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OVERVIEW: ROLE OF RWD (!) IN DRUG DEVELOPMENT AND FOR POST-AUTHORISATION EVIDENCE GENERATION

Robert Hemmings

Consilium Salmonson and Hemmings

HISTORICALLY

Pre-authorization

- RCTs
  - Promoting unbiased estimates of treatment effect
- SATs
  - Limited use of external controls

Post-authorization

- Clinical trials for variations
- "Descriptive" uncontrolled, extensions for long-term effects
- Observational studies for PhV with best epi.
  - Signal generation.

What role for RWD?

Where are we in implementing change?

WHY RCT?

- **Data source**
  - CRFs
- **Experimental design**
  - Randomisation, blinding, I/E criteria and trial population; con-meds; visit schedule; assessment tools; independent review etc etc.
- **Data handling and statistical analysis**

- To isolate and estimate a treatment effect.
  - "The most important design techniques for avoiding bias in clinical trials are blinding and randomization" … and pre-specification…

CHANGING LANDSCAPE

- **Societal**
  - Cost of drugs
  - Access to new drugs
  - Ethics
  - Feasibility
- **Science**
  - Novel treatments
  - Better understanding of diseases
  - Disease modification
- Access to **other data sources**

- **We should "use the right tool from the toolbox", right?**
- **BUT… change is slow …**
- **Is that wrong?**

CHANGING LANDSCAPE

- "The RCT is dead…" is good for publication.
- "Because it is old … and old is bad."
- "Parachute use to prevent death and major trauma when jumping from aircraft: randomized controlled trial" BMJ, Christmas 2018
- I agree … in some very specific cases (see later).
- Perhaps the parachute is a good analogy. The design may be old, but if I want to jump an aeroplane, I want to use one – if I want to jump from a step, I don't .
- Similarly, RCTs may be old, but if I want to estimate an incremental treatment effect, I want to use one.

WHAT NEXT?

- Too expensive?
- Unnecessary?
- Over-regulated?
- Lacking “external validity”?

REMOVING THE "GOLD PLATE"

- Perhaps we went too far?
- Perhaps to increase internal validity we have compromised external validity.
  - Patient selection, extensive inclusion/exclusion criteria
  - "stable" conditions, allow "difficult" patients to withdraw, impute it they don't etc.
- To maximise quality we have costly monitoring, GCP requirements. CTA requirements for patient safety.
- Investigators and service providers can make money.
- All of these relate to implementation; they are not problems of R C or T per se. Other data sources don't (yet) have the "problems" of promoting quality.

RWD (!)

- Data generated in clinical practice
  - i.e. a different data source … NB: not necessarily a different experimental design etc…
- Planning … YES
- **Estimating treatment effects for decision making … ?**
- Post-authorisation … ?

ESTIMATING TREATMENT EFFECTS - WHEN MIGHT WE NOT 'RCT'?

1. We can't, e.g.
   - Population is extremely (I mean extremely) rare
   - Ethics / Feasibility
- Use best epidemiology

2. We can, but we don't need to, because:
   - The treatment effect is unequivocal: rate on control arm is well-known (<1% or >99% helps!)
   - I have a "RW" data source and a clever methodologist. **This remains harder than we are told.**

SINGLE ARM TRIALS, INDIRECT COMPARISONS AND "AUGMENTED CONTROL ARMS"

- **Similar patients?**
- **Similar experimental conditions?**
  - Assessments, patient management, adherence, withdrawals, estimand…
- **Similar data handling and statistical analysis?**

- Hemmings' μ (mu) test
  - Is the size of the treatment effect justifiably bigger than the extent of confounding that might be introduced? Or:
  - P(Success) ≈ rigour of methods * effect size

SINGLE ARM TRIALS, INDIRECT COMPARISONS AND "AUGMENTED CONTROL ARMS"

- Gene therapy
- Literature says babies with condition X all die before 2 years of age…
- SAT shows treated babies alive at 4 years of age.
- Passes Hemmings' μ test

- Cell therapy
- Literature says 55% of grafts survive with standard immunosuppression
- SAT shows 65% of grafts survive with cell therapy
- Fails Hemmings μ test

MIXING DATA SOURCES

- Is difficult …

- **Patients**
  - Quantitative, e.g. propensity score matching.
  - Validation?

- **Experimental design**
  - ~~Randomisation, blinding,~~ I/E criteria and trial population; con-meds; visit schedule; assessment tools; independent review etc etc.

