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Additional offer of sigmoidoscopy in colorectal cancer screening in Germany: rationale and protocol of the decision-analytic modelling approach in the SIGMO study

Leonie Diedrich ,[1] Melanie Brinkmann ,[1] Maren Dreier,[1] Wendelin Schramm,[2] Christian Krauth[1]

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[1]Institute for Epidemiology, Social Medicine and Health Systems Research, Hannover Medical School, Hannover, Niedersachsen, Germany
[2]GECKO Institute for Medicine, Informatics and Economics, Heilbronn University, Heilbronn, Baden-Württemberg, Germany

Correspondence to
Ms Leonie Diedrich;
Diedrich.Leonie@mh-hannover.de

ABSTRACT

Introduction In Germany, statutory insured persons are entitled to a stool test (faecal immunochemical test (FIT)) or colonoscopy for colorectal cancer (CRC) screening, depending on age and sex, yet participation rates are rather low. Sigmoidoscopy is a currently not available screening measure that has a strong evidence base for incidence and mortality reduction. Due to its distinct characteristics, it might be preferred by some, who now reject colonoscopy. The objective of this study is to estimate the economic consequences of the additional offer of sigmoidoscopy for CRC screening in Germany compared with the present screening practice while considering the preferences of the general population.

Methods and analysis A decision-analytic modelling approach will be developed that compares the present CRC screening programme in Germany (FIT, colonoscopy) with a programme extended by sigmoidoscopy from a societal perspective. A decision tree and Markov model will be combined to assess both short-term and long-term effects, such as CRC and adenoma detection rates, the number of CRC cases, CRC mortality as well as complications. The incremental cost per quality-adjusted life year gained for each alternative will be calculated. The model will incorporate the general population's preferences based on a discrete choice experiment. Further, input parameters will be taken from the literature, the German cancer registry and health insurance claims data.

Ethics and dissemination Ethical approval for the study was obtained from the Ethics Committee of Hannover Medical School (ID: 8671_BO_K_2019). The findings of the study will be published in peer-reviewed journals and presented at national and/or international conferences.

Trial registration number DRKS00019010.

Strengths and limitations of this study

- The decision-analytic model enables estimations about the potential effects of the additional offer of sigmoidoscopy without real-life implementation.
- The incorporation of preferences from a discrete choice experiment into decision-analytic modelling for the screening of colorectal cancer is an innovative approach.
- The conceptualisation of the modelling approach will be based on extensive systematic literature search as well as in consultation with experts.
- As with all model-based economic evaluations comes a trade-off between feasibility on the one side and the comprehensive representation of reality on the other side.

INTRODUCTION

Colorectal cancer (CRC) is of high public health relevance as it is the third-leading cancer type worldwide. In 2020, it accounted for over 9% of cancer-related deaths, ranking it second after lung cancer. The majority of CRC cases and related deaths are found in countries with high or very high human development index.[1] In Germany, 25 990 women and 32 300 men were diagnosed with CRC in 2016.[2] The 5-year relative survival is about 60%, but can be significantly higher if detected in earlier stages.[3] Due to the slow development of colorectal carcinomas along the adenoma–carcinoma sequence and the available screening methods, CRC can often be detected at an early stage and in some cases even be prevented.[4] Common screening methods are colonoscopy and a guaiac-based or immunochemical stool test (gFOBT/faecal immunochemical test (FIT)). Colonoscopy is considered the gold standard, as precursor lesions, such as adenomas, can usually be removed directly. The effectiveness and cost-effectiveness of screening measures has been shown in several studies.[5–7] Observational studies demonstrated that colonoscopy is associated with an incidence and mortality

reduction of 69% (95% CI 23% to 88%) and 68% (95% CI 57% to 77%), respectively.[6]

As a consequence, many countries have implemented opportunistic or organised screening for CRC. In Germany, people with statutory health insurance are entitled to a colonoscopy or FIT within the framework of an organised and quality-assured screening programme, depending on their age and sex.[8] Currently, only 26% of men and 27% of women between 55 and 64 years of age undergo a preventive colonoscopy in Germany.[9] Participation for endoscopic screening measures is similarly low in other countries[10] and tends to be overall lower than for non-invasive stool tests.[11] Reasons for this can be the effort involved in preparation and colonoscopy itself. The required drinking of about 2 L of laxative in advance is often perceived as unpleasant and burdensome. In addition, colonoscopy is usually carried out with sedation, which leads to an inability to work on the day of the examination and makes it necessary to be accompanied home.[12] Complications and side effects such as intestinal injuries or pain after the examination are possible.[13] The risk for perforations is estimated to be 4 in 10 000 procedures (95% CI 2 to 5 in 10 000) and for major bleeding 8 in 10 000 procedures (95% CI 5 to 14 in 10 000).[14]

