Cochrane Methods Prognosis

Cochrane Netherlands

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

University Medical Center Utrecht

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?

Answer

(BMJ series 2009 (Altman, Moons, Royston, Vergouwe) + Progress series BMJ/Plos Med 2013

F**orecast** 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

Answer

- Why prognosticate:
  - To provide information to patients
  - Identify groups for treatment or other management – including abstine
  - 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

Answer

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

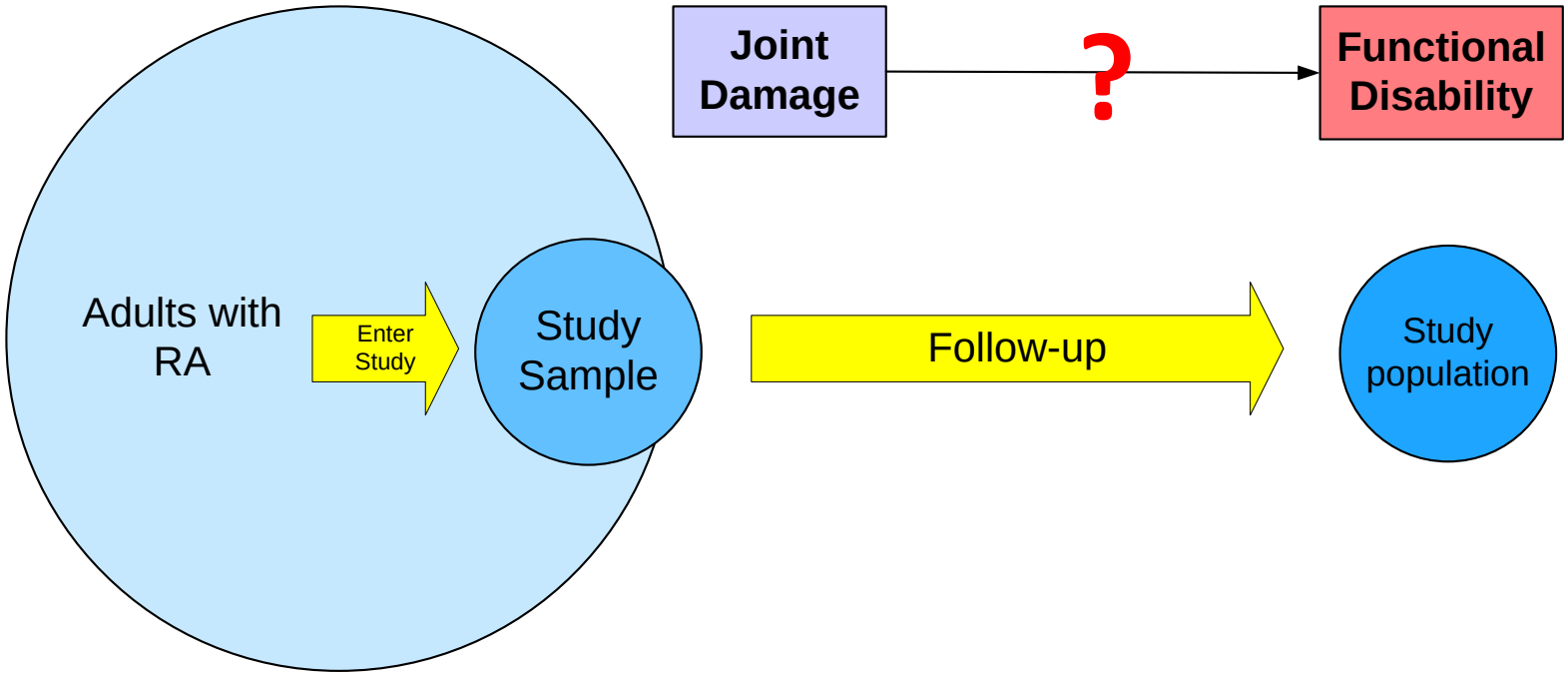
Conducting a systematic review of prognosis studies

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** → J Haydn, Ann Int Med 2006 + 2013
- Prognostic (prediction) model studies (development and validation)
  - **PROBAST** – Ann Int Med 2018

Prognostic Factor Studies



Adapted from: *Fletcher & Fletcher, Clinical Epidemiology – The Essentials. Chapter 6. Williams & Wilkins, Baltimore. 1996*

QUIPS (J Hayden, Ann Int Med 2006 + 2013)

Table 2. Domains Included in the Framework of Potential Biases and the Proportion of Reviews Assessing the Biases*

