



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

## **Identifying opportunities for 'Big Data' in medicines development and regulatory science.**

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## Attitudes to Big Data

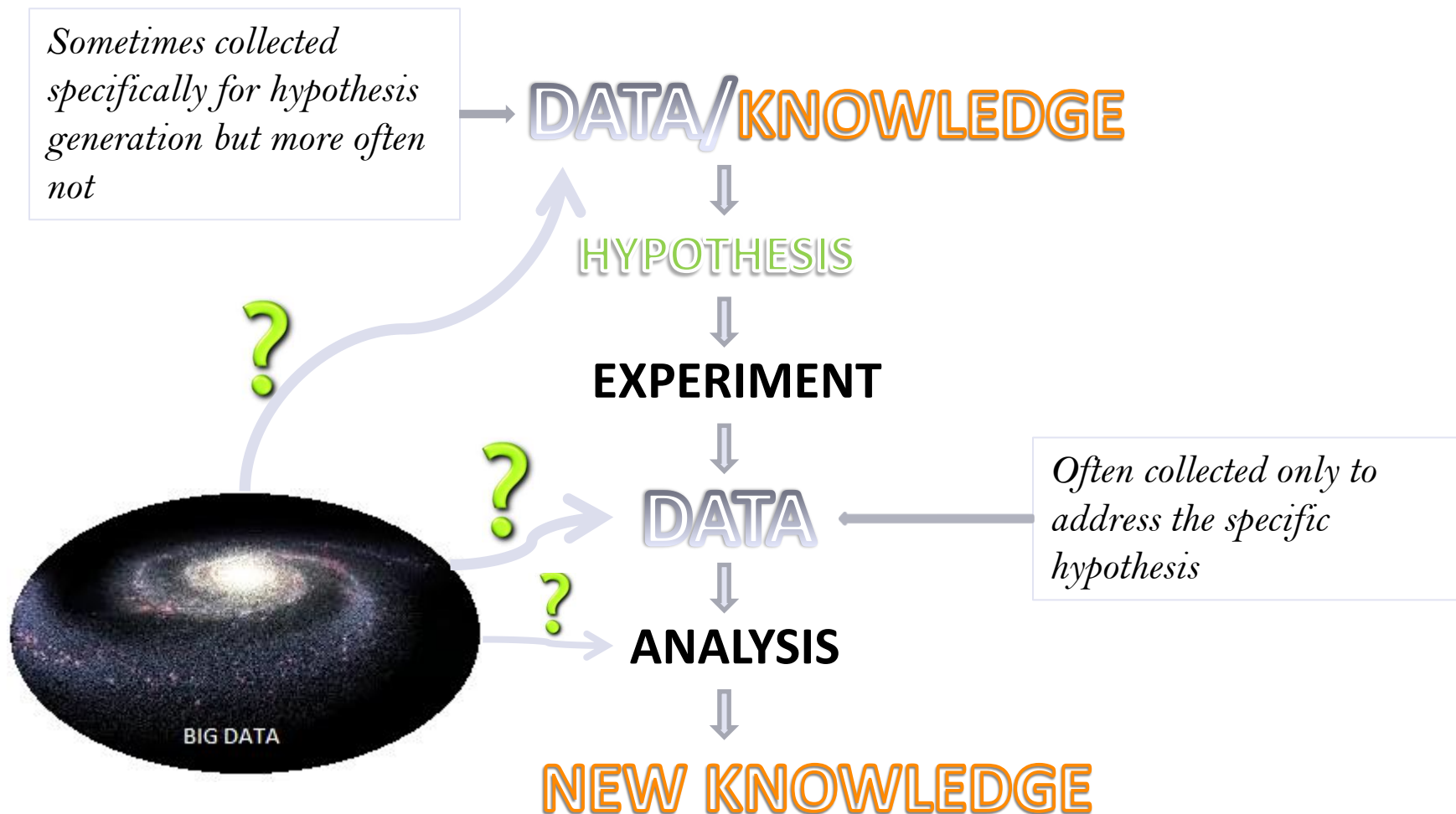
- A huge advance that will allow computers to find the answers to everything
- A resource that appears promising across many areas of science and business
- A useful tool for hypothesis generation
- An asset we should try to use because it is there
- A ploy to attract funding for data scientists



## **Big Data**

**Data that arise as a product of the widespread use in human activities of digital equipment with storage capabilities**

- **Examples of human activities are communication, sales, professional consultations, monitoring, mapping etc**
- **Includes most data sources advertised as ‘Real World’.**





