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SCIENCE MEDICINES HEALTH

Regulator's learnings from the Adaptive Pathways pilot on the use of RWD to support drug development

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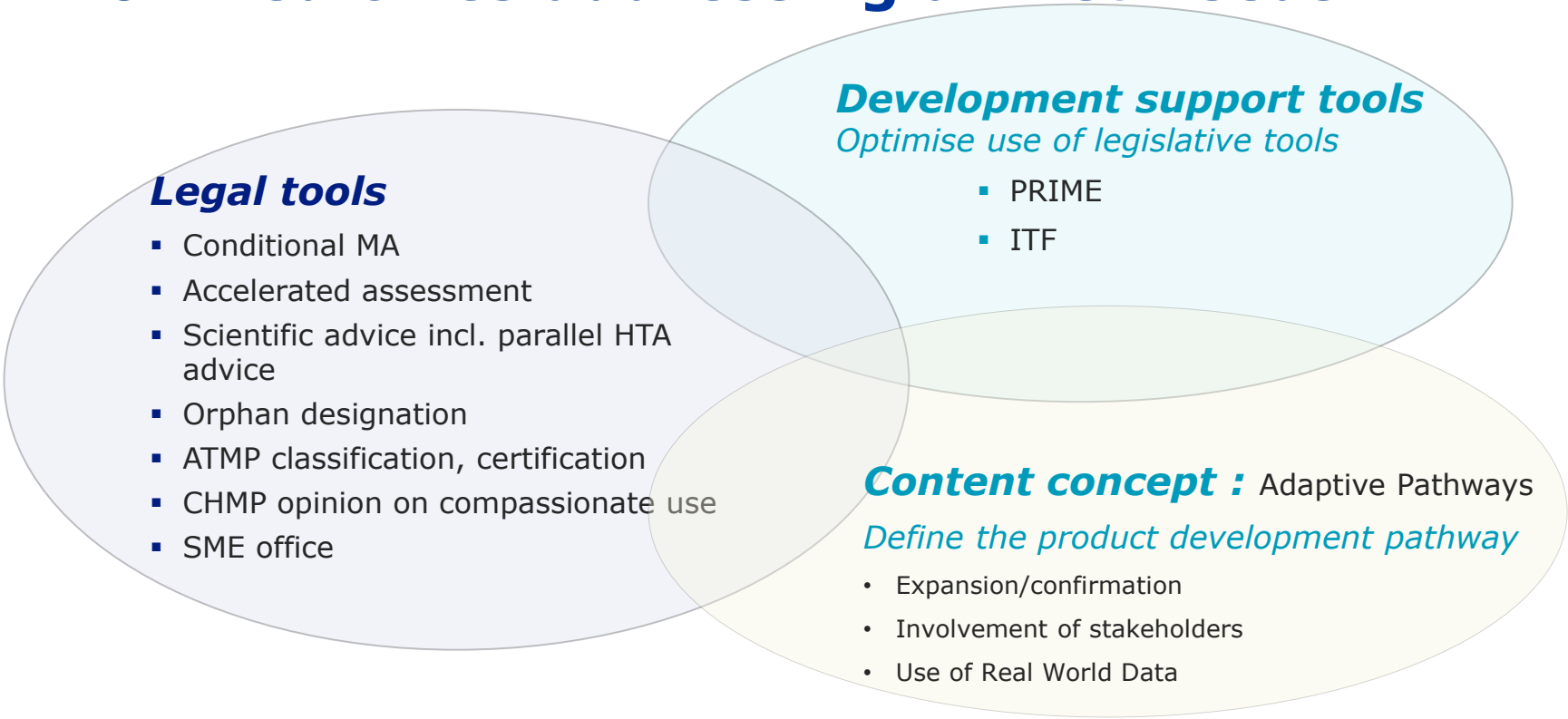
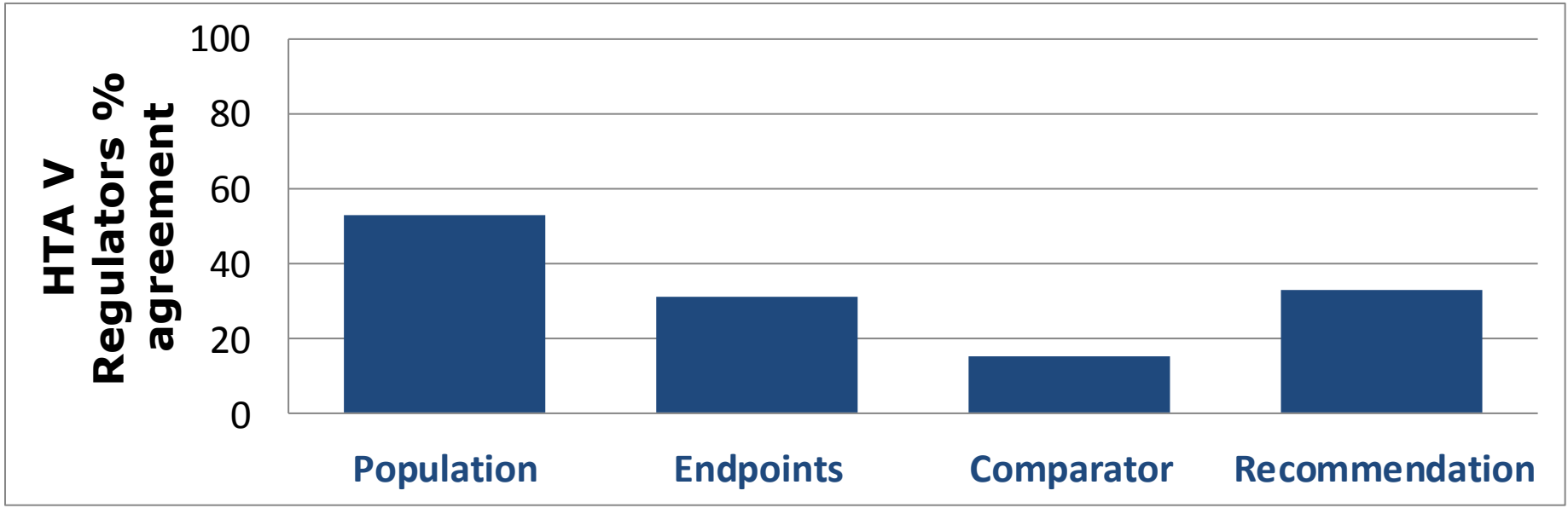
EMA development support and early access for medicines addressing unmet needs



