Real World Data, Real World Evidence, Big Data

A few perspectives

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The views expressed are personal views and not necessarily the views of CBG-MEB or EMA.

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Potential

- Era of personalized treatment.
- Abundance of data.
- Better information on diseases and performance of treatments.
- Reducing research waste.
- Faster access to new treatments in difficult situations.

Concerns

- Bias, bias as we know from the past & present.
- Level of evidence at crucial decision points.
- Increased difficulty in assessing the evidence.
- Increasing research waste.
- Institutional challenges on data and data sharing.

Overview

- Introduction of terminology
- Some relevant (regulatory / research) initiatives
- Regulatory decision making context & Methodological challenges
- Wishes for the future

- What I will not talk about as much……..

RWD, RWE

What Is Real-World Data? A Review of Definitions Based on Literature and Stakeholder Interviews

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38 definitions evaluated: Most non-interventional.

"Data used for decision making that are *not collected in conventional RCTs*."

" For the purposes of this guidance, "RWD" will refer to data obtained by *any non-interventional* methodology that describe *what is happening in normal clinical practice*."

…….data regarding the *effects of health interventions* (e.g., benefit, risk, and resource use) that are *not collected in the context of conventional RCTs*. ……..collected both *prospectively and retrospectively* from observations of routine clinical practice. Data collected include, but are not limited to, clinical and economic outcomes, patient-reported outcomes, and health-related quality of life. RWD can be obtained from many sources including patient registries, electronic medical records, and observational studies.

