What happened in the last two years in industry?

Frank Bretz (Novartis)

7th EFSPI Regulatory Statistics Workshop
September 14, 2022

Acknowledgement: Mouna Akacha, Mireille Muller, Stephen Ruberg, Emmanuel Zuber

Disclaimer

The views and opinions expressed in this presentation are solely my own and reflect my personal biases.

Outline

Clinical trial disruptions and estimands

Decentralized clinical trials

Master protocol designs

Augmenting our Phase 3 trials

Discussion

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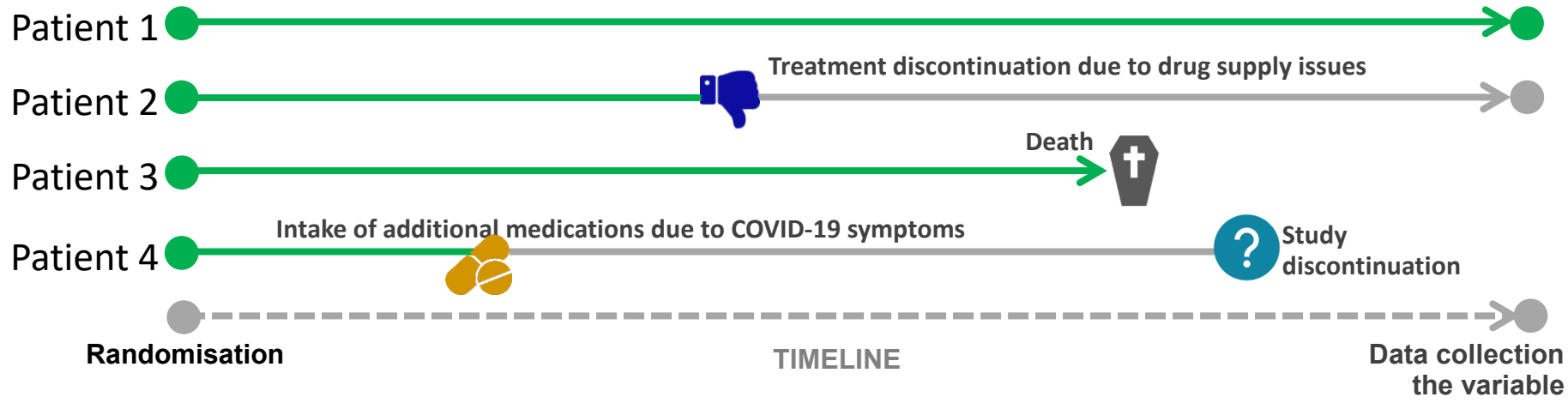
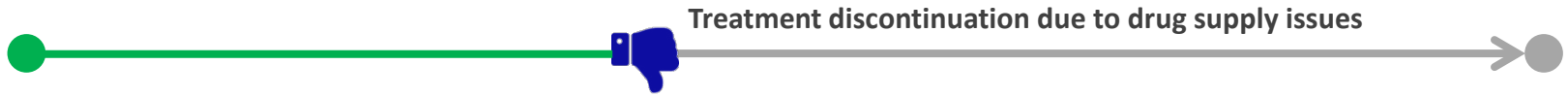
Complications due to COVID-19

- COVID-19 outbreak led to complicating events during the conduct of many clinical trials
- Some of these events affect either the interpretation or the existence of the measurements associated with the clinical question of interest (intercurrent events)
  - Administrative/operational challenges, e.g. treatment discontinuation due to drug supply issues, missed visits due to lockdown,...
  - Events directly related to impact of COVID-19 on health status, e.g. death due to COVID-19, treatment discontinuation due to COVID-19 symptoms,...



