated saliva will be collected, the salivary flow rate will be measured using standardized procedures, and patients and caregivers will fill in two questionnaires regarding perceived taste and smell dysfunction. Taste and smell dysfunction will be assessed with taste strips and Sniffin' Sticks. To assess subjective taste and smell perception, and the impact of taste and smell dysfunction, the Chemotherapy-induced Taste Alteration Scale (CiTAS) questionnaire, the Patient-Generated Subjective Global Assessment (PG-SGA) questionnaire, the Appetite, Hunger and Sensory Perception (AHSP) and the Questionnaire of Olfactory Disorders (QOD) will be used. Subjective xerostomia will be assessed with the Dutch versions of the Xerostomia Inventory (XI) and the Regional Oral Dryness Inventory (RODI). The results of the patients will be compared with the caregivers. Salivary flow rate and pH will be measured immediately after collection, and subsequently the saliva will be stored at -80^{0}C until biochemical analysis. Below, the tests and examinations are explained in more detail.

Taste dysfunction

Taste dysfunction will be objectively measured with "Taste Strips" (Burghart, Wedel, Germany)(23). Strips with an impregnated taste solution will be placed on the participants' tongue. The taste solutions contain the basic tastes bitter, sweet, sour and salty in four different concentrations, thus 16 tests will be performed. The strips will be randomly administered and participants are asked which taste they notice. A right answer gives one point and a total of 16 point can be obtained.

Smell dysfunction

Smell dysfunction will be objectively measured with "Sniffin' Sticks" (Burghart, Wedel, Germany)(24). Pens filled with liquid odorants are presented to the participants' nose. Participants will smell 16 different scents with an interval of minimal 30 seconds to

prevent desensitization. For each scent, participants will choose between four options from a multiple choice card. Smell threshold will be measured with “Sniffin’ Sticks” with different odor concentrations.

Saliva (flow rate, pH and elektrolytes)
Saliva flow will be measured, both stimulated and unstimulated(25). The pH of saliva will be determined immediately after collection using an electronic pH meter. The composition of the saliva is determined by measuring electrolyte concentration (Na, K, Cl, HCO_3, Zn) and the enzyme activity/concentrations of chitinase, amylase, lysozyme, Mucin5B, total protein, and carbonic anhydrase.

Questionnaires
Dysfunction in taste will be subjectively measured with the validated Dutch version of the **CiTAS** questionnaire(26). The CiTAS questionnaire consists of 18 questions on a 5-point Likert-scale and identifies the type and severity of taste dysfunction. The **PG-SGA** assesses weight, food intake, symptoms, and activities and function in 8 questions(27). The **AHSP** questionnaire consists of 29 multiple choice questions and assesses appetite, hunger and sensory perception(28). Impact on quality of life will be measured with the **QOD** questionnaire(29). Xerostomia will be quantified with the internationally validated **XI** (a questionnaire with 11 items on a 5-point Likert-scale) and the **RODI**(30,31). The RODI consists of a schematic representation of 9 intra-oral areas, and the patient can indicate the severity of the xerostomia at these areas on a 5-point Likert scale.

8.3 Withdrawal of individual subjects

Subjects 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.

8.3.1 Specific criteria for withdrawal

Occurrence of signs or symptoms of progressive disease during study visit (after informed consent was signed).

8.4 Follow-up of subjects withdrawn from treatment

Subjects withdrawn from the study will not be assessed at a later time.

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 procedure. 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)

A serious adverse event is any untoward medical occurrence or effect that

- results in death;
- is life threatening (at the time of the event);
- requires hospitalisation or prolongation of existing inpatients' hospitalisation;
- results in persistent or significant disability or incapacity;
- is a congenital anomaly or birth defect; or
- any other important medical event that did not result in any of the outcomes listed above due to medical or surgical intervention but could have been based upon appropriate judgement by the investigator.

An elective hospital admission will not be considered as a serious adverse event.

The sponsor will report the SAEs through the web portal *ToetsingOnline* to the accredited METC that approved the protocol, within 7 days of first knowledge for SAEs that result in death or are life threatening followed by a period of maximum of 8 days to complete the initial preliminary report. All other SAEs will be reported within a period of maximum 15 days after the sponsor has first knowledge of the serious adverse events.

