Handling Missingness in Real-World Data (RWD)

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What is particular to missingness in RWD vs. RCT?

- Common to all cases
  - Missingness can induce bias in study results, as well as decrease statistical power/precision.
  - The issue and varying guidelines of handling of missing data in clinical trials have been addressed through regulatory and GCP stakeholders to include ICH, FDA, NIH, and numerous private and peer reviewed publication sources.
- Pattern of missingness can differ between RWD and RCT
  - Frequently higher missingness in RWD than in RCTs (retrospective vs prospective data collection)
  - Subject selection; data is often right and/or left censored
  - Joint and comparative evaluation of measures of clinical benefit/utility and costs
  - “Spikes” in HEOR outcomes (e.g., unit QALYs, costs)
  - HEOR outcomes can have different distributions (eg, hospital visits, costs, utility…) -> issues with Multiple Imputation (MI)

Missingness occurs in different ways both within and across types of RWD studies

RWD sources	RW study types	Sources of missingness
• Medical records/electronic health records (EHRs) • Product and disease registries • Claims and billing databases • Lab result databases • Patient and physician self-report (surveys) • Health-monitoring devices	• Retrospective claims studies • Cross-sectional & longitudinal survey studies • Medical record/EHR studies • Safety/epidemiology studies • Registries • Pragmatic Control Trials (PCTs) • Combination of the above	**Sources** • Non-response/participation • Attrition • Item/variable non-response • Survey non-completion • Patient non-compliance

Slide adapted from Dr. Judith Stephenson

Examine methods to handle missingness in RWD: on-going work at ISPOR SIG

- **Missing data in RWD: One of two focus points for the ISPOR Statistical Methods in HEOR Special Interest Group (SIG)**
- SIG Mission
  - To provide statistical leadership for strengthening the use of appropriate statistical methodology in health economics and outcomes research and improve the analytic techniques used in real world data analysis.
- SIG Co-Chairs
  - Rita M. Kristy, MS, Senior Director, Medical Affairs Statistics, Astellas Pharma Global Development, Northbrook, IL, USA
  - David J. Vanness, PhD, Professor, Health Policy and Administration, The Pennsylvania State University, State College, PA, USA

On-going work in our ISPOR "HEOR stats SIG"

1. **Literature reviews**

- Methods to handle missing data in general (not HEOR specific)
- Existing examples and guidance for addressing missing data in the HEOR literature by type of data source

2. **Evaluation and critical appraisal**

- A comparison of methods in terms of assumptions, complexity, and context for use in the HEOR analysis setting
- Further exploration of specific challenges due to missingness faced when conducting HEOR analyses

Which are the estimand(s) relevant for HEOR?

Longitudinal aspects of covariate missingness

Dealing with multiple (i.e. repeated) measures of an outcome (i.e. what is the best approach to deal with multiple measures of an outcome when aiming to predict the value of that outcome)

Use of auxiliary variables to improve power and reduce bias

Inclusion of interactions in the missing data model (i.e. what is the best approach to account for correlations/interactions between covariates in a repeated measures setting, in particular with treatment)

On-going work in our ISPOR "HEOR stats SIG"

3.Guidance and best practices

- Reporting of estimands, missing data and identifying magnitude of missingness
- Determining/confirming missing at random or missing completely at random (MAR/MCAR) underlying the missing data in a specific study.
- Methods used for addressing missing data, and under what circumstances, in particular Availability and dissemination of relevant and specific software (STATA, R).

4. Practical application/ example

- Possibly using real and simulated data to test and compare methods.

Using RWD to replace missing data for regulatory submissions

RWD to replace fully-missing data in regulatory submissions

- Context: prudent introduction of RWD into FDA/EMA submissions
- Trend on submitting RWD as part of regulatory dossiers = when there is no other option? i.e., data is fully missing?

RWD to replace missing data

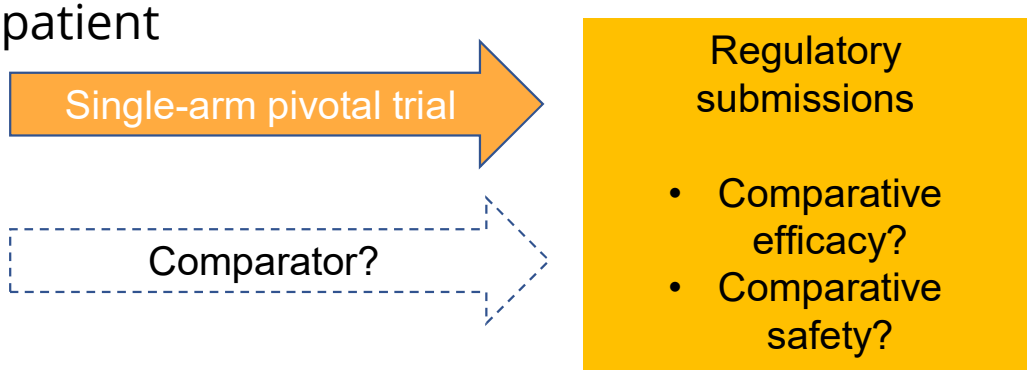
- Case 1: on comparative effectiveness (e.g., in cancer and rare diseases)
- Case 2: on dynamic drug effects on long term outcomes (e.g., Alzheimer's disease)