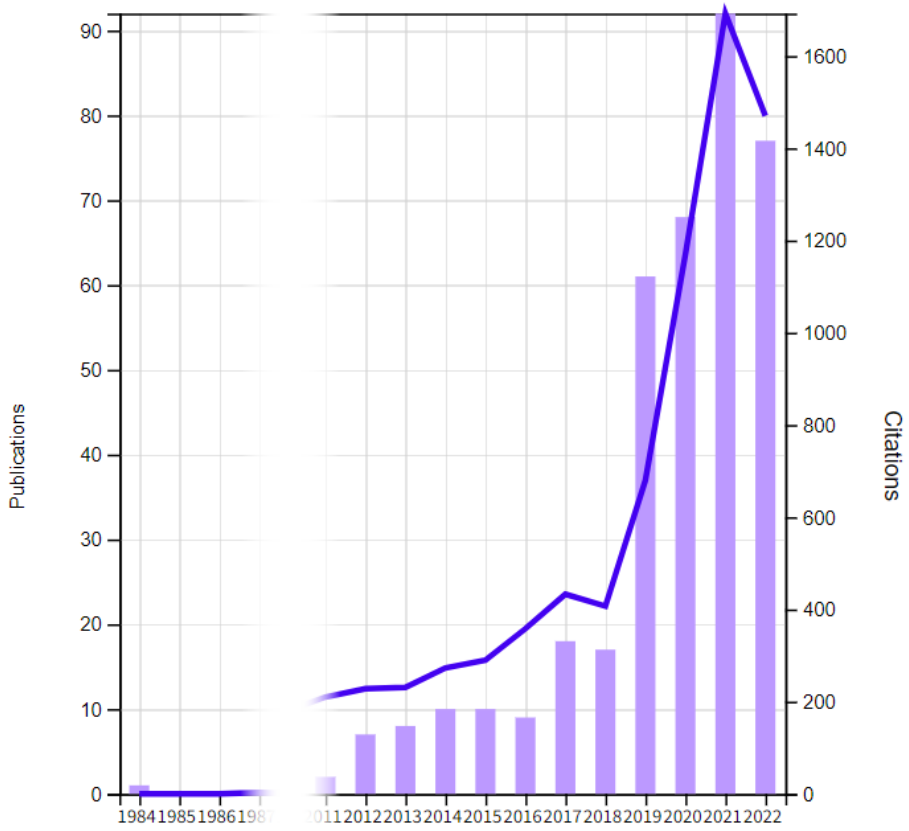
Example: Treatment discontinuation



- Treatment policy strategy: Intercurrent event as part of the ‘treatment’
  - No adaptation of the original estimand implicitly suggests a treatment policy approach
- Hypothetical strategy: ‘Had patients not discontinued treatment’
  - Need to predict the outcome in a hypothetical setting
  - More than one hypothetical setting is conceivable → precision in language is needed
- For details on estimands and estimators, see
  - Van Lancker et al. (2022) Estimands and their estimators for clinical trials impacted by the COVID-19 pandemic
  - Lasch, Guizzaro (2022) Estimators for handling COVID-19-related intercurrent events with a hypothetical strategy

Estimands beyond COVID-19

Uptake of the estimand framework per ICH E9(R1)



'estimands' (Web of Science, 2022-09-09)

- Many working groups across all major regions, for example:
  - Estimand Implementation Working Group
  - DIA Blue Book V2
  - Neuroscience Estimand Working Group
  - Oncology Estimand Working Group
  - Tripartite Working Team
- Increasing reference to estimands in disease specific guidelines (next slide)
- Increasing awareness about the need of causal inference methods in pharmaceutical statistics

Estimands are increasingly referred to in disease specific guidelines by EMA and FDA

EMA	FDA
Diabetes	Eosinophilic esophagitis
Alzheimer's disease	Acute myeloid leukemia
Registry-based studies	Chronic rhinosinusitis w/ nasal polyps
Chronic non-infectious liver diseases	COVID-19
Crohn's disease	Crohn's disease
Ulcerative colitis	Ulcerative colitis

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Decentralized clinical trials (DCT)

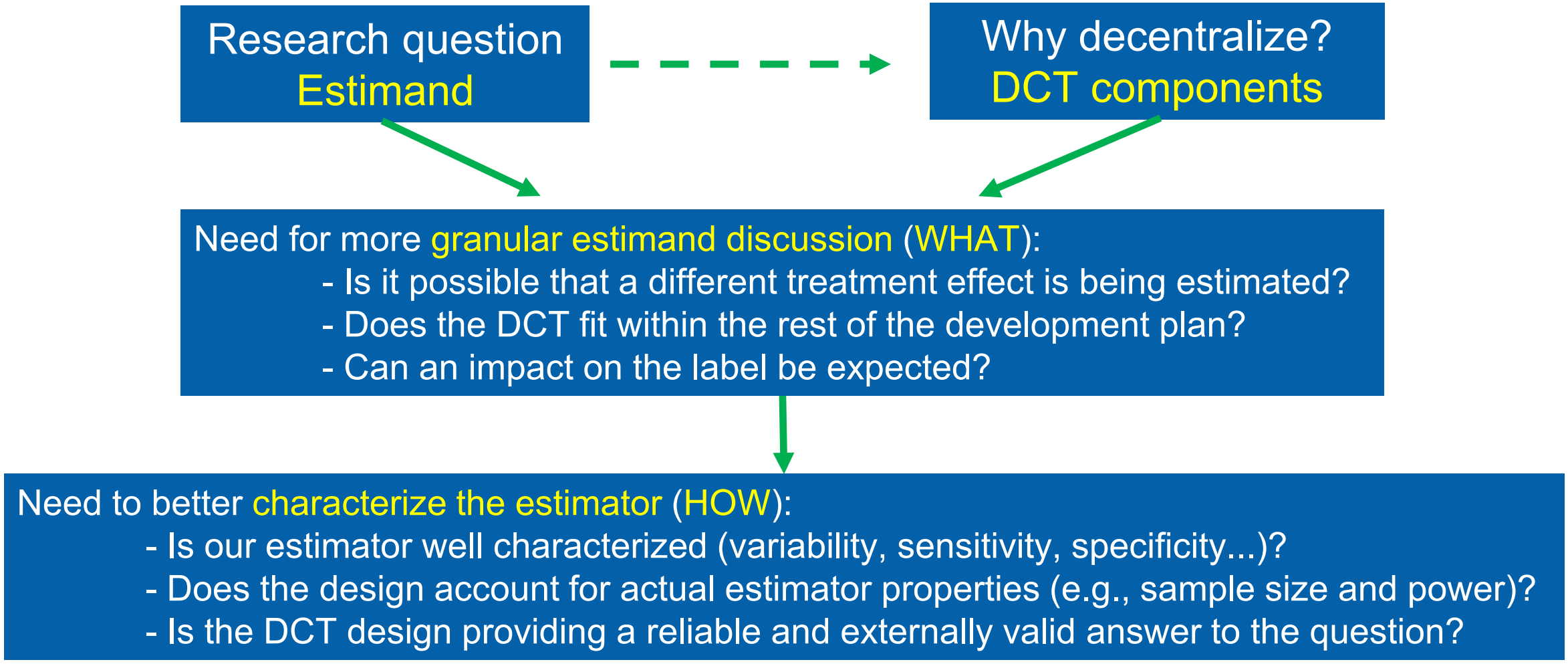
From the COVID-19 experience...

