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# Protocol for the development of a global core outcome set for the surgical treatment of differentiated thyroid cancer: a literature review and international Delphi survey

Daniël J van de Berg ,[1] Christiaan F Mooij,[2] A S Paul van Trotsenburg,[2] Faridi S Jamaludin,[3] Hanneke M van Santen,[4,5] Sarah C Clement,[4] Menno R Vriens,[6] Eveline Bruinstroop,[7] Schelto Kruijff,[8,9] Robin P Peeters,[10] Frederik A Verburg,[11] Romana T Netea-Maier,[12,13] Angelique Seur,[14] Els J M Nieveen van Dijkum,[15] Anton F Engelsman,[15] Joep P M Derikx[1]

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For numbered affiliations see end of article.

**Correspondence to**
Dr Daniël J van de Berg; d.j.vandeberg@amsterdamumc.nl

## ABSTRACT

**Introduction** There is a lack of consensus on the optimal surgical strategy for differentiated thyroid cancer (DTC), partly due to inconsistent reporting of outcomes. This limits the ability to compare study results, hindering the ability to draw conclusions regarding novel treatment strategies. The development of a core outcome set (COS) reduces heterogeneity in the selection and reporting of clinical trial outcomes. Currently, there is no COS for the surgical treatment of DTC. We aim to reach a global consensus among patients and physicians on the COS for the surgical treatment for patients with DTC of all ages.

**Methods and analysis** The DTC-COS development will consist of three phases: first, an extensive literature review will be performed to identify reported outcomes in studies regarding surgical treatment for DTC in patients of all ages. Second, a 2-step or 3-step Delphi procedure will be performed to identify a final set of core outcomes out of the selected outcomes from the literature review. For this Delphi survey, both healthcare professionals and patients will be invited. Third, an (online) expert meeting with participants from every stakeholder group is organised to ratify the final core outcome set. The final COS will be reported in accordance with the COS-Standards for Reporting statement.

**Ethics and dissemination** The medical research ethics committee of the Amsterdam UMC confirmed that the Dutch Medical Research Involving Human Subjects Act (WMO) does not apply to this study and that full approval by the committee is not required. The study is registered in the COMET initiative database (registration number 2597). Results will be presented in peer-reviewed academic journals and at (international) conferences.

**Trial registration number** COMET initiative database 2597

## STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The invitation for this international Delphi study will be distributed through the European Thyroid Association, the EU Reference Network Rare Endocrine Conditions, the European Organisation for Research and Treatment of Cancer—Endocrine Tumour Group, the European Reference Network EURACAN and the African Head and Neck Society, ensuring broad, worldwide inclusion of experts.

⇒ This Delphi study will include healthcare professionals and patients as participants, ensuring a core outcome set that reflects both patients and healthcare professional perspectives.

⇒ A patient representative from the Dutch thyroid patient federation (SON) is involved in the study design and during the Delphi rounds to ensure seamless patient participation.

⇒ The Delphi questionnaire will only be available in English.

## INTRODUCTION

Differentiated thyroid cancer (DTC) is the most common endocrine malignancy, accounting for ~2.1% of all cancer diagnoses worldwide.[1] Moreover, its incidence is increasing.[2]

Surgery is the cornerstone of treatment for DTC. In the last decade, there have been several developments in the surgical treatment of DTC, leading to a trend of de-escalating treatment strategies.[3] However, many controversies about the ideal surgical approach for DTC remain. For instance, the benefit of prophylactic central neck dissection (CND) remains controversial. Some studies show that prophylactic CND in selected patients reduces the rate of loco regional recurrence,[4–6] whereas others report no effect on recurrence.[7 8] Moreover, results on the complication rates of prophylactic CND are inconsistent.[4–8]

One of many reasons for the lack of consensus on the optimal surgical strategy for DTC is inconsistent selection and reporting of outcomes. This limits the ability to adequately compare and interpret study results.[9] Furthermore, it hampers synthesising data and data pooling for systematic reviews and meta-analyses and impairs drawing conclusions regarding the effect of novel treatment strategies. To adequately compare and interpret treatment strategies, it is crucial that studies select and report similar and appropriate outcomes. The development and implementation of a core outcome set (COS) reduces heterogeneity in the selection, measurement and reporting of clinical trial outcomes.[10 11] A COS is an agreed standardised set of outcomes that should be measured and reported, as a minimum, in all clinical trials in specific areas of healthcare.[11] The implementation of a COS can enhance data comparison and data pooling, enable adequate and efficient comparison of treatment strategies, and improve the interpretation and implementation of clinical trial results.[9 11] Currently, there is no COS for the surgical treatment of DTC. An international COS for the surgical treatment of DTC could improve appropriate and uniform outcome selection in future studies, which, subsequently, would enhance comparing and interpreting future treatment strategies. Therefore, we aim to reach a global consensus among patients, researchers and physicians on the minimal set of core outcomes that should be measured and reported in all future clinical research investigating any surgical treatment for patients of all ages with DTC.

