Within-registry trials: Do they work?

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Conflicts of interest

Grants, consultancy:

Abbott, Amgen, AstraZeneca, Bayer, BMS, Daiichy Sankyo, Novartis, Vifor Pharma

Publishing:

EHJ Quality of Care and Clinical Outcomes

Research funding:

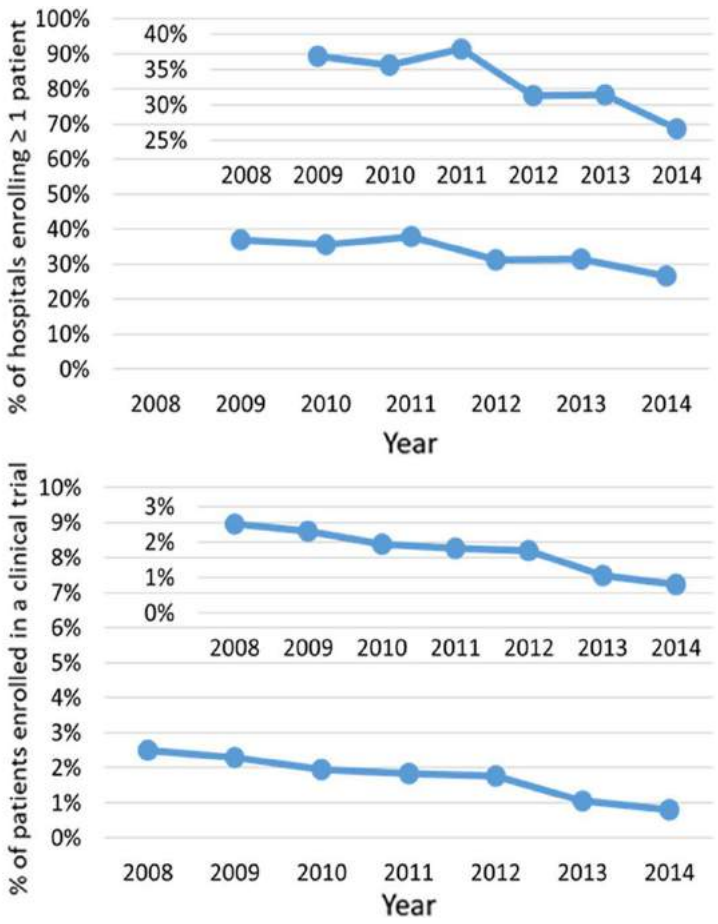
British Heart Foundation, Horizon 2020, NHS England, National Institute for Health Research, Wellcome Trust

Chief Investigator of UKGRIS and ISCOMAT trials

Traditional RCTs are challenging

- Scientific & operational complexity
- Waning site & patient participation
- Regulatory issues
- Inefficient and costly

Hospitals participating in studies of MI, NCDR



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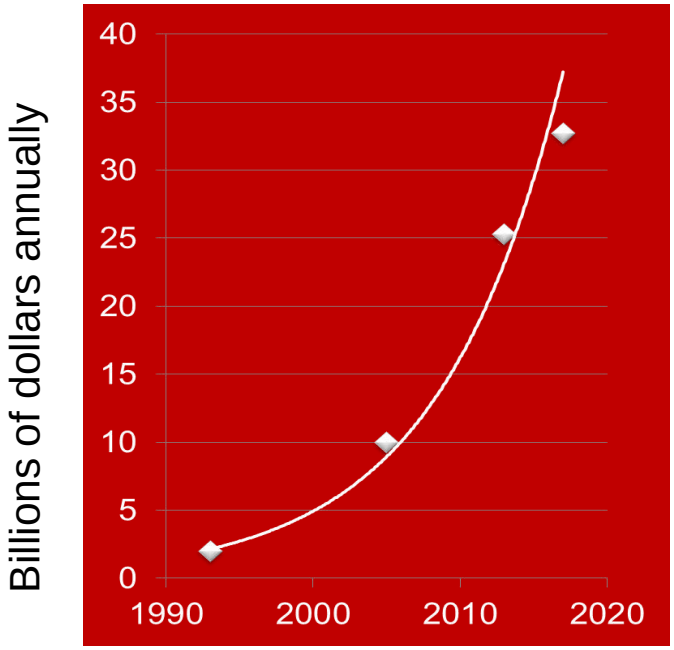
Jones WS.J Am Coll Cardiol 2016;68:1898-1907
Fanaroff AC. Am Heart J 2019; 214:184-193

