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Use of real world data pre-authorisation – what can it answer?

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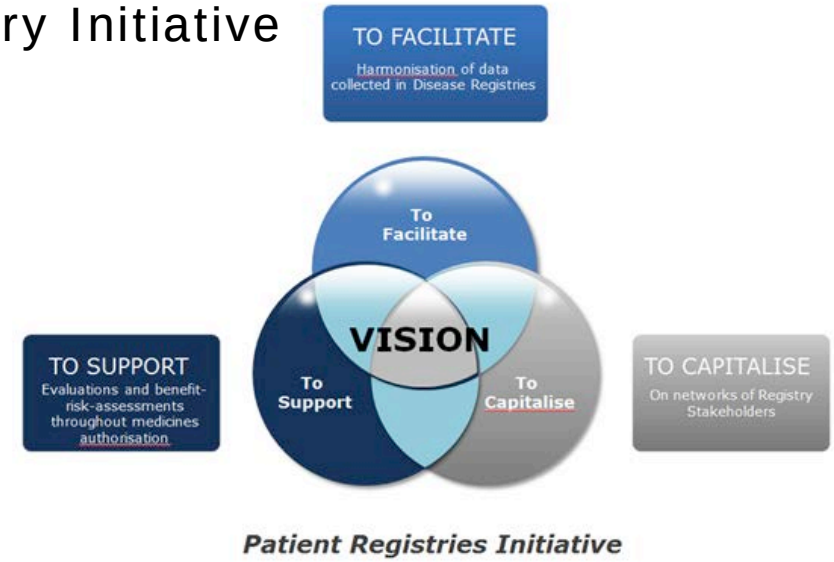
Disclaimer

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

Use of RWD in Scientific Advice Procedures

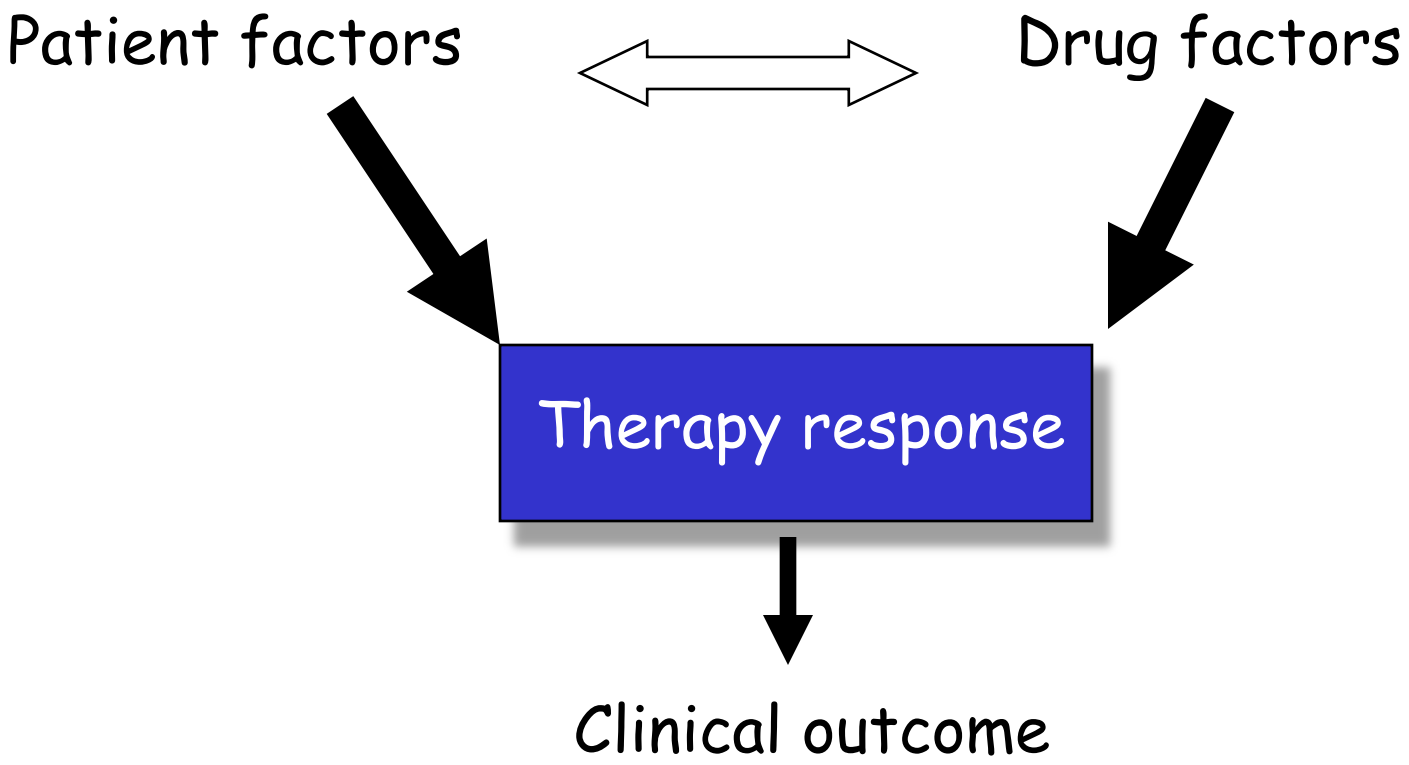
- SAWP
  - Meeting monthly to discuss drug development programs
  - 600+ advices annually
  - Questions on quality (~20%), pre-clinical (~25%) and clinical (~55%) development
- Patient Registry Initiative