- **Case 1: RWD to replace missing data on comparative effectiveness**

Case 1: how to palliate a lack of data on comparative efficacy and safety for regulatory approval?

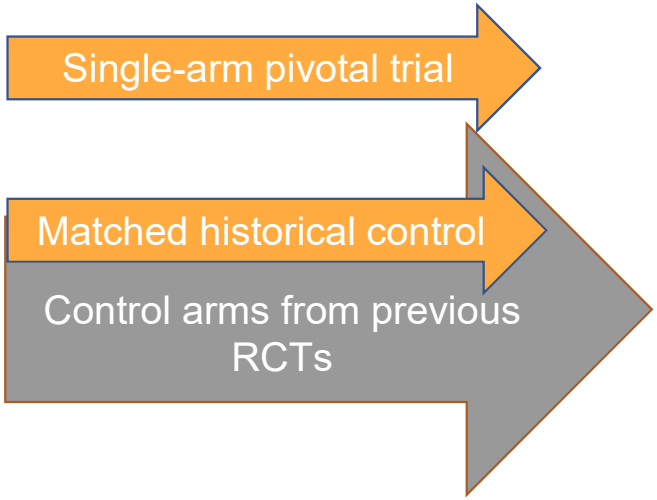
- Case when only single-arm pivotal trials are available
  - Ethical reasons: no standard of care, off-label use of other therapies
  - Operational reasons. too few patients to recruit (very rare indications)

→ Only available information on drug efficacy and safety is an improvement from baseline for each patient



Classical solution: use control arm of previous RCTs as historical control

- *Historical data choice*: to fit the Pocock[1] criteria for suitability (similarity of population, geography, endpoints, standard of care..)
- *Analysis*: population adjustment technique: propensity score, matched-adjusted indirect comparison (MAIC)
- Many examples submitted to FDA/EMA
  - Secukinumb in Crohn´s disease[2] and Ankylosing Spondylitis[3]
  - Lamotrigine XT in epilepsy[4]
  - 44 indications approved by EMA, 60 by FDA[5] in total between 1999-2014:

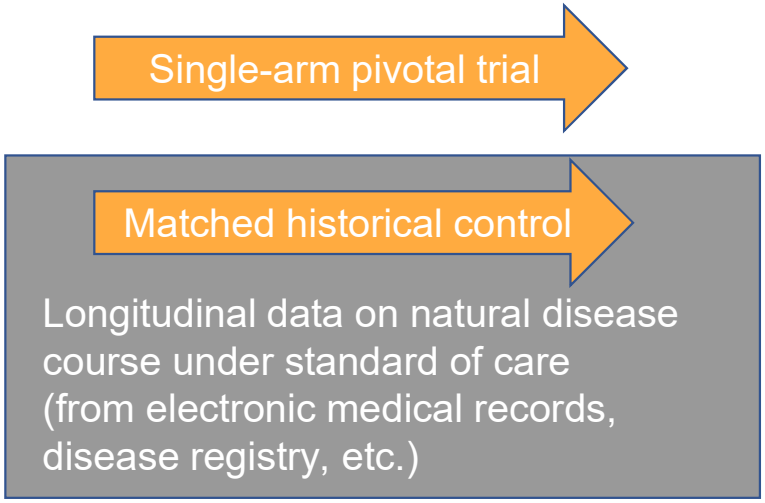


[1]*Pocock 1976. J. Chron. Dis. 29:175-178;* [2]*Hueber et al. Gut. 2012 61(12):1693-700;* [3]*Baeten et al. Lancet 2013; 382;1705-13.*
[4]*French et al. Neurotherapeutics 2012. 9:176-184;* [5]Hatswell et al. BMJ open. 2017.

What to do when no RCT exist to use as historical control?