## METHODS AND ANALYSIS

In the development of this protocol, we will adhere to the Core Outcome Measures in Effectiveness Trials (COMET) handbook[11] and the Core Outcome Set-Standards for Development (COS-STAD) recommendations.[12] The COS-STAD recommendations provide a structured approach for COS development, emphasising stakeholder engagement and consensus-building to ensure the selected outcomes reflect both clinical and patient perspectives. Involvement of patients and public will be described using the Guidance for Reporting on Involvement of Patients and Public (GRIPP2) short form reporting checklist.[13] This study was registered with the COMET initiative database (registration number 2597) on 21 March 2023.[14] The COMET initiative promotes the development and use of COS, ensuring that essential outcomes are consistently measured across clinical trials to improve comparability and applicability of research findings. The final core outcome set will be reported in accordance with the Core Outcome Set-Standard for reporting statement.[15] The methods described in this protocol replicate, in part, those outlined in the protocols by our colleagues Maat *et al* and Knaapen *et al*.[9 16]

### Study design

This COS development will consist of three phases:

1. An extensive literature review will be performed to identify reported outcomes in studies regarding surgical treatment for DTC in patients of all ages. The methods for the literature search are described in phase 1.
2. A 2-step or 3-step Delphi procedure to identify a final set of core outcomes out of the selected outcomes from the literature review. Development of the Delphi is reported according to the checklist of Sinha *et al*.[17] The methods for the Delphi procedure are described in phase 2.
3. An (online) expert panel meeting with participants from every stakeholder group is organised to ratify the final core outcome set (see phase 3).

### Study management group

The study management group will consist of Professor Joep Derikx (paediatric surgeon), Dr Anton Engelsman (endocrine surgeon), Professor Els Nieveen van Dijkum (endocrine surgeon), Professor Paul van Trotsenburg (paediatric endocrinologist) and Daniël van de Berg (MD, PhD candidate).

The study management group will have regular meetings throughout the project to discuss the progress of the project.

### Steering committee

A steering committee will be formed with experts from different medical expertise and academic hospitals, and a patient representative from the Dutch thyroid patient federation (SchildklierNL).

The steering committee will agree on the final version of the protocol at the start of the project and will be informed of the process and be asked for input during the project. The steering committee members will not be involved in the Delphi study. However, they will be involved in the expert panel meeting to ratify the final definition.

### List of outcomes

We will perform an extensive literature review to identify all reported outcomes in studies regarding surgical treatment interventions of DTC. The study management group will discuss similar outcomes and will group these outcomes under a common outcome term to obtain a manageable and cohesive list of outcomes that is appropriate for a Delphi study.

## PHASE 1

### Literature review

#### Search strategy

A systematic literature search for the surgical treatment of DTC is performed in MEDLINE and EMBASE. The search terms are formulated in collaboration with a medical information specialist (FSJ). All outcomes after surgical treatment of DTC are being sought. Publication dates extend from January 2020 till April 2023. Limitations are set to retrospective studies, prospective studies,

randomised controlled trials (RCTs) and systematic reviews and/or meta-analyses, English language and human studies. Unpublished studies are not sought. A total of 2585 studies are found. The full search with search terms can be found in the online supplemental appendix.

### Study selection

Selection of studies will be performed by DJvdB, according to the inclusion and exclusion criteria. In case of doubt, a second independent reviewer (JPMD) will make the final decision.

### Inclusion/exclusion criteria

Retrospective studies, prospective studies, RCTs and systematic reviews and/or meta-analyses studies reporting on surgical treatment interventions (or as a component of treatment) of patients of all ages with DTC will be included in this review. Studies that explicitly report on the surgical treatment interventions of patients with incurable (ie, palliative care) DTC, studies reporting on non-surgical treatment only, studies comparing one or more diagnostic techniques, studies that include any patient with a diagnosis other than DTC, PTC or FTC, studies that report in abstract form only, such as conference proceedings, and studies that are not written in English will all be excluded. Case studies and case series will be excluded.