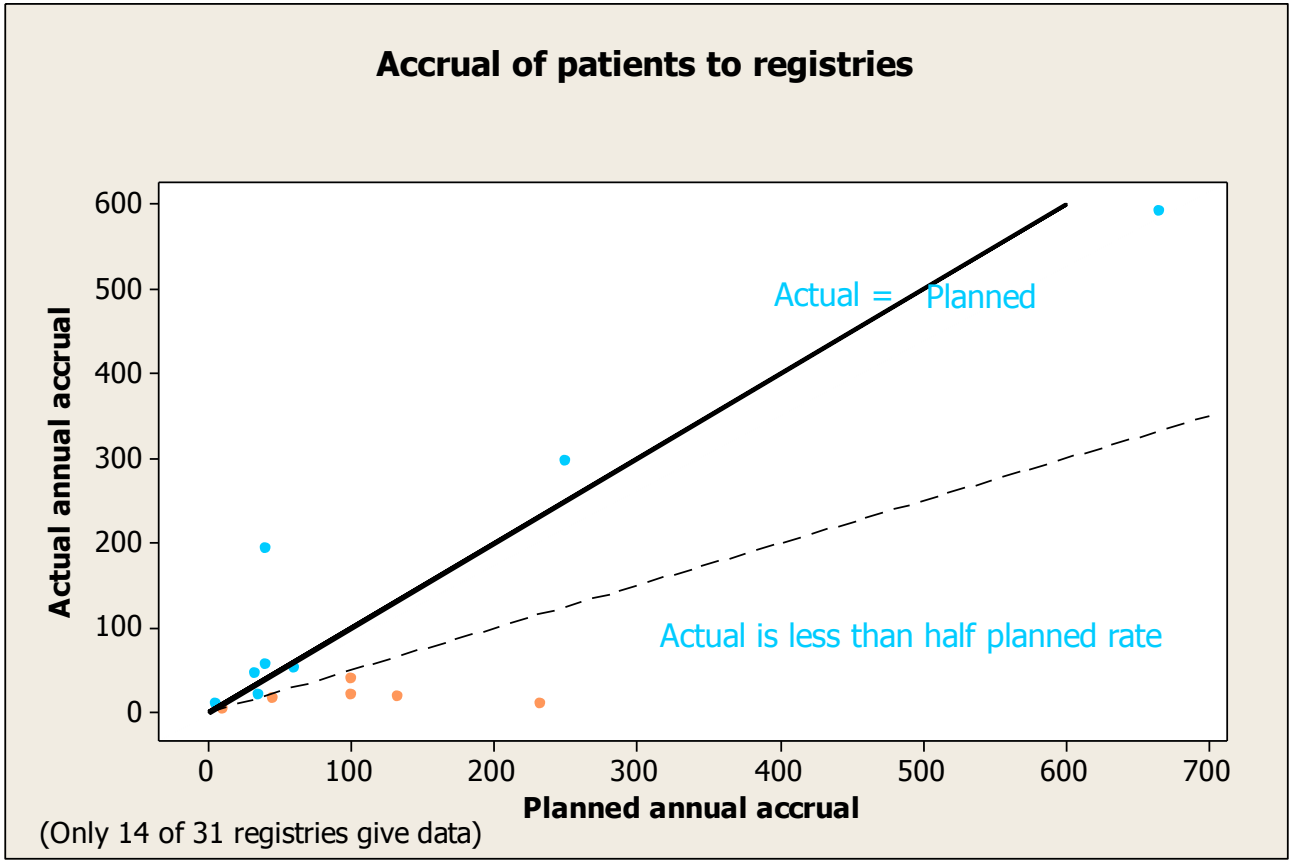
The status quo: HTA/regulators agreement on RCT design

