Real-World Evidence: What, Why and How

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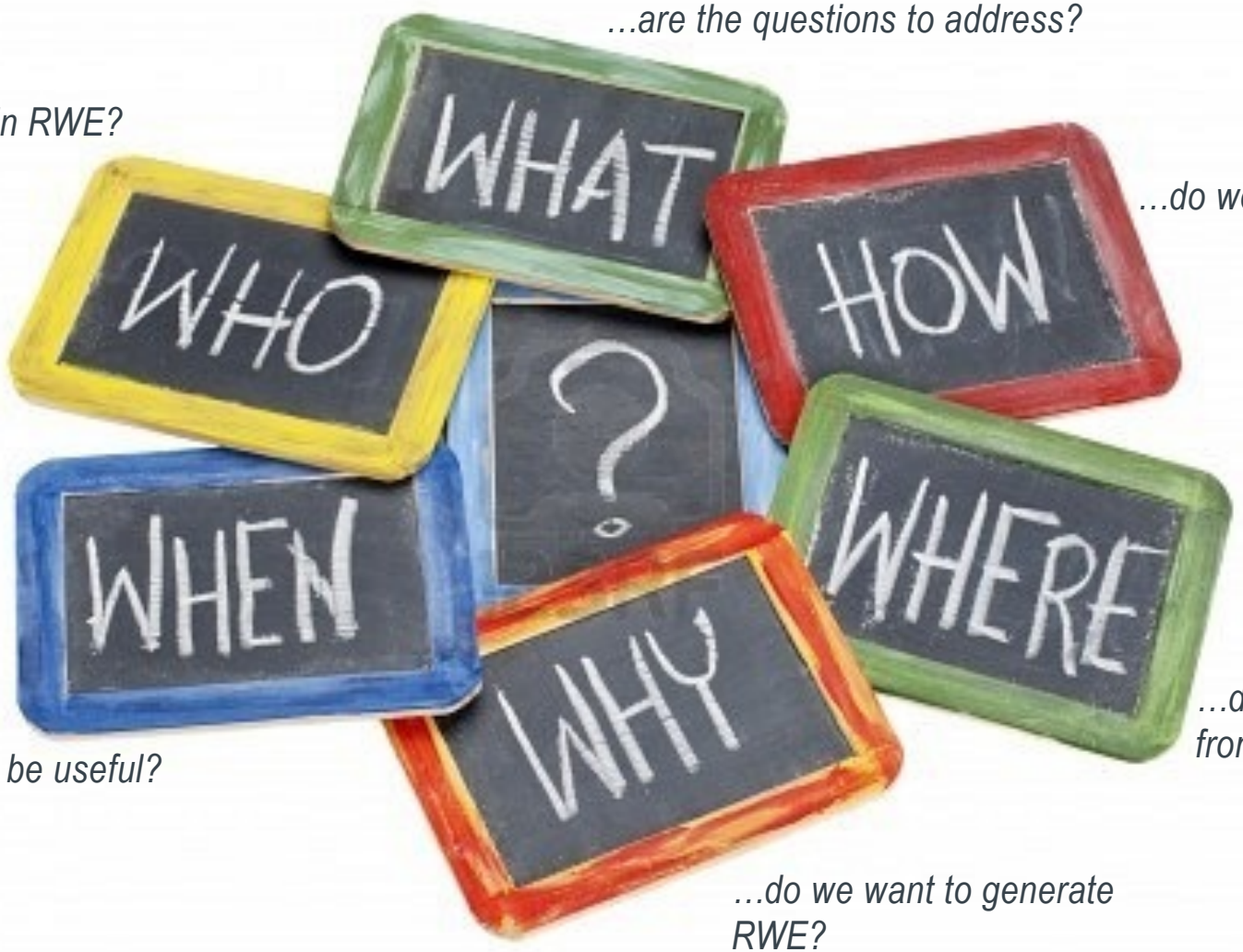
Selected issues on RWE

…are the questions to address?

…are interested in RWE?



…do we approach it?

…do the data come from?

… can RWE be useful?

…do we want to generate RWE?

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Some definitions to start with…

REAL-WORLD DATA

- Health-related data obtained outside the typical clinical research (e.g RCTs)
- Generated during routine clinical practice or claims processing or reported by patients, etc.

- RWD are raw materials and alone are non-informative

≠

REAL-WORLD EVIDENCE

- Output of RWD analysis
- Generated and interpreted according to a research plan

- Provides insight beyond RCTs and inform decision making by healthcare stakeholders

Berger et al (2017): Value in Health, 20:1003-1008

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What is driving Real-World Evidence generation?

Regulators, Payers, Prescribers and the HC Industry are eager to understand more the performance and the impact of (new) treatments in a real-world setting. RWE can help fill the knowledge gap between RCTs and real-life clinical practice. *

Changes in data sciences, HC policy and stakeholders' priorities drive RWE

- New technologies = new opportunities to capture and analyze data (companies specialized in data infrastructure and analytics, Apps, digital services, etc.)
- New types of data = tremendous growth in volume, source and complexity of RWD
- Challenges for Governments/Insurers/Payers = high quality and affordable HCS
  - Improve health care quality and outcomes
  - Control rising costs
  - Improve efficiency of the HCS, reduce wastes
  - Motivate HC providers for better performance
  - Implement innovative contracting solutions (e.g. performance-based payment)

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** http://www.appliedclinicaltrialsonline.com/real-world-evidence-studies*

