NATIONELL KONFERENS OM
KLINISKA STUDIER

6–7 september 2016, Uppsala

Pragmatiska patientnära studier - större, smartare och snabbare

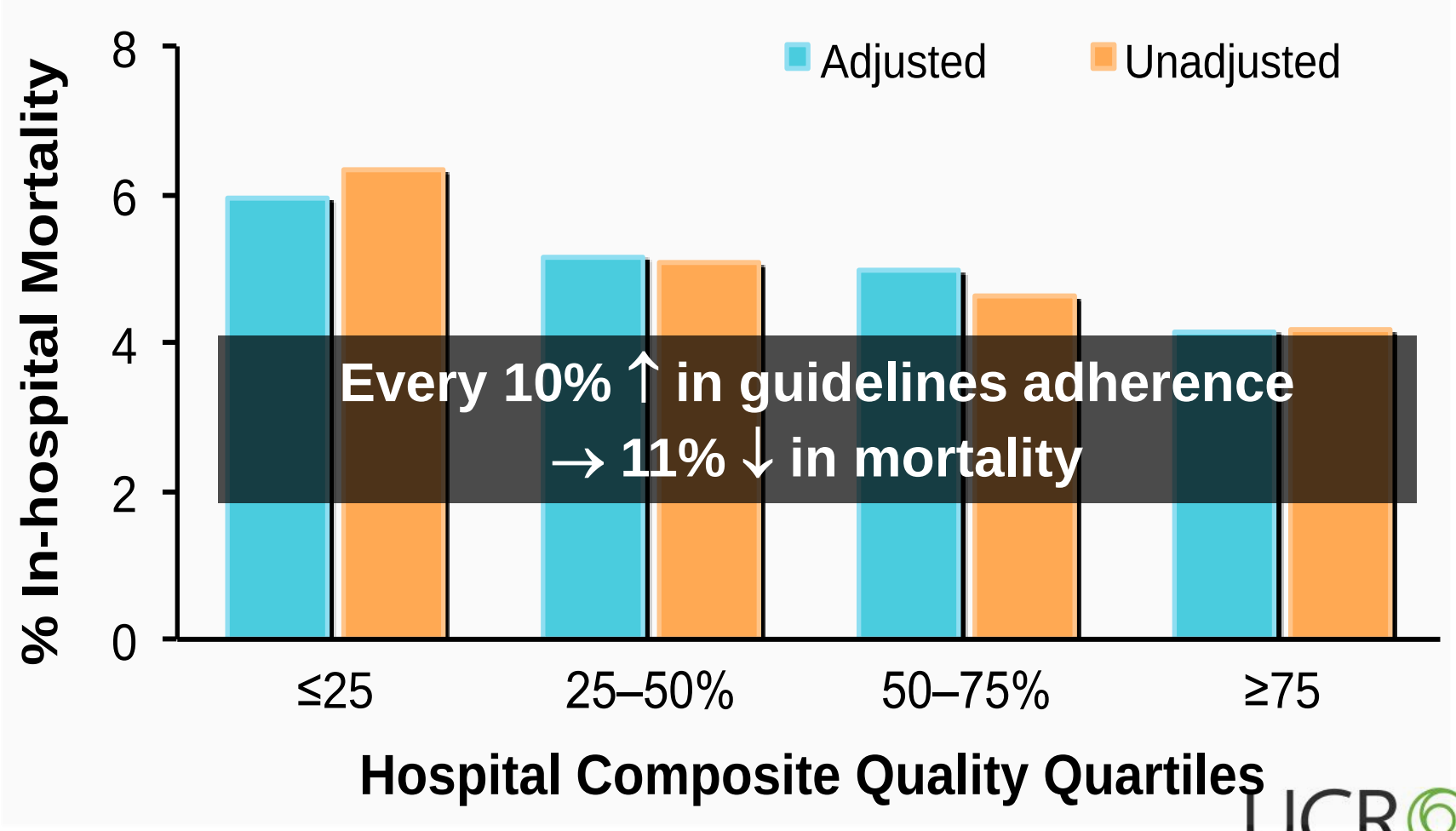
Stefan James

Professor of Cardiology

Uppsala Clinical Research Center
Uppsala University Uppsala, Sweden

UCR

Link Between Overall ACC/AHA Guidelines Adherence and Mortality



UCR

Peterson et al, ACC 2004

ORIGINAL CONTRIBUTION

Which Treatment is Best for Whom? High-Quality Evidence is Scarce
< 15% of guideline recommendations supported by high quality evidence

