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COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Regulator's view on RWD in Alzheimer's disease

Peter Mol
CHMP member, NL
Professor of drug regulatory science, UMCG, NL

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Conflicts of interest

I am participating in IMI-EPND, and receive unrestricted research grants from CBG-MEB, HORIZON EUROPE (PRIME-CKD, **More-EUROPA**)

All my views presented today are my own, and may not necessarily reflect the opinion of the CBG-MEB, the EMA or one of its committees or working parties

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RCTs and RWD

- RCTs mainstay of drug efficacy and safety information for regulators & HTA bodies
- Value of RWD increasingly acknowledged
  - transform, accelerate and de-risk decision making
  - improve efficiency in design and conduct of trials
  - increase public health
- Around licensing: contextualize study results, ensure generalisability of results to target population
  - E.g., Yescarta SmPC (Crump et al. 2017 https://doi.org/10.1182/blood-2017-03-769620)
- Post-licensing: appreciate real-world value, long-term B/R

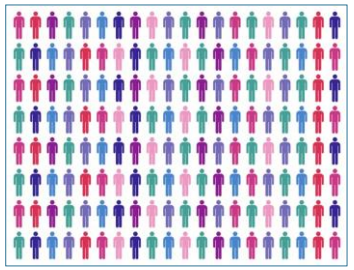
Patients in randomized trials

In- and exclusion criteria!

Exclusion for melanoma trials:

- Brain metastases
- ECOG score ≥2
- Auto-immune disease
- Immunosuppression
- Other malignancies
- Not Recist evaluable
- Etc.

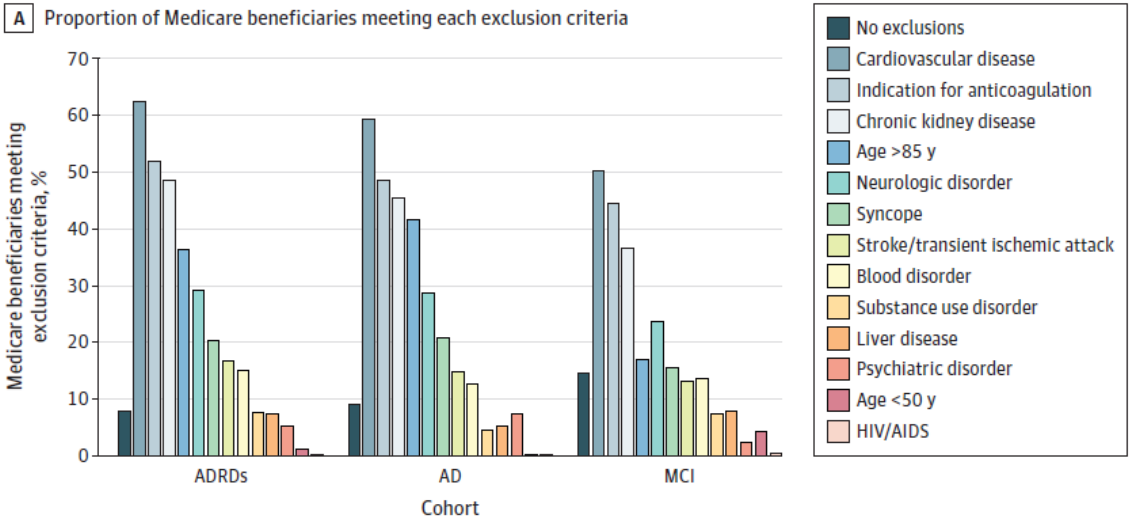
Patients in daily practice



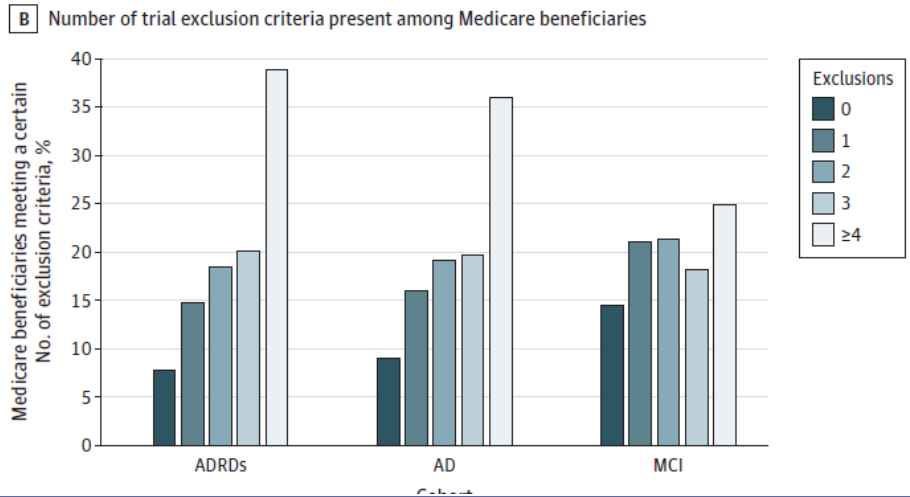
Donia et al. EJC, 2017

Old questions : RCT Representativeness

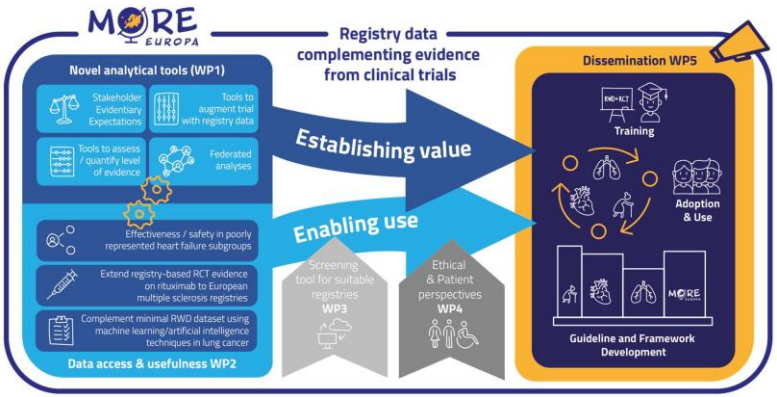
RW population meeting exclusion criteria



Trial exclusion criteria per RW patient



Richness of use of registries- *illustrated.*



Early development

- Biomarker & to support **probability of success** & clinical outcome associations full development decisions.

Full development & decision making

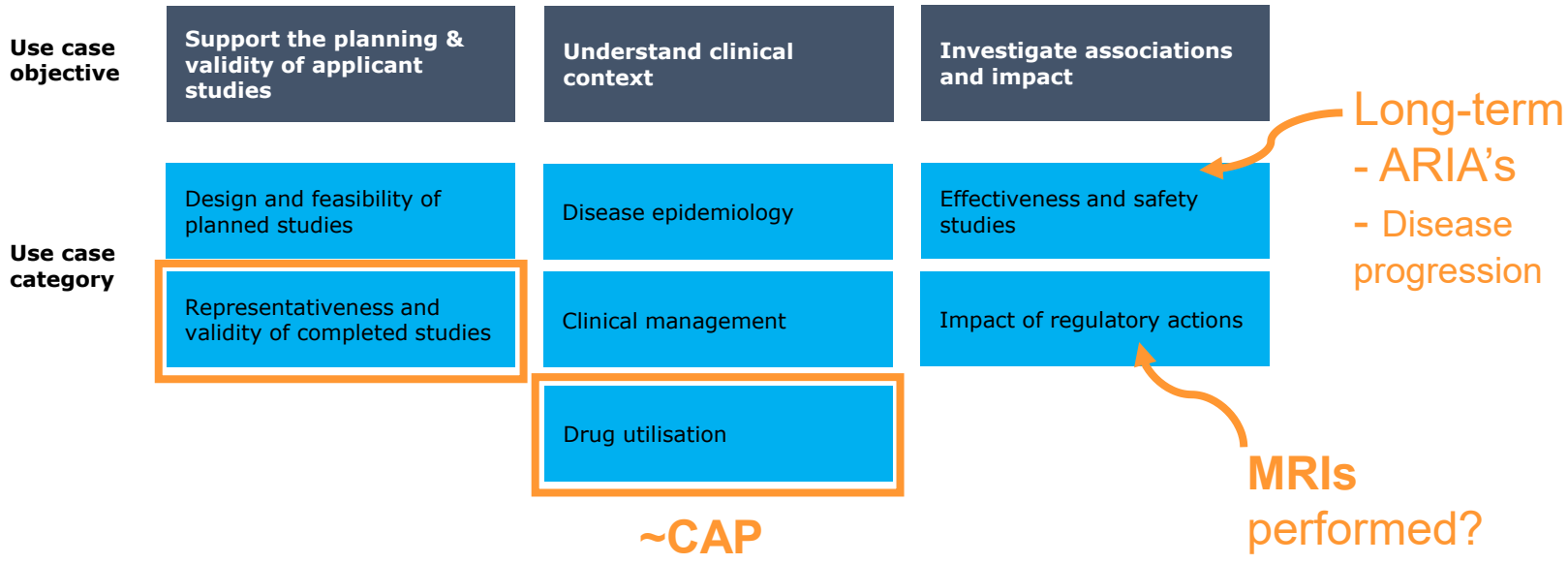
- Contextualisation.
- Direct augmentation of clinical trial data (hybrid).
- **Modeling efficacy / effectiveness in broad population** based on clinical trial data.

Beyond Full development

- **Target trial emulation** for observational studies.
- Registry-based clinical trials.
- Modelling for **HTA support**, including external controls.