Real World Evidence

- RWE is defined as the evidence derived from the analysis and/or synthesis of real world data (RWD) (imi get real).
  - RWD is an umbrella term for data regarding the effects of health interventions that are not collected in the context of ***highly-controlled RCTs***. Instead, RWD
  - can either be primary research data collected in a manner which reflects how interventions would be used in routine clinical practice
  - or secondary research data derived from routinely collected data

Determinants of drug response: a balanced view



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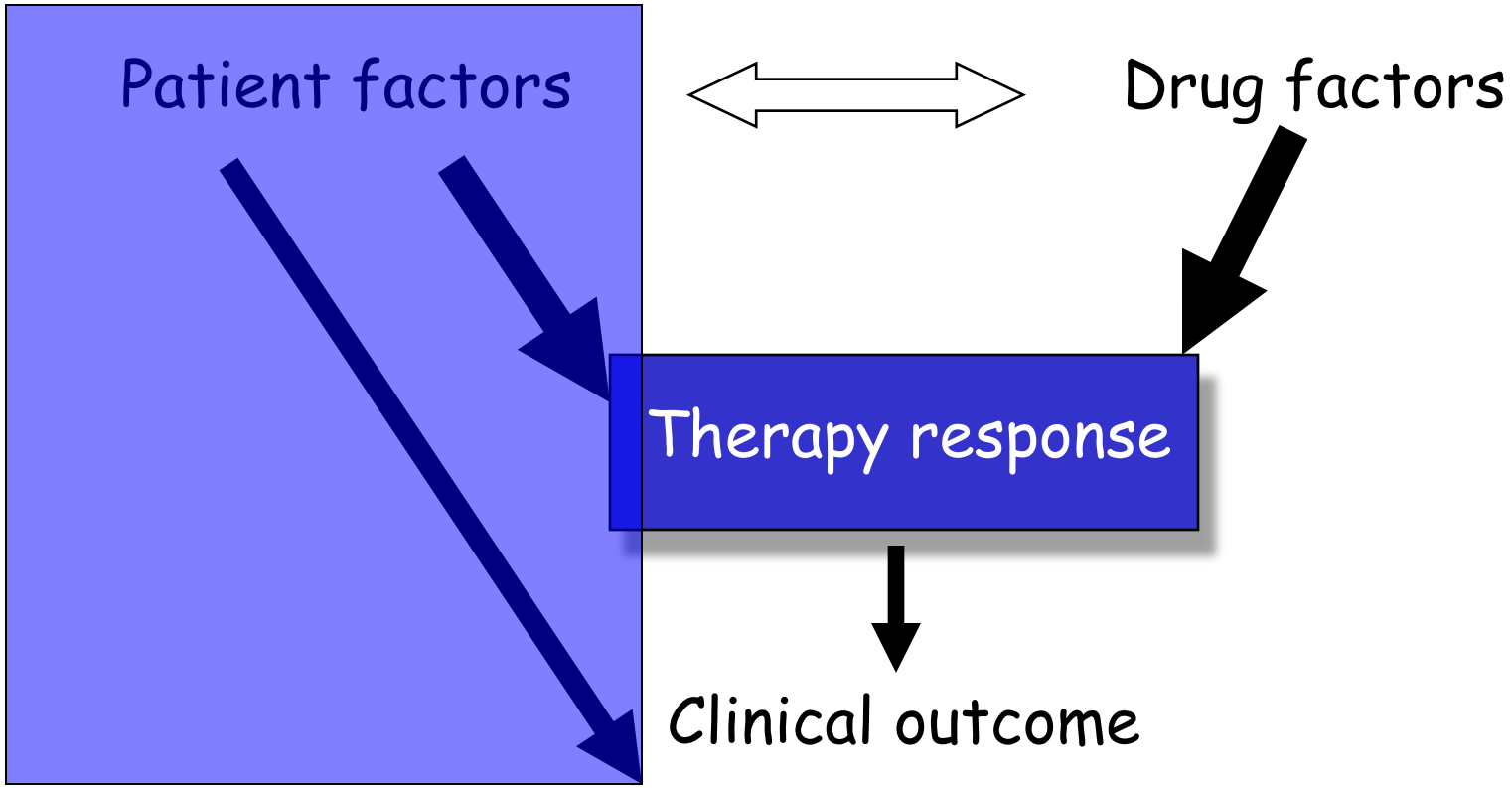
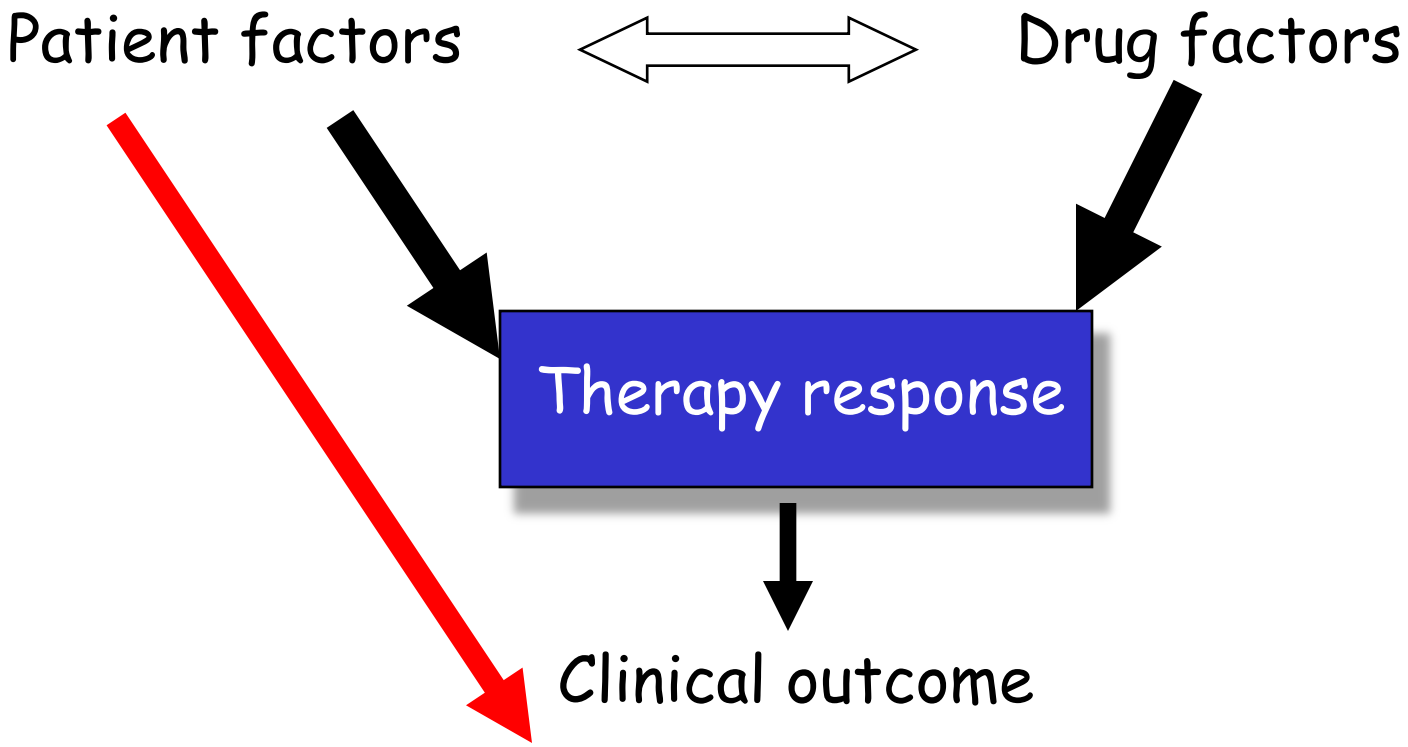


Comparative clinical trial: Randomization to ELIMINATE patient factors

Determinants of drug response: a balanced view



Comparative clinical trial: Randomization to ELIMINATE patient factors

Review of 12 months SA procedures – Jane Moseley / Ines Lucas *(July '16- June '17)*

To identify the objective for which RWD data are proposed and the study designs employed

To identify which sources of RWE drug manufacturers are using.