### Data extraction

First, the reported outcomes from the included studies will be extracted. A risk of bias assessment of the individual studies is not applicable as we will only use the reported outcomes. Outcomes will initially be reported exactly as mentioned in the original study. After data extraction is complete, the study management group will discuss similar outcomes and will group these outcomes under a common outcome term to obtain a manageable and cohesive list of outcomes that is appropriate for a Delphi study.

## PHASE 2

## International online Delphi study

This study is a prospective, Delphi consensus-seeking exercise, iterative survey of international experts for a core outcome set of the surgical treatment of DTC. The Delphi consensus methodology will be used to survey a panel of experts who will fill in the online survey as individual participants. A balanced mix of patients and professional healthcare experts from different medical areas of expertise that treat patients with DTC will be sought. The primary users of core outcome set for the treatment of DTC will mostly be healthcare professionals that treat patients with DTC, researchers and patients. The study is scheduled to start in January 2024 and is expected to conclude by November 2024.

### Participants

#### Stakeholders selection: professionals

To reflect the views of different stakeholders, a variety of healthcare professionals will be part of the development of this COS. We will also include non-surgeons in this surgical COS, as diagnostics and follow-up are mostly done by other medical specialties (eg, (paediatric) endocrinologists, nuclear medicine physicians, oncologists). Therefore, including experts from multiple medical areas is essential for this COS. Moreover, involving professionals from different countries and continents will lead to the development of a global 'minimal' COS that reflects the opinion of the international community. Non-clinical researchers can be involved in this Delphi procedure but will not be formed into a separate stakeholder group in the analysis. Since most clinical research regarding the treatment of DTC is initiated by healthcare professionals that treat these patients, it is likely that researchers will be well represented in the healthcare professional stakeholder group.

#### Stakeholders selection: patients

Involving patients as participants for development of a COS is imperative as patients may report different outcomes than physicians.[18 19] Therefore, we will make efforts to involve 10–15 patients from the Dutch thyroid patient federation (SchildklierNL). Patients will be provided with plain language information about the Delphi method, the Delphi rounds and the expert panel meeting. They will also be offered the opportunity to call the coordinating research fellow for further explanation of the study. After the first Delphi round, patients will, like the experts, have the opportunity to suggest new outcomes, including patient-reported outcomes not identified in the initial literature search.

#### Stakeholder recruitment

First, we will invite groups of healthcare professionals who are currently conducting clinical trials on the treatment of DTC. Groups will be identified through www.clinicaltrials.gov by searching 'differentiated thyroid cancer'.[9 16] No age limitation will be set. Studies completed before 2018 or studies without an update after 2019 will be excluded. Second, we aim to include healthcare professionals who were last authors on more than two included studies in our literature review. Thirdly, we will include experts/research groups that were involved in the development of international thyroid guidelines, such as the European Society for Medical Oncology, American Thyroid Association and European Thyroid Association (ETA) (paediatric) clinical practice guidelines.[3 20–22] Fourth, we will invite members via the boards of the ETA-Cancer Group, EU reference Network Rare Endocrine Conditions, European Organisation for Research and Treatment of Cancer—Endocrine Tumour Group, European Reference Network-EURACAN, African Society of Paediatric and Adolescent Endocrinology, and African Head and Neck Society. Lastly, we will ask input from the

Study Steering Group to give suggestions regarding international experts not yet part of the list.

Patients will be invited by contacting the patient thyroid group/federation, along with an explanation of the study objectives, instructions and outputs.

Potential participants will be invited per email that will contain a link to an online registration system with all the study information. Potential participants can reach the study coordinator (DB) of this Delphi by email or telephone to ask additional questions, if necessary.[9 16] After registration in our online system (Welphi software), participants will be invited to the Delphi questionnaire. Participants will not receive any form of (financial) compensation. They can discontinue the study at any moment without giving a reason. There will be no questions related to personal health information.

