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T A B L E   O F   C O N T E N T S

[Prognosis Protocol]

The added value of different biomarkers to the Revised Cardiac Risk Index to predict major adverse cardiac events and all-cause mortality after noncardiac surgery

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A B S T R A C T

This is a protocol for a Cochrane Review (Prognosis). The objectives are as follows:

The primary objective of this Cochrane Review is to quantify the added predictive value of several biomarkers to the Revised Cardiac Risk Index (RCRI) and to estimate the predictive performance of biomarkers compared to the RCRI alone to predict major adverse cardiac events (MACEs) and all-cause mortality in patients undergoing noncardiac surgery. Table 1 represents the PICOTS of the review based on the CHARMS checklist (Moons 2014).

Table 1. PICOTS of the review based on the CHARMS checklist

Population targeted	Patients undergoing noncardiac surgery
Intervention (index model)	Prognostic model; Revised Cardiac Risk Index (RCRI)
Comparator model	Addition of biomarkers to the RCRI or comparison of biomarkers alone to the RCRI
Outcome(s) to be predicted	Major adverse cardiac events (MACEs) and all-cause mortality
Time span of the prediction	All time spans

(Continued)

Setting (intended role and use of the model)	To inform physicians preoperatively of the patient's risk of developing events after noncardiac surgery

Investigation of sources of heterogeneity between studies
We will assess sources of heterogeneity based on the population, outcome definitions and prediction horizons. The RCRI was originally developed for a noncardiac, nonvascular surgical population to predict in-hospital MACEs. However, the RCRI has also been externally validated in vascular surgical patients (Gillmann 2014; Scrutinio 2014), in which the predictive performance was found to be moderate (Ford 2010). In addition, prediction horizons vary between studies from in-hospital to long-term events (e.g. postoperative 1-year all-cause mortality). Finally, the composition of items that defines MACEs varies among different studies.

BACKGROUND

Description of the condition

Worldwide, over 300 million patients undergo intermediate to high risk noncardiac surgery every year (Rose 2015), and this number has been increasing continuously (Weiser 2015). Despite the beneficial aspects of surgery, approximately 19% of these patients will suffer an in-hospital major adverse postoperative event (MAPE; ISOSG 2016). The most common MAPE had an infectious (33%) or cardiovascular origin (19%), with the highest mortality rates (7.0%) observed in patients with a major adverse cardiac event (MACE; ISOSG 2016). Such complications are difficult to diagnose, as typical symptoms are often not present in most postoperative patients (e.g. chest pain may be masked by pain medication). Therefore, preoperative risk stratification in these patients using available clinical information is an important component of any strategy to prevent these complications, and this has been recommended in clinical guidelines (Fleisher 2014; Kristensen 2014). Informing patients and physicians about perioperative risks might result in changes in patient management and optimisation before surgery by for example, performing additional diagnostic tests or interventions.

Description of the prognostic model

The Revised Cardiac Risk Index (RCRI) is a predictive tool to preoperatively estimate the postoperative probability of a MACE in patients undergoing noncardiac surgery (Lee 1999). The RCRI contains six equally weighted predictors, including high risk surgery (suprainguinal vascular, intrathoracic, or intraperitoneal procedures), history of myocardial infarction, history of cerebrovascular disease, chronic heart failure, renal insufficiency (creatinine concentration > 177 μmol/L (> 2 mg/dL)) and insulin dependent diabetes. Notably, all six predictors were independent

