Supplementary Online Content


eAppendix. PRISMA-P Review Protocol

eTable 1. Risk of Bias

eTable 2. Safety Concerns Related to Management Guided by the EOS Calculator, Other Than Missed EOS Cases

eTable 3. Management of Symptomatic and Asymptomatic EOS Cases in as Guided by the EOS Calculator or Conventional Strategy

This supplementary material has been provided by the authors to give readers additional information about their work.
eAppendix. PRISMA-P Review Protocol

Systematic Review Sepsis Calculator – Review Protocol – Version 1.4

Administrative information

Title
1a. Title Evaluation of the neonatal sepsis calculator; a systematic review.
1b. Update This review is not an update of a previous investigation

Registration
2. Registration This review was registered in PROSPERO as of Nov 12, 2018. Significant amendments to the protocol will be reflected in updated of the registration where possible.

Authors
3a. Contact Protocol corresponding authors:
N.B. Achten, Tergooi, MD, niek.achten@gmail.com
F.B. Plötz, Tergooi, MD PhD, fbplotz@tergooi.nl
R. Bokelaar, Tergooi, MD, rbokelaar@tergooi.nl
3b. Contribution NA: authored protocol
FP: reviewed protocol, guarantor.
RB: reviewed protocol

Amendments
4.
22-11-2018; version 1.1
Finalizing additions and refinements in Appendix 2, made to enhance and precise data extraction and collections. If necessary, data-extraction was repeated according to protocol, for any changed definitions.
14-12-2018; version 1.2
Adding refinements to outcomes related to missed EOS cases and delay in antibiotics, as discussed and used in data extractions. If necessary, data-extraction was repeated according to protocol, for any changed definitions.
29-1-2019; version 1.3
Enhancement of definitions regarding missed EOS cases. Adding methodology and decision-making for meta-analysis as a result of insights and expertise of additional co-authors.
Addition of MOOSE guideline/checklist adherence.
24-4-2019; version 1.4
Refining exclusion criteria in order to ensure independence of results by preventing datasets involved in EOS calculator development entering the analysis.

Support
5a. No sources of financial or other support for the review to be reported.
5b. No external sponsors to be reported.
5c. No role of external funders, sponsors or institutions to be reported.
Introduction

Rationale
6. There is worldwide a growing interest in using the newborn sepsis calculator because of its promising results to reduce empiric antibiotic use in early onset sepsis (EOS). Studies evaluating the effects of the sepsis calculator in different neonatal populations are critical for responsible and successful adoption. A comprehensive overview of such studies hitherto performed will allow informed decision-making when practitioners consider the sepsis calculator, and can help identify current lacunas and shortcomings that need to be addressed.

Objectives
7. PICO statement
   Patients: Newborns born at 34 weeks of gestational age or later
   Intervention: Use of sepsis calculator as provided bij Kaiser Permanente
   Comparison: Current, previous, or alternative management of suspected EOS
   Outcomes: Primary: reduction in empiric antibiotics
             Secondary: amount of adverse events
Methods

Eligibility criteria

8. Eligibility criteria:

Studies will be selected according to the criteria below.

Study characteristics

- Any study design validating the sepsis calculator or comparing sepsis calculator results with alternative management strategies according to PICO characteristics previously stated under Objectives.
- Original data; we will exclude studies without original data, but we will include any studies generating new information by pooled analysis of previously included studies such as meta-analysis.
- We will include studies that report results related to either the primary outcome (use of antibiotics in the first 72 hours of life) and/or the secondary (safety) outcomes; including to EOS incidence/cases, blood and or cerebrospinal fluid cultures, readmissions, EOS mortality, severe EOS disease, prolonged hospital stay, and adversities mentioned by authors.
- To ensure independence of outcome estimates, we excluded datasets that were used to develop the EOS calculator. (Post-hoc decision; amendment 24/4-2019)
- No other restrictions on study characteristics.