Scientific Evidence Underlying the ACC/AHA Clinical Practice Guidelines

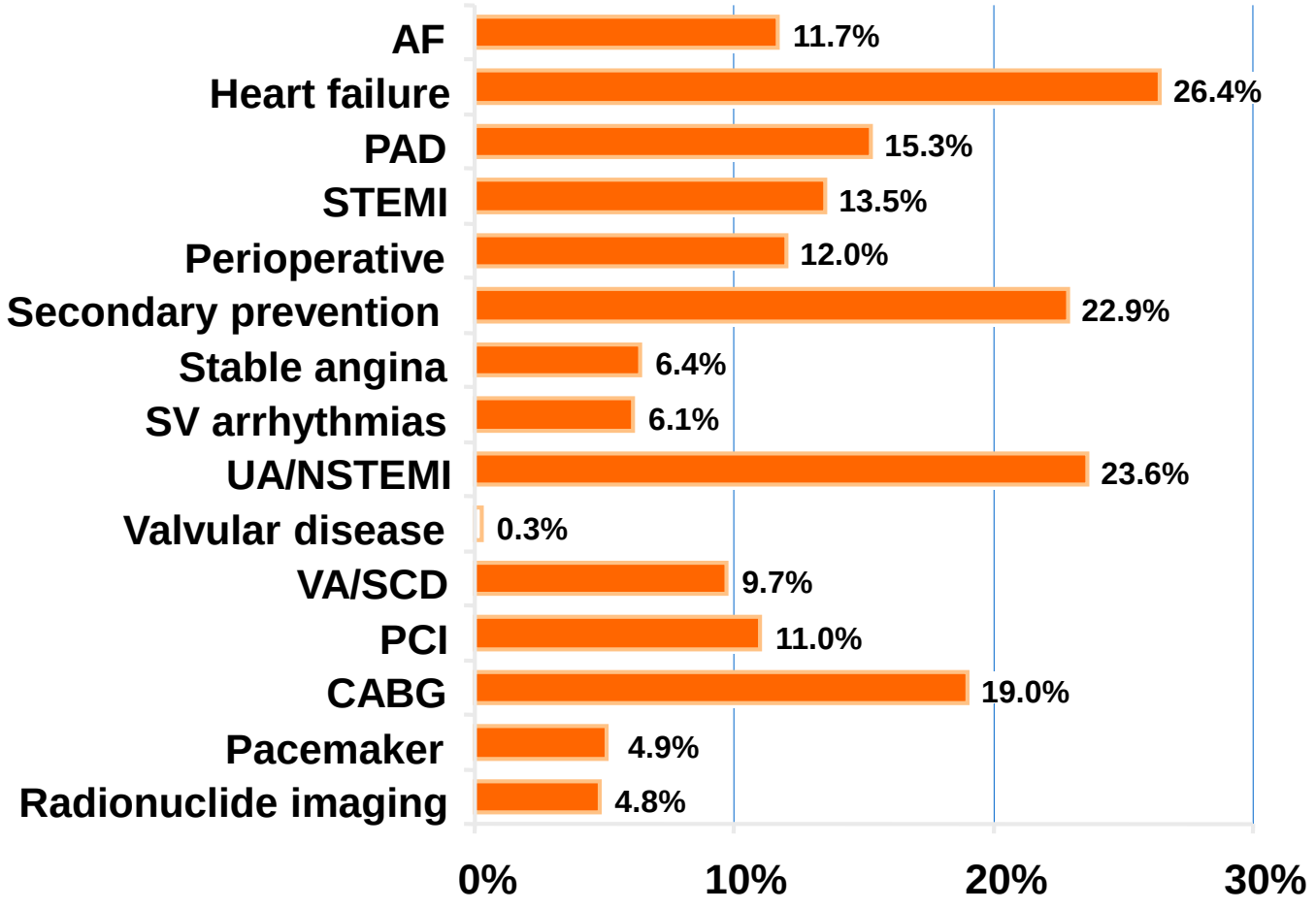
Pierluigi Tricoci, MD, MHS, PhD
Joseph M. Allen, MA
Judith M. Kramer, MD, MS
Robert M. Califf, MD
Sidney C. Smith Jr, MD