Potential Bias	Studies Adequately Assessing Bias, %†	Domains Addressed	Studies Assessing Domain, %
1. The study sample represents the population of interest on key characteristics, sufficient to limit potential bias to the results (study participation).	55	1. Source population clearly defined 2. Study population described 3. Study population represents source population or population of interest	50 21 50
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).	42	4. Completeness of follow-up described 5. Completeness of follow-up adequate	19 42
3. The prognostic factor of interest is adequately measured in study participants to sufficiently limit potential bias (prognostic factor measurement).	59	6. Prognostic factors defined 7. Prognostic factors measured appropriately	31 59
4. The outcomes of interest are adequately measured in study participants to sufficiently limit potential bias (outcome measurement).	51	8. Outcome defined 9. Outcome measured appropriately	42 51
5. Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest (confounding measurement and account).	13	10. Confounders defined and measured 11. Confounding accounted for	21 53
6. The statistical analysis is appropriate for the design of the study, limiting potential for presentation of invalid results (analysis).	33	12. Analysis described 13. Analysis appropriate 14. Analysis provides sufficient presentation of data	8 33 32

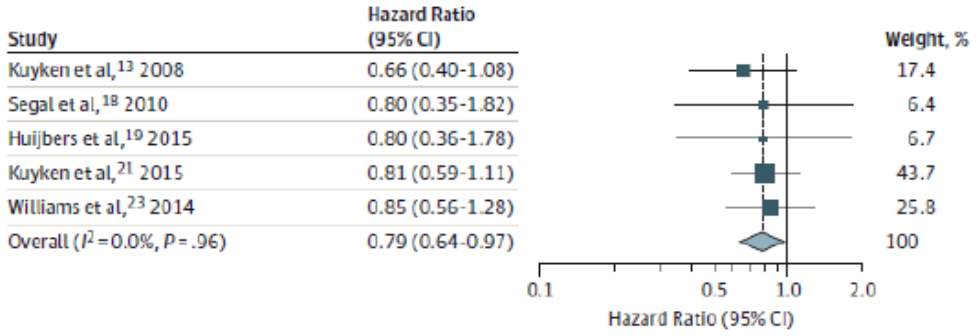
* Data are from 163 prognostic systematic reviews with quality items that could be extracted.

†Adequate assessment included 1) study participation: "source population clearly defined" and "study population described" or "study population represents source

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
  - **QUIPS** → J Haydn, Ann Int Med 2006 + 2013
- Prognostic (prediction) model studies (development and validation)
  - **PROBAST** – Ann Int Med 2018

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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

BMJ series 2009/Bouwmeester 2012/PROGRESS series 2013 (BMJ/Plos Med)