# Potential use - 1

## Hypothesis generation

- **Signalling safety issues**
- **Suggesting new directions for research**



## Potential uses - 2

**Elucidating the causal process underlying an association. In the pharmaceutical area these processes are those linking the products to alterations in the health of the recipient.**

- Appropriate targeting of medicines**





# Potential uses - 3

## Regulatory decision making

- **Supporting assumptions**
  - **Validation of surrogate outcomes**
  - **Validation of modelling and simulation**
  - **Extending clinical trial data**
    - **Longer term outcomes**
    - **Clinical pathways for cost-effectiveness analyses**
- **Outcome evaluation of regulatory interventions**
- **Evaluation of safety concerns**
- **Evaluation of efficacy**



## A BIG QUESTION

How do we decide if the data are 'fit for purpose'?



## Fundamental requirement

- **Data whose form might be influenced by subject matter we are interested in investigating.**
- **Sometimes barn-door. E.g. Gene data.**
- **More often, for Big Data, the area of interest will only affect a small part of the data and hence preliminary analysis involves statistical screening to identify the relevant parts of the data. E.g. Drug effects from social media.**



## **Additional considerations**

- Are the data available at the right time?
- Are they easily accessible?
- Are they sufficiently reliable for the current decision?
- Are they the only way of answering the question?
- If not, do they add value when used in parallel with the alternative methods?



# An expert opinion on Big Data

Things can go wrong, but that's where the power of big data comes in. If you're looking at ten tweets and you're getting a few wrong, you've got problems. If you're looking at ten billion tweets, basically it washes out as noise. The real patterns are the ones that survive the noise.

[Kalev Leetaru](#)

- Stated objective may look like hype but is in fact quite modest - to find 'real patterns'
- Real patterns are either truth or consistent untruths



# Big data for hypothesis generation (1)

- Hypothesis generation is not free of prior conceptions
  - We know what kind of ideas interest us
  - Hence fundamental requirement can be applied for the class of interesting hypotheses
- Low standards of evidence may be acceptable
- **BUT** Every hypothesis carries a cost associated with further verification



## Big data for hypothesis generation (2)

- Are the data we are considering the best way of generating this class of hypotheses?
- If not, do they add anything new to the other available sources of hypotheses?
- What is the (incremental) cost of generating hypotheses from these data?



## Example 1

- Rapid learning for precision oncology
  - Statistical reverse engineering methods to hypothesize the putative driver networks for a given patient's tumour
  - Information from 'exceptional' responders
  - Information about cancer associated mutations
  - Feedback from personal treatment episodes

Shrager J, Tenenbaum J. Rapid learning for precision oncology. *Nat. Rev. Clin. Oncol* 11, 109-118 (2014)





# Rapid learning for precision oncology

- Method of analysis unclear
- Vast assumptions. Responders or just resilient?
- Huge multiplicity issues and numerous sources of bias
- But, if no established treatment strategy, can a system like this help your doctor to choose a promising treatment?
- A valid use of big data but not a new paradigm for drug development



## Example 2 Detection of unknown ADRs

- **From spontaneous reports:** large body of research characterising performance of methods and added value compared to other established pharmacovigilance techniques. Routine use at EMA.
- **From EHR:** An evolving area with mixed results
- **From social media:** early research shows:
  - That ADRs are mentioned in social media and can sometimes be mapped to formal coding dictionaries
  - As yet no clear characterisation of signal detection performance
  - No proof of added value compared to SR data

Freifeld C, et al. Digital drug safety surveillance: Monitoring pharmaceutical products in Twitter. *Drug Saf* 2014; 37: 343-350

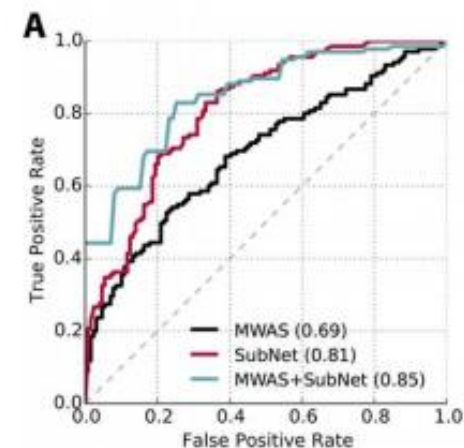
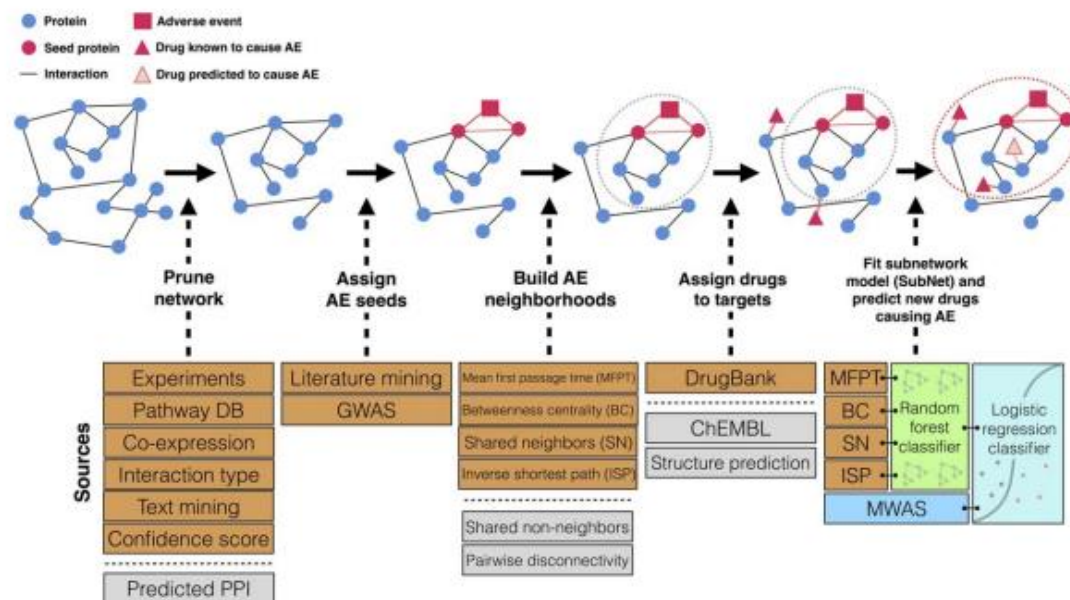


## Big data for model building

- Are data available on variables that may modify the effects of drugs?
- Person/group-level data - Need these data to be linked to individuals or groups with known drug exposures and outcomes.
- Can the data be used to give prior probabilities for selecting among hypotheses?
- Growth area in research

# Example – Systems pharmacology

- Using data on drug's target proteins and pathways to guide ADR detection



Lorberbaum T, Nasir M, Keiser M, Vilar S, Hripsak G, Tatonetti N. Systems pharmacology augments drug safety surveillance. *Clin Pharm & Ther* 2015; 97(2): 151-158



# Messages

- Some quite non-specific information about chemical interactions seems to improve detection of adverse drug reactions
- Big data used to inform prior beliefs looks like a very exciting area for development



## Regulatory decision: Safety

- Use of observational data is well-established in safety analyses.
- Often based on large detailed clinical datasets collected for routine clinical care
- Often the highest standard of evidence available
- Evaluation of such evidence is already a major component of the work of the Pharmacovigilance Risk Assessment Committee.