Typical situation for rare and/or very specific cancer indications

→ Leverage RWD to fill missingness in control data and evaluate comparative efficacy



Recent FDA approvals where RWD was used as historical/external control of the pivotal single-arm study

Drug	Indication	Sponsor Year	Type of RWD submitted as historical control	Endpoint for comparative efficacy
Blincyto[1]	Sub-type of acute lymphoblastic leukemia (ALL)	Amgen 2018	Medical records for 121 patients over 8 years from 14 institutions in the US, Canada, Australia - Prospectively-planned, retrospective study	CR
Brineura[2]	Batten disease (CLN2)	BioMarin 2017	Disease registry of 69 children (42 included): records & patient interviews - Prospectively-planned, mostly retrospective study	CLN2 rating scale (motor, language)
Bavencio[3]	Metastatic Merkel cell carcinoma	EMD Serono 2017	Electronic medical records from 686 patients (14 included) from community and academic centers - Prospectively planned, retrospective study	RECIST
Exondys 51[4]	Duchenne Muscular Distrophy	Sarepta 2016	2 natural disease history cohorts (Belgium & Italy) of about 90 patients each (13 included) - Post-hoc retrospective study	6-min walking test

[1]BLA 125557 S-005 Blincyto (blinatumomab); [2]BLA 761052 Brineura (cerliponase α); [3]BLA 761049 Bavencio (avelumab)
[4]NDA 206488 Exondys 51 (eteplirsen) and Mendell 2016 Ann. Neurol. 79:257-271

Recent FDA approvals where RWD was used as historical/external control of the pivotal single-arm study

On the 4 examples on the previous slide:

- Thorough protocol for population selection (e.g., independent reviewers to adjudicate cases), which led to much reduced population size
- Compared endpoints with low missingness
- Missingness addressed through sensitivity analyses, and in one instance through prospective data collection

EMA: cases where RWD was proposed or used as historical/external control of the pivotal single-arm study

Study from all procedures brought to Scientific Advice Working Party (SAWP) during 12 months (2016-2017)*

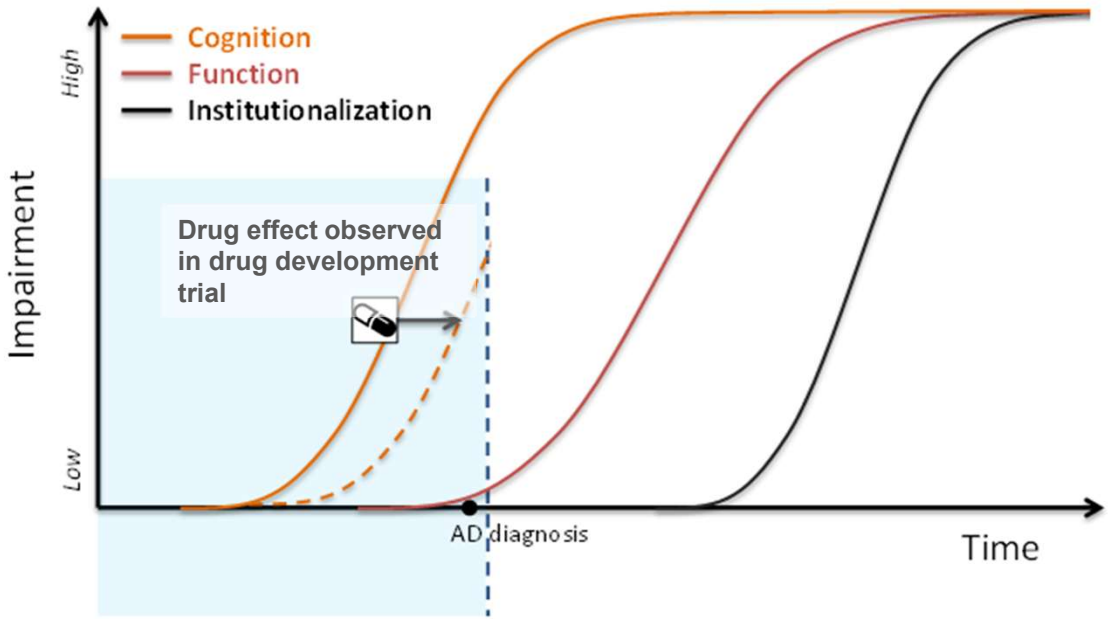
- 10 requests to use RWD as historical control for efficacy
- 6 partially agreed; 3 declined; 1 agreed for setting threshold clinical cut-off value (biomarker)
- Typical answer:“The preferred option is to run a small randomised controlled trial, even if unpowered. External controls are supportive/for contextualisation”

Other examples(*) beyond study year – Agreed for an ultra rare disease – SAWP rejected historical control data in a proposal with a Bayesian approach: “incorporation of external data into the analysis of the trial is not supported” – Company changed to RCT - registry inadequate for consistent and comprehensive control data

*Peter Mol, EMA https://www.ema.europa.eu/documents/presentation/presentation-session-1-use-real-world-data-pre-authorisation-what-can-it-answer-peter-mol_en.pdf
Study by Jane Moseley / Ines Lucas.