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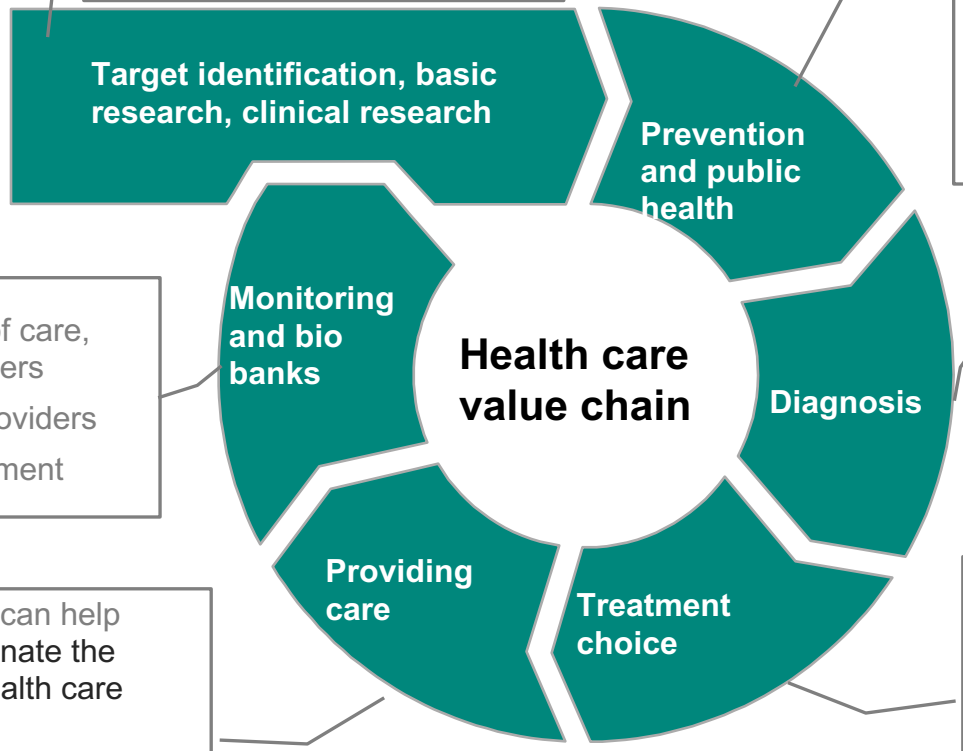
RWE can help optimize health care provided as well as the health care system



- » Input to R&D
- » Trial design, patient cohort
- » Safety/quality/efficacy concerns

- » Lifestyle, risk behavors
- » Identification of population groups with unmet needs, identify treatment gaps
- » Identification and quantification of patients at risk sub-groups
- » Optimizing cost of prevention versus the cost to cure/control

- » Early identification of patients
- » Assess the timeliness of diagnosis

- » Measuring effectiveness of therapy in the “real life” setting help select the most suitable intervention
- » Compare real-life usage with treatment guidelines

- » National databases can help integrate and coordinate the treatment across health care system
- » Measure health care resource utilization
- » Analyze patient pathways in the HC system

- » Monitoring of quality of care, performance of providers
- » Build incentives for providers
- » Patient health assessment

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RWE is essential in all stages of product life cycle

Use RWE to shape design of clinical trials

Burden of disease

Unmet medical need

Treatment pattern (current)

Cost-effectiveness

Health care resource utilization

Safety follow up

Adherence to guidelines

Assessment of real-life effectiveness

Real-life utilization patterns

Support market access

Product differentiation

Safety follow up, AE monitoring

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To generate RWE we need to collect RWD

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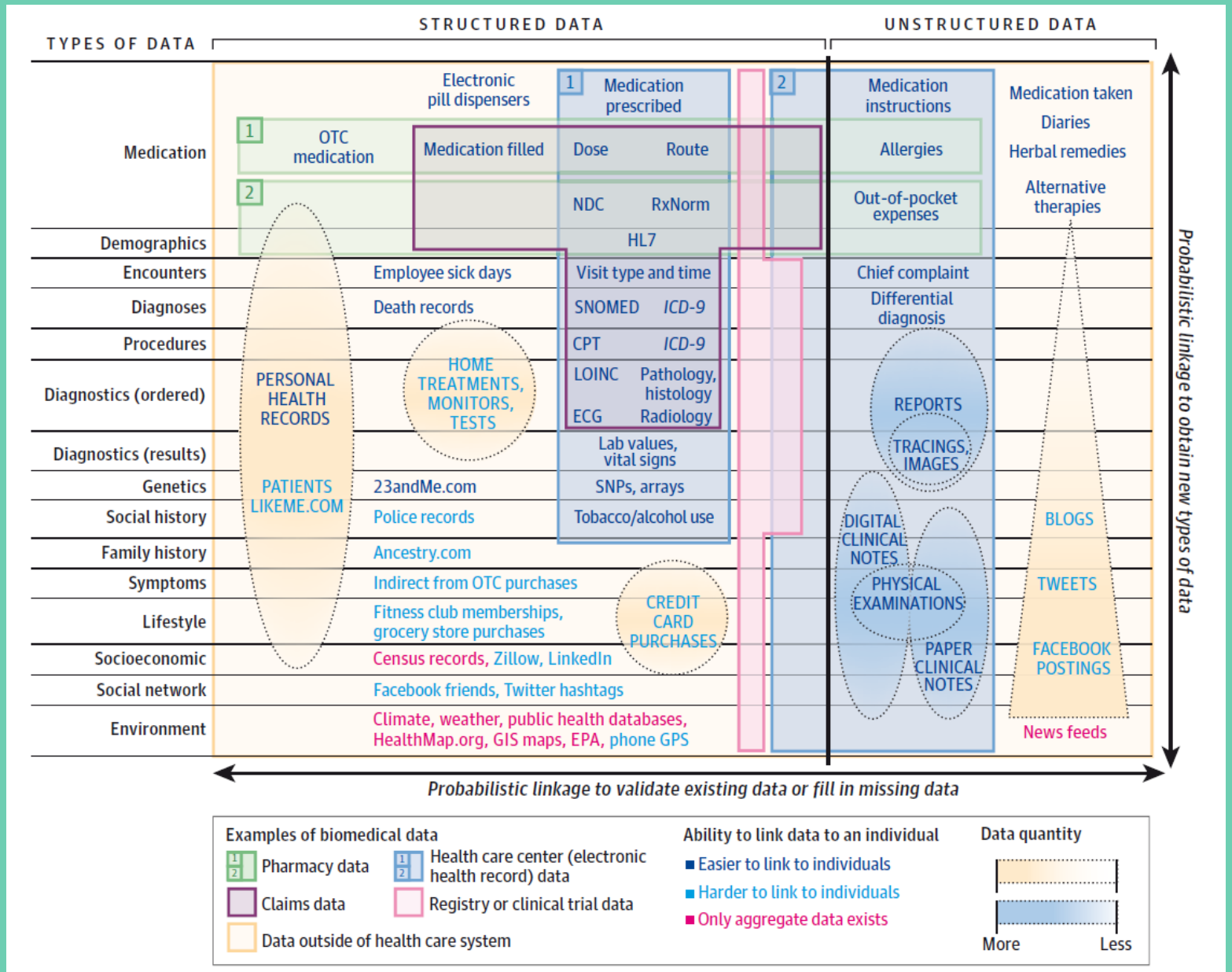
Potential sources of biomedical data