CLINICAL PRACTICE GUIDELINES are systematically developed statements to assist practitioners with decisions about appropriate health care for spe-

Context The joint cardiovascular practice guidelines of the American College of Cardiology (ACC) and the American Heart Association (AHA) have become important documents for guiding cardiology practice and establishing benchmarks for quality

Objec
cular gu
dations

Data S
issued
ence ar
recomm



ORIGINAL CONTRIBUTION

Characteristics of Clinical Trials Registered in ClinicalTrials.gov, 2007-2010

Robert M. Califf, MD
Deborah A. Zarin, MD
Judith M. Kramer, MD, MS
Rachel E. Sherman, MD, MPH
Laura H. Aberle, BSPH
Asba Tasneem, PhD

Context Recent reports highlight gaps between guidelines-based treatment recommendations and evidence from clinical trials that supports those recommendations. Strengthened reporting requirements for studies registered with ClinicalTrials.gov enable a comprehensive evaluation of the national trials portfolio.

Objective To examine fundamental characteristics of interventional clinical trials registered in the ClinicalTrials.gov database.

Methods A data set comprising 96 346 clinical studies from ClinicalTrials.gov was downloaded on September 27, 2010, and entered into a relational database to analyze aggregate data. Interventional trials were identified and analyses were focused

Conclusion Clinical trials registered in ClinicalTrials.gov are dominated by small trials and contain significant heterogeneity in methodological approaches, including reported use of randomization, blinding, and DMCs.

CLINICAL TRIALS ARE THE CEN-

the International Committee of Medical Journal Editors (ICMJE) announced a policy, which took effect in 2005, of requiring registration of clinical trials as a prerequisite for publication.[6,7] The Food and Drug Administration Amendment Act (FDAAA)[8] expanded the mandate of

0.91), and mental health trials vs those in the other 2 specialties. In similar comparisons, randomization and blinding were less frequently reported in earlier-phase, oncology, and device trials.

Conclusion Clinical trials registered in ClinicalTrials.gov are dominated by small trials and contain significant heterogeneity in methodological approaches, including reported use of randomization, blinding, and DMCs.

JAMA. 2012;307(17):1838-1847 www.jama.com

Cost of doing trials

How Much They Cost: R&D Spending Per New Drug

	Company	Number of new drugs	10 year R&D spending ($MIL)	R&D per drug ($MIL)
1	Abbott	1	13183	13183
2	Sanofi	6	60768	10128
3	AstraZeneca	4	38245	9561
8	Bayer			
9	Schering-Plough	3	18845	6282
10	Nov			
11	Take			
12	Mer			
13	Glax			
14	J&J			
15	Nov			

'Current clinical trials are too slow, too expensive, not reliable, and not designed to answer the important questions…'

Rob Califf, Commissioner for medical products & tobacco FDA. *"Applied clinical trials.*

'There is a peculiar paradox that exists in trial execution - we perform clinical trials to generate evidence to improve patient outcomes; however, we conduct clinical trials like anecdotal medicine'

Monica Shah NHI, quoted in Gheorghiade et al 2014

www.forbes.com

It takes A LOT of work

- 9 Data Safety Monitoring Board Reviews
- 33 Investigator Meetings
- 14,709 CEC events sent for adjudication
- 15,000+ SAEs processed
- 30,000+ Monitoring visits
- 300,000 Patient visits completed
- 2.7 Million CRF data forms completed

Big Cost Drivers in Traditional Clinical Trials

- Data collection – size of case report form
- Site monitoring - % source document verification
- Number of study-specific procedures and tests
- Number of study-specific contacts and visits
- Volume and complexity of safety reporting requirements
- Investigational drug storage and accountability
- **Total trial timeline!!!!!**

