Data-enabled RCTs: examples from registry-based and EHR-based trials

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Trials Methodology TMRP Research Partnership

My RCT experience

- CTU Director - predominantly comparative effectiveness trials
- Have (almost) always considered best source of data at the design stage (particularly for eligibility assessment, outcome data)
- Common to access HES data for cost-effectiveness analysis
- Lesson learnt: do not underestimate the Information Systems resource requirements



"NHS digital transformation ….. making data captured for care available for clinical research"

"How can randomised trials become part of routine care and best utilise current clinical care pathways?"

PRioRiTy
Prioritising Recruitment in Randomised Trials

Examples

- **CF START** – a registry-based randomised CTIMP
- **DECIDE** – an EHR-based point-of-care RCT
- **UK IBD Registry** – maximising the registry's potential
- **ISDR** – an NHS screening programme-based RCT

Issues to consider: Design

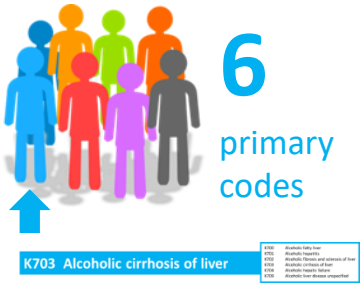
- Data quality – upfront investment of time
- **Patient identification**
- **Outcome data**
- Treatment data - more or less likely to be available?
- Information systems resource

ARLD: Identifying patients

Standard approach: Primary

3,201 spells - 36,119 bed days

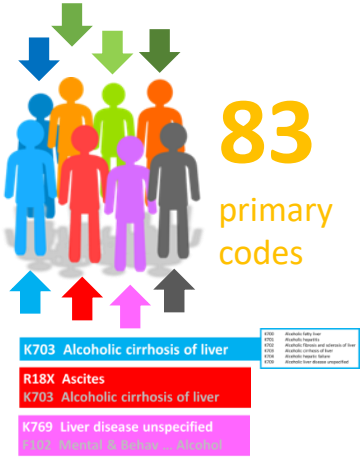
SEVEN ACUTE TRUSTS, CHESHIRE & MERSEY (3 YEARS)



Clinical approach: Algorithm

6,054 spells - 57,736 bed days

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Outcome data

- Relevance, accuracy, completeness

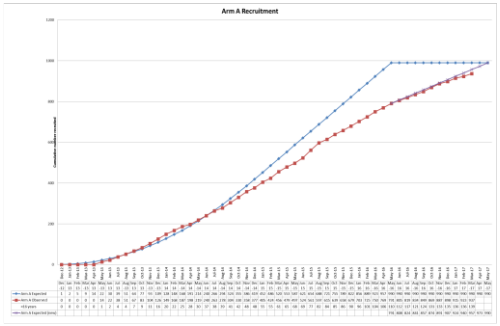
- What is missing visit in this context?

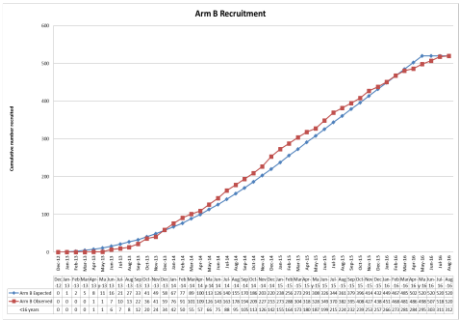
- informative measurement (patient unwell)

- absence (does not affect patient so outcome not discussed/recorded)

- Visit timing windows (e.g. 52 weeks +/- 2 weeks) – more or less of a problem than usual?