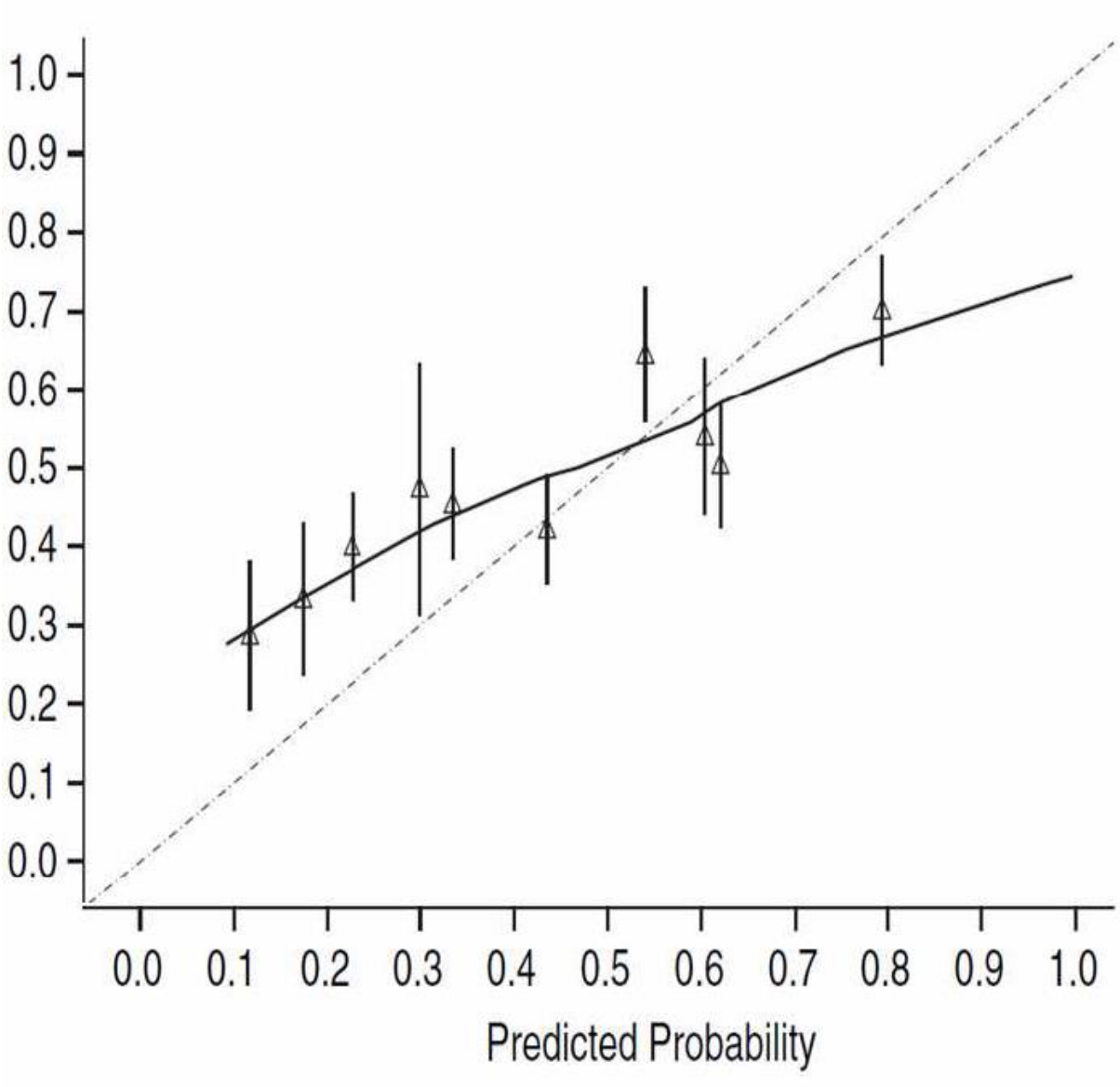
1. Model development studies – to develop prediction model from data: identify important predictors; estimate predictor weights; construct model for individualised predictions; quantify predictive performance; internal validation

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.

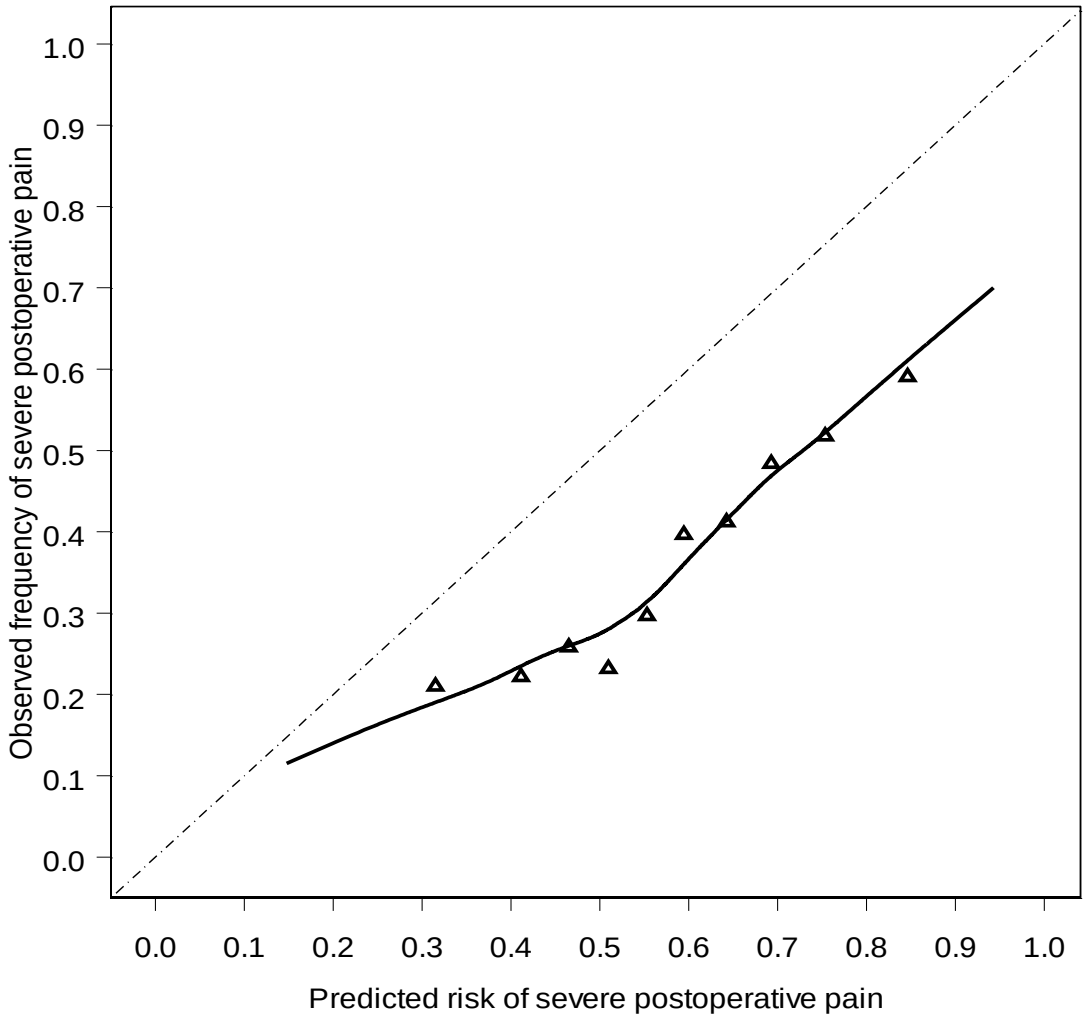
Specific issue in Prediction Model studies