predictors of postoperative MACE in the derivation cohort, however both elevated creatinine and insulin dependent diabetes were not in the validation cohort. In addition, a systematic review that examined the performance of the RCRI in external validation studies, concluded that the RCRI discriminated moderately well between patients at low versus high risk for predicting cardiac events after noncardiac surgery (Ford 2010). However, the predictive ability of the RCRI for patients undergoing vascular surgery was less accurate (Ford 2010).
Several authors reported the added predictive value to the RCRI of one (or more) biomarkers to improve risk prediction. These biomarkers are among others, troponin (Gillmann 2014; Kopec 2017; Weber 2013), N terminal pro-brain natriuretic peptide (NT-proBNP) (Choi 2010; Kopec 2017; Scrutinio 2014; Weber 2013), estimated glomerular filtration rate (eGFR) (Cywinski 2015; Davis 2013), C-reactive protein (CRP) (Choi 2010; Scrutinio 2014), electrocardiography (ECG) (Noordzij 2006; van Klei 2007), and transthoracic echocardiography (Rohde 2001). They all reflect different disease mechanisms. For example, NT-proBNP and transthoracic echocardiography reflect heart failure, troponin and ECG are associated with myocardial infarction and eGFR with kidney failure. The addition of troponin, NT-proBNP, CRP, or all three, to the RCRI seems promising for the prediction of MACE, as the predictive performance significantly improves compared to the RCRI by itself (Choi 2010; Gillmann 2014; Kopec 2017; Scrutinio 2014; Weber 2013).
As well as the addition of biomarkers to the RCRI, various studies compared the predictive ability of biomarkers alone to the RCRI to predict postoperative outcomes. The biomarkers included were among others brain natriuretic peptide (BNP) (Katsanos 2015; James 2014; Mercantini 2012; Park 2011), eGFR (James 2014), cardiopulmonary exercise testing (James 2014), transthoracic echocardiography (Park 2011), and CRP (James 2014). Similar to adding biomarkers to the RCRI, the predictive performance improves using biomarkers alone for postoperative

risk predictions compared to the RCRI.

Health outcomes

The RCRI was originally developed to predict postoperative in-hospital MACEs. MACEs are a leading cause of morbidity and mortality and occur in over 10 million patients undergoing noncardiac surgery (Devereaux 2012; Ekeloef 2016). MACEs account for the highest postoperative mortality rates (ISOSG 2016), and they are associated with prolonged hospitalisation and increased medical costs (Mackey 2006). A MACE is a composite outcome and includes, among others, cardiac death, myocardial infarction, cardiac arrest, arrhythmias, revascularisation and emergent coronary bypass graft surgery. However, the composition of cardiac outcomes to define MACE varies notably between different research groups and publications (Kip 2008), as there is no standardised definition of MACE existing. Although the outcome predicted in the development paper was MACE (Lee 1999), the RCRI has also been used to predict all-cause mortality in patients undergoing noncardiac surgery (Katsanos 2015; Weber 2013).

Why it is important to do this review of these prognostic models

The addition of one or multiple biomarker(s) to the RCRI for postoperative risk prediction will likely result in improved predictive accuracy, and thereby could lead to a recommendation to routinely measure these biomarker(s) preoperatively. Accordingly, routine measuring of these biomarkers will result in a better preoperative stratification of patients at high risk for a MACE, or all-cause mortality, or both, and thus better postoperative monitoring and patient management. More intensified monitoring of patients at increased postoperative risk could result in prevention of major complications, including MACE, in these patients. On the other hand, additional measuring of biomarkers in clinical care might also lead to overtreatment of patients without clinical signs and symptoms in which deviations in biomarkers were observed. Currently, the advantages and disadvantages of measuring such biomarkers in routine care are not yet fully understood. To date, several authors have reported on the added predictive value of biomarkers to the RCRI (Choi 2010; Gillmann 2014; Kopec 2017; Scrutinio 2014; Weber 2013), or compared the predictive performance of biomarkers themselves to the RCRI (James 2014 ;Katsanos 2015; Mercantini 2012; Park 2011), but no systematic review has been conducted on this topic yet. Therefore, the aim of this Cochrane Review is to quantify the added predictive value of one or multiple biomarker(s) to the RCRI and to estimate the predictive performance of biomarkers themselves compared to the RCRI to predict MACEs and all-cause mortality in patients undergoing noncardiac surgery.

O B J E C T I V E S

The primary objective of this Cochrane Review is to quantify the added predictive value of several biomarkers to the Revised Cardiac Risk Index (RCRI) and to estimate the predictive performance of biomarkers compared to the RCRI alone to predict major adverse cardiac events (MACEs) and all-cause mortality in patients undergoing noncardiac surgery. Table 1 represents the PICOTS of the review based on the CHARMS checklist (Moons 2014).

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Setting (intended role and use of the model)	To inform physicians preoperatively of the patient's risk of developing events after noncardiac surgery

Investigation of sources of heterogeneity between studies

We will assess sources of heterogeneity based on the population, outcome definitions and prediction horizons. The RCRI was originally developed for a noncardiac, nonvascular surgical population to predict in-hospital MACEs. However, the RCRI has also been externally validated in vascular surgical patients (Gillmann 2014; Scrutinio 2014), in which the predictive performance was found to be moderate (Ford 2010). In addition, prediction horizons vary between studies from in-hospital to long-term events (e.g. post-operative 1-year all-cause mortality). Finally, the composition of items that defines MACEs varies among different studies.