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Griffin et al (2014): JAMA, Vol. 311, No 24

Huge opportunities with big challenges because…

„…big data becomes transformative when disparate data sets can be linked at the individual level." *

But…

- **Health related data are scattered** across institutions
  - If a national Unique Patient Identifier is lacking, other algorithms need be developed to link data at individual level
- Many times **data sets are isolated to protect patient privacy** and security
  - Societal, legislative and ethical standards needed to ensure that benefits outweigh risks
- Data collected are greatly different by **depth of information and time horizon**
- Data collected for variable purposes, in **different formats**, following **different standards**
  - Data collection procedures and rigor, data storage are hugely varying
  - Primary data: collected specifically for research purposes (case reports, outcomes assessment, surveys, EMR, registries, etc.)
  - Secondary data: collected for varying reasons (medical charts, payer claim database, registry, EMR, etc.)

** Griffin et al (2014): JAMA, Vol. 311, No 24*

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Examples for MSD's Local partnerships in Europe

Local collaborations centered around specific research projects to understand more the disease areas and our own products.

Strategic parterships of MSD worldwide

Longer-term collaborations to conduct research in different therapeutic areas, to advance analytics and methodology, to develop RWE for innovative research.

DBMI HARVARD MEDICAL SCHOOL (Dec 2013-)

NHS (Jul 2014-)

Karolinska Institutet (Nov 2016-)

Regenstrief Institute (Sep 2012-)

Maccabi Healthcare Services (Sep 2013-)

FLATIRON (Dec 2014-)

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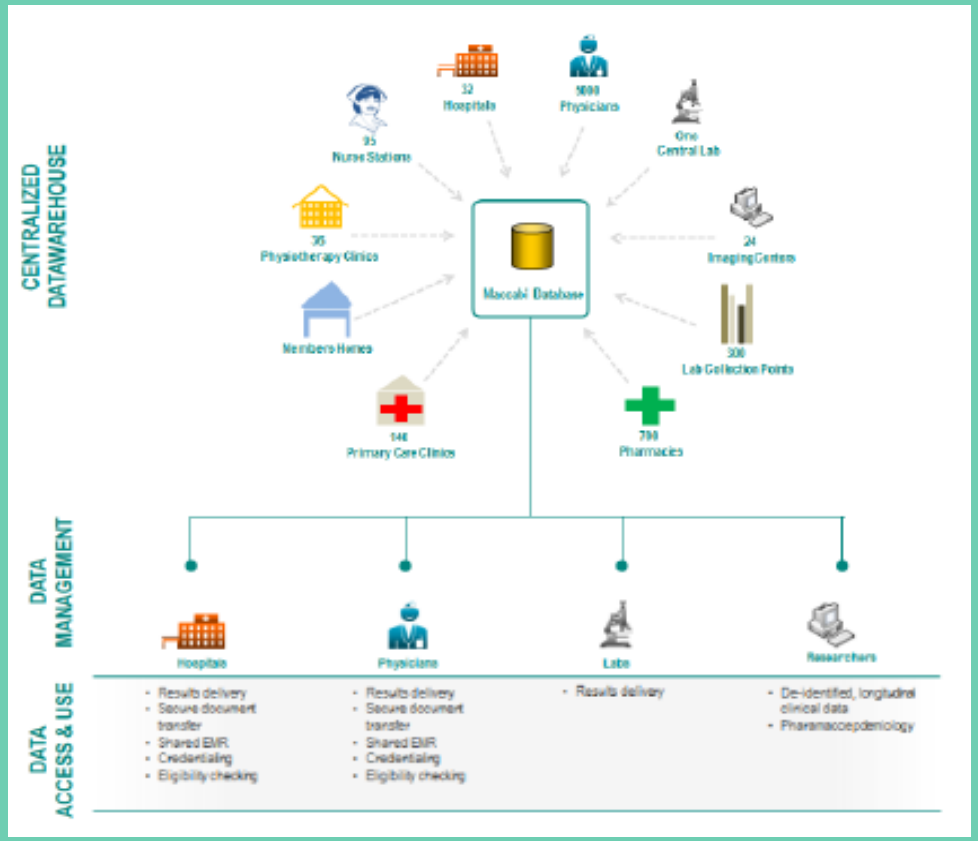
Example: Maccabi Clinical Database Offers Unique Real-World Evidence View

- 2nd largest HMO* in Israel ~25% of the population, i.e. 2 million members
- Owns the largest private hospital network in Israel
- Fully computerized and integrated, longitudinal EMR for 20 years, linking different segments of the HCS



** HMO: health maintenance organization*

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More than 20 publications in 3 years

