Risk of Bias in systematic reviews of prognostic factor and model studies

Carl Moons, Lotty Hooft, Anneke Damen, Robert Wolff, Katrina Williams, Jill Hayden, Richard Riley, Sue Mallett, Penny Whiting, Hans Reitsma
We have no actual or potential conflicts of interest in relation to this presentation
In short

1. What is prognosis, as compared to treating and diagnosis?

2. Why do we prognosticate?

3. Types of prognosis studies?
Forecast of the course and outcome for an individual in a certain health state (given a specific treatment management)

- Not necessarily sick people

• More technical: probable course/prediction of specific future outcomes in subjects with certain health condition

• Disease does not have a prognosis → an individual does
Why prognosticate:

- To provide information to patients
- Identify groups for treatment or other management – including abstinence
- To target specific prognostic factors that modify treatment effects
- Select high/low risk patients for inclusion in RCTs
- Adjust for case-mix differences in comparison health care of institutes
- Service developers make decisions about what services are needed
- Policy makers what to support/advocate
Types of prognosis studies?

PROGRESS series 2013: BMJ and Plos Med

1. Average/overall prognosis: 'What is most likely course (outcome) of individuals with certain health condition?'

2. Prognostic factor studies: 'Which factors are associated with specific outcome in individuals with certain health condition?

3. Prognostic modeling studies: ‘What combination of prognostic factors predict, and how well, a certain outcome in individuals with a certain health condition?’

4. Treatment selection factors: ‘Which factors lead to/predict different treatment effect in individuals to be treated?’

Focus on 2 +3
Conducting a systematic review of prognosis studies

1. Formulate review question (PICOTS)
2. Searching and selection for studies
3. Extraction of data (CHARMS)
4. **Risk of Bias assessments (QUIPS and PROBAST)**
5. Meta-analysis of prognostic factor studies
6. Meta-analysis of prognostic model studies
7. Interpretation + conclusions
Risk of Bias tools

- Prognostic factor/predictor finding studies
  - QUIPS \(\rightarrow\) J Haydn, Ann Int Med 2006 + 2013

- Prognostic (prediction) model studies (development and validation)
  - PROBAST \(\rightarrow\) Ann Int Med 2018
Prognostic Factor Studies

Adapted from: Fletcher & Fletcher, Clinical Epidemiology – The Essentials. Chapter 6. Williams & Wilkins, Baltimore. 1996
**Table 2. Domains Included in the Framework of Potential Biases and the Proportion of Reviews Assessing the Biases**

<table>
<thead>
<tr>
<th>Potential Bias</th>
<th>Studies Adequately Assessing Bias, %†</th>
<th>Domains Addressed</th>
<th>Studies Assessing Domain, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. The study sample represents the population of interest on key characteristics, sufficient to limit potential bias to the results (study participation).</td>
<td>55</td>
<td>1. Source population clearly defined</td>
<td>50</td>
</tr>
<tr>
<td>2. Loss to follow-up (from sample to study population) is not associated with key characteristics, sufficient to limit potential bias (i.e., the study data adequately represent the sample) (study attrition).</td>
<td>42</td>
<td>2. Study population described</td>
<td>21</td>
</tr>
<tr>
<td>3. The prognostic factor of interest is adequately measured in study participants to sufficiently limit potential bias (prognostic factor measurement).</td>
<td>59</td>
<td>3. Study population represents source population or population of interest</td>
<td>50</td>
</tr>
<tr>
<td>4. The outcomes of interest are adequately measured in study participants to sufficiently limit potential bias (outcome measurement).</td>
<td>51</td>
<td>4. Completeness of follow-up described</td>
<td>19</td>
</tr>
<tr>
<td>5. Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest (confounding measurement and account).</td>
<td>13</td>
<td>5. Completeness of follow-up adequate</td>
<td>42</td>
</tr>
<tr>
<td>6. The statistical analysis is appropriate for the design of the study, limiting potential for presentation of invalid results (analysis).</td>
<td>33</td>
<td>6. Prognostic factors defined</td>
<td>51</td>
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<td></td>
<td>7. Prognostic factors measured appropriately</td>
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<td>8. Outcome defined</td>
<td>42</td>
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<td>9. Outcome measured appropriately</td>
<td>51</td>
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<td></td>
<td></td>
<td>10. Confounders defined and measured</td>
<td>21</td>
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<td></td>
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<td>11. Confounding accounted for</td>
<td>53</td>
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<tr>
<td></td>
<td></td>
<td>12. Analysis described</td>
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<td>13. Analysis appropriate</td>
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<td></td>
<td></td>
<td>14. Analysis provides sufficient presentation of data</td>
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</tbody>
</table>