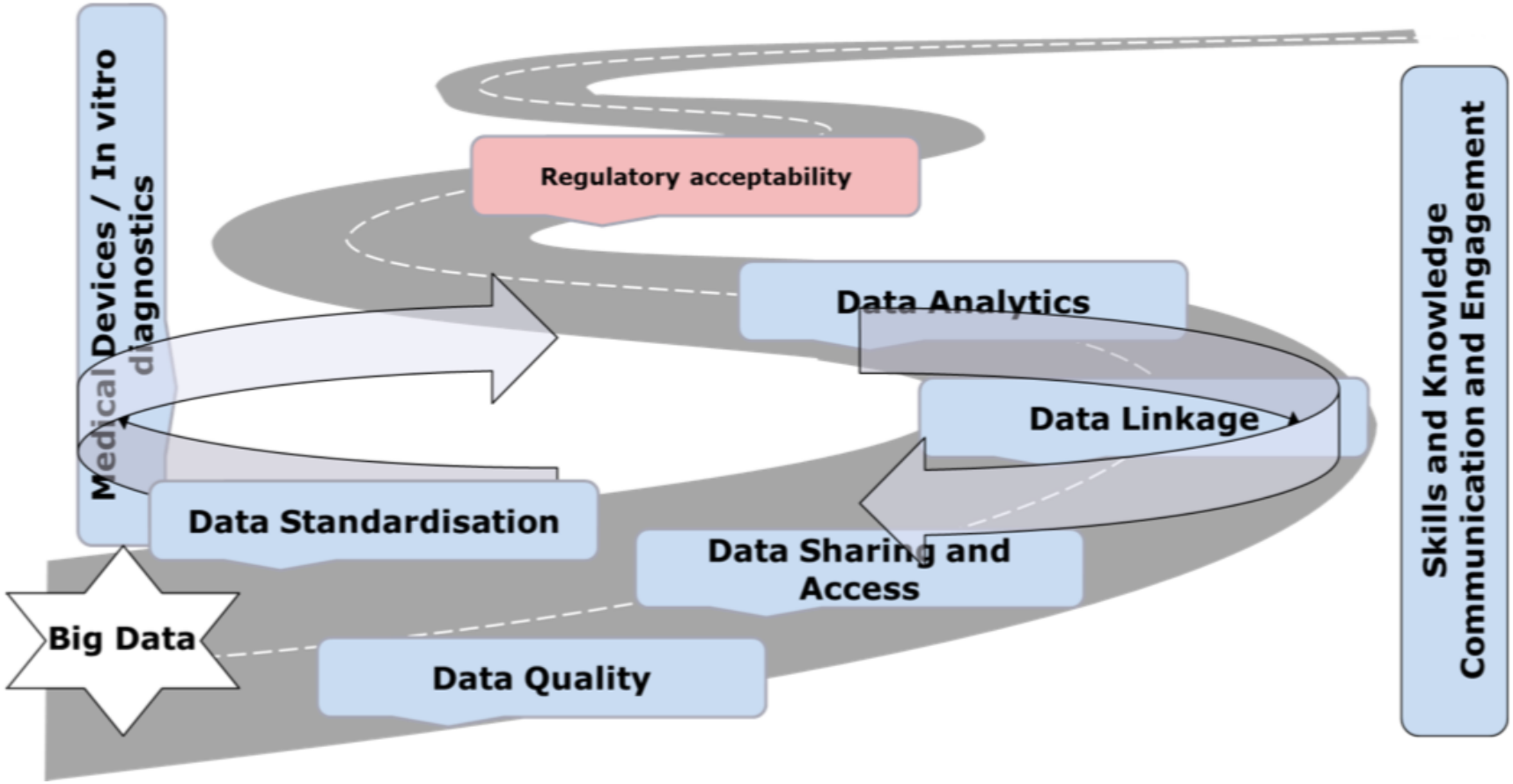
RWD

		Data collection control	
		Experimenter	**External**
Intervention	**Experimenter**	RCT, Single Arm Trials, Trials within cohort, cluster RCT	Pragmatic trials
	External	Patient Registries Cohort studies	e-HR Claims dB

Big Data

'extremely large datasets which may be complex, multi-dimensional, unstructured and heterogeneous, which are accumulating rapidly and which may be analysed computationally to reveal patterns, trends, and associations. In general big data sets require advanced or specialised methods to provide an answer within reliable constraints'.

Big Data Taskforce



Initiatives

5 November 2018

EMA/763513/2018

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

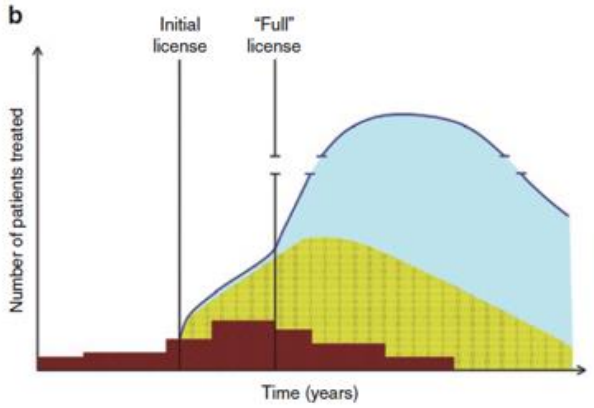
Discussion paper:

Use of patient disease registries for regulatory purposes – methodological and operational considerations

The Cross-Committee Task Force on Patient Registries

Adaptive pathway thinking

Complex trials



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Regulatory decision making context

Perspective of treating physician and her patient

Evidence based decision for the (next) patient to treat, selecting from the available treatment options.

Perspective of market authorisation of a new drug

Evidence based decision of allowing physicians to add a new drug to their treatment options.

Enable subsequent decision making (reimbursement)

Provide information to guide the prescribing physician.

Provide information to guide the patient.

Regulatory decision making context

Intended and unintended effects of therapy*

Intended effects of therapy

- RCT
- Prospective follow-up
- Retrospective follow-up
- Case-control
- Anecdotal

Discovery and explanation

- Anecdotal
- Case-control
- Retrospective follow-up
- Prospective follow-up
- RCT

*(Unknown) Adverse effects are “unintended”, usually not associated with indication: no “confounding by indication“-> observational evidence can be strong.

J.P. Vandenbroucke (2008). Observational Research, Randomised Trials, and Two Views of Medical Science, PLoS Medicine

Regulatory decision making context

Main drivers for considering RWD *for effectiveness.*

- **Generalizability of pre-licensing RCTs (“gap”)**
- Efforts to increase efficiency for clinical development.
- Perceived obstacles to RCTs in challenging settings.
- Improve continuum of evidence generation across the life cycle.