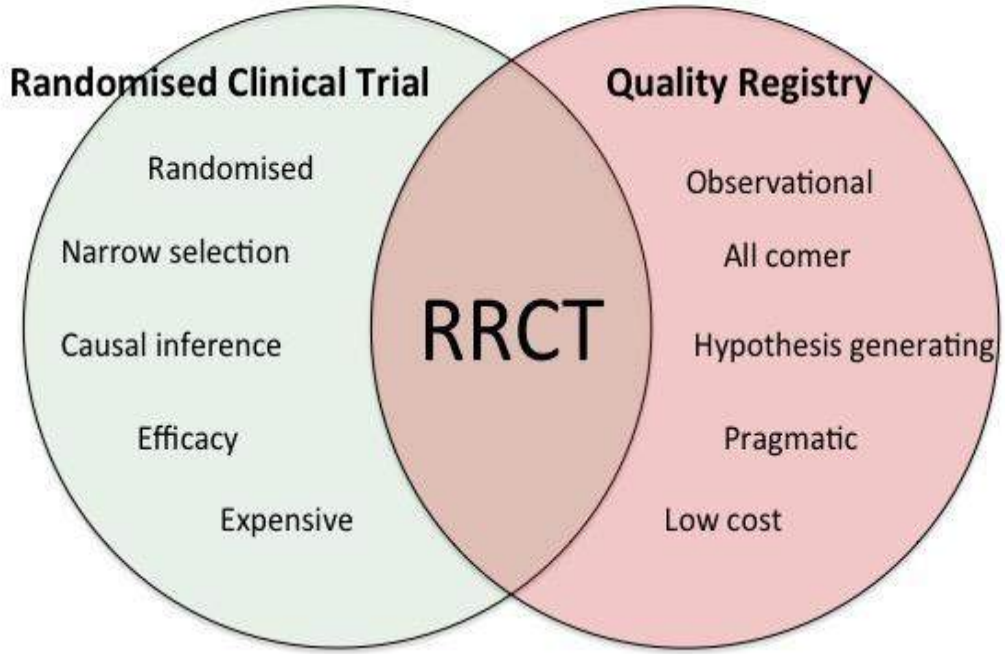
RCT landscape inhibits research

- Regulatory obstacles, delays and costs
- Focus on regulation rather than innovation
- Therefore, fewer developments by industry and less research by academia

Growth in the Contract Research Organization (CRO) market since the creation of International Conference on Harmonisation (ICH) in 1990



Derivation of registry-RCTs



Yndigegn T. Heart. 2018 Oct;104(19):1562-1567

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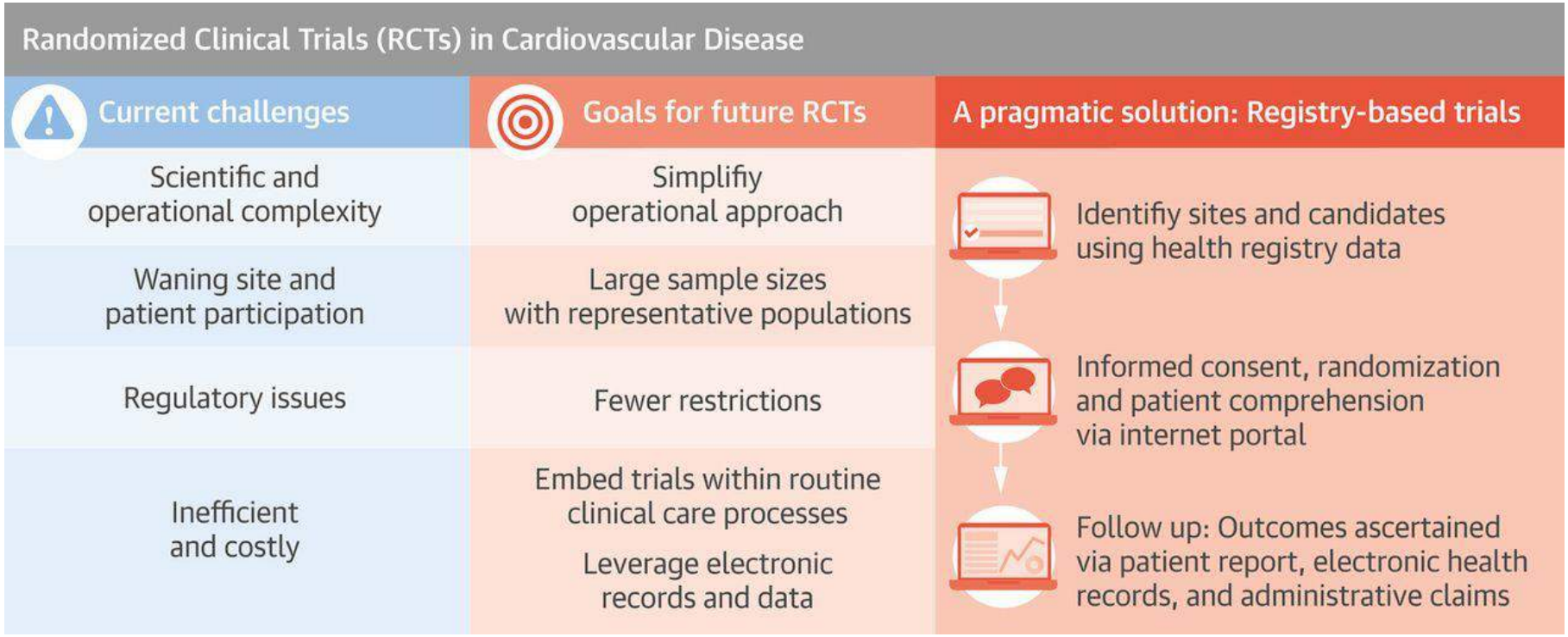
From challenges to solutions