To identify timing of request advice pre MAA or post MAA, to RWE, type of marketing authorisation they are planning to apply for (conditional, under exceptional circumstances, accelerated assessment, full marketing authorisation

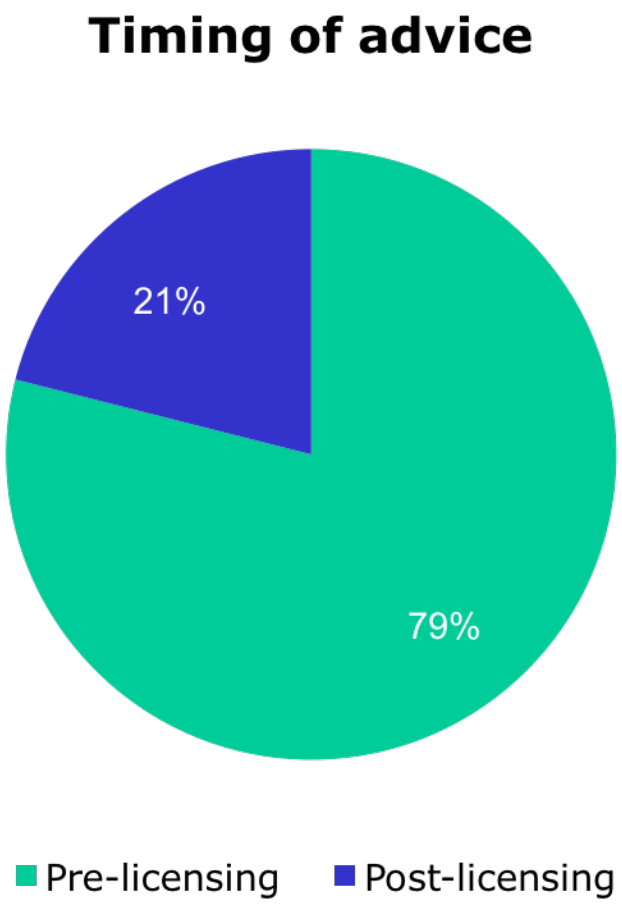
To analyse the content of the answers provided by the CHMP (qualitative analysis) and if CHMP agreed with the manufacturer's proposal.

RWD
It is a bit diverse: 30 keywords/variations

- Case-control
- Case-report
- Cohort study
- Cross-sectional
- Drug utilisation/ utilization
- Electronic health record
- External control
- Historical control
- Historical data
- Historically controlled
- Large simple trial
- Natural history
- Non randomised / randomized
- Only "registry"
- PAES
- PASS
- Pass study
- Post-approval effectiveness study
- Post-approval efficacy study
- Post-approval safety study
- Post-authorisation/authorization effectiveness study/studies
- Post-authorisation/authorization efficacy study/studies
- Post-authorisation /authorization safety study/studies
- Pragmatic study/studies
- Real world
- Registry/ registries
- RWE
- Simple trial
- Uncontrolled
- Uncontrolled trial