Report characteristics

- Peer-reviewed; we will only include publications that are peer-reviewed, meaning the exclusion of dissertations, thesis, abstracts and other non-peer-reviewed publications.
- Publishing date in or after the 2011 calendar year; we will only include publications from 2011 or later, since the model of subject was not published until 2011.
- Language: we aim to include published reports in all languages. If required title and/or abstract, or required full-text publications are not available in languages spoken by one of the main reviewers, other authors will be consulted for translations. If the publication was in a language that could not be translated, we will attempt to contact main authors for a translation or to confirm non-eligibility of the publication. If unsuccessful, we will review if translation of title/abstract through Google Translate is sufficiently adequate to confirm non-eligibility. If this is unsuccessful, publications will be excluded from the review.

Information sources

9.

Literature searches will be developed using the resources below. We will use a search strategy developed by NA and reviewed by FP to find eligible publications in Cochrane, PubMed/Medline and EMBASE libraries. To ensure literature saturation, we will additionally search Google Scholar and Web of Science for publications that cite one or both of the publications detailing the sepsis calculator itself (section 10A).

<table>
<thead>
<tr>
<th>Source</th>
<th>Coverage date</th>
<th>URL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cochrane library</td>
<td>Nov 9, 2018</td>
<td>cochranelibrary.com</td>
</tr>
<tr>
<td>MEDLINE/PubMed</td>
<td>Nov 9, 2018</td>
<td>ncbi.nlm.nih.gov/pubmed</td>
</tr>
<tr>
<td>EMBASE</td>
<td>Nov 9, 2018</td>
<td>elsevier.com/solutions/</td>
</tr>
<tr>
<td></td>
<td></td>
<td>embase-biomedical-research</td>
</tr>
<tr>
<td>Google Scholar</td>
<td>Nov 9, 2018</td>
<td>scholar.google.com</td>
</tr>
<tr>
<td>Web of Science</td>
<td>Nov 9, 2018</td>
<td>apps.webofknowledge.com</td>
</tr>
</tbody>
</table>
Search strategy

10. General search strategy for primary electronic databases

General search terminology and strategy for electronic databases is detailed in the table below. Exact search syntax for each electronic database can be found in Appendix 1.

<table>
<thead>
<tr>
<th>Search terms</th>
</tr>
</thead>
<tbody>
<tr>
<td>All fields</td>
</tr>
<tr>
<td>'sepsis calculator'</td>
</tr>
<tr>
<td>'eos calculator'</td>
</tr>
<tr>
<td>'sepsis risk calculator'</td>
</tr>
<tr>
<td>'eos risk calculator'</td>
</tr>
<tr>
<td>OR</td>
</tr>
<tr>
<td>Title/abstract</td>
</tr>
<tr>
<td>'predictive' AND 'model' AND 'quantitative' AND 'stratification'</td>
</tr>
<tr>
<td>'risk' AND 'algorithm' AND 'early onset sepsis' AND 'early onset neonatal sepsis' AND 'EOS'</td>
</tr>
</tbody>
</table>

Like ‘OR’ Dotted lines mark interchangeable search terms.

Search strategy for reviewing citations

A. Reviewing papers citing original sepsis calculator publications:

  
  https://scholar.google.com/scholar?cites=17123481009097227542&as_sdt=2005&sciodt=0,5&hl=en
  
  http://apps.webofknowledge.com/CitingArticles.do?product=WOS&SID=E3Fh1qobGFDBM1NV1f6&search_mode=CitingArticles&parentProduct=WOS&parentQid=1&parentDoc=1&RECID=424305078

  
  https://scholar.google.com/scholar?cites=2777091998604103995&as_sdt=2005&sciodt=0,5&hl=en
  

B. Reviewing Citations of Included articles

For all publications included after full-text review, all publications cited by these articles will be evaluated. Title and abstract and if necessary full-text of any publications not present among results of initial search will be evaluated according to eligibility criteria. If any eligible publications, we will evaluate the reason for exclusion from the initial search. If deemed necessary, this will prompt a more broaden search, and possibly amendments to protocol.