* Data are from 153 prognostic systematic reviews with quality items that could be extracted.
† Adequate assessment included 1) study participation: “source population clearly defined” and “study population described” or “study population represents source population or population of interest.”
Intermezzo Challenge
Meta-analysis/Pooling of prognostic factor studies

Exercise 10 minutes:

1. Assume this forest plot is of RCTs on intervention X to prevent outcome Y in patients with disease Z.
   – Is this pooling ok?
   – Why or why not?

2. Assume this forest plot is of studies on prognostic factor X, to predict outcome Y in patients with disease Z.
   – Is this pooling ok?
   – Why or why not?
Meta-analysis/Pooling in prognostic factor studies

Answers:

• If RCTs
  – Pooling is ok – provided correctly randomised
  – Then the 3 HRs are unbiased (provided no other risks of biases) so can easily pool them
  – Clear effect of intervention X to prevent outcome Y
  – In frequentistic world, at alpha 0.05 – even statistically significant result.

• If prognostic factor studies?
  – Non randomised → even if a study was based on a RCT – the prognostic factor analysis is per arm and thus non randomised
  – Can not assume that the 3 HRs are unbiased
  – Only pool them if studies have adjusted for the same co-variates – or largely for the same co-variates – e.g. the same big 6 or 7 (the eighth co variate probably did not change the HR further)
  – So pooling of prognostic factor studies only if same adjustment –-- otherwise do stratified pooling (e.g. over studies with similar adjustment)
Risk of Bias tools

• Prognostic factor/predictor finding studies

• Prognostic (prediction) model studies (development and validation)
  – PROBAST – Ann Int Med 2018
In Short

1. There are three phases of prediction modelling – which three?

2. What is the biggest difference between phase 1+2 versus 3?
3 Phases of Prediction Modelling studies

1. Model development studies – to develop prediction model from data: identify important predictors; estimate predictor weights; construct model for individualised predictions; quantify predictive performance; internal validation

2. Model validation studies – test (validate) predictive performance of previously developed model in participant data other than development set

3. Model impact studies – quantify effect/impact actually using model on participant/physician management and health outcomes – relative to not using the model → comparative studies.
Specific issue in Prediction Model studies

• Bias in prognostic model development exhibited by:
  • Overfitted models
    • too large ROC area
    • too optimistic calibration plot or outcome classification
      • Wrong estimated predictor weights
      • Wrong estimated intercept
  • Unfortunately: often don’t know from development study
    → only visible until model validation → ideally external
Slope plot $< 1.0$

- Low prob too low
- High prob too high
Systematic overestimation predicted probabilities

Intercept (outcome incidence) development study too high!
PROBAST
Prediction model Risk Of Bias
Assessment Tool

Karel Moons, Robert Wolff, Penny Whiting, Richard Riley, Gary Collins, Johannes Reitsma, Marie Westwood, Jos Kleijnen, Sue Mallett

Annals of Internal Medicine 2018
Structure of PROBAST

• Also domain-based: each with risk of bias + applicability
• Follows QUADAS-2, ROBINS-I, ROB 2.0 tool

Bias Likelihood that a prediction model leads to distorted predictive performance (discrimination, calibration, classification) for its intended use in the targeted individuals.

