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

Tim Williams (MHRA) and Dipak Kotecha (University of Birmingham)

15th September 2021

Medicines & Healthcare products Regulatory Agency

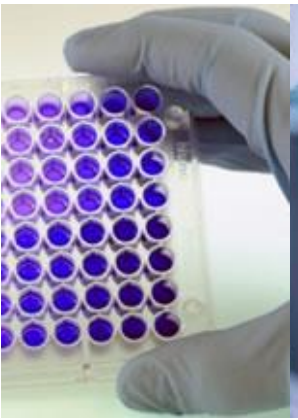
NIHR | National Institute for Health Research

Medicines & Healthcare products Regulatory Agency

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

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.

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






CPRD NIBSC MHRA

What is CPRD?

Medicines & Healthcare products Regulatory Agency

NIHR | National Institute for Health Research

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

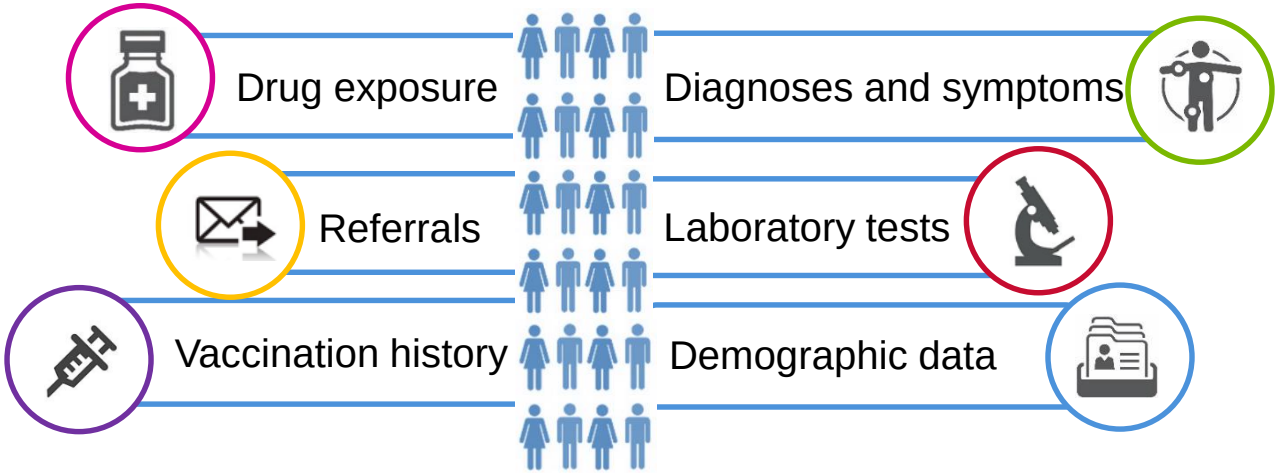
25% UK population coverage

Representative data

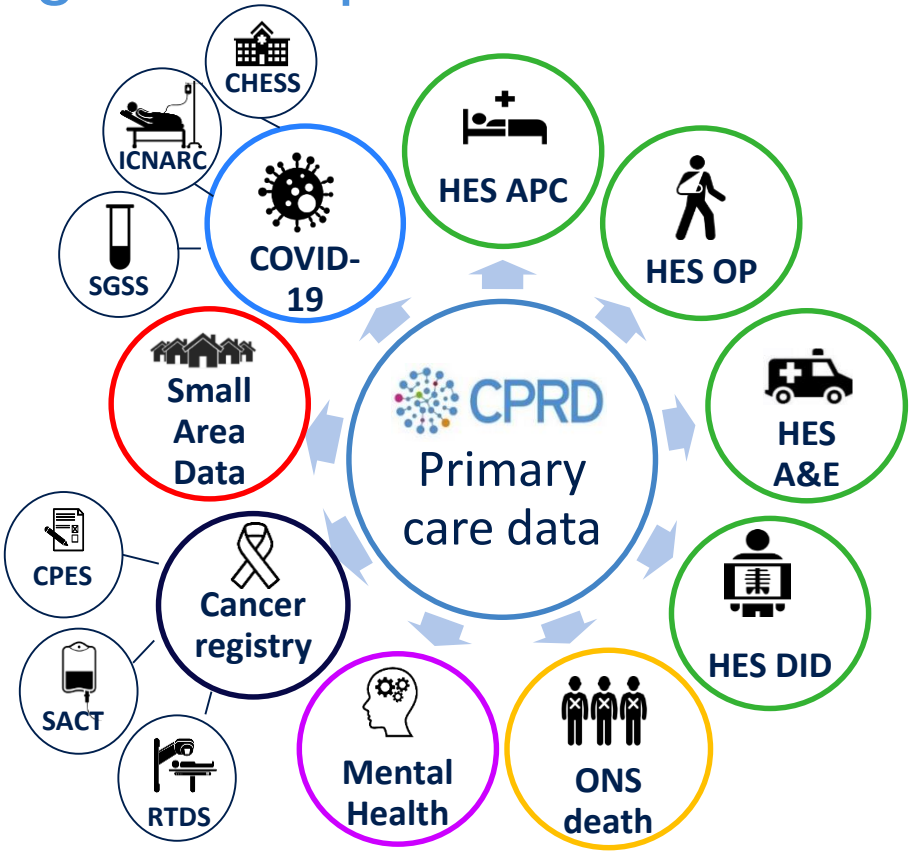
CPRD

Collect all coded data in EHR except patient identifiers

Over 14 billion consultations

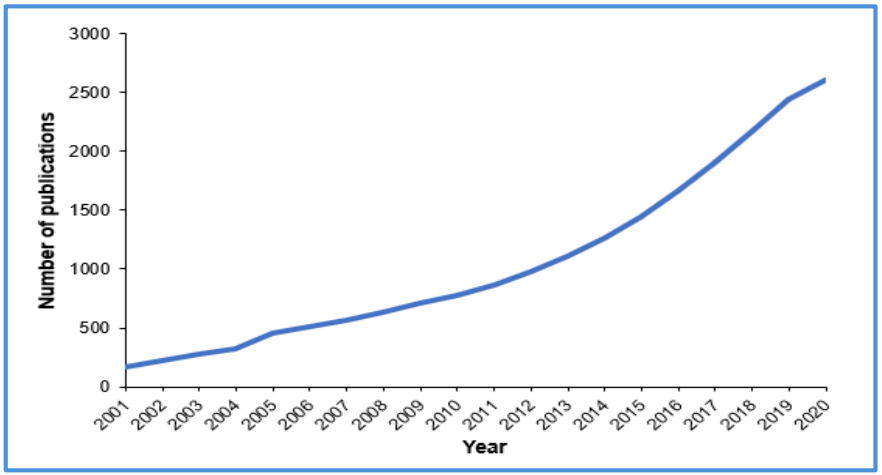


Extending the scope of research through linkage



Impact of CPRD data on public health

2600 peer-reviewed publications using CPRD data



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

British Journal of General Practice
bringing research to clinical 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

BMJ Open
https://bmjopen.bmj.com/content/8/9/e022404

Are noise and air pollution related to the incidence of dementia? A cohort study in London, England

PDS Pharmacoepidemiology & Drug Safety
Original Report

Use of selective serotonin reuptake inhibitors in pregnancy and cardiac malformations: a propensity-score matched cohort in CPRD†

PHARMACOEPIDEMIOLOGY AND DRUG SAFETY 2013; 22: 942–951

FDA

The NEW ENGLAND JOURNAL of MEDICINE

N Engl J Med 2016; 374:1145-1154 | March 24, 2016 | DOI: 10.1056/NEJMoa1506115

A Multicenter Observational Study of Incretin-based Drugs and Heart Failure

thebmj
Papers

Antidepressant treatment and the risk of fatal and non-fatal self harm in first episode depression: nested case-control study

THE LANCET
Volume 364, Issue 9438, 11–17 September 2004, Pages 963–969

MMR vaccination and pervasive developmental disorders: a case-control study

thebmj
RESEARCH

Safety of pertussis vaccination in pregnant women in UK: observational study

Suspected Cancer Clinical Guidance

NICE National Institute for Health and Care Excellence

CPRD

COVID-19 studies using CPRD data

