Prognosis Research in Healthcare:

initiatives to improve methodology standards

Wednesday, March 30, 1:30 pm – 4:40 pm

Speakers:

Richard Riley (Keele University, UK)
Gary Collins (University of Oxford, UK)

DAGStat Conference 2022

Education for Statistics in Practice

Prognosis Research in Healthcare:

initiatives to improve methodology standards

Wednesday, March 30, 1:30 pm – 4:40 pm

1:35 – 2:15: The PROGRESS Framework (Riley)

2:15 – 2:55: Reporting Guidelines for Prognosis Research (Collins)

(Break)

3:10 – 4:10: Sample Size Calculations For Prognostic Model Research (Riley)

4:10 – 4:35: IPD Meta-Analysis for Prognosis Research (Riley)

The PROGRESS Framework

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PART 1

What is prognosis research?

"Patient trust was essential in the healing process. It could be won by a punctilious bedside manner, by meticulous explanation, and by mastery of prognosis, an art demanding experience, observation and logic"

Galen, 2nd Century AD

(as quoted within: Porter, R. (1999). The greatest benefit to mankind : a medical history of humanity from Antiquity to the present, London, FontanaPress)

Prognosis

- The study of the risk (probability, likelihood) of future outcomes and events

- Greek: *πρόγνωση* (fore-knowing, foreseeing)

- We are all interested in understanding the future

  - will it rain today?
  - will my favourite team win the league?
  - will I live until at least 70?
  - will Brexit ever deliver at least one benefit?

What is prognosis research?

- In healthcare, the term ***prognosis*** refers to the risk of future health outcomes in people with a given disease or health condition.

- ***Prognosis research*** is thus the study of future outcomes ("endpoints") among people with a given baseline health state ("startpoint"), ***in order to improve health***.

- It aims to **summarise, understand and predict outcomes** in clinically relevant populations and individuals
- Thereby inform clinical research & clinical practice

PART 2

Is prognosis research relevant?

Is prognosis research relevant?

- **The study of prognosis is vital**:

  - globally more people are living with one or more diseases or health-impairing conditions than at any previous time

  - governments and funders want to see that medical research ***improves patient outcomes***

- In the UK, our government state wanting to:
  - improve health outcomes
  - reduce variation in outcomes across the country
  - ensure our outcomes are not below other countries'

Is prognosis research relevant?

- A few years ago the UK NHS Commissioning Board proposed to spend £80bn per year:

  - its red thread was outcomes.

Read 'Developing the NHS Commissioning Board':

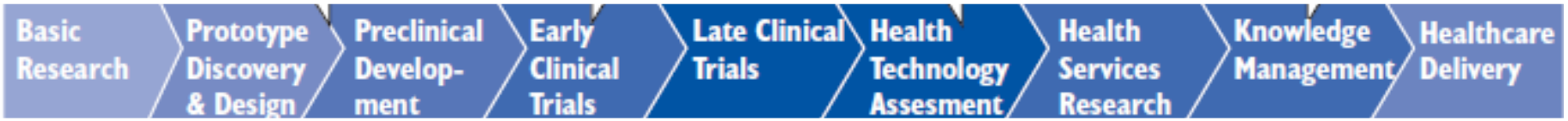
The Government has set out a clear vision for a modernised NHS driven by a new commissioning system focused relentlessly on improving outcomes for patients

The Board's overarching role is to ensure that the NHS delivers better outcomes for patients within its available resources

The purpose of the Board will be to use the £80bn commissioning budget to secure the best possible outcomes for patients

Is prognosis research relevant?

- Prognosis research can impact many routes toward improved health outcomes
- Consider the 'translational' pathway below, used to reflect translational clinical research that ultimately leads to *improved patient outcomes*



- Prognosis research can impact upon all components
  - from basic research (e.g. disease definition)
  - to discovery (e.g. targets for treatment)
  - to clinical trials (e.g. sample size calculations)
  - to HTA (e.g. develop, validate & assess prognostic models)
  - to delivery (e.g. prioritising highest risk, precision medicine)

PART 3

PROGRESS:

A framework for researching clinical outcomes

Poor quality prognosis research

- Sadly, much of prognosis research is poor quality

"**The (prognostic factor) literature is probably cluttered with false-positive studies that would not have been submitted or published if the results had come out differently**"

Simon R (2001) Evaluating prognostic factor studies. In: Gospodarowicz M. Kea, editor. Prognostic factors in cancer. Wiley-Liss. pp. 49–56

Poor quality prognosis research

"**As a consequence of the poor quality of research, prognostic markers may remain under investigation for many years after initial studies without any resolution of the uncertainty. Multiple separate and uncoordinated studies may actually delay the process of defining the role of prognostic markers**"

Altman DG (2001) Systematic reviews of evaluations of prognostic variables. BMJ 323: 224–228

Poor quality prognosis research

"Categorising continuous predictors is unnecessary, biologically implausible and inefficient and should not be used in prognostic model development"

Collins GS et al. (2016) Quantifying the impact of different approaches for handling continuous predictors on the performance of a prognostic mode. Stat Med 35: 4124–4135