Applicability refers to extent to which prediction model from primary study matches your systematic review question, in terms of participants, predictors or outcomes of interest
# PROBAST 4 phases

<table>
<thead>
<tr>
<th>Step</th>
<th>Task</th>
<th>When to complete</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Specify your systematic review question</td>
<td>Once per systematic review</td>
</tr>
<tr>
<td>2</td>
<td>Classify the type of prediction model evaluation</td>
<td>Once for each model of interest in each publication being assessed, for each relevant outcome</td>
</tr>
<tr>
<td>3</td>
<td><strong>Assess risk of bias and applicability</strong></td>
<td>Once for each evaluation (development and/or validation) of each distinct model</td>
</tr>
<tr>
<td>4</td>
<td>Overall judgment</td>
<td>Once for each evaluation (development and/or validation) of each distinct model</td>
</tr>
</tbody>
</table>
Split group in 2
Practical

Apply QUIPS to the article by Kettlewell et al. 2006

Value of sentinel node status as a prognostic factor in melanoma: prospective observational study

Stephen Kettlewell, Colin Moyes, Caroline Bray, David Soutar, Alan MacKay, Dominique Byrne, Taimur Shoaib, Barun Majumder, Rona MacKie

Abstract

Objective To establish the prognostic value of knowledge of sentinel node status in melanoma.
Design Single centre prospective observational study, with sentinel nodes identified by lymphoscintigraphy, γ probe, and intraoperative blue dye and examined by both conventional histopathology and immunopathology.
Setting Specialist surgical service in west of Scotland.
Participants 482 patients with melanoma who consented to sentinel node biopsy in 1996-2003.
Main outcome measure Time to recurrence of or death from melanoma.
Results Of 472 patients who consented to sentinel node biopsy and in whom at least one sentinel node was identified, 367 (78%) had no tumour in the sentinel node. At mean follow-up of 43 months, 200 (82%) of this group were alive and free from multicentre randomised trial (MSLT1) is in progress with the aim of determining if patients with melanoma who have a positive SNB and proceed immediately to full node dissection have a superior disease-free survival or overall survival compared with patients who have node dissection only when nodes draining the site of the primary melanoma are clinically palpable. Definitive results are awaited.19

This study started before MSLT1. We aimed to gain clinical experience of the technique of SNB in a single centre and determine whether sentinel node status adds prognostic information to that gained from measuring tumour thickness.

Methods

We identified 482 patients, who gave written consent to take part in the study. All patients had an appropriate wide excision of
Table: A summary of the bias domains, prompting items and ratings of the QUIPS tool (reproduced from Hayden et al., 2013[62]); a copy of the full QUIPS tool is available at www.annals.org.