Generalisation (1)

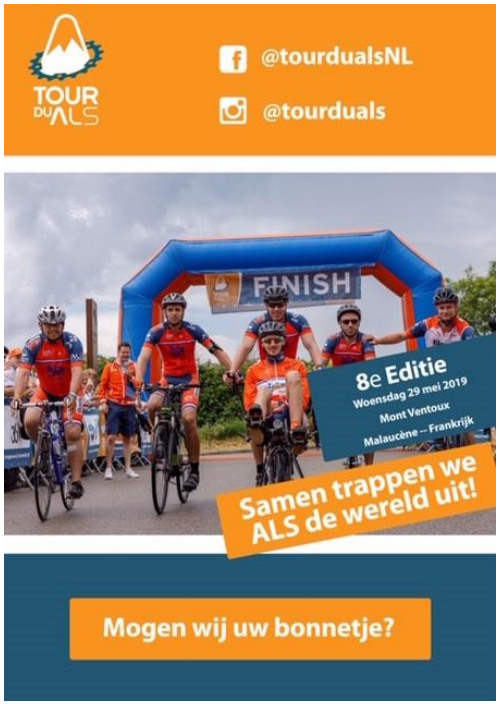
Randomisation is not the root cause of the generalizability problem.

Going “ beyond” randomisation will not be the solution.