- 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!

Julius Center
UMC Utrecht

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

Step	Task	When to complete
1	Specify your systematic review question	Once per systematic review
2	Classify the type of prediction model evaluation	Once for each model of interest in each publication being assessed, for each relevant outcome
3	**Assess risk of bias and applicability**	**Once for each evaluation (development and/or validation) of each distinct model**
4	Overall judgment	Once for each evaluation (development and/or validation) of each distinct model

Split group in 2

Group Exercise QUIPS

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

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.[12]

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

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

Modified from: Hayden JA, Côté P, Bombardier C. Evaluation of the Quality of Prognosis Studies in Systematic Reviews. Annals of Internal Medicine. 2006;144:427-437, with the assistance of the QUIPS-LBP Working Group.

Author and year of publication				
Study identifier				
Reviewer				
Biases	**Issues to consider for judging overall rating of "Risk of bias"**	**Study Methods & Comments**	**Rating of reporting**	**Rating of "Risk of bias"**
Instructions to assess the risk of each potential bias:	These issues will guide your thinking and judgment about the overall risk of bias within each of the 6 domains. Some 'issues' may not be relevant to the specific study or the review research question. These issues are taken together to inform the overall judgment of potential bias for each of the 6 domains.	Provide comments or text exerpts in the white boxes below, as necessary, to facilitate the consensus process that will follow.	Click on each of the blue cells and choose from the drop down menu to rate the adequacy of reporting as yes, partial, no or unsure.	Click on the green cells; choose from the drop-down menu to rate potential risk of bias for each of the 6 domains as High, Moderate, or Low considering all relevant issues
1. Study Participation	**Goal: To judge the risk of selection bias (likelihood that relationship between *PF* and *outcome* is different for participants and eligible non-participants).**			
Source of target population	The source population or population of interest is adequately described for key characteristics (LIST).			
Method used to identify population	The sampling frame and recruitment are adequately described, including methods to identify the sample sufficient to limit potential bias (number and type used, e.g., referral patterns in health			
Recruitment period	Period of recruitment is adequately described			
Place of recruitment	Place of recruitment (setting and geographic location) are adequately described			
Inclusion and exclusion criteria	Inclusion and exclusion criteria are adequately described (e.g., including explicit diagnostic criteria or "zero time" description).			
Adequate study participation	There is adequate participation in the study by eligible individuals			
Baseline characteristics	The baseline study sample (i.e., individuals entering the study) is adequately described for key characteristics (LIST).			
Summary Study participation	**The study sample represents the population of interest on key characteristics, sufficient to limit potential bias of the observed relationship between PF and**			
2. Study Attrition	**Goal: To judge the risk of attrition bias (likelihood that relationship between *PF* and *outcome* are different for completing and non-**			
Proportion of baseline sample available for analysis	Response rate (i.e., proportion of study sample completing the study and providing outcome data) is adequate.			
Attempts to collect information on participants who dropped out	Attempts to collect information on participants who dropped out of the study are described.			
Reasons and potential impact of subjects lost to follow-up	Reasons for loss to follow-up are provided.			
Outcome and prognostic factor information on those lost to follow-up	Participants lost to follow-up are adequately described for key characteristics (LIST).			
	There are no important differences between key characteristics (LIST) and outcomes in participants who completed the study and those who did not.			
Study Attrition Summary	**Loss 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 outcome)**			
Definition of the PF	A clear definition or description of 'PF' is provided (e.g., including dose, level, duration of exposure, and clear specification of the method of measurement).			
Valid and Reliable Measurement of PF	Method of PF measurement is adequately valid and reliable to limit misclassification bias (e.g., may include relevant outside sources of information on measurement properties, also characteristics, such as blind measurement and limited reliance on recall).			
	Continuous variables are reported or appropriate cut-points (i.e., not data-dependent) are used.			
Method and Setting of PF Measurement	The method and setting of measurement of PF is the same for all study participants.			
Proportion of data on PF available for analysis	Adequate proportion of the study sample has complete data for PF variable.			