### QUIPS Risk of Bias Assessment Instrument for Prognostic Factor Studies


<table>
<thead>
<tr>
<th>Blases</th>
<th>Issues to consider for judging overall rating of &quot;Risk of bias&quot;</th>
<th>Study Methods &amp; Comments</th>
<th>Rating of reporting</th>
<th>Rating of &quot;Risk of bias&quot;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Study Participation</td>
<td><strong>Goal:</strong> To judge the risk of selection bias (likelihood that relationship between PF and outcome is different for participants and eligible non-participants).</td>
<td>Provide comments or text except in the white boxes below, as necessary to facilitate the continuous process that SEMMOM click on each of the bias tabs and choose from the drop-down menu(s) to select the severity of bias as: High, Moderate or Low.</td>
<td>Click on the green area; choose from the drop-down menu(s) to select the severity of bias as: High, Moderate or Low.</td>
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<tr>
<td></td>
<td>Source of study population</td>
<td><em>The source population or population of interest is adequately described for key characteristics (LS1).</em></td>
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<td></td>
<td>Inclusion and exclusion criteria</td>
<td><em>Selection of participants is adequately described (e.g., excluding patients with baseline characteristics as: High, Moderate or Low).</em></td>
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<td></td>
<td>Selection of participants</td>
<td><em>The sample frame and recruitment are adequately described, providing methods to identify the sample sufficient to control potential bias (number and type used, e.g., referral patterns in health.</em></td>
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<td></td>
<td>Recruitment period</td>
<td><em>Recruitment is adequately described.</em></td>
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<td></td>
<td>Place of measurements</td>
<td><em>Place of measurements (setting and geographic location) are adequately described.</em></td>
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<td></td>
<td>Adequate randomization</td>
<td><em>Randomization is adequate (e.g., using random number generators).</em></td>
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<td></td>
<td>Baseline characteristics</td>
<td><em>Baseline characteristics (e.g., individual entering the study is adequately described for key characteristics [LS1].</em></td>
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<td></td>
<td>Summary: Study participation</td>
<td>The study sample represents the population of interest on key characteristics, sufficient to limit potential bias of the observed relationship between PF and outcome.</td>
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</table>

| 2. Study Attrition | **Goal:** To judge the risk of attrition bias (likelihood that relationship between PF and outcome are different for completing and non-completing patients). | Provide comments or text except in the white boxes below, as necessary to facilitate the continuous process that SEMMOM click on each of the bias tabs and choose from the drop-down menu(s) to select the severity of bias as: High, Moderate or Low. | Click on the green area; choose from the drop-down menu(s) to select the severity of bias as: High, Moderate or Low. | |
| | Proportion of baseline sample available for analysis | *The proportion of study sample completing the study and providing outcome data (adherence).* | | |
| | Attempts to collect information on participants who dropped out | *Attempts to collect information on participants who dropped out of the study are described.* | | |
| | Reasons for patients lost to follow-up are provided | | | |
| | Outcome assessment center | *Outcome assessment center (e.g., measurement or observer) are adequately described for key characteristics (LS1).* | | |
| | Summary: Study Attrition | Losses to follow-up (from baseline sample to study population analyzed) is not associated with key characteristics (i.e., the study data adequately represent the sample) sufficient to limit potential bias to the observed relationship between PF and outcome. | | |

| 3. Prognostic Factor Measurement | **Goal:** To judge the risk of measurement bias related to how PF was measured (differential measurement of PF related to the level of agreement). | Provide comments or text except in the white boxes below, as necessary to facilitate the continuous process that SEMMOM click on each of the bias tabs and choose from the drop-down menu(s) to select the severity of bias as: High, Moderate or Low. | Click on the green area; choose from the drop-down menu(s) to select the severity of bias as: High, Moderate or Low. | |
| | Definition of PF | *A clear definition or description of PF is provided (e.g., including how, when, duration of exposure, and how the measurement of the key characteristic is performed).* | | |
| | Valid and Reliable Measurement of PF | *The method of PF measurement is adequately validated and reliable (e.g., through correlation between ratings, different raters, or validation with other measures).* | | |
| | Estimation of PF | | | |
| | Continuous variables are measured or appropriate transformations (e.g., data depending on measurement)* | | | |
| | Summary: Prognostic Factor Measurement | Adequate proportion of the study sample has positive data for PF usable. | | |
Suggested answers QUIPS practical

- Study Participation – MODERATE
- Study Attrition – LOW
- Prognostic Factor Measurement – MODERATE
- Outcome Measurement – LOW
- Covariate adjustment – LOW
- Statistical Analysis and Reporting - LOW
Predicting early death in patients with traumatic bleeding: development and validation of prognostic model

OPEN ACCESS

Pablo Perel senior clinical lecturer¹, David Prieto-Merino lecturer, medical statistics², Haleema Shakur senior lecturer¹, Tim Clayton senior lecturer, medical², Fiona Lecky clinical professor³ honorary professor⁴ honorary consultant⁵, Omar Bouamra medical statistician⁶, Rob Russell senior lecturer², Mark Faulkner paramedic advisor⁸, Ewout W Steyerberg professor⁹, Ian Roberts professor¹
Suggested answers PROBAST practical