Randomisation is not the problem

1. Systematic review of RCTs in ALS (2000 - 2017)
   - Placebo-controlled
   - Clinical endpoint
   - Single agent

2. Incidence-cohort UMC Utrecht (N = 2904)
   - 2006 - 2016
   - Survival & functional (ALSFRS-R) data



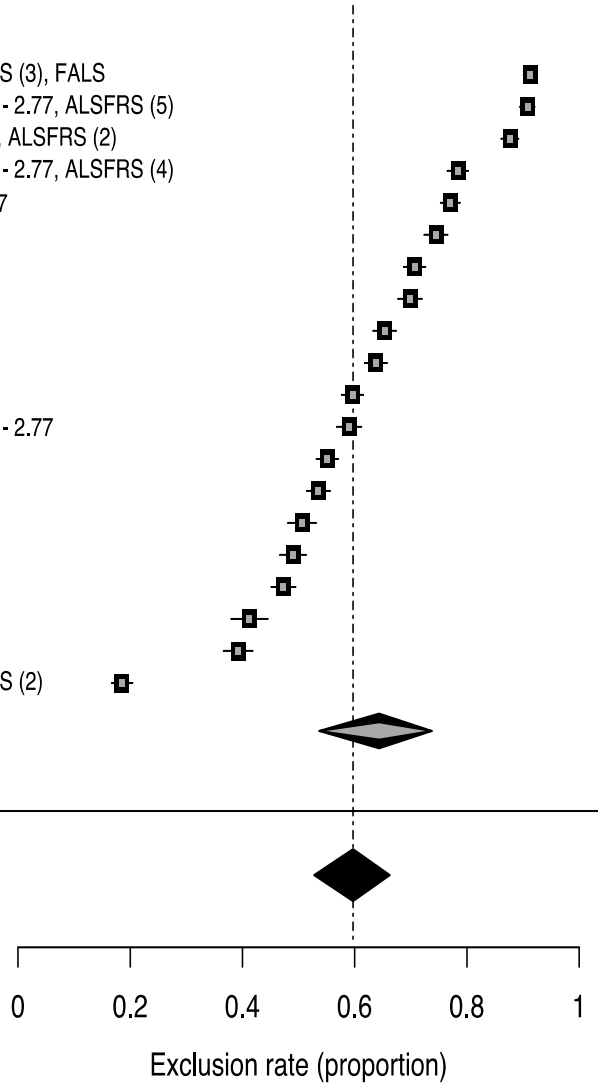
Randomisation is not the problem

Period: 2010 - 2017

Acetyl-L-carnitine	2013	II	82	Def, Prob (LS)	≥ 80%	6 - 24	40 - 70	ALSFRS (3), FALS
Edaravone	2017	III	137	Def, Prob	≥ 80%	0 - 24	20 - 75	LI 0.36 - 2.77, ALSFRS (5)
Memantine	2010	II	63	Def, Prob (LS)	≥ 60%	0 - 36	18 - 75	LI >1.0, ALSFRS (2)
Edaravone	2014	II	205	Def, Prob (LS)	≥ 70%	0 - 36	20 - 75	LI 0.36 - 2.77, ALSFRS (4)
TUDCA	2016	II	29	Def, Prob	≥ 75%	0 - 18	18 - 75	LI <2.77
Pioglitazone	2012	II	218	All	50%-95%	6 - 36	≥ 18	
Erythropoietin	2015	III	200	Def, Prob (LS)	≥ 70%	0 - 18	18 - 75	FALS
Olesoxime	2014	III	512	Def, Prob (LS)	≥ 70%	6 - 36	18 - 80	
Lithium	2012	II	133	Def, Prob (LS)	≥ 70%	6 - 36	18 - 85	-
Flecainide	2015	II	54	Def, Prob	≥ 50%	0 - 60	18 - 75	
NP001	2015	II	136	Def, Prob	≥ 70%	0 - 36	21 - 80	-
Bromocriptine	2016	II	36	All	≥ 70%	0 - 36	20 - 75	LI 0.36 - 2.77
Talampanel	2010	II	59	Def, Prob	≥ 60%	0 - 24	18 - 85	-
G-CSF	2010	II	39	Def, Prob	≥ 50%	0 - 72	18 - 85	FALS
Ozanezumab	2017	II	303	All	≥ 65%	0 - 30	18 - 80	
Dexpramipexole	2013	III	942	All	≥ 65%	0 - 24	18 - 80	
Lithium	2013	III	214	All	≥ 60%	6 - 36	≥ 18	
Lithium	2010	II	84	All	≥ 60%	0 - 36	≥ 18	-
Ceftriaxone	2014	III	513	All	≥ 60%	0 - 36	≥ 18	-
Tirasemtiv	2016	II	388	All	≥ 50%	-	≥ 18	ALSFRS (2)

Exclusion rate 2010 - 2017: 0.64 (0.54-0.74)

Pooled exclusion rate: 0.60 (0.53-0.66)



Improvements based on the cohort

- Validated prediction model to predict speed of progression.
- On average 60% excluded, but slow & fast progressors still in trials.
- Inclusion based on risk score:
  - Larger - more diverse - inclusion
  - Smaller sample size
- Design of multinational master protocols

van Eijk RPA et al. Refining eligibility criteria for ALS clinical trials. *Neurology* 2019

Generalisation (2)

Two key questions **must** be addressed for benefit (in benefit/risk):

- Can causality ("direct drug effect") be concluded? Does the drug cause the (positive) effect in the target population?
- What is the estimated clinical benefit (compared to best standard of care) in the target population?

These are separate steps in inference.

The calibration of treatment effects from clinical trials to target populations
Constantine Frangakis
Clin Trials 2009 6: 136
DOI: 10.1177/1740774509103868

RWD & Experimental Design

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RWD & Experimental Design

Type 1 Error for a clinical trial

- Imaginary quantity.
- Associated with “decision procedure”, based on a specific statistical model.
- **Which we (have to) agree to be plausible before the data are collected.**

Control

- Has brought us many good things for confirmatory trials.
  - A rational approach to sample size choice
  - Careful pre-planning of the whole trial (good experimental design)
  - No “free lunches”
  - Clear threshold for proceeding to secondary assessment
  - At least some control of regulatory error rate
  - Level playing field
- **In settings with sufficient prior data and knowledge.**

RWD & Experimental Design

Cornerstones of good experimental design

Control

- The well known potential for bias (however used)
- If used as external control: Can we consider it one experiment?

Pre-specification: What to value more:

- An analysis that is pre-specified, but (obviously) wrong given the data?
- An analysis that was not fully pre-specified, but supported by the data?
- And how to assess the level evidence from the latter?

Replication

- Independent replication in different RWD sources.

Wishes for the future…..

Potential

- Era of personalized treatment.
- Abundance of data.
- Better information on diseases and performance of treatments.
- Reducing research waste.
- Faster access to new treatments in difficult situations.

To address

- **Reinforce randomization as essential to inference.**
- Trial design for generalisability.
- Data quality and institutional arrangements for data sharing.
- New approach to level of evidence at crucial decision points.
- Adapt regulatory assessment process in case of RWD.