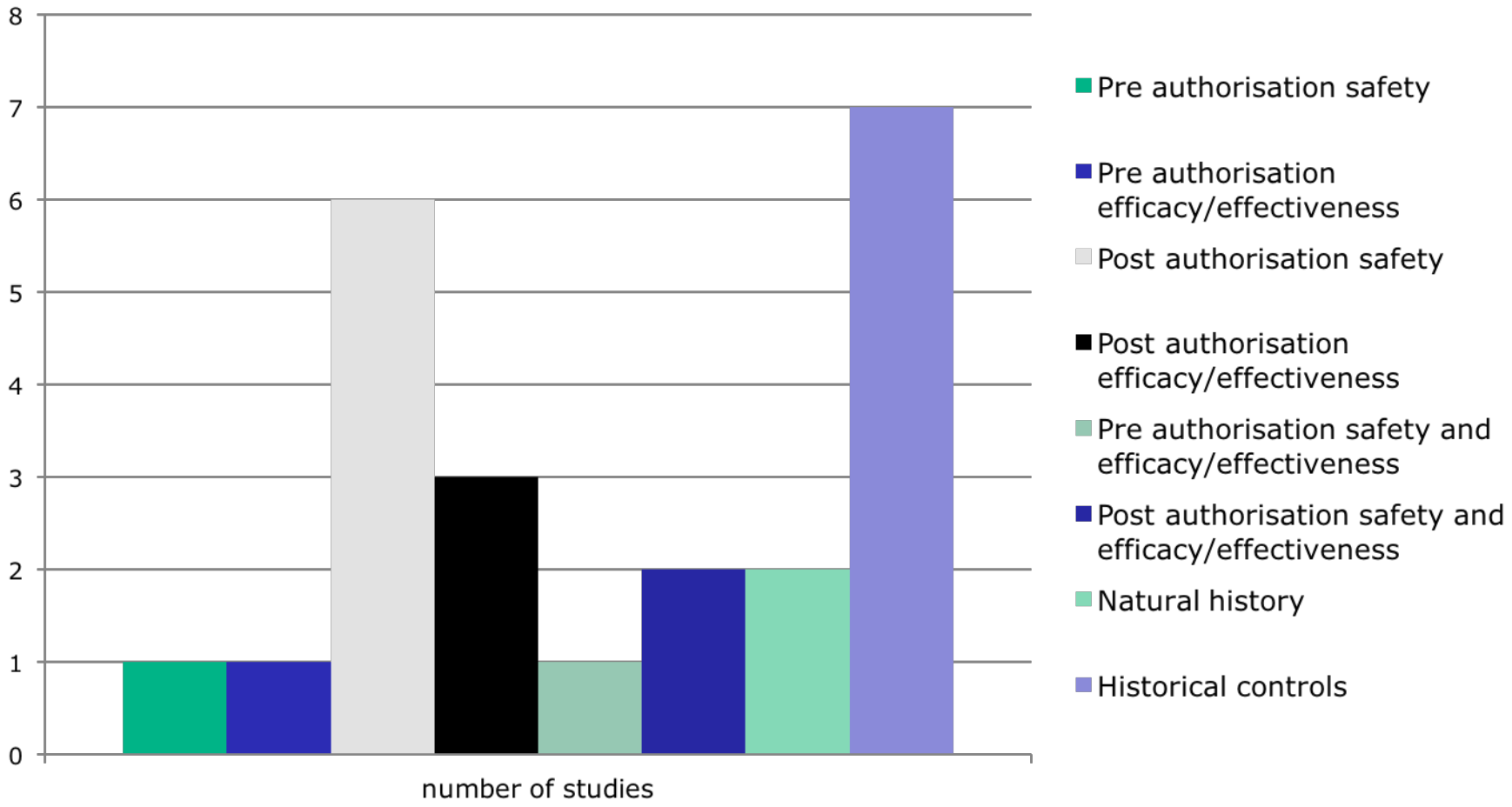
*FALs issued between 07/2016 - 06/2017

Results

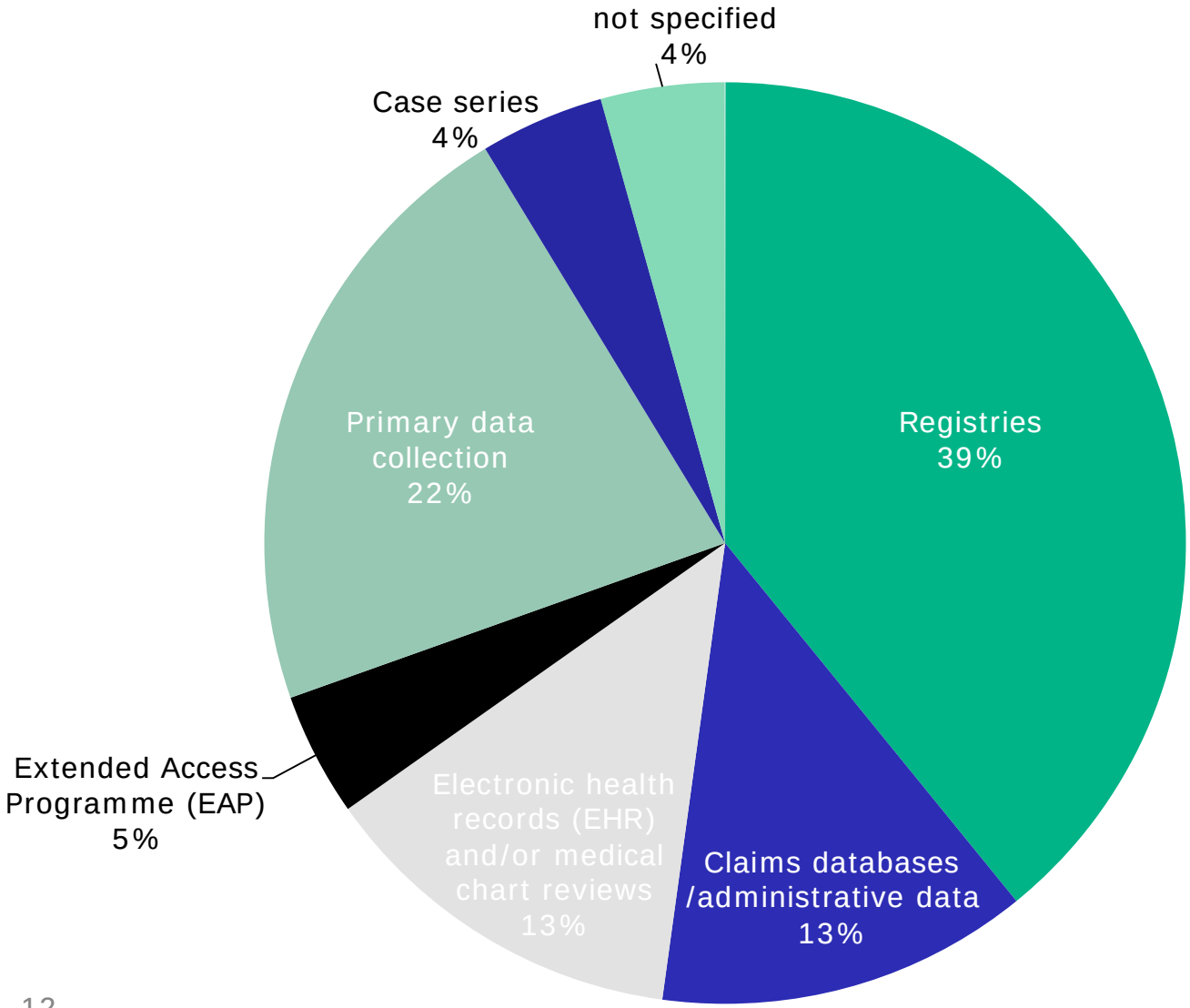


- 19 procedures fulfilled the search criteria
- 23 questions related to the use of RWE were identified
- Timing of requests:
  - Pre MAA requests (15/19) vs
  - Post MAA (4/19)

Purpose of the studies



Data sources



Pre-licensing evidence
Historical controls

- **Historical controls / efficacy**
- 10 requests (2 orphan) 6 partial agreed, 3 no, 1 agreed for setting threshold *clinical cut-off value (biomarker)*
  - Typical answer "option of a small randomised controlled trial, even if unpowered, could be preferred. External controls could be 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

Post-licensing evidence efficacy with RWE

- Efficacy ± safety : 5 cases; 3 partially agreed, 2 agreed
- Studies (1 pragmatic trial breast cancer, 1 RCT but also with external controls, 3 cohorts)
- Data sources (primary data collection, registries x2, claims database, expanded access program)
- Other notable examples A *pragmatic* trial
- 10 year report CMA, and sample of PASS 2/3 of imposed studies are ongoing; Mix of randomised and nonrandomised trials
- **Further issues** (concerns on eligibility, outcome, SUSAR reporting, safety for participants, extrapolation to EU) Other study designs? Get Real?