M E T H O D S

Criteria for considering studies for this review

Types of studies
We will consider all studies regardless of study design, language or publication status for inclusion in this review.

Types of participants (target population)
We will include studies reporting on patients of all ages undergoing noncardiac surgery.

Types of prognostic models
We will assess all studies reporting the external validation of the Revised Cardiac Risk Index (RCRI) both without the biomarkers, as well as with one or more biomarkers. The predictive accuracy of the extended RCRI model should thus be compared to the original RCRI model. In addition, we will also include studies reporting on the comparison between the predictive performance of biomarkers themselves to the RCRI alone (i.e. without model updating). We will exclude studies in which the RCRI is solely externally validated without extending the model with biomarker(s) or comparison of the predictive accuracy of biomarker(s) to the RCRI.

Types of primary outcomes to be predicted
The outcome of interest is postoperative in-hospital MACE, as was used for the original model development paper (Lee 1999). As mentioned before, the composition of MACE varies extensively among different studies, but we will assess and consider all for this review. Although the prediction horizon varies among different studies, we will not make any restrictions based on this and will select all for this review. Depending on the heterogeneity of the definition of MACE, we will conduct a meta-analysis to estimate the probability of a postoperative MACE in the extended model, for biomarkers alone and the RCRI itself.

Types of secondary outcomes to be predicted
Although the RCRI was developed to predict MACE (Lee 1999), several authors have reported the prognostic ability of the RCRI to predict all-cause mortality (Katsanos 2015; Weber 2013). Therefore, we will include all prognostic studies that report the added value of one or more biomarker(s) to the RCRI to predict all-cause mortality. Similar to the primary outcome, we will include all studies reporting on the external validation of RCRI both without the biomarkers, as well as with biomarker(s), or studies reporting on the comparison of the predictive ability of biomarkers alone to the RCRI independent of the prediction horizon. In case we encounter other outcomes predicted by the RCRI in which one or more biomarkers are added or compared to, we will include these studies as well.

Search methods for identification of studies

Electronic searches
We will search the following databases: Ovid MEDLINE and Ovid Embase. The search strategy will include an adjusted version of the Geersing search filter for prognostic studies (Geersing 2012). We adjusted the filter to identify studies reporting on the validation or updating of prediction models, as well as the added value of variables to existing prediction models. Further, we used synonyms of the RCRI, including 'revised Goldman index' and 'Lee index'. The Geersing search filter was originally designed for searches in Ovid MEDLINE (Geersing 2012), however for this review we also adapted the search strategy for use in Ovid Embase. The search strategies we will use are reported in Appendix 1.

In addition, we will search in both ISI Web of Science and SCOPUS (1999 - current date) for articles referring to the original study that reported the development of the RCRI (Lee 1999). As the RCRI is a revised model from the Cardiac Risk Index by Goldman 1977 and Detsky 1986, we will include all references from these articles from 1999 onwards in the search as well. We will search online trial registries, i.e. ClinicalTrials.gov (www.clinicaltrials.gov), and the World Health Organization (WHO) International Clinical Trials Registry platform (ICTRP) for potential new studies investigating the predictive ability of biomarkers or the added value of one or multiple biomarker(s) to the RCRI (apps.who.int/trialsearch). For included studies we will search PubMed to check if there are any comments or retractions. We will also check the Retraction Watch Database for retractions of included articles (retractiondatabase.org/ RetractionSearch). We will not apply any language restriction so as to reduce language bias.

Searching other resources

We will perform a cross-reference check in the retrieved articles and relevant review articles to identify other eligible articles, including the Ford 2010 review.

Data collection and analysis

Selection of studies

Two review authors (JAD, LMV) will independently screen the results of the searches for eligibility on title and abstract for study selection. The same two review authors will independently retrieve and assess full reports for potentially relevant studies for inclusion and exclusion according to the above criteria using a predefined electronic spreadsheet. In case of disagreement, consensus will be achieved by involving a third independent review author (LMP). We will document study selection in a detailed flow chart based on the PRISMA guidelines (Moher 2009).

Data extraction and management

Two review authors will independently extract data from the selected articles according to the CHARMS checklist (Moons 2014) (JAD, LMV). These items address potential issues regarding risk of bias and issues that may affect applicability of the results in relation to the intended use of the prediction model. A data extraction form will contain the following items.