9.3 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 need to be reported till end of study within the Netherlands, as defined in the protocol.

10. STATISTICAL ANALYSIS

This study aims to investigate the prevalence of taste and smell dysfunction in a predefined cohort of melanoma, NSCLC and urogenital cancer patients. Results will be reported as mean (standard deviation) and median (range) for parametric and non-parametric continuous variables, respectively. Categorical data will be presented as N and percentages.

Participants and their caregivers will be compared using Mann Whitney U test or independent T-test, depending on data distribution. For ordinal data, Chi-square tests will be performed. Correlations between perceived and objective taste and smell dysfunction will be studied with Pearson's rho or Spearman's rho, depending on data distribution.

10.1 Primary study parameter(s)

Taste strip and Sniffin' Stick scores will be presented as mean scores and standard deviations. A higher score corresponds to a higher level of taste and/or smell dysfunction.

10.2 Secondary study parameter(s)

Salivary flow rates, saliva electrolytes, salivary proteins, salivary enzyme activity and pH, perceived taste and smell dysfunction will be presented as mean scores and standard deviations.

Relationships between taste and smell dysfunction and salivary flow rates, saliva electrolytes, salivary proteins, salivary enzyme activity and pH will be analyzed using Pearson or Spearman correlation tests.

11. ETHICAL CONSIDERATIONS

11.1 Regulation statement

The 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 section 10, subsection 1, of the Medical Research Involving Human Subjects Act (WMO). The protocol will be approved by the local Medical Ethical Committee.

11.2 Recruitment and consent

A patient cohort with 70-120 patients and 70-120 caregivers is already built up and patients and caregivers have given permission to be approached again. Potential participants will receive written study information. A week later, they will be called to ask if they want to participate. If a potential participant is willing to participate, he/she/they will sign written informed consent. The investigator will co-sign the informed consent form. The investigator will make a single appointment during a regular follow-up visit to the outpatient clinic.

11.3 Objection by minors or incapacitated subjects

Minors or incapacitated subjects will not be included in this study.

11.4 Benefits and risks assessment, group relatedness

This is a study without risks. Participation in the study will include one study visit of approximately 1,5 hour. If possible, the study visit will be combined with a regular follow-up visit. In this study, no invasive procedures are performed. The results of the full study group will be used to guide future interventions and support for cancer patients treated with ICIs. The participants will not have benefit by participating in this study.

11.5 Compensation for injury

The sponsor/investigator has a liability insurance which is in accordance with article 7 of the WMO.

The sponsor is in accordance with the legal requirements in the Netherlands (Article 7 WMO). As this study carries no risks for the participant, exemption is requested for the WMO clinical trial participants insurance.

11.6 Incentives

Participants will receive travel allowance if the study visit is not combined with a regular follow-up visit.

12. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

12.1 Handling and storage of data and documents

Data of patients will be handled confidentially and a coded identification number will be used to link the data to the specific patients. The patients' code will contain the abbreviation of the short study title, 'TS', and a number, starting with '01'. The principal investigator and coordinating investigator safeguard the key to the code. The handling of personal data complies with the EU General Data Protection Regulation and the Dutch Act on Implementation of the General Data Protection Regulation. (in Dutch: Uitvoeringswet AVG, UAVG). All research data will be stored for 15 years after the data collection has been completed (i.e. last research assessment for the last patient has been performed) in accordance with the NFU guidelines for WMO-compliant research. The saliva will be stored for three years.

12.2 Monitoring and Quality Assurance

The current study is considered to hold negligible risk. Therefore, monitoring will consist of checking the most important study procedures and data in a patient sample once a year.

12.3 Amendments

Amendments are changes made to the research after a favorable opinion by the accredited METC has been given. All amendments will be notified to the METC that gave a favorable opinion. Non-substantial amendments will not be notified to the accredited METC and the competent authority, but will be recorded and filed by the sponsor.

12.4 Annual progress report

The sponsor/investigator will submit a summary of the progress of the trial 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 trial, 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 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

The results of this study will be disclosed unreservedly after the end of the study, either by publication in a peer-reviewed scientific journal or by publication on trial registers or websites. The published results cannot be traced back to the participants. All manuscripts derived from this protocol will be reviewed by the investigating group before submission.

13. STRUCTURED RISK ANALYSIS

Not applicable.

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