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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

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Group Exercise PROBAST

BMJ 2012;345:e5166 doi: 10.1136/bmj.e5166 (Published 15 August 2012)

RESEARCH

Predicting early death in patients with traumatic bleeding: development and validation of prognostic model

Pablo Perel *senior clinical lecturer*[1], David Prieto-Merino *lecturer, medical statistics*[2], Haleema Shakur *senior lecturer*[1], Tim Clayton *senior lecturer, medical*[2], Fiona Lecky *clinical professor*[3] *honorary professor*[4] *honorary consultant*[5], Omar Bouamra *medical statistician*[6], Rob Russell *senior lecturer*[7], Mark Faulkner *paramedic advisor*[8], Ewout W Steyerberg *professor*[9], Ian Roberts *professor*[1]

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)

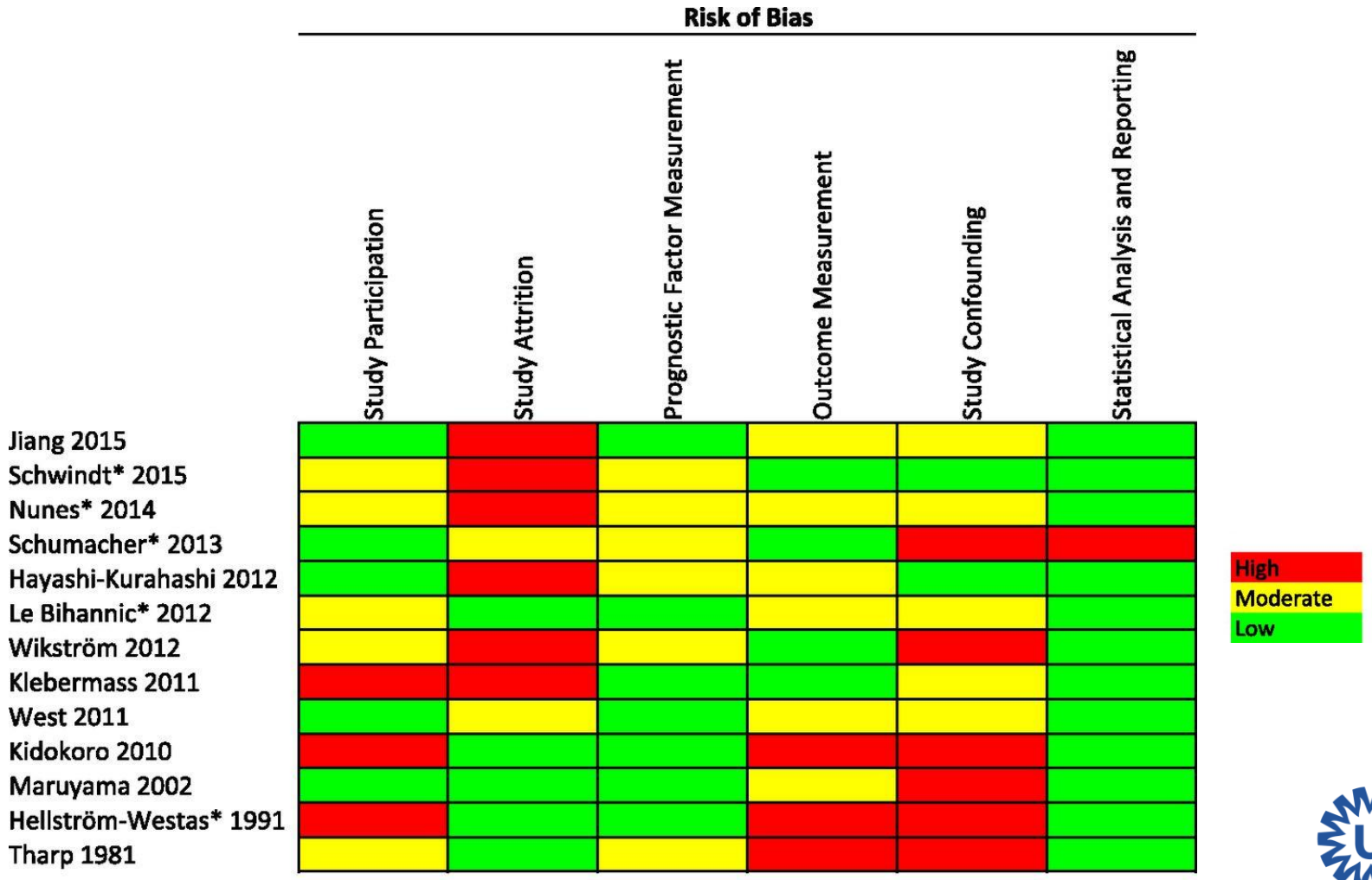
Judge the specific domains for each study:

