Harnessing the power of AI in RWD: Enhanced insights through machine learning and causal inference advances

ISPOR Europe 2024

Monday, 18 November

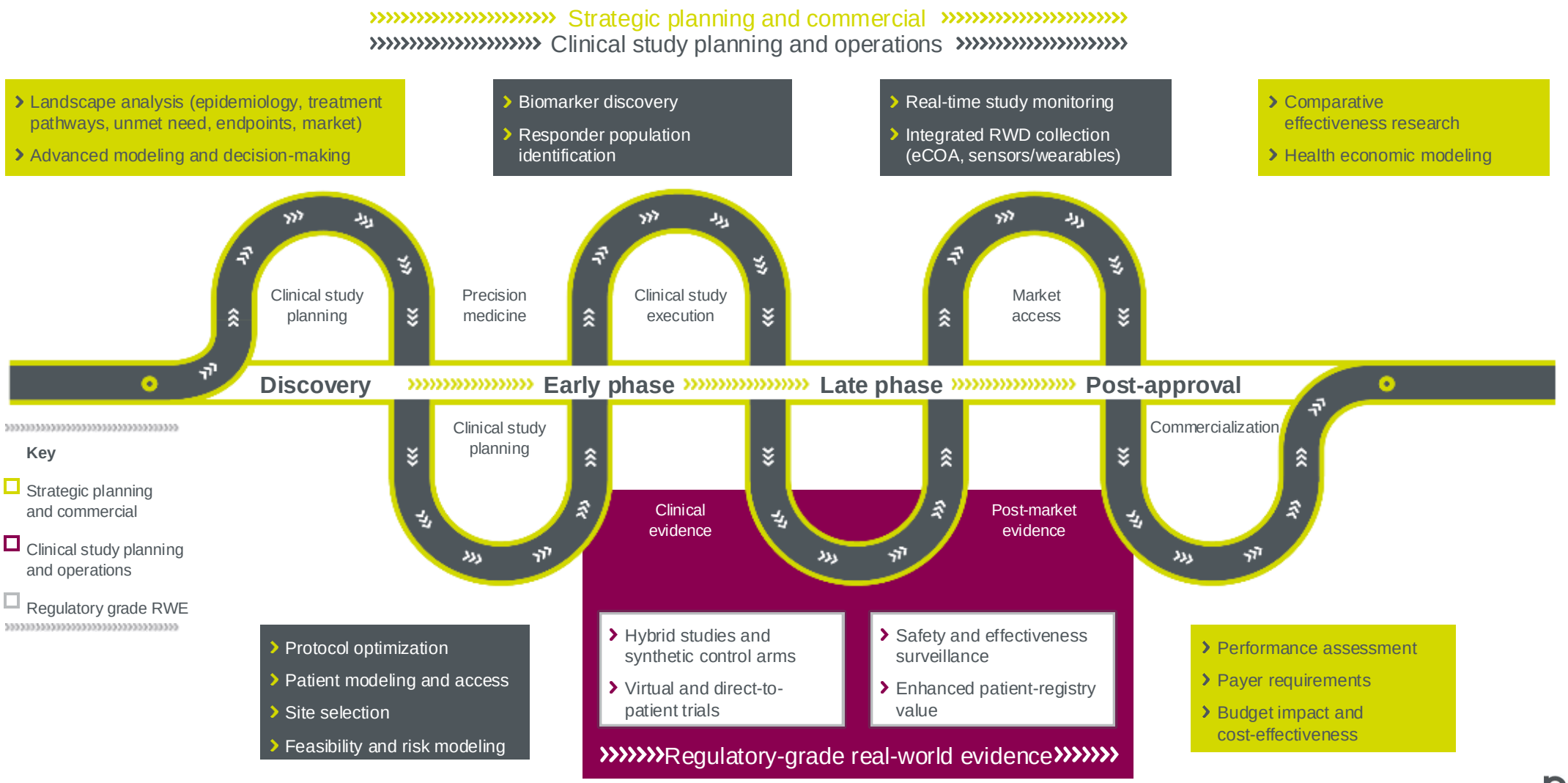
Our agenda for today

Jacqueline Vanderpuye-Orgle, PhD

Vice President and Global Head
of Advanced Analytics, Parexel

- **General overview:** RWD, causal inference, and AI
- **Regulatory perspective:** Drivers for AI in healthcare, EMA's initiatives and workplan, and stakeholder engagement
- **Pharmaco-epidemiological perspective:** Causal inference, target trial emulation, and AI applications
- **Statistical perspective:** Causal methods in RWD and AI use cases (TMLE and super learners)
- **Manufacturer perspective:** Strategic evidence generation needs and use of AI in RWE

There is potential for us to deploy of Big Data and RWE across the clinical development and life cycle management spectrum



There are some critical considerations when using RWD given the nature of the data generation process

- Missing data
- Sample size
- Sources of bias (selection bias, confounding
- Comparability issues
- Uncertainties in covariate matching
- Lack of transparency
- No pre-specified protocol / statistical analysis plan

Methodological considerations regarding causal inference and AI applications can help bridge the gap in some instances

Regulatory guidance on the fast-evolving landscape

RWE guidance*

Design

- **Considerations for the design and conduct of externally controlled trials for drugs and biologic products** : Draft guidance for industry – Feb 2023
- **Real-world Evidence: Considerations regarding non-interventional studies for drugs and biologic products:** Draft guidance for industry – Mar 2024

Submissions

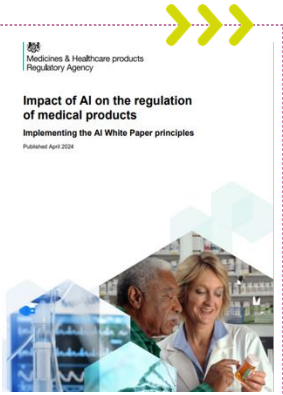
- **Data standards for drug and biologic submissions containing real-world data:** Draft guidance for industry – Oct 2021
- **Considerations for the use of RWD and RWE to support regulatory decision making for drug and biologic products:** Draft guidance for industry – Dec 2021

Data sources

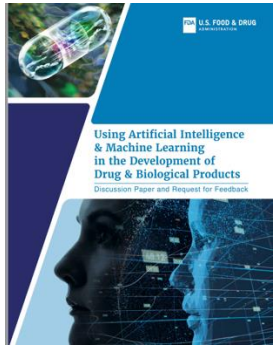
- **Real-world Data: Assessing electronic health records and medical claims data to support regulatory decision making:** Draft guidance for industry – Sep 2021
- **Real-world Data: Assessing registries to support regulatory decision making:** Draft guidance for industry – Nov 2021

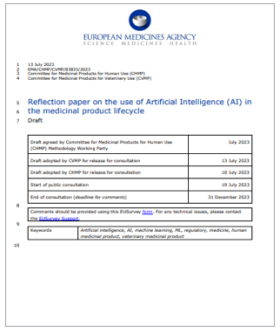
AI guidance*

- Regulatory and legislative compliance needs to be engineered into AI application development pipeline from the outset
- Regulatory agencies seem set to take a risk-based approach, but as yet no clear and aligned position on expectations
  - MHRA implementation paper for AI in regulation of medical products (April 2024)
  - FDA discussion paper (May 2023 – draft guidance anticpated)
  - EMA reflection paper on AI in medicinal product development (September 2024)



Per MHRA:
"… the changes our customers make will not impact how we regulate."





There is a need to drive consensus on how we harness AI in RWE, with the right theoretical underpinning, in service of expediting patient access to much-needed drugs.

*Examples only, not an exhaustive list

Our speakers

Patrice Verpillat MD, MPH, PhD

Head of Real World Evidence, European Medicines Agency

Katja Hakkarainen PhD

Vice President, Epidemiology, Parexel

Andy Wilson PhD

Head of Innovative RWD Analytics, Parexel

Ipek Özer Stillman MS, MBA

Global Leader, Value, Evidence, Access - Vice President, Global Head of Health Economics at Takeda

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Harnessing the power of AI in EU regulatory environment

An overview of the approach of the European Medicines Regulatory Network

ISPOR Europe 2024

Presented by Patrice Verpillat on 18 November 2024
Head of Real-World Evidence, Data Analytics and Methods Taskforce

An agency of the European Union

Disclaimer

The presenter does not have any conflict of interest.

The views expressed in this presentation are personal views and may not be understood or quoted as being made on behalf of, or reflecting the position of the European Medicines Agency or one of its committees or working parties.

AI in Healthcare | Regulatory Drivers

- Regulatory submissions
- Process Analytics
- Healthcare Analytics

AI in Healthcare | Regulatory Drivers

Regulatory submissions

Regulate applications of AI in medicines to help create value for public health

Process Analytics

Healthcare Analytics

AI in Healthcare | Regulatory Drivers

Regulatory submissions

Process Analytics

Improve **efficiency** by automating and digitalizing processes

Healthcare Analytics

AI in Healthcare | Regulatory Drivers

Regulatory submissions

Process Analytics

Healthcare Analytics

Structure information and increase insights into data to inform decision-making

European Medicines Regulatory Network | Key initiatives

Key initiatives of the European Medicines Regulatory Network

Big Data Task Force | European Medicines Regulatory Network Strategy | Regulatory Science Strategy

European Medicines Regulatory Network | Key initiatives

Guidance

Offer clear, balanced, guidance to developers, marketing authorisation holders, etc.