Using mutiple registries
Federated inference

Areas of decision-making for which registries can be useful



Throughout the entire drug development life cycle

The system will ensure appropriate and relevant information on the specified data fields (such as amyloid pathology, MCI or mild AD, APOE4 genotype, MRI, history of cerebral haemorrhage, anticoagulant therapy, patient card and PIL, acknowledgment of risks) prior to the first infusion of lecanemab, for all patients.

However: Rare tumour

The ***comparisons*** of XXXXX efficacy endpoints to ***external control data*** were ***not pre-specified*** in the study protocol. They were entirely defined in a SAP addendum, finalised after the data cut-off date of the pivotal single-arm trial. In this situation, it cannot be excluded that several aspects of planned analyses (historical data sets and selection criteria, endpoint selection and definition, propensity score weighting/matching methods and associated covariates, planned statistical models and adjustment…) ***could be at least partially data-driven***. The ***lack of pre-specification is a clear limitation of these external control comparisons***. Moreover, it is highly likely that relevant prognostic factors (known or unknown) were not accounted for and may have biased the estimates of external control comparisons.

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ADNI cohort

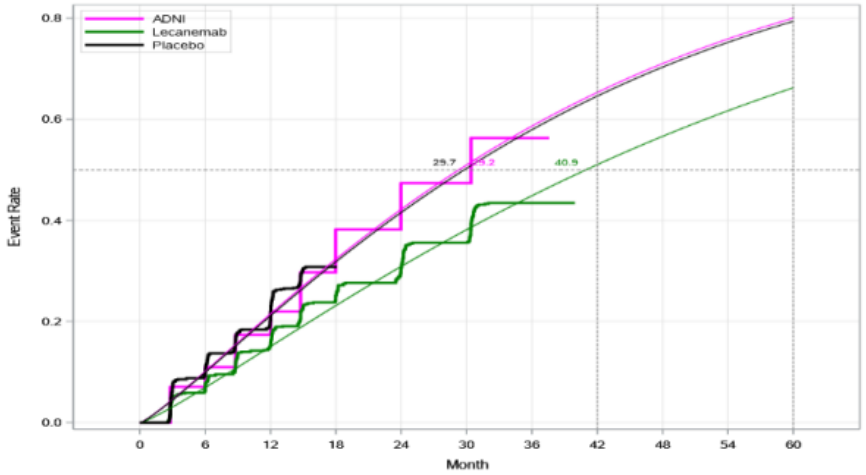

Figure 80. Event rate of time to worsening to next stage under Weibull distribution

Source: Data on file.

Table 104. Proportion of patients converting to the next stage of disease

Month	Lecanemab 10 mg/kg Biweekly	Placebo	ADNI
42	51.1%	**65.4%**	**64.7%**
60	**66.3%**	80.1%	79.4%

Source: Data on file.

*"This analysis illustrates how the treatment effect observed with LEC10-BW at 18 months translates to a 5-year period of treatment and follow-up, demonstrating increasing benefit of treatment over time and a **clinically relevant delay** in disease progression with preservation of cognition and function relative to PBO."*

ADNI cohort – external cohorts – many caveats

*"There are **uncertainties** on the long-term efficacy, since the placebo-controlled data are limited to 18 months with further data from the OLE period up to 36 months. A **formal statistical comparison** between LEC10-BW and the Alzheimer's Disease Neuroimaging Initiative (ADNI) natural history cohort at 36 months could not be performed. However, the trajectories of the PBO in study 301 Core and ADNI natural history cohort for the first 18-month period were almost overlapping. The presented information beyond 18 months are based on **extrapolation** using **unverifiable models** and **assumptions**. Moreover, **ADAS-COG** and **ADCS-MCI-ADL** are **not available** for the ADNI cohort. **Missing data** in the ADNI cohort is **considerable** (**60%** in the restricted population). Thus, treatment effect estimates at 36 months may be **biased**."*

https://www.ema.europa.eu/en/documents/assessment-report/leqembi-epar-public-assessment-report_en.pdf

Conclusion

Registry-based RWD can complement trial data

- describe natural history
- clinical context (all AD patients targeted)
- long-term **safety** & efficacy

Need for:

- Adverse events of special interest monitoring (e.g., ARIAs, ICH, …)
- Clinical outcomes (CDR-SB, disease stageing, …)
- Risk factors (APOE status, …)

Studies in registries to

- pre-planned, early interaction with EMA
- registy study registered in EMA RWD catalogue
- state-of-the-art design, e.g., use TTE framework, HARPER protocol
- registries in EMA RWD catalogue, Qualification Procedure

Note: Alzheimer's Disease is prevalent and full clinical development program is expected with at least one long-term pivotal RCT

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Questions?

p.mol@cbg-meb.nl / p.g.m.mol@umcg.nl

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