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

N Engl J Med. 2020 Jul 23;383(4):397-400. doi: 10.1056/NEJMc2005396. Epub 2020 May 8.

Association between Angiotensin Blockade and Incidence of Influenza in the United Kingdom

Sheng-Chia Chung [1], Rui Providencia [2], Reecha Sofat [3]

Antihypertensive Medications and COVID-19 Diagnosis and Mortality: Population-based Case-Control Analysis in the United Kingdom

Emma Rezel-Potts, Abdel Douiri, Phil J Chowienczyk, Martin C Gulliford

doi: https://doi.org/10.1101/2020.09.25.20201731

Safety of hydroxychloroquine, alone and in combination with azithromycin, in light of rapid wide-spread use for COVID-19: a multinational, network cohort and self-controlled case series study

Jennifer C.E Lane, James Weaver, Kristin Kostka, Talita Duarte-Salles, Maria Tereza F. Abrahao, Heba Alghoul, Osaid Alser, Thamir M Alshammari, Patricia Biedermann, Edward Burn, Paula Casajust, Mitch Conover, Aedin C. Culhane, Alexander Davydov, Scott L. DuVall, Dmitry Dymshyts, Sergio Fernández Bertolín, Kristina Fišter, Jill Hardin, Laura Hester, George Hripcsak, Seamus Kent, Sajan Khosla, Spyros Kolovos

Patient characteristics, risk factors and predictors of COVID-19

COVID-19 in Great Britain: epidemiological and clinical characteristics of the first few hundred (FF100) cases: a descriptive case series and case control analysis

Nicola L Boddington, Andre Charlett, Suzanne Elgohari, Jemma L Walker, Helen Mcdonald, Chloe Byers, Laura Coughlan, Tatiana Garcia Vilaplana, Rosie Whillock, Mary Sinnathamby, Nikolaos Panagiotopoulos, Louise Letley, Pauline MacDonald, Roberto Vivancos, Obaghe Edeghere, Joseph Shingleton, Emma Bennett, Daniel J Grint, Helen Strongman, Kathryn E Mansfield, Christopher Rentsch, Caroline Minassian, Ian J Douglas, Rohini Mathur, Maria Peppa, Simon Cottrell, Jim McMenamin, Maria Zambon, Mary Ramsay, Gavin Dabrera, Vanessa Saliba, Jamie Lopez Bernal

doi: https://doi.org/10.1101/2020.05.18.20086157

LSHTM Data Compass

UK prevalence of risk factors for severe COVID-19 disease, by age and region: point prevalence estimates in 2019 and 2014, using electronic health records

Health service use during the COVID-19 pandemic

Estimating excess 1-year mortality associated with the COVID-19 pandemic according to underlying conditions and age: a population-based cohort study