SANAD II





- Core outcome set exists (ILAE, patients' views)
- 12-month remission (98 patients):

  46% (CRFs) vs 74% (EHR)
- Follow-up seizures poorly recorded in the EHR
- EPiNET system

MRC HTMR PhD – Dr Graham Powell

- Review of the use of UK routine data sources **in RCTs** published before 2016

- registry mortality and secondary care data most common
- primary care data infrequently accessed

Systematic review of 37 studies assessing agreement between routine data with that collected in RCTs using typical methods

- reasonable agreement for all-cause mortality
- variable agreement for other clinical and resource use data

a new journey

CF START

CF START

The Cystic Fibrosis (CF) anti-STaphylococcal Antibiotic prophylaxis Trial; a randomised Registry Trial to assess the safety and efficacy of flucloxacillin as a long-term prophylaxis agent for infants with CF

Newborn Screening Laboratory
Positive NBS result (14-21 days)

Early Diagnosis from another route
Family history, meconium ileus or antenatal screening

Regional CF Centre
Diagnosis Confirmed

Excluded from CF START
CF Diagnosis excluded
Equivocal diagnosis (CFSPID)
Age > 70 days
PsA already identified

Treatment options discussed with local CF team

Families informed about CF START
Information sheet/website/video

One week Routine CF treatments gradually introduced (including home visits, admission if concerns)

Decline consent
No permission to use Registry data

Consent for CF START
And Registry

Decline consent
Permission to use Registry data

CENTRAL RANDOMISATION (IVRS, linked to Registry with prompts)

"Prevent and Treat"
(Flucloxacillin)
220 infants

"Detect and Treat"
(Antibiotics in a more targeted manner)
220 infants

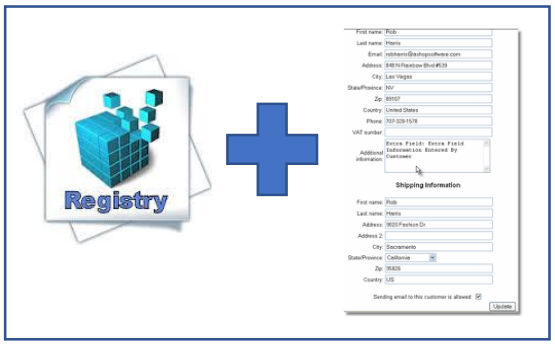
CF Network Care | CF Centre Care | CF Network Care | CF Centre Care

Routine clinical care Encounter based Registry data entry (at least every 3 months)
Primary outcome, time to first growth of PsA. Secondary outcomes include, SA infection, resistant bacteria, need for extra antibiotics (oral and intravenous), need for hospital admission and respiratory symptom questionnaire.

Multiple Breath Washout Measurement 40-48 months at GOSH (200 children)

Data Analysis at 48 months ITT and CACE, reporting and dissemination

CF START cohort Longterm follow-up (registry) and knowledge translation



a new journey
CF START



- First registry-based CTIMP RCT in children
- National CF registry (UK CF Trust - custodians of the registry) used to:
  - Assess eligibility
  - Randomise – linked to registry
  - Collect trial outcomes including
    - Primary outcome measure – already collected in registry
    - Secondary measures – 'need for acute antibiotics' added in
    - Safety outcomes - built-in email alert if SAR form is triggered