Upskilling

Provide training across the network to foster competent and responsible use/regulation of AI

Collaborations

Leverage collaborations to improve knowledge, reduce uncertainty and facilitate alignment

European Medicines Regulatory Network | Key initiatives

Guidance

AI Reflection Paper

Published on Sep 30

Upskilling

Digital Academy
Big Data Steering Group Curricula
Other change management activities

Collaborations

EU Agencies (e.g. EFSA)
EU regulatory network
Academia
International agencies incl. ICMRA

AI RP | General considerations & risk

- AI and ML tools can, if used correctly, **effectively support the acquisition, transformation, analysis, and interpretation of data** within drug lifecycle
- A **risk-based approach** for development, deployment and monitoring of AI and ML tools allows developers to pro-actively and systematically define and manage risks throughout the AI lifecycle
- The degree of risk may depend on
  - the AI technology
  - the context of use
  - the degree of influence the AI technology exerts
  - …

AI RP | Benefit-risk

- If an AI/ML system is used in the context of medicinal product development, evaluation or monitoring, and is expected to impact, even potentially, on the benefit-risk of a medicinal product, **early regulatory interaction is advised**
  - E.g., qualification of innovative development methods for a specific intended use in the context of research and development in relation to pharmaceuticals, or scientific advice
- The level of scrutiny would depend on the level of risk and regulatory impact posed by the system
- For all requests for advice or opinions, the applicant or MAH is expected to provide a scientific base along with sufficient technical details to allow **comprehensive assessment of any AI/ML systems used** in the medicinal product lifecycle, the integrity of data and generalizability of models to the target population and for a specific context of use

Multi-annual AI workplan 2023-2028

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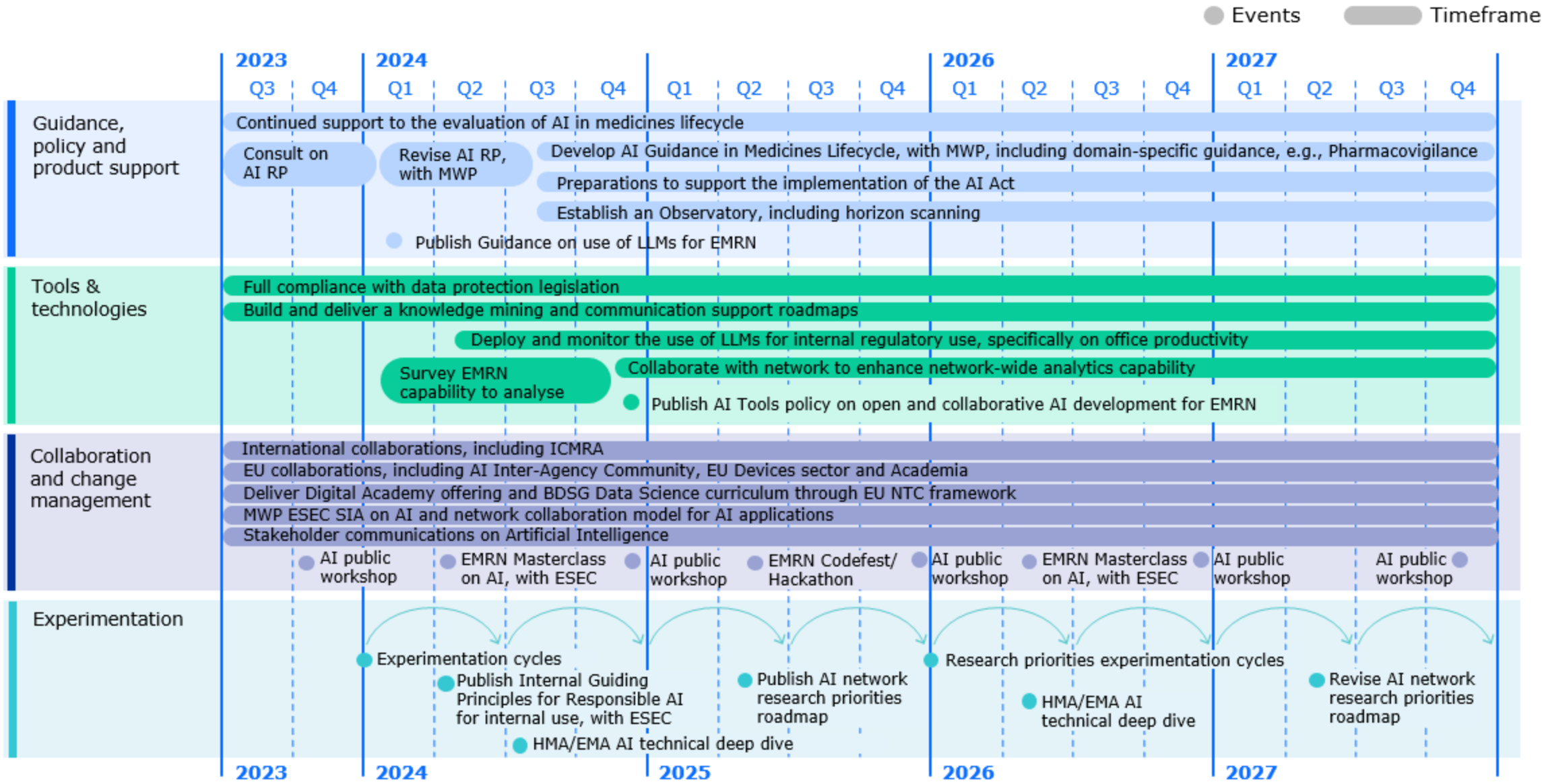

Experimentation | For what purpose?

Increase learning and reduce uncertainty

Fail faster and learn from failure

Discover new insights and solutions

Test new system designs and identify conditions for success

Feed the knowledge into regulatory activity space

Experimentation | EMA

Digital Innovation Lab (DigiLab)

Established 2021 to accelerate digital innovation and experimentation

Infrastructure

Analytics Centre of Excellence

Explore analytics, AI, ML and robotics to **build pragmatic solutions and experiment with new technology**

Process analytics

Health Data Lab

Develop innovative analytics to **extract insights from healthcare data**, to provide answers/recommendations and maximise intelligence

Healthcare data analytics

Information Processing and Analytics

Aim to improve the organisation's performance through streamlining information processing across the regulatory lifecycle.

Data analytics tools and platforms

Scientific Explorer / From multiple unstructured sources to a single structured target

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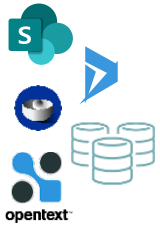
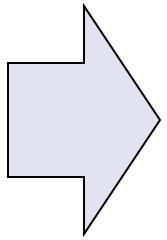
Data Sources

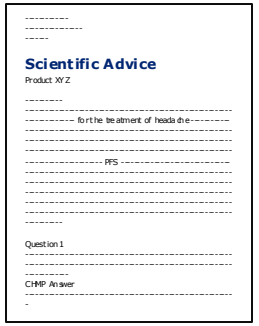
Ingestion and Pre-processing

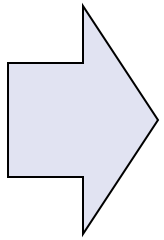
Extracted Terms

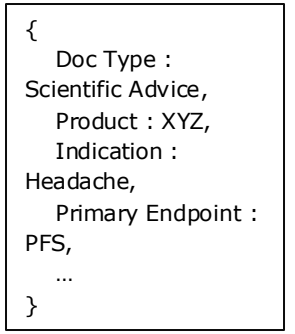
Search engine & UI

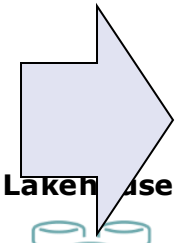












Scraping Websites
Ingest .doc .docx .pdf…

Pattern Matching
NER models
Large Language Models

Index, store and share structured data

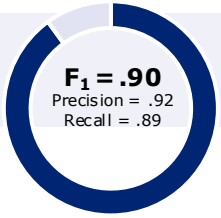
Engineered Prompt

```
Extract the following set of information from the
letter. For each extraction …

- Comparator: The Comparator, control, reference group,
cohort or arm. A few relevant example are placebo,
active comparator, low dose, historical, standard of
care, sham, vehicle, uncontrolled, noncomparative,
intrapatient, within patient
- Primary Endpoint(s): …
```

GPT-4 Output

```
Trial : Paediatric IL-23 platform trial
- Comparator
  = Proposal by the Applicant : Using adult placebo as
an external control group
  = CHMP level of Agreement : Partially agreed
  = CHMP Caveats : Comparison should be adequately
adjusted for all possible relevant differences between
patient populations.
  = References : Question 2
```



From
~ 300 validations

Summary

- Several, and increasing number of, opportunities to leverage AI for regulatory purposes, and especially in pharmacoepidemiology
  - Generative AI will likely increase productivity/efficiency but will likely still play a limited role e.g., in the actual analytics real-world data where data tends to be structured
  - Machine learning will become increasingly part of the analytical arsenal of the pharmacoepidemiologist but not likely to replace existing tools (e.g., for the most part, logistic regression models still are the best option)
- Experimentation and collaboration will be essential – a European Medicines Regulatory Network workplan including experimentation and fora for interactions with, e.g. Academics

Thank you!

Further information

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Epidemiological perspective on the causal inference methods

Katja Hakkarainen, PhD
VP Epidemiology at Parexel

Content of today's session

..will provide the (**pharmaco**)**epidemiological perspective** on the **causal inference methods**, especially the adoption of the **target trial emulation framework** in observational research **within pharmacoepidemiology**… the principles of target trial emulation, **motivations for using the framework**, and **examples of applications of the framework in observational research**.