C. Repetition of search

To avoid missing recent publications, the search of this review will be repeated towards the end of this review. Any publications not included in the original search results will be
evaluated as detailed before.

Study records

11a. Data management
Search results will be imported in reference software (Mendeley). Duplicates will be merged manually. Where possible, citations will be completed with full (English) title an abstract if not already available through search results, will be obtained. After the selection process, reviewers will examine studies for overlap in study process and/or study population. If the data from the same study is published multiple times, these publication will combined to avoid overrepresentation of study data in review results.

11b. Selection process
Independent review of title and abstract of each unique search result using the eligibility criteria will be performed by two reviewers (NA, RB). Discrepancies were resolved by discussion. If necessary, the full-text publication will be obtained to help with discussion. Next, for all search results that required obtaining of full-text publication, said full-text publication will be independently reviewed by two reviewers (NA, RB), for eligibility. Discrepancies will be resolved through discussion, if necessary using the expertise of a third reviewer (FP). We will record the reasons for exclusion at both stages (title/abstract and full-text screening) using predefined categories based on eligibility criteria: ‘non relevant’ (i.e. not concerning the sepsis calculator), ‘no original data’, ‘no data on outcomes’, ‘not peer-reviewed’, and ‘ineligible due to language’.

11c. Data collection process
Using pre-specified data extraction sheets (appendix 2), two reviewers will (NA, RB) will independently extract relevant data on study design, setting, population, methods, and results for each included study. Discrepancies be resolved by discussion, and a third reviewer (FP) will help unresolved disagreements. We will contact study authors to resolve any uncertainties.

Data items

12. Data items
For each study, we will extract data on the authors, year of publication, location, setting, design, sepsis calculator implementation method, study population (size of birth cohort, size of sepsis calculator population, size of comparison population, gestational age, presence of EOS risk factors), population EOS incidences, used EOS incidence for sepsis calculator.

Outcome and prioritization

13. Outcome and prioritization
For the primary outcome, we will look at (changes or differences in) rate/number of newborns treated with or selected for empiric antibiotics for (suspected) EOS, which may translate to all (start of) empiric antibiotic therapy within 24 and/or 72 hours. Preference will be given to the 72 hours timeframe, and for studies to be included in meta-analysis, original authors of the study will be contacted to resolve any uncertainty and ensure data is valid for the 72 hours timeframe.

Wherever possible, primary outcome data (reduction in empiric antibiotics), we will calculate the relative reduction (RR) that occurs by using the sepsis calculator compared to the compared approach in the respective study, to ensure a consistent outcome measure across studies. Calculations will be reviewed by a second (NA or RB) and third reviewer (FP), to check and correct for mistakes.

For secondary (safety) outcomes, we will extract data on ‘missed’ or delayed EOS cases, readmissions, changes in EOS incidence, changes in use of antibiotics, changes in mortality, changes in morbidity, changes in need for intensive care. To allow for nuanced interpretation of safety results, we will extract description of these safety outcomes where reported by the authors. To ensure no safety data is missed, reviewers will extract all adverse events or safety concerns given by the authors of the studies. We will also distinct between ‘not reported’ and ‘absence’ for each safety outcome. An EOS case was defined as missed if the management strategy did not allocate antibiotics within 24 hours after birth. In case of before-after implementation studies, we will look at actual management of the case in the cohort/epoch in which the respected management strategy was used. In case of the calculator, a
case assigned observation with check of vitals, which showed clinical symptoms within 24 hours is seen as a missed EOS case. ‘Well-appearing’ was considered asymptomatic, unless otherwise specified by the study. However reported EOS cases that were assigned vitals will be included in the safety outcome table, for completeness.

For delay in antibiotics as outcome, we will include any delay in antibiotics reported by authors, or any increase in antibiotics between 24 and 72 hours after birth as possible EOS delays.