1. General information: author, year of publication, journal, country, language.
2. Source of data: study design, prospective or retrospective data collection, derivation from routinely collected data or previous conducted study, data collected in academic or peripheral hospital.
3. Participants: eligibility and recruitment method (e.g. consecutive participants, location, number of centres, setting, inclusion and exclusion criteria), whether all patients were used for model validation, number of included patients, study dates (i.e. study period), surgical specialty, surgical intervention and other case mix variables, including age, sex, comorbidities and chronic medication use.
4. Outcomes to be predicted: definition of each of the items representing the composite outcome, number of individual component outcomes as part of the composite outcome, number of patients diagnosed with each of the individual component outcomes, assessor of the outcome was blinded from candidate predictors, whether candidate predictors were part of the outcome, timing of outcome occurrence or duration of follow-up.
5. Candidate predictors; RCRI predictors: definition of each of the original RCRI predictors used in the validation study, whether the number of RCRI predictors were used for risk

prediction (i.e. combination of predictors is not important for risk prediction) or whether the individual items were used for risk prediction (i.e. the combination of predictors is important for risk prediction).

6. Candidate predictors; biomarkers: the number, type (i.e. biomarker derived from blood, imaging or patient characteristics) and definition of new (candidate) predictors, whether the biomarker added or compared to the RCRI, assay used for biomarker determination, optimal cut-off point in case of biomarkers, predefined cut-off point, handling of the biomarkers in the modelling (e.g. continuous, dichotomous, transformations).
7. Sample size: number of patients included in the study, number of patients with outcome of interest, number of events-per-variables.
8. Missing data: number of patients with any missing value, number of missing values for each predictor, type of missing data (e.g. missing at random, missing not at random), handling of missing data (i.e. complete-case analysis, multiple imputation, other methods).
9. Model performance: calibration (calibration plot, observed-to-expected ratio (O:E ratio), Hosmer-Lemeshow (Hosmer 1997)) with confidence interval, discrimination (c-statistic) with confidence interval, classification (sensitivity, specificity, negative and positive predictive value, net reclassification index, integrated discrimination improvement), overall measures of performance.
10. Model updating: method used for updating, performance for all different updates.
11. Results: each of the model performance measures reported for both the RCRI alone as for the extended model or biomarker to which the RCRI was compared, whether these performance measures were statistically compared (e.g. using P value, Aikake's Information Criterion (AIC)), whether the new model was statistically significantly improved in comparison with the RCRI alone.
12. Interpretation and discussion: comparison with other studies, discussion of generalisability, strengths and limitations.

Three independent review authors (JAD, LMV, LMP) will pilot the data extraction form by extracting data from two selected articles. We will compare the extracted data and discuss potential issues to optimise the data extraction form.

Assessment of risk of bias of included studies

We will use the PROBAST-tool to assess risk of bias and applicability of individual studies (Wolff 2018).

Two review authors will independently assess these studies. As reported in PROBAST, we will assess risk of bias for all models reported in the selected articles according to the following domains.

1. Patient selection
   i) What study design was used?

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ii) Was the inclusion and exclusion of participants appropriate?

iii) Was participant selection similar to the development study?

2. Predictors

i) Was the predictor definition similar for all participants and similar to the development study?

ii) Are all predictors available at the intended time of prediction?

3. Outcome

i) Was the outcome definition prespecified?

ii) Was the same definition and assessment used for predictors and outcomes in all patients?

iii) Were outcome assessors blinded to predictor information?

4. Analysis

i) Was the number of participants with the outcome reasonable?

ii) Was there appropriate handling of continuous and categorical predictors?

iii) Was there appropriate evaluating of model performance measures, e.g. discrimination and calibration?

We will judge each of the domains for risk of bias (high, low, unclear). Judgement will be facilitated by signalling questions which can be answered with 'yes', 'probably yes', 'probably no' , 'no' or 'no information'. Questions answered with 'yes' indicate low risk of bias. We will judge risk of bias for each domain and for the model as a whole by using the answers of the signalling questions. In addition, we will judge applicability of the model to the research question using the PROBAST-tool. We will assess each of the selected articles on applicability using the first three domains, as data analysis is not related to the contribution of the review question. Two independent review authors (JAD, LMV) will assess the risk of bias using the PROBAST-tool. In case of disagreement, a third independent review author (LMP) will be involved to reach consensus.