Current State of Clinical Trials

VIEWPOINT

Transforming Clinical Trials in Cardiovascular Disease

Mission Critical for Health and Economic Well-being

Elliott M. Antman, MD
Robert A. Harrington, MD

Perhaps the most exciting opportunity for CVD research-ers is to capitalize on the advances in systems and computa-tional biology that can inform first-in-human, proof-of-

"As large trials became popular…the original simplicity was lost…leading to increasingly complex trials. The unintended consequence has been to threaten the very existence of RCTs, given the operational complexities and ensuring costs. An ideal opportunity would be to embed randomization in the EMR… introducing randomization into registries sponsored by societies."

-Antman E, Harrington RA. JAMA 2012;338:1743-4.

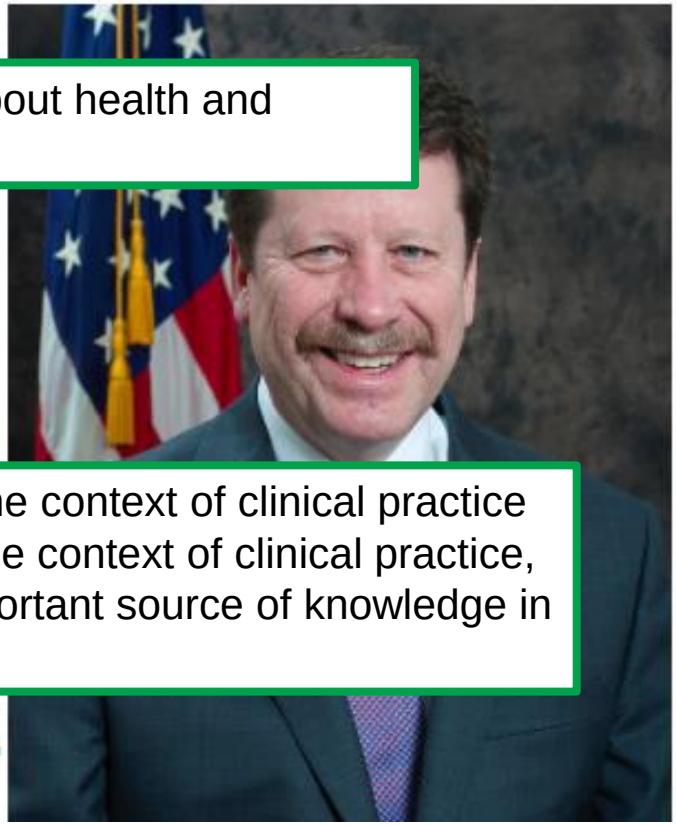
UCR

Califf: Leveraging Real World Evidence is 'Top Programmatic Priority' for FDA

Posted 11 May 2016

By Michael Mezher

"Unfortunately, too many of the decisions made today about health and healthcare are not supported by high quality evidence,"



Food and Drug Law Institute's annual conference last week.