### Sample size

There is no rationale for determining the number of respondents for a Delphi survey.[11] A minimum of seven respondents per stakeholder group is suggested to be a large enough group

to allow for a consensus process.[23] Understanding that some panellists may be experts in more than one category, we will invite at least 15–20 participants per medical area of expertise and we aim to include at least 10–15 patient representatives. This should lead to a sample size of approximately 100–120 participants and solidify the generalisability of the consensus findings, allowing for a 10–15% non-response (or non-desire to participate) rate and 10% drop-out rate. In case the number of respondents per country is significantly higher than other countries, we will consider a weighing per country in the analyses. There will be no maximum number of respondents.

## Delphi rounds

The Delphi study will be conducted online and managed by Welphi software. The Delphi questionnaire will be formulated in English. The list of outcomes from the literature review will be formatted into questions for the Delphi questionnaire. These questions will be accompanied by plain language question in layman's terms for the patients. The questionnaires and letters of invitation will be piloted by a layperson from the Dutch thyroid patient federation (SchildklierNL) and two other laypersons to check for ambiguity and readability. The questionnaires will be open simultaneously to all respondents of all participating countries.

In this Delphi study, we will use a 9-point Likert scale from 1 to 9 as recommended by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) working group and COMET initiative.[11 24] Each candidate outcome will be scored by each individual Delphi participant. A score of 7–9 indicates that an outcome is considered critically important for assessing the effect of a treatment, 4–6 the outcome is considered important but not critical and 1–3 indicates an outcome has low importance for assessing the treatment effect and should not be included in the core outcome set. In addition, it will be possible to select 'unable to score/not my area of expertise' per question, for respondents that do not feel equipped to score certain outcomes.[9 16]

### Delphi round one

Participants will be divided into two stakeholder groups: healthcare professionals and patients. Both groups will be asked to provide basic demographic characteristics (eg, country of residence, patient/healthcare professional). Healthcare professionals will be asked for specialty (surgeon, endocrinologist, etc) and current affiliation. All participants in both stakeholder groups will be asked to score all previously identified outcomes according to their perceived importance for assessing the effectiveness of treatment.[9 16] In the first round, participants can propose additional outcomes that were not included in the initial list of outcomes.

The timeframe to complete each Delphi round will be 3 weeks. In that time, we will send two reminder emails to the participants that did not yet complete the questionnaire.

### Delphi round one: analysis

Results of the Delphi procedure will be analysed separately for each stakeholder group, using descriptive statics, since patients are expected to appoint different scores to outcomes compared with professionals, which has the potential to influence eventual outcome selection.[9 16 25] In the absence of a formal guideline, we will define and analyse consensus based on the approach most commonly used in the literature and by our research group.[9 16]

'Consensus-in' will be defined as:

- 70% or more of the participants in both stakeholder groups (excluding 'Not my area of expertise) rating the outcome as 7–9 and less than 15% rating the outcome as 1–3.
- 90% or more of participants within one stakeholder group rate the outcome as 7–9 'consensus-in'. This entails that the outcomes that are only of interest to one stakeholder group can also be included.

'Consensus-out will be defined as:

1. 70% or more of the participants in both stakeholder groups rating the outcomes as 1–3 and less than 15% of participants in both stakeholder groups rating it 7–9. Consensus-out can only be reached if there is consensus across both stakeholder groups.

Outcomes that do not meet any of these criteria will be labelled as 'no consensus'. After analysis of the first round, the study management group will determine if new outcomes suggested by respondents are added as new outcomes. Questions are rephrased if misinterpretation is suspected. A stratified analysis can be performed to check for skewing because of a divergent opinion from a single country or type of physicians. In case of skewing, the analysis will be corrected accordingly.

### Delphi round two

All participants who have completed the first round will be asked to participate in round two. Outcomes that have been identified as 'consensus-in' or 'consensus-out' will be excluded from round two. An overview of all the included and excluded outcomes will be available. Any newly suggested outcomes from the previous rounds will also be included. In round two, participants will be provided with a histogram showing the scoring distribution or with the median score of the answers of the other participants and a reminder of their individual answer in round one, according to the Delphi principle. Respondents will be asked to rate the outcomes in round two of the Delphi process in the same manner as in round one.[9 16]

### Delphi round two: analysis

The results of round two will be analysed per stakeholder group and for all participants, using descriptive statistics with the same definitions for consensus in/out as in the first Delphi round. In the case of consensus in both stakeholder groups on more than 10 outcomes with 'consensus in', the study management group will determine whether to refrain from a third round. Again, a stratified analysis can be performed to check for skewing because of a divergent opinion from a single country or type of physicians. In case of skewing, the analysis will be corrected accordingly.[9 16]