**Risk of bias in individual studies**

14. **Risk of bias in individual studies**

Given the nature of the intervention covered by this systematic review – a prediction modeling tool designed for use in daily clinical practice – we will deviate from standard risk of bias assessment as described in the Cochrane Handbook for Systematic Review of Interventions, and use instead the dedicated CHARMS-checklist (CHecklist for critical Appraisal and data extraction for systematic Reviews of prediction Modelling Studies) to assess individual studies for risk of bias. In accordance with this checklist, we will evaluate risk of bias for each study on the following domains: data source, outcomes, candidate predictors, sample size, missing data, model performance, model evaluation and results. As the review intends to review studies evaluating results sepsis calculator, items that refer to model development will not be assessed, as they not applicable (appendix 3).

Using these items, two reviewers (NA, RB) will discuss each study and categorize the risk of bias as ‘high’, ‘low’ or ‘unclear’. Disagreements will be resolved through expertise of a third reviewer (FP). We will not attempt blinding for this process, as by this stage the reviewers will have sufficient knowledge of the studies to render true blinding impossible.

We plan to include studies regardless of risk-of-bias, but we will discuss the general risk of bias of included studies in our discussion to allow for a balanced interpretation of results.

**Data synthesis**

15a. **Describe criteria under which study data will be quantitatively synthesized.**

At the time of commencement of this review, we do not plan to quantitatively synthesize study data, mainly for two reasons:

First, the goal of this review is to provide a comprehensive overview of available sepsis calculator evidence rather than calculating a precise, universal estimate of the effect size(s) of sepsis calculator implementation. Because actual implementation and use of the sepsis calculator is likely to be different for each institution according to the particular setting and dynamics of early onset sepsis, a universal estimate would be of little relevance.

Second, based on the wide variation in strategies for management of newborns at risk for early onset sepsis, significant heterogeneity in study population, comparators and sepsis calculator implementation strategies is expected, limiting the possibilities for reliable and useful meta-analysis.

However, we cannot rule out the development of different insights through either the nature of initial review results, the input of a large group of co-authors/collaborators, and/or the input and viewpoints of peer reviewers. In that case, providing sufficient homogeneity among studies, we plan to conduct meta-analysis using a random-effects model, because of expected differences in study population sizes. Exact methods of handling and combining of data, assessing of consistency and additional analysis however, will depend on aforementioned insights and viewpoints. Before commencing any meta-analysis, this protocol will be amended with precise protocols for data synthesis and analysis.

**Amendment**

Following review of our data and initial results by added co-authors with specific expertise in meta-analyze, we will explore possibilities to meta-analyze primary outcomes for those studies that provide reasonably comparable, separate populations for the management guided by the EOS calculator and existing management strategies, such as before-after implementation studies. Pooling of results missed EOS cases will be performed if deemed appropriate by consulted epidemiologists.

15b. **Planned methods for data synthesis**

Not applicable, see 15a.

**Amendment**
Data will be tested for statistic heterogeneity before pooling using $I^2$ and comparison of confidence intervals. 0-40 % might not be important, whereas higher $I^2$ values may represent moderate (30-60 %), substantial (50-90 %) or considerable heterogeneity (75-100 %). Subgroups analysis may be performed if deemed logical and useful given heterogeneity in results and study designs or populations. Analysis will be performed using using RevMan version 5.3 (The Nordic Cochrane Centre, Copenhagen, Denmark).

Reporting of all outcomes and

15c. Proposed additional analyses
Not applicable, see 15a.

15d. Type of summary
Data on number and characteristics of included studies will presented in results. Systematic tables will be provided for both main and secondary outcomes, including detailed study characteristics for each included study. Narrative synthesis for both main and secondary outcomes will be provided, highlighting congruencies as well as discrepancies within study results. We plan on including results regardless of risk of bias in synthesis of results. For safety outcomes, results will be accompanied with descriptions of events or cases as provided by authors of included studies when relevant for interpretation.