Amitava Banerjee, Laura Pasea, Steve Harris, Arturo Gonzalez-Izquierdo, Ana Torralbo, Laura Shallcross, Mahdad Noursadeghi, Deenan Pillay, Neil Sebire, Chris Holmes, Christina Pagel, Wai Keong Wong, Claudia Langenberg, Bryan Williams, Spiros Denaxas, Harry Hemingway

Characteristics and outcomes of 627 044 COVID-19 patients with and without obesity in the United States, Spain, and the United Kingdom

Martina Recalde, Elena Roel, Andrea Pistillo, Anthony G Sena, Albert Prats-Uribe, Waheed Ul-Rahman Ahmed, Heba Alghoul, Thamir M Alshammari, Osaid Alser, Carlos Areia, Edward Burn, Paula Casajust, Dalia Dawoud, Scott L DuVall, Thomas Falconer, Sergio Fernandez-Bertolin, Asieh Golozar, Mengchun Gong, Lana Yin Hui Lai, Jennifer C.E Lane, Kristine E Lynch, Michael E Matheny, Paras P Mehta, Daniel R Morales, Karthik Natarjan, Fredrik Nyberg, Jose D Posada, Christian G Reich, Lisa M Schilling, Karishma Shah, Nigham H Shah, Vignesh Subbian, Lin Zhang, Hong Zhu, Patrick Ryan, Daniel Prieto-Alhambra, Kristin Kostka, Talita Duarte-Salles

doi: https://doi.org/10.1101/2020.09.02.20185173

Health outcomes among patients with COVID-19

Estimating excess mortality in people with cancer and multimorbidity in the COVID-19 emergency

Alvina G Lai, Laura Pasea, Amitava Banerjee, Spiros Denaxas, Michail Katsoulis, Wai Hoong Chang, Bryan Williams, Deenan Pillay, Mahdad Noursadeghi, David Linch, Derralynn Hughes, Martin D Forster, Clare Turnbull, Natalie K Fitzpatrick, Kathryn Boyd, Graham R Foster, Matt Cooper, Monica Jones, Kathy Pritchard-Jones, Richard Sullivan, Geoff Hall, Charlie Davie, Mark Lawler, Harry Hemingway

doi: https://doi.org/10.1101/2020.05.27.20083287

Now accepted for publication in *BMJ Open*

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

Richard Williams, David A Jenkins, Darren M Ashcroft, Ben Brown, Stephen Campbell, Matthew J Carr, Sudeh Cheraghi-sohi, Navneet Kapur, Owain Thomas, Roger T Webb, Niels Peek

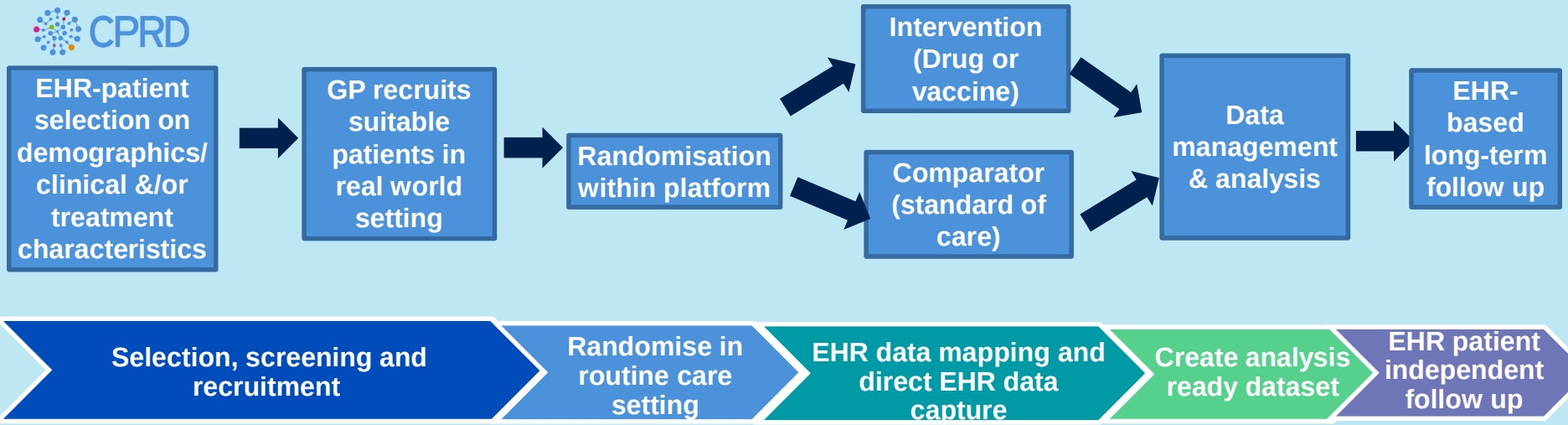
Impact of COVID-19 on the diagnoses, HbA1c monitoring and mortality in people with type 2 diabetes: a UK-wide cohort study involving 13 million people in primary care

Matthew J. Carr, Alison K. Wright, Lalantha Leelarathna, Hood Thabit, Nicola Milne, Naresh Kanumilli, Darren M. Ashcroft, Martin K. Rutter

doi: https://doi.org/10.1101/2020.10.25.20200675

CPRD

EHR-enabled trial management in routine primary care



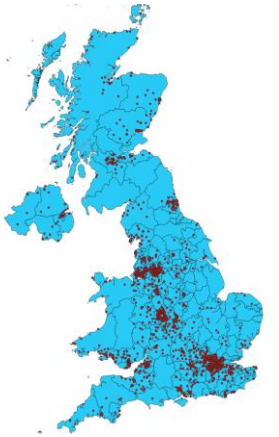
CPRD Interventional Research Services Platform

CPRD

EHR-enabled patient location and recruitment across the UK

CPRD

16+ million patients



Central search of CPRD primary care database for eligible patients

CPRD network of 2000 GP practices

GP reviews eligible patients for suitability

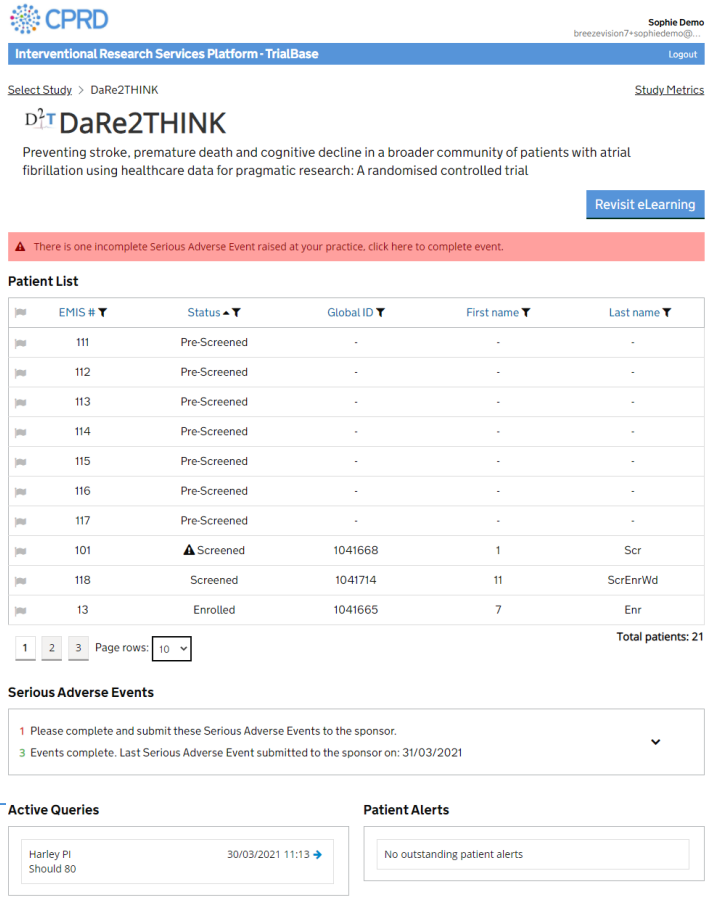
GP invites only suitable patients

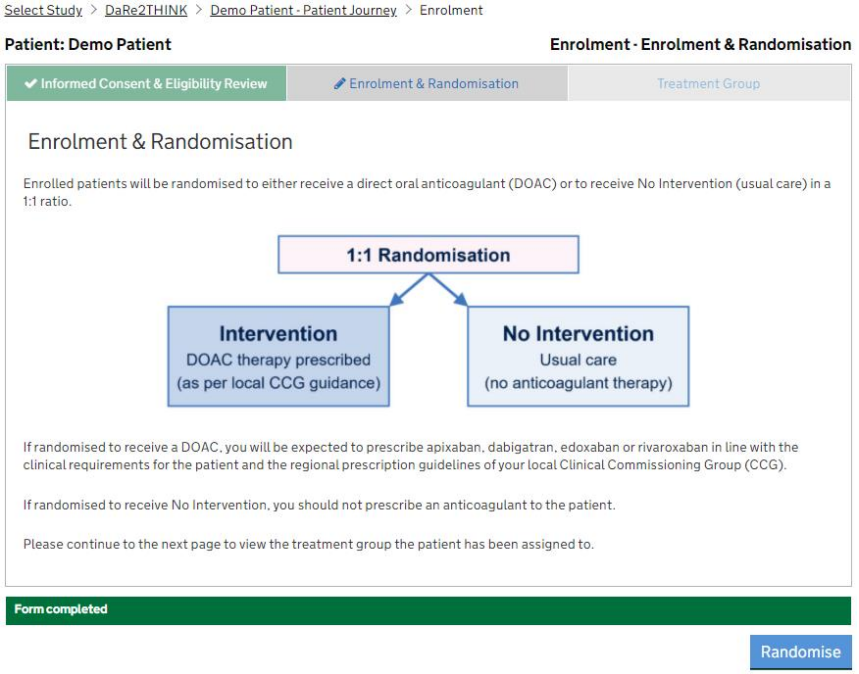
High quality patients contact study centre

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

CPRD

IRSP Platform Interface





CPRD

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

Dipak Kotecha, Professor of Cardiology & Consultant Cardiologist

UNIVERSITY OF BIRMINGHAM | INSTITUTE OF CARDIOVASCULAR SCIENCES

University Hospitals Birmingham NHS
NHS Foundation Trust

Disclosures

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Advisory board / Speaker fees – Bayer, Amomed, Myokardia, Atricure.

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British Heart Foundation – PG/17/55/33087 and AA/18/2/34218
EU Innovative Medicines Initiative – BigData@Heart Consortium #116074

FUNDED BY NIHR | National Institute for Health Research

British Heart Foundation FIGHT FOR EVERY HEARTBEAT bhf.org.uk

efpia imi innovative medicines initiative

This work has received support from the EU/EFPIA Innovative Medicines Initiative [2] Joint Undertaking BigData@Heart grant n° 116074

Need for new trial approaches

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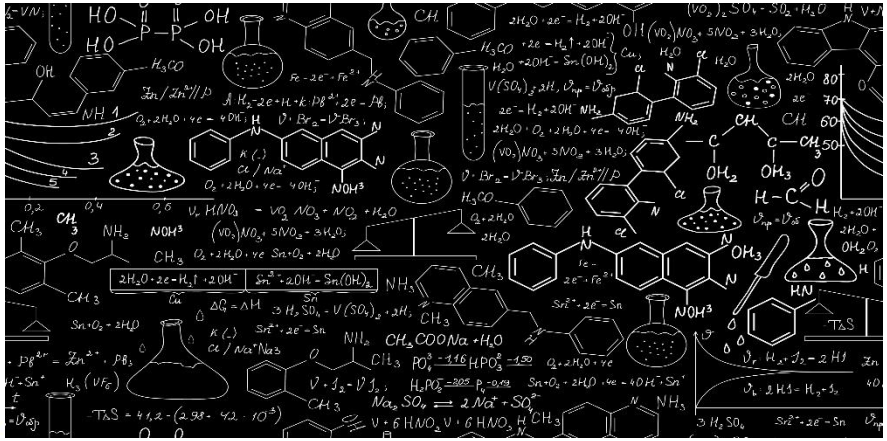
Challenges of conventional RCTs…

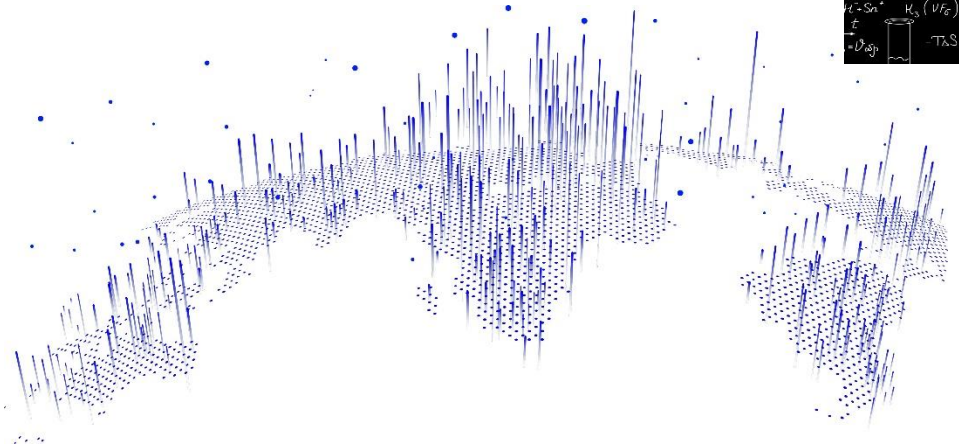
Prolonged design phase

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

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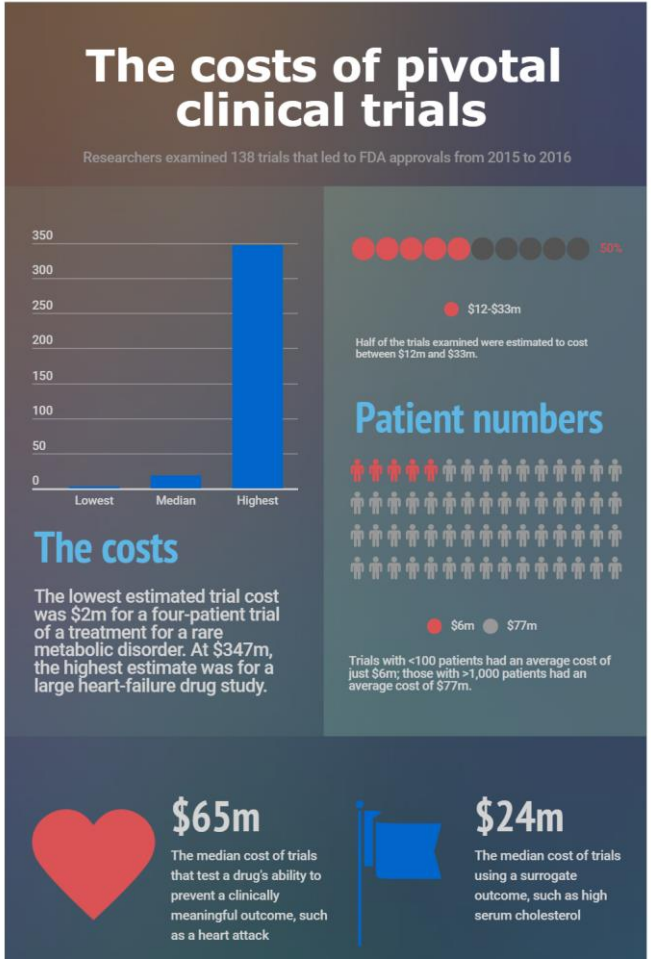
Generalisability with the 'real' population…

Source	MERIT-HF RCT	PARADIGM -HF RCT	SWEDE-HF cohort
Year	1997-8	2009-12	2000-12
Mean age	64 years	64 years	72 years
Women	22%	22%	31%
AF	17%	37%	50%

High and increasing cost…



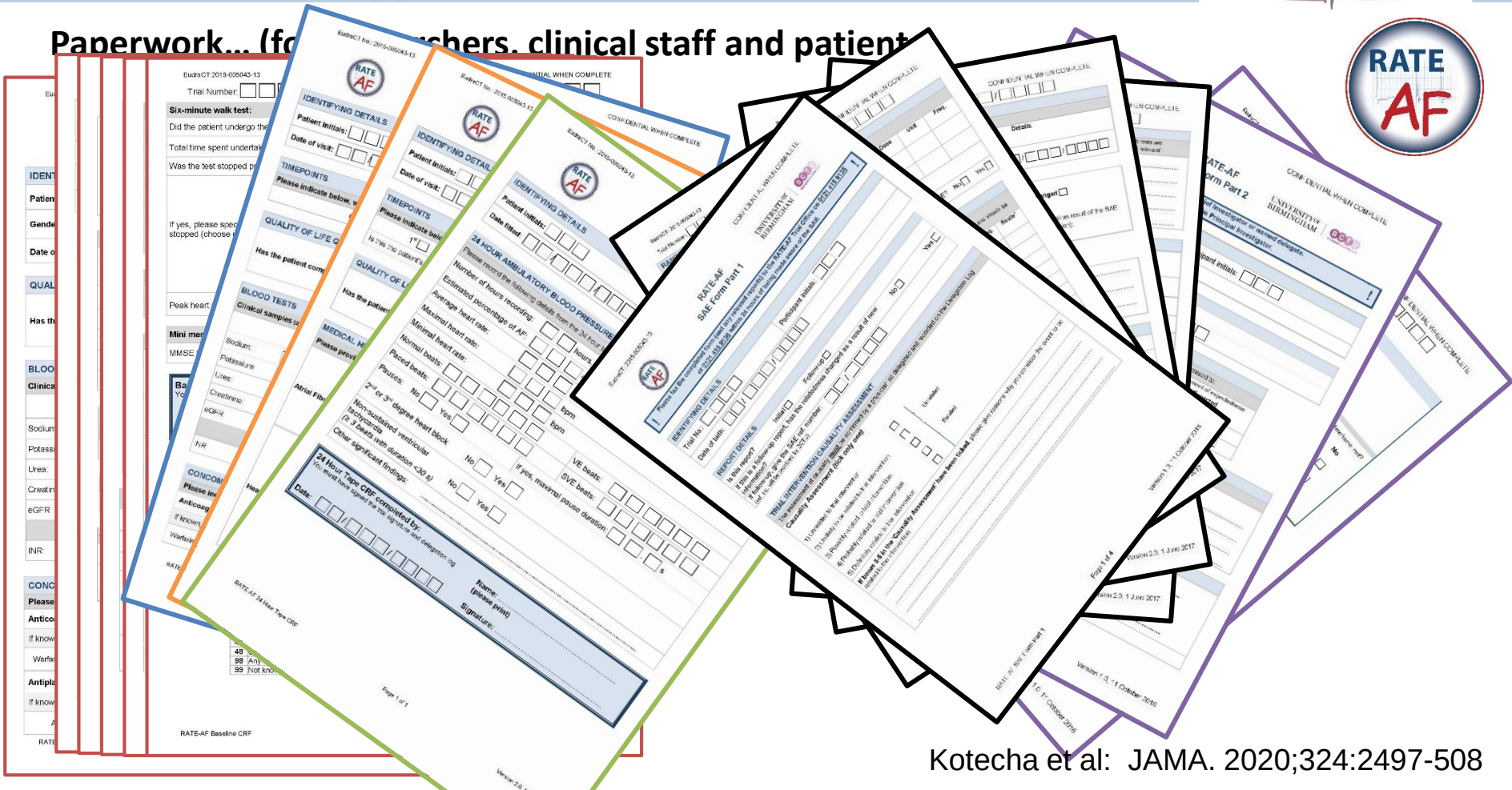
Moore: JAMA Intern Med. 2018;178:1451-1457

Infographic: outsourcingpharma.com

Need for new trial approaches

DaRe2THINK

Paperwork… (fo[illegible]chers, clinical staff and patient



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 ?

DaRe 2 THINK

Indicates data-driven automated process

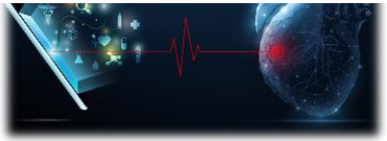
Automated screening of health record:

Inclusion criteria:
- a
- b
- c

Exclusion criteria:
- w
- x
- y

Targeted recruitment of sites and patients

Screening before and during trial



healthcare DAta for pragmatic clinical REsearch

DaRe 2 THINK

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

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University Hospitals Birmingham NHS Foundation Trust

CPRD

NIHR | Clinical Research Network West Midlands Primary Care

www.birmingham.ac.uk/d2t

HDRUK Health Data Research UK

CPROR

CTSU University of Oxford Clinical Trial Service Unit & Epidemiological Studies Unit Nuffield Department of Population Health

biobank uk

UNIVERSITY OF BIRMINGHAM | Institute of Applied Health Research

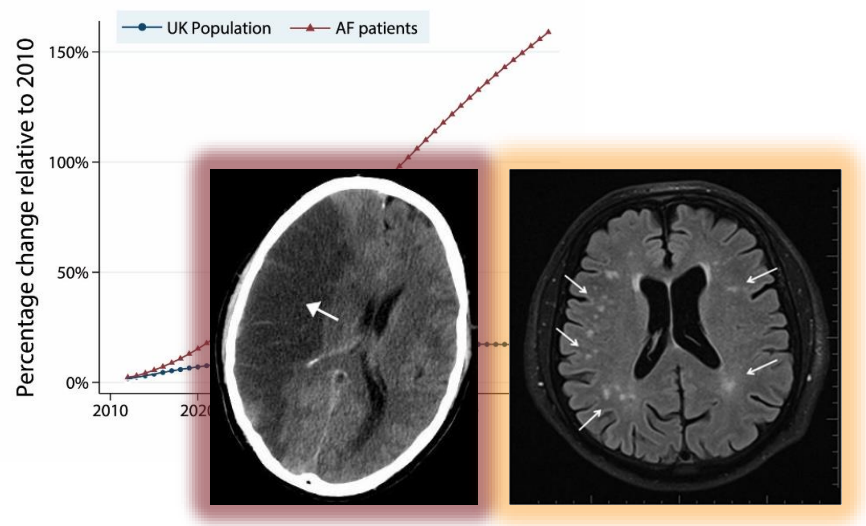
LSE The London School of Economics and Political Science