Poor quality prognosis research

"Prediction models for covid-19 are quickly entering the academic literature to support medical decision making at a time when they are urgently needed. This review indicates that proposed models are poorly reported, at high risk of bias, and their reported performance is probably optimistic. Hence, we do not recommend any of these reported prediction models for use in current practice"

Wynants et al. (2020) Prediction models for diagnosis and prognosis of covid-19: systematic review and critical appraisal. BMJ 369:m1328

The PROGRESS framework

- PROGRESS refers to **PROGnosis RESearch Strategy**
- Originally relates to a group of UK and non-UK researchers who met (unfunded) for 2-3 years, with the aim of improving prognosis research
- Founders: Hemingway, Riley & Altman
- Members: clinicians, statisticians, economists, epidemiologists, editors & Royal Society of Medicine
- Led to being awarded an MRC Partnership Grant

The PROGRESS framework

- The PROGRESS series of 4 articles was published in the BMJ & PLoS Med in Feb 2013
- This series outlines four key strands of prognosis research & explains why they are important at multiple stages on the translational pathway to improved outcomes

I: Overall prognosis research

II: Prognostic factor research

III: Prognostic model research

IV: Predictors of treatment effect research

NB Themes overlap & thus not distinct

But generally move from population to individual prognosis

I: Overall prognosis research

- Aims to describe and explain future outcomes in relation to current diagnostic and treatment practices, often in relation to quality of care

- Also known as *fundamental prognosis*, *outcomes research*, *average prognosis, baseline risk, natural history*

- To improve quality of health care, evidence is required on how specific patterns of care received (e.g. investigation, treatment) & their variations (e.g. underuse, overuse) impact on future endpoints

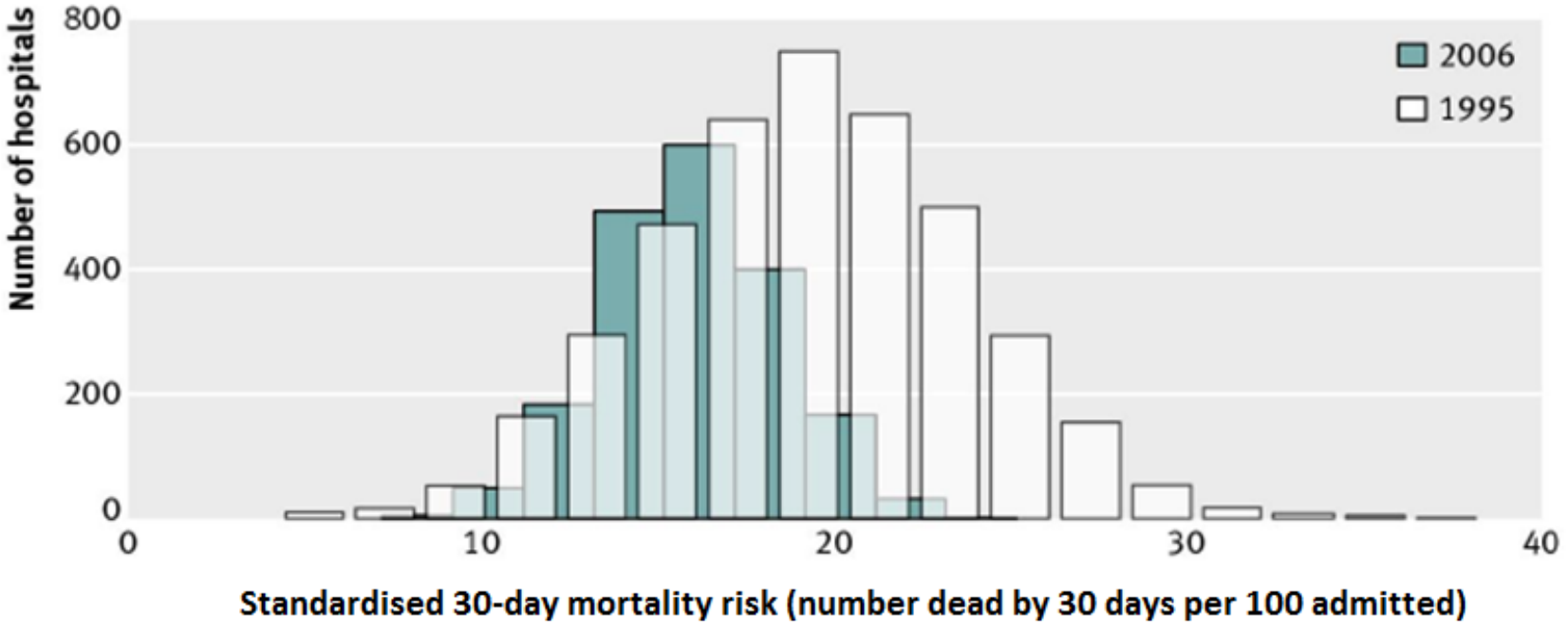
I: Overall prognosis research

- Reveals average outcome risk for a condition and variations in this average risk across populations defined by treatment, care, location, etc

- Provides initial answers to the question "**What is the prognosis of people with a given disease?**", and so quantifies the impact/quality of current care, and motivates & prioritises further inquiry