Amendment
For pooling or meta-analysis of data of multiple studies, results will be presented as a forest-plot with effect size estimates and confidence intervals for each study as well as the overall effect, or by pooled data results in table format and appropriate statistical test results where necessary.

Meta-bias(es)
16. Planned assessment of meta-bias(es)
Currently, there is no register widely used for validation and impact studies, limiting the potential to assess and control for publication bias. Selective outcome reporting bias will be limited for the main outcome, since this is represented by a single outcome measure that is defined as a criterion for study eligibility. As for secondary outcomes, we will report on any selective outcome reporting by comparing methods with results within studies.

17. Assessment of strength of evidence
Using the GRADE (Grading of Recommendations, Assessment, Development and Evaluations) framework as a guideline, we evaluate evidence on both the main outcome as well as secondary outcomes for strengths. Where applicable and possible, authors will assess the available evidence on the GRADE domains; risk of bias, imprecision, inconsistency, indirectness, and/or publication bias. Rather than reporting the strength of evidence as a main study result, this review will use these assessments as a ground for recommendations for future research or implementation efforts.

Protocol appendix 1 – Search syntax

Cochrane
("sepsis calculator" OR "eos calculator" OR "sepsis risk calculator" OR "eos risk calculator") OR (("predictive":ti,ab OR "risk":ti,ab OR "quantitative":ti,ab OR "stratification":ti,ab) AND ("model":ti,ab OR "algorithm":ti,ab) AND ("early onset sepsis":ti,ab OR "early onset neonatal sepsis":ti,ab OR "EOS":ti,ab))

MEDLINE/PubMed
((("EOS"[Title/Abstract]) OR "early onset sepsis"[Title/Abstract]) OR "early onset neonatal sepsis"[Title/Abstract]) AND ((("predictive"[Title/Abstract]) OR "risk"[Title/Abstract]) OR "quantitative"[Title/Abstract]) OR "stratification"[Title/Abstract]) AND ("model"[Title/Abstract]) OR "algorithm"[Title/Abstract]) OR ("sepsis calculator" OR "eos calculator" OR "eos risk calculator" OR "sepsis risk calculator") AND ("2011/01/01"[PDat] : "3000/12/31"[PDat]))

© 2019 American Medical Association. All rights reserved.
**EMBASE**
('eos calculator' OR 'sepsis calculator' OR 'sepsis risk calculator' OR 'eos risk calculator' OR ('predictive':ti,ab OR 'risk':ti,ab OR 'quantitative':ti,ab OR 'stratification':ti,ab) AND ('model':ti,ab OR 'algorithm':ti,ab) AND ('early onset sepsis':ti,ab AND 'early onset neonatal sepsis':ti,ab OR 'early onset neonatal sepsis'/exp OR 'early onset neonatal sepsis' OR 'eos':ti,ab))) AND [2011-2018]/py

**Protocol appendix 2 – Search syntax**

**Data extraction sheet**

The following data will be recorded for each study. If no data was available on a particular item/variable ‘NR’ will be reported. Data will be noted as reported by the authors, but also recalculated by reviewers using listed formulas. In case of discrepancies, both numbers were extracted.