Measures of model's predictive accuracy to be extracted

We will extract the reported predictive performance measures from the selected articles and use the recommended methodology for meta-analysing the predictive performance of prognostic models (Debray 2017). These performance measures include among others calibration, discrimination and reclassification measures. Calibration refers to the predictive accuracy of the model and indicates the extent to which expected outcomes (i.e. outcomes predicted by the prediction model) and the observed outcomes agree (Steyerberg 2009). Calibration performance can be presented as calibration plots, calibration slopes and observed to expected ratios (O:E ratios). Discrimination refers to the ability of the prediction model to discriminate between those with and without the event

(Steyerberg 2009). The most commonly used discrimination measure is the concordance-statistics, i.e. c-statistic. Examining the added value of each biomarker to the RCRI or the biomarker itself compared to the RCRI is the primary aim of this review, in particular the delta c-statistics and the net reclassification index (NRI) are of primary interest.

Dealing with missing data

We will contact the corresponding authors to provide additional data for our analyses. In case of any non-response, we can estimate performance measures and standard errors such as the O:E ratio and c-statistic using formulas described by Debray 2017. If this is impossible due to limited data, these articles will be thought to introduce serious bias. We will report thisand we will explore the impact of the missing data in a sensitivity analysis.

Assessment of heterogeneity

We will investigate and discuss clinical and statistical heterogeneity based on the items mentioned in the section 'Data extraction and Management'. To assess between-study heterogeneity across the included studies, we will inspect the forest plots and compute the I^2-statistics and Tau^2 to quantify the extent of the heterogeneity. We will report on heterogeneity and explore its causes by conducting subgroup analyses.

Assessment of reporting biases

Current guidelines recommend reporting both discrimination and calibration measures for all prognostic models (Collins 2015). However, several systematic reviews focusing on the methodological conduct and reporting of prognostic models found that these performance measures are frequently not reported (Bouwmeester 2012). Therefore, we will report the reporting deficiencies in the selected studies. Furthermore, most studies reporting on prognostic models are not prospectively registered and no protocol has been published (Peat 2014), which makes assessment of potential publication bias difficult. However, in case a study protocol is available, we will check articles for protocol violations.

Data synthesis

Data synthesis and meta-analysis approaches

We will provide an overview of the included articles which will be sorted on the biomarker added to the RCRI and on predicted outcome. We will present the author, publication year, number of patients included, biomarker(s) added, outcome definition, number of patients with the event, c-statistics and O:E ratios of RCRI

alone and the extended model using a tabular display. We will present a similar table for the articles reporting on the comparison of the predictive accuracy of a particular biomarker to the RCRI. If possible, we will meta-analyse articles reporting on the added value of a particular biomarker to the RCRI to predict a particular outcome (O:E ratio, (delta) c-statistic and net reclassification index (NRI)) and will report the pooled measure with the confidence intervals and prediction intervals. We will compare these to the 'pooled' RCRI alone to assess improved risk prediction for the extended model. Currently, no methodology is available on meta-analysing NRIs including handling of different thresholds for reclassification. In case of appropriate included articles, we will consider development of such methods. In addition, we will construct a random-effects model as we expect heterogeneity among the selected articles (Riley 2011). We will weight studies based on inverse variance analysis. We will performs meta-analyses through methods proposed by Debray 2017 using the meta-analysis packages in the R statistics language, which includes metafor (Viechtbauer 2010), mvmeta (Gasparrini 2012), metamisc (Debray 2018), and lme4 (Bates 2015). We will conduct similar analysis for 'pooled' performance measures comparing the predictive ability of the biomarkers alone compared to the RCRI alone.

Subgroup analysis and investigation of heterogeneity

We will perform the following subgroup analyses for the comparison of predictive performance measures between:

1. vascular surgical patients and non-vascular surgical patients;
2. patients undergoing elective or emergency surgery;
3. different prediction horizons, e.g. in-hospital, 30-day and long-term events;
4. patients in different age categories.

We will examine potential causes of heterogeneity by assessing case mix variation and differences in study characteristics (e.g. study design and prospective versus retrospective data collection). We will conduct meta-regression, if needed, to explore the cause and extent of the between-study heterogeneity (Debray 2017; Riley 2011).