- e.g. in 2006 an average of about 15% of people aged > 65 admitted to a US hospital with a heart attack died within 30 days, compared with 19% in 1995

Example 1: 30-day mortality after acute myocardial infarction (hospitals USA)

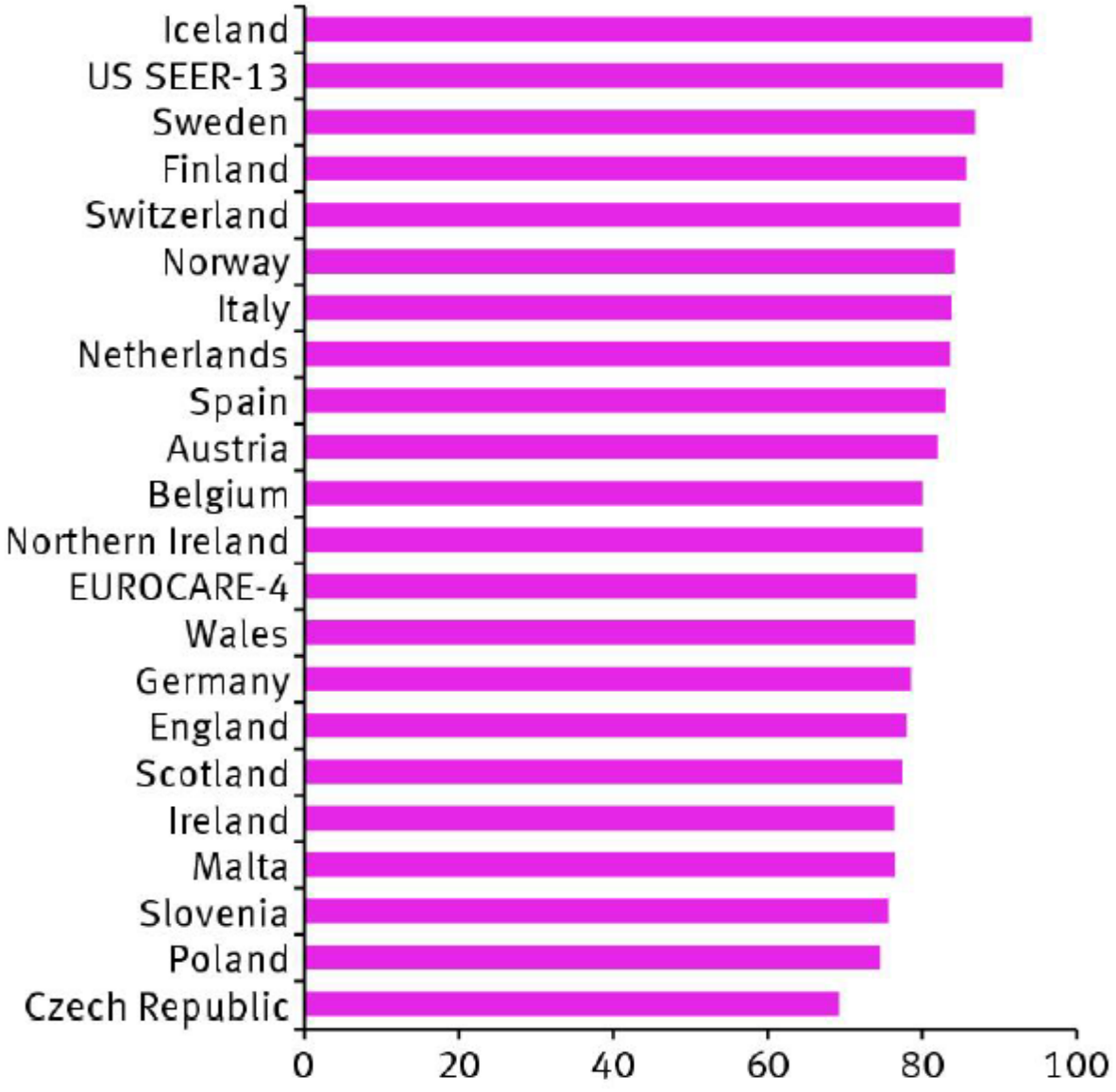


- Improvement in 30-day mortality risk
- Decrease in variability between hospitals

Fictional data, based on Krumholz et al. JAMA 2009

Example 2:
Differences in average prognosis across countries

Age-adjusted 5-year survival (breast cancer)



Cancer Research UK , 2009

II: Prognostic factor research

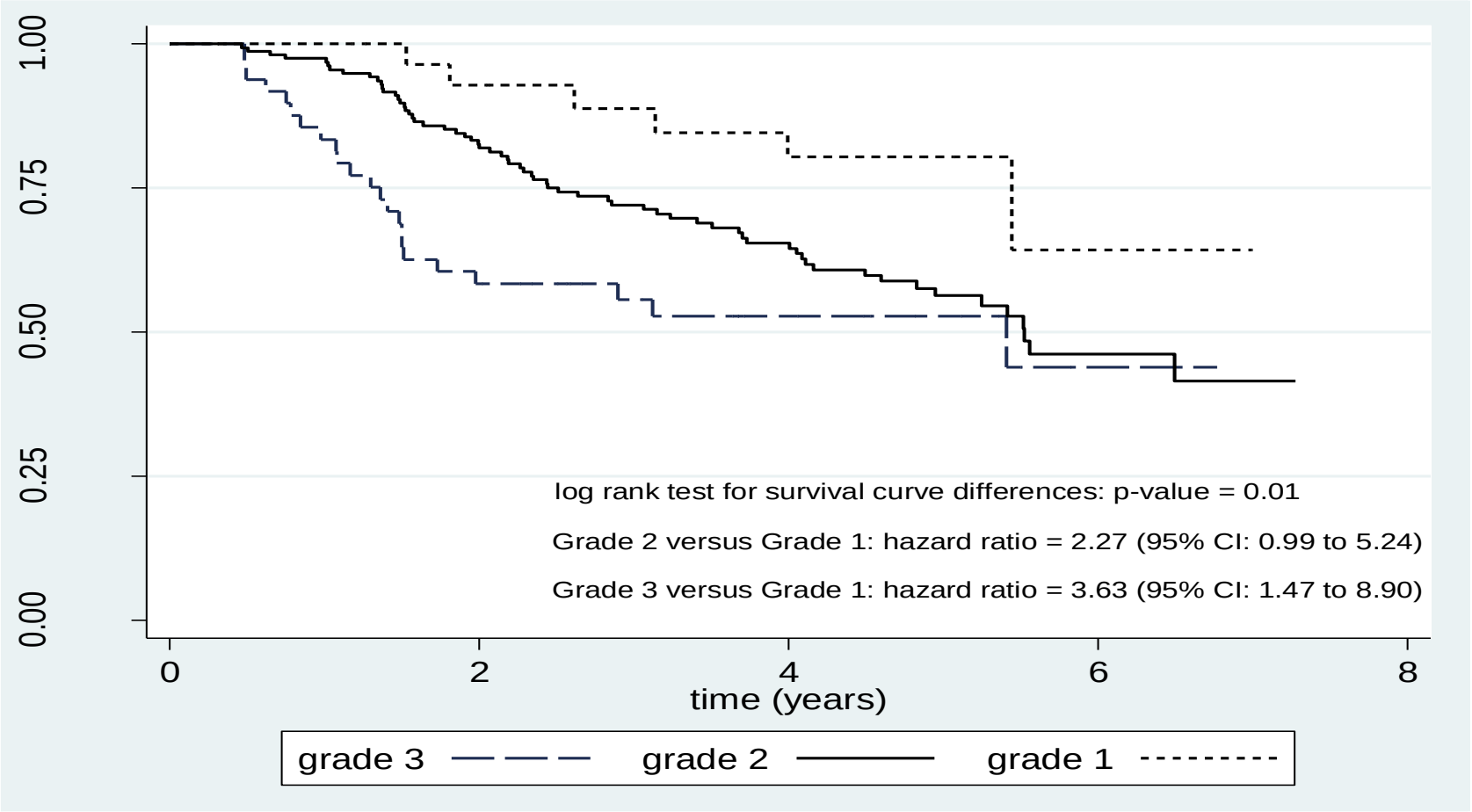
- **A prognostic factor** is any measure that, among people with a given health condition, **is associated with a subsequent clinical outcome**

  e.g. age, weight, family history, biomarkers

- Each prognostic factor level has a different average prognosis ... they thus refine (enhance) the basic 'overall prognosis' summarised in PROGRESS I

Example: Prognostic factor in breast cancer

Kaplan-Meier curve below suggests that tumour grade is a prognostic factor: ***on average, higher grades have worse time to recurrence/death***



II: Prognostic factor research

- *Many potential benefits*
  - define disease at diagnosis
  - inform clinical and therapeutic decisions
  - used within multivariable prognostic models
  - may even be targets for new treatments

- But current prognostic factor research *riddled with problems* (e.g. low study quality, dichotomisation of continuous variables, publication bias)

- A key issue is to examine whether a factor adds prognostic value over existing prognostic factors

III: Prognostic model research

- **Prognostic models** utilise *multiple prognostic factors in combination* to **predict the risk** of future clinical outcomes in **individual patients**.

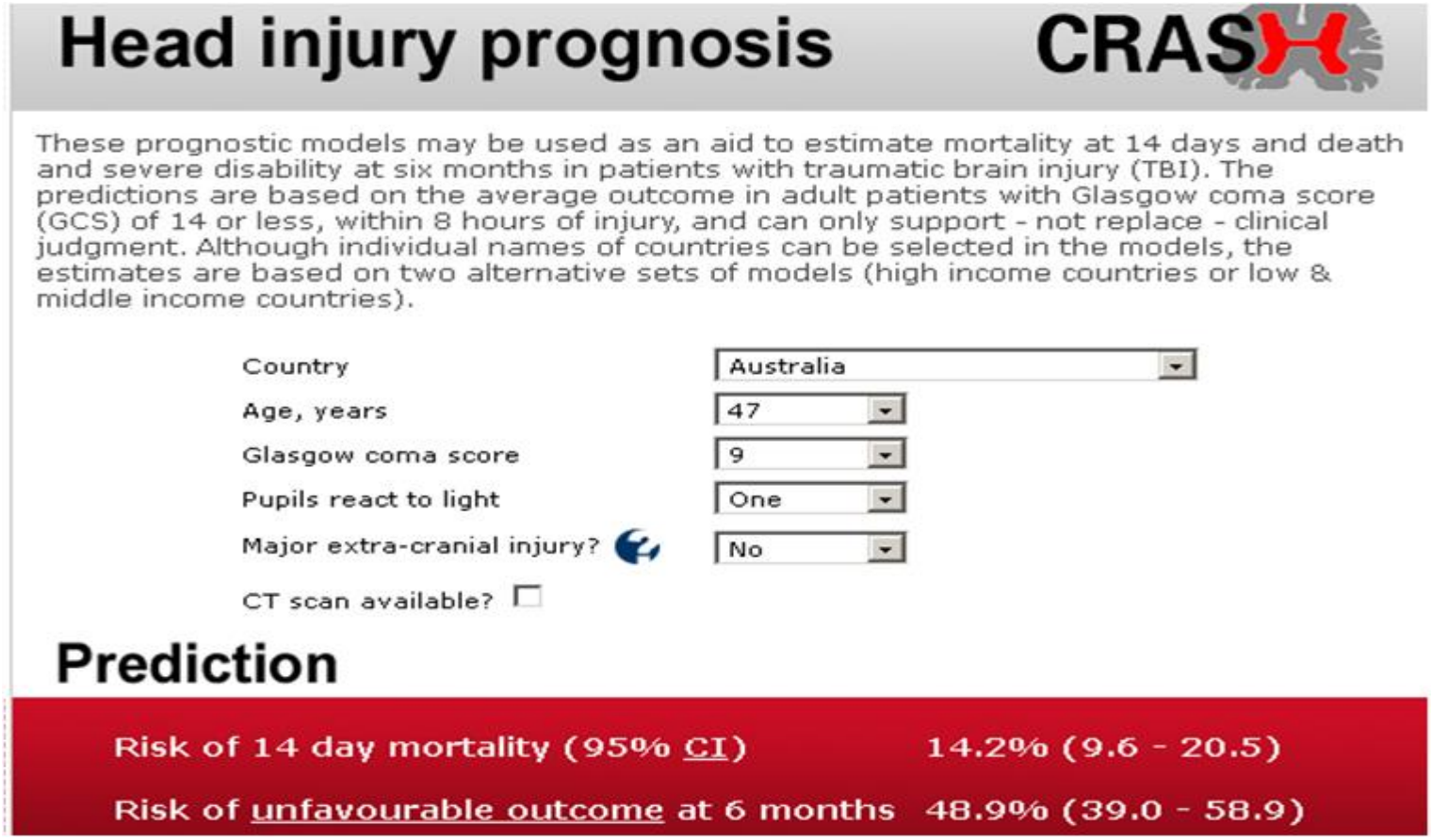
- A **useful** prognostic model provides accurate predictions that:
  - inform patients & their caregivers
  - support clinical research (e.g. trial randomisation)
  - allow more informed decisions to improve outcome

- Prognostic model research moves away from average prognoses in PROGRESS I & II
- Focus on predicted risk for **individuals**

Example: Prognostic model for predicting mortality risk in patients with traumatic brain injury

Web-tool below used to calculate 14 day mortality risk,

& 6-month unfavourable outcome risk ***for an individual based on multiple prognostic factors in combination***



III: Prognostic model research

- Prognostic model research has three main phases:
  - **model development**
  - **external validation**
  - **investigations of clinical impact**

- Current research focuses mostly on development
  - many methodological problems (small sample sizes, no adjustment for overfitting, no internal validation …)

- Much fewer studies on external validation
  - small sample sizes, calibration rarely assessed, etc

- Impact studies (e.g. RCTs) are extremely rare

IV: Predictors of treatment effect

- **Stratified or precision medicine (care)** involves tailoring clinical and therapeutic decisions for specific, often biologically distinct individuals

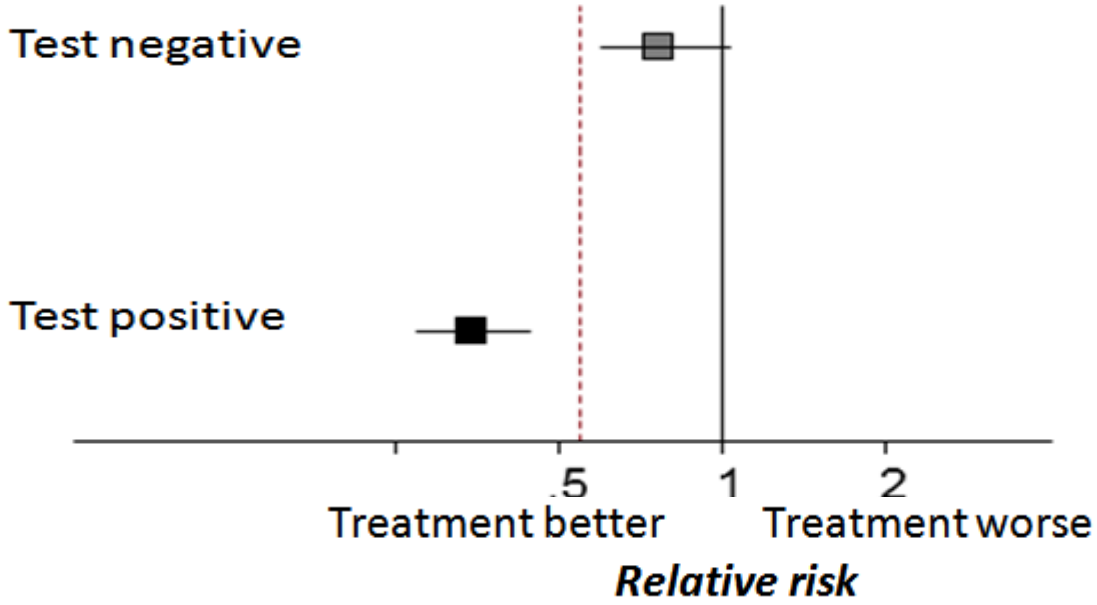
- ***Aim to maximise treatment related benefit & reduce treatment related harm***

- May rescue treatments which fail to show overall benefit across all patients, but do benefit specific patients

- A key part is to identify **tests** (e.g. biomarker levels or genotypes) **that predict an individual's response to treatment** ... Aims to help healthcare professional identify patients for whom a treatment is (most) effective

IV: Predictors of treatment effect

e.g. Trastuzumab most effective in +ve human epidermal growth factor receptor 2 (HER-2) breast cancer patients



IV: Predictors of treatment effect

- Current clinical use of such predictors is small
- Evidence to support them often weak

- Field is riddled with many problems

- Flaws in study design, analysis & reporting can lead to spurious evidence either for or against a test, e.g.
  - small sample sizes (low power)
  - data dredging (lack of replication)
  - dichotomisation of continuous predictors & outcomes
  - lack of adjustment for prognostic factors, …