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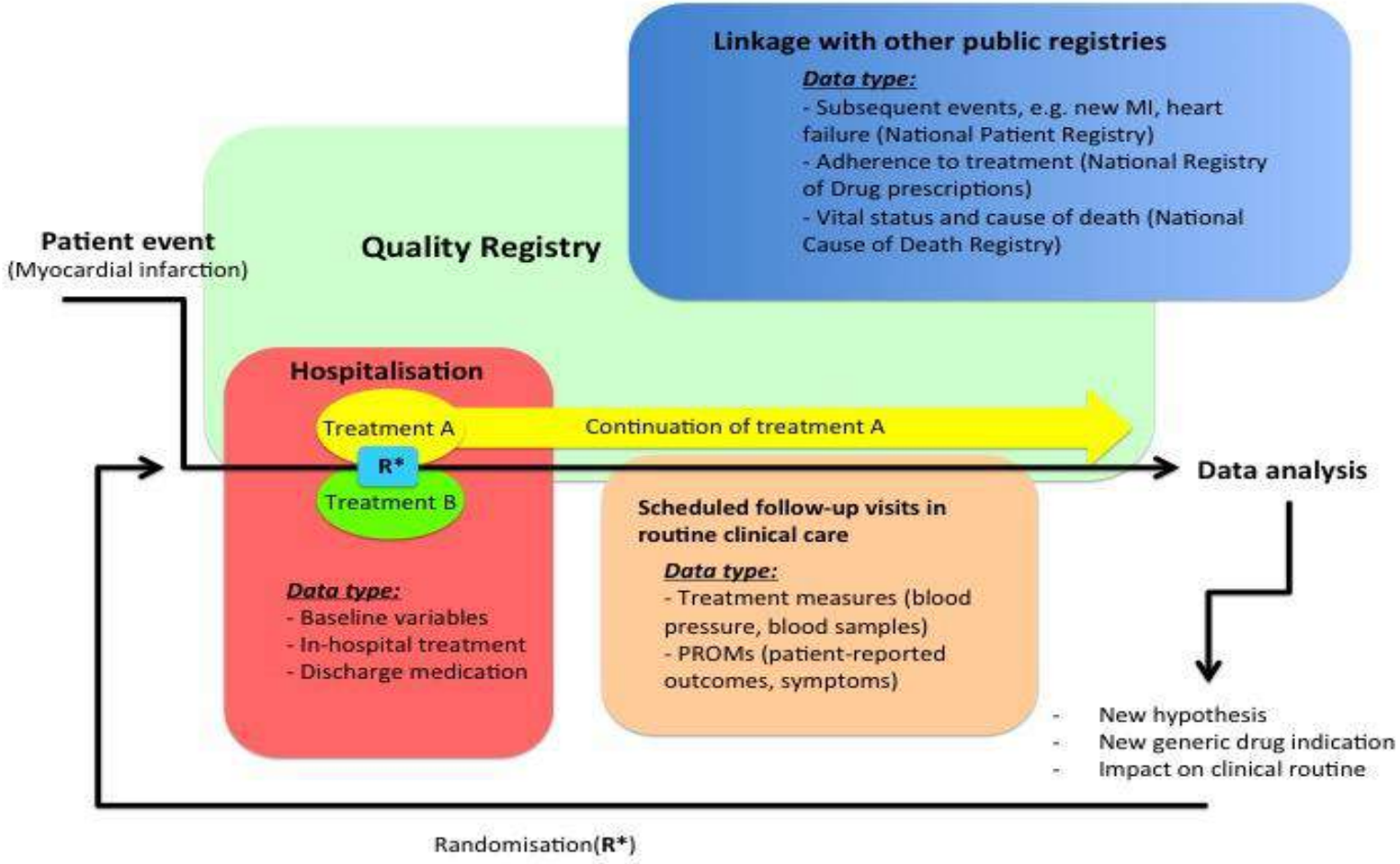
Data flow from registers to RCT timeline



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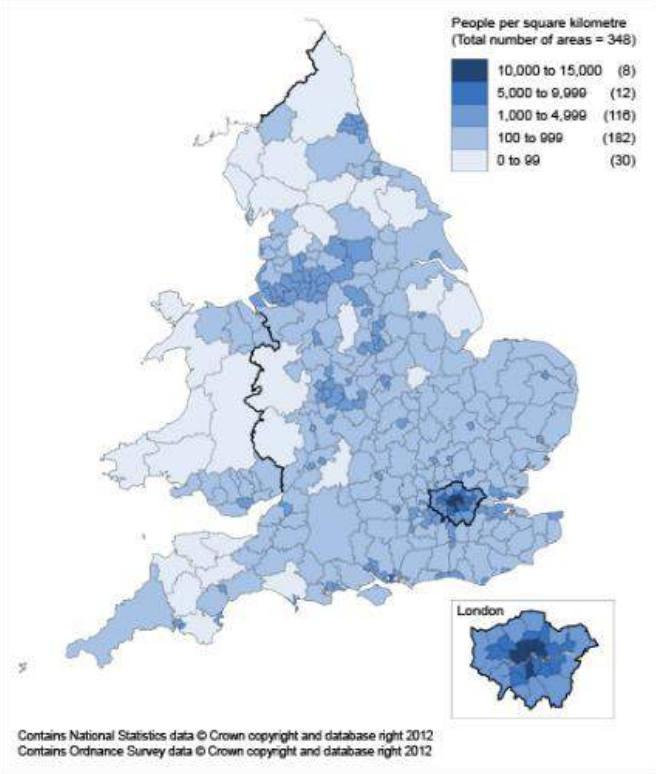
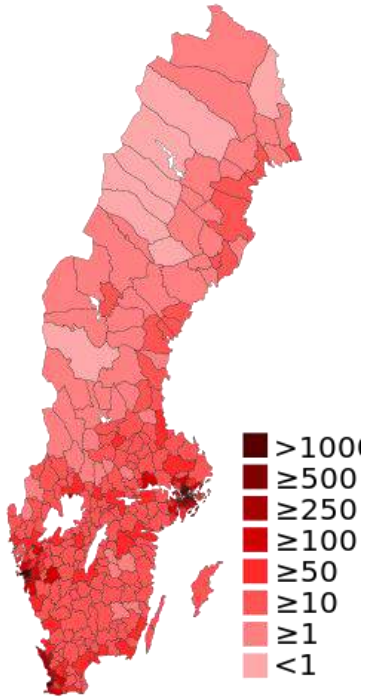
Population-based registers