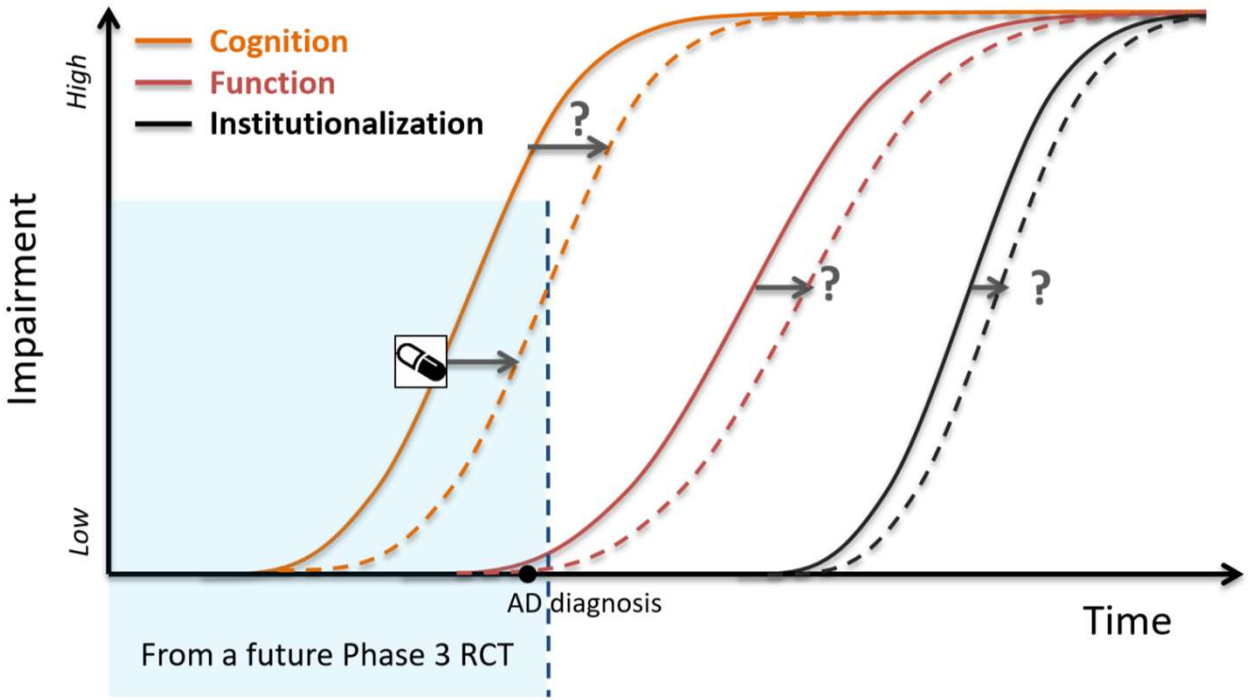
- **Case 2: RWD to replace missing data on long term outcomes**

Case 2: Missing data on dynamic effects of early drugs on long term outcomes.



- New therapeutic concept in **Alzheimer's disease**
  - Act early
  - New compounds target pre-diagnosis, at-risk patients
- Challenge
  - Impact of early drugs can only be tested on cognition (and time to disease onset)
  - Cognition will still be „good“ in the control group, even with long trial duration (5-8 years)