When we want to understand the effect of a drug
– safety outcome or effectiveness –
through comparative observational (non-interventional) studies

Counterfactual theory in pharmacoepidemiology

- Fundamental concept in causal inference
- Asks: *What would have happened had the exposure been different, given all other things are equal?*
  - Leads to causal contrast
- **Disease experience** (outcome), given exposed (treated) ← factual
- **Hypothetical disease** (outcome), if was unexposed (not treated) ← **counter**factual
- Outcomes only have meaning when defined in contrast to an alternative

Counterfactual theory: Assumptions for causal inference, applied to pharmacoepidemiology

Exchangeability = comparable groups

- No **confounding** → Requires attention in observational studies
- Achieved by randomization in trials

Received most attention

Consistency = well defined counterfactual outcomes, plus interventions

- Observed outcome for each patient is one of the potential outcomes: the one corresponding to the treatment actually received
- Solved by protocol in trials; requires attention in observational studies

Positivity = both groups treated and untreated

- The conditional probability of receiving every value of treatment is greater than zero, i.e. positive

Strucural/theroterical positivity violations = impossible for a subject to receive treatment

Practical positivity violations = no one receives a treatment in a sub-group, e.g. due to small study size

Additionally biases need to be considered and addressed

	Key biases associated with Study Population	
	Confounding by indication	Occurs “when the underlying diagnosis or other clinical features that affect the use of a certain drug are also related to the outcome under study”
	Channeling bias	Occurs “when interventions having similar indications are differentially prescribed to groups of patients at varying levels of risk or with prognostic differences”
	Healthy user bias	Refers to “the propensity for patients who receive one preventive therapy to also seek other preventive services or partake in other healthy behaviors” *Healthy Adherer Bias (Subtype of Healthy User Bias)*: Refers to “when patients who adhere to preventive therapy are more likely to engage in other healthy behaviors than their non-adherent counterparts”
	Protopathic bias	Refers to “interpreting a factor to be a result of an exposure when it is in fact a determinant of the exposure, and can occur when an early sign of the disease under study led to the prescription of the drug under study”
Time zero!	**Key biases associated with Study Design**	
	Prevalent user bias	Refers to systematic distortion of study findings associated with “the extent that time-dependent risk can result in the early attrition of those individuals most susceptible to the event and in the follow-up of low-risk individuals”
	Immortal time bias	Refers to systematic distortion of study findings resulting from the misclassification or exclusion of immortal time, “a period of follow-up during which, by design, death or the study outcome cannot occur”
	Key biases associated with Data Source	
	Misclassification bias (exposure/outcome/confo under misclassification)	*Exposure misclassification*: Refers to “the error resulting from classifying study subjects as exposed when they truly are unexposed, or vice versa” *Outcome misclassification*: Refers to the error resulting from classifying study subjects as having an outcome when they truly did not have the outcome, or vice versa *Confounder misclassification*: Refers to the error resulting from classifying study subjects as having a specific confounding factor when they truly did not have the confounding factor, or vice versa
	Missing data/ loss to follow up	Refers to the unavailable information in a study which can result from subjects that are not able to be followed for the duration of the study, as well as multiple other factors including “failure to attend medical appointments, lack of measurements, failure to send or retrieve questionnaires, and inaccurate transfer of data from paper registration to an electronic database”

Acton et a. 2022: Core concepts in pharmacoepidemiology: Key biases arising in pharmacoepidemiologic studies

Articles on examples of biases

Received: 30 April 2020 | Revised: 29 June 2020 | Accepted: 6 July 2020

DOI: 10.1002/pds.5083

ORIGINAL REPORT

Time-related biases in pharmacoepidemiology

Samy Suissa[1,2] | Sophie Dell'Aniello[1]

Especially time-related biases – Time zero!

Published in final edited form as:
Epidemiology. 2008 November ; 19(6): 766–779. doi:10.1097/EDE.0b013e3181875e61.

Observational studies analyzed like randomized experiments: an application to postmenopausal hormone therapy and coronary heart disease

Miguel A. Hernán[1,2], Alvaro Alonso[3], Roger Logan[1], Francine Grodstein[1,4], Karin B. Michels[1,4,5], Meir J. Stampfer[1,4,6], Walter C. Willett[1,4,6], JoAnn E. Manson[1,4,7], and James M. Robins[1,8]

Published in final edited form as:
Nat Med. 2019 October ; 25(10): 1601–1606. doi:10.1038/s41591-019-0597-x.

Avoidable flaws in observational analyses: an application to statins and cancer

Barbra A. Dickerman, PhD[1], Xabier García-Albéniz, MD, PhD[1,2], Roger W. Logan, PhD[1], Spiros Denaxas, PhD[3,4,5], Miguel A. Hernán, MD, DrPH[1,6,7]

There are numerous aspects to consider in study design and methods....

Target trial emulation increasingly recommended

- **Consistent with counterfactual theory**
  - Framework to help address the assumptions
  - **Consistency** facilitated by well-defined protocol
  - **Exchangeability** considered by defining treatment assignment instead of randomization (also inclusion criteria)
  - **Positivity** considered e.g. in inclusion criteria and choice of treatment strategies
- Additionally: Helps to avoid biases related to defining time zero (follow-up start)
  - Time zero vs eligibility criteria vs treatment assignment

  → Avoiding prevalent user bias (new-user design!) and immortal time bias
- Yet: many more biases to be considered, such as those related to data, as well as other methodological aspects

TTE protocol specifies
- Eligibility criteria
- Treatment strategies (exposure groups)
- Treatment assignment, instead of randomization
- Outcomes
- Follow-up, start-end
- Causal contrasts (intent-to-treat, per-protocol)
- Statistical analysis

Regulators and scientific community, etc…

15 April 2024
EMA/CHMP/150527/2024
Committee for Human Medicine Products (CHMP)

Reflection paper on use of real-world data in non-interventional studies to generate real-world evidence

Draft

4.4. Studies with causal objectives

The causal interpretation of any treatment effect requires a comparator in order to isolate and quantify the effect. The aim of the study design in studies with causal objectives should be to achieve valid comparisons between exposure groups by dealing with the risk of selection bias, information bias and confounding.

The target trial emulation (TTE) framework should be considered as a strategy that uses existing tools and methods to formalise the design and analysis of NIS using RWD with causal objectives (3-5). The first step of this framework is to envision the key elements of a hypothetical (target) trial that would answer the research question, including its target population, eligibility criteria, assignment procedure, treatment conditions, outcome, causal contrasts (i.e. the estimand) and analysis plan. The second step is to design a NIS as close as possible to the hypothetical trial using epidemiological methods.

The TTE framework is considered useful for the following reasons:

- It provides a structured and coherent framework for the design of NIS with a causal objective, with similarities with CTs in terms of terminology, definition of the estimand and analytical approaches.
- It helps the investigators to consider potential bias and adequate methods to address them.
- Given the need to explicitly describe the design elements needed to emulate the CT, it provides a high level of transparency on the study design, the assumptions needed to emulate the trial and the definition of causal effects; this level of transparency may facilitate the evaluation and the replication of the study.
- The detailed and structured definition of inclusion/exclusion criteria and allocation of time periods defined by study entry and estimated start of treatment have been shown to reduce bias, such as the prevalent user bias (6) and the immortal-time bias (7).

Although the TTE framework can improve the internal validity of the NIS, the lack of randomisation and blinding still requires attention to the prevention and/or control of selection bias, information bias and confounding described in Chapter 4.5.

To increase the coherence between definitions of exposures, endpoints and intercurrent events, the estimand framework described in the ICH E9 (R1) Addendum on Estimands and Sensitivity Analysis in Clinical Trials should be considered in the design of the hypothetical trial, such as the attributes of the estimand, intercurrent events and strategies to manage ICEs. The main statistical analysis may also be aligned with the estimand framework, e.g. concerning the approach to missing data handling and sensitivity analyses.

ICH harmonisation for better health

General Principles on Plan, Design and Analysis of Pharmacoepidemiological Studies That Utilize Real-World Data for Safety Assessment of Medicines

M14

Draft version
Endorsed on 21 May 2024
Currently under public consultation

4.1 Research Question

The research question is a concise statement of the study purpose and the prespecified hypotheses to be tested; the purpose of the study may also be to generate hypotheses for future research. The research question may be formulated by use of the population, intervention (exposure in the case of non-interventional studies), comparator, outcome, and timing (PICOT) template. In the case of non-interventional studies, "intervention" can be considered the same as an exposure. The specific question should be formulated after a review of the literature to identify and understand any knowledge gaps, strengths and weaknesses of prior studies, the expected magnitude of effect, and important confounding factors. When defining the research question, researchers should provide a clear rationale on how it will be addressed by the study objectives. In the protocol, researchers should document and support decisions about the study design and the types of data required/available. Careful formulation of the research question will highlight unknowns that will need to be addressed through information derived from the feasibility assessment and this information may further refine the question and drive protocol development. Researchers may also consider a principled framework for study design and estimation of the risks of a medicine, such as the ***target trial*** approach or the ***estimands*** framework as they initiate work on the research question and conduct initial design and feasibility analyses [3, 5].