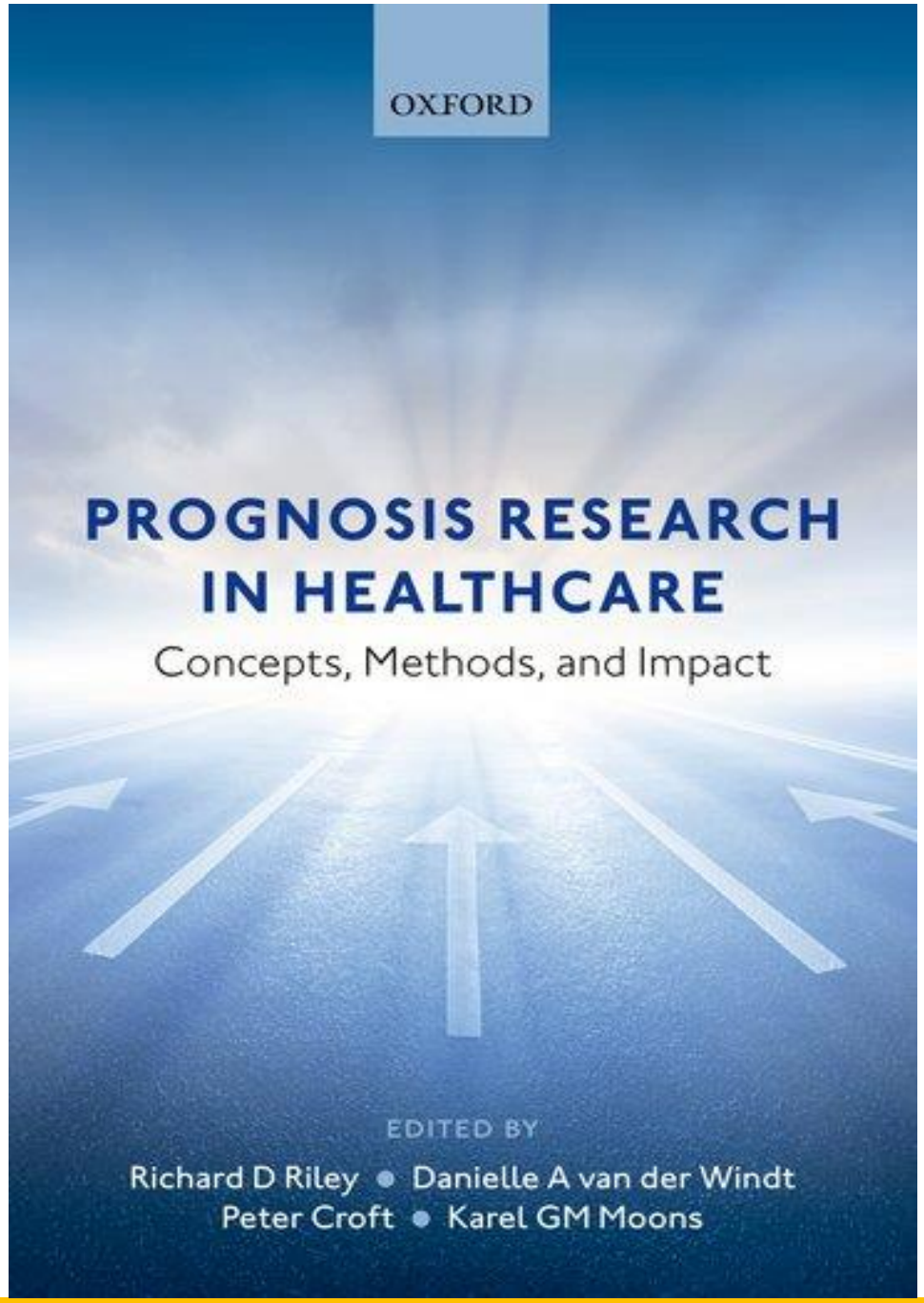
PART 4

Time to improve prognosis research

Some pointers

When setting up your prognosis research study

- What are your startpoints & endpoints?
- What prognosis questions are you interested in? (where does it fit in the PROGRESS framework?)
- What previous prognosis evidence is there?
- Replicate / externally validate previous findings first
- Look at added value of novel prognostic factors
- Design new studies appropriately: protocols, sample size, statistical methods, reporting guidance, etc



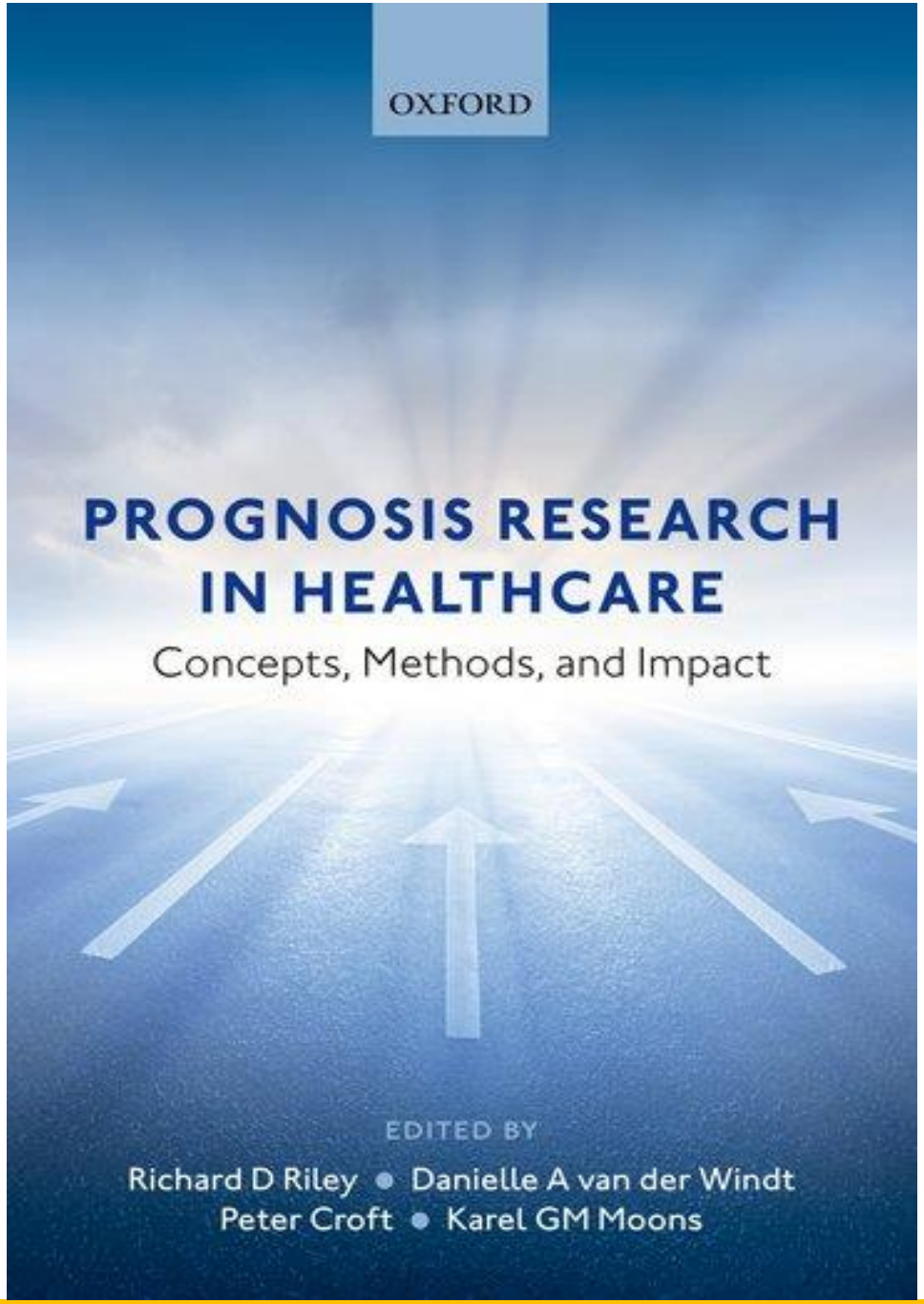
Comprehensive guide to doing prognosis research

- Overall prognosis
- Prognostic factors
- Prognostic models
- Predictors of treatment effect