EFPIA analysis on 56 products



http://www.efpia.eu/documents/189/61/HTA-Accelerator-In-Depth-Analysis-Final-report

The status quo: planned vs actual number of patients in registries



RWD can be important for populations absent from RCT

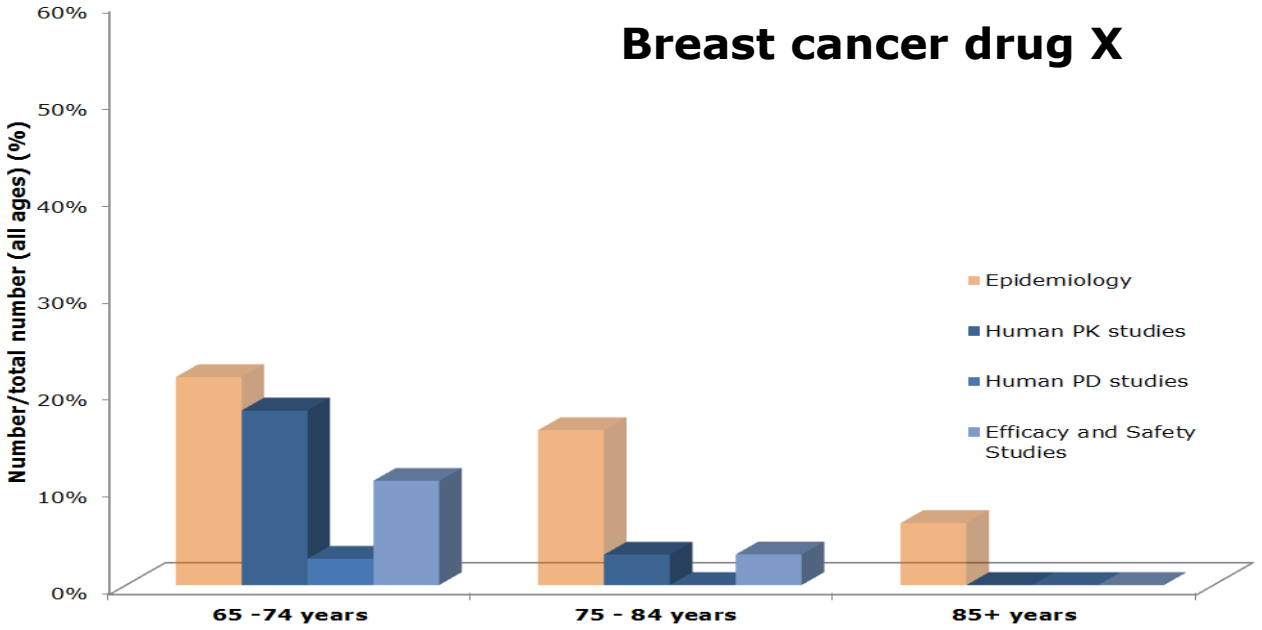
% of elderly patients (i.e. 65 to 85+ years) in human PK, human PD, efficacy and safety studies

Inclusion criteria

- Age: 20 to 74 years at time of consent
- ECOG performance 0 to 1 (i.e. good performance able to carry out normal activity)

Exclusion criteria

- cardiac failure, coronary artery disease hypertension
- Patients with serious uncontrolled intercurrent illness, including poorly controlled insulin dependent diabetes mellitus.
- Patients assessed by the investigator to be unable or unwilling to comply with the requirements of the protocol.