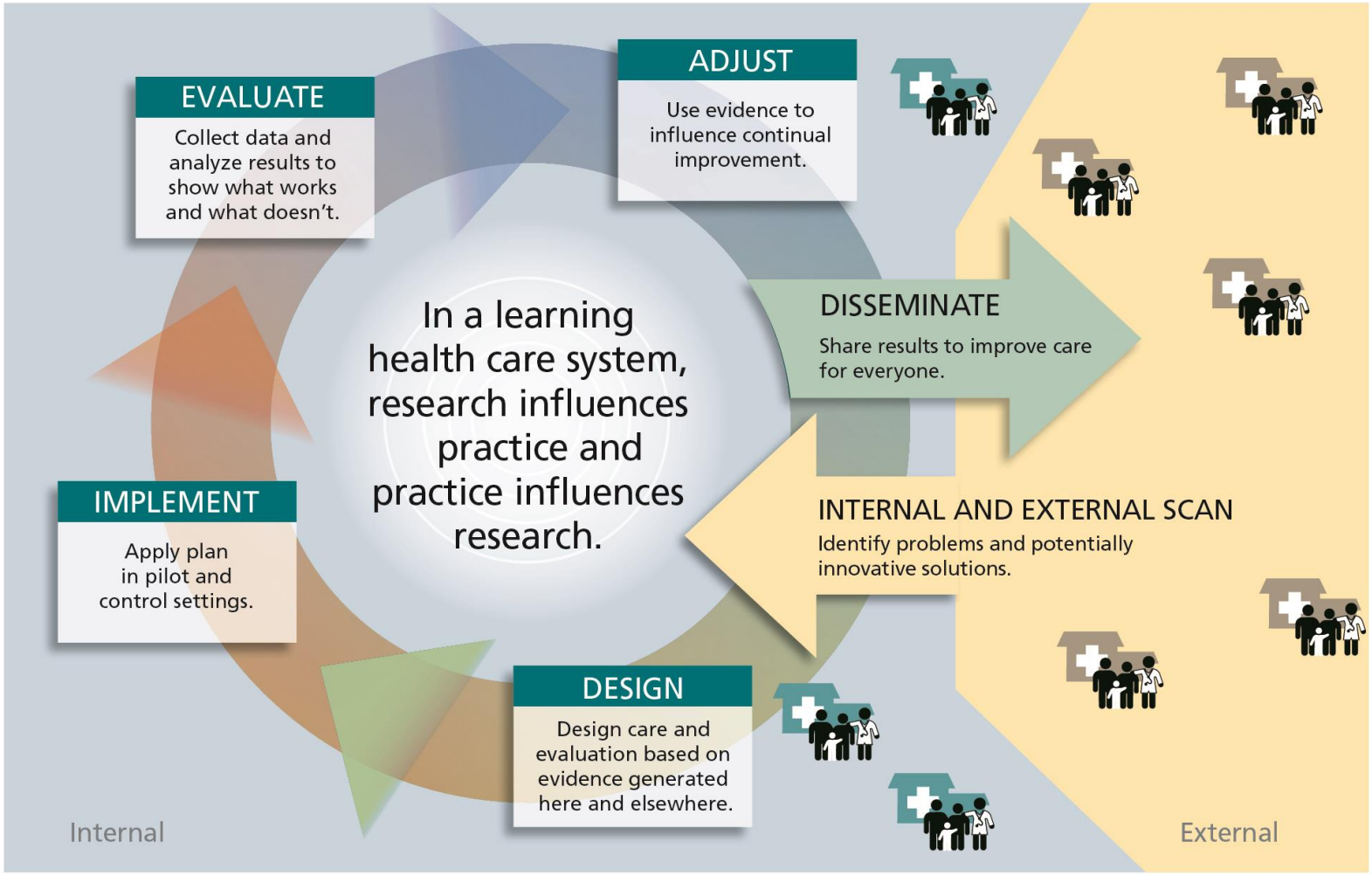
While Califf said his first priority as commissioner is to strengthen FDA's workforce, that stronger workforce will be critical to achieving FDA's goals in specific program areas such as real world evidence.

"Prospectively designed registries and cohort studies in the context of clinical practice are highly valuable, and randomized trials conducted in the context of clinical practice, often called a pragmatic clinical trial may be the most important source of knowledge in the future,"

through recent developments in electronic health records, patient registries and FDA-led initiatives such as Sentinel and unique device identifier (UDI) adoption, he added.

UCR

Learning health care systems



Summary

- Enormous gap between evidence and need for evidence
- Costs are skyrocketing
- Technical development growing
- Digitalized health records, clinical registries
- A new path is needed- to facilitate better, faster, easier, and more cost effective clinical research

UCR

General Classification

- **Explanatory or mechanistic trials**
  - aimed at impact of a treatment on biological or mechanistic measures
- **Pragmatic or evaluative trials**
  - aimed at impact of a treatment on what matters to patients and their care providers (living longer, feeling better, avoiding unpleasant experiences, spending less money) and to inform decision makers about health and healthcare

