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Randomised evaluation of accepted choices in treatment (REACT) trials

Tjeerd van Staa
Clinical Practice Research Datalink
Utrecht University
London School of Hygiene & Tropical Medicine

Disclosures

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CPRD is owned by the UK Department of Health and operates within the Medicines and Healthcare products Regulatory Agency (MHRA). CPRD has received funding from the MHRA, Wellcome Trust, Medical Research Council, NIHR Health Technology Assessment programme, Innovative Medicine Initiative, UK Department of Health, Technology Strategy Board, Seventh Framework Programme EU, various universities, contract research organisations and pharmaceutical companies.

Content of presentation reflects my personal views and not those of my employer

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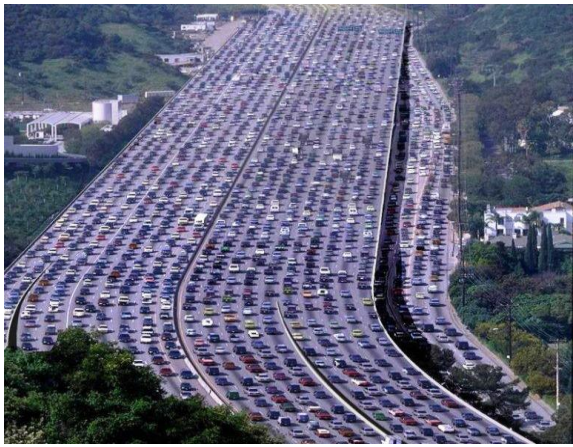
Phases of drug development (one view)

=>



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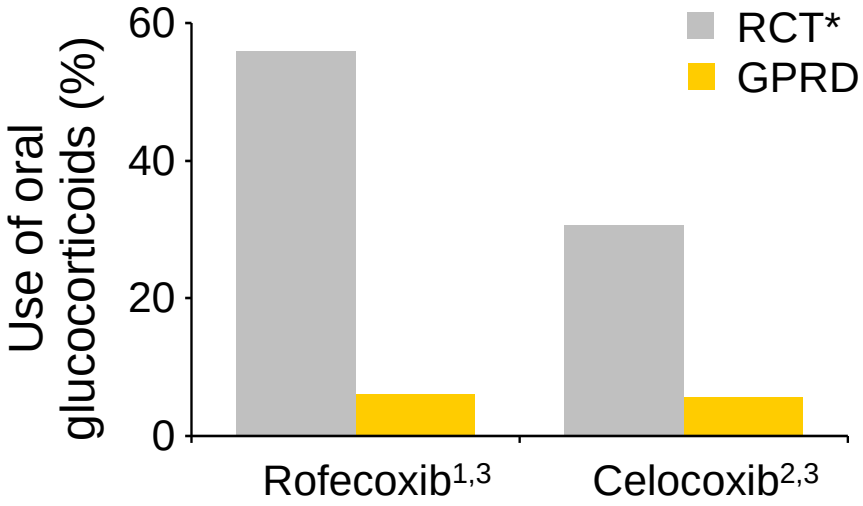
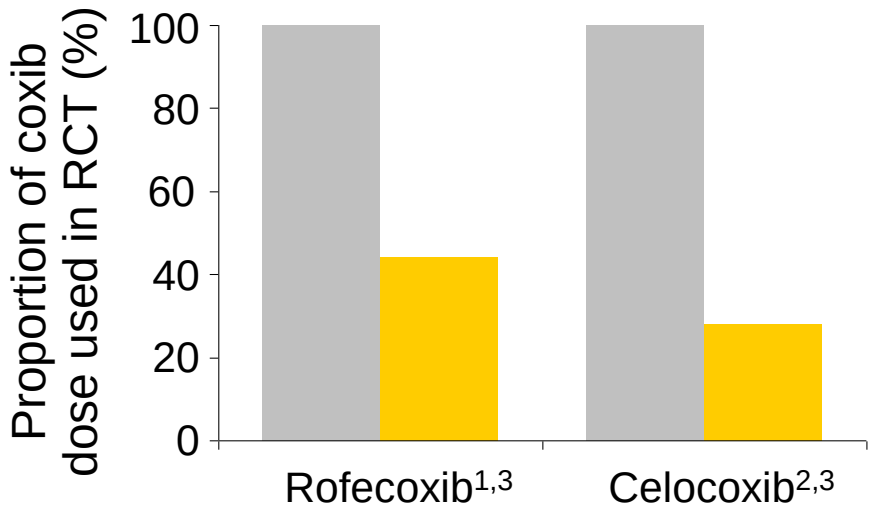
Trial population ≠ population in actual clinical practice