### Delphi round three

If necessary, a third round will be organised. All participants that completed the first and second round of the Delphi process will be asked to participate in the last round. On the outcomes for which no consensus has been reached, participants will be provided with a histogram showing the scoring distribution or with the median score of the answers of the other participants, and a reminder of their individual answer in round one, according to the Delphi principle. Respondents will be asked to rank the remaining outcomes 1–9.[9 16]

### Delphi round three: analysis

The results of round three will be analysed with the same definitions for consensus in/out as in the first two Delphi rounds using descriptive statistics. Results will be analysed per stakeholder group and for all participants. Again, a stratified analysis can be performed to check for skewing because of a divergent opinion from a single country or type of physicians. In case of skewing, the analysis will be corrected accordingly.[9 16]

To estimate the (lack of) agreement between respondents, the width of the IQR of the median ranking score will be calculated, ranging from 0.00 meaning complete agreement to 8.00 meaning least possible agreement.

If deemed necessary by the study management group or steering group, a fourth round can be organised, in case of no sufficient consensus on proposed outcomes. However, this is not expected.

## PHASE 3

### Formal consensus meeting

A formal consensus meeting will not be organised, as face-to face consensus meetings lead to a selection of participants that are able to attend the meeting, which is introducing a risk of bias. However, if consensus cannot be reached in the Delphi process, we will attempt to organise a formal face-to-face consensus meeting with an appropriate representation of all stakeholder groups.[9 16]

### Expert panel meeting

After consensus in the Delphi study is reached, a face-to-face expert panel meeting will be organised with selected individuals from every stakeholder group to ratify a pragmatic and well-defined set of outcomes. Through purposive sampling, approximately 30 individuals from the stakeholder group 'professionals' and 5 individuals from the stakeholder group 'patients' will be invited to participate in the face-to-face meeting.[9 16] We aim to organise a physical meeting. However, participants that are not able to participate physically can join the meeting digitally. During the meeting, the outcomes will be introduced by patient representatives who participated in the Delphi process, in order to make them a more integral part of the meeting and to ensure their contribution has a greater impact alongside the experts. The patient representatives will introduce each outcome by sharing a personal story, highlighting why they believe it is important to include the outcome in the surgical COS.

The goal of this study is to achieve a pragmatic COS that is applicable and feasible for all future clinical research regarding treatment of DTC. Therefore, we aim to only include outcomes in the final COS that are:

1. Relevant.
2. Measurable by an accepted tool or instrument.
3. Specific to be improved by surgical interventions for DTC.

During the expert panel meeting, the outcomes on which consensus has been reached will be evaluated based on these criteria. After a moderated discussion, experts and patient representatives will vote again to determine whether each outcome met these criteria and should thus be included in the final COS. Consensus will be defined as 80% or more of the participants voting for the outcome to be included in the final COS, as a lower number of participants in the expert panel meeting, compared during the Delphi rounds, requires a higher consensus threshold.

As a minimum, we aim to reach 1 outcome per OMERACT domain. In total, we aim to develop between 8 and 15 outcomes in the DTC-COS. If consensus is reached on more than 15 outcomes, the 15 outcomes with the highest level of consensus will be considered part of the suggested COS. This will ensure that the final COS is a pragmatical list of the most relevant outcomes for future research and to collect in clinical setting. Highest level of consensus depends on whether there is consensus in both stakeholder groups, the median score that was appointed

Table 1 Reclassification of outcomes, according to the OMERACT filter 2.0

| Core area | Example(s) |
|---|---|
| Life impact | Quality of life |
| Pathophysiological manifestations | Complications, oncological effects (eg, recurrence rate, survival) |
| Resource use | Length of hospital stay, healthcare costs, readmission |
| Death | Disease specific survival |

to the outcome and the IQR of the median score as an estimate of the degree of consensus. Only outcomes for which international consensus is reached will be selected. These criteria will ensure that the final COS reflects the perspectives of both experts and patients across all participating countries.

## Final COS

Outcomes will be reclassified according to the four core areas (table 1), suggested by the OMERACT filter 2.0.[26 27] The OMERACT Filter 2.0 explicitly describes a comprehensive conceptual framework and a recommended process to develop core outcome measurement sets.

## Patient and public involvement

Patient and public involvement will be according to the GRIPP2 short form reporting checklist.[13] A patient representative from the Dutch thyroid patient federation (SchildklierNL) is involved in the design of this Delphi study. The patient representative will agree on the final version of the study protocol at the start of the project and will be informed of the process and asked for input during the project. Furthermore, the questionnaires and letters of invitation will be piloted by this patient representative to check for ambiguity and readability. Patients will be involved in the Delphi procedure in rating the outcomes and proposing additional outcomes, if necessary. Patients will be invited to a (digital) consensus meeting, if consensus cannot be reached. As mentioned above, patients will be invited to join the (digital) expert panel meeting to ratify the final COS.

## Data collection and confidentiality

The handling of the collected personal data complies with the EU General Data Protection Regulation and the Dutch Act on Implementation of the General Data Protection Regulation.[28] The study will be conducted following the Good Clinical Practice guidelines.[29] The Delphi study will be conducted online and managed using online Welphi software. To ensure participants' privacy, the personal information is stored separately, in a secured environment at a hard drive of Amsterdam UMC, from the answers given in the questionnaire and is only accessible by the study management group. Survey responses will be anonymous and tabulated by groups only. Request for data sharing will be considered by the project leaders on written request. Deidentified participant data will only be made available after receipt of a written proposal and a signed data-sharing agreement. Furthermore, an amendment will be handed in to the MEC for ethical approval before starting this additional research.

## Ethics and dissemination

The non-WMO committee of the Medical Ethics Review Committee of Amsterdam University Medical Centres has confirmed that the Medical Research Involving Human Subjects Act (WMO) does not apply to this study (METc2023.0677). Consent to participate in the survey will be implied by answering and returning the survey. No explicit consent will be obtained, as only limited personal information is requested from patients during the online registration. The findings from this Delphi study will be disseminated through publication in an international peer-reviewed journal and presentations at (international) conferences. Inclusion of a significant number of experts and international federations engaged in the treatment of DTC is intended to enhance the adoption of the final COS in forthcoming clinical studies on the surgical treatment of DTC.

**Author affiliations**
[1]Department of Pediatric Surgery, Emma Children's Hospital, Amsterdam UMC, Amsterdam, Noord-Holland, The Netherlands
[2]Department of Pediatric Endocrinology, Emma Childrens' Hospital, Amsterdam UMC, Amsterdam, North Holland, The Netherlands
[3]Medical Library AMC, Amsterdam UMC location University of Amsterdam, Meibergdreef 9, Amsterdam, Netherlands
[4]Department of Pediatric Endocrinology, Wilhelmina Children's Hospital University Medical Center, Utrecht, Utrecht, The Netherlands
[5]Department of Pediatric Oncology, Princess Maxima Center for Pediatric Oncology, Utrecht, Utrecht, The Netherlands
[6]Department of Surgery, UMC Utrecht, Utrecht, Utrecht, The Netherlands
[7]Department of Endocrinology, Amsterdam UMC Location AMC Department of Internal Medicine, Amsterdam, North Holland, The Netherlands
[8]Department of Surgery, University Medical Centre Groningen, Groningen, Groningen, The Netherlands
[9]Department of Molecular Medicine and Surgery, Karolinska Institutet, Stockholm, Sweden
[10]Department of Internal Medicine, Erasmus Medical Center, Rotterdam, South Holland, The Netherlands
[11]Department of Radiology & Nuclear Medicine, Erasmus Medical Center, Rotterdam, Zuid-Holland, The Netherlands
[12]Department of Internal Medicine, Radboud University Medical Center, Nijmegen, Gelderland, The Netherlands
[13]Research Center for Functional Genomics, Biomedicine and Translation Medicine, Iuliu Hatieganu University of Medicine and Pharmacy, Cluj-Napoca, Romania
[14]SchildklierNL, Bussum, The Netherlands
[15]Department of Surgery, Amsterdam UMC, Amsterdam, North Holland, The Netherlands

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revisions to the manuscript from all co-authors. All authors (CFM, ASPvT, HMvS, SCC, MRV, EB, SK, RPP, FAV, RN-M, EJMNvD, AFE, JPMD, AS) contributed to the design of this study by providing advice and contributed with provision of critical revisions to this manuscript, either as study management group or as study steering group. AS contributed to the patient participation in the study. All authors approved the final version of this manuscript. JPMD is the guarantor.

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**ORCID iD**

Daniël J van de Berg http://orcid.org/0000-0003-3670-7422

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