- Low risk of bias
- Moderate risk of bias
- High risk of bias

- Provide complete descriptions from studies supporting judgments

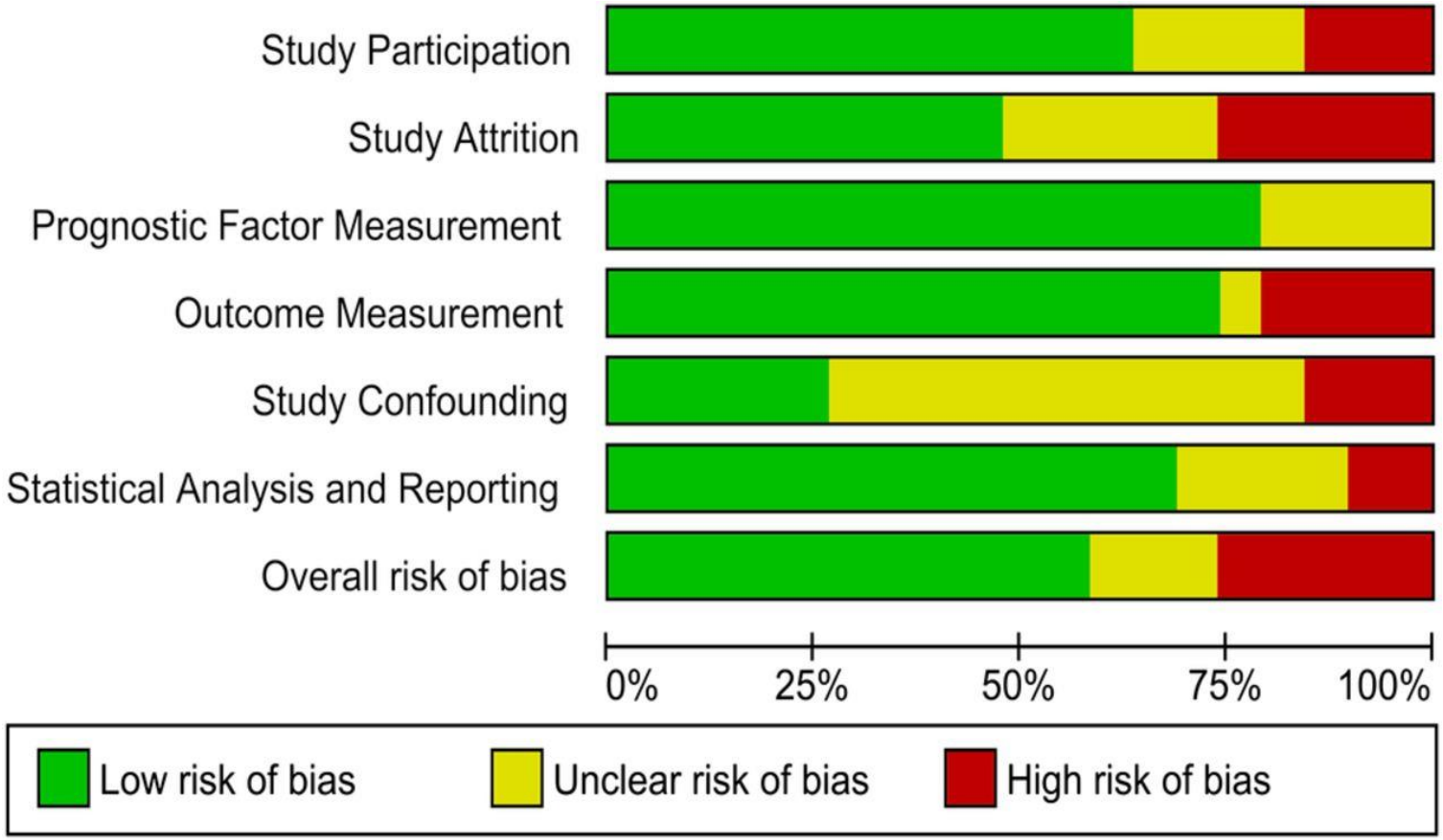
Quality assessment/Risk of Bias Tool prognostic factor studies