A different method for the early detection and prevention of CRC is sigmoidoscopy, which is an endoscopic procedure where only the lower part of the intestine is examined. Currently, sigmoidoscopy, similar to colonoscopy, is included in only few screening programmes, for example, parts of Italy.[15] Until the end of 2020, sigmoidoscopy was also a screening measure in parts of England[16] and has recently been replaced by FIT mainly due to a lack of qualified personnel.[17]

Compared with colonoscopy, where only observational studies exist, sigmoidoscopy has a superior evidence base. A recently published meta-analysis taking into account four large randomised controlled trials concludes that sigmoidoscopy leads to a 24% reduction in CRC incidence (95% CI 17% to 30%) and a 26% reduction in CRC mortality (95% CI 20% to 31%).[18] For sigmoidoscopy, a previously administered enema is usually sufficient for bowel preparation.[13] Moreover, it is less invasive than colonoscopy and does not require sedation. The risks of perforation and major bleeding are less common in sigmoidoscopy than colonoscopy (1 perforation in 10 000 sigmoidoscopies (95% CI 0.4 to 1.4 in 10 000); 2 major bleeding in 10 000 sigmoidoscopies (95% CI 0.7 to 4 in 10 000)).[14] In addition, sigmoidoscopy, similar to other screening strategies, is cost-effective in health economic systematic reviews compared with no CRC screening.[7 19 20]

Given the different characteristics of screening measures in terms of costs, benefit, harm and effort, the choice of screening is a preference-sensitive decision. Preference elicitations for CRC screening showed ambiguities regarding the most favoured measure and differences in subgroups.[21–23] Sigmoidoscopy might be preferred by specific populations who would otherwise reject colonoscopy. Nonetheless, sigmoidoscopy is currently not available to insured persons in Germany. Due to limited reimbursement options, it cannot be used for CRC screening, even though sigmoidoscopy is recommended in the German S3 guideline in case of a refusal of colonoscopy.[24]

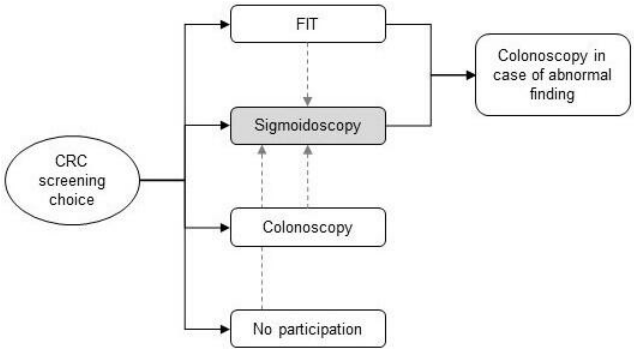

Figure 1 Potential participation shifts with the additional offer of sigmoidoscopy (dotted arrows). CRC, colorectal cancer; FIT, faecal immunochemical test.

With the currently low participation rates, the substantial evidence body of sigmoidoscopy, and the different preferences for screening procedures, the question arises whether sigmoidoscopy is a reasonable addition to the CRC screening programme in Germany. It is difficult to estimate, how an additional offer of sigmoidoscopy would impact uptake and cost-effectiveness of CRC screening. Participation rates might increase by mobilising more insured persons. But also, the number of participants can shift between the procedures (eg, from FIT to sigmoidoscopy) (figure 1). This has implications for the number of detected CRC cases as well as for CRC mortality. To assess the economic consequences of an extended screening offer, a broader approach is necessary. A mere focusing on the technology (level), as is the case in most existing economic evaluations trying to identify the single optimal screening strategy, is not sufficient.[7] Insured persons can choose between several measures (eg, colonoscopy or FIT), so that alternative procedures are used by different groups of individuals. Preferences of the relevant population need to be incorporated to estimate the potential take-up of the screening programme. This systemic perspective constitutes a novel approach to economic evaluations in CRC screening.