UCR

Robert Harrington, Stanford 2015

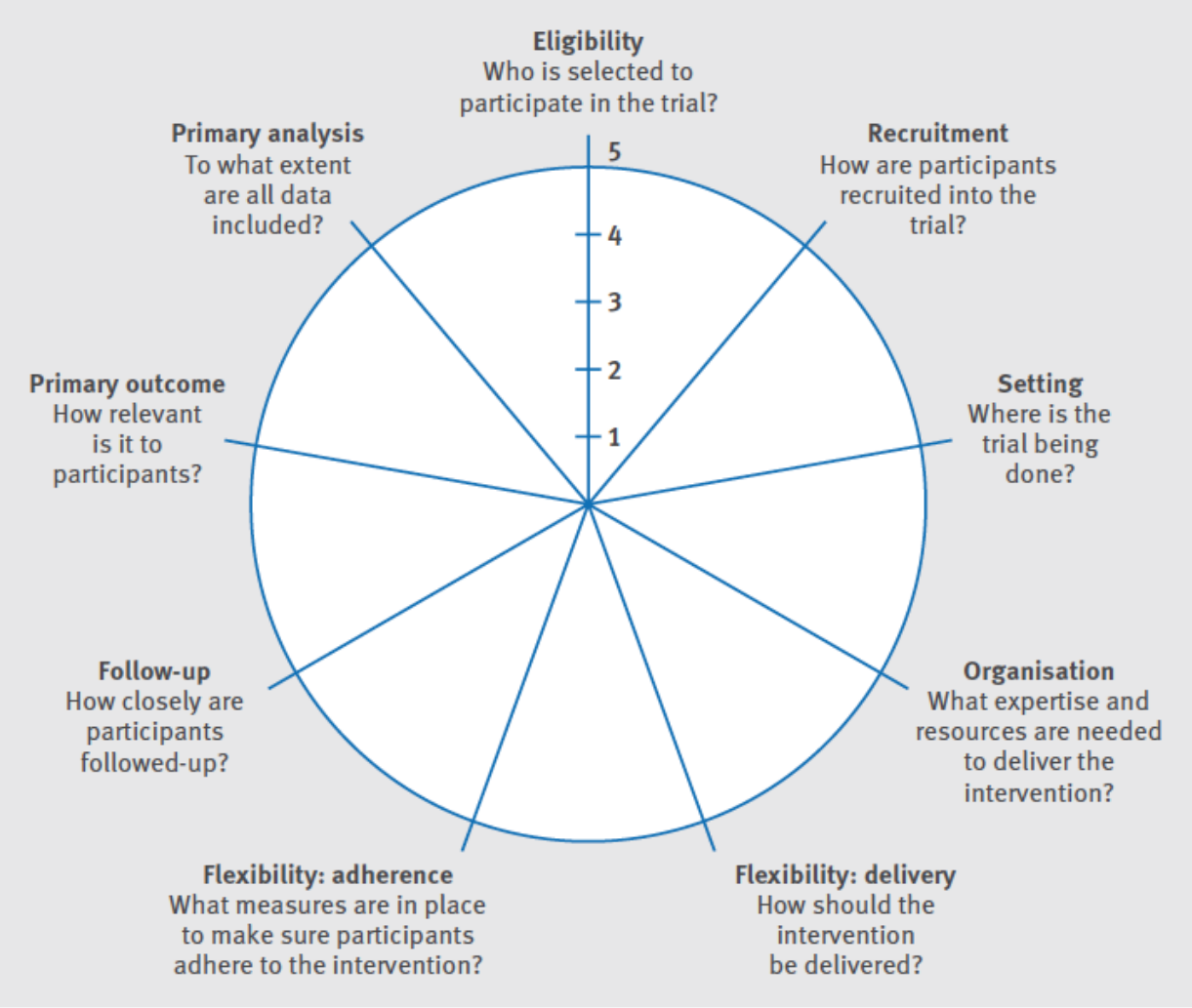
Elements of PCTs

	Traditional Clinical trial	Pragmatic Clinical trial
Research question	Is the treatment effective under ideal circumstances	Is the treatment effective in clinical reality
Patient selection	Narrow	Broad, representative
Goal	Deeper scientific understanding	Treatment choice
Endpoints	Surrