Pragmatic trials in the real world: DaRe2THINK – a novel approach to healthcare-embedded clinical trials

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The Medicines and Healthcare products Regulatory Agency regulates medicines, medical devices and blood components for transfusion in the UK.

The National Institute for Biological Standards and Control (NIBSC) plays a leading national and international role in assuring the quality of biological medicines and diagnostics.

Clinical Practice Research Datalink (CPRD) is a real-world research service supporting retrospective and prospective public health and clinical studies.
What is CPRD?

UK Government health data research service supporting observational & interventional public health and clinical studies by academics, industry and regulators worldwide.

Services based on > 30 years of collecting longitudinal primary care EHR across UK.

- **60 million** Patients for observational studies
- **16 million** Patients for trials & clinical studies
- **Median 10 years follow-up** 25% 20 years follow-up
- **GP Network** 1 in every 5 GP practices in UK

Daily data collection, 25% UK population coverage, Representative data.
Collect all coded data in EHR except patient identifiers

Over 14 billion consultations

Drug exposure
Diagnoses and symptoms
Referrals
Laboratory tests
Vaccination history
Demographic data
Extending the scope of research through linkage

Primary care data

- Small Area Data
- Cancer registry
- Mental Health
- ONS death
- COVID-19
- SGSS
- CHESS
- ICNARC
- CPES
- SACT
- RTDS

HES APC
HES OP
HES A&E
HES DID
ONS death
Impact of CPRD data on public health

2600 peer-reviewed publications using CPRD data

- Drug safety
- Drug use
- Disease epidemiology
- Incidence/prevalence
- Care delivery

Sources:
- BMJ Open: https://bmjopen.bmj.com/content/8/9/e022404
- THE LANCET: MMR vaccination and pervasive developmental disorders: a case-control study
- NICE: National Institute for Health and Care Excellence
- British Journal of General Practice: https://bjgp.org/content/69/684/e462
- Use of multiple inflammatory marker tests in primary care: using Clinical Practice Research Datalink to evaluate accuracy
COVID-19 studies using CPRD data

Pharmacological risk factors and safety of emergent treatment for COVID-19

Patient characteristics, risk factors and predictors of COVID-19

Health outcomes among patients with COVID-19

Health service use during the COVID-19 pandemic

Diagnosis of physical and mental health conditions in primary care during the COVID-19 pandemic: a retrospective cohort study
EHR-enabled trial management in routine primary care

**Selection, screening and recruitment**

- **GP recruits suitable patients in real world setting**
- **Randomisation within platform**
- **Intervention (Drug or vaccine)**
- **Comparator (standard of care)**
- **Data management & analysis**
- **EHR-based long-term follow up**

**EHR-patient selection on demographics & treatment characteristics**

**Interventional Research Services Platform**
EHR-enabled patient location and recruitment across the UK

- Central search of CPRD primary care database for eligible patients
- CPRD network of 2000 GP practices
- GP reviews eligible patients for suitability
- GP invites only suitable patients
- High quality patients contact study centre

Recruitment of patients with Chronic Obstructive Pulmonary Disorder (COPD) from the Clinical Practice Research Datalink (CPRD) for Research
www.nature.com/articles/s41533-018-0089-3
IRSP Platform Interface

Interventional Research Services Platform - Trialbase

Select Study > daRe2THINK

Patient List

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<th>Status •</th>
<th>Global ID</th>
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<th>Last name</th>
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<td>Pre-Screened</td>
<td>-</td>
<td>-</td>
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<tr>
<td>2</td>
<td>112</td>
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<td>13</td>
<td>Enrolled</td>
<td>1041690</td>
<td>7</td>
<td>Err</td>
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</table>

Total patients: 21

Serious Adverse Events

1. Please complete and submit these Serious Adverse Events to the sponsor.
2. Events complete. Last Serious Adverse Event submitted to the sponsor on: 31/03/2021

Enrolment & Randomisation

Enrolled patients will be randomised to either receive a direct oral anticoagulant (DOAC) or to receive No Intervention (usual care) in a 1:1 ratio.

- **Intervention**: DOAC therapy prescribed (as per local CCG guidance)
- **No Intervention**: Usual care (no anticoagulant therapy)

If randomised to receive a DOAC, you will be expected to prescribe apixaban, dabigatran, edoxaban or rivaroxaban in line with the clinical requirements for the patient and the regional prescription guidelines of your local Clinical Commissioning Group (CCG).