- Increase in trial activities conducted remotely and in participant's home, by necessity
- Development of regulatory guidelines:
  - Initially on the management of clinical trials during the COVID-19 pandemic
  - Focus shifting to the implementation of decentralized elements in clinical trials
- Sponsor's reactions: Develop a strategic approach to trial decentralization:
  - Where does it help?
  - What are the technical solutions, tools and capabilities to develop or acquire?
  - How do we enable organizations to change?

...to deeper considerations

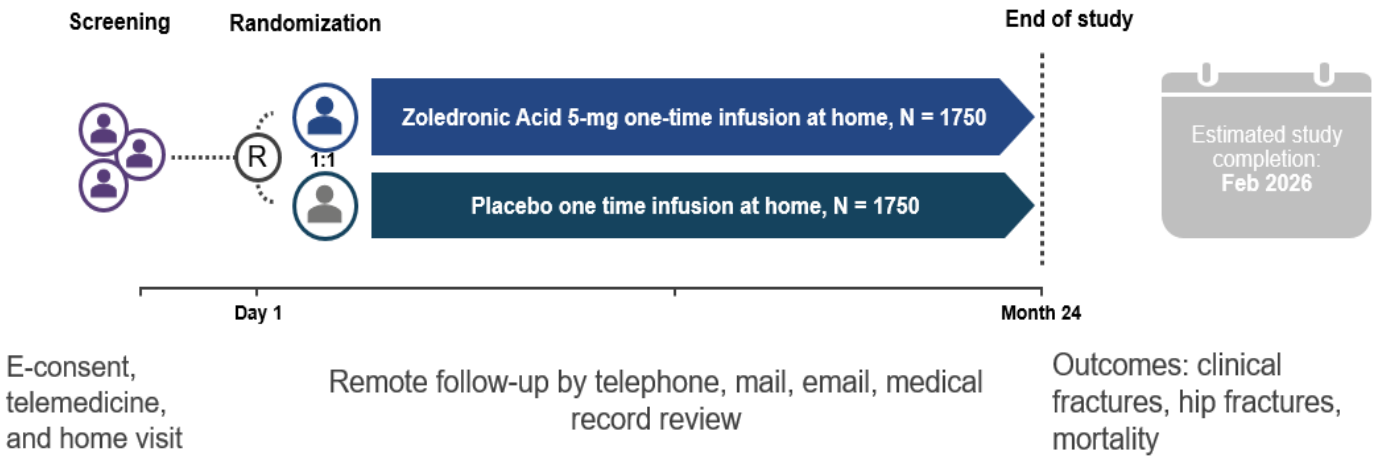
- Increasing number of publications, reports, forums and web resources
- Enhanced access to devices, tools, platforms and technological solutions
- More published design examples
  - 'DCT Methodology studies': Validation of novel technology or endpoint, comparison of DCT vs. on site components
  - 'Drug development studies': Fully decentralized or hybrid trials to assess a treatment effect
- What about scientific challenges and outcomes?

Evaluating the scientific ramifications of DCTs



TOPAZ: A fully decentralized trial

- US-wide, double-blind, home-based, Phase 4 trial
- Single infusion of zoledronic acid vs. placebo to prevent fractures in patients aged >65 years with neurodegenerative parkinsonism



NPJ Parkinsons Dis. 2021; 7: 16

NCT03924414

- Detailed DCT discussion by estimand attribute: Zuber et al. (2022, EFSPI workshop)