1. Bombardier C, et al. *N Engl J Med* 2000;343:1520-28.
2. Silverstein FE, et al. *J Am Med Assoc* 2000;284:1247-55.
3. Van Staa et al Plos Medicine.

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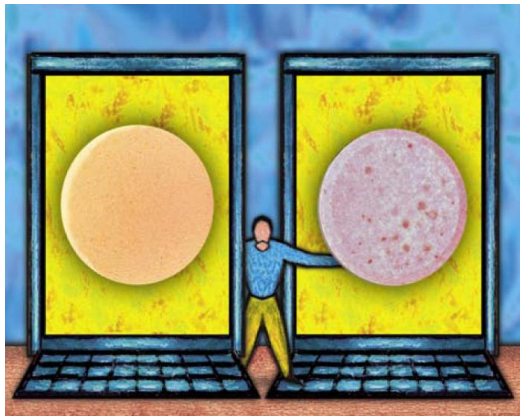
Pragmatic randomised trials using routine electronic health records

What to prescribe for a patient in general practice when the choice of treatments has a limited evidence base? **Tjeerd-Pieter van Staa and colleagues** argue that using electronic health records to enter patients into randomised trials of treatments in real time could provide the answer



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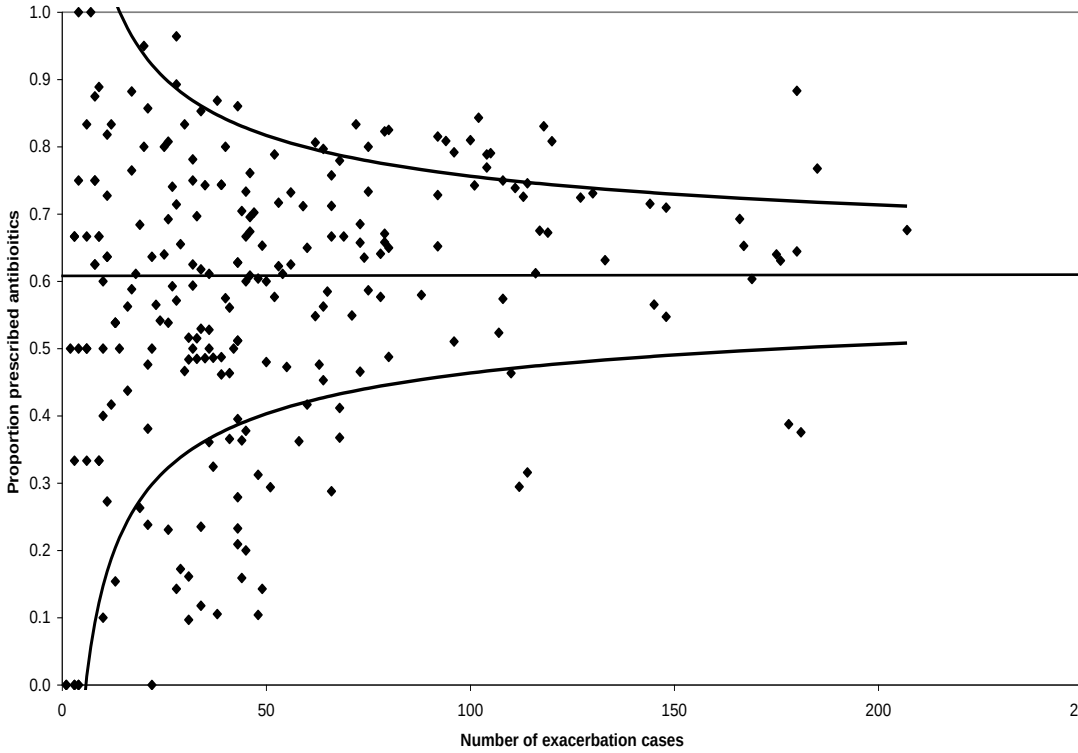
REACT trials: when to do and when not!



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Impetus for REACT trials

- Confounding often insurmountable in epidemiological studies

- Randomisation with systematic data collection is the most rational and ethical way to resolve uncertainties

- EHR + linked databases
  - Identification of eligible patients
  - Clinician to confirm + recruit
  - Long-term unobtrusive follow-up of major clinical outcomes

- Simple trials (for clinicians) integrated with standard care
  - ‘randomise and then forget’ trials (misnomer)

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- Central repository of anonymised EHRs
- EHR records of General Practitioners across the UK = central healthcare provider; EHR for record keeping
- About 8% of the population included
- Pseudo-anonymised records (using opt-out system)
- Linked to other datasets using NHS number (e.g. hospital data, death certificates, registries)
- Quality standards
- Regular transmission of data from practice to CPRD (monthly update of research database)
- Number of practices to increase

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Ongoing individual pragmatic trials

-RETRO-PRO: the effectiveness of simvastatin compared to atorvastatin—a feasibility study (ISRCTN33113202)

-eLUNG: the effectiveness of antibiotics compared to no antibiotics for exacerbations of chronic obstructive pulmonary disease: a feasibility study (ISRCTN72035428)

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Recruitment models in REACT

- Hot recruitment: e.g. COPD exacerbations
  - Flagging software
  - Clinicians directly go to study website

- Cold recruitment: e.g. statins in CVD
  - Regular email to clinician of list of potentially eligible patients
  - Clinicians directly go to study website
  - (Flagging software)

Data flow in REACT trials

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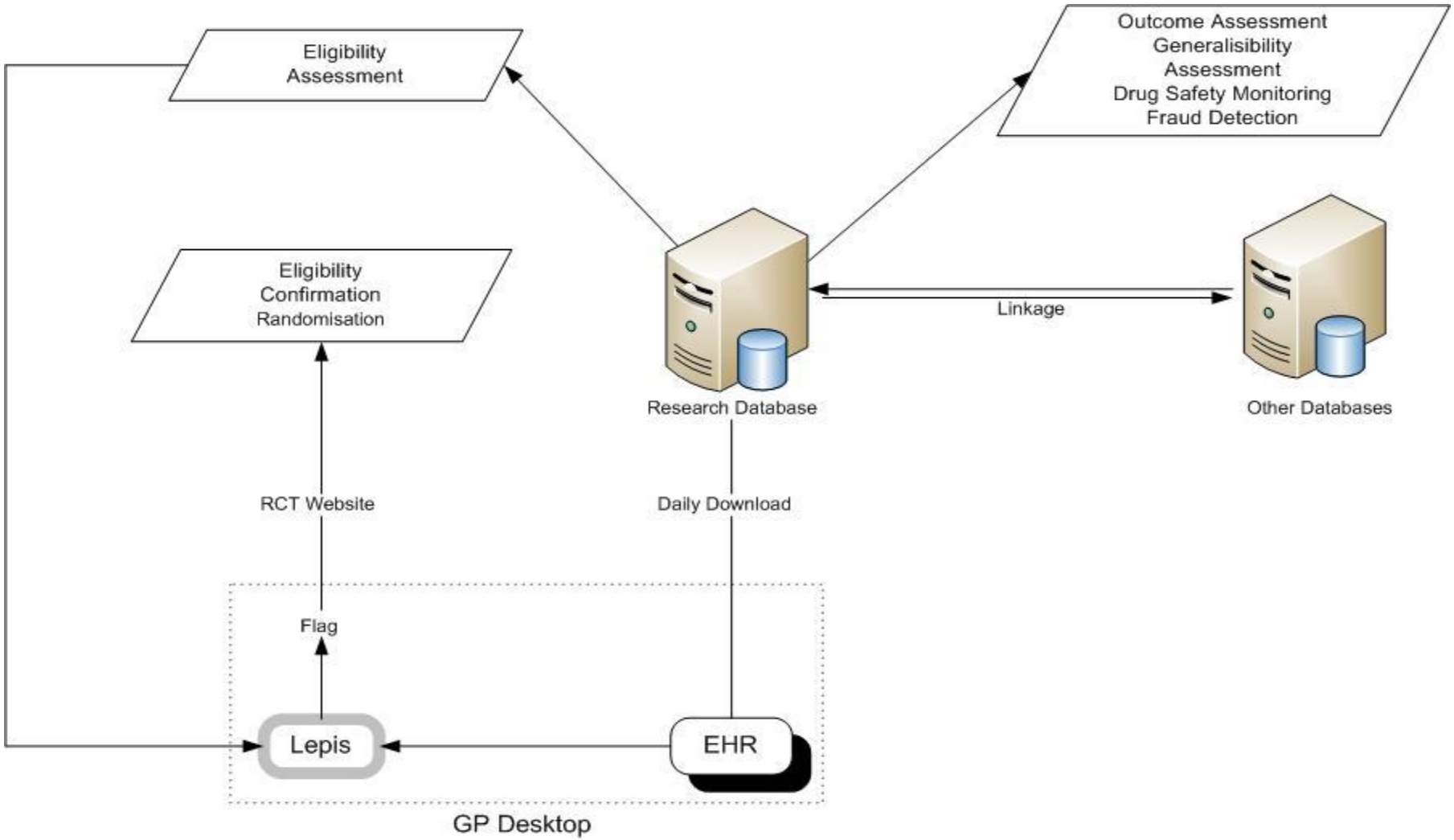

Follow-up in REACT trials

- Treatment allocation not blinded

- Major clinical outcomes
- Persistence to treatment
- Additional data may be collected
  - QoL+FEV1 with eDiary in eLung
  - Blood test for genetic analyses at month 3
- Daily checks for ADRs (study website / EHR data) => email to PI => if SUSAR, then electronically reported to regulator
- Monthly analyses of recruited patients versus non-trial patients
- Fraud detection (in development)

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Examples of monitoring in REACT trials

	rct recruited patients	Non-recruited statin starter in RCT Practice	statin starter in non-RCT Practice
	N=10	N=260	N=2743
men	7 (70%)	134 (51.5%)	1398 (51%)
mean age_index	64.5 (5.3)	61.8 (9.9)	62.2 (11)
mean cholesterol_hdl_ratio	5.5 (0.6)	5 (1.9)	4.9 (1.5)
amlodipine use at baseline	2 (20%)	37 (14.2%)	408 (14.9%)

			number of cases	rate	Crude RR
coronary artery disease	rct_patient	yes	0	0	0 (0 -.)
		no	9	5.21	
	rct_practice	yes	2	12.14	2.89 (0.6 -13.93)
		no	7	4.47	

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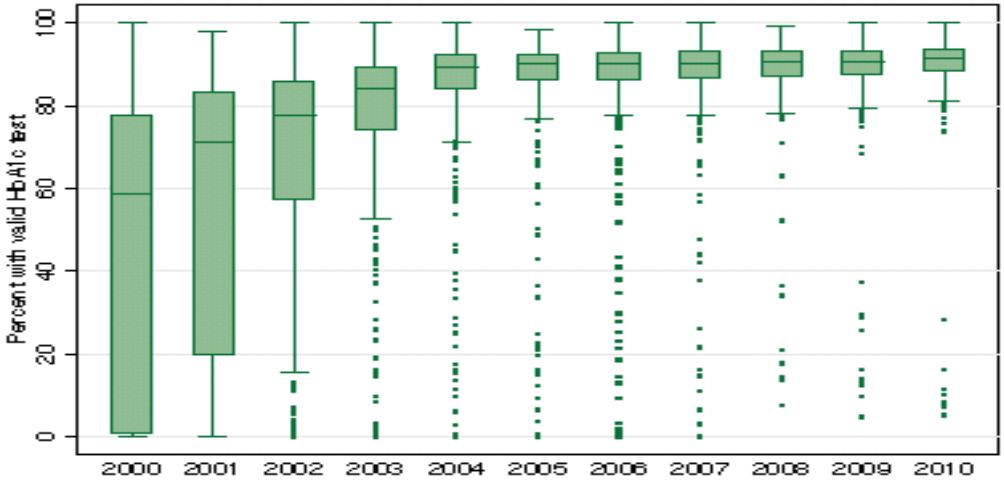
Data quality in REACT

- Linked observational databases (e.g long-term follow-up)
- Clinician to confirm outcome (eCRF)
- Collect e.g. pharmacogenetic information
- Blinded outcome assessment
- Systematic data quality measurement across clinics:



DROWNING in DATA

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Infrastructure challenges + opportunities in REACT

- Opportunities:
  - UK GPs central healthcare providers – all use EHR
  - Ability to link to other datasets using NHS number
- Challenges:
  - Hospitals: limited EHR (use of disease registries / admission data collected for administrative purposes)
  - Medical data rarely uniformly recorded (will they ever???)
  - Linked datasets: not interoperable (will they ever???)
  - Data / systems change over time
  - Flagging system for REACT
    - loading software / firewall issues

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Integrate REACT with clinical care

- Statins not being used in accordance with the license
- Prescribing guidelines:
  - e.g. need to switch patients to simvastatin at official end of trial (3 months)
- Prescribing habits of clinicians
- Safety information updates affect one drug:

Simvastatin: updated advice on drug interactions - updated contraindications : MHRA

MHRA

Drug Safety Update

Volume 6, Issue 1 **August 2012**

Latest advice for medicines users

Simvastatin: updated advice on drug interactions – updated contraindications

Article date: 20 August 2012

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Stakeholders in REACT trials

- Patients: qualitative study ongoing including refusers / representatives on Trial Steering Committee very supportive
- Clinicians:
  - "too cumbersome and time intensive"
  - UK ethics guidelines (GMC): clinician's duty to help to resolve uncertainties
- Local healthcare funders / health technology organisations: not yet fully appreciative
- Research funders: very interested but closely monitoring our 'trials and tribulations'
- Regulatory authorities
- Pharmaceutical industry
- Academic researchers

Resources for REACT trials

- IT systems: developed for generic use + re-apply to new studies
- EHR data collection: routinely done
- Daily processing and ADR system: automated

- *Staff costs for approval processes*
- *Costs to reimburse clinician*

- Staff costs to identify and monitor trial patients and analyse results
- Costs for trial team

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Policy-related challenges

- Research governance seems to be based on high risk trials:
  - e.g. need to train GPs
- Informed consent procedures: ‘skimpiest ever’ form
- GCP: from paper to EHR
- To do research on prescribing guidelines (e.g. to address low-level evidence)
- What is the end of a REACT trial?
- SUSAR reporting requirements
- Clinicians’ incentives: research not always recognised as part of professional development
- Research agenda to be set by clinicians and patients

The good and the bad…

- The positives:
  - EHR rather than paper is the future!
  - System works for daily eligibility assessment / on-off recruitment / ADR review / comparison non-RCT patients / central data monitoring / fraud detection / long-term follow-up
  - Patient representatives on Steering Committee supportive!
  - Some clinicians are interested

- The challenges:
  - Not all outcomes may be recorded well in EHR
  - *Simple* trials do not (yet) exist - research governance / informed consent procedures
  - Additional data collection (e.g. QoL / eDiary)
  - Most clinicians are not interested in research

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So where do we go?

- REACT trials work!

- Research governance: safeguarding trial subjects <u>but also</u> promoting research
  - What is cost of not doing trial?
  - Why always so complex?

- Why not randomise in case of uncertainty as a matter of routine rather than exception: learning Health Care System?

- REACT trials may also directly benefit trial participants

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