Aston University Birmingham UK

FUNDED BY NIHR | National Institute for Health Research

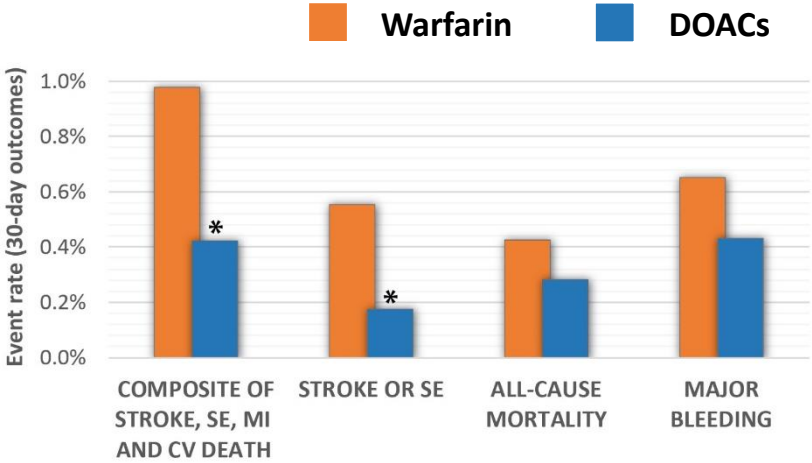
DaRe2THINK rationale

Why study atrial fibrillation?



Better therapy to prevent stroke and clots?

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



* p<0.05

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

Kotecha et al: J Am Coll Cardiol. 2018;72:1984-1986

DaRe2THINK EHR-embedded approach

DaRe^{2}THINK

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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

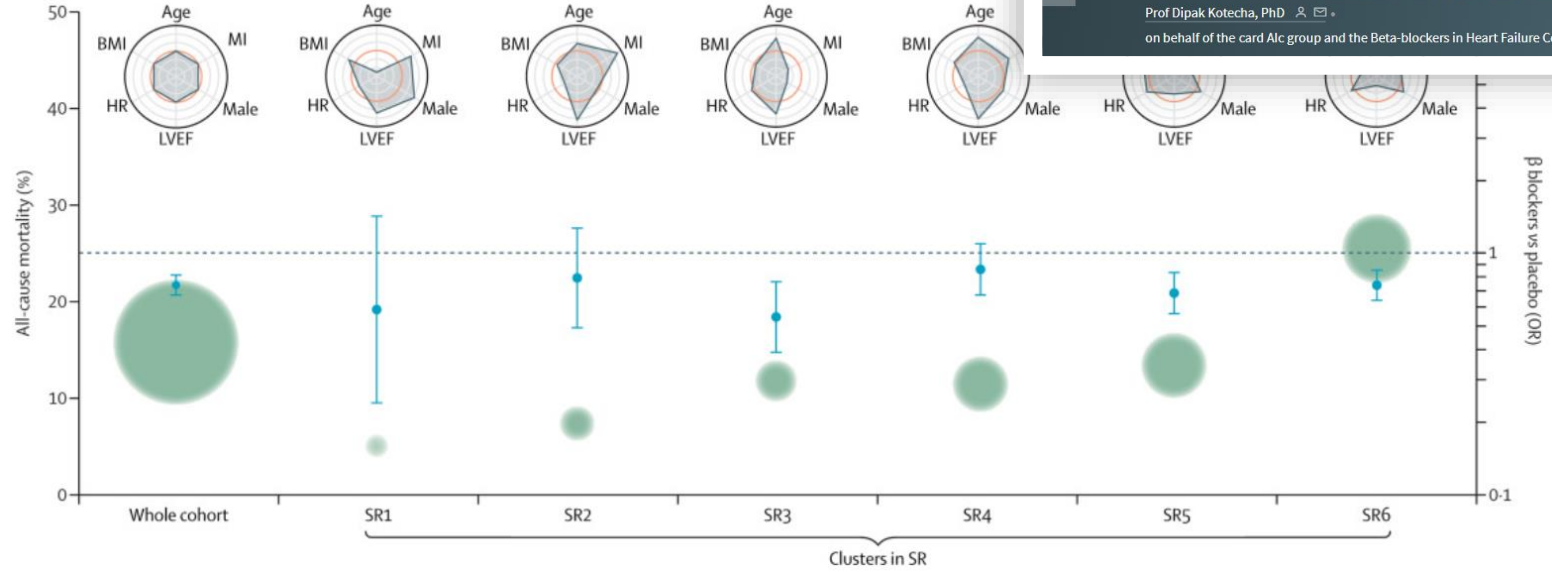
Auto SAE reporting

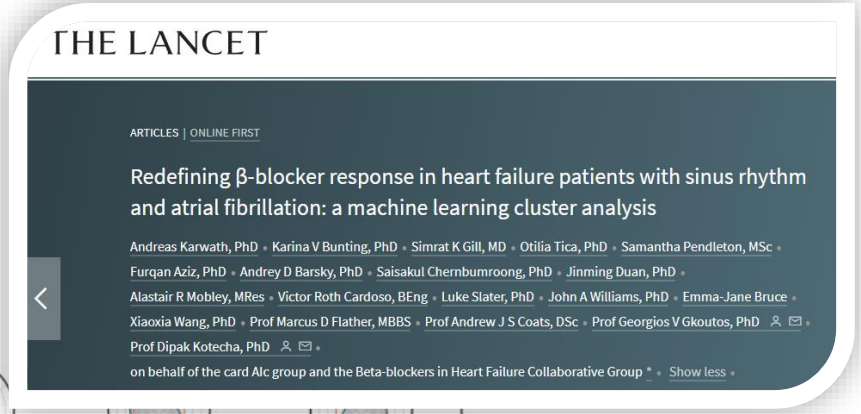
Better patient selection pre and post-recruitment