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From an idea…

The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

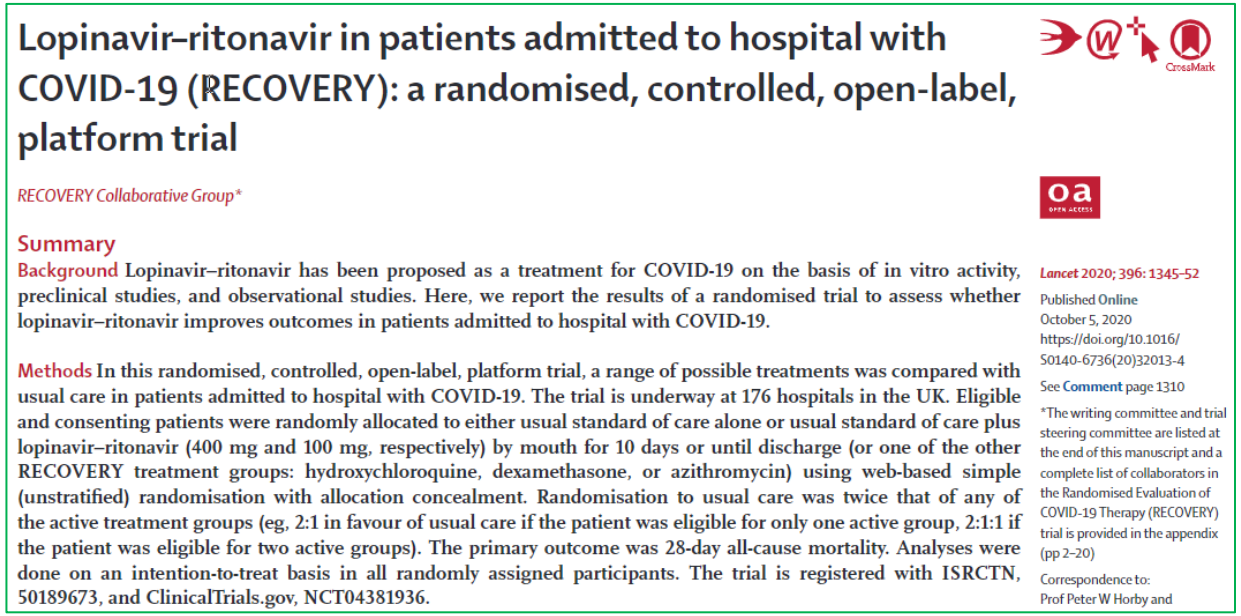
THE CHANGING FACE OF CLINICAL TRIALS

Jeffrey M. Drazen, M.D., David P. Harrington, Ph.D., John J.V. McMurray, M.D., James H. Ware, Ph.D., and Janet Woodcock, M.D., *Editors*

Master Protocols to Study Multiple Therapies, Multiple Diseases, or Both

Janet Woodcock, M.D., and Lisa M. LaVange, Ph.D.

…to action during the pandemic



Lopinavir–ritonavir in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial

*RECOVERY Collaborative Group**

Summary

Background Lopinavir–ritonavir has been proposed as a treatment for COVID-19 on the basis of in vitro activity, preclinical studies, and observational studies. Here, we report the results of a randomised trial to assess whether lopinavir–ritonavir improves outcomes in patients admitted to hospital with COVID-19.

Methods In this randomised, controlled, open-label, platform trial, a range of possible treatments was compared with usual care in patients admitted to hospital with COVID-19. The trial is underway at 176 hospitals in the UK. Eligible and consenting patients were randomly allocated to either usual standard of care alone or usual standard of care plus lopinavir–ritonavir (400 mg and 100 mg, respectively) by mouth for 10 days or until discharge (or one of the other RECOVERY treatment groups: hydroxychloroquine, dexamethasone, or azithromycin) using web-based simple (unstratified) randomisation with allocation concealment. Randomisation to usual care was twice that of any of the active treatment groups (eg, 2:1 in favour of usual care if the patient was eligible for only one active group, 2:1:1 if the patient was eligible for two active groups). The primary outcome was 28-day all-cause mortality. Analyses were done on an intention-to-treat basis in all randomly assigned participants. The trial is registered with ISRCTN, 50189673, and ClinicalTrials.gov, NCT04381936.

Lancet 2020; 396: 1345–52

Published Online October 5, 2020 https://doi.org/10.1016/S0140-6736(20)32013-4

See Comment page 1310

*The writing committee and trial steering committee are listed at the end of this manuscript and a complete list of collaborators in the Randomised Evaluation of COVID-19 Therapy (RECOVERY) trial is provided in the appendix (pp 2–20)

Correspondence to: Prof Peter W Horby and

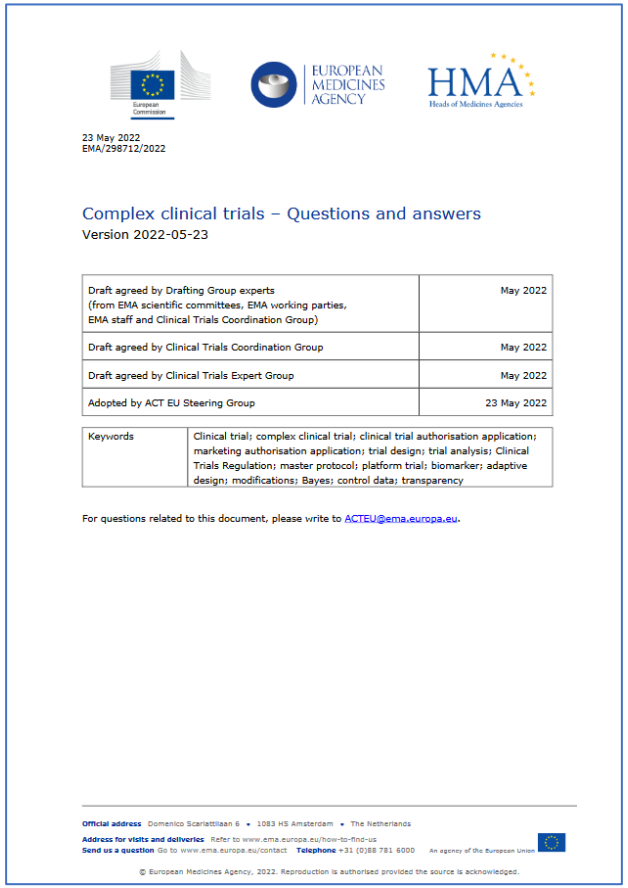
Many, *many* open questions

From master protocol designs…

Statistical challenges

- Non-concurrent controls
- Change of control arm
- Multiplicity adjustment
- Complex adaptive design elements
- Trial integrity
- …

…to complex clinical trials



23 May 2022
EMA/298712/2022

Complex clinical trials – Questions and answers
Version 2022-05-23

Draft agreed by Drafting Group experts (from EMA scientific committees, EMA working parties, EMA staff and Clinical Trials Coordination Group)	May 2022
Draft agreed by Clinical Trials Coordination Group	May 2022
Draft agreed by Clinical Trials Expert Group	May 2022
Adopted by ACT EU Steering Group	23 May 2022

Keywords	Clinical trial; complex clinical trial; clinical trial authorisation application; marketing authorisation application; trial design; trial analysis; Clinical Trials Regulation; master protocol; platform trial; biomarker; adaptive design; modifications; Bayes; control data; transparency

For questions related to this document, please write to ACTEU@ema.europa.eu.