UK

Area 243,610 km2

Inhabitants 65M; 259 p/km2

8M living in/around London

Unique identifiers

943 476 5870

Randomly generated at birth/point of first contact with NHS

Sweden

Area 447,435 km2

Inhabitants 10M; 23 p/km2

5M living in/around Stokholm, Göteborg and Malmö

Unique identifiers

390202-1439

Derived from DOB, place, sex

Data linkage for tracking care and outcomes

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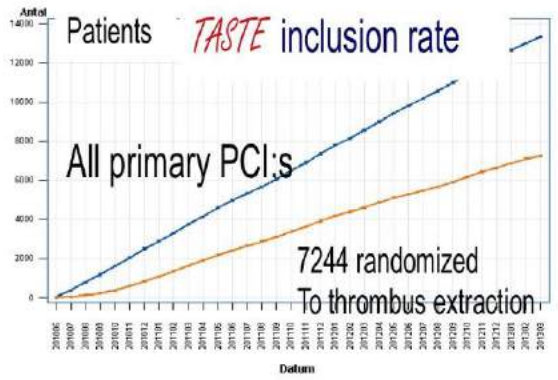
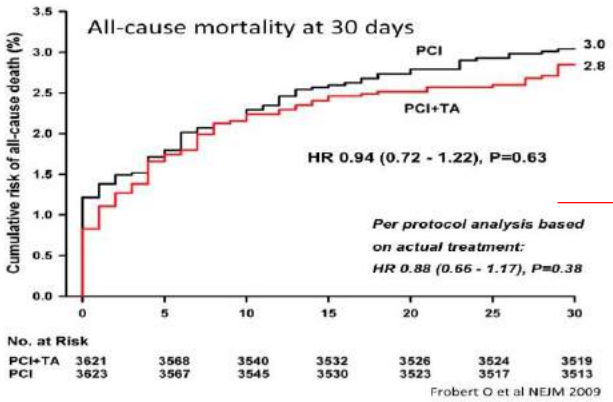
Disruptive technology in clinical research

The Randomised Registry Trial – The Next Disruptive Technology in Clinical Research?

Michael S. Lauer, M.D., and Ralph B. D'Agostino, Sr., Ph.D.





Registry Randomised Clinical Trial - RRCT

- New concept for clinical research
- Integrates a randomised study with a clinical registry
- Complement to classical RCT

The success of the registry based randomised trials (RRCT) on patient recruitment & generating evidence in real life care

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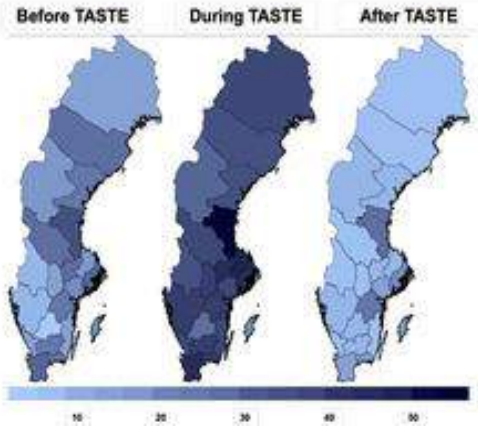
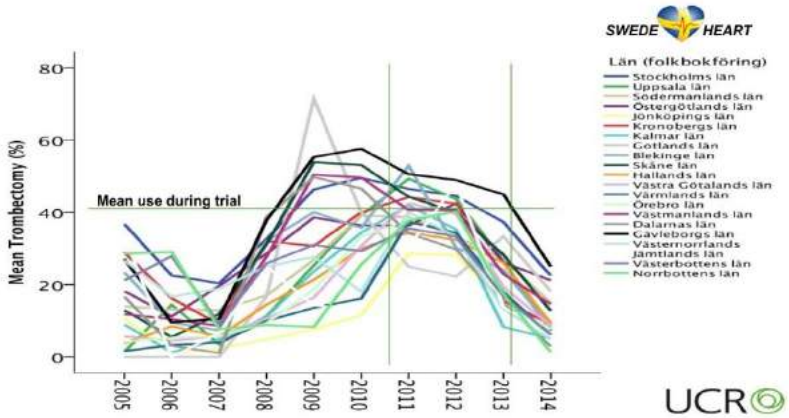
System-wide changes following RRCT