This Issue | Views 43,118 | Citations 187 | Altmetric 124

JAMA Guide to Statistics and Methods

December 12, 2022

Target Trial Emulation

A Framework for Causal Inference From Observational Data

Miguel A. Hernán, MD, DrPH[1]; Wei Wang, PhD[2]; David E. Leaf, MD, MMSc[3]

ISPOR Europe 2024

17-20 November 2024 | Barcelona, Spain

Sunday, 17 November — EXPAND ALL

8:00 - 12:00 SHORT COURSE MORNING SESSIONS

006: Causal Inference and Causal Estimands From Target Trial Emulations Using Evidence From Real-World Observational Studies and Clinical Trials +

Monday, 18 November

11:45 - 12:45 EDUCATIONAL SYMPOSIA

115: Harnessing the Power of AI in RWD: Enhanced Insights Through Machine Learning and Causal Inference Advances +

17:00 - 18:00 BREAKOUTS: IP, WS, & OBS

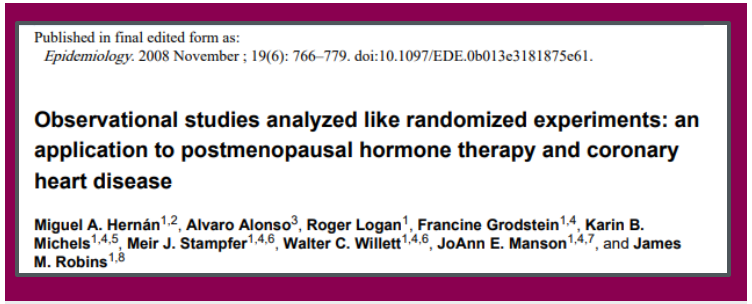
150: Innovation or Stagnation? Unpacking Issues and Solutions in the Uptake of Advanced Methods for Real World Evidence +

Tuesday, 19 November

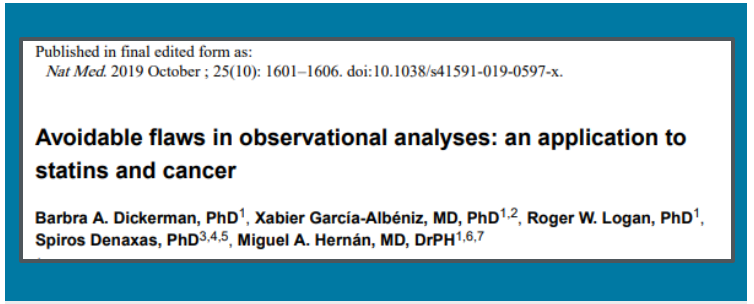
10:15 - 11:15 BREAKOUTS: IP, WS, & OBS

201: Advanced Methods for Comparing Treatment Sequences or Pathways Using Real-World Data +

Examples of target trial emulation



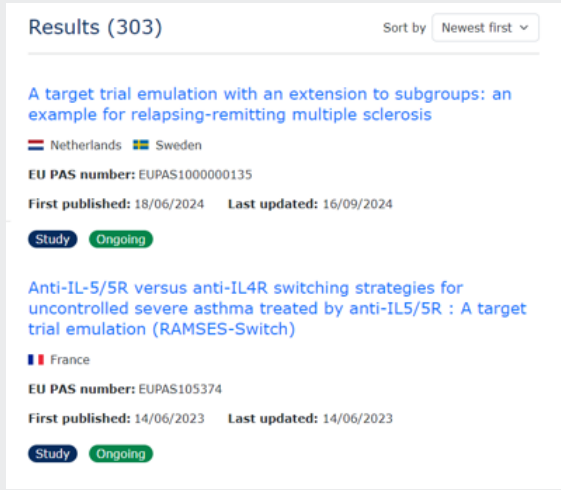
- RCT: HRT increases the risk of CRD
- Observational studies: HRT increases the risk of CRD
- **Observation study repeated with TTE framework: results aligned with the RCT**
- Protective effect in prior observational studies influenced by prevalent user bias (depletion of susceptible)
- HRT users were prevalent users: assignment before start of follow-up
  - Early CHD undetected among HRT users
  - Less CHD detected



- Meta-analysis of RCT: no effect (HR 1.02)
- Observational studies: protective effect of statins on cancer incidence
- **Observation study repeated with TTE framework: results aligned with the RCTs**
- Protective effect in prior observational studies predominantly caused by immortal time bias
- Assignment (long-term use of statins) was defined after start of follow-up
  - Statin users had to survive until assignment
  - Less cancer detected (also prevalent user bias also contributed protective effect)

EMA | RWD Catalogues

- Numerous ongoing studies
- Search of “target trial emulation”: 300+ hits
- E.g.



How does AI play in?

Target trial emulation increasingly recommended

- **Consistent with counterfactual theory**
  - Framework to help address the assumptions
  - **Consistency** facilitated by well-defined protocol
  - **Exchangeability** considered by defining treatment assignment instead of randomization (also inclusion criteria)
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- Additionally: Helps to avoid biases related to defining time zero (follow-up start)
  - Time zero vs eligibility criteria vs treatment assignment

  → Avoiding prevalent user bias (new-user design!) and immortal time bias
- Yet: many more biases to be considered, such as those related to data, as well as other methodological aspects

Data-driven confounder selection

TTE protocol specifies
- Eligibility criteria
- Treatment strategies (exposure groups)
- Treatment assignment, instead of randomization
- Outcomes
- Follow-up, start-end
- Causal contrasts (intent-to-treat, per-protocol)
- Statistical analysis

Analysis

Data extraction and structuring of data

Concluding remarks

- **Causal inference – Epidemiological and methodological aspects crucial to consider in study design**
- **Target trial emulation can facilitate optimal study design**
- **AI can support in some elements**
  - Knowledge and understanding of causal/epidemiological methods and risk/mitigation of biases still needed

Thank you

Useful references

- Acton et al. **Core concepts in pharmacoepidemiology: Key biases arising in pharmacoepidemiologic studies**. Pharmacoepidemiol Drug Saf. 2022;32:9–18. doi: 10.1002/pds.5547
- Dickerman et al. **Avoidable flaws in observational analyses: an application to statins and cancer**. Nat Med. 2019;25(10):1601–1606
- Hernán and Robins, **Causal Inference: What If**. Boca Raton: Chapman & Hall/CRC, 2020
- Hernán et al. **Target trial emulation: A framework for causal inference from observational data**. JAMA 2022;328:2446–2447
- Hernán et al. **Observational studies analyzed like randomized experiments: an application to postmenopausal hormone therapy and coronary heart disease**. Epidemiology 2008;19:766–779
- Lash et al. **Modern epidemiology**. 4th ed. Philadelphia: PA. L Wolters Klouwer; 2020 (**Chapter 3. Formal causal models**)
- Rough et al. **Core concepts in pharmacoepidemiology: Principled use of artificial intelligence and machine learning in pharmacoepidemiology and healthcare research**. Pharmacoepidemiol Drug Saf. 2024;33:e70041
- Suissa and Dell'Aniello. **Time-related biases in pharmacoepidemiology**. Pharmacoepidemiol Drug Saf. 2020;29:1101–1110

Introduction to causal methods: the statistical approach to causal inference & intro to methods

Andy Wilson, PhD Mstat

Head of Innovative RWD Analytics at Parexel

10’ish minute flow ~

- The importance of causal methods in real-world data (RWD) and real-world evidence (RWE) settings
- $Cause_1$ ~ more formal definition(s) & philosophy
- $Cause_2$ ~ History and evolution of causal methods
- $Cause_3$ ~ practical perspective : Frontiers in Causal Methods and evolving (regulatory) landscape ~ From PS to TMLE & beyond
- Concluding thoughts

In theory there is no difference between theory and practice.

In practice there is.

Yogi Berra

The importance of causal methods in real-world data (RWD) and real-world evidence (RWE)

Data are …

- Beautiful, powerful, informative, persuasive…
- **But also, *deceitful***
  - **Example: "Pneumococcal vaccines increase pneumonia incidence"**
    - In fact, the more you interrogate, the more confidently it will confess
    - Keep squeezing (torture leads to false confession)

> "The causes aren't in the data."
>
> – Judea Pearl

Briefly, what are identifiability assumptions
Your passport to causal island (but “heroic assumptions”)

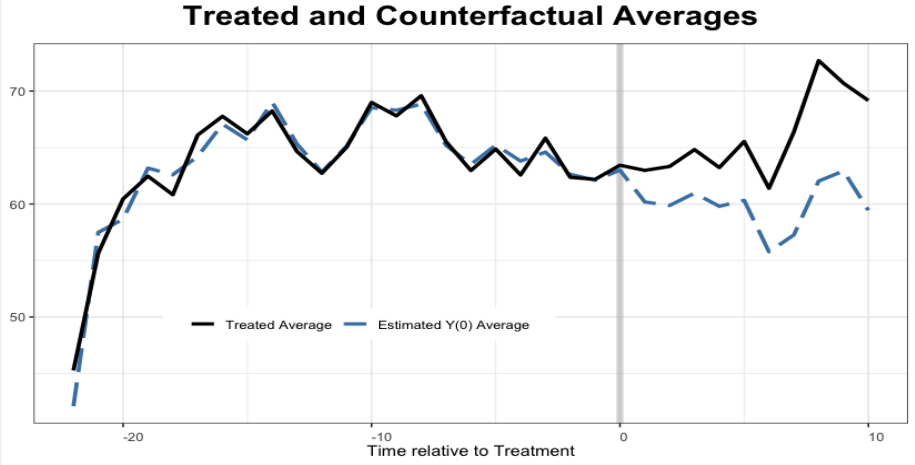
- **Exchangeability** (no-unmeasured confounding?)
- **Positivity (**everyone have a chance to be treated?)
- **Consistency** (Did you have an authentic potential outcome?)