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EU-PEARL
EU PATIENT-CENTRIC CLINICAL TRIAL PLATFORMS

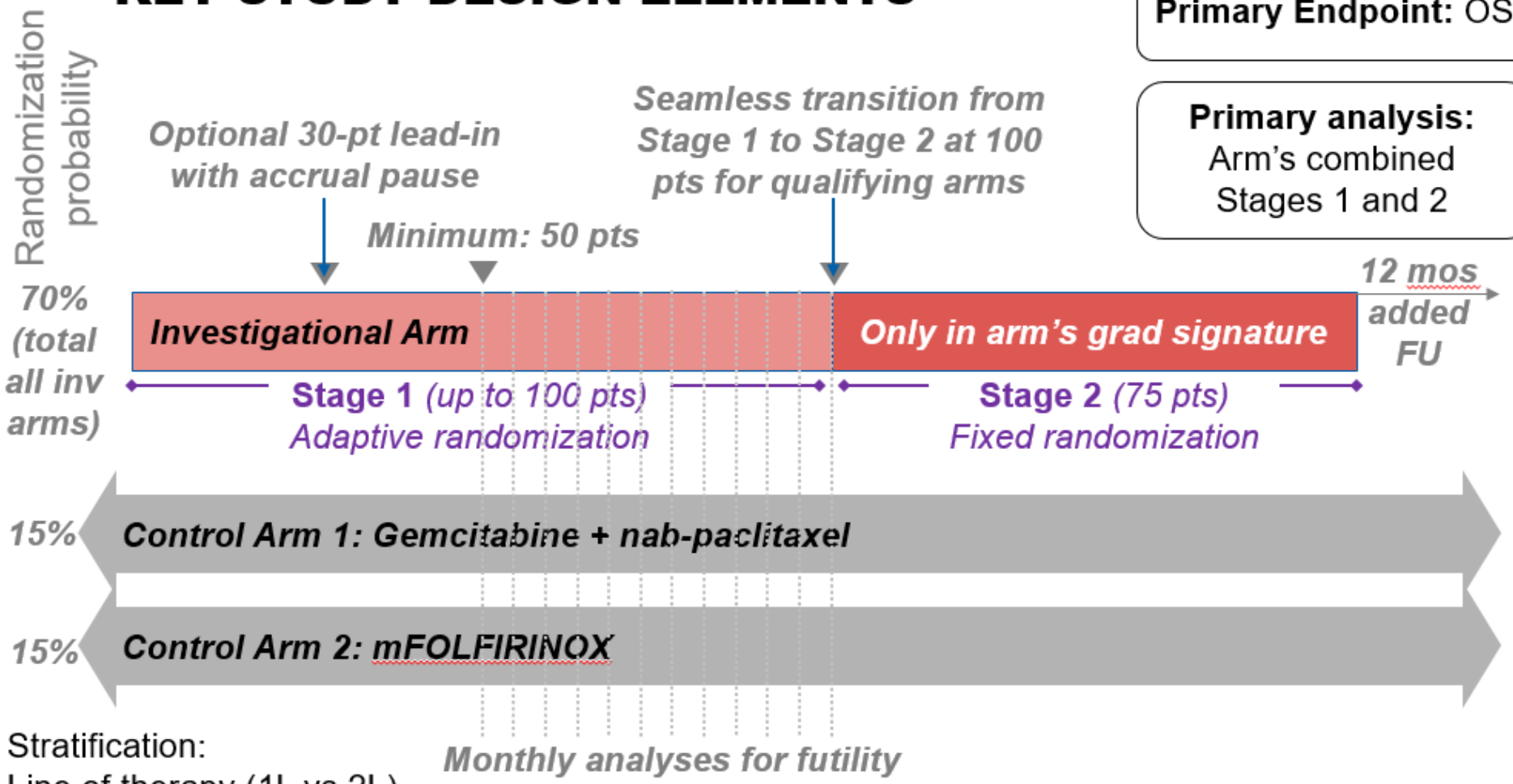
Slide presented by Don Berry and Alexandra Vaury at the 6th EFSPI Regulatory Statistics Workshop (2021)

PRECISION PROMISE^{SM}

KEY STUDY DESIGN ELEMENTS

Primary Endpoint: OS

Primary analysis: Arm's combined Stages 1 and 2



Stratification:
Line of therapy (1L vs 2L)