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Cystic Fibrosis Trust

a new journey
CF START

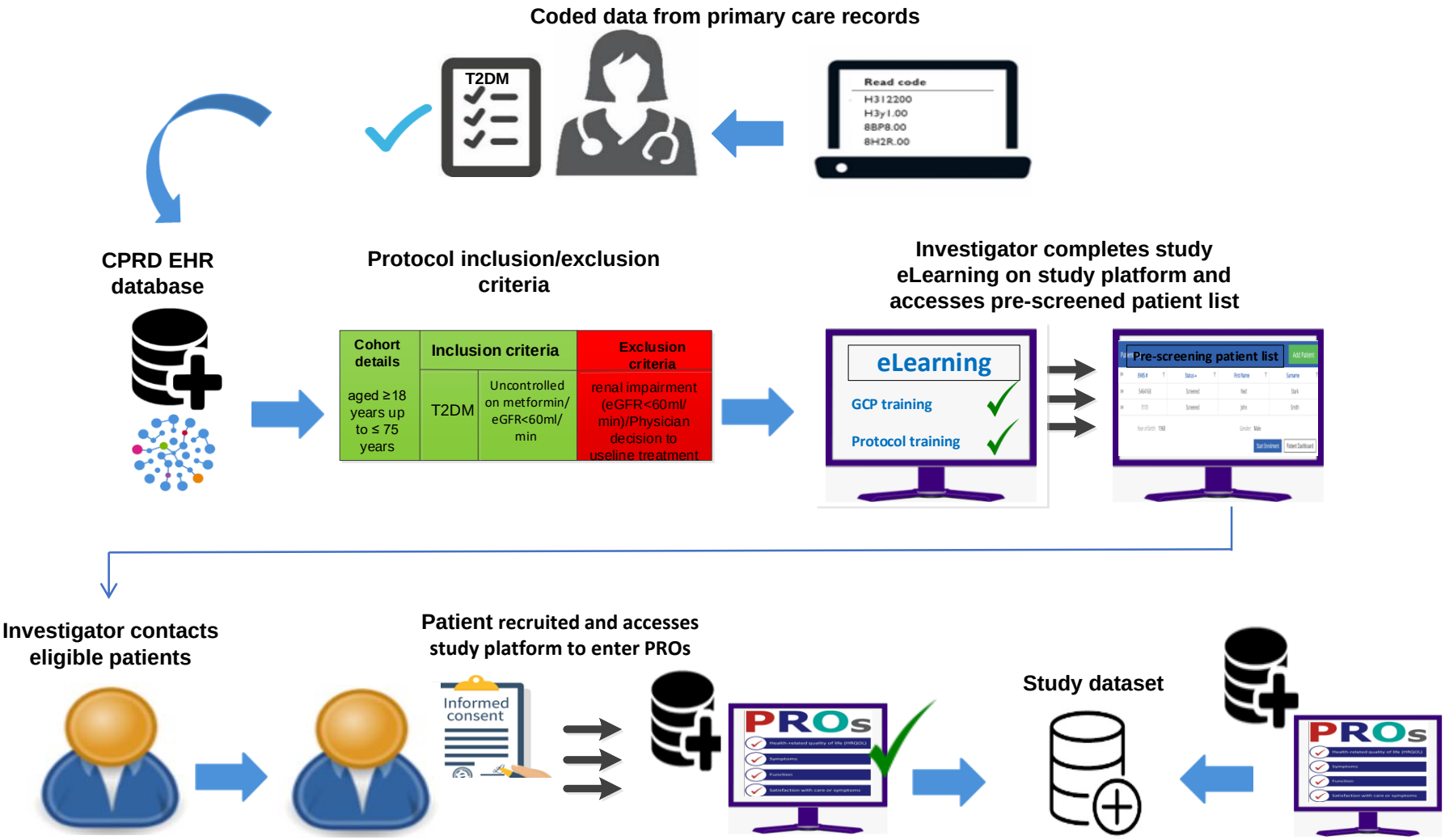
- Registered and randomized - %
- Assessment of external validity
- Condition-specific registry

- organic and ever evolving database; several updates a year
- testing to ensure registry and trial data remain robust
- close working between the registry and CTU teams

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CPRD recruitment process for DECIDE



DECIDE: Recruitment and outcome data

- Cohort eligibility algorithm created in search engine (TrialViz)
- Study platform (interoperable search engine; Clinical Trial Management System; Site Management System; Study Database) built in 6 months)
  - Study Designer (configurator)
  - Portal for patient and investigator
  - eLearning controlled access
  - User Dashboard and journey
  - Mapping from EHR
  - Real-time pre-screened patient list*
  - Consent and randomisation
  - EDC for EHR and eCRF
  - SAE reporting

  - * on platform for vision users and in EMIS system for EMIS users

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Trials Methodology

TMRP

Research Partnership

Health Informatics Working Group

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https://www.methodologyhubs.mrc.ac.uk/about/tmrp/