# Example: Fluoroquinolones + Retinal Detachment

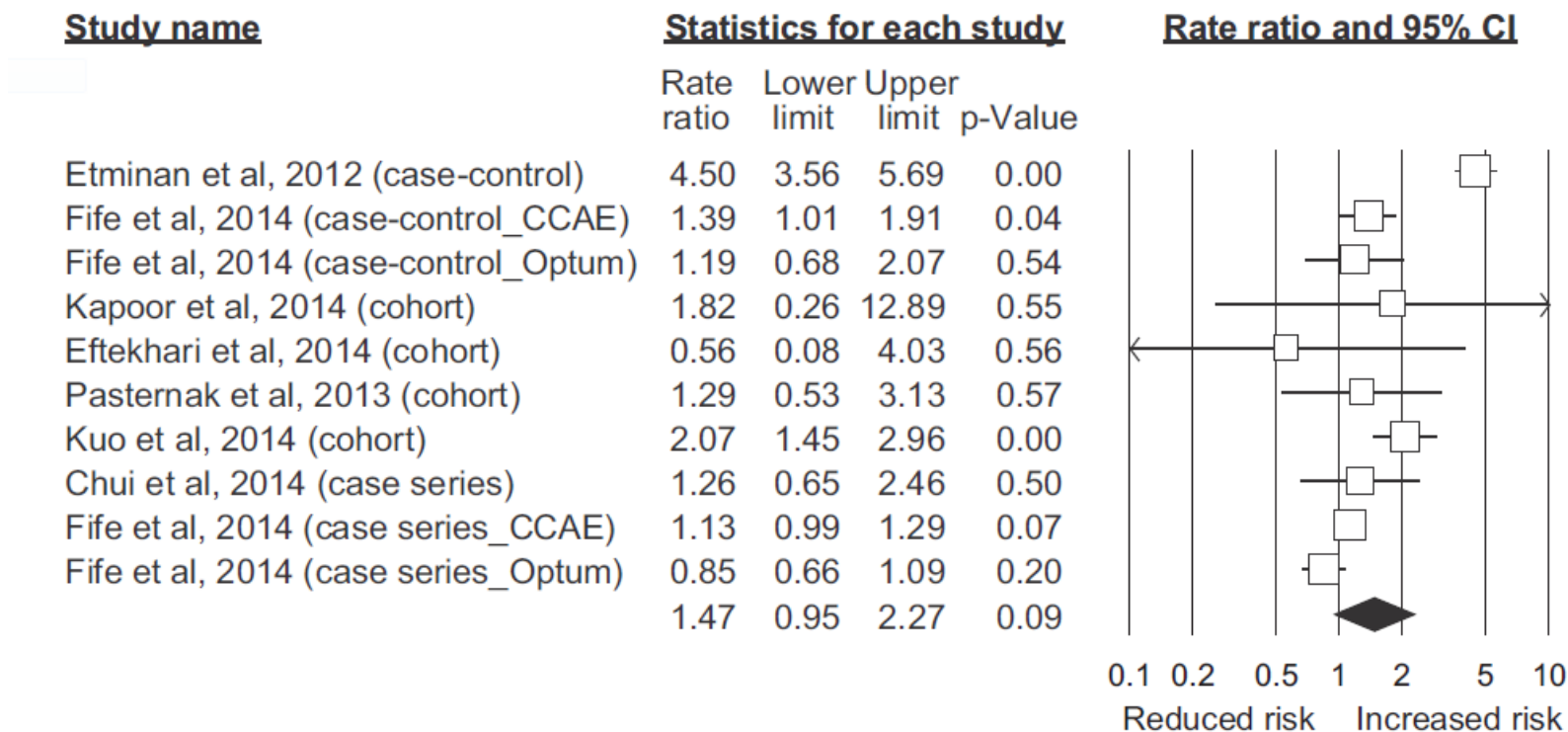


Fig. 2. Pooled rate ratio and 95% CI of retinal detachment associated with fluoroquinolones.

Alves C, Penedones A, Mendes D, Marques F. A systematic review and meta-analysis of the association between system fluoroquinolones and retinal detachment. *Acta Ophthalmol.* 2016; 19: e251-e259



## Context

- These are all carefully designed studies by researchers who understood the data and adjusted estimates appropriately.
- $I^2$ , a statistic that describes the proportion of total variation in study estimates that is due to heterogeneity, was 92.8%.
- For PRAC to reach agreement on results of this nature requires extended deliberation.
- Use of RWE is essential – but not a quick or easy option!





# Regulatory decision: Verifying Efficacy

- Extend time horizon for efficacy
- Validating assumptions of modelling and simulation
- Linking surrogate outcomes to clinically important effects
  - E.g. Is BMD associated with fractures?
    - In untreated subjects?
    - In treated patients?
      - In patients with this specific treatment?



## Context

- Attempts using RWE/Big data to extend limited but reliable observations within the same patient group can start by matching the initial results – A reality check.
- Even if the absolute results do not match it may be reasonable to estimate relative measures from the observational data.
- RWE/Big data often supply insights not otherwise obtainable but need careful interpretation