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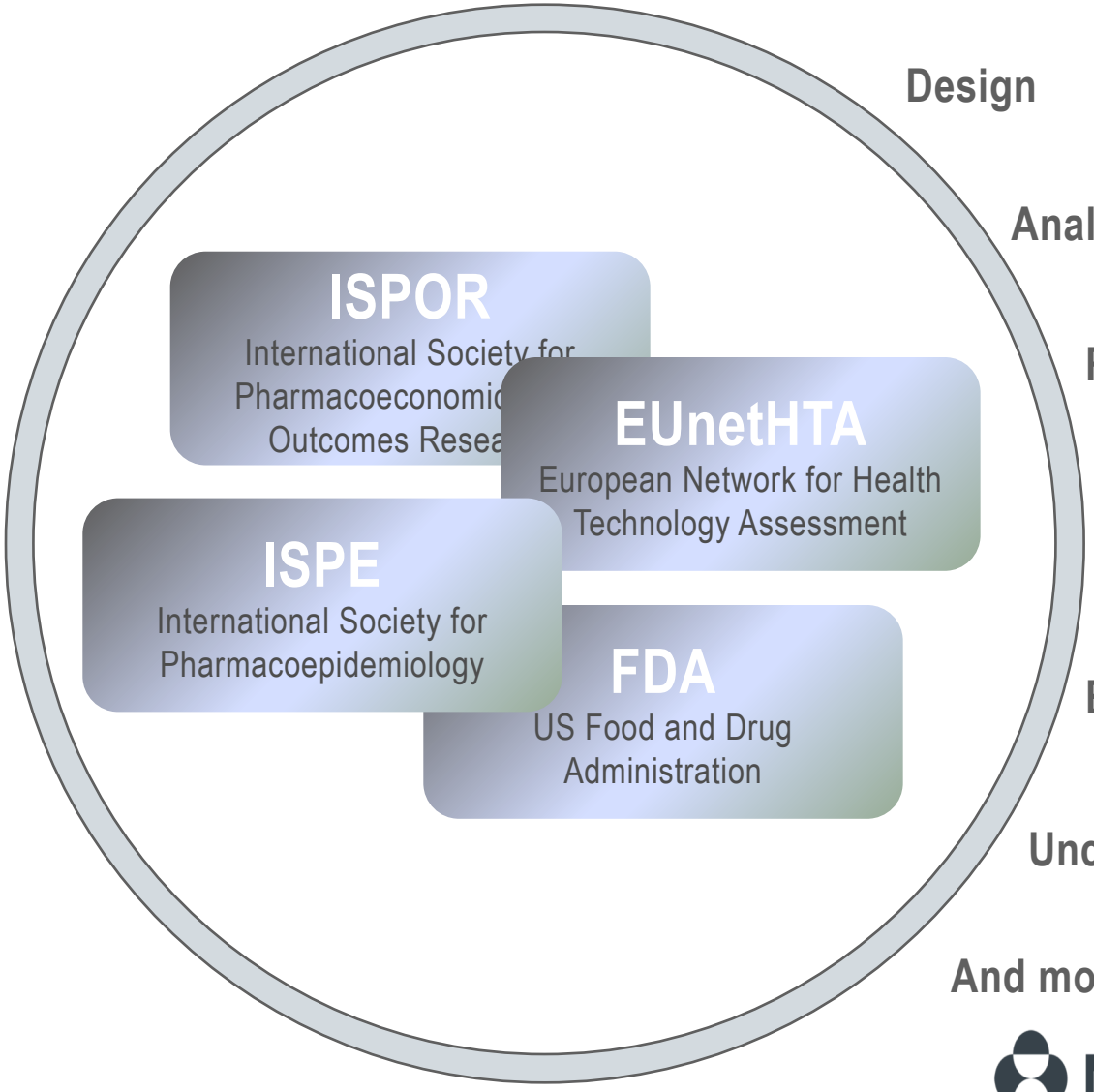
Guidances for good practices are available to improve the validity and relevance of RWD studies and to provide standards



Design

Analysis

Reporting

Confounding

Bias

Uncertainty

And more…

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THE UK EXPERIENCE

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Objectives

- To understand the potential for utilising electronic health records for observational research
- To understand the basic steps needed to produce valuable real world evidence using EHRs
- To provide a real life example from the UK

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Overview

- Electronic health records (EHRs) for observational research
- Components of an observational study
  - Formulating the research question
  - Defining the patient cohort
- Data collection and analysis
  - Types of data
  - Developing code lists
  - Missing data
  - Confounders
  - Data analysis
- Example from UK CPRD

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Potential of EHRs in research

- Real world settings
- Representative
- Richness of recording
- Real time
- Cost effective
- Population size
- Longitudinal
- Retrospective and prospective
- Add value by linking to other datasets

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Uses of primary care EHR for observational research

- **Pharmaco-epidemiology**
  - Drug safety / AEs
  - Drug effectiveness
  - Drug unexpected benefits
- **Disease epidemiology**
  - Incidence, prevalence and demographics of disease
  - Identification of risk factors / association between diseases
- **Health outcomes and healthcare resource utilisation (HCRU)**
  - Hospital and outpatient (re) admissions
  - Tests/ surgeries
  - Drug utilisation
  - Cost of disease to HC system

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Components of an observational study

Research question

Study population

Outcome

Exposures

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Components of an observational study using EHRs

Research question

Study population →

- Individuals registered in routinely recorded databases

Outcome

Exposures

→

- Linkage to other routinely recorded data sets
- Diagnostic codes (e.g. ICD-10)
- Free text

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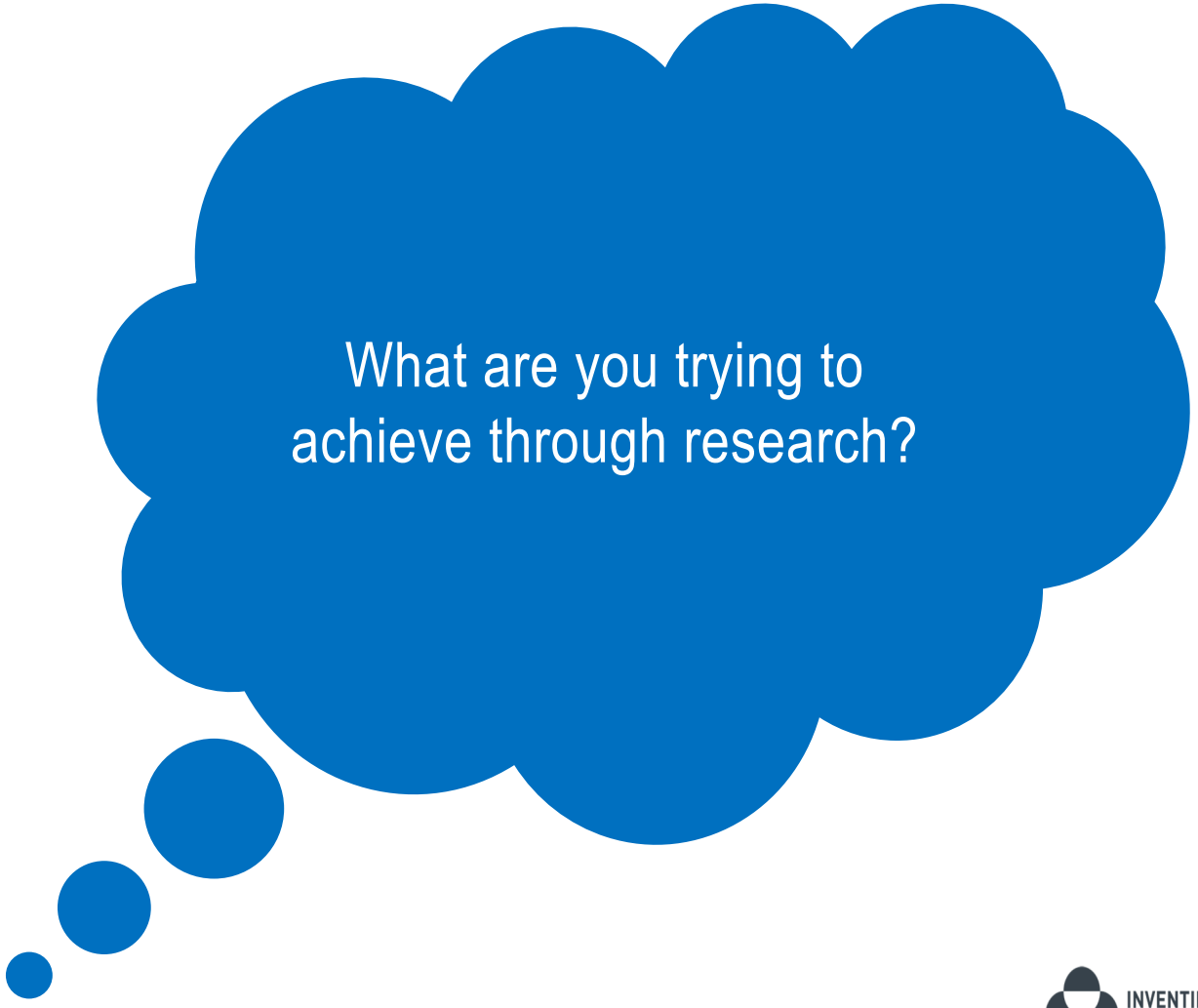
Formulating the research question



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Formulating the research question

Some questions to consider …

1. Who is your audience?
2. Has the question already been asked and/or answered?
3. What data already exists in the literature?
4. Is it feasible?

*Critical to have clear **focus** – too broad of a question will not deliver valuable results and more likely to not deliver an answer to your question*

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Defining the patient cohort

- Invest time and effort in this step – failing to do so may lead to downstream inefficiencies
- Identify potential bias, confounding, and missing-data within patient population
- Balance accuracy with generalisability
  - *Too broad* → inaccurate results
  - *Too narrow* → unable to generalise results
- Isolating specific patient phenotypes requires collaboration between clinicians and data scientists

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skowitz A., Chen K. (2016) Defining the Patient Cohort. Secondary Analysis of th Records. Springer, Cham.

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Defining the patient cohort

1) Select **exposure** of interest
   - Patient centric – traits intrinsic to a group of patients (e.g. gender or LT condition)
   - Episode centric – transient condition (e.g. sepsis)
   - Encounter centric – single intervention (e.g. arterial line placement)

2) Select **outcome** of interest
   - Should relate to exposure of interest
   - Be specific as possible
   - Watch out for broad outcomes (e.g. mortality) as they may be confounded w/ too many variables
   - Surrogate outcome measures (e.g. blood pressure, LDL level) are less prone to confounding

skowitz A., Chen K. (2016) Defining the Patient Cohort. Secondary Analysis of th Records. Springer, Cham.

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Defining the comparison group

- Ideally phenotypically similar to study cohort but lacking exposure of interest
- Should be equally at risk of developing study outcome
  → Can be done through propensity score development
- Same size or larger than the study cohort to maximise power of the study

kowitz A., Chen K. (2016) Defining the Patient Cohort. Secondary Analysis of th Records. Springer, Cham.

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Types of Data

- **Data is at the centre of all research: ensuring good practices are in place from the start will result in downstream savings**

- When using routinely captured data, know *what* type & *why* it was captured initially. **Often NOT recorded for the purpose of research**
  - Subject to variation in clinician perception, interpretation & recording
  - Timestamps may differ in meaning for different categories of data
  - Biases may be seen depending on where data is collected
    - Specific demographics (given locality or speciality of site)
    - Variation in treatment approach or prescribing
  - Patient attendance (specific demographics attend more) not representative of individual (snapshot of condition) and population

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Types of Data & Potential Challenges

Category	Example	Challenges
Billing	Prescriptions, tests	Not documented for clinical purposes so may be misrepresented; influenced by financial incentives
Demographics	Age, gender, ethnicity	Can be highly sensitive – anonymising is key
Laboratory	Microbiology results	Sample quality and testing may be variable resulting in inaccuracies
Physiologic	Heart rate, blood pressure	HCPs may not consistently record data so often missing results
Medication	drug, dose, timing	Captures prescription but not whether patient took the drug
Notes	Admission notes, discharge summary	“free text” makes it difficult to analyse and inconsistent

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ard T., Dernoncourt F., Finlayson S., Velasquez A. (2016) Data Preparation. In:
lysis of Electronic Health Records. Springer, Cham

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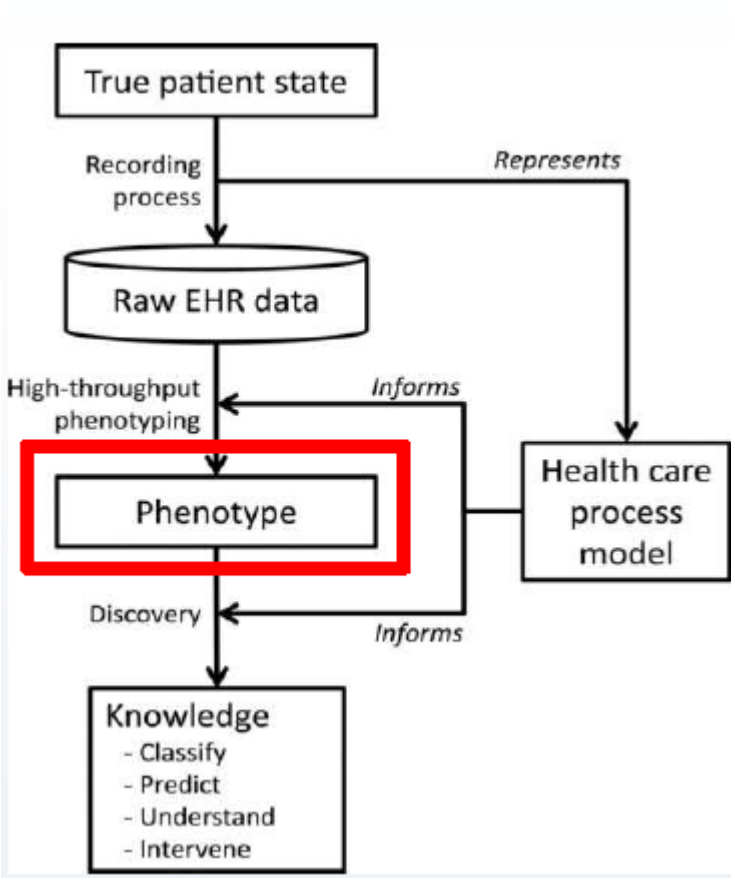
Developing code lists

In EHRs, often Read codes or ICD-10

Developing code lists is an iterative process

1. Identify existing, ideally validated lists
2. Compile keywords – clinical input essential
3. Search for additional terms in code dictionaries
4. Review stem codes, refine accordingly, and exclude any irrelevant codes
5. Final code list check with clinician review



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ıikam L., Blackburn R. (2017) Developing code lists for EHR. UCL.

Missing data is inevitable and must be accounted for

- Exclude variables with incomplete records → may lead to bias due to confounding
- Create missing data categories → severe bias can arise
- **Imputation**: replace missing values with an estimated value based on other information available
  - **Single methods** (e.g. mean/mode substitution) More favourable than exclusion or missing data category but does not account for uncertainty, which reduces variability and disregards relationship between variables
  - **Model-based methods** (e.g. regression): predictive model created to estimate values that will substitute the missing data

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Types of missing data

- **'Missing completely at random' (MCAR):** the reasons for the missing data are *not* associated with the observed or missing values (e.g. not possible to measure blood pressure due to equipment failure)
- **'Missing at random' (MAR)**: the reasons for the missing data are *not* associated with the values of the missing data conditional on the observed data (e.g. once you know someone's age, their chance of having blood pressure recorded is independent of their blood pressure level)
- **'Missing not at random' (MNAR):** even given the observed data the reasons for the missing data *are* associated with the missing values (e.g. patients with a high blood pressure are more likely to have blood pressure measured)

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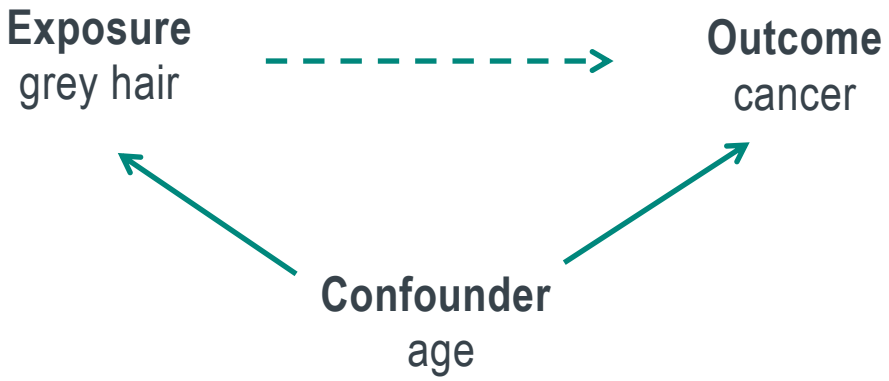
iamson E. (2018) Multiple Imputation for missing data in longitudinal EHRs. UCL.

Confounders

A confounder provides an *alternative explanation* for the association between the exposure and outcome

- It must be associated with the outcome
- It must be independently associated with the exposure of interest
- It must not be on the causal pathway



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ren-Gash C. (2018) Analytic approaches to dealing with confounding.

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Confounders

Can control for confounding

- In the analysis, through *stratification* – display data separately for each level of a potential confounding factor
- Through *multivariable modelling* – measure exposure and outcome and a range of confounders and adjust for these in the analysis
- Through *propensity scores* – estimate the likelihood a patient receives an intervention based on observed population risk factors for receiving the intervention and do matched comparison or adjust in the analysis

Self-controlled case series

- Subject is used as his own control during different time periods
- Eliminates between-person comparison and therefore eliminates between-person confounding

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ren-Gash C. (2018) Analytic approaches to dealing with confounding.

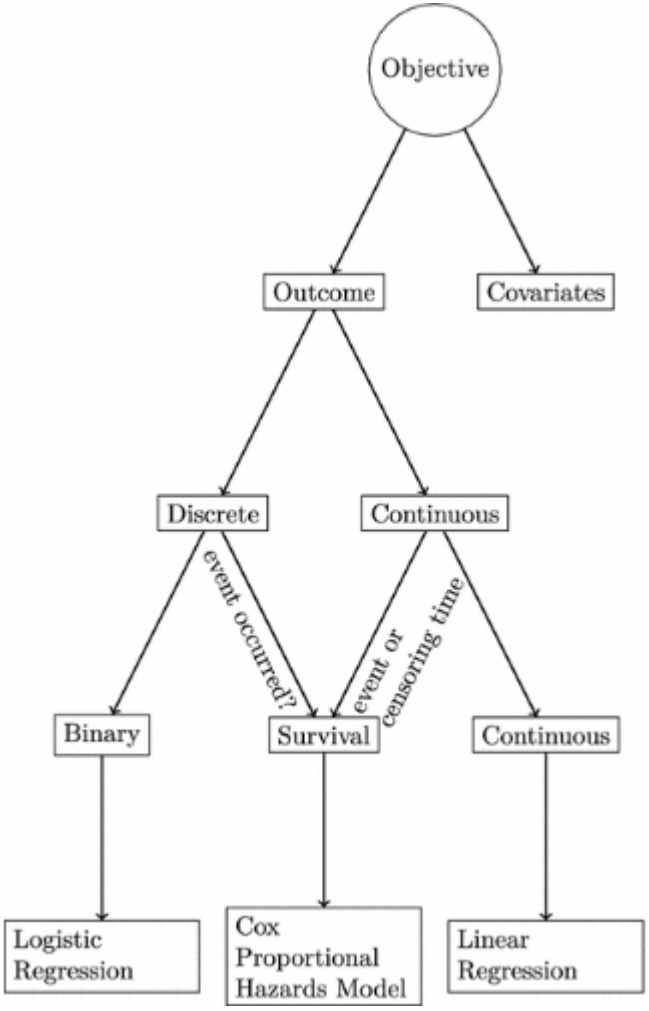
Data analysis

Type of outcome data will inform method for data analysis:

- Discrete (e.g. gender)
- Continuous: can plausibly take on any numeric value

Three common methods of analysis:

- Logistic regression
- Cox proportional hazard model
- Linear regression



Raffa J.D., Ghassemi M., Naumann T., Feng M., Hsu D. (2016) Data Secondary Analysis of Electronic Health Records. Springer, Cham

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UK example using CPRD

Link between autism and MMR vaccine?

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Clinical Practice Research Datalink (CPRD)

- Not for profit research service funded by NHS NIHR & MHRA
- Research using CPRD data has resulted in over 1,800 publications which have led to improvements in drug safety, best practice and clinical guidelines
- Database of longitudinal anonymised NHS healthcare records collecting data from GP practices across UK for over 25 years (1987)
- Covering >710 practices and 14.86 million patients
  - 80% England; 8& Wales; 9% Scotland; 3% NI

Participating UK GP practices

Vision (•) and EMIS (•) practices

NIHR - National Institute for Health Research
MHRA - Medicines and Healthcare products Regulatory Agency
w.cprd.com/home/; Rebecca Ghosh, CPRD presentation, NIHR, 2018

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UK example: MMR and autism

- MMR vaccine: combined vaccine against measles, mumps, and rubella – introduced in the UK in 1988
- To ensure all children are protected in the community from measles, 95% must be fully vaccinated (known as herd immunity)
- In 1998, a study published in The Lancet: MMR vaccination might cause autism
- Following this, MMR vaccine coverage fell internationally
  - At its lowest, herd immunity fell to 80%
  - Measles outbreaks occurred

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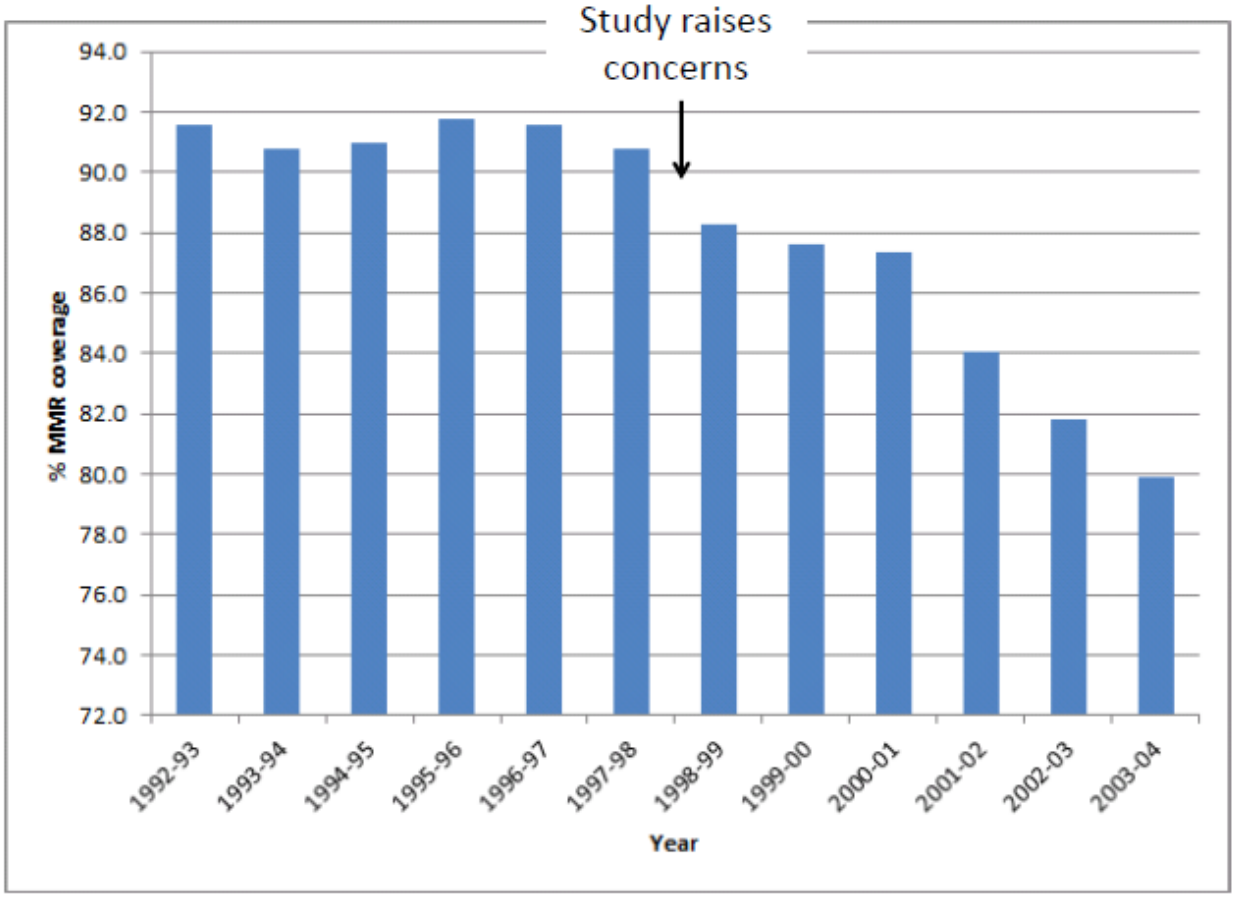
ɔsh R. (2018). Using Primary Care EHRs for Research. CPRD.