Berry Consultants Statistical Innovation

PANCREATIC CANCER ACTION NETWORK PRECISION PROMISE

NOVARTIS

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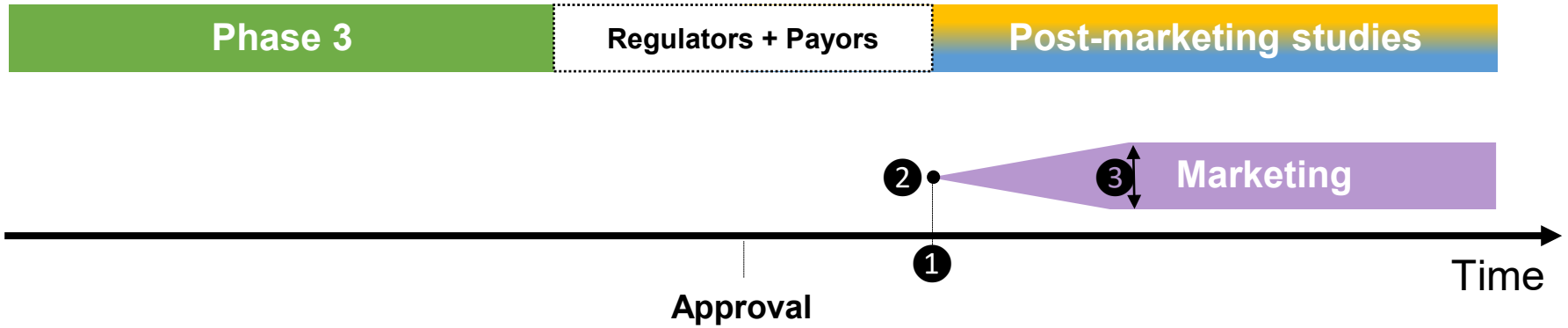
Increasing demand for using RWD in drug development

- Increasing number of initiatives aimed at integrating information generated outside confirmatory trials (e.g., RWD) into drug development
- However,
  - the scientific questions these data could serve to answer often remain vague and/or may not align with the objectives of a development program
  - such data are often generated/identified later and through observational studies, such that results are difficult to compare with earlier clinical trial data (e.g., using the target trial framework, see Hampson et al. (2022) for an application)
- At the same time, clinical trial data collected in regular development programs for market authorisation may not be sufficient for HTA decisions

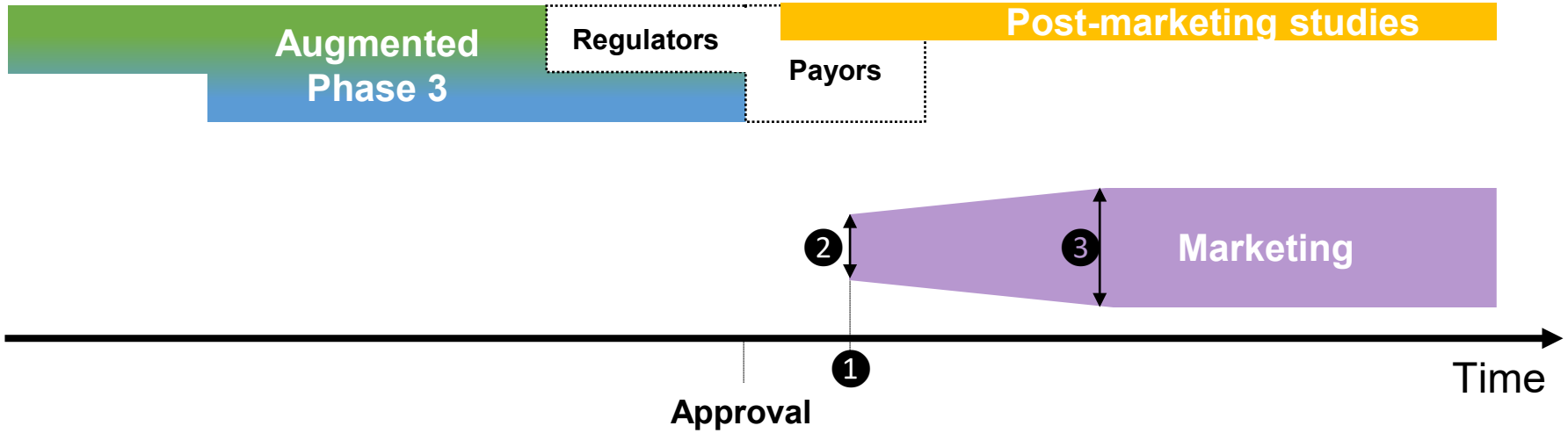
Generating the right evidence at the right time: A Proposal

- New class of study designs enabling flexible augmentation of confirmatory RCTs with concurrent RW elements to facilitate:
  - estimation of treatment effects in the confirmatory part and other, complementary treatment effects in a 'close-to-real-world' (cRW) part
  - stakeholder use of the evidence that is relevant within their own decision-making framework
- Benefits:
  - high quality data are generated under one single protocol
  - use of randomization ensures rigorous statistical inference and interpretation within and between the different parts of the experiment
  - earlier evidence for HTA decision-making than is currently the case

What we did in the past

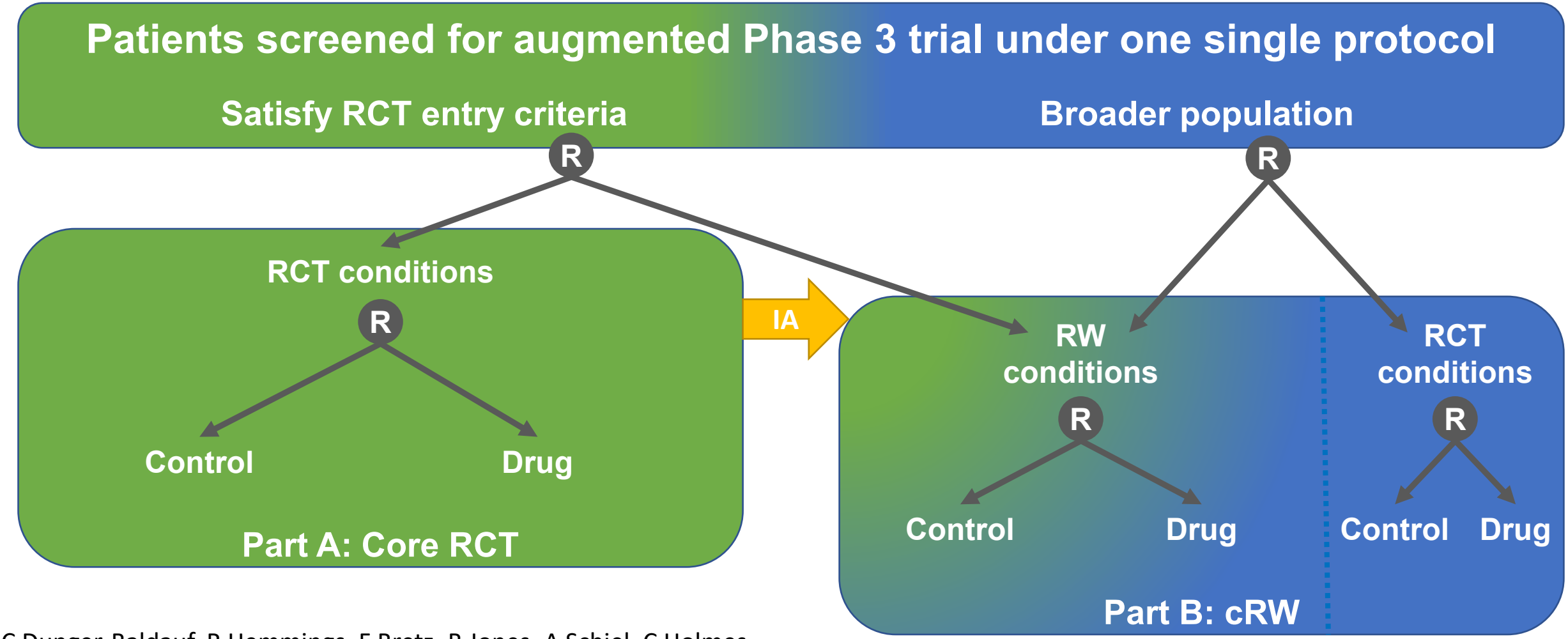


What we might do in the future



1. First availability of new treatment to patients
2. Initial uptake of new treatment use
3. Maximum uptake of new treatment use

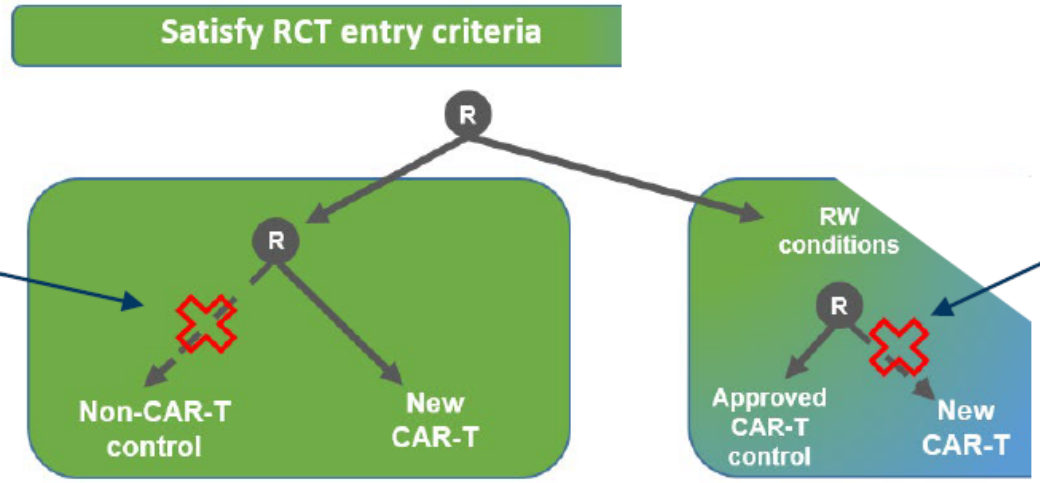
FACTIVE: Flexible Augmented Clinical Trial design for Improved eVidencE generation[1]



[1] C Dunger-Baldauf, R Hemmings, F Bretz, B Jones, A Schiel, C Holmes

Slide presented by Nigel Yateman at the BBS Seminar on July 15, 2022

Example application to new CAR-T



Cannot randomize to non-CAR-T if SoC = approved CAR-T

Cannot randomize until after 1st approval

Remains highly beneficial to randomize

i.e., investigator choice – but expected mainly **approved CAR-T** as study would need to be conducted in CAR-T centers

In some geographies (e.g., US) the 2 arms could be aligned on eCRFs, visit schedule, independent review of response

SoC = standard of care; eCRF = electronic case report form

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Acknowledgments

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- Byron Jones
- Anja Schiel
- Chris Holmes
- Rima Izem
- Pascal Edrich
- Nadia Daizadeh
- Evgeny Degtyarev
- Nikos Sfikas
- Alex Sverdlov
- Adrian Cassidy
- Janice Branson
- Insa Gathmann