**Study characteristics and primary outcome**

<table>
<thead>
<tr>
<th><strong>Author</strong></th>
<th>Last name of 1st author of study, et al if applicable</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Year of publication</strong></td>
<td>Last name of 1st author of study, et al if applicable</td>
</tr>
<tr>
<td><strong>Location</strong></td>
<td>Country where study was conducted. ‘Multiple’ if conducted in multiple countries.</td>
</tr>
<tr>
<td><strong>Setting</strong></td>
<td>‘Tertiary’ for academic, referral, or university-affiliated institutions, ‘Regional’ for other institutions, ‘Mixed’ for a combination of tertiary and regional.</td>
</tr>
<tr>
<td><strong>Study design</strong></td>
<td>Retrospective/Prospective/Cross-sectional and Cohort/(nested) Case-Control/Clinical (randomized) trial</td>
</tr>
<tr>
<td><strong>Implementation</strong></td>
<td>‘Yes’ if sepsis calculator was actually (partly) or completely implemented in daily clinical workflow.</td>
</tr>
<tr>
<td><strong>Gestational age</strong></td>
<td>(range) of gestational age of newborns in whom the sepsis calculator was tested.</td>
</tr>
<tr>
<td><strong>N (births)</strong></td>
<td>Number of live births during the study period, in the range of gestational age used in the particular study.</td>
</tr>
<tr>
<td><strong>Included subset</strong></td>
<td>If applicable, criteria/selection for the subset in which the sepsis calculator was tested. ‘N/A’ newborns in the study if the sepsis calculator was tested in all.</td>
</tr>
<tr>
<td><strong>N (subset)</strong></td>
<td>If applicable, N=number of newborns in subset among which the sepsis calculator was tested.</td>
</tr>
<tr>
<td><strong>Comparison</strong></td>
<td>Description of alternative approach used as comparison management strategy as opposed to the sepsis calculator. I.e. CDC guidelines, National guideline, local protocol, ‘AB in all cases of chorioamnionitis’, etc.</td>
</tr>
</tbody>
</table>
N (comparison)  If applicable, N=number of newborns in comparison strategy. Only if sepsis calculator and comparison estimates results were derived from different data (actual implementation studies).

AB (calculator)  Rate (%) of newborns included treated with empiric antibiotics for (suspected) EOS when the sepsis calculator was used. Preferably ≤72 hrs for EOS indication, but any antibiotics ≤72 hrs, ≤48hrs or 24 hrs postpartum or antibiotics described as EOS-related allowed as proxy. (Refer to section 13 for more detail.)

AB (comparator)  Rate (%) of newborns included treated with empiric antibiotics for (suspected) EOS when the comparative management strategy was used. Refer to ‘AB (calculator)’ and section 13 for more detail.

AB (change, absolute)  Absolute reduction (or increase) in empiric antibiotics, if the sepsis calculator was used, compared to the comparator strategy. Both as reported by the authors (if reported and as calculated using: \[
[AB \text{ (comparator)}] - [AB \text{ (calculator)}]
\]

AB (change, relative)  Relative reduction (or increase) in empiric antibiotics, if the sepsis calculator was used, compared to the comparator strategy. Both as reported by the authors (if reported and as calculated using:
\[
100 - \frac{[AB \text{ (calculator)}]}{[AB \text{ (comparator)}]}
\]

EOS incidence  Population EOS incidence among newborns in study, or for newborns in the study institution. As reported by the authors, and as calculated using \([\text{proven EOS cases}] / [\text{newborns in study period}]\)

Subset incidence  EOS incidence among newborns included for sepsis calculator testing, as reported by the authors, and as calculated using \([\text{proven EOS cases}] / [\text{newborns eligible for inclusion}]\).

Calculator incidence  EOS incidence as used for sepsis calculator appliance in the study; the particular setting used in the calculator when the calculator was applied.
**Secondary outcomes - safety**

To ensure no safety data is missed, reviewers will extract all adverse events or safety concerns given by the authors of the studies. We will also distinguish between ‘not reported’ and ‘absence’ for each safety outcome.

**Missed EOS cases**
Description of EOS proven cases that were not selected for antibiotics by the sepsis calculator and/or the comparative strategy. Description preferably include:
- if the case was or would have been selected for antibiotics using the different strategy in the study
- if the case was or would have been selected for antibiotics using national guidelines
- if antibiotics were started within 24hrs, within 72hrs, after 72hrs, or not at all
- if the newborn deteriorated, and if this happened within 24hrs
- if cultures were taken at start of antibiotics and what the results were
- a brief description of the clinical course
- other remarks deemed relevant by the authors of the study.

**Incidence change**
If a change in sepsis calculator was seen after implementation of the sepsis calculator.

**Antibiotics change**
If the rate (%) of empiric antibiotics started ≥24 hrs after birth changed after implementing the sepsis calculator.

**Mortality/morbidity**
If a change in mortality and or morbidity (such as need for intensive care) was seen after implementation of the sepsis calculator.

**Adverse events**
Any adverse events or safety concerns listed by the authors of the studies. We will also distinguish between ‘not reported’ and ‘absence’ for each safety outcome.
Protocol appendix 3 – Evaluation of Risk of Bias

Using items below, based on the CHARMS checklist, reviewers will discuss each study and categorize the risk of bias as ‘high’, ‘low’ or ‘unclear’.

**Source of data**
Source of data (e.g., cohort, case-control, randomised trial participants, or registry data)

**Participants**
Participant eligibility and recruitment method (e.g., consecutive participants, location, number of centres, setting, inclusion and exclusion criteria). Participant description; details of treatments received, if relevant; study dates.

**Outcomes**
Definition, consistency, blinding.

**Predictors**
Definition, method of measuring. Specifically; whether a priori sepsis risk was adequately adjusted for study population.

**Sample size**
Number of participants, number of EOS cases, number of events per predictor.

**Missing data**
Number of participants with any missing data (on predictors or outcomes); number of participants with missing data for each predictor; handling of missing data.

**Model performance**
Calibration (calibration plot, calibration slope, Hosmer-Lemeshow test) and Discrimination (C-statistic, D-statistic, log-rank) measures with confidence intervals; Classification measures (e.g., sensitivity, specificity, predictive values, net reclassification improvement) and whether a priori cut points were used.

**Model evaluation**
Method used for testing model performance: development dataset only (random split of data, resampling methods, e.g., bootstrap or cross-validation, none) or separate external validation (e.g., temporal, geographical, different setting, different investigators); In case of poor validation, whether model was adjusted or updated (e.g., intercept recalibrated, predictor effects adjusted, or new predictors added)

**Results**
Comparison of the distribution of predictors (including missing data) for development and validation datasets
**eTable 1. Risk of Bias**

<table>
<thead>
<tr>
<th>Study</th>
<th>Source of data</th>
<th>Participants</th>
<th>Outcomes</th>
<th>Predictors</th>
<th>Sample size</th>
<th>Missing data</th>
<th>Model evaluation</th>
<th>Results</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kuzniwicz 2017</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Achten 2018</td>
<td>High</td>
<td>High</td>
<td>Low</td>
<td>High</td>
<td>High</td>
<td>Low</td>
<td>Low</td>
<td>Unclear</td>
<td>High</td>
</tr>
<tr>
<td>Dhudasia 2018</td>
<td>High</td>
<td>Low</td>
<td>Low</td>
<td>High</td>
<td>High</td>
<td>Low</td>
<td>Low</td>
<td>Unclear</td>
<td>Low</td>
</tr>
<tr>
<td>Strunk 2018</td>
<td>Low</td>
<td>High</td>
<td>High</td>
<td>Low</td>
<td>High</td>
<td>Unclear</td>
<td>Low</td>
<td>Unclear</td>
<td>High</td>
</tr>
<tr>
<td>Gievers 2018</td>
<td>High</td>
<td>Low</td>
<td>High</td>
<td>Low</td>
<td>High</td>
<td>Unclear</td>
<td>Low</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>Beaver 2018</td>
<td>High</td>
<td>Low</td>
<td>Unclear</td>
<td>Unclear</td>
<td>High</td>
<td>Low</td>
<td>Low</td>
<td>Unclear</td>
<td>Uncl</td>
</tr>
<tr>
<td>Shakib 2015</td>
<td>High</td>
<td>High</td>
<td>High</td>
<td>Low</td>
<td>High</td>
<td>Low</td>
<td>Low</td>
<td>Unclear</td>
<td>High</td>
</tr>
<tr>
<td>Kerste 2016</td>
<td>High</td>
<td>High</td>
<td>High</td>
<td>Low</td>
<td>High</td>
<td>Low</td>
<td>High</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>Warren 2017</td>
<td>High</td>
<td>High</td>
<td>High</td>
<td>Low</td>
<td>High</td>
<td>High</td>
<td>Low</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>Money 2017</td>
<td>High</td>
<td>High</td>
<td>High</td>
<td>Low</td>
<td>High</td>
<td>High</td>
<td>Low</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>Carola 2017</td>
<td>High</td>
<td>Low</td>
<td>High</td>
<td>High</td>
<td>High</td>
<td>Low</td>
<td>High</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>Joshi 2019</td>
<td>High</td>
<td>High</td>
<td>Low</td>
<td>High</td>
<td>Unclear</td>
<td>Low</td>
<td>Low</td>
<td>Unclear</td>
<td>High</td>
</tr>
<tr>
<td>Klingaman 2018</td>
<td>Low</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Unclear</td>
<td>High</td>
<td>Unclear</td>
<td>Low</td>
<td>Unclear</td>
<td>Uncl</td>
</tr>
</tbody>
</table>

**Abbreviations:** n/a: not applicable.
**eTable 2. Safety Concerns Related to Management Guided by the EOS Calculator, Other Than Missed EOS Cases**

<table>
<thead>
<tr>
<th>Study</th>
<th>Incidence</th>
<th>Delay in AB</th>
<th>Readmissions</th>
<th>Mortality/morbidity</th>
<th>Other adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kuzniewicz 2017</td>
<td>No change</td>
<td>No increase in AB 48-72hrs postpartum</td>
<td>No change</td>
<td>No change</td>
<td>None reported</td>
</tr>
<tr>
<td>Achten 2018</td>
<td>No change</td>
<td>No delay in AB</td>
<td>n/a</td>
<td>NR</td>
<td>None reported</td>
</tr>
<tr>
<td>Dhudasia 2018</td>
<td>No change</td>
<td>NR</td>
<td>NR</td>
<td>No change</td>
<td>'No safety concerns'</td>
</tr>
<tr>
<td>Strunk 2018</td>
<td>No change</td>
<td>No increase in AB 48-72hrs postpartum</td>
<td>No change</td>
<td>No change</td>
<td>'No adverse events'</td>
</tr>
<tr>
<td>Gievers 2018</td>
<td>No change</td>
<td>NR</td>
<td>No change</td>
<td>NR</td>
<td>None reported</td>
</tr>
<tr>
<td>Beavers 2018</td>
<td>No change</td>
<td>NR</td>
<td>NR</td>
<td>No change</td>
<td>'No negative outcomes'</td>
</tr>
<tr>
<td>Klingaman 2018</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>None reported</td>
</tr>
</tbody>
</table>

Abbreviations: NR, not reported
**eTable 3. Management of Symptomatic and Asymptomatic EOS Cases in as Guided by the EOS Calculator or Conventional Strategy**

<table>
<thead>
<tr>
<th>Study design</th>
<th>EOS cases (n)</th>
<th>Management guided by EOS calculator</th>
<th>Conventional management strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>N</td>
<td>Symptomatic</td>
</tr>
<tr>
<td>Before-after studies</td>
<td>AB &lt;24 hrs, n (%)</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>AB &gt;24 hrs (‘missed ’), n (%)</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Hypothetical database analysis studies</td>
<td>AB &lt;24 hrs, n (%)</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>AB &gt;24 hrs (‘missed ’), n (%)</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Totals</td>
<td>AB &lt;24 hrs, n (%)</td>
<td>2 0</td>
<td>18 (90)</td>
</tr>
<tr>
<td></td>
<td>AB &gt;24 hrs (‘missed ’), n (%)</td>
<td>1 0</td>
<td>6 (60)</td>
</tr>
</tbody>
</table>