DaRe 2 THINK

New advances in linked artificial intelligence for personalised medicine…

Karwath... Kotecha: Lancet 2021 – online now!




THE LANCET

ARTICLES | ONLINE FIRST

Redefining β-blocker response in heart failure patients with sinus rhythm and atrial fibrillation: a machine learning cluster analysis

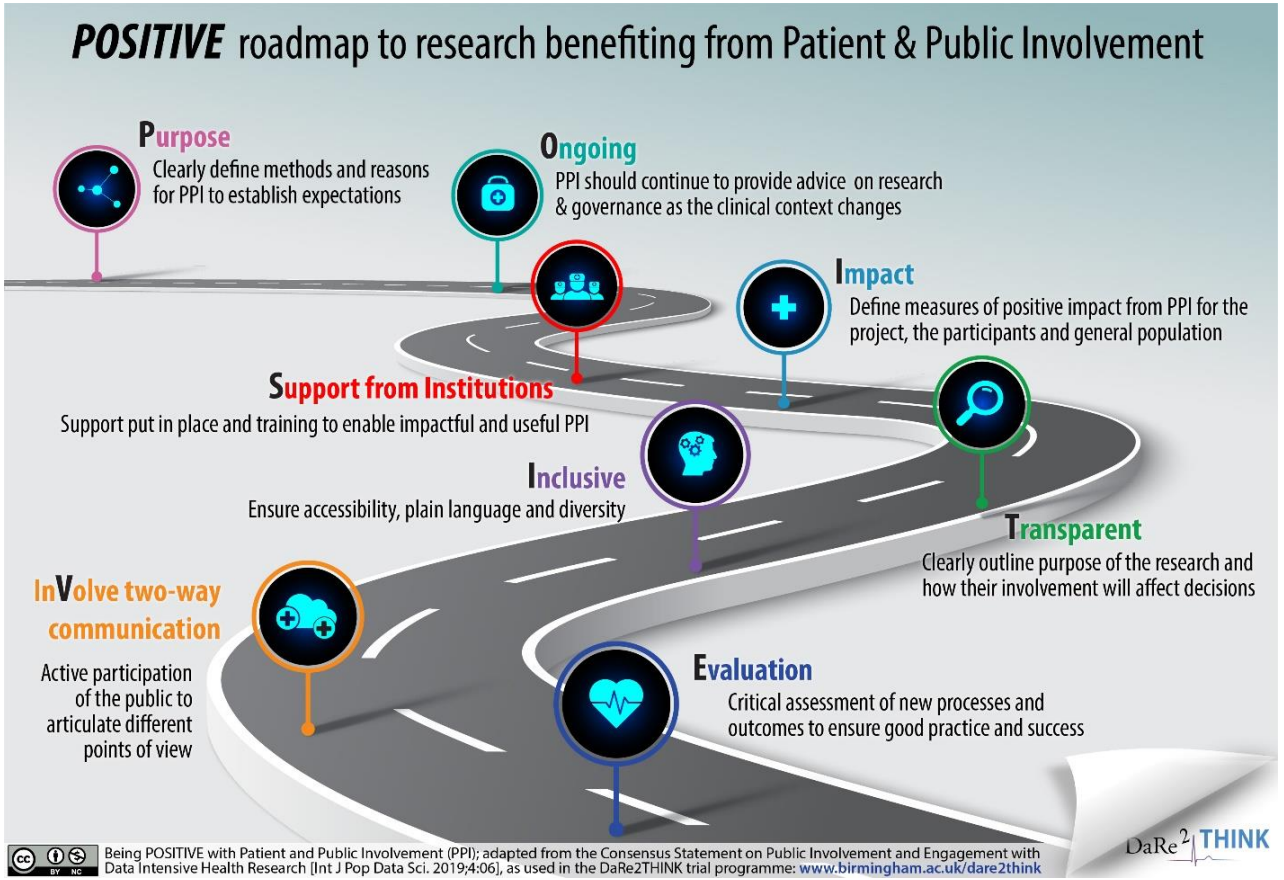
Andreas Karwath, PhD • Karina V Bunting, PhD • Simrat K Gill, MD • Otilia Tica, PhD • Samantha Pendleton, MSc • Furqan Aziz, PhD • Andrey D Barsky, PhD • Saisakul Chernbumroong, PhD • Jinming Duan, PhD • Alastair R Mobley, MRes • Victor Roth Cardoso, BEng • Luke Slater, PhD • John A Williams, PhD • Emma-Jane Bruce • Xiaoxia Wang, PhD • Prof Marcus D Flather, MBBS • Prof Andrew J S Coats, DSc • Prof Georgios V Gkoutos, PhD • Prof Dipak Kotecha, PhD •

on behalf of the card AIc group and the Beta-blockers in Heart Failure Collaborative Group * • Show less •

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



Bunting, Kotecha: Eur Heart J. 2021:42:2411-2414