Objectives

The 'sigmoidoscopy as an evidence-based CRC screening test—a possible option?" study (SIGMO) combines (1) a discrete choice experiment (DCE) to determine the preferences of the general population on CRC screening with (2) a decision-analytic modelling approach comparing the current CRC national statutory cancer screening programme (standard care) with a screening programme additionally offering sigmoidoscopy. To the best of our knowledge, this is the first model-based economic evaluation of CRC screening that takes the general population's preferences in Germany into account.

The present protocol describes the decision-analytic modelling approach (second part of the SIGMO study). The protocol of the DCE was published elsewhere.[25] The specific objectives of the modelling approach are to evaluate the effects of the extended screening offer on:

1. The participation rates and participation shift between the different screening measures.
2. Benefit (life years, quality of life, CRC deaths and CRC cases averted), harm (complications), cost and cost-effectiveness (cost per quality-adjusted life year (QALY)).

METHODS

Decision-analytic modelling combines various sources for input parameters with defined assumptions on the course of events in a mathematical framework.[26] In this way, it is possible to draw conclusions about the consequences of certain interventions even before implementation in the healthcare system. The methodology of this study is based on the guidelines for good practices in modelling by the International Society for Pharmacoeconomics and Outcomes Research and the Society for Medical Decision Making joint working group.[26] The decision problem must be specified first. This is followed by the conceptualisation of the model and the development of the model structure. Furthermore, suitable input parameters will be determined. The model is then analysed and validated. An overview of the methodological approach is presented in table 1. The SIGMO study will be conducted from March 2019 to February 2023.

Specification of the decision problem

The current CRC screening practice in Germany (standard care) will be compared with a screening offer extended by sigmoidoscopy. The relevant population group is the 50-to-75-year-old general population with an average, age-appropriate risk of CRC.

According to the Cancer Screening Directive of the Federal Joint Committee,[8] the current standard care includes an annual FIT at the ages of 50–54 (since 2017 replacing gFOBT). In addition, the statutory insured persons are eligible for a screening colonoscopy from the age of 55, which can be repeated once after 10 years, unless the first colonoscopy was performed after the age of 65. In 2019, the eligibility age of men for a colonoscopy has been lowered to 50 years, because of their relatively higher risk of developing CRC compared with women. If colonoscopy is rejected, FIT can be performed every 2 years for those persons over 55 years of age.

As the alternative, a screening programme is evaluated that includes sigmoidoscopy in addition to the screening strategies outlined above (colonoscopy and FIT). There is no recommendation on the optimal interval of the use of sigmoidoscopy in CRC screening. Since the German S3 guideline recommends sigmoidoscopy when colonoscopy is rejected, the considered interval should be similar to that of colonoscopy.[24] Also, the European Guideline for Quality Assurance in Colorectal Cancer Screening and Diagnosis concludes the optimal interval being not less than 10 years for endoscopic screening measures.[27] The analysed interval of sigmoidoscopy will thus be analogous to colonoscopy in standard care with a target age range

Table 1 Overview of methodological key points

Methodological aspects of health economic evaluations	Study design
Modelling approach	Decision tree and Markov model
Medical benefit	Life years gained, quality-of-life, CRC cases averted, CRC deaths averted
Comparators	Current CRC screening Programme (FIT+colonoscopy) versus screening programme extended by sigmoidoscopy
Participation rates in the intervention	Based on preferences from a Discrete Choice Experiment (first part of the SIGMO study)
Cost types	Direct and indirect
Health-economic perspective (societal, employer, etc)	Societal
Methods for determining medical benefits	Literature search, cancer registry data
Methods for determining economic benefits	Literature search, health insurance claims data
Methods for health economic outcomes (eg, ICER, NMB, etc)	ICER
Time horizon	Lifetime
Discounting: effect and/or cost	Effect and cost discounted by 3%
Population/patient characteristics	50-to-75-year-old general population at average risk of CRC
Validation	Consultation of experts; validation against dependent and independent data

CRC, colorectal cancer; FIT, faecal immunochemical test; ICER, incremental cost-effectiveness ratio; NMB, net monetary benefit.