With contributions from

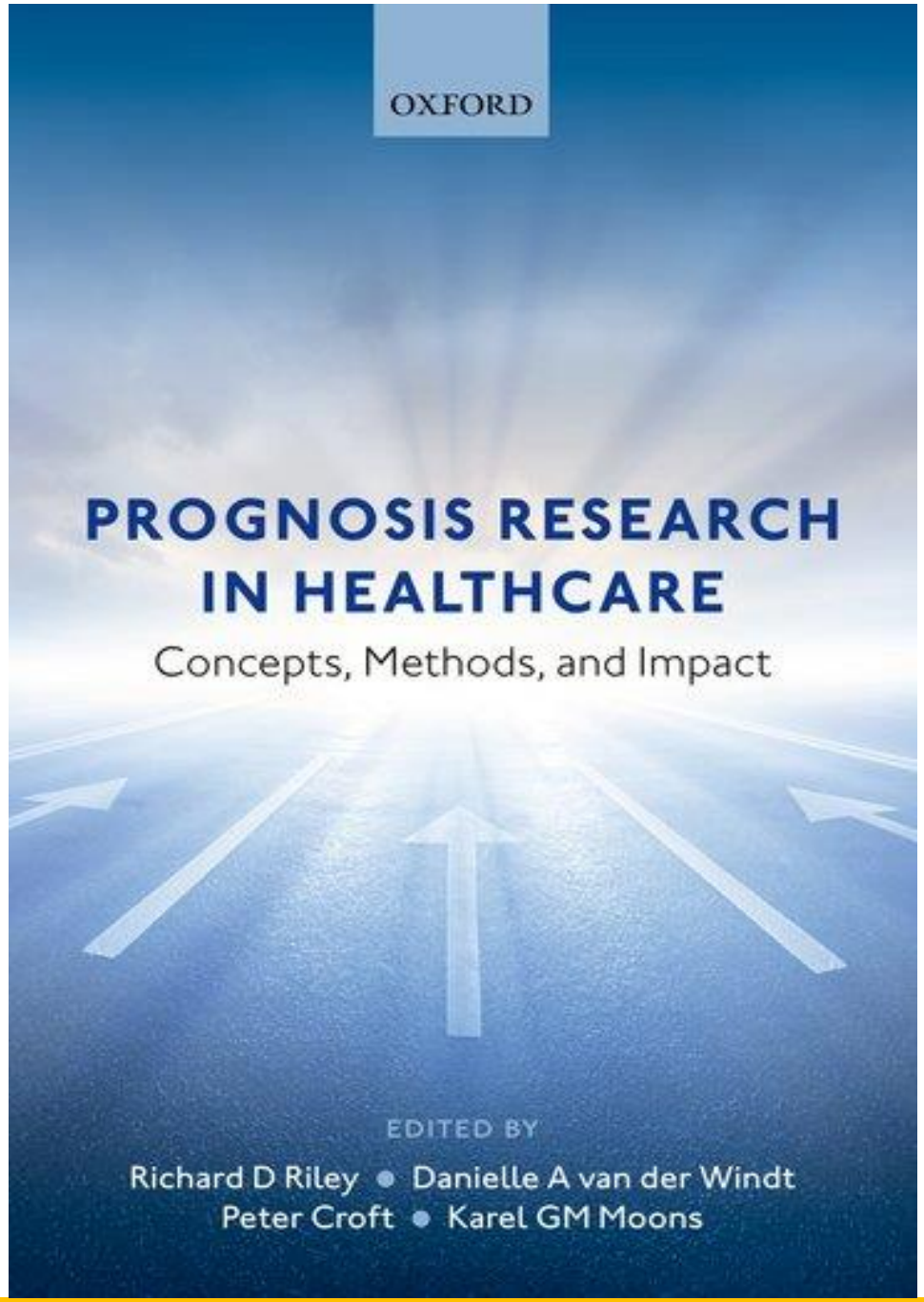
- Doug Altman
- Gary Collins
- Kym Snell
- Harry Hemingway

amongst many others



Dedicated to Doug Altman

"Our inspiration to improve prognosis research"



Dedicated to Doug Altman

"Our inspiration to improve prognosis research"

Also see:

Sauerbrei et al.

Doug Altman: Driving critical appraisal and improvements in the quality of methodological and medical research

Biometrical Journal (2020)

Positive initiatives

- There are growing initiatives to improve prognosis research methods and standards
- Joining forces to promote & develop better practice

e.g.

- Reporting guidelines (e.g. REMARK & TRIPOD)
- Quality appraisal tools: (e.g. QUIPS & PROBAST)
- STRATOS
- Methodological guidance (e.g. sample size)
- Cochrane Prognosis Methods Group
- IPD meta-analysis
- Conferences and symposiums (e.g. MEMTAB)
- Training courses (e.g. Keele, Utrecht)

www.prognosisresearch.com

- Entry-level website to prognosis research

- Promote good practice in prognosis research
- Disseminate PROGRESS framework

- Highlight relevant papers, blogs, videos, etc
- Provide training resources, and software

- Promote training courses and conferences

- Companion to **Prognosis Research in Healthcare**