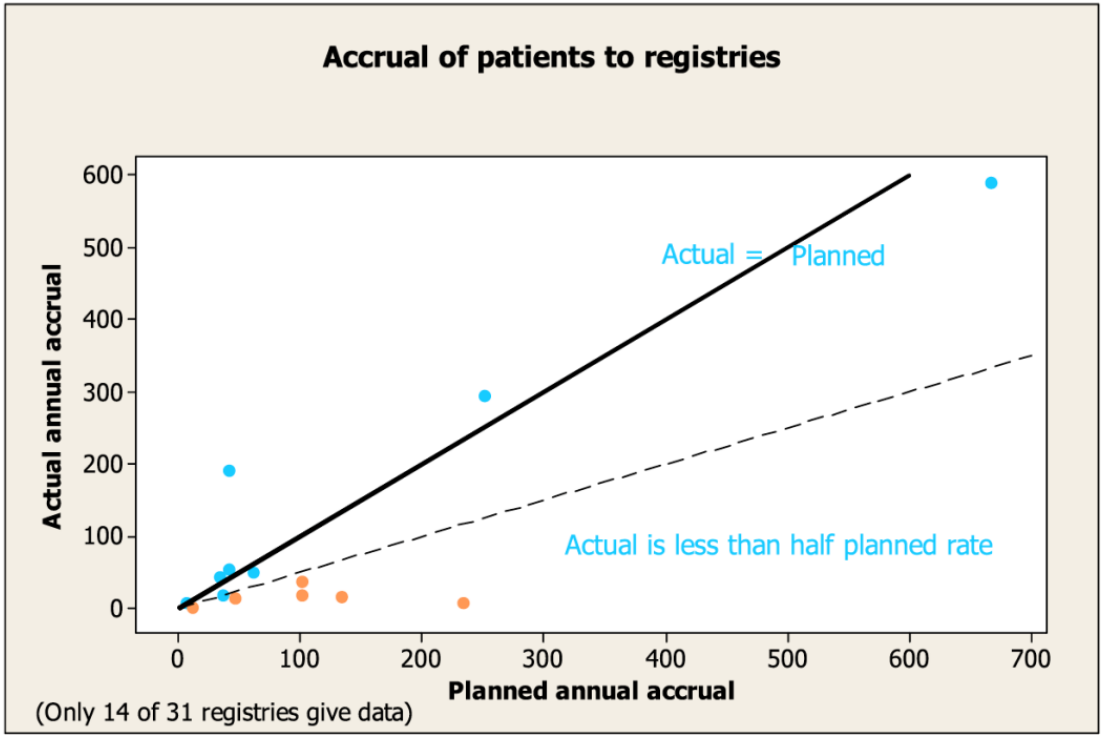
Post authorisation evidence - safety

- Safety - 6 cases; 4 disagreements, 2 agreed* (1 change to OLE)
- 4 pre MAA Discussions, 3 registries, 2 EHR
- Proposals tend to be weak; Answers tend to be shorter
- **Issues on safety studies discussed at SAWP**
  - Encourage proactive PreMAA discussions
  - Need detailed proposals if possible to give advice pre MAA
  - Pre MAA:
    Can we progress? *"Drug Registry will be evaluated when the dossier is submitted for marketing approval. If there are uncertainties regarding safety or efficacy, which can be addressed by a post-approval registry study, the Applicant could be requested to perform such a study"*
  - Other notable examples CAR-T, PASS protocols

Registry studies supporting new drug applications

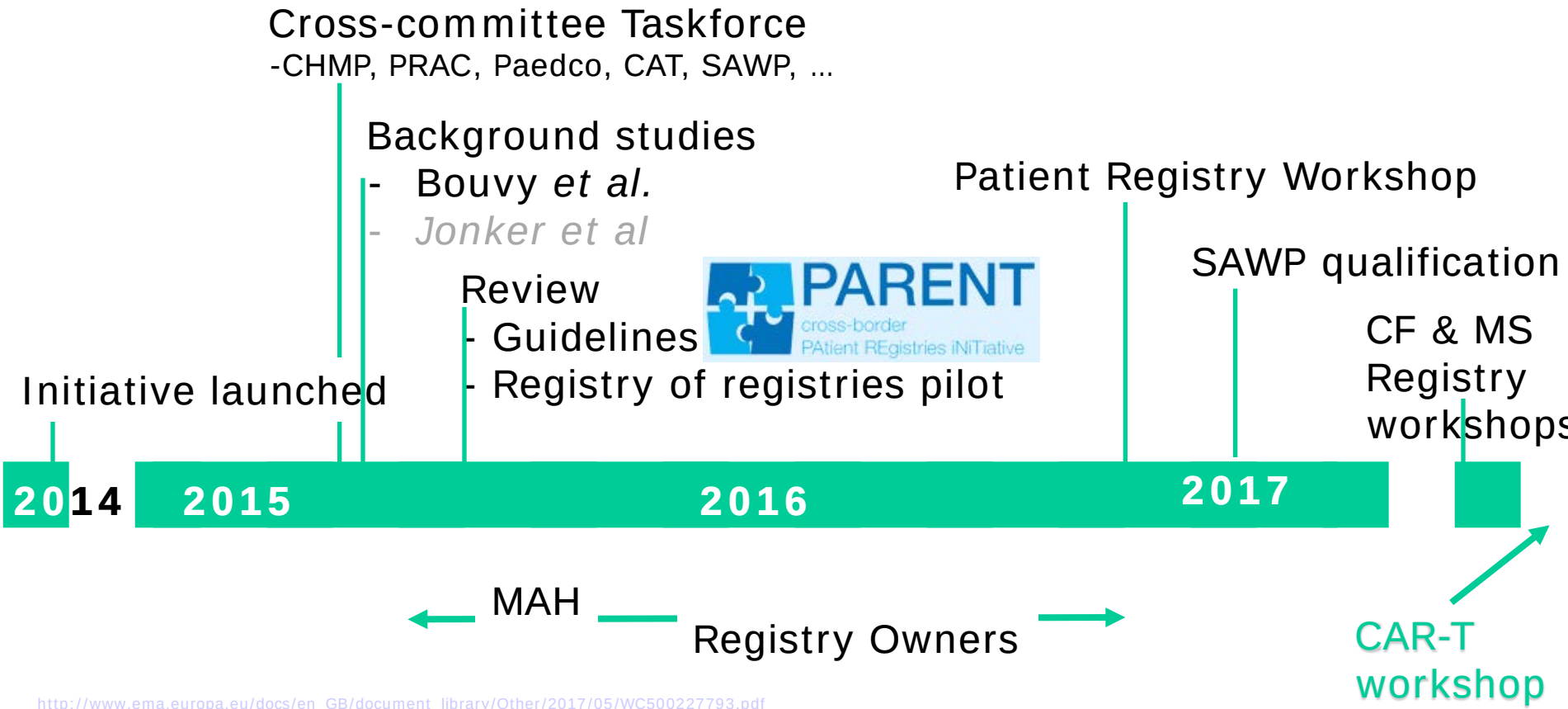
- Bouvy *et al.*
  - 335 CAP (‘05-’13); 31 (9%) imposed registries
- Obective
  - 22 (71%) safety
  - 3 (10%) effectiveness/efficacy
  - 3 (10%) pregnancy
  - 3 (10%) other
- Type of registries
  - 11 (35%) disease
  - 20 (65%) product
  - 24 (77%) new
- Jonker *et al.*
  - *43 (37%) of 116 CAPs one or more registry (‘07-’11)*
- *73 registries*
  - *9 (12%) imposed*
- *Objective*
  - *38 (54%) safety*
  - *5 (7%) effectiveness/efficacy/safety*
  - *26 (37%) pregnancy*