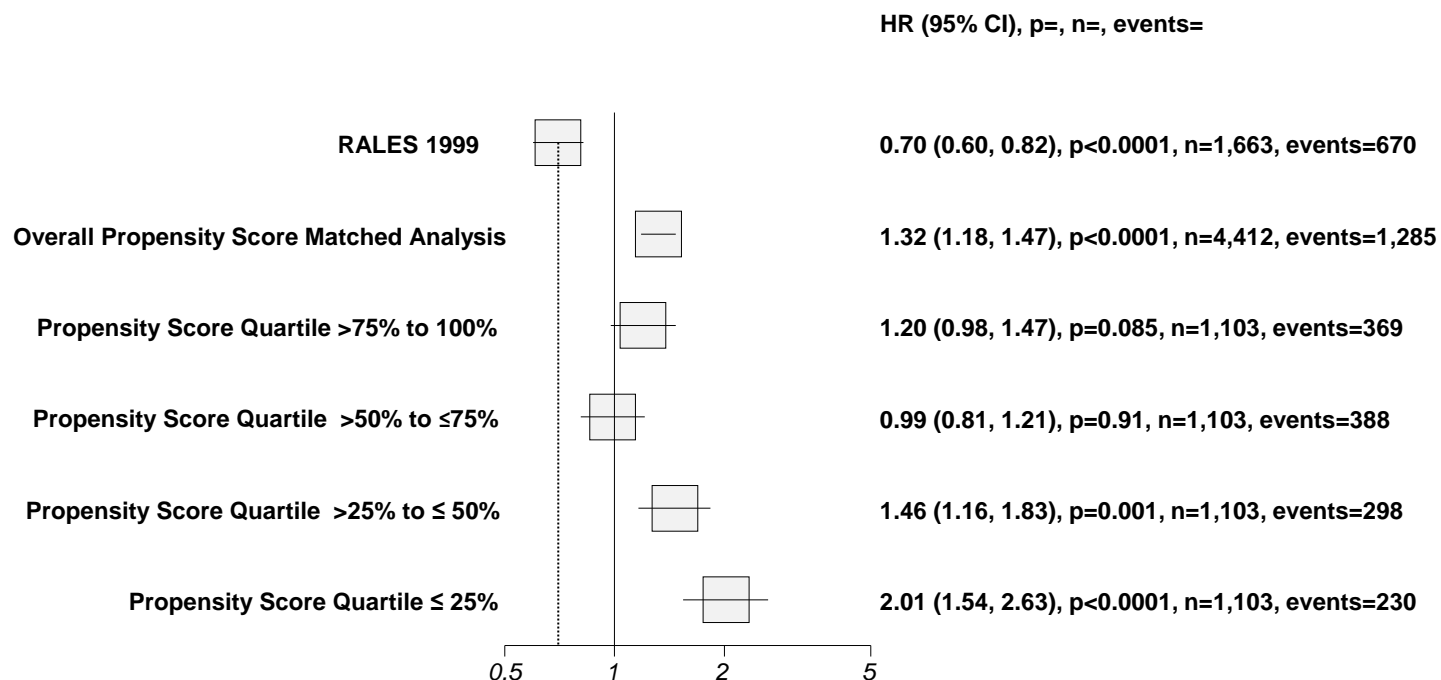
## Level of evidence for efficacy?

- Spironolactone in heart failure
- Case study attempting to replicate results of randomised clinical trial

Freemantle N, Marston L, Walters K, et al. Making inferences on treatment effects from real world data: propensity scores, confounding by indication, and other perils for the unwary in observational research. *BMJ* 2013;347:f6409.



# Propensity scores, confounding by indication and other perils for the unwary in observational research





# Take home messages for propensity score based analyses of treatment effects

- Start from somewhere you know
  - Replicating an existing trial
- Examine the behaviour of the propensity score across its range
  - Test for interaction with exposure
- Estimates of efficacy for treatments given according to well-defined rules based on known variables are less likely to be biased.
- Doubts about standard of evidence may limit regulatory use.



## **Regulatory decision: Efficacy in new patient groups**

- Pre-authorisation RCTs enrol patients for whom no licence yet exists
- Exposure of patients beyond the current label demands extreme caution
- Where would observational data on a well-characterised group of off-label patients arise?
- Main limitation of observational approach.



## **Efficacy: An aside**

**RCT:** The right answer to (maybe) the wrong question  
OR

**Observational study:** The (maybe) wrong answer to the right question

**If we chose to put one of these right, which would it be?**



# Conclusions

- 1. Optimism:** Big data/RWE hold promise. They are already used productively in safety evaluation and can provide an evidence-base in confirmation of efficacy and support of modelling assumptions.
- 2. Realism:** Big Data/RWE have multiple uses in regulation but no data analytics approach can free the analyst from having to understand the data
  - Big Data are an accumulation of diverse datasets with heterogeneous properties
  - Regulatory data uses are also diverse with heterogeneous requirements
  - Every data source must be evaluated relative to its potential use
  - Clear and rational criteria for use of each dataset in each purpose are required.





## Conclusions

- 3. Caution:** Some regulatory decisions require very robust and reliable standards of evidence and this limits use of observational data.
- 4. Future:** EMA considers that RWE might have a role in medicines regulation as a source of insights and it will explore this in the future by working with stakeholders to evaluate the reliability and utility of available sources of big data.