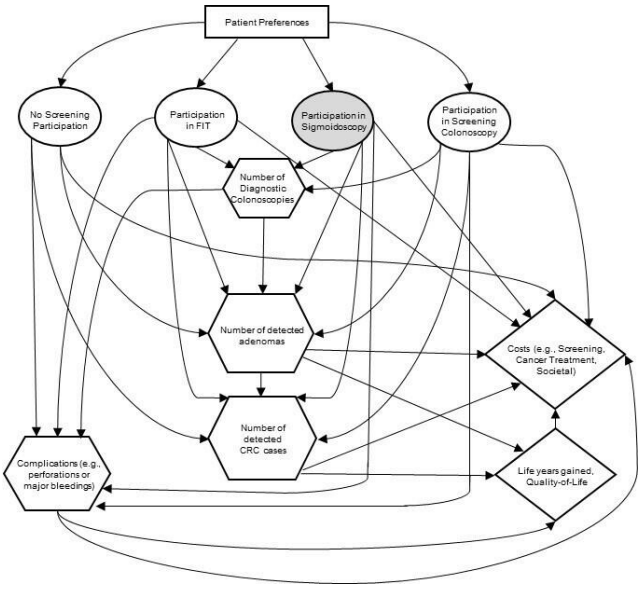

Figure 2 Influence Diagram of the additional offer of sigmoidoscopy. CRC, colorectal cancer; FIT, faecal immunochemical test.

of 50–75 years of age for men and 55–75 years of age for women, respectively. If any abnormal findings (precursor lesions or CRC) are detected during sigmoidoscopy, a follow-up diagnostic colonoscopy will be performed.

Both short-term and long-term outcomes are of interest, when evaluating the additional offer of sigmoidoscopy. The short-term detection rates of CRC and the precursor lesions are to be assessed. Furthermore, the costs per case detected (including indirect costs and costs for treatment and screening) and the total costs of screening will be determined. The economic evaluation will identify the long-term effects of the extended offer on the number of CRC cases, CRC-related mortality, complications (eg, perforations or major bleeding), life years gained and quality of life. CRC cases averted and CRC-related deaths averted will also be assessed. The cost per QALY gained (incremental cost-effectiveness ratio, ICER) of the extended programme compared with standard care will be calculated.

The time horizon applied in the economic model will be lifetime to represent the prospective consequences of CRC and screening. The study will be conducted from a societal perspective. As recommended by the German Institute for Quality and Efficiency in Health Care, the annual discount rate of costs and effects will be 3% and varied to 0% and 5% in sensitivity analyses.[28]

Figure 2 illustrates the anticipated influence effects if sigmoidoscopy is additionally offered for CRC screening.[29] The underlying assumption is that divergent preferences in the general population lead to disparate participation rates in screening measures. The measures differ in their sensitivity, specificity and predictive values. Cost of CRC treatment increases with progressing cancer stages. The impact on costs and QALYs results therefore primarily from altered detection rates of adenomas and CRC cases.

Conceptualisation of the model

The conceptualisation of the model will be based on an extensive systematic literature search in MEDLINE, Embase, EconLit, Web of Science, the British National Health Service Economic Evaluation Database, as well as the Cost-Effectiveness Registry (Tufts Medical Center). The search complies with the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) checklist[30] and aims to identify already existing models in the field of CRC screening. From this, approaches for the model structure can be derived. The search strategy consists of two blocks describing 'colorectal cancer screening' and 'economic evaluation'". Both blocks include various search terms, which are then combined.

The conceptualisation and development of the model structure will be undertaken in consultation with experts from the field of decision-analytical modelling. First, an appropriate modelling approach must be identified to correctly model the natural development of CRC and the effects of screening. Since both short-term and long-term effects of an extended screening offer are to be investigated, a combined approach of decision tree and Markov model is recommended.[31]

A decision tree is a visual representation of all possible decision options and the events that may follow each option.[32 33] It starts with a decision node. Following, each possible consequence is represented as a branch. At a chance node, different events can occur which are not predictable and thus embody the uncertainty of the decision problem. Therefore, there are various paths that lead from the root to the end node and end there with an outcome. The expected value for each alternative is formed by the sum of the individual values on the branches, weighted according to their probabilities. Due to its simplicity, a decision tree is a suitable method for representing a short time horizon.

