# How to appraise Individual Participant Data (IPD) meta-analysis in diagnostic and prognostic risk prediction research

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## Background & Objective

The development and (external) validation of clinical prediction models for diagnosis and prognosis is an important aspect of contemporary epidemiological research. During the past few years, evidence synthesis and meta-analysis of individual participant data (IPD) has become increasingly popular for improving the development, validation and eventual generalizability of prediction models. IPD meta-analyses provide additional opportunities to better understand the generalizability of prediction models across different (sub)populations and settings. There is, however, little guidance on how to conduct an IPD meta-analysis aimed at developing and validating prediction models, and how to interpret their findings. We provide methodological recommendations for both authors and reviewers in appraising IPD meta-analyses that aim to develop and/or validate a prediction model . We discuss (potential) advantages, the selection and inclusion of relevant studies, risk of bias assessments, and statistical methods of IPD-MA.

## What is the main difference between intervention and risk prediction research?

- controlled versus observational study design
- causal versus predictive associations
- relative effects versus absolute risk probabilities

**Diagnostic prediction models**

- predict the absolute probability that a certain disease or condition is currently present
- inform the referral of patients for further testing, initiate treatment directly or reassure patients that a serious cause for their complaints or symptoms is unlikely

**Prognostic prediction models**

- predict the absolute probability that an outcome will occur within a specific follow-up period (example in **Fig 1**).
- planning lifestyle or therapeutic decisions

## What are the (potential) advantages of an IPD meta-analysis in prediction research?

- standardize variable definitions of predictors and outcomes and overcome differences in censoring and length of follow-up
- Increase the total sample size and the number of included study populations as compared to prediction research that is based on a single dataset. It therefore enables the development and validation of prediction models in a wider range of study populations with an increased variation of subject and study characteristics.
- Facilitate simultaneous development and validation of risk prediction models. This may help to verify whether there is consistent evidence that the model is reliable and applicable to the intended populations of individuals, and thereby improve insight into a model's external validity.
- Investigate between-study heterogeneity in baseline risk (such as outcome occurrence, typically reflected by the intercept term of the prediction model), predictor effects, and thus in model performance. This may help to identify under which circumstances a certain prediction model yields accurate predictions across different study populations, but also lead to an increased model performance by accounting for between-study heterogeneity.
- Examine more complex associations, such as non-linearity of predictor effects, covariate interaction and time-varying predictor effects.

## What aims can be addressed by an IPD meta-analysis in prediction research?

1. To develop and directly validate a new prediction model using IPD from all relevant studies
2. To evaluate the performance of an existing prediction model across various study populations
3. To compare the performance of competing prediction models developed for the same target population and outcome
4. To adjust and combine the most promising prediction model(s) developed for the same target population and outcomes.
5. To examine the added value of a specific predictor or (bio)marker across different study populations.

## Identifying the relevant studies for the IPD meta-analysis

- Perform a (systematic) literature review and seek IPD from the relevant studies identified
- Set-up a collaborative group of selected researchers who agree to share their IPD

## Pre-specifying the IPD meta-analysis

- information on the outcomes and (candidate) predictors and their definitions
- in- and exclusion criteria of study participants
- sample size considerations
- methods for quantifying and accounting for heterogeneity across studies
- model performance statistics of interest
- testing against optimism and incidental findings

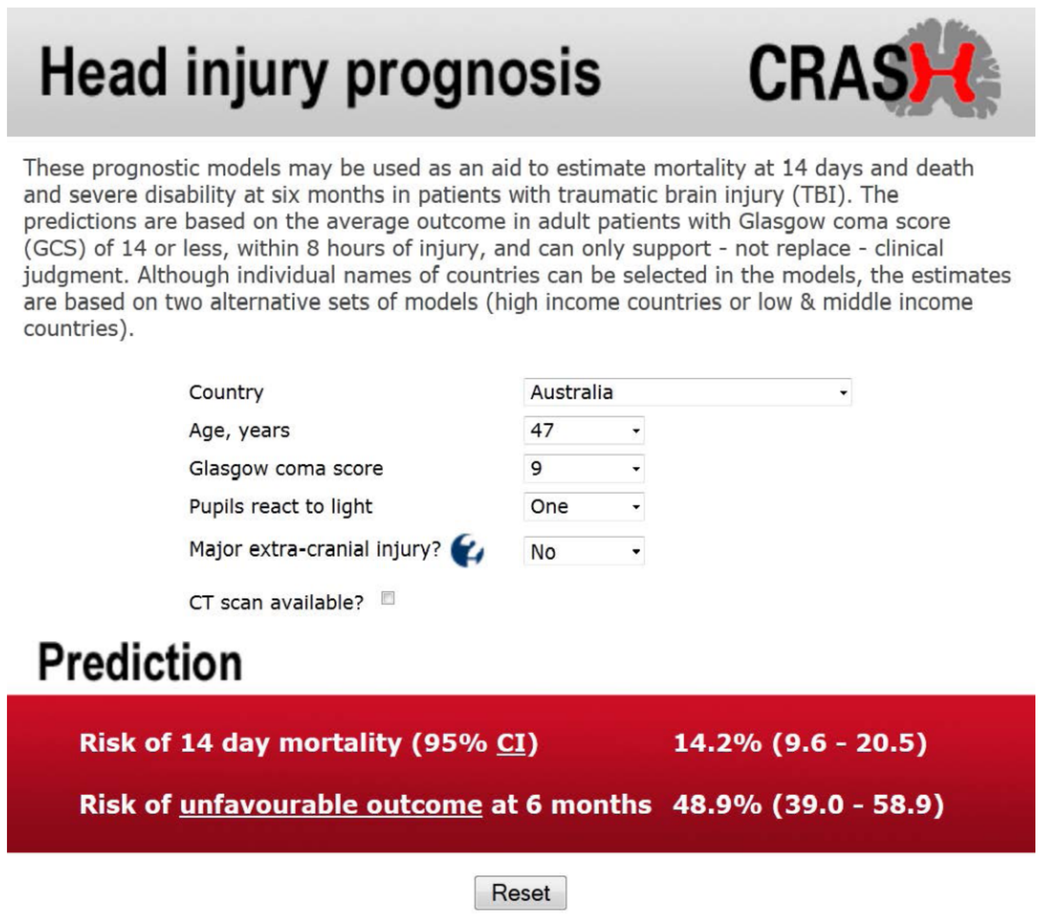


**Fig 1**: Web tool for prognosis of patients with head injury (CRASH trial) (reproduced from Steyerberg et al 2013. Prognosis Research Strategy (PROGRESS) 3: Prognostic Model Research. PLOS Medicine 10(2):e1001381).

## Assessing the risk of bias of included studies

Check adherence to methodological recommendations (study design, participant selection, length-of follow-up, outcome and predictor definitions)

- QUIPS checklist for appraisal of prognostic factor studies
- PROBAST risk of bias tool for prediction modeling studies
- Checklists from Centre for Evidence-Based Medicine (Toronto)

## Which statistical methods can be used?

- Missing data: account for heterogeneity across studies (impute study datasets separately or adopt hierarchical imputation model) (aim 1 – 5)
- Investigate degree of variation in baseline risk (or hazard) and predictor effects (aim 1, 5)
- Investigate degree of variation in model performance (aim 2, 3, 5)
- Investigate relatedness between study populations (aim 2, 3): comparison of case-mix differences
- Facilitate updating of prediction models in new study populations (aim 1, 4): estimate study-specific baseline risk (or hazard) and report outcome prevalence (or incidence) in that study
- Minimize heterogeneity in predictor effects (aim 1, 4)
- Facilitate the calculation of absolute risks over time (aim 1, 4)
- Sensitivity analyses: internal-external cross-validation, hierarchical bootstrap (aim 1)

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