This is the answer to the question:
“What makes your association have a causal interpretation”?

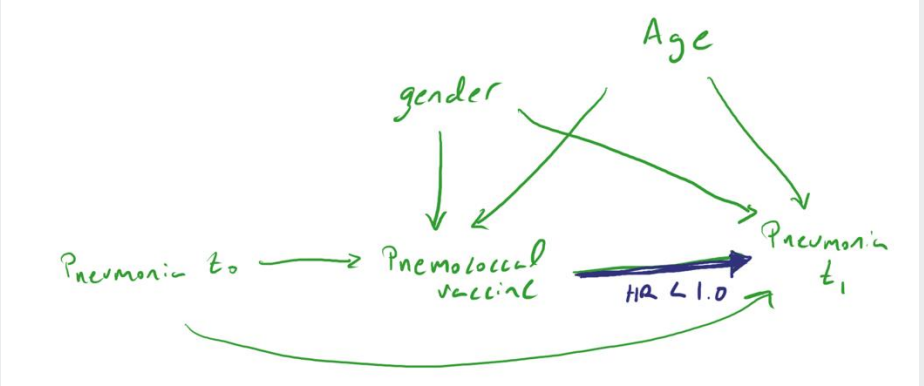
For some, *Causal* is the new “Bayesian” : aka “fancy”

Introduction to causal methods: the two predominant schools of thought

- Neyman-Rubin counterfactual framework [and the fundamental problem of causal methods is we can't have both outcomes]



- Causal **Structural** (Pearl-graphical) approach - where variables 'listen' to each other



  - Gender
  - Age
  - Prior pneumonia & pneum. vaccine.

- Practically, use "right to inform left"

"Draw your assumptions before your conclusions"
– Miguel Hernan

Metaphor ~

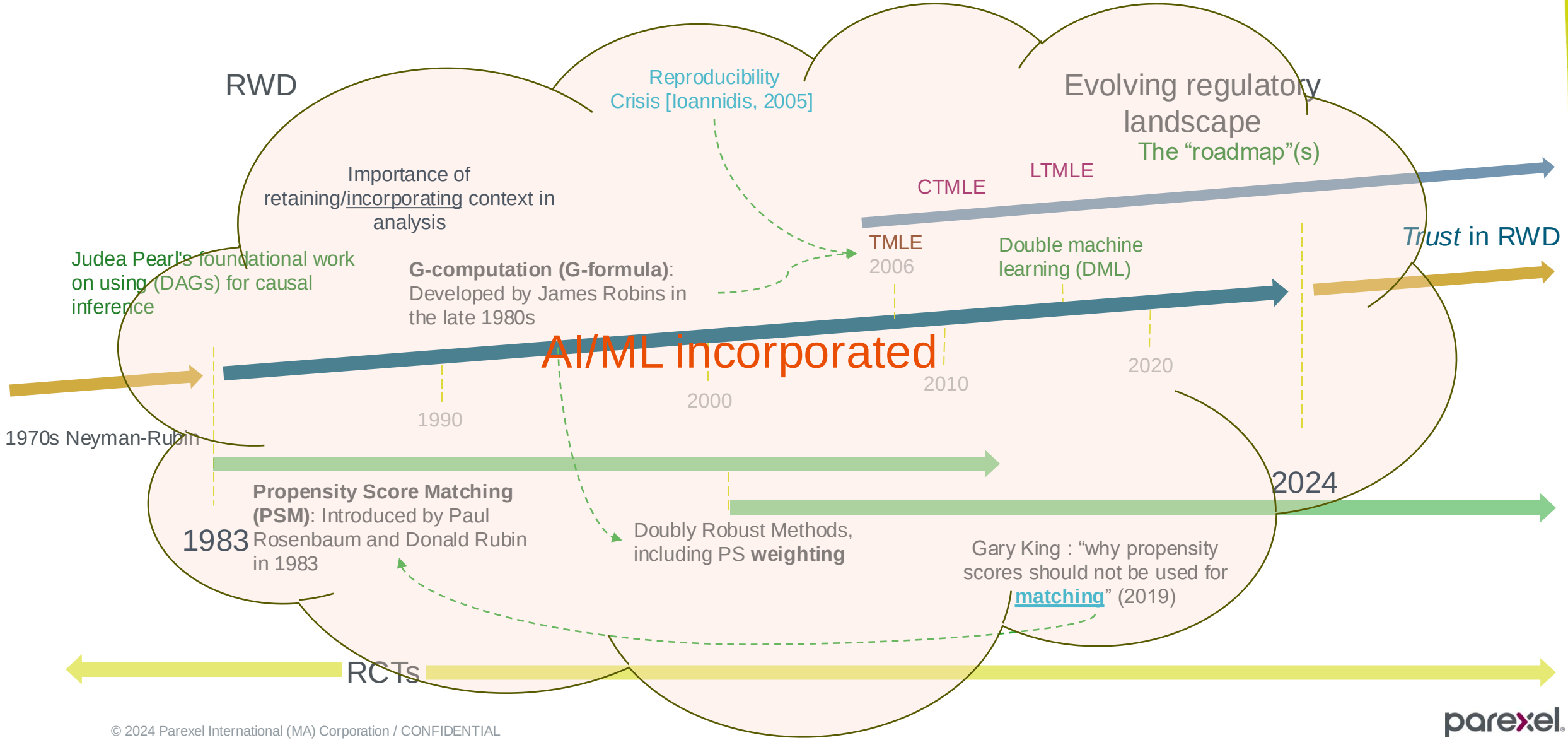
Causal estimate : identifiable in data
Suspect : crime scene + plausible story

Just as a detective needs not only evidence but also a coherent story to link the suspect to the crime, causal inference requires not only data but a plausible mechanism that explains the relationship between cause and effect. Without that, the cause could be misleading, just like having the wrong suspect with circumstantial evidence.

Annual Review of Statistics and Its Application: Causal Inference in the Social Sciences – Guido W. Imbens (2023)

- **1920s-1930s: Fisher and Neyman** - The foundations of Randomized Controlled Trials (RCTs), marking the traditional method for causal inference in experimental settings
- **1983: Rosenbaum and Rubin** - Introduction of the concept of *propensity scores* to address confounding in observational studies, revolutionizing the field of causal inference in observational settings
- **1990s: Increased focus on causal inference** - A dramatic increase in methodological and empirical research into causality, driven by fields like economics, statistics, and social sciences*
- **Early 2000s: Pearl's Structural Causal Models (SCM)** - Judea Pearl's work on Directed Acyclic Graphs (DAGs) and SCMs offered a graphical approach to causal inference, providing a framework to model causal relationships and analyze interventions
- **2000s: Double Machine Learning and Targeted Maximum Likelihood** - Integration of machine learning methods like double machine learning, and approaches such as targeted maximum likelihood estimation (TMLE) for robust causal effect estimation in observational data
- **2010s: Synthetic Control Methods and Difference-in-Differences (DID)** - These approaches became prominent for dealing with time-series data or cases where randomization is not feasible, especially in econometrics and policy evaluations
- **Recent Years & future: Causal AI and Machine Learning** - The advent of causal AI and the increasing integration of machine learning techniques with causal inference methodologies, helping automate causal effect estimation in real-world data settings

Recent History and Evolution of Causal Methods (according to AW)



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What's so special about *Targeted Learning*?

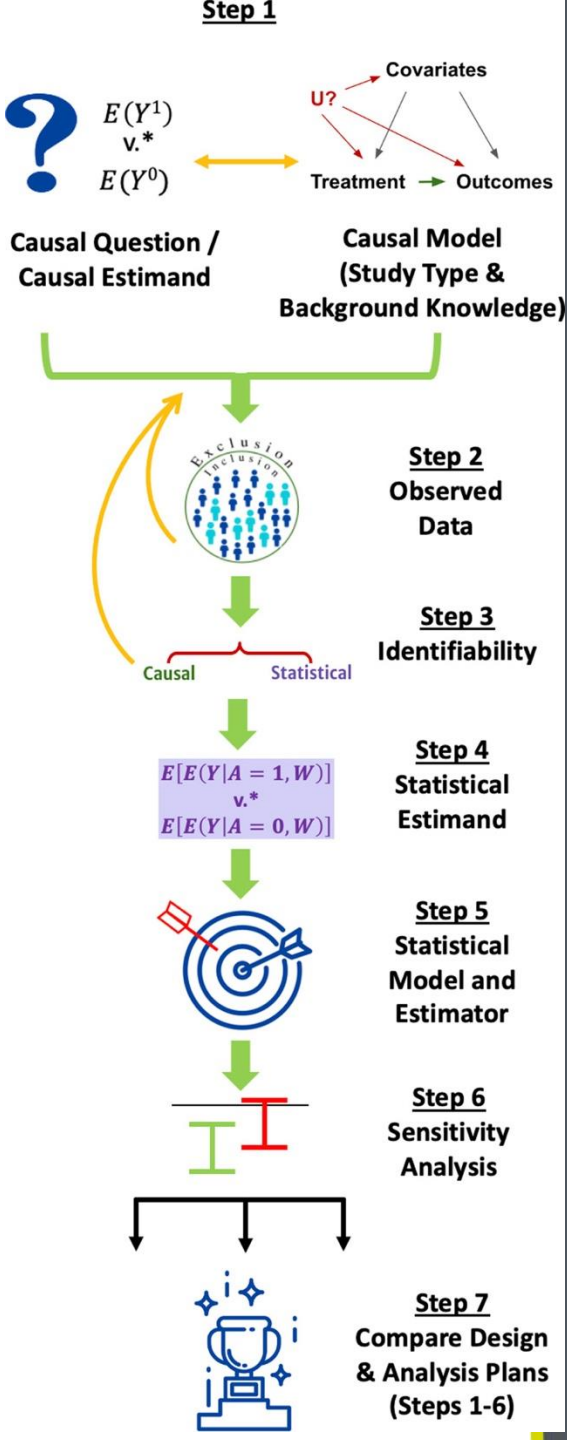
Two core innovations + a *roadmap*

Targeted Learning (TMLE)

- Ability to focus in on the question, e.g., “what is the improved outcome in the treated population”? (especially important in high-dimensional space, where traditional methods get worse with big data)
- Applies innovative “Targeting Step” (analytically, a second chance to get estimate right)
- Optimizes bias/precision tradeoff for the target

Super Learning (SL)

- Works on a collection of input models
- Builds data-adaptive composite model
- Cross-validates to guarantee best overall fit



TMLE/SL has great performance

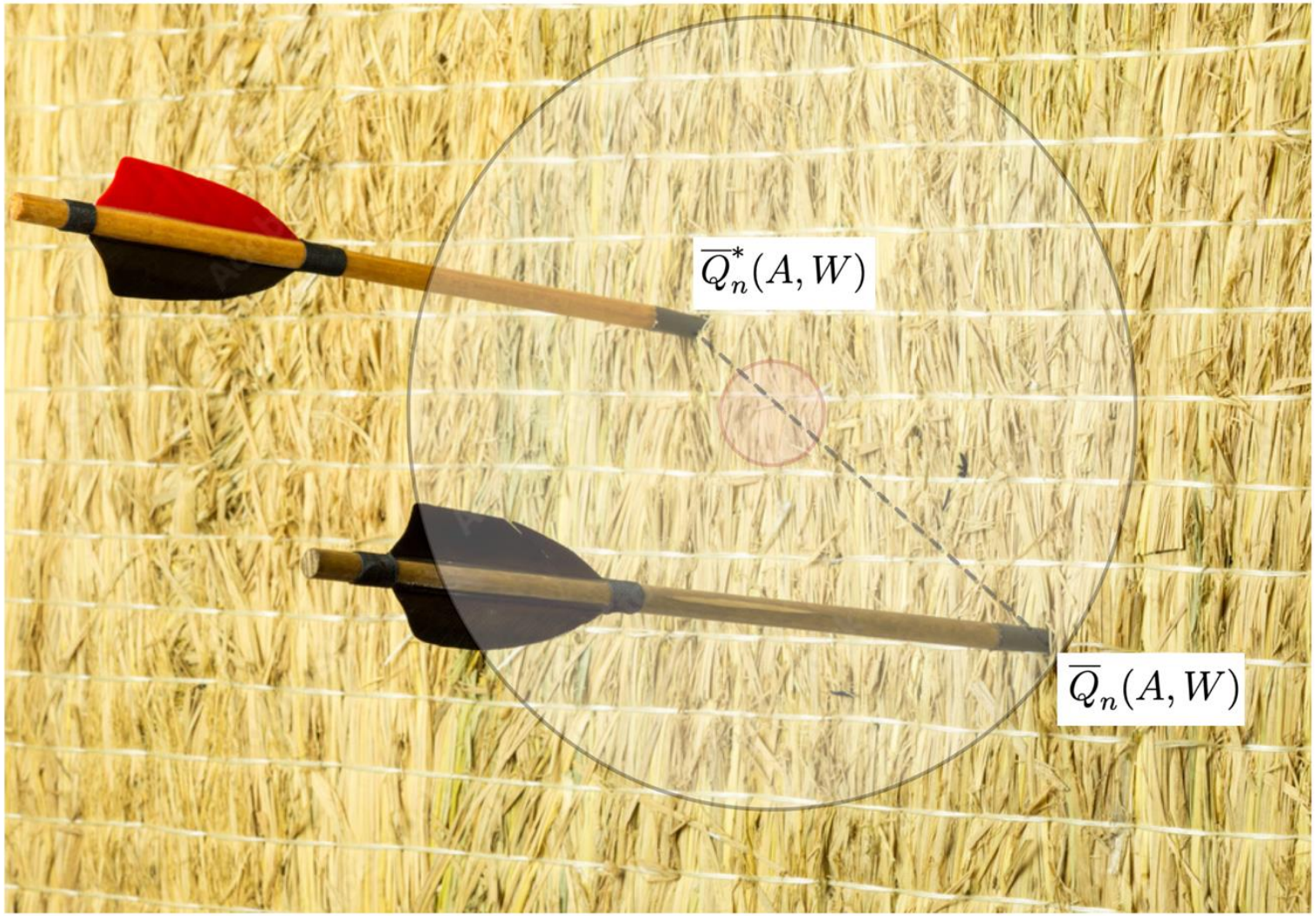
Motivating characteristics of TMLE

- An algorithm for the construction of double-robust, semiparametric, efficient substitution estimators.
- Allows for data-adaptive estimation while supporting valid statistical inference.
- Does use the G-computation estimand (G-formula).
- Incorporates the ensemble Super Learner, which is a weighted composite model from a library of algorithms. Candidate learners and weights are chosen to minimize the cross-validated empirical risk loss function.

Targeted Maximum Likelihood Estimation (TMLE)

When we are interested in one particular parameter of the data distribution and consider the remaining parameters to be nuisance parameters, we would prefer an estimate that has smaller bias and variance **for the targeted parameter**, at the expense of increased bias and/or variance in the estimation of nuisance parameters.

TMLE takes an initial estimate $\overline{Q}_n(A, W)$ as well as an estimate of the propensity score and produces an updated estimate $\overline{Q}_n^*(A, W)$.



A second chance to get it right.

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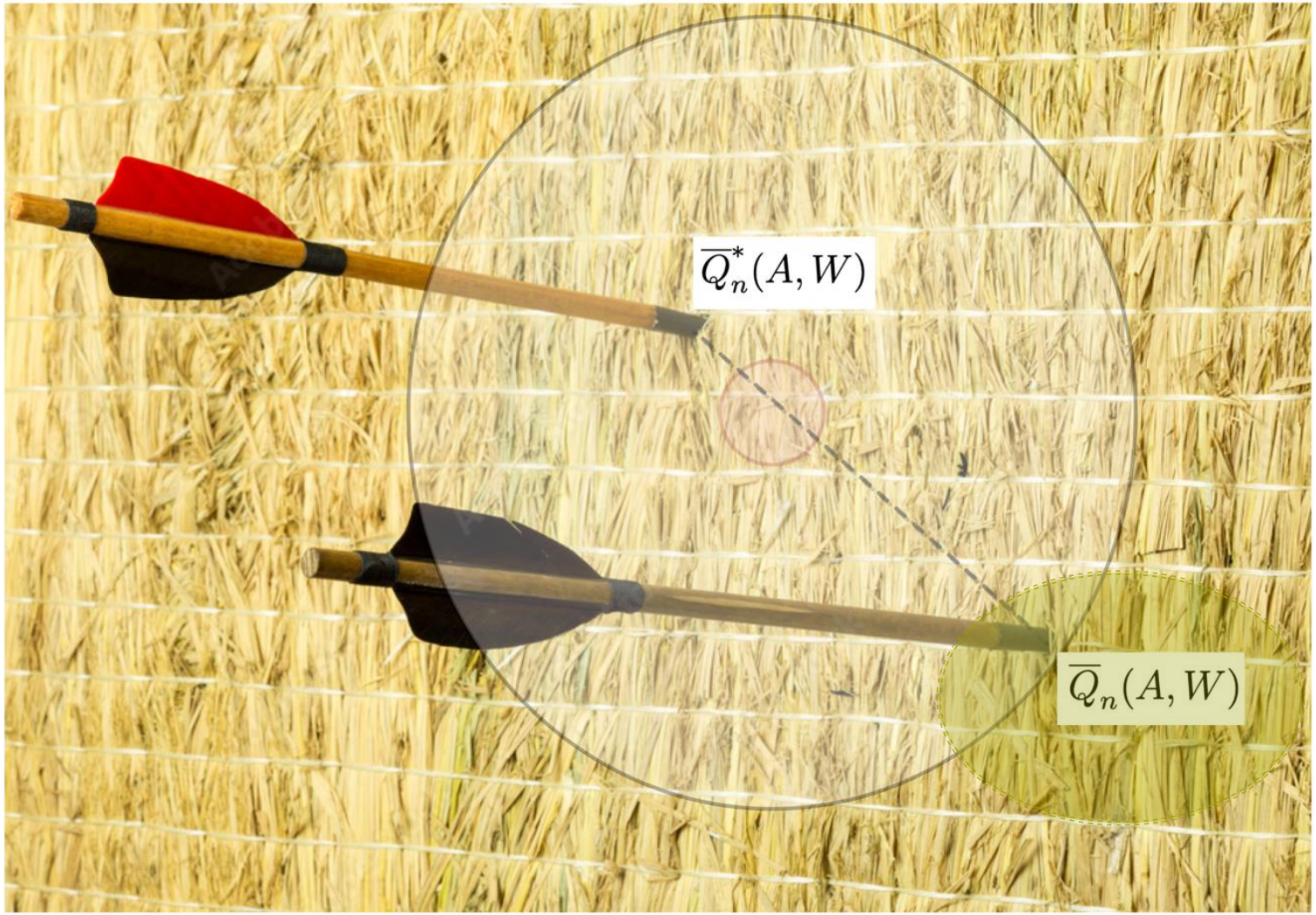
In fact

The initial estimate*, even before the *targeting* step, is already an incredibly attractive estimate compared to traditional methods

TMLE takes an initial estimate $\overline{Q}_n(A,W)$ as well as an estimate of the propensity score and produces an updated estimate $\overline{Q}_n^*(A,W)$.