Real World Data–making the best use of all information

RWD are viewed in contrasting ways, often in the same publication:

Case reports: a reliable source of information on safety

Well planned registry: unreliable to investigate effectiveness.

Methodological challenge
to RWD acceptability for decision making.

RWD should:

- **Address justified uncertainties** emerging during the evaluation.
- **Confirm long term effects** if initial approval is based on early or surrogate endpoints

Already done-could be improved!

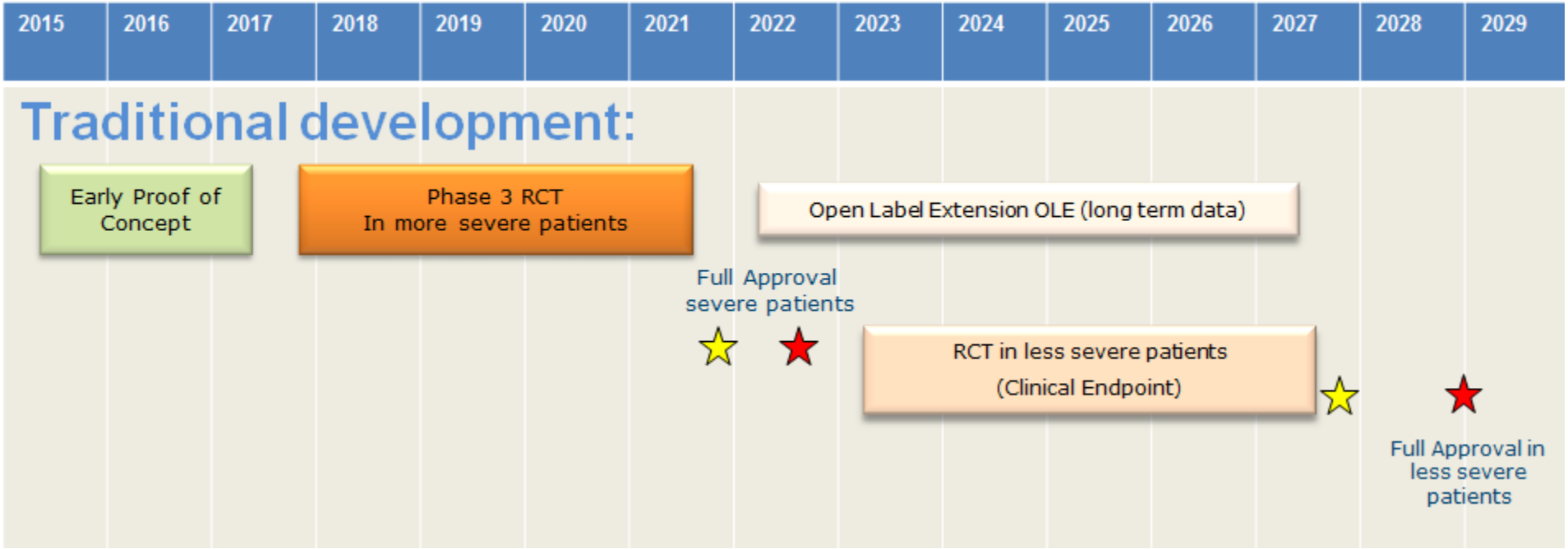
- Prospectively
- Optimised
- Use all data sources