If randomised to receive No Intervention, you should not prescribe an anticoagulant to the patient.

Please continue to the next page to view the treatment group the patient has been assigned to.

Form completed

Randomise
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UNIVERSITY OF BIRMINGHAM  INSTITUTE OF CARDIOVASCULAR SCIENCES

University Hospitals Birmingham NHS Foundation Trust
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British Heart Foundation – PG/17/55/33087 and AA/18/2/34218
EU Innovative Medicines Initiative – BigData@Heart Consortium #116074
Need for new trial approaches

Challenges of conventional RCTs...
- Prolonged design phase
- Over 50% fail to recruit
- Most require amendment
- 80% delayed

Duplication of effort...
- especially follow-up visits and outcomes which are recorded within electronic health records (EHRs)
# Need for new trial approaches

## Generalisability with the 'real' population...

<table>
<thead>
<tr>
<th>Source</th>
<th>MERIT-HF RCT</th>
<th>PARADIGM-HF RCT</th>
<th>SWEDE-HF cohort</th>
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<td><strong>Year</strong></td>
<td>1997-8</td>
<td>2009-12</td>
<td>2000-12</td>
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<td><strong>Mean age</strong></td>
<td>64 years</td>
<td>64 years</td>
<td>72 years</td>
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<tr>
<td><strong>Women</strong></td>
<td>22%</td>
<td>22%</td>
<td>31%</td>
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<tr>
<td><strong>AF</strong></td>
<td>17%</td>
<td>37%</td>
<td>50%</td>
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High and increasing cost...

Moore: JAMA Intern Med. 2018;178:1451-1457

Infographic: outsourcingpharma.com
Need for new trial approaches

Paperwork... (for researchers, clinical staff and patients)

Kotecha et al: JAMA. 2020;324:2497-508
In-practice
EHR-embedded
No case reports forms
Patient-centred
Totality of follow-up
Tech-enabled
Low impact on staff
Cost-efficient
Generalisable results
High-quality evidence
Data-driven EHR trials... pipe dream?

Automated screening of health record:
- a
- b
- c

Inclusion criteria:

Exclusion criteria:
- w
- x
- y

Indicates data-driven automated process

Targeted recruitment of sites and patients

Screening before and during trial

COVID-19
Preventing stroke, premature death and cognitive decline in a broader community of patients with atrial fibrillation using healthcare data for pragmatic research: A randomised controlled trial

Clinicaltrials.gov NCT04700826  EudraCT: 2020-005774-10

www.birmingham.ac.uk/d2t
Why study atrial fibrillation?

Meta-analysis of AF patients undergoing cardioversion in RCTs (n=5203):

- Warfarin
- DOACs

DaRe2THINK will test the effectiveness of starting DOACs age 60-73 with low to intermediate risk of stroke

Lane... Kotecha: J Am Heart Assoc. 2017;6:e005155
DaRe2THINK EHR-embedded approach

**SCREENING**
- Automated screening of CPRD for selection criteria across >12 million NHS patients at study start
- Weekly CPRD updates to notify each General Practice of potentially eligible participants
- Opportunistic screening at participating GPs of patients seen in daily practice

**ENROLMENT**
- Eligible patients given the Participant Information Sheet and invited to enrolment visit
- GP / Primary Care research team go through trial information and obtain informed consent

**RANDOMISATION**
- Randomisation 1:1 within CPRD portal
- Intervention arm: DOAC therapy prescribed (as per local CCG guidance)
- Control arm: Usual care (no anticoagulant therapy)

**FOLLOW-UP**
- ‘No-visit’ follow-up
- Technology-supported patient reported cognitive function (yearly) and quality of life assessment (6-monthly)
- Key secondary & additional secondary outcomes
- Adverse events acquired from routine clinical records across all primary and secondary NHS care (yearly)
- Primary & additional secondary outcomes

**Remote e-consent**
- Phone/video consult to enrol patients
- No visits

**Auto SAE reporting**
Better patient selection pre and post-recruitment

New advances in linked artificial intelligence for personalised medicine...

Karwath... Kotecha: Lancet 2021 – online now!
Public engagement to design the right trials

Essential to bring patients and the public into the design process for this next generation of clinical trials...

- Social license for use and linkage of EHR data
- Patient-focused approaches
- Better clinical research and dissemination