- Participant selection – LOW
- Predictors – LOW
- Outcome – LOW
- Analysis – LOW
EXTRA

What to do with your risk of bias assessments?
Presentation of Risk of Bias

• ‘Risk of Bias’ table (transparent reporting)

Judge the specific domains for each study:
– Low risk of bias
– Moderate risk of bias
– High risk of bias

• Provide complete descriptions from studies supporting judgments
### Quality assessment/Risk of Bias Tool prognostic factor studies

#### Presentation across studies

<table>
<thead>
<tr>
<th>Study Participation</th>
<th>Study Attrition</th>
<th>Prognostic Factor Measurement</th>
<th>Outcome Measurement</th>
<th>Study Confounding</th>
<th>Statistical Analysis and Reporting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jiang 2015</td>
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<td>Schwindt* 2015</td>
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<td>Nunes* 2014</td>
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<td>Schumacher* 2013</td>
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<td>Hayashi-Kurahashi 2012</td>
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<td>Le Bihannic* 2012</td>
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<td>Wikström 2012</td>
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<td>Klebermass 2011</td>
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<td>West 2011</td>
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<td>Kidokoro 2010</td>
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<td>Maruyama 2002</td>
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<td>Hellström-Westas* 1991</td>
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<td>Tharp 1981</td>
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</table>

- **High**
- **Moderate**
- **Low**

*Note: * indicates that the study included in the analysis.*
Quality assessment/Risk of Bias Tool prognostic factor studies

Presentation RoB summary

- Study Participation
- Study Attrition
- Prognostic Factor Measurement
- Outcome Measurement
- Study Confounding
- Statistical Analysis and Reporting
- Overall risk of bias

Legend:
- Green: Low risk of bias
- Yellow: Unclear risk of bias
- Red: High risk of bias
Incorporating Assessments into Analyses

• Not appropriate to ignore potential biases

• Trade-off between bias and precision
  • Including all eligible studies will produce a result with high precision
  • But results may be biased due to flaws

• Cautious analysis and interpretation
Approaches to Include RoB Results in Analysis

• Restrict primary analysis to ONLY studies with low risk of bias (e.g. on all domains)
  • Threshold-type of approach (arbitrary)
  • Sensitivity analysis including higher risk studies

• Explore the impact of individual bias domains
  • Graphically according to risk of bias
  • Comparison of subgroups
## Take home messages

**Predictor finding studies** - which predictors contribute to prediction of particular prognostic/diagnostic outcome - aim not to develop a model for individualised predictions

**Model development studies** – to develop prediction model from data: identify important predictors; estimate predictor weights; construct model for individualised predictions; quantify predictive performance; internal validation

- **QUIPS** (Hayden, Ann Intern Med 2005)

**Model validation studies** – test (validate) predictive performance of previously developed model in participant data other than development set

- **CHARMS** (Moons 2014) – Data extraction + Critical Appraisal
- **PROBAST** (2018) – Formal Risk of Bias tool

**Model impact studies** – quantify effect/impact actually using model on participant/physician management and health outcomes – relative to not using the model → comparative studies.

**Comparative, intervention studies** – RoB Cochrane (Higgins BMJ 2011)

Reporting guideline prediction modeling studies

Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD): The TRIPOD Statement
Gary S. Collins, PhD; Johannes B. Reitsma, MD, PhD; Douglas G. Altman, DSc; and Karel G.M. Moons, PhD

Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD): Explanation and Elaboration
Karel G.M. Moons, PhD; Douglas G. Altman, DSc; Johannes B. Reitsma, MD, PhD; John P.A. Ioannidis, MD, DSc; Petra Macaskill, PhD; Ewout W. Steyerberg, PhD; Andrew J. Vickers, PhD; David F. Ransohoff, MD; and Gary S. Collins, PhD

www.tripod-statement.org
Cochrane PMG title registration form for SRs of prognostic studies

Cochrane Methods
Prognosis

Prognosis Studies review proposal form

Review Proposal Form

Please complete this form to outline your proposal for a Cochrane systematic review. Email the completed form to [email address], or send to [name], Managing Editor, Cochrane XXX Group, [postal address]. Ph: +XX XXXXXXXX Fax: +XX XXXXXXXX.