In Markov models on the other hand, uncertain events are modelled as transitions between defined health states. For this reason, Markov models are also referred to as a form of state-transition modelling.[32] The health states are mutually exclusive and collectively exhaustive. They reflect the natural history of the disease and the effects of the intervention. The time horizon is divided into equal increments of time (Markov cycles) with fixed event rates. Within the Markov model, a hypothetical cohort is progressing through the health states in a defined time frame at given cycles. As the cycles proceed, transitions to other health states are possible based on defined transition probabilities. A special characteristic of the Markov model is the assumption that transition probabilities depend solely on the state of the current cycle, known as the Markovian 'memoryless' property.[34] The health states are assigned with certain utility values and costs. The expected values for the costs and effects of the alternatives result from the accumulation of the cycle-specific values. This allows the derivation of ICERs. The advantage of Markov models is that time-varying parameters such as

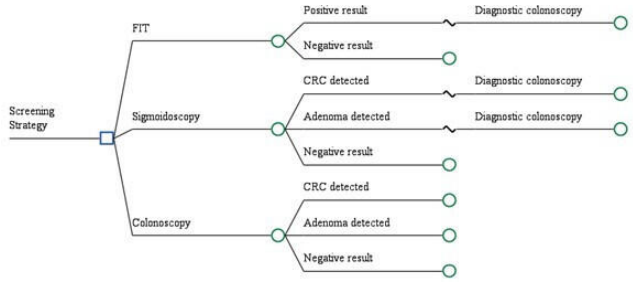

Figure 3 Exemplary decision tree illustrating different screening measures. CRC, colorectal cancer; FIT, faecal immunochemical test.

quality of life or costs can be incorporated enabling to analyse a longer time horizon.[31]

The combination of different modelling approaches for the evaluation of CRC screening seems appropriate, as the Markov model can build on the results of the decision tree. It can take into account the time-to-event or time-to-progression, which is particularly crucial in cancer screening. Moreover, the progression of the disease can be adequately represented as the different stages (Markov states) correspond to the stage-based natural history of CRC along the adenoma–carcinoma sequence. The moderate number of possible states, as well as the repeated occurrence of screening events also supports the planned modelling approach.

Model structure

Decision tree

A decision tree will first be developed for each of the two comparative alternatives of standard care and the extended offer. In the tree structure, each screening strategy (FIT, sigmoidoscopy, colonoscopy) represents a branch (figure 3). The relative distribution of the general population between the strategies will be an expression of preferences. Following events, such as 'CRC detected', will be represented by subsequent branches of the tree and the assigned probabilities. From the two decision trees the number of detected cases, the screening costs and costs per case detected can be derived. The comparison of standard care and the extended offer will indicate potential participation shifts towards sigmoidoscopy. It can be concluded whether more cases of CRC and its precursors can be detected by the additionally offered sigmoidoscopy. Furthermore, statements about potential additional costs compared with the standard care are supported.

Markov model

The subsequent Markov model will be based on the results from the decision tree analysis. Standard care and the extended screening offer will be each represented through a Markov model. In either scenario, the different screening strategies will be linked with the natural history. The health states can be simplified as 'healthy', 'detected/non-detected precursor lesions (adenomas)', 'CRC' and 'dead'. The stages of the adenomas as well as of the carcinomas in the final model will be further specified with regard to their histological character or state (eg, localised, regional, distant). The cycle length will be set for 1 year. In each cycle, a remaining in a state or transitions will be possible, for example from 'healthy' to 'adenoma' or from 'CRC' to 'dead'. The different screening strategies influence the probabilities of the detection of the precursors as well as the disease itself, depending on their sensitivity and specificity. In both compared alternatives, a diagnostic colonoscopy is performed in case of abnormal findings in FIT and/or sigmoidoscopy. It is assumed that adenomas are removed in endoscopic procedures and that the surveillance of precursor lesions and the disease is carried out in compliance with current guidelines. The hypothetical cohort will run through as many cycles until a defined amount reaches the state "dead". In this way, the lifetime of the cohort is represented.

Input parameters

The model will be based on various data from different sources: first, the DCE we conducted; second, systematic literature search; and thirdly, cancer registry and health insurance data.

Discrete choice experiment

The public preferences regarding the screening strategy will be identified with a DCE (first part of the SIGMO study). This is a method rooted in random utility theory for measuring stated preferences.[35] Individuals are presented with several choice sets that have two or more hypothetical alternatives. These choice sets are characterised by different attributes and differ in the characteristics of these attributes (level). Preferences are derived from the discrete choices between these alternatives. The attributes and levels in the unlabelled DCE will represent the different screening measures (colonoscopy, sigmoidoscopy, and FIT). Therefore, it will be possible to identify subgroups that prefer certain measures (eg, a non-invasive procedure like FIT). Based on the preference weights, the potential uptake will be determined and incorporated into the model. To collect the choice data, a written questionnaire will be sent to a random sample of 50–60-year-old insurees of the health insurance company AOK Lower Saxony. A detailed study protocol describing this survey has already been published.[25]

Systematic literature review

The parameters for health utilities, costs as well as the transition probabilities will be based on further extensive systematic literature search in order to support the model on the best possible evidence. To model the screening strategies, the test performance characteristics will also be taken from the literature. A separate systematic search will be carried out for each parameter in compliance with PRISMA,[30] with the reasoning and selection of the data being documented. Various appropriate databases, like Medline, Embase or the Tufts Cost-Effectiveness Registry will be used. Data from national statistics and guidelines will also be included where

relevant. German data will be preferred, as the model depicts the German healthcare system. Whenever necessary, meta-analysis will be applied to aggregate multiple data. The data obtained will be checked for plausibility by experts.

Cancer registry and health insurance data

To represent the natural history of CRC in the model, current localisation-based data on CRC incidence and mortality by age and gender will be used, which is provided by the German Centre for Cancer Registry Data. In addition, data on healthcare utilisation from the statutory health insurance company AOK Lower Saxony will be included in the model to adequately reflect the German healthcare context.

Analysis and validation

Analyses will be performed in TreeAge Pro (TreeAge Software, Williamstown, Massachusetts, USA). We will estimate the ICERs of the extended offer with sigmoidoscopy compared with standard care. In the base case analysis, model calculations will be done with the most probable parameter constellations. In sensitivity analyses, the robustness of the results will be tested. Different parameters and assumptions, such as the starting age of sigmoidoscopy, will be systematically changed stratified by sex to evaluate the effect of these modifications on the results of the analysis. The choice of sensitivity analysis and the varied parameter is to be made with reasonable deliberation. Probabilistic sensitivity analysis will be conducted to assess parameter uncertainty. For validation of the model, clinical experts as well as experts in the field of modelling will be consulted. The results will also be validated against the literature.

Patient and public involvement

No patients were involved in the development of the research question or the conceptualisation of the decision-analytic modelling approach.

DISCUSSION

Strengths

The presented study enables an estimation of the potential effects of a new strategy for cancer screening without real-life implementation. It can provide decision-makers with important information on whether or not sigmoidoscopy should be made available as a screening method. The incorporation of preferences into decision-analytic modelling for the screening of CRC is an innovative approach. Since sigmoidoscopy is de facto not available in Germany at present, no data on participation exists. The DCE in the SIGMO study provides valuable information on the potential uptake, which is influenced by diverging preferences. By parameterizing this data in a model, it is possible to make predictions about a feasible screening strategy that is potentially preferred by some. The results of the DCE reflect thereby the preferences of the directly eligible population, which ensures more accurate estimations. Above that, the decision-analytic modelling approach is based on several different data sources to generate valid results.

Limitations

There are limitations to this modelling approach. With all model-based economic evaluations comes a trade-off between feasibility on the one side and the true depiction of reality on the other side. The more details are included in a model, the more accurate the results are. Yet, this reduces transparency and comprehensibility. It is also important to note that the model relies on the data included, which will be partially obtained through systematic research. A lack of high-quality data would limit the validity of the study. Even though the model structure will be based on the literature and experts' opinions, the structural assumptions might not reflect all consequences of the events of interest. Since modelling is an iterative process, possible changes and deviations from the study protocol are possible, which will be documented.

ETHICS AND DISSEMINATION OF THE RESULTS

Ethical approval for the study was obtained from the Ethics Committee of Hannover Medical School (ID: 8671_BO_K_2019). Informed consent is not required for this part of the SIGMO study since no patient-related data are included in the economic evaluation. The findings of the study will be published in peer-reviewed journals and presented at national or international conferences. Additionally, the study results will be communicated to the funder by annual progress reports and a final report within 6 months after completion of the study.

Contributors Conceptualisation: MD and CK. Funding acquisition: MD and CK. Methodology: LD, WS and CK. Project administration: MD and CK. Supervision: MD, WS and CK. Writing—original draft: LD. Writing—review and editing: LD, MB, MD, WS and CK. All authors have provided input to, reviewed, edited and approved the final version.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

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ORCID iDs

Leonie Diedrich http://orcid.org/0000-0002-3960-961X
Melanie Brinkmann http://orcid.org/0000-0003-2636-2328

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