UK example: MMR and autism



MMR coverage by time of 2nd birthday, England

NHS Immunisation Statistics, HSCIC

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UK example: MMR and autism

Objectives: Assess the risk of autism and other pervasive developmental disorders (PDD) associated with MMR vaccination

→ Case control using CPRD

- All people registered with a practice contributing to the CPRD during the practice 1988 to 2001
- Born in 1973 or later: therefore eligible to be offered MMR vaccine
- Cases – first diagnosis of a PDD during the study period while registered with a practice contributing to CPRD

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ısh R. (2018). Using Primary Care EHRs for Research. CPRD.

UK example: MMR and autism

- **Cases**
  - first diagnosis of a PDD during the study period while registered with a practice contributing to CPRD

- **Controls**
  - Five controls were selected for each case
  - No diagnosis of PDD
  - Alive and registered with a participating practice on the date of the PDD diagnosis in the case
  - Individually matched to cases by year of birth (+/- 1 year), sex, and GP

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UK example: MMR and autism

- **Exposure**
  - Algorithm to identify children in the CPRD with recorded MMR vaccination was developed; single MMR code not widely used initially

- **Analysis**
  - Conditional logistic regression: primary analysis examined the relationship between MMR vaccination and the odds of being diagnosed with a PDD
  - Adjusted for a range of potential confounding factors

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UK example: MMR and autism

- **Results**
  - 1294 cases and 4469 controls
  - 17.2% female
  - Median age of cases at the recorded diagnosis of PDD was 5.4 years
  - ~ ¾ of cases were classified as autism
  - Any MMR vaccination prior to the diagnosis of PDD or index rate
    - 78% of cases 82.1% of controls
  - Odds ratio for the association between MMR vaccination and autism: 0.86 (95% CI 0.68 to 1.09), P=0.21

- **Conclusions**
  - No convincing evidence that MMR vaccination increases the risk of autism or other PDDs
  - No association found in rigorously conducted studies in a range of different settings

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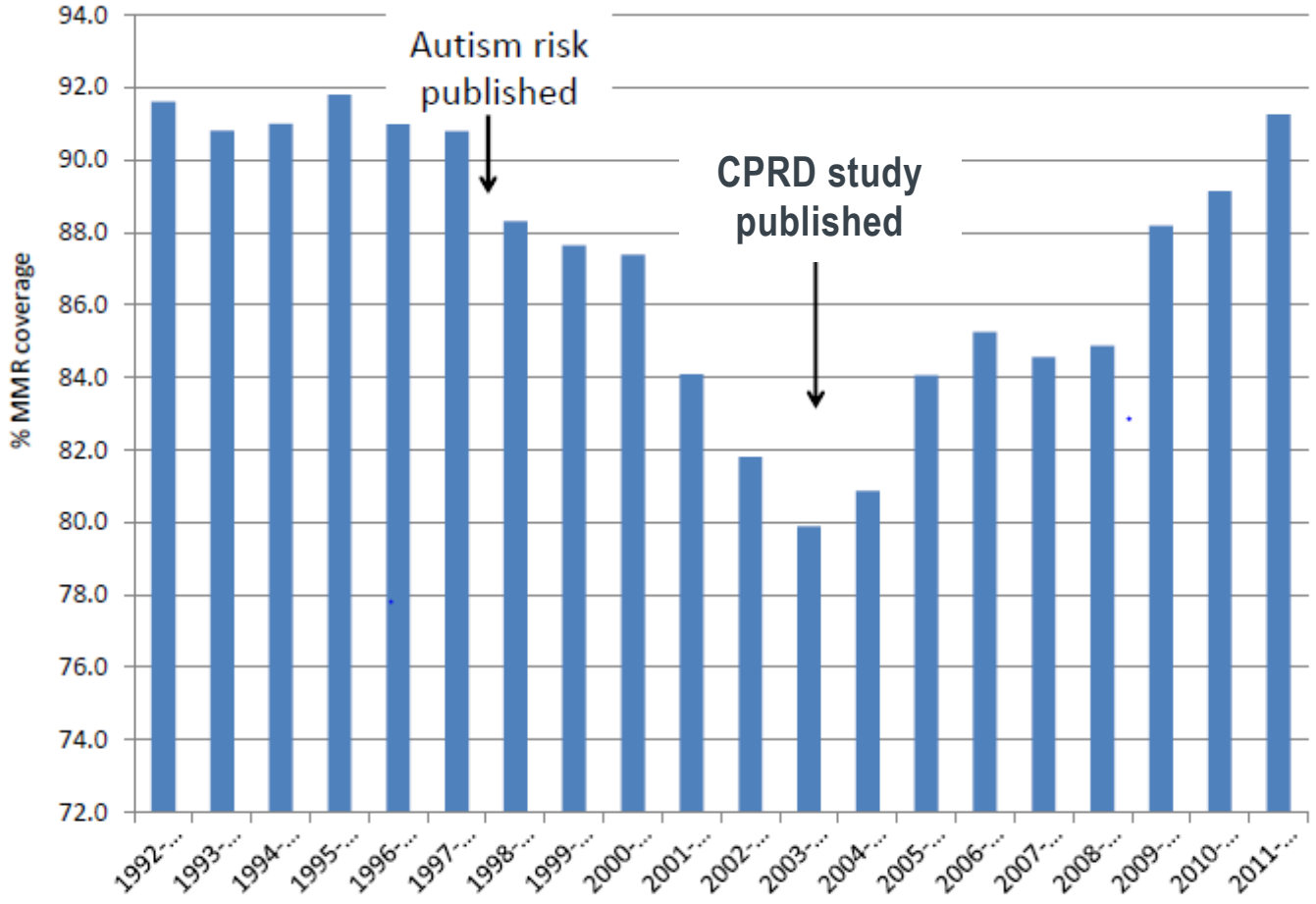
UK example: MMR and autism



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THANK YOU! QUESTIONS?

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