Use of thrombectomy before and after Taste



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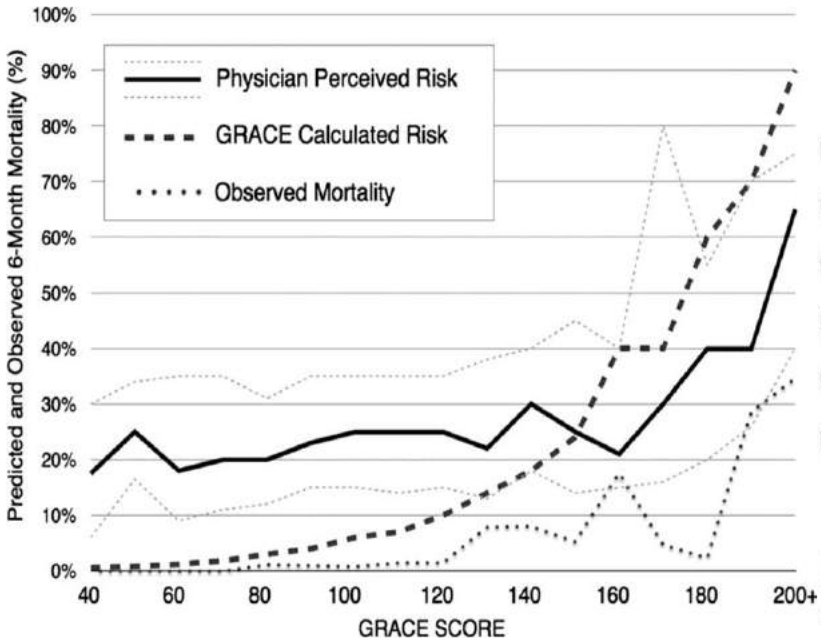
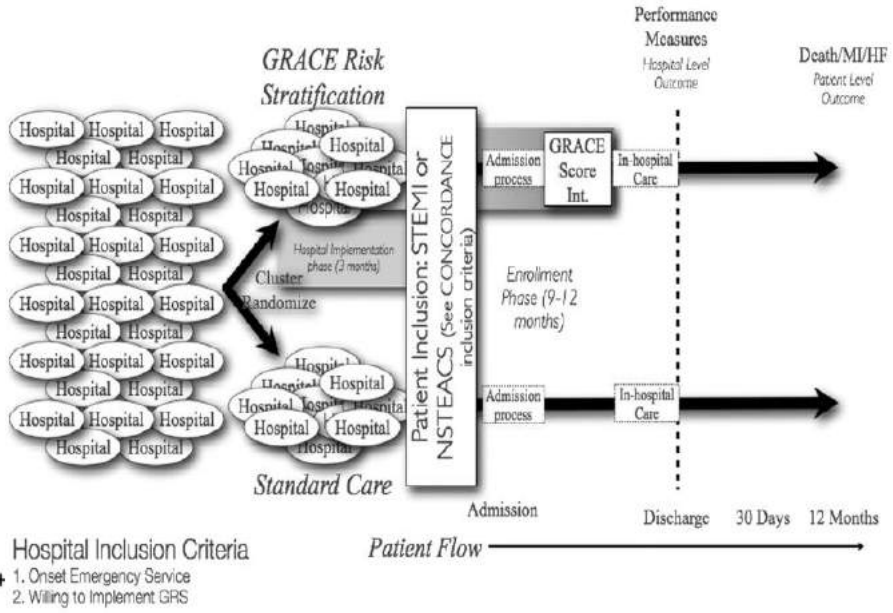
Buccheri S. Circ cardiovasc Int. 2019;12:e007381

Objective vs subjective risk assessment: testing decision tree prompts for treatment of AMI





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Chew DP. Am Heart J. 2015;170;995
Bebb O. Euro Heart J. 2018; 39 (42),3798
Everett C. BMJ Open. 2019;9(9):e032165

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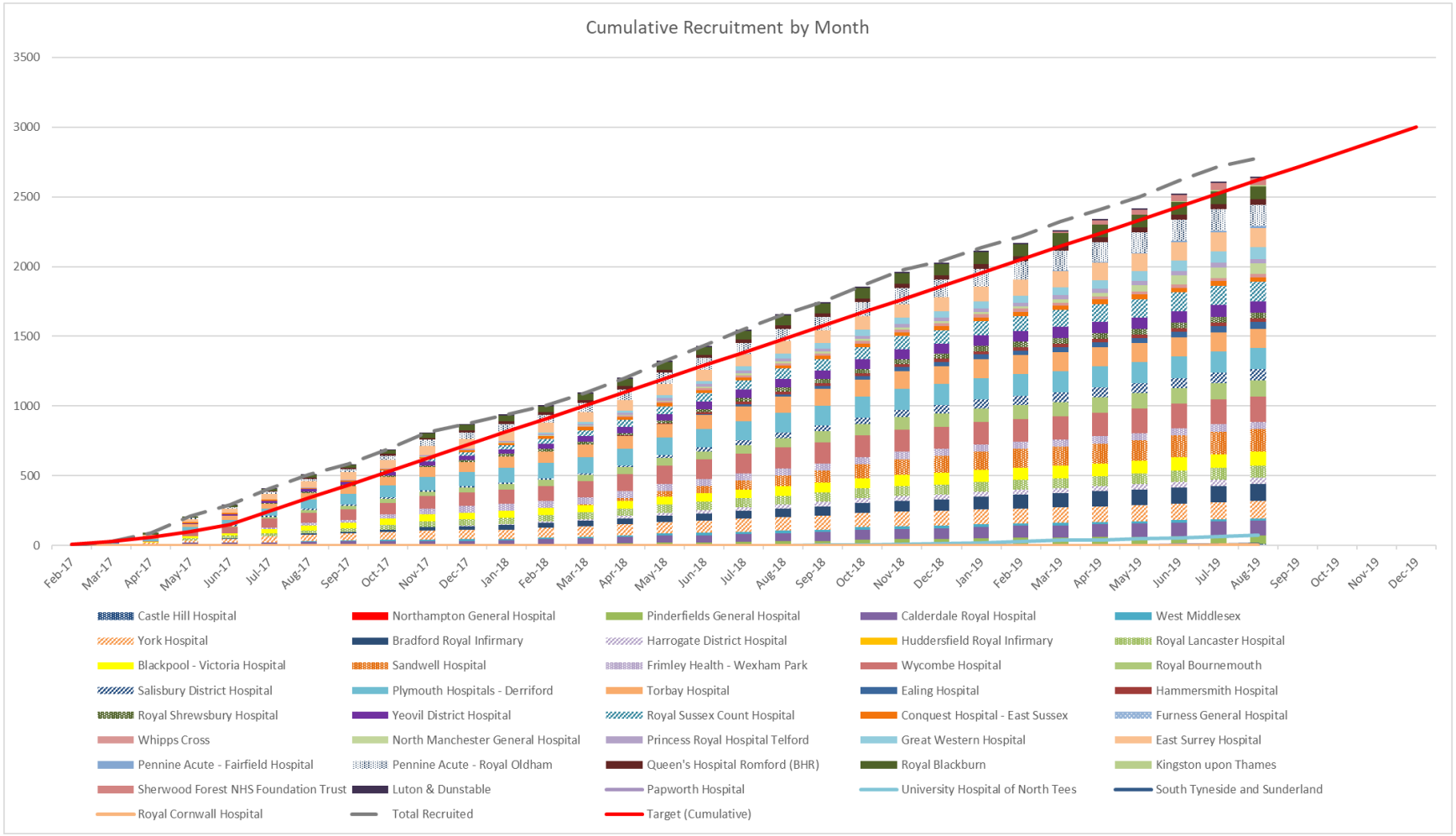
Recruiting ahead of time, target and budget: UKGRIS