A second chance to get it right.

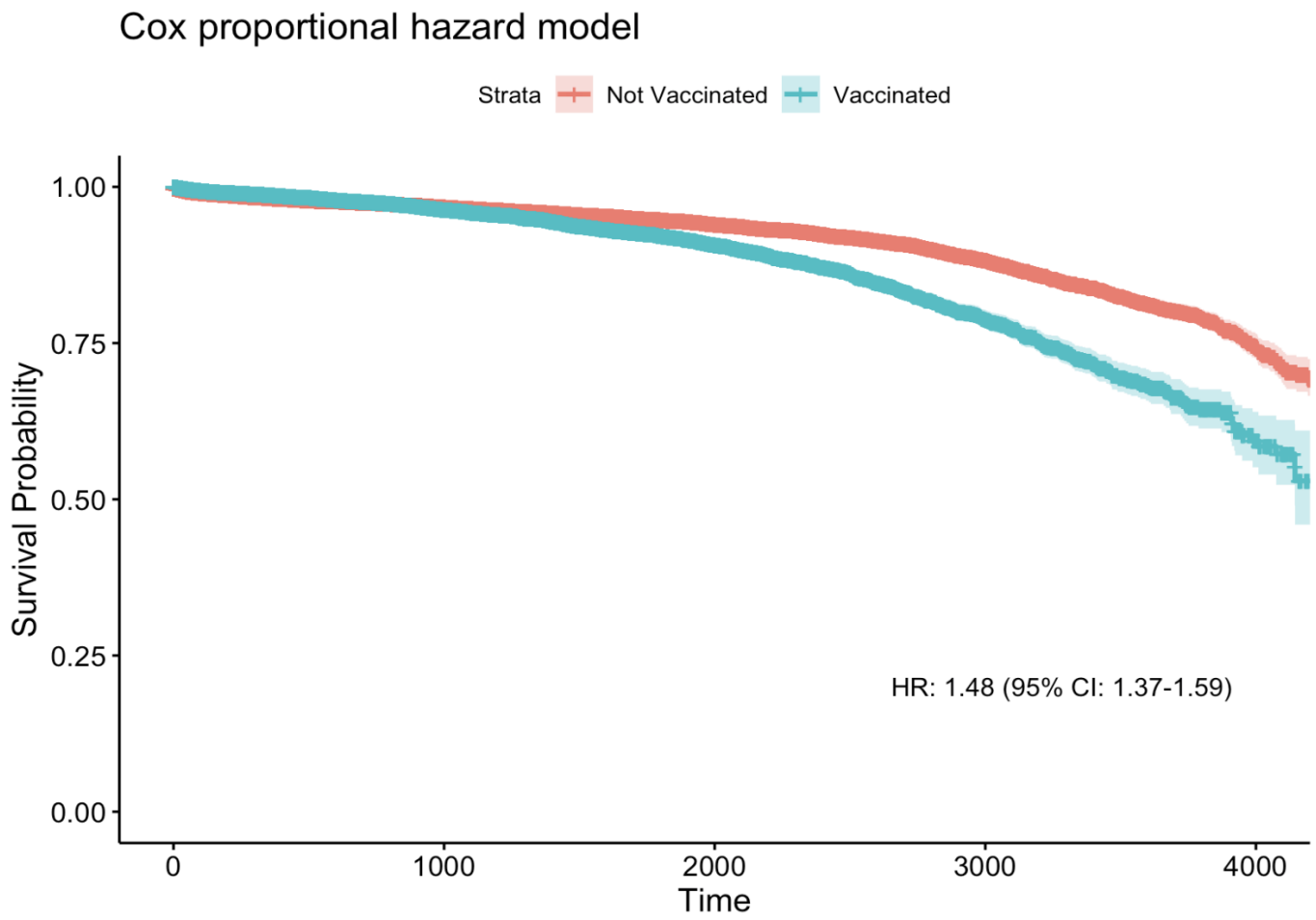
*Super-learner-based g-computation

Removes **assumptions!**

- Traditional parametric methods make many assumptions which are known to be false. Let's remove these assumptions.
- Best statistical approximation given the study design
- No miracles – still need assumptions for causal claims, e.g., sequential randomization (no unmeasured confounding) and positivity
- Researchers can focus more on setting up design of experiment

Performs well :: back to our demonstration ~ pneumonia

Crude estimate from MIMIC IV – about 300,000 patients in Massachusetts (>154 million Rx records)



Looks bad for the vaccine

HR : 1.48

😬

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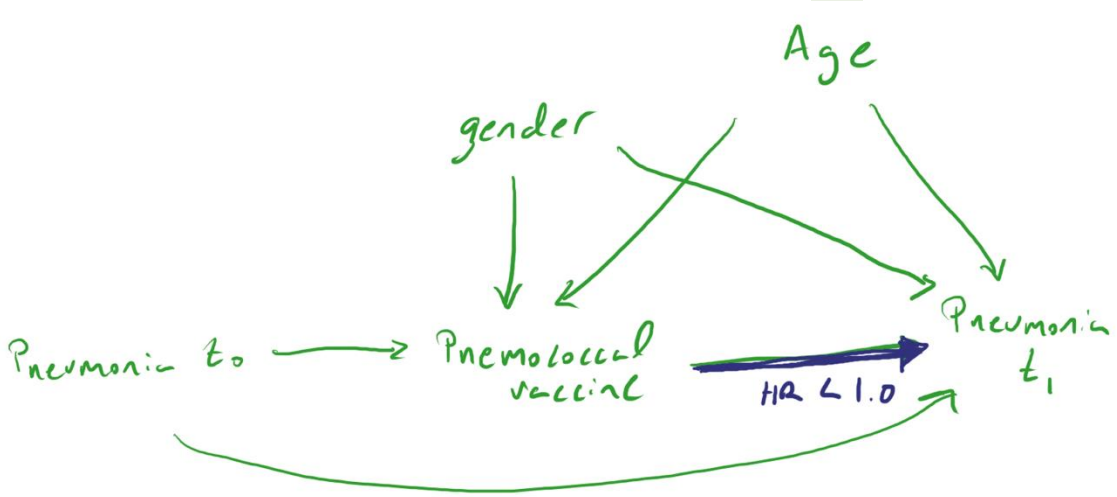
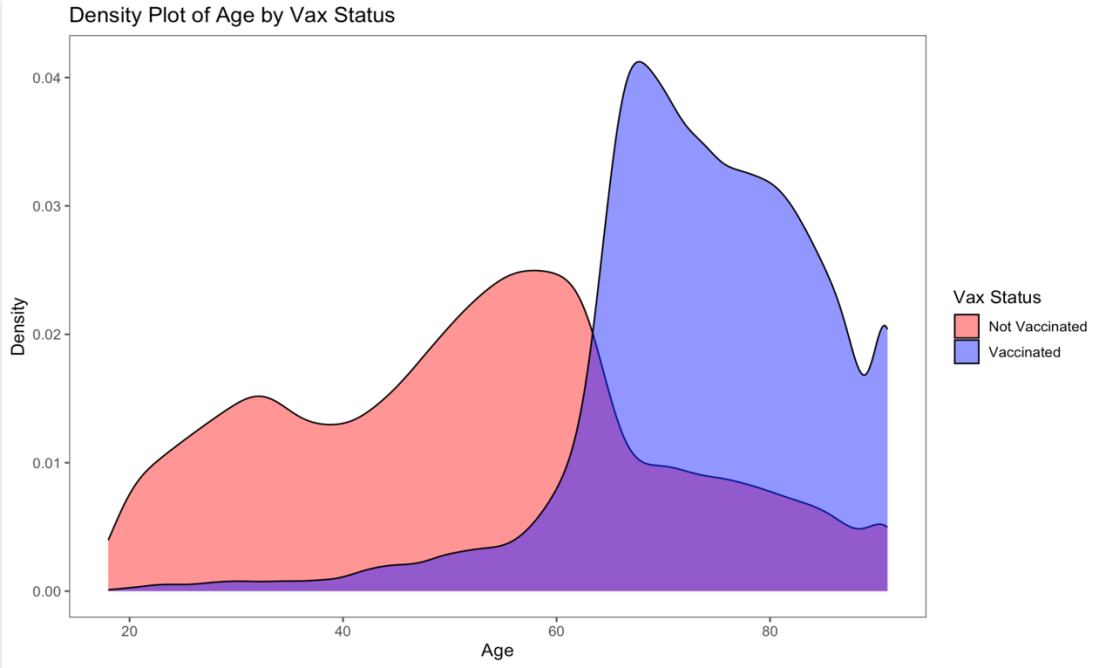
Performs well :: back to our demonstration ~ pneumonia

But wait:

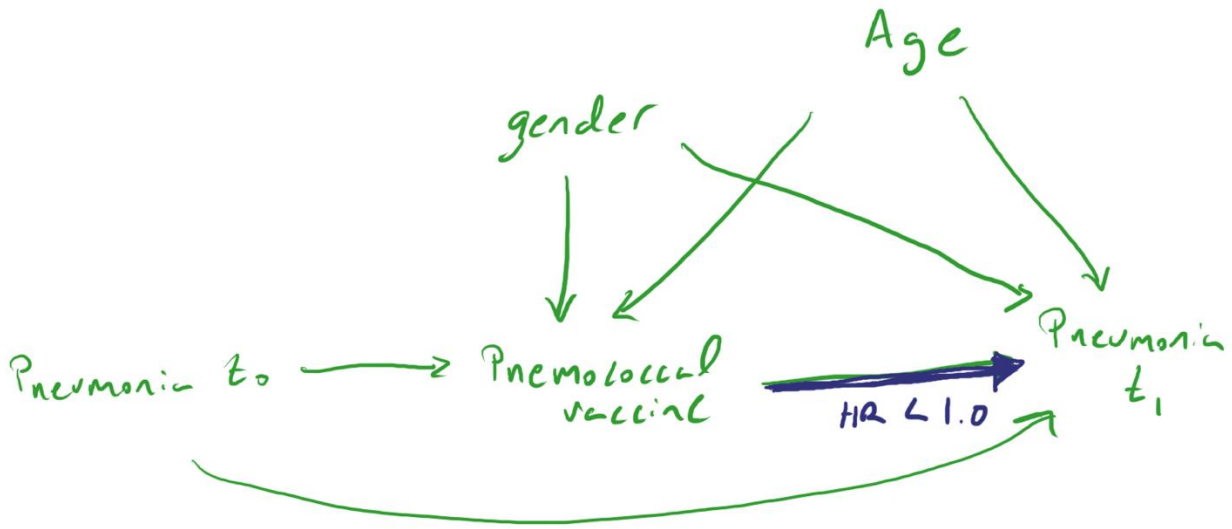
E.g., Age





Performs well :: back to our demonstration ~ pneumonia

But wait:



\+ TMLE

HR : 0.77516

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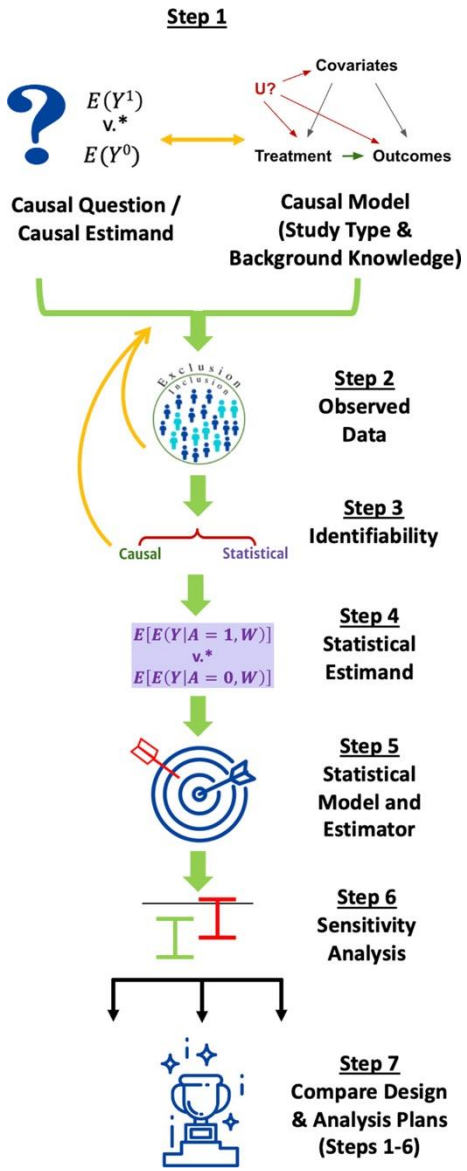

A causal roadmap for generating high-quality real-world evidence

Lauren E. Dang[1], Susan Gruber[2], Hana Lee[3], Issa J. Dahabreh[4], Elizabeth A. Stuart[5], Brian D. Williamson[6], Richard Wyss[7], Iván Díaz[8], Debashis Ghosh[9], Emre Kıcıman[10], Demissie Alemayehu[11], Katherine L. Hoffman[12], Carla Y. Vossen[13], Raymond A. Huml[14], Henrik Ravn[15], Kajsa Kvist[15], Richard Pratley[16], Mei-Chiung Shih[17,18], Gene Pennello[19], David Martin[20], Salina P. Waddy[21], Charles E. Barr[22,23], Mouna Akacha[24], John B. Buse[25], Mark van der Laan[1] and Maya Petersen[1]

+

JAMA Guide to Statistics and Methods

December 12, 2022

Target Trial Emulation
A Framework for Causal Inference From Observational Data

Miguel A. Hernán, MD, DrPH[1]; Wei Wang, PhD[2]; David E. Leaf, MD, MMSc[3]

Start with the Target Trial Protocol, Then Follow the Roadmap for Causal Inference

Lauren E. Dang[a] and Laura B. Balzer[a]

Epidemiology • Volume 34, Number 5, September 2023

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Concluding thoughts on the evolving regulatory landscape and promising frontiers

- Continue “trial & evidence” framework: open to best evidence (will never pre-render a verdict)
  - It’s a conversation (engage early – they request it)
  - “**Engage us (regulatory agencies). Don’t go through the process and then get to the end and be rejected. We invite it**”!
  - No downside

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Thank you

- Special thanks to Meghann Gregg, Jenny Alderden, and Lexi Pasi

Harnessing the Power of AI in RWD/ RWE

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Global Head of Health Economics

Takeda Pharmaceuticals

18. November 2024

DISCLAIMER

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Any suggestions, proposals, or recommendations made herein are not made on behalf of Takeda and should be considered as my personal opinions.

Legislation around access and reimbursement is changing across the EU and US

Aug 2022

Inflation Reduction Act (IRA)

- *Need for greater speed & efficiency in clinical development*
- *Drive up clinical trial complexity & burden of data generation*

Apr 2023

EU pharmaceutical reform

- **Reimbursement of novel therapies,** especially costly therapies, will increasingly require **new payment agreements** between payers and manufacturers

Jan 2025

EU HTA

- Adapt to a new regulatory process and **increased data generation requirements** to meet assessment criteria

Recent and upcoming legislative changes across regions is impacting manufacturers' clinical strategy as well as market access and reimbursement

As a result, pharmaceutical research is evolving to include real-world data (RWD) as a powerful complement to traditional clinical trials.

RWD provides a window into how patients respond to treatments in everyday settings, delivering invaluable insights into effectiveness and safety.

However, these studies bring challenges, especially from selection biases, time-related biases, and unobserved patient characteristics, which can obscure true treatment effects.

Improving early-phase decisions impacts the entire drug development process and the likelihood for reimbursement

Informed decisions in early phases are critical for establishing safety and efficacy, minimizing downstream costs and ensuring that interventions reach patients who are most likely to benefit.

With the use of AI, techniques such as causal ML, we can improve patient insights, reduce misclassification, and better understand the impact of patient characteristics on treatment responses.

These techniques ultimately enhance the precision and reliability of our early-phase decisions, and also help in setting up the right benchmarks for later phases, ultimately enhancing the product's real-world relevance and impact.

Potential use cases:
Protocol optimization

Eligibility Criteria Optimization

Using ML-based causal models, we can predict the most effective inclusion and exclusion criteria for participants by analyzing how different patient characteristics impact treatment efficacy and safety.

Feasibility analysis

For instance, causal ML can reveal which comorbidities or baseline characteristics significantly influence treatment outcomes, helping us to tailor protocols that target patients who are more likely to benefit while minimizing risks.

- This approach can also adjust treatment regimens based on predicted treatment responses, leading to fewer adverse events and improved trial efficiency.

Potential use cases:

Patient subgroup identification and stratification

Enhanced patient selection and prediction of subgroups

By examining heterogeneous treatment effects across patient subgroups, we can stratify patients based on likely treatment response.

- This understanding helps in crafting personalized protocols or exploring combination therapies for specific groups, such as elderly patients or those with comorbidities.
- Causal ML thus empowers us to make evidence-based decisions on optimal treatment strategies, reducing the time and resources spent on unpromising pathways.

Potential use cases:

Observational studies to support access & reimbursement needs

Beyond causal ML: Potential use cases

Adaptive Trial Design: AI-driven simulations allow for adaptive trial designs that adjust based on interim results. This can speed up the decision-making process by identifying early signals of efficacy or safety and potentially reduce sample sizes and costs.

Synthetic Control Arms: By leveraging RWD and historical trial data, AI can generate synthetic control arms, allowing some early-phase trials to proceed without a traditional control group, which can make trials faster and more ethical, especially in rare diseases.

Early Efficacy Prediction: AI models can predict a treatment's potential efficacy using biomarkers, genomic data, and early patient responses, allowing for early-phase go/no-go decisions.

Safety Profile Analysis: AI helps analyze early signals in clinical data, anticipating adverse events and refining dose selection to maximize safety in subsequent trial phases.

In closing

ML use cases help address some of the concerns in the application of RWD in causal construct, however, there are some limitations on use.

- Not all confounders can be accounted for, especially if they're unobserved.
- Furthermore, model complexity can sometimes obscure interpretability, requiring ongoing collaboration with clinical and biostatistical experts.
- Ethical considerations in the data generation process also remain essential to ensure patient privacy and adherence to regulatory standards.

ML can not only increase the efficiency of drug development but also ensure that treatments are optimized for real-world application, improving both patient outcomes and the long-term value of our therapies.

Questions?

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