Presentation across studies



Quality assessment/Risk of Bias Tool prognostic factor studies

Presentation RoB summary



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

QUIPS (Hayden, Ann Intern Med 2005)

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

CHARMS (Moons 2014) – Data extraction + Critical Appraisal

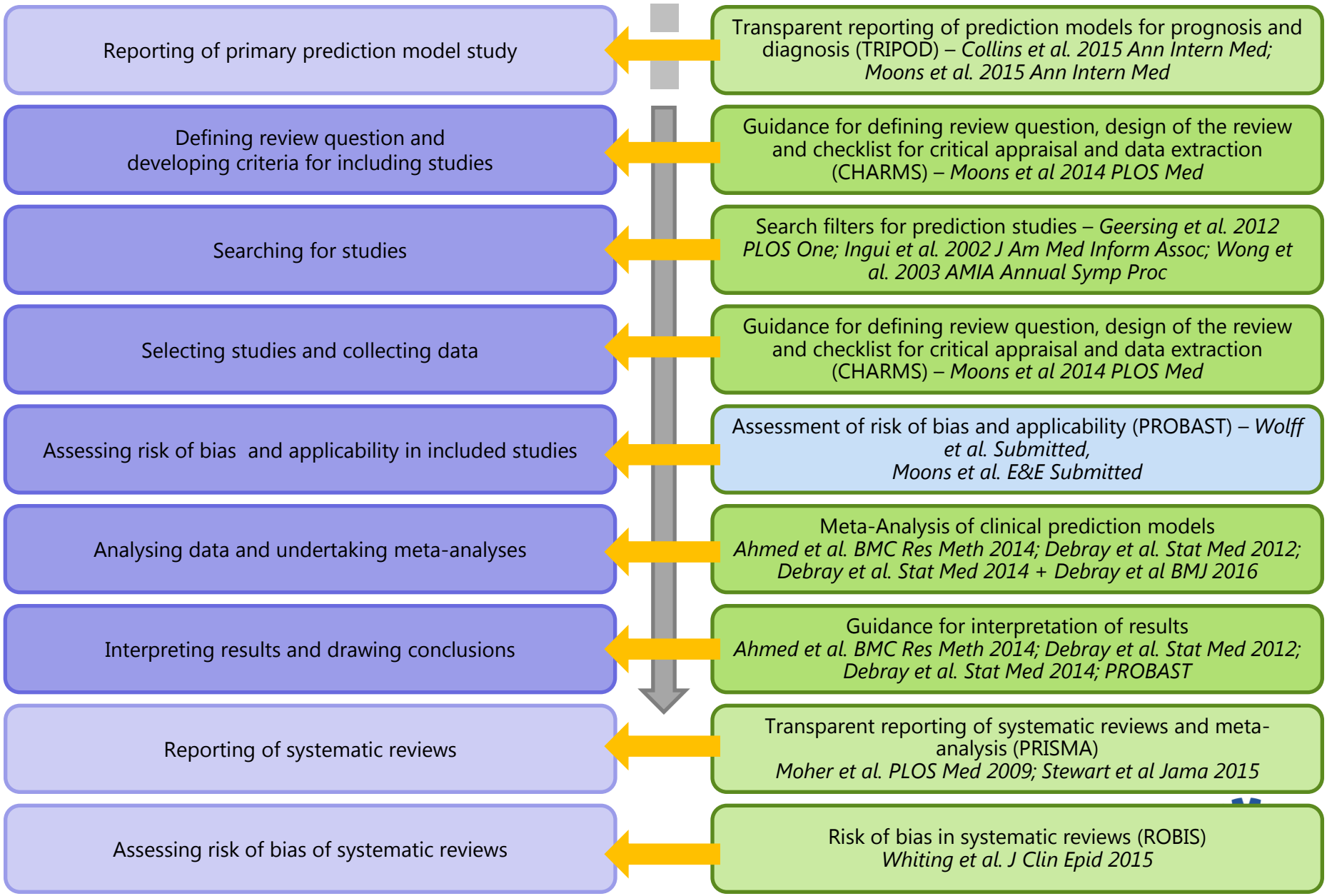
Model validation studies – test (validate) predictive performance of previously developed model in participant data other than development set

PROBAST (2018) – Formal Risk of Bias tool
Prognostic and Diagnostic

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)

Bouwmeester et al. PLoS Med 2012


Reporting of primary prediction model study
Transparent reporting of prediction models for prognosis and diagnosis (TRIPOD) – *Collins et al. 2015 Ann Intern Med; Moons et al. 2015 Ann Intern Med*
Defining review question and developing criteria for including studies
Guidance for defining review question, design of the review and checklist for critical appraisal and data extraction (CHARMS) – *Moons et al 2014 PLOS Med*
Searching for studies
Search filters for prediction studies – *Geersing et al. 2012 PLOS One; Ingui et al. 2002 J Am Med Inform Assoc; Wong et al. 2003 AMIA Annual Symp Proc*
Selecting studies and collecting data
Guidance for defining review question, design of the review and checklist for critical appraisal and data extraction (CHARMS) – *Moons et al 2014 PLOS Med*
Assessing risk of bias and applicability in included studies
Assessment of risk of bias and applicability (PROBAST) – *Wolff et al. Submitted, Moons et al. E&E Submitted*
Analysing data and undertaking meta-analyses
Meta-Analysis of clinical prediction models *Ahmed et al. BMC Res Meth 2014; Debray et al. Stat Med 2012; Debray et al. Stat Med 2014 + Debray et al BMJ 2016*
Interpreting results and drawing conclusions
Guidance for interpretation of results *Ahmed et al. BMC Res Meth 2014; Debray et al. Stat Med 2012; Debray et al. Stat Med 2014; PROBAST*
Reporting of systematic reviews
Transparent reporting of systematic reviews and meta-analysis (PRISMA) *Moher et al. PLOS Med 2009; Stewart et al Jama 2015*
Assessing risk of bias of systematic reviews
Risk of bias in systematic reviews (ROBIS) *Whiting et al. J Clin Epid 2015*

Reporting guideline prediction modeling studies

Annals of Internal Medicine RESEARCH AND REPORTING METHODS

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 *Ann Intern Med.* 2015;162:55-63. doi:10.7326/M14-0697

Annals of Internal Medicine RESEARCH AND REPORTING METHODS

Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD): Explanation and Elaboration

Ann Intern Med. 2015;162:W1-W73. doi:10.7326/M14-0698

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 XXXXXXXXX Fax: +XX XXXXXXXXX.

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-publishing-policy-resource/cochrane-review-development/managing-expectations Note: this information is particularly 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 understanding 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 question addressing the available expertise in the author team, and whether external expertise (e.g. from 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] 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 in/exclusion 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 *Indicate what type of review you are going to perform (double click to check a box). See PROGRESS series in the reference list.*	☐ 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; is it 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 prognostication (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 this 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 abstention, 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 Box 1 in the paper of Debray 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 exemplar 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 exemplar reviews of prognostic model(s). See at the end of this document relevant references that may be helpful when writing the protocol.

Header*	Description
Title	Choose preferably one of the following formats: 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] Performance of [prognostic model] for predicting [outcome] in [population] Added/Incremental value of [prognostic factor] on top of [existing prognostic factors/prognostic model] 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]
Authors	List names and affiliations of all authors.
Contact person	
Background [Fixed, level 1 heading]	
Description of the health condition and context [Fixed, level 2 heading]	A description of the targeted health condition and clinical context for which the (overall) prognosis 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. If there are existing Cochrane reviews of interventions or diagnostic tests for the targeted health condition they should be cross-referenced here.
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

Protocol Cochrane Review Prognosis Studies

	disease recurrence, or even lifelong incidence of certain outcome events.
Why it is important to do this review [Fixed, level 2 heading]	Explain the rationale for the review and why the prognosis questions being asked are important.
Objectives [Fixed, level 1 heading]	
Primary objectives [Optional, level 2 heading]	State the review question, including a table in the PICOTS format. (See Box 1 in the paper of Debray et al, BMJ 2017, and Table 1 of the CHARMS 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. overall prognosis ons may categorise their Objectives'. For example, the primary objectives may be to quantify the added predictive value of several biomarkers to an existing prognostic model; the secondary objective may be to compare the performance of this existing prognostic model to the performance of the biomarkers alone. Secondary objectives related to investigating heterogeneity between study results should not be listed under this subheading but under the next subheading.
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 a priori 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