- **Data handling and statistical analysis**

MIXING DATA SOURCES

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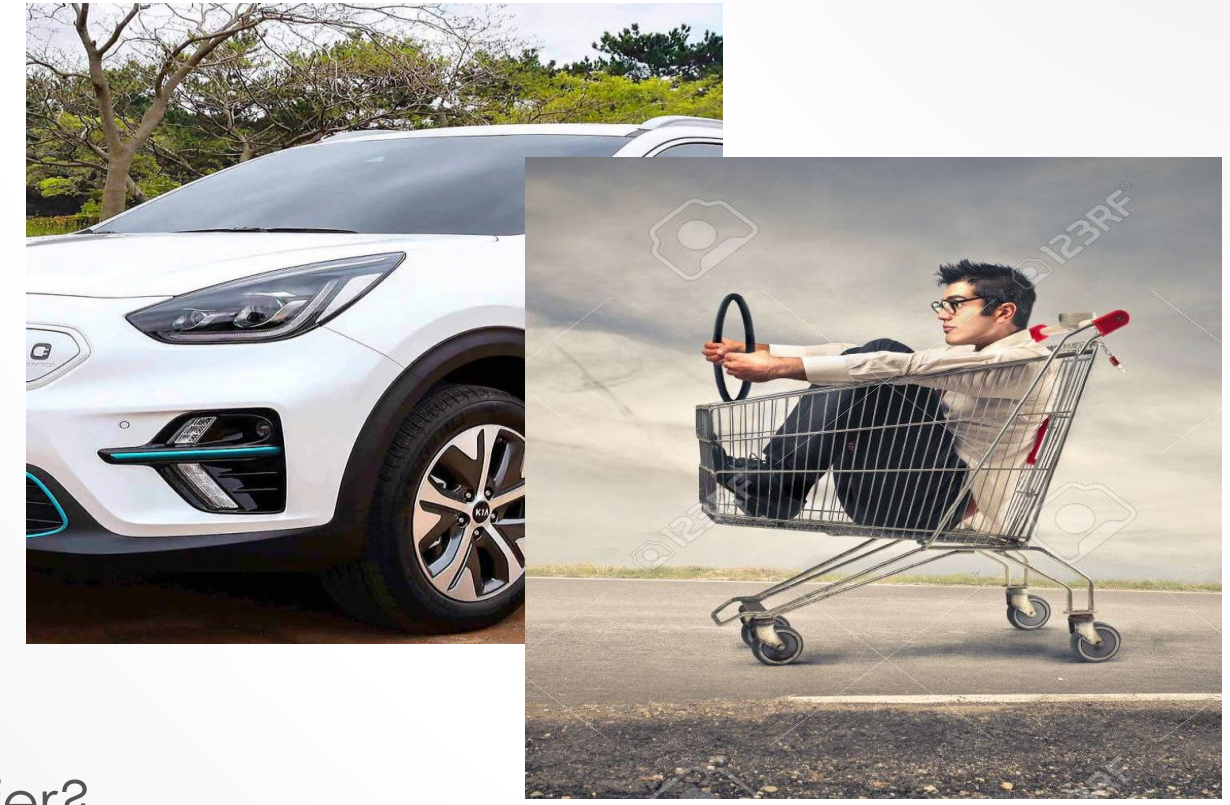
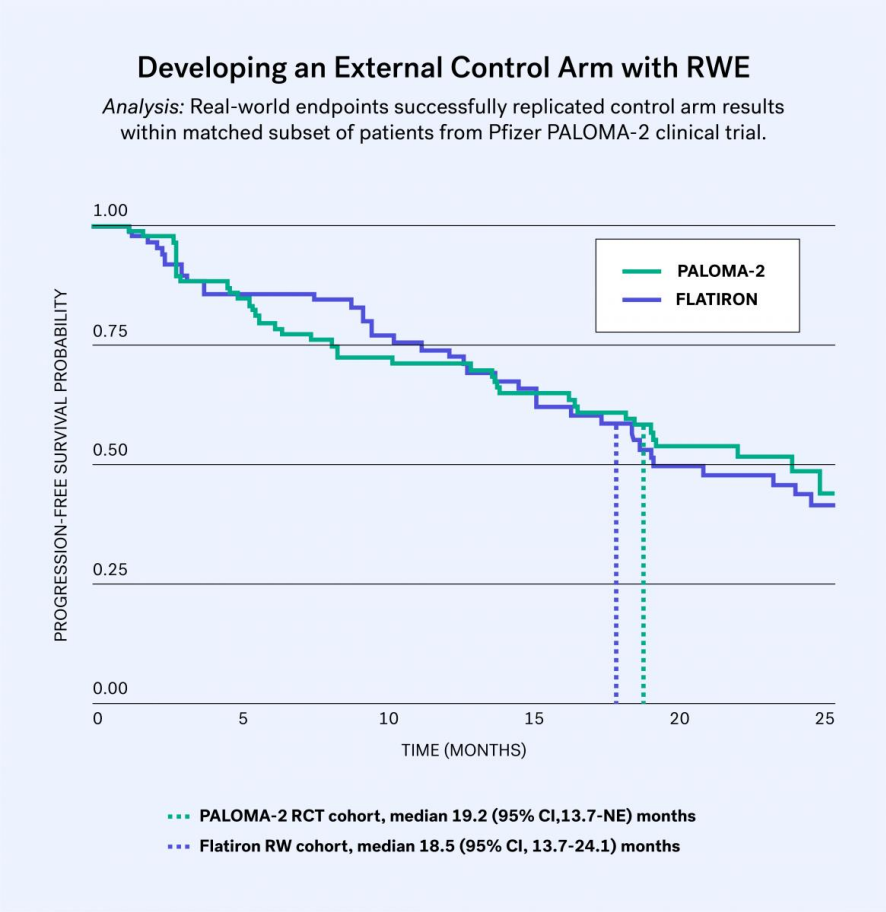


- Which should the regulator prefer?
- When should the regulator trust this type of comparison?
- Which should society prefer?

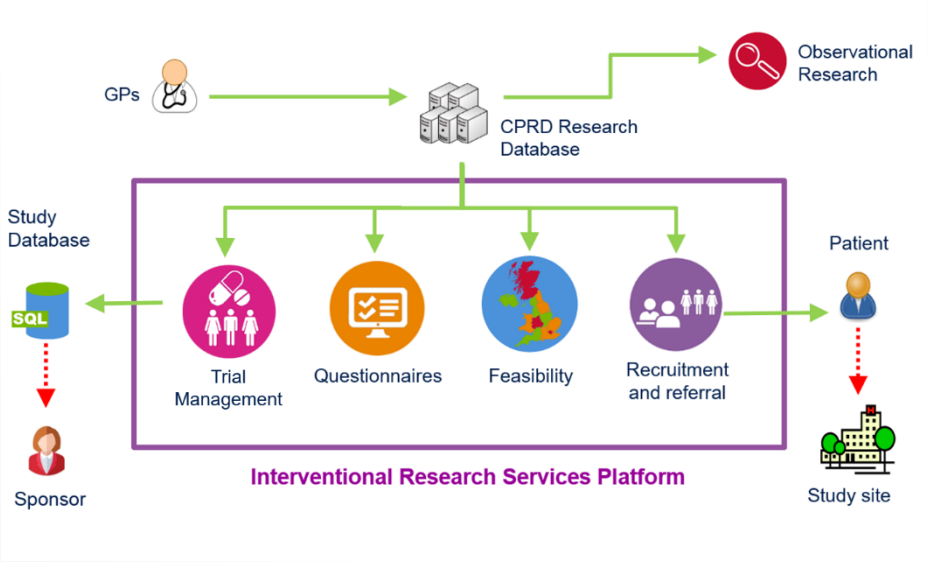
PROGRESS

- e.g. Flatiron
- TransCelerate Placebo/Standard of Care (PSoC) initiative
  - Repository established with converted PSoC data that contains 119 trials, >82,500 patients across 17-Therapeutic Areas (TAs) (2018)
- … but for how long…



PROGRESS

- Examples of randomised study designs in other data sources
  - Registry, EHRs
- CPRD
- FDA RWE program
- Multiple data sources emerging



POST-AUTHORISATION

- CAR-T as a poster child …
- … but can be misleading …
- Some questions best answered / only answered outside (R)CT
  - Alzheimer's
    - Long-term outcomes
    - When to stop treatment?
- Variations – largely as before, though relevant data might be available.
- Re-purposing – signal generation?

CONCLUSIONS

- Continue to evolve the CT
- Some questions don't need RCT. Some questions can't use RCT.
- Retain the R even in other data sources
- Mixing data sources is harder than we are told
- When is "best epidemiology" good enough
  - = how to persuade stakeholders that you don't have a shopping trolley?
- (More) expensive (R)CTs -vs- cheaper and quicker observational studies: which is better for public health?