Introduction to Real World Evidence Studies

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Forbes Magazine May 2018:

Will Real World Performance Replace RCTs as Healthcare's Most Important Standard?

IPI Technology

Social Media-sourced Real-world Evidence – A Novel, Cheap, Effective Method

Big Data: Prescription for the Pharmaceutical R&D Plight

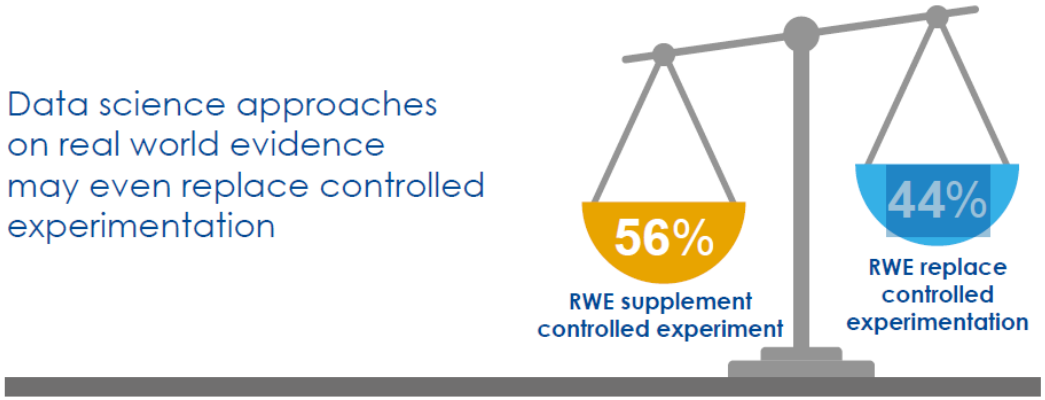
THE BENEFITS OF SOCIAL MEDIA SOURCED RWE:

- Low-cost solution in comparison to RCTs; often up to a tenth of the cost
- Data is collected on a large scale, enabling detailed / granular analysis
- Studies can be conducted into areas where conventional healthcare research is not possible, or difficult
- The data collection process is not governed by clinical trial regulations, offering greater control
- It provides eviden
  strengthen existin
  develop new ones

SURVEY HIGHLIGHTS

Cytel

Data science approaches on real world evidence may even replace controlled experimentation



CEBM
CENTRE FOR EVIDENCE BASED MEDICINE

UNIVERSITY OF OXFORD

The Institute of Clinical Research

Levels of Evidence (March 2009)

www.cebm.net

Level 1A	Therapy/Prevention, Aetiology/Harm	1a SR (with homogeneity*)of RCTs
	Prognosis	SR (withhomogeneity*) of inception cohort studies; CDR† validated in different populations
	Diagnosis	SR (with homogeneity*) of Level 1 diagnostic studies; CDR† with 1b studies from different clinical centres
	Differential diag/symptom prevalence	SR (with homogeneity*) of prospective cohort studies
	Economic and decision analyses	SR (with homogeneity*) of Level 1 economic studies
Level 1b	Therapy/Prevention, Aetiology/Harm	Individual RCT (with narrow Confidence Interval‡)
	Prognosis	Individual inception cohort study with > 80% follow-up; CDR† validated in asingle population
	Diagnosis	Validating** cohort study with good††† reference standards; or CDR† tested within one clinical centre
	Differential diag/symptom prevalence	Prospective cohort study with good follow-up****
	Economic and decision analyses	Analysis based on clinically sensible costs or alternatives; systematic review(s) of the evidence; and including multi-way sensitivity analyses
Level 1c	Therapy/Prevention, Aetiology/Harm	All or none§
	Prognosis	All or none case series
	Diagnosis	Absolute SpPins and SnNouts††
	Differential diag/symptom prevalence	All or none case-series
	Economic and decision analyses	Absolute better-value or worse-value analyses ††††
Level	Therapy/Prevention, Aetiology/Harm	SR (with homogeneity*) of cohort studies
	Prognosis	SR (withhomogeneity*) of either retrospective cohort studies or untreated control groups in RCTs

Levels of Evidence for Therapy

- 1A – Systematic Review (with homogeneity) of Randomised Clinical Trials
- 1B – Individual RCT with narrow Confidence Interval
- 2A - Systematic Review (with homogeneity) of cohort studies
- 2B – individual cohort study
- 3 – Case control studies
- 4 – Case series (and poor quality cohort and case control studies)
- 5 – Expert opinion without explicit critical appraisal

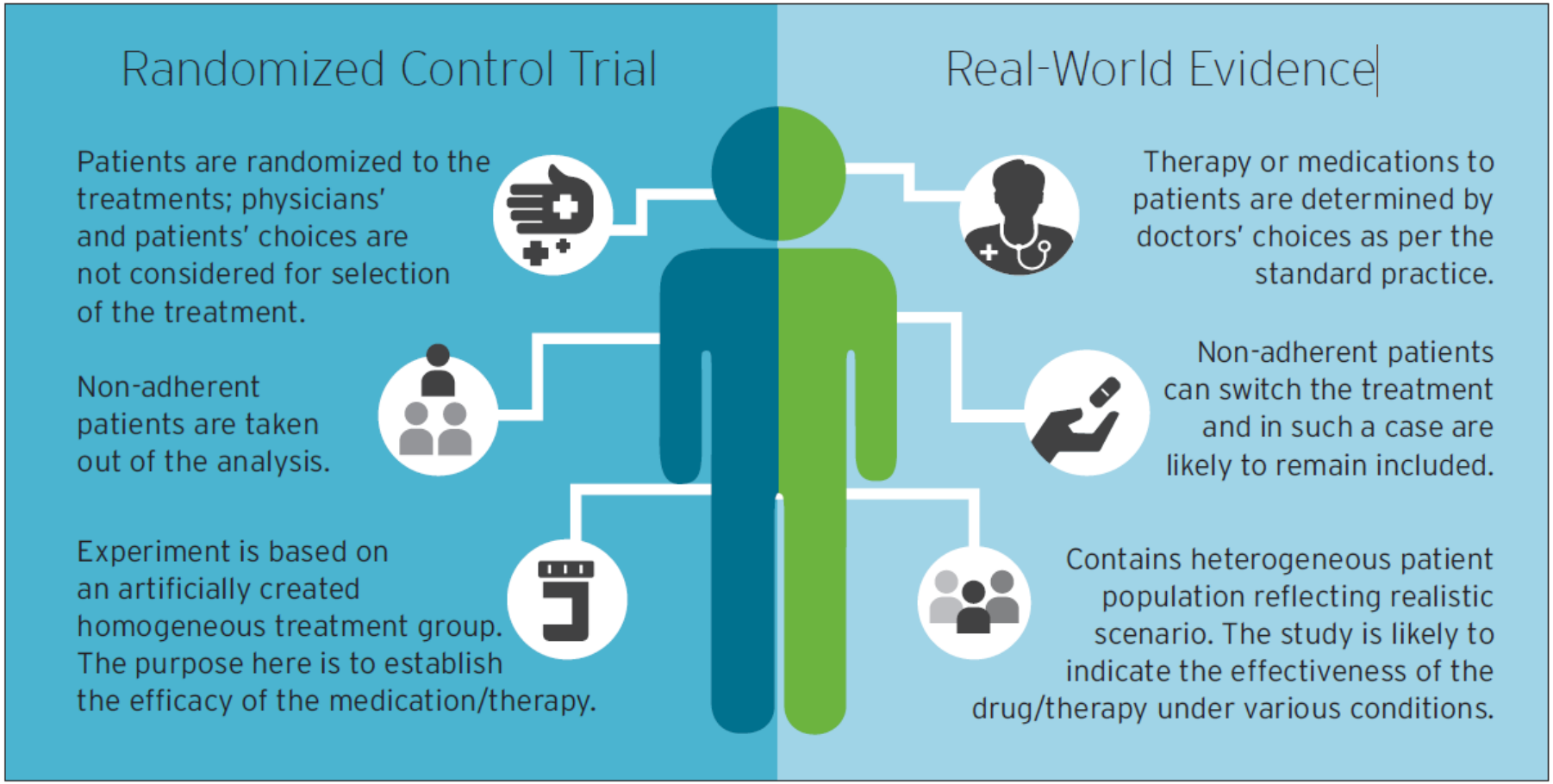
Why are RCTs seen as the "Gold Standard"?

- Randomisation ensures that treatment groups are similar in every respect other than the investigative treatment applied;
  - For factors which are known to be important
    - Could stratify the randomisation to improve precision
  - And for factors whose impact is unknown
- Blinding ensures that assessment of outcome is not affected by knowledge of the patient's assigned treatment (by patient or investigator or operational staff)
- Avoids bias
- High internal validity

But …

- “Your trials include
  - Patients from 18-65
  - Generally healthy apart from disease you are investigating
  - Taking no other drugs
- “The patients I see are
  - Mostly over 65
  - Suffering from several diseases
  - Taking multiple drugs
- “How can I be sure that your trial results are applicable to my patients?”
- Does your drug work in the real world?

RCT vs. RWE


Randomized Control Trial
Real-World Evidence
Patients are randomized to the treatments; physicians' and patients' choices are not considered for selection of the treatment.
Non-adherent patients are taken out of the analysis.
Experiment is based on an artificially created homogeneous treatment group. The purpose here is to establish the efficacy of the medication/therapy.
Therapy or medications to patients are determined by doctors' choices as per the standard practice.
Non-adherent patients can switch the treatment and in such a case are likely to remain included.
Contains heterogeneous patient population reflecting realistic scenario. The study is likely to indicate the effectiveness of the drug/therapy under various conditions.

Sources of RWE

- Patient claims
  - Hospital claims – episode level
  - Provider claims – procedure level
  - Prescription claims
- Patient / Medical registries
  - Focused on target populations
- Electronic Health Record (EHR) / Electronic Medical Record (EMR)
  - Patient-level record from single provider practice (EMR) or multiple practices (EHR)
- Social data
  - Patient interaction on diseases, treatment experiences and side effects
  - Facebook, Twitter, Medhelp, PatientsLikeMe …

Real World studies

- Follow up patients in a normal environment, rather than using artificial clinical trial procedures
- Examine use of the product in patients with
  - Co-morbidities
  - Concomitant medication
- Can be much cheaper with computerised databases
  - Though the data owner may charge you heavily!
- Good external validity
- So why less highly regarded?

Example - Nurses Health Study 1976

- After menopause, rate of heart disease in women rises
- Is it worth giving oestrogen and progesterone after menopause to lower rate of heart disease?
- 127,000 nurses aged between 30 and 55 entered study and completed questionnaires every two years
  - 90% of questionnaires returned
- Grodstein et al (NEJM 1996) showed oestrogen users had 40% fewer heart attacks than those taking no hormones
- Later paper showed similar result in women taking oestrogen and progesterone
- Millions of prescriptions followed

Women's Health Initiative 1991

- Randomised 16,000 women aged 50-79 to
  - oestrogen and progesterone
  - Or placebo
- Study was stopped 3 years early because of higher rates of
  - Breast cancer, Heart disease, stroke, pulmonary embolism
  - 7 / 8 / 8 / 8 more events per 10,000 women
  - In the active group.
- The well-designed NHS observational study had missed these effects: why?

The women who took hormones in NHS

- Were less likely to
  - Have family history of heart disease
  - Have hypertension or diabetes
  - Smoke
- Were more likely to
  - Take aspirin, birth control pills, vitamins
  - Be Younger
  - Drink more alcohol
  - Eat more saturated fat
- And they were wealthier
- These are called CONFOUNDING VARIABLES

Confounding variables

- Maybe one of the differences in confounding variables masked the effect, eg aspirin or …
- Any one explanation is plausible but their effects are all mixed up together or confounded.

Example RWE paper

Current Medical Research and Opinion

ISSN: 0300-7995 (Print) 1473-4877 (Online) Journal homepage: http://www.tandfonline.com/loi/icmo20

Real-world glycemic, blood pressure, and weight control in patients with type 2 diabetes mellitus treated with canagliflozin—an electronic health-record-based study

Patrick Lefebvre, Dominic Pilon, Marie-Noëlle Robitaille, Marie-Hélène Lafeuille, Wing Chow, Michael Pfeifer & Mei Sheng Duh

Quality questions

- Focussed issue?
  - Defined goals for HbA1c, blood pressure and weight control
  - Simple summary analyses: no claims for anything dramatic
- Recruitment of cohort acceptable = free of bias?
  - IMS Real-World Data
    - Includes primary care / specialists, Medicare / Medicaid / commercial / cash patients
    - March 2012 – September 2014 (product approved by FDA in March 2013)
    - 18 years plus (so includes older patients)
    - Diagnosis for T2DM
    - CANA prescription
    - 12 months plus clinical records before index date

Recognised limitations in paper

- No link to secondary care data
- Prescribing drug does not guarantee it was taken
  - Correct in real world study?
- Ignores use of drug samples to initiate patients
- Missing information may affect the results
- Changes in anti-hypertensive / anti-hyperglycaemic / weight loss medication not tracked
- Duration of CANA treatment under-estimated as it may continue
- Adverse events not reported

Follow-up of subjects – Table 2

- Are patients with two years complete IMS data representative?
  - 20,725 patients with T2DM and CANA
  - 16,163 (78%) had 12 month pre-baseline data and were 18+ years
  - 11,984 had HbA1c assessment pre-index with 10,478 over 7%
  - 6,912 had HbA1c assessment within 45 days of index date
  - 3,612 had HbA1c assessment at 3 month timepoint
    - 17% of original cohort
  - 619 at 12 months - 3% of original cohort
  - Are those with more frequent measurements the more problematic patients?

COMPROMISES BETWEEN RWE AND RCTs: Pragmatic trials

- In cases where genuine uncertainty exists about best treatment
  - Allow medical practitioners to randomise patients to treatments
  - Then follow up as normal
  - Randomisation ensures that treatment groups are comparable
- Or randomise practices to treatment
  - Then treat all patients within that practice the same
- Following up Overall Survival in an oncology trial where patients have crossed over to other treatments uses a technique related to Propensity Score matching

PROBE TRIALS

- Prospective
- Randomised
- Open
  - For patient and investigator
  - Operational study team may be blinded to avoid bias
- Blinded endpoint
  - Assessed by blinded individual not connected to study
- Example of FAST study

Open Access Protocol

BMJ Open

Protocol of the Febuxostat versus Allopurinol Streamlined Trial (FAST): a large prospective, randomised, open, blinded endpoint study comparing the cardiovascular safety of allopurinol and febuxostat in the management of symptomatic hyperuricaemia

Thomas M MacDonald,[1] Ian Ford,[2] George Nuki,[3] Isla S Mackenzie,[1] Raffaele De Caterina,[4] Evelyn Findlay,[1] Jesper Hallas,[5] Christopher J Hawkey,[6] Stuart Ralston,[3] Matthew Walters,[7] John Webster,[8] John McMurray,[7] Fernando Perez Ruiz,[9] Claudine G Jennings[1]

FAST study

- Post Approval Safety Study (PASS) to address CV safety concerns when febuxostat was approved by EMA (2008)
- Recruited patients are
  - Aged over 60
  - Prescribed allopurinol for symptomatic hyperuricemia
  - Have at least one additional CV risk factor
- Patients randomised to optimal dose allopurinol or febuxostat (80-120mg)
- Followed up for at least 2 years through electronic records *
  - average of 3 years
  - Expected 2 year recruitment period
    - * EMA insisted on annual face-to-face assessments

FAST study

- Primary endpoint is occurrence of APTC event
  - Non-fatal MI
  - Non-fatal stroke
  - CV death
- Secondary endpoints
  - All-cause mortality
  - Hospitalisation for specified CV events
- Objective to demonstrate that febuxostat is non-inferior to allopurinol
  - Hazard ratio < 1.30

What to do?

- '*I keep saying the sexy job in the next ten years will be statisticians … those skills – of being able to access, understand, and communicate the insights you get from data analysis – are going to be extremely important.' (*Google Chief Economist Hal Varian, 2009)
- '*What sets statisticians apart? … our understanding of and ability to quantify uncertainty … guarding against false discovery, bias, and confounding*.' (Lisa Lavange, FDA Director of Statistics 2014)

Key statistical questions

- Is there scope for bias in
  - Data collection?
  - Data presentation?
  - Selective presentation of results?
- Have all data been included?
  - Does the fact that data is missing tell you something about the treatment?
- Are claims made backed up by
  - Full data disclosure?
  - Estimates of false discovery rates?

RCT or RWE?

- Both bring great value
- RCT assesses efficacy
  - Can the drug work?
- RWE assesses effectiveness
  - Does the drug work in practice?
- If RWE contradicts results of RCT would you change your drug label?

QUESTIONS?