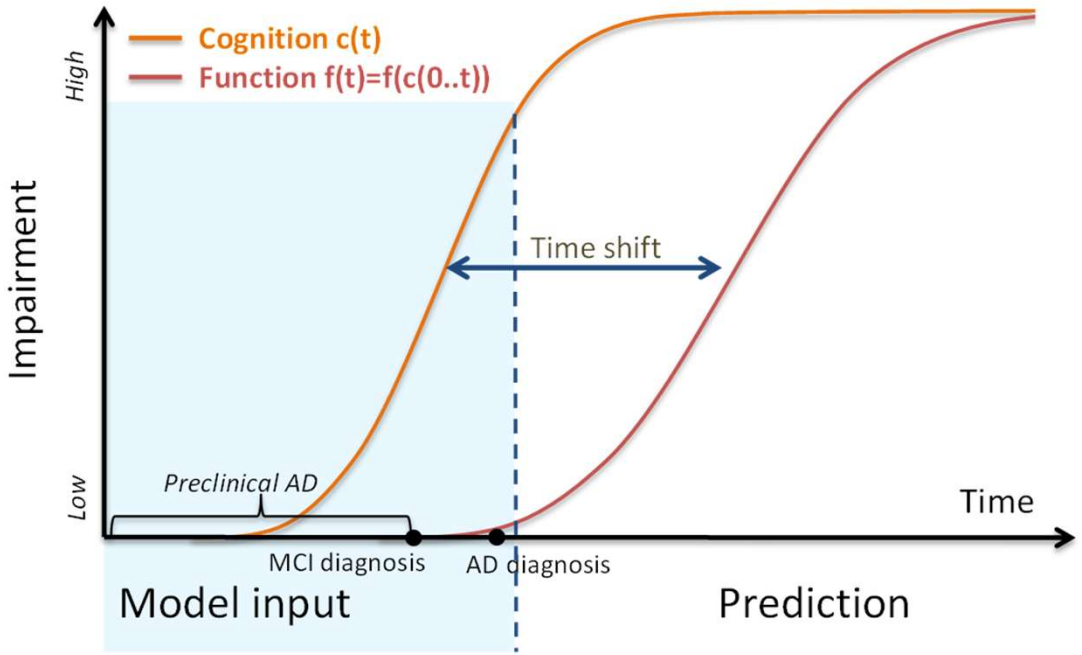
Drug effect on long term Alzheimer´s disease outcomes that are clinically relevant?



- Drug-induced changes on later, more severe cognitive impairment?
- Changes to functional impairment?
- Changes to behavior & time to insitutionalization?

Classical endpoint surrogacy methods (with thresholds) lack power to predict changes

Solution: use several disease registries to develop a series of dynamic models that stitch together outcomes sensitive in different parts of the disease spectrum



Data sources

Disease registries of subjects visiting a memory clinic

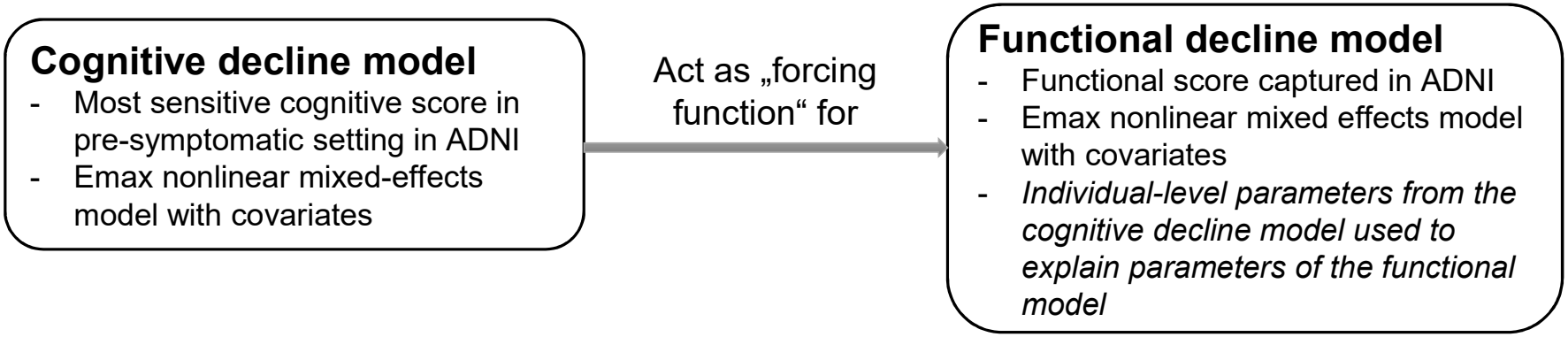
E.g.: ADNI, NACC, Rush, Memento, Goetenburg...

- Solution vetted by a panel of regulatory & HTA experts in February 2018 as part of the European Roadmap consortium.

ROADMAP
Real world Outcomes across the AD spectrum for better care

An example of such model developed on ADNI data*

Link longitudinal decline in cognition to later decline in function



- Use the model-derived relationship between longitudinal decline in cognition to predict decline in function for each individual, treated or not.

*Karcher, Qi, Hummel, Risson, Capkun-Niggli, Savelieva. Dynamic Alzheimer's disease model to predict functional decline from a patient´s longitudinal data on cognitive decline. Manuscript in preparation.

Conclusion

We are still at the beginning of using real-world data (RWD) in regulatory submissions.

Regulators may be more likely to accept RWD when it is used to fill missingness in critical data, not obtainable from RCTs, and is of high quality, low missingness.

Two examples are:

- For comparative efficacy/safety when only single-arm trials are available
- For estimation of clinically-relevant outcomes when only earlier ones can be measured