Sensitivity analysis

We will perform sensitivity analysis by excluding studies with high risk of bias (at least 4 domains to be 'high') and by excluding unpublished studies and studies with missing data.

Conclusions and summary of findings

We will present the 'Summary of findings' table using GRADE to assess the body of evidence of the included prognostic studies for both MACE and all-cause mortality (Iorio 2015). We will assess the quality of evidence as being high-quality to moderate-, low- or very low-quality. Two review authors (LMV and JAD) will independently undertake grading the quality of evidence and they will reach agreement by consensus. We will judge characteristics of evidence based on considerations of ideal study design and inconsistency (i.e. variability in point estimates, extent of overlap in confidence intervals, and where point estimates lie in relation to decision thresholds), imprecision, indirectness (i.e. the studied population corresponds to their population of interest) and evidence for publication bias (Iorio 2015).

ACKNOWLEDGEMENTS

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* *Indicates the major publication for the study*

The added value of different biomarkers to the Revised Cardiac Risk Index to predict major adverse cardiac events and all-cause mortality after noncardiac surgery (Protocol)

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APPENDICES

Appendix 1. MEDLINE Ovid search strategy

1 ("Revised Cardiac risk index" or RCRI or "Lee index" or "Lee-index" or "Lee's index" or "revised goldman index" or goldman or detsky or LCRI or RCI or "revised cardiac index" or "pre-operative variable*" or "preoperative variable*" or "revised cardiac risk" or "cardiac risk factor*").ti,ab,kf.
2 Reproducibility of Results/ or calibration/ or Area Under Curve/ or Validation Studies.pt. or (validat* or stratification or overfit* or overpredict* or underfit* or underpredict* or overestimation or underestimation or pooled or recalibration or re-calibration or calibration or discrimination or cohort or discriminate or c-statistic* or "c statistic*" or "Area under the curve*" or AUC or Indices or Algorithm or Multivariable or "added value" or incremental or "receiver operating curve" or roc or "receiver operating characteristic" or "c index" or "c-index" or "predictive accuracy" or "prognostic accuracy" or "reclassifi*" or "prognostic value" or "predictive value" or MACE).ti,ab,kf.
3 1 and 2
4 (exp animals/ not humans/) or (equine or cattle or bovine or canine or mice or mouse or rat or rats or guinea-pig* or dog).ti.
5 3 not 4

Appendix 2. Ovid Embase search strategy

1 ("Revised Cardiac risk index" or RCRI or "Lee index" or "Lee-index" or "Lee's index" or "revised goldman index" or goldman or detsky or LCRI or RCI or "revised cardiac index" or "pre-operative variable*" or "preoperative variable*" or "revised cardiac risk" or "cardiac risk factor*").ti,ab,kw.
2 reproducibility/ or validation study/ or validation process/ or calibration/ or area under the curve/ or (validat* or stratification or overfit* or overpredict* or underfit* or underpredict* or overestimation or underestimation or pooled or recalibration or re-calibration or calibration or discrimination or cohort or discriminate or c-statistic* or "c statistic*" or "Area under the curve*" or AUC or Indices or Algorithm or Multivariable or "added value" or incremental or "receiver operating curve" or roc or "receiver operating characteristic" or "c index" or "c-index" or "predictive accuracy" or "prognostic accuracy" or "reclassifi*" or "prognostic value" or "predictive value" or MACE).ti,ab,kw.
3 1 and 2
4 ((exp experimental organism/ or animal tissue/ or animal cell/ or exp animal disease/ or exp carnivore disease/ or exp bird/ or exp experimental animal welfare/ or exp animal husbandry/ or animal behavior/ or exp animal cell culture/ or exp mammalian disease/ or exp mammal/ or exp marine species/ or nonhuman/ or animal.hw.) not human/) or (equine or cattle or bovine or canine or mice or mouse or rat or rats or guinea-pig* or dog).ti.
5 3 not 4
6 limit 5 to (conference abstract or conference paper or "conference review")
7 5 not 6

CONTRIBUTIONS OF AUTHORS

Lisette M Vernooij: protocol development, content input and medical input

Johanna A Damen: methodological, statistical and content input

Wilton A van Klei: medical and content input

Karel G Moons: methodological, statistical and content input

Linda M Peelen: methodological, medical and content input

DECLARATIONS OF INTEREST

Lisette M Vernooij: none known

Johanna A Damen: none known

Wilton A van Klei: none known

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External sources

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