Registries – caveat!
Enrolment was poor



Bouvy, J PDS 2017

Patient Registry Initiative



http://www.ema.europa.eu/docs/en_GB/document_library/Other/2017/05/WC500227793.pdf

Recommendations Patient Registry Workshop

28 October 2016

- Explore mechanisms for regulators and marketing authorisation applicants to ***systematically*** consider the ***need for registries*** and interact with registry holders
- ***Share*** information on patient registries in specific disease areas – 'Registry of Registries' [PARENT JA & ENCEPP]
- ***Governance principles*** and ***standards*** for stakeholder interactions; EMA guideline!?
- **Core data** elements and ***quality standards*** acceptable for *regulatory decision-making*
- Registry holders' needs for ***methodological*** and ***technical*** guidance
- ***Patient-reported outcomes*** in registries!?
- Explore measures to improve the ***sustainability*** of registries

Conclusion

- Limited number of advices concern RWD
  - 19 (4%) of 646 procedures
- Majority of studies with RWD in context of safety studies

– But, do not always deliver
– Patient Registry Initiative

- Experience with RWD pre approval limited

– Benefit risk- across product lifecycle
– Conditional Approval
– Historical Control
– Natural History
– Biomarker validation / End point development

Conclusion II

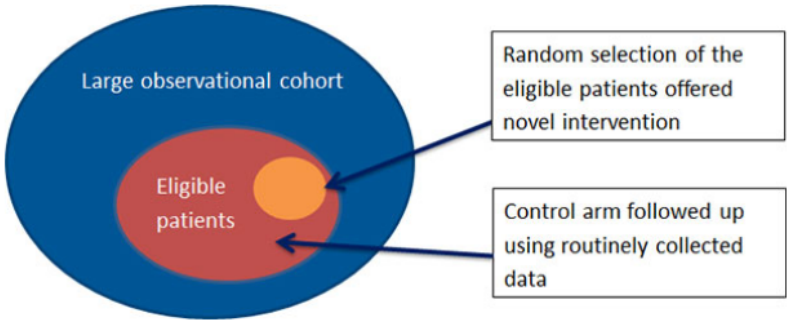
- Main issues
  - Lack of randomisation & contemporaneous control
  - Data content <> core data set -> but, often missing are non-routine lab, PD parameters and ADR (MedDRA)
  - Data quality - verification
- Yet, innovative RWE approaches of value
  - Rare conditions, to *identify prognostic markers and endpoints* suitable for phase III -> sample size & duration of f-up!
  - Rare conditions for natural history controls for pivotal study -> match per country/setting…but, still confirmatory RCT
  - And perhaps in *preventive* indications / slowly progressive disease, confirmation of surrogate outcomes (post approval):
    - Large simple trials / Registry-based RCTs (e.g. IMI Get-Real)

GetREAL output; novel study designs

Study design: Cohort multiple randomised controlled trial (cmRCT)

The cmRCT study design is a type of pragmatic trial. It is also known as a 'trial within cohort' study design (TwiCs).

Figure. Cohort multiple randomised controlled trial



Cluster cmRCTs are a variation on this design using groups (clusters) of patients rather than individuals randomised to different treatments (similar to cluster RCTs). For example, a cluster might be within a GP practice, hospital or community. This can increase the speed of recruitment to the trial and help reduce costs because interventions are administered in fewer places.

A large cohort of patients with the condition of interest is recruited and followed-up over a period of time. Each intervention is offered to a randomly selected sample of patients eligible for that intervention, who are then compared with the rest of the eligible patients from the cohort that are still being treated as usual
Randomisation can occur either at a patient or a cluster (site) level.

https://rwe-navigator.eu/use-real-world-evidence/generate-real-world-evidence/study-design-pragmatic-trials/study-design-cmrct/

Conclusion III

- If you intend to do so:
  - Engage early for scientific advice (SAWP)
  - Agree on
    - Protocol,
    - Alternative/additional data sources,
    - Data quality
    - Representativeness for Europe
  - Stakeholders; registry owners, HTA-bodies [HTA-SAWP advice], Paedco, PRAC,…
  - Product specific OR Qualification Procedure

Thank you for your attention

- For further information:

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- Thanks to Jane Moseley & Ines Lucas who reviewed SAWP procedures