Many other topics

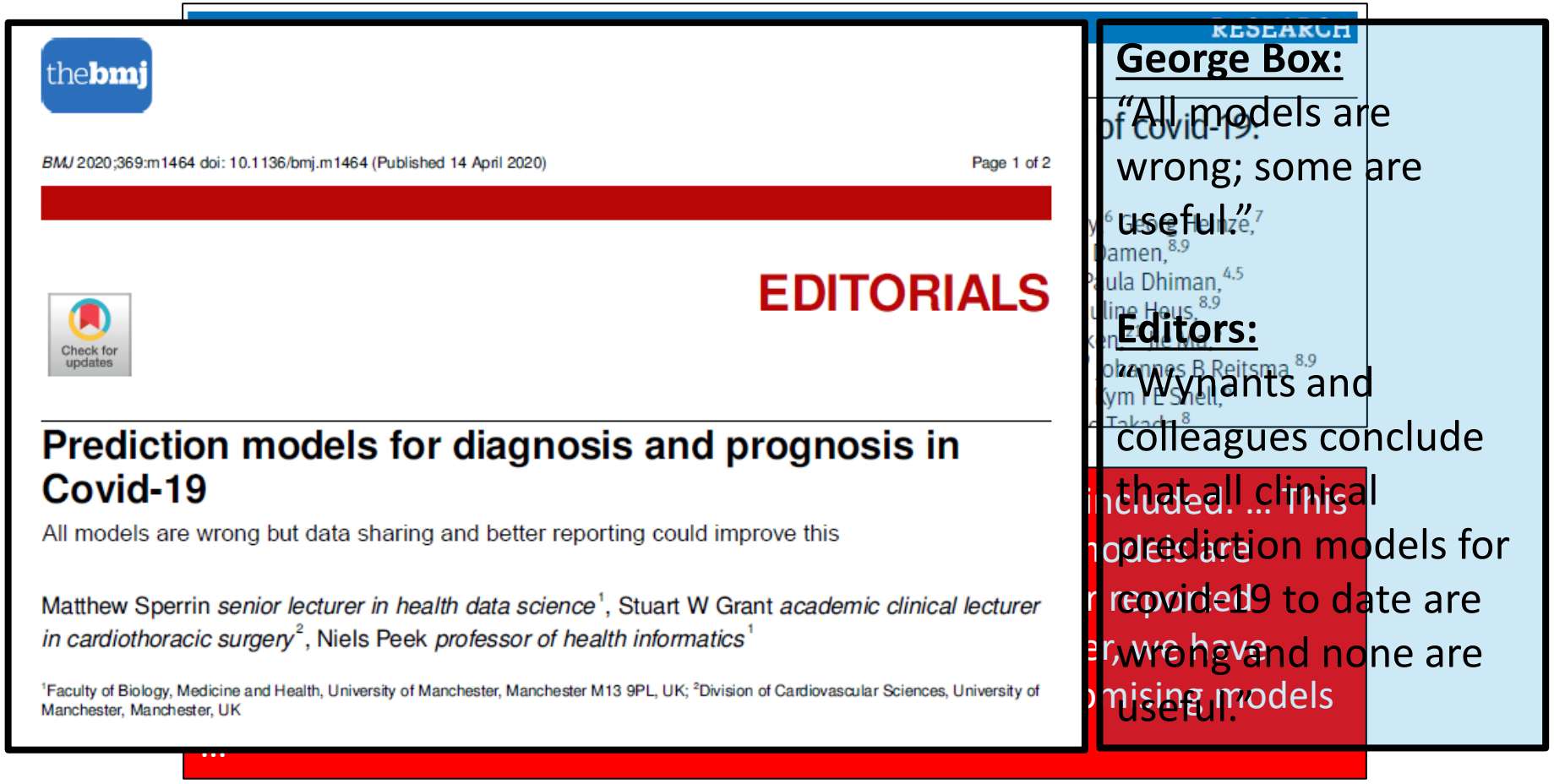
- Other methodological areas
  - Covariate adjustment, patient-focused drug development, tokenization, differential privacy,...
- Industry uptake of recent changes in the regulatory and reimbursement landscape
- Broader impact triggered by pandemic
  - Virtual communication (meetings, workshops, conferences...), resulting in broader (= global) outreach, in particular to lesser developed regions
  - Role / perception of Statistics in society

What did *really* change?

- Uptake of estimand framework and principled missing data approaches, but...
  - limited uptake outside Statistics and inconsistent application of the estimand framework (e.g., misalignment between estimand, analysis approach and drug label)
- Flexible drug development programs (e.g., RECOVERY platform trial), but...
  - not every drug development program addresses a global health crisis
- Stream of subgroup identification methods, but...
  - post-hoc subgroup analyses still prevail
- Pivotal Bayesian adaptive design for Pfizer COVID-19 vaccine, but...
  - progress about appropriate statistical inferences in drug development remains slow

➔ Many promising sparks of innovation, less clear about changes 'on the ground'

What happened to ‘Data Science’ in the past two years?



thebmj

BMJ 2020;369:m1464 doi: 10.1136/bmj.m1464 (Published 14 April 2020) Page 1 of 2

EDITORIALS

Check for updates

Prediction models for diagnosis and prognosis in Covid-19

All models are wrong but data sharing and better reporting could improve this

Matthew Sperrin *senior lecturer in health data science*[1], Stuart W Grant *academic clinical lecturer in cardiothoracic surgery*[2], Niels Peek *professor of health informatics*[1]

[1]Faculty of Biology, Medicine and Health, University of Manchester, Manchester M13 9PL, UK; [2]Division of Cardiovascular Sciences, University of Manchester, Manchester, UK

George Box:

“All models are wrong; some are useful.”

Editors:

“Wynants and colleagues conclude that all clinical prediction models for covid-19 to date are wrong and none are useful.”

Acknowledgement: S Ruberg