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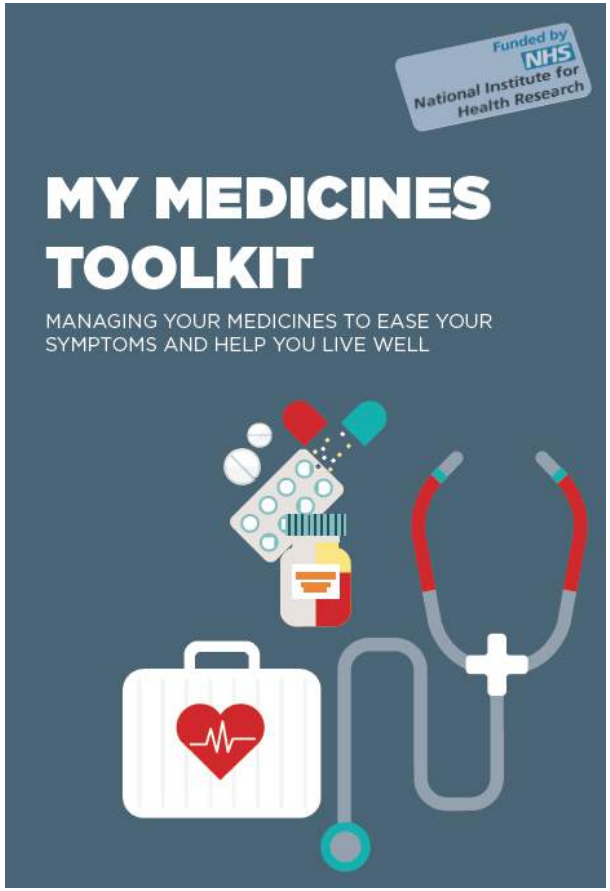
Medications management at the transition between hospital and home for heart failure



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Randomised trials based on health records: Spectrum of Studies

	Cost	Design & Data	Study Population	Randomisation	Summary
Observational studies (including registry studies)	$	Can be retrospective or prospective in design; data quality is variable	Typically unselected population (e.g., Medicare)	Without randomization, comparative effectiveness studies cannot be performed	Large population; often many unmeasured variables or unexplained factors
Traditional RCTs	$$$$-$$$$$	Prospective design; data collection occurs at specialized study centers	Highly-selected patient population at study centers; may lead to results that are not generalizable	Randomization eliminates confounding bias	Current gold standard for comparative-effectiveness studies
Registry-based RCTs	$$-$$$	Prospective design; data collection often occurs at diverse clinical sites	Typically designed to study a specific patient population (e.g., those undergoing PCI)	Randomization eliminates confounding bias	Large number of outcomes; harnesses power of already-established clinical registry
Large, pragmatic clinical trials	$$-$$$$	Prospective design; data is collected ubiquitously as part of clinical care	Depending on electronic infrastructure, can be broad or selective; can incorporate enrichment criteria	Randomization eliminates confounding bias	Simple design; large number of outcomes; requires infrastructure that can facilitate easy and quick enrollment

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RCTs from eHRs

	SCOT-HEART Trial	PROMISE Trial
Country	UK	North America
Sample Size	4,146	10,003
Follow Up	Electronic Health Records	Site contact
Primary Endpoint	Certainty of diagnosis of angina due to coronary heart disease 5-Year CHD Death or non-fatal MI	Death, non-fatal MI, hospitalization for unstable angina, major procedural complications (anaphylaxis, bleeding and renal failure)
Cost	£0.5 Million	$40 Million
Long-term Follow-up	£718	Estimated at $20 Million (Funding declined)

Lancet 2015;385:2383-2391
N Engl J Med 2018; 379:924-933
N Engl J Med 2015;372:1291-1300

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Cochrane Library

Cochrane Database of Systematic Reviews

Comparison of central adjudication of outcomes and onsite outcome assessment on treatment effect estimates (Review)

Ndounga Diakou LA, Trinquart L, Hróbjartsson A, Barnes C, Yavchitz A, Ravaud P, Boutron I

"On average, treatment effect estimates for subjective outcome events assessed by onsite assessors did not differ from those assessed by Adjudication Committees."

In the real world, what matters is what the healthcare system sees and experiences not what is adjudicated.

Cochrane Database of Systematic Reviews 2016;3: MR000043

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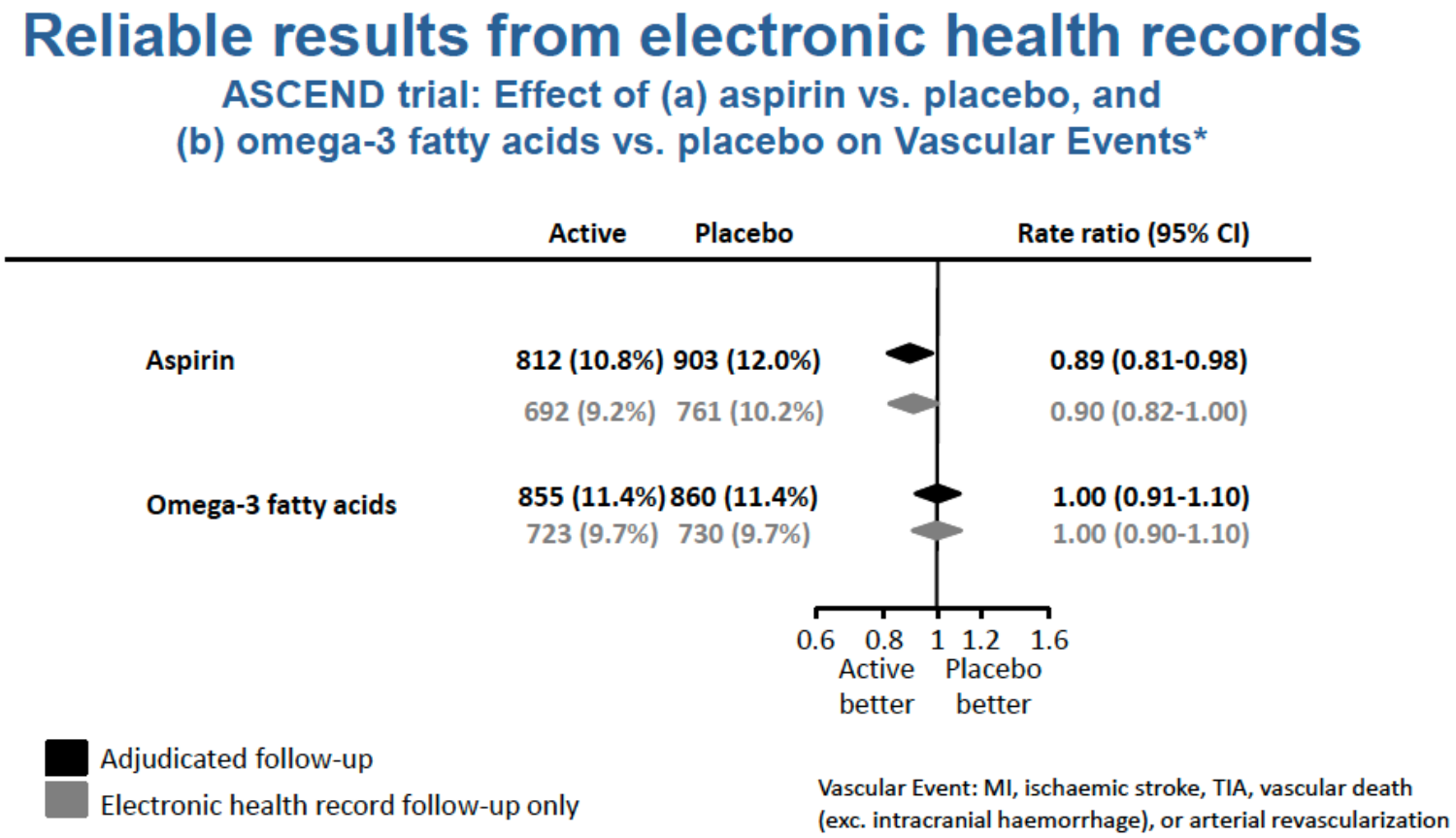
eHR data as the (composite) outcome



N Engl J Med. 2018;379:1540-1550

Jane Armitage, (via D Newby) Personal Communication: *Unpublished Data*

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The need for internationally recognised definitions of disease derived from eHRs

"An anonymous Tweeter brought the unusu
ICD codes to light. But investigators were q
to provide answers on numbers"

"When is an MI not an MI? Sometimes in SCOT-HEART, apparently."

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EuroHeart: an ESC initiative

EuroHeart is an ESC coordinated and sponsored programme that:

- Supports continuous development of quality of care based on individual patient data.
- Is based on development of and collaboration between national programmes that use common data sets and quality criteria.
- Integrates tools for device surveillance.
- Integrates tools for randomised clinical trials (RRCT).
- Provides an optional common IT-infrastructure.
- Is aligned with the ESC mission to reduce the burden of CVD.

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EuroHeart – the project

EuroHeart is an ESC coordinated and sponsored programme that:

- Covers the common disease areas ACS-PCI, valve disease, heart failure and atrial fibrillation.
- Starts with development of standardised data sets and quality indicators for diseases and devices.
- During the pilot phase, it tests the system in 2 – 4 countries.
- Will develop a data science centre localised with options for remote data access.
- Will include representatives from the interested countries in the development and in all subcommittees.