Before completing this form:

- Read “Managing expectations: what does The Cochrane Collaboration expect of authors, and what can authors expect of The Cochrane Collaboration?” (see http://community.cochrane.org/editorial-and-quality-policy-resource/cochrane-review-development/managing-expectations. Note: this information is particularly useful for systematic reviews of intervention studies. A page for prognosis reviews is under construction.)

- Note that a Cochrane review of prognosis studies clearly differs from that of intervention studies and diagnostic test accuracy studies. In, e.g., searching, data extraction, critical appraisal and meta-analysis, step-by-step guidance to help you understand prognosis studies and the processes of conducting a review of prognosis studies is given in the papers in the reference list below.

- Cochrane reviews of prognosis require a multidisciplinary team. Below you find several questions addressing the available expertise in the author team, and whether external expertise (e.g. information specialists or methodologists) is needed to conduct this review. If additional expertise is needed, e.g. an information specialist, or methodological or statistical expertise, please provide this request to the Prognosis Methods Group (PMG) timely.

Proposed title

Choose one of the formats below. See also the generic guidance on defining a review question for prognosis studies in the CHARMS/Checklist.

- Incidence of [outcome] within [time] in [population]
- [Prognostic factors] for predicting incidence of [outcome] in [population]
- Prediction of [outcome] in [population] using [prognostic factors]
- Prognostic models for predicting [outcome] in [population]
- Predictive performance of [prognostic model] for predicting [outcome] in [population]
- Added value of [prognostic factor] on top of [existing prognostic factors/prognostic model(s)] for predicting [outcome] in [population]
- [Predictive factors] predicting the [outcome of treatment] in [population]
- [Factors / Models] predicting differential treatment response in [population]
- [Factors / Models] for predicting treatment response in [population]

Short description of review proposal

Provide brief but enough information to make sure that the clinical context and the actual question that is being asked is clear for non-content experts as well.

For explicit guidance to help filling in this title registration form and for the conduct of the review, from framing the review question, search strategy, study inclusion criteria, critical appraisal, risk of bias assessment, meta-analysis and reporting, please see the papers mentioned in the reference list below.

Type of prognosis review

- Overall prognosis
- Prognostic factors
- Prognostic models
- Predictive/Treatment selection factors

Motivation for the review

For example, is this going to be part of a PhD thesis? A part of a larger project? Is it particularly topical at the present time?

Background

i) The clinical problem.

A short description of the existing clinical pathway of the targeted individuals/patients, their starting condition and moment of progression (time point in the clinical pathway); what prognostic outcomes are relevant to the targeted individuals. For predictive factor reviews also refer to the role of treatment.

ii) Why is the review relevant, including how might the results of the review be used, e.g., the prognostic or predictive factor(s), or model(s) under review may be used to determine treatment allocation or stratification, decide on closer follow-up or monitoring, etc.

Reference to an existing systematic review on this topic outside Cochrane is helpful.

Review objective(s)

What is the review question, according to the PICOTS format? (see line 1 in the paper of Shemlay et al, BMJ 2017, see reference list below)

Primary objective:

Secondary objective(s):

Participants/ setting

Short outline of the targeted population and clinical setting, to be included and excluded for the review.
# Cochrane PMG Protocol Template for SRs of prognostic studies

**Protocol Cochrane Review Prognosis Studies**

*Prognosis extracter protocols are published in the Cochrane Library using the "Flexible (Prognosis)" type. The Prognosis Methods Group recommends inclusion of specific sub-headers relevant to the type of prognostic review being undertaken. This document includes the recommended sub-headers for example reviews of prognostic model(s). See at the end of this document relevant references that maybe helpful when writing the protocol.*

## Why it is important to do this review

| [Fixed, level 2 heading] | The rationale for the review and why the prognostic questions being asked are important. |

## Objectives

| [Fixed, level 2 heading] | State the review question, including a table in the PICOTS format. (See Box 1 in the paper of Debraay et al, BMJ 2017, and Table 1 of the CHARMPS guidance Moons et al, PLOS Med 2014). The PICOTS format consists of the following elements: Population—define the target population in which the overall prognosis or factor(s)/model(s) will be used. Intervention (model/factor)—define the factor(s)/model(s) under review. Comparator—if applicable, one can address competing factor(s)/model(s) for the factor(s)/model(s) under review. Outcome(s)—define the outcome(s) of interest that is/are studied for the overall prognosis estimation or predicted with the factor(s)/model(s). Timing—define when and over what time period the outcome occurrence is studied or predicted. |

## Description of the targeted health condition and context

| [Fixed, level 2 heading] | A description of the targeted health condition and clinical context for which the (overall) prognostic or prognostic/predictive factor or model under review is intended (frequency, severity, and possible treatments). A health condition can for example be people undergoing surgery, having a certain disease or diagnosis, being pregnant, or healthy individuals of the general population within a certain age range. Also clearly define the moment of prognostication or prediction in the targeted population. For example, within two weeks after receiving a certain diagnosis, the day of intensive care admission, being 3 months pregnant, or visiting the emergency department with a trauma. |

## Description of the prognostic/predictive model(s)/factor(s)

| [Fixed, level 2 heading] | Not applicable for review on overall prognosis. Clearly state in which of the types of prognosis studies you are interested in: prognostic factor, prognostic model, or predictive factor (see PROGRESS series for definitions, see below for references). Describe the factor(s) or model(s) under review in more detail. |

## Health outcomes

| [Fixed, level 2 heading] | Description of the health outcomes that are being studied in the targeted population—e.g. the outcomes of the overall prognosis or that are to be predicted by the factor(s)/model(s) under review. Also clearly define the time horizon (relative to the moment of prognostication or prediction) of the outcomes. |

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Authors

Contact person

| [Fixed, level 1 heading] | The names and affiliations of all authors. |

Background

| [Fixed, level 2 heading] | A description of the targeted health condition and clinical context for which the (overall) prognostic or prognostic/predictive factor or model under review is intended (frequency, severity, and possible treatments). A health condition can for example be people undergoing surgery, having a certain disease or diagnosis, being pregnant, or healthy individuals of the general population within a certain age range. Also clearly define the moment of prognostication or prediction in the targeted population. For example, within two weeks after receiving a certain diagnosis, the day of intensive care admission, being 3 months pregnant, or visiting the emergency department with a trauma. |

Investigation of sources of heterogeneity between studies

| [Fixed, level 2 heading] | Heterogeneity investigations explore factors which may affect, e.g. the overall prognosis or the prognostic accuracy of factors or models. These explorations are essential because they provide a framework by which the observed heterogeneity may be explained and to provide a more clinically useful review. For example, the predictive performance of a certain prognostic model for predicting 10-year cardiovascular disease outcomes in the adults above 40 in the general population, may vary when different definitions of cardiovascular disease outcomes are applied, when different age ranges, ethnic groups or genders have been studied, or when different study designs were used in the prognostic model studies. |

Methods

| [Fixed, level 1 heading] | The Methods section in a protocol should be written in the future tense. Often a review is unable to implement all of the methods outlined in the protocol. |

Available via [http://methods.cochrane.org/prognosis](http://methods.cochrane.org/prognosis)