RWD can offer a **monitoring advantage**

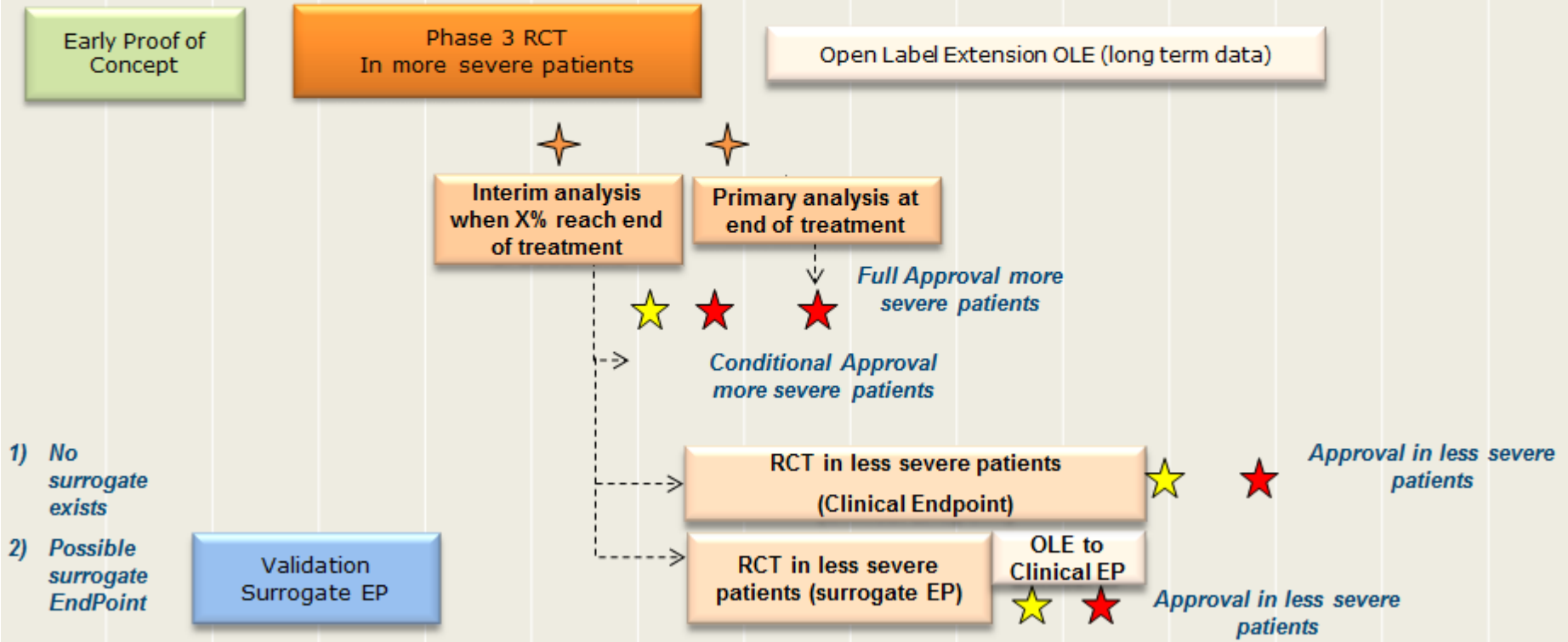
- Capture real clinical practice, adherence, compliance
- Capture rare, long-term events (safety and/or efficacy)
- Less costly way to monitor long-term outcomes – important for degenerative and chronic diseases
- Useful for geriatrics and paediatrics (PIP examples of RWD use: historical control arms, safety and tolerability investigation if efficacy could be extrapolated from the adult trials)
- Useful to validate biomarkers
- Personalised medicine: capture more strata than RCT

Generic Adaptive Pathways example

this is what a traditional development proposal may look like



Adaptive scenarios:



Some RWD examples in AP applications

- Registries: natural history of the disease, SoC, resource utilisation, adherence to treatment, effectiveness, long-term outcomes, drug utilisation, PROs, time to treatment failure..
- Single arm studies for rare diseases vs outcomes in disease registries;
- Open label salvage studies to obtain expansion of the indication;
- Efficacy and safety data from early access/compassionate use to supplement RCTs in small populations;
- Linking drug registries to risk-sharing schemes for reimbursement (pay per performance, annuity payments…)
- Investigation of non-serological outcomes for vaccines

A RWD plan to address downstream stakeholders needs

A managed entry approach is essential to the AP paradigm

Value may change both upwards and downwards with further data acquisition

resource investment – minimum impact on clinical practice

Must be designed to be **useful to patient and prescriber, correctly communicated**

clear-cut ACTIONABLE performance measures should be chosen (eg Sustained Virologic Response, survival rates) for re-assessment of B/R value and P&R

Risk-sharing price reductions are simpler to implement and easier to negotiate solution for drugs with marginal benefit :not affect practice of treatment and low burden of additional data collection, but miss the opportunity of RWD collection and B/R refinement.

Little experience on data collection from **compassionate use programs**. Opportunity to use better?

Learnings on RWD use from AP pilot

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- A **prospective, life-span** discussion of product development with different stakeholders is possible and desirable in cases where decision making could be delayed by suboptimal planning.
- Increase **patient participation** (product selection, risk management, feasibility, ethical aspects, support enrolment in trials and registries).
- Making the most use of available RWD data, feedback/access to other stakeholders for their decision making.
- Prescription controls are important (STAMP discussion March'16)
- Choose clear-cut, **actionable** endpoints for decision making (for B/R, value, pricing)
- **Trust** in capability to conduct the studies is important.

Conclusion

RWD can offer advantages in supplementing RCTs

Their use might accelerate development –if all goes well, particularly if requirements from disffernt stakeholders are prospectively optimised.

Checkpoints and choice of endpoints are important

There are still methodological challenges to be explored