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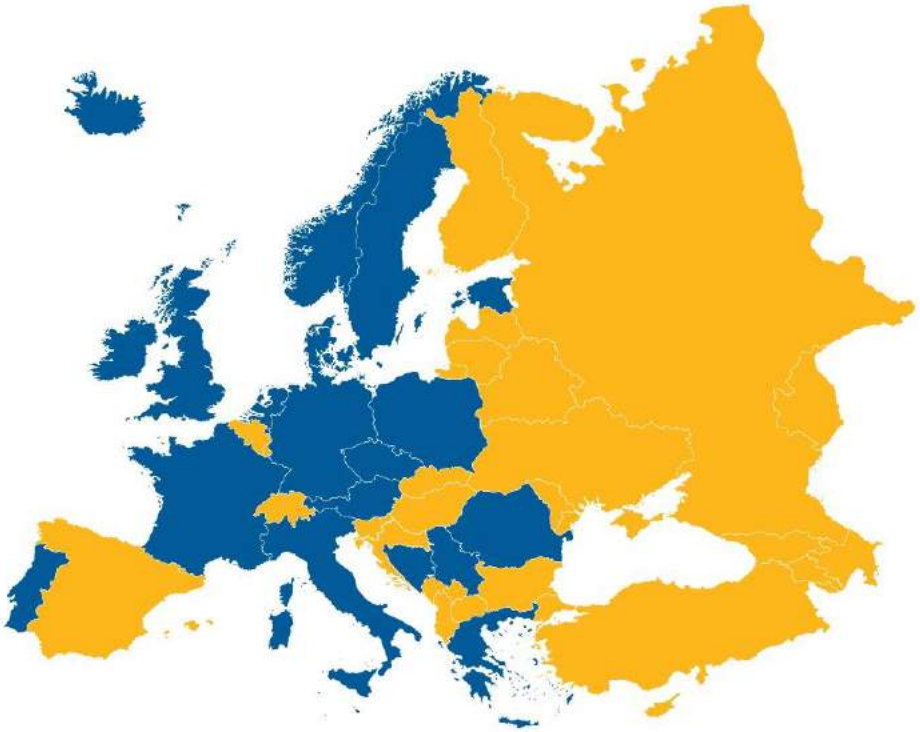
EuroHeart – EoIs

Potential Pilot Phase countries

- Sweden
- Iceland
- United Kingdom
- Scotland
- Ireland
- Poland
- Romania
- Serbia
- Check Republic
- Hungary
- Portugal
- Germany
- Austria
- Italy
- Israel
- Estonia
- Bosnia and Herzegovina
- Greece
- France
- The Netherlands
- Denmark
- Norway



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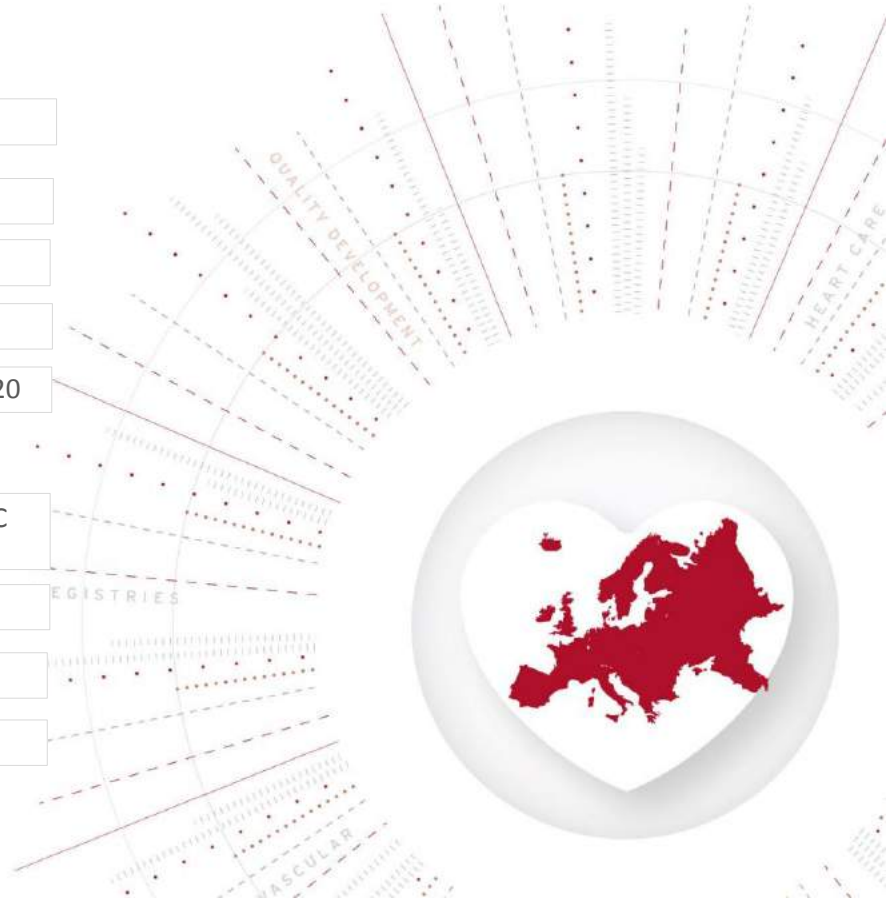
EuroHeart – schedule

EuroHeart - Milestones

Dec, 2019	Decision on protocol and standardized variables for ACS-PCI
March, 2020	Final decision on 2 – 4 pilot countries
April, 2020	IT-platform ready for development of ACS-PCI registry
June, 2020	Launch of the EuroHeart ACS-PCI
Sep 1, 2020	Report on the first included patients at the ESC Congress 2020
June, 2021	Decision on protocol & variables for valve disease
Sep 1, 2021 Congress 2021	Report on the 1-year outcomes of the ACS-PCI registry at ESC
Oct, 2021	EuroHeart ACS-PCI registries running in all pilot countries
	Start of development of TAVI registry
Dec , 2021	Decision on expansion of the EuroHeart system



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Registry-based RCTs

- Ideal for simple important clinical questions
- Cheap, real world and highly relevant for healthcare systems
- Many advantages over and above ‘gold-standard’ double blind RCTs
- Less resource intensive and more inclusive than registry-based RCTs
- Relies on strong and widespread registries / eHR systems to be in place

Are registries-based RCTs the future gold-standard for real world testing and implementation of therapies?

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