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REVIEW

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A scoping review of metamodeling applications and opportunities for advanced health economic analyses

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ABSTRACT

Introduction: Metamodels, also known as meta-models, surrogate models, or emulators, are used in several fields of research to negate runtime issues with analyzing computational demanding simulation models. This study introduces metamodeling and presents results of a review on metamodeling applications in health economics.

Areas covered: A scoping review was performed to identify studies that applied metamodeling methods in a health economic context. After search and selection, 13 publications were found to employ metamodeling methods in health economics. Metamodels were used to perform value of information analysis (n = 5, 38%), deterministic sensitivity analysis (n = 4, 31%), model calibration (n = 1, 8%), probabilistic sensitivity analysis (n = 1), or optimization (n = 1, 8%). One study was found to extrapolate a simulation model to other countries (n = 1, 8%). Applied metamodeling techniques varied considerably between studies, with linear regression being most frequently applied (n = 7, 54%).

Expert commentary: Although it has great potential to enable computational demanding analyses of health economic models, metamodeling in health economics is still in its infancy, as illustrated by the limited number of applications and the relatively simple metamodeling methods applied. Comprehensive guidance specific to health economics is needed to provide modelers with the information and tools needed to utilize the full potential of metamodels.

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Metamodeling; surrogate modeling; emulators; health economic analyses; computational burden

1. Introduction

Health economic decision modeling is common practice in evaluations of health care interventions informing policy decisions on reimbursement, resource allocation, and research prioritization. However, ongoing personalization within health care creates additional complexities for commonly used health economic modeling methods, such as cohort state-transition models, with multiple clinical pathways based on individual risk profiles and preferences [1–3]. Consequently, there seems a trend towards the use of microsimulation methods, such as patient-level state-transition modeling [4] and discrete event simulation [5]. Although such modeling methods allow individual patients to be traced throughout simulations, their development may be more complex, and their analysis requires more computational power compared to traditional cohort simulation models [6].

Long runtimes required for simulating sufficient hypothetical patients to obtain stable outcomes has been a major drawback of the analysis of patient-level simulation models [7]. Despite advances in computational power, there are still scenarios in which available computer resources are insufficient to perform computationally demanding analyses within reasonable time horizons. Depending on the analysis that needs to be performed, runtime may increase in magnitude and become infeasible. For example, a runtime of a single (deterministic) model simulation of one minute can result in a runtime of several days, if a probabilistic sensitivity analysis of 10,000 samples is performed using that model. Even if this runtime would be considered feasible, repeatedly performing this analysis, for example to apply optimization algorithms or to perform value of information analysis using an inner and outer simulation loop [8,9], would no longer be feasible.

Metamodels, also referred to as meta-models, surrogate models, or emulators, can be used to negate runtime issues of complex models and analyses, by approximating the outcome of computationally demanding models within feasible time [5,10]. More specifically, a metamodel is defined as a function that approximates the output of a simulator (i.e. original model) based on input provided to that simulator [11]. Since such an approximation function can typically be evaluated almost instantaneously, it can be used to reduce runtime issues with computationally demanding analyses as simulator substitute. For example, regression techniques can be used to estimate relations between model inputs and outputs based on results of a probabilistic sensitivity analysis. This regression model can subsequently be used to provide a fast approximation of model outcomes based on model inputs and, thereby,

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perform other computationally demanding analyses. This application of metamodels as substitutes to perform additional simulation-based analyses can be classified as simulation modeling. Alternatively, metamodeling applications can be classified as statistical modeling if their objective and use is to obtaining insights into relations between simulator inputs and outputs.

Although the field of metamodeling has been studied well in areas such as engineering [12,13] and environmental modeling [14,15], implementation in health economics appears to be limited so far. Besides that modelers might not feel a need to apply metamodeling methods, this may also be due to unfamiliarity or a lack of guidance on the development of metamodels, which involves design choices such as selecting the method to be used, structuring the model, structuring the dataset used to fit the metamodel, and fitting the metamodel [16–18]. Although development of metamodels may seem challenging, when developed, metamodels of complex (patient-level) health economic models have great potential to substantially decrease model runtime and, thereby, enable complex analyses to be performed within feasible time horizons.

This study aims to provide an overview of previous and potential applications of metamodeling methods in health economics. To this end, a scoping review is performed to identify prior metamodeling studies and, thereby, potential metamodeling applications in a health economic context. Although metamodeling is primarily introduced here as a means towards reducing runtime issues with computationally demanding analyses, the scope of this review is not restricted to simulation modeling, as applications classifiable as statistical modeling are also considered. Results of this study should create awareness of, and provide an introduction to, the application of metamodeling methods in health economics.

2. Scoping review on metamodeling applications in health economics

A literature review was performed to identify possible applications of metamodeling in health economics. The search was performed in PubMed on 19 February 2018, employing primary search terms on metamodeling, meta-modeling, surrogate modeling, and emulators, combined with well-known and previously used key words on modeling, simulation, and health economics in title or abstract [19]. Refer to Supplementary Materials 1 for the exact search strategy. PubMed was consulted as single database, as result of an iterative strategy in which additional potentially relevant databases were identified by cross-referencing from the initial search results. Since studies that apply metamodeling methods in a health economic context were expected to be published in the general health economic literature, and PubMed has good coverage of this literature, this database was selected first. Because no publications from journals that are not indexed in PubMed were obtained by cross-referencing, no additional databases were searched. Health economic MeSH terms were not included in the search strategy, since a recommended search strategy including MeSH terms [20] was considered too narrow. Hence, a previously used broader strategy for identifying health economic publications was adopted. No exclusion criteria were applied during the search in PubMed, i.e. all results were included in an initial sample for screening based on title and abstract.

Publications were assessed based on title and abstract by one reviewer (KD) and excluded if no modeling methods were applied or if a modeling study did not relate to: health economics, health logistics, or epidemiology, as the objective of the review was to identify previous and potential applications of metamodeling methods in health economics. Consequently, methodological studies discussing a theoretical framework for metamodeling in a health economic context without an (illustrative) application were excluded. Next, publications in the refined sample were assessed for inclusion based on full-text and the same exclusion criteria. In this process, a proposition whether to include or exclude a publication was made by KD. For each publication in the refined sample, the final decision to include a publication was based on consensus between KD and HK by either adopting or rejecting the proposed inclusion or exclusion. Excluded publications were categorized according to the reason for exclusion. The included sample was enriched by cross-referencing based on full-text [21], which resulted in the final sample used for analysis. Inclusion of cross-references was also based on consensus between KD and HK following a proposition by KD.

The final sample was analyzed to identify general study characteristics, metamodeling specific information, and cross-references. More specifically, the following general study characteristics were identified: year of publication, journal of publication, clinical context, type of study, and method used for developing the original model (i.e. simulator). Identified information specifically on metamodeling included: metamodeling technique used, analysis performed using the metamodel, design of experiments used for generating input data for fitting metamodels, type of input parameters, type of output parameters, and software used for metamodel development. These aspects were selected to identify why a metamodel was developed, which methods were used to develop this metamodel, and how these metamodeling methods were applied. Study characteristics and metamodeling information were extracted by KD following a full-text review of all publications, the results of which were discussed with HK for validation.

3. Results

The literature search yielded 478 publications, which were all included in the initial sample for title and abstract screening (Figure 1). A total of 452 publications (95%) were excluded based on title and abstract. These publications predominantly related to in vitro and in vivo research (n = 186, 41%), engineering research (n = 68, 15%), environmental research (n = 57, 13%), and biomedical research (n = 45, 10%). From the resulting 26 publications in the refined sample, 16 publications (62%) were excluded based on full-text screening. These publications were excluded, because the referred-to metamodels were: 1) models developed using an identical modeling technique yet with different model parameters (n = 3, 19%), 2) meta-analyses for defining prediction or classification models (n = 3, 19%), 3) (prediction) models developed for use in non-health economic contexts (n = 3, 19%), 4) ensembles or comparisons of

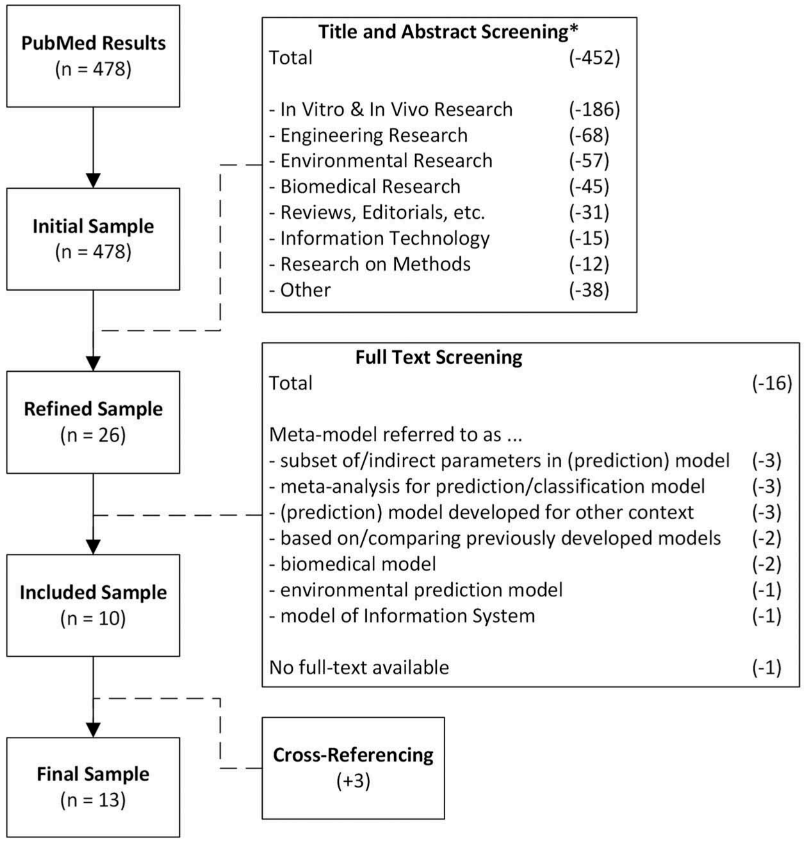

Figure 1. Graphical representation of the search and selection process.

* Exclusion categories not mutually exclusive.

previously developed models (n = 2, 13%), 5) related to biomedical research (n = 2, 13%), 6) related to environmental research (n = 2, 13%), or 7) related to information systems research (n = 1, 6%). One publication (6%) was excluded because the full-text was not available, and could also not be obtained from the publication authors [22]. The included sample [23–32] was enriched by three cross-references [33–35], resulting in a final sample of 13 publications for analysis, representing a total of 14 case studies, as one publication includes two different case studies [27].

Characteristics of publications included in the final sample are presented in Table 1 and results following extraction of key features with respect to the applied metamodeling methods are presented in Table 2. As presented in Table 1, clinical contexts of the studies included: inflammatory arthritis, human immunodeficiency virus, excessive alcohol consumption, influenza, varicella, breast cancer, renal transplantation, multiple sclerosis, osteoporosis, and deep vein thrombophlebitis. One study did not focus on a specific disease area but modeled an emergency department. Three studies employed fictitious models, representing a hypothetical case study. Most publications represented traditional health economic studies that compare cost and effectiveness outcomes for different treatment strategies (n = 10/13, 77%), two represented infectious disease modeling studies (15%), and one represented a health care logistics study (8%). Applied modeling techniques for the original model (i.e., simulator) were: cohort state-transition modeling (n = 6/14, 43%), agent based modeling (n = 3/14, 21%), decision tree analysis (n = 2/14, 14%), microsimulation state-transition modeling (n = 2/14, 14%), and hybrid microsimulation modeling (n = 1/14, 7%). Finally, an upward trend in applications of metamodeling methods over time can be observed from Tables 1 and 2.

Metamodels were most often developed and applied to perform value of information analyses (n = 5/13, 38%), followed by deterministic sensitivity analyses (n = 4/13, 31%). With regard to the latter, metamodels were either used to obtain stable outcomes over multiple runs with the same input values, or to obtain insights into parameter importance directly. Single studies employed metamodeling for model calibration, optimization, probabilistic sensitivity analysis, and extrapolation to other countries. The metamodel used for extrapolation to other countries was developed based on a parameter subset of a country-specific simulator, and applied to estimate outcomes for other countries after gathering data on the included parameters for these countries. Of these applications, obtaining stable outcomes over multiple runs, performing model calibration, probabilistic sensitivity analysis, value of information analyses, and optimization, directly relate to negating runtime issues as reason for employing metamodeling methods. Most publications included metamodels that were based on linear (logistic) regression (n = 8/13, 62%) or Gaussian Process modeling (n = 4/13, 31 %). Other applied metamodeling techniques were (ensembles of) neural networks, symbolic regression, and regression splines. Methods used to generate samples

Table 1. Study characteristics of publications included in the final sample for analysis.

First Author	Year of Publication	Journal of Publication	Clinical Context	Type of Study	Simulator Type
Merz	1992	Medical Decision Making	Deep Vein Thrombophlebitis	Health Economic Modeling	Decision Tree Model
Tappenden	2004	Health Technology Assessment	Multiple Sclerosis	Health Economic Modeling	Cohort State-transition Model
Stevenson	2004	Medical Decision Making	Osteoporosis	Health Economic Modeling	Microsimulation State-transition Model
Woodroffe	2005	Health Technology Assessment	Renal Transplantation	Health Economic Modeling	Microsimulation State-transition Model
Rojnik	2008	Value in Health	Breast Cancer	Health Economic Modeling	Cohort State-transition Model
Jalal	2013	Medical Decision Making	NA (Fictitious)	Health Economic Modeling	Cohort State-transition Model
Willem	2014	PLoS Computational Biology	Influenza & Varicella	Infectious Disease Modeling	Agent-Based Model
Jalal	2015	Medical Decision Making	NA (Fictitious)	Health Economic Modeling	Decision Tree Model & Cohort State-transition Model
Andrianakis	2015	PLoS Computational Biology	HIV	Infectious Disease Modeling	Agent-Based Model
Angus	2016	European Journal of Public Health	Excessive Alcohol Consumption	Health Economic Modeling	Hybrid Microsimulation Model
Jutkowitz	2017	Pharmacoeconomics	Gout, Inflammatory Arthritis	Health Economic Modeling	Cohort State-transition Model
Yousefi	2018	Artificial Intelligence in Medicine	Emergency Department	Health Care Logistics	Agent-Based Model
Jalal	2018	Medical Decision Making	NA (Fictitious)	Health Economic Modeling	Cohort State-transition Model

NA = not applicable.

Table 2. Results of analyzing the final sample to identify metamodeling specific information.

First Author	Year of Publication	Metamodeling Technique	Analysis with Metamodel	Design of Experiments	Simulator Parameters	Metamodeling Outcome	Metamodeling Software
Merz	1992	Logistic Regression	Deterministic Sensitivity Analysis (Parameter Influence)	Random Sampling (MC)	All	Preferred Treatment Strategy	GLIMS
Tappenden	2004	Linear Regression & Gaussian Process	Value of Information	Random Sampling (MC) & Unknown Efficient Design	All & Subset	ENB	Matlab
Stevenson	2004	Gaussian Process	Probabilistic Sensitivity Analysis	Random Sampling (MC)	Subset	Costs, QALYs & Years on Pharmaceutical Treatment	-
Woodroffe	2005	Linear Regression	Deterministic Sensitivity Analysis (Stable Outcomes)	Deterministic Ranges	Subset	Costs & QALYs	-
Rojnik	2008	Linear Regression & Gaussian Process	Value of Information	Latin Hypercube Sampling & Random Sampling (Uniform)	All	Costs & QALYs	SAS & GEMSA
Jalal	2013	Linear Regression	Deterministic Sensitivity Analysis (Parameter Influence)	Random Sampling (MC), One-Factor-at-a-Time & Full Factorial Design	All	Costs, QALYs & NHB	Stata
Willem	2014	Symbolic Regression	Deterministic Sensitivity Analysis (Parameter Influence)	Latin Hypercube Sampling	Subset & All	Clinical Attack Rate, Moment of Epidemic Peak & QALYs	Mathematica
Jalal	2015	Linear Regression	Value of Information	Random Sampling (MC)	All	Incremental Net Benefit	R & MS Excel
Andrianakis	2015	Gaussian Process	Model Calibration	Latin Hypercube Sampling	Subset	Population size, Incidence & Prevalence	-
Angus	2016	Linear Regression	Extrapolation to other countries	Fractional Factorial Design	Subset	Costs & QALYs	Stata
Jutkowitz	2017	Linear Regression	Value of Information	Random Sampling (MC)	All	Opportunity Loss	R
Yousefi	2018	(Ensembles of) Neural Networks	Optimization	Latin Hypercube Sampling	Subset	Average Length of Stay	Matlab
Jalal	2018	Spline Regression	Value of Information	Random Sampling (MC)	All	Opportunity Loss	R

MC = Monte Carlo; GLIMS = Generalized Linear Interactive Modeling System; ENB = Expected Net Benefit; QALYs = Quality Adjusted Life-Years; GEMSA = Gaussian Emulation Machine for Sensitivity Analysis; NHB = Net Health Benefit.

for fitting metamodels, i.e. design of experiments, included: sampling using deterministic ranges for one parameter at a time, random sampling using either uniform or parameter-specific distributions (i.e. Monte Carlo sampling), Latin Hypercube sampling, and fractional and full factorial designs. Eight studies (62%) defined their metamodel using the same parameters that defined the simulator, whereas others (also) used subsets of simulator inputs (n = 7/13, 54%). Outcomes of interest, i.e. dependent variables or response variables, included (aggregated) health economic outcomes (e.g. costs, quality adjusted life-years, and opportunity loss), as well as epidemiological outcomes (e.g. disease population size and clinical attack rate) and process outcomes (e.g. average length of stay).

4. Conclusions

Applications of metamodeling methods in health economics are scarce. Studies applying metamodeling methods to negate runtime issues with computational demanding analyses of health economic models illustrate its potential to serve several objectives, such as obtaining stable outcomes over multiple runs with the same input values, performing model calibration, probabilistic sensitivity analyses, value of information analyses, and optimization. Additionally, not directly relating to runtime issues, metamodels have been used to obtain insights into parameter importance (i.e. deterministic sensitivity analyses) and for extrapolation to other countries. Linear (logistic) regression, symbolic regression, regression splines, Gaussian Processes, and neural networks were techniques used to develop metamodels. Most original health economic models, i.e. simulators, were cohort-based, rather than microsimulation, i.e. patient-level, simulation models. Different design of experiments methods were used to generate input data for fitting metamodels, including: random designs, full factorial designs, fractional factorial designs, and Latin Hypercube designs. Predicted outcomes, i.e. response variables or dependent outcomes, were mostly health economic outcomes, such as costs and quality adjusted life-years.

5. Expert commentary

Metamodeling methods have traditionally been applied to address runtime issues with computationally expensive simulation models and their corresponding analysis in different fields of research, such as engineering and environmental modeling. Although computational burden in health economics may typically be perceived as matter of concern only for microsimulations, results show that runtime issues are not only applicable to analyses of patient-level simulation models, but also to analyses of cohort-based simulation models. The growth in metamodeling applications over time may, therefore, not only be due to an increase in health economic publications or the use of microsimulation methods, such as patient-level state-transition modeling and discrete event simulation, but also due to an increase in applications of advanced model analyses, such as value of information analyses [36].

According to its aim of reducing runtime issues associated with computational demanding analyses [5,10], most identified applications of metamodeling in health economics were aimed at addressing runtime issues with analyzing cohort-based or patient-level simulation models, for example to perform model calibration, probabilistic sensitivity analyses, value of information analyses, or optimization. Interestingly, applications were not limited to those addressing computational issues, as metamodels have also been developed to obtain insights into parameter importance [26,27,33] and to extrapolate simulation models to other countries [30]. One publication developed and used a metamodel to obtain stable outcomes over multiple simulator runs [24], though this indirectly relates to addressing runtime issues, because running this simulator for a sufficiently large number of hypothetical patients would also stabilize outcomes. The required number of simulated individuals might be so high, however, that it becomes infeasible to perform the required analyses, i.e. runtime is an issue.

The different identified reasons for applying metamodels show these methods' potential to address several challenges in the field of health economic modeling, not only from a simulation modeling perspective but also from a statistical modeling perspective. Especially the use of metamodeling methods to obtain insights in characteristics of simulators, i.e. original models, appears from the review results. Such analyses can be classified as statistical modeling, and general methods to this end have been described previously [37]. Although straightforward structures to interpret, such as simple linear regression models, can be used as a first step in performing comprehensive sensitivity analyses [38], no useful information regarding simulator characteristics can be obtained from more complex metamodeling structures, such as symbolic regression or Gaussian processes, as these structures are hard to interpret. Use of such complex structures in a simulation modeling context to perform fast simulations to approximate simulator outcomes, however, is straightforward, which may be an explanation of why most identified applications used metamodeling as a toolbox to this end.

Despite computational challenges, successful applications, and ample utilization opportunities, metamodeling in health economics appears to be in its infancy, as only a small number of applications could be identified. Reasons for this limited number of applications may include the absence of a need to perform computer resource demanding analyses, for example because these are not required by decision makers, or that only few health economic modelers are aware of these methods and their potential. Another reason for the limited number of applications may be the lack of comprehensive guidance, specifically in a health economic context. Some guidance has been identified in the reviewed sample [23,25,27,32], though this guidance is not coherent, nor comprehensive. Furthermore, guidance available for metamodeling in other fields of research [16–18,39–41] is not completely transferrable to, and comprehensive for, application in health economic analyses.

The limited uptake of, and guidance for, metamodeling in health economics is also illustrated by the diversity of metamodeling methods identified in the review. Linear regression was the technique applied for developing the majority of metamodels, and although linear regression is well known due to its prominent role in statistics, it is rarely used for metamodeling in other fields of research, because more accurate and flexible methods are available. These more advanced methods, however, are more complex to fit, interpret, and apply compared to linear regression models. Furthermore, the variety of design of experiments methods used, and the lack of reasoning why these were applied, suggests that comprehensive guidance in health economic literature as a central source of information would be valuable to guide such design choices.

Our study has certain limitations. First of all, only one database was searched, which may have partly caused a low number of publications to be included in the final sample. This limitation might have caused publications just outside the standard health economic context, e.g. in operations research journals that are not indexed in PubMed, to be excluded from our results. Cross-referencing was applied to minimalize the potential impact of this limitation. The three publications identified by cross-referencing do not compromise our search strategy. One cross-reference used the term emulator, though this was not identified in the full-text by the search machine [34]. The two remaining cross-references did not contain any health economic terms in their title or abstract [33,35]. Finally, results of literature reviews of modeling studies are generally prone to underreporting, which also relates to the limited space available for publications in peer-reviewed journals, potentially causing authors to exclude details about metamodeling methods from their publications.

6. Five-year view

In order for health economic models to persist in informing decision-making by meaningfully representing increasingly complex clinical pathways, these models will continue becoming more and more sophisticated, and their corresponding analysis will thus become progressively computationally demanding. Additionally, new consensus guidance on advanced analyses in health economics, such as for value of information analyses and optimization [42], is expected to become available on the short term, and will boost the application of these analyses. Since these analyses may place a large burden on computational resources, it may not be possible to carry them out within feasible time horizons using standard health economic modeling methods. Metamodeling methods provide opportunities to address these challenges by providing (almost) instant approximations of simulator outcomes. Consequently, the use of metamodels in health economics is expected to rise with an increase in applications of demanding analyses.

Currently, comprehensive guidance on the application of metamodeling methods in health economics is being developed as part of a successive study. When this guidance becomes available, and health economic modelers become aware of the potential of these methods, applications of metamodeling methods in health economics may increase substantially. Health economic modelers will be provided with an extensive set of tools to perform advanced computationally demanding analyses, which were largely infeasible to perform beforehand. This is likely to work both ways, as not only more studies will utilize the value of metamodeling methods in health economics, but more studies will also perform advanced analyses with their simulation models. Eventually, when results of analyses that are currently not being performed due to unacceptable runtime become available, decision makers may be better informed and, thereby, health economics outcomes, both in terms of patient outcomes and health care costs, may improve.

Key issues

- Metamodels estimate the output of a simulator (i.e. original model) using an approximation function or structure that can be evaluated (almost) instantaneously.
- Metamodeling methods can be used to negate runtime issues associated with advanced analyses of health economic models, such as model calibration, probabilistic sensitivity analyses, value of information analyses, and optimization.
- Metamodeling in health economics is in its infancy, both in terms of the number of applications and in the methods that are being applied.
- Comprehensive guidance on how to apply metamodeling methods in health economics is needed to provide modelers the information and tools needed to utilize the full potential of these methods.

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Author contributions

The research design, including the search strategy and inclusion criteria, was developed as a combined effort of all authors. Performing the search and primary analysis was done by KD in close cooperation with, and under supervision of HK. Interpretation of the results was a combined effort of all authors. The initial manuscript was drafted by KD and revised by HK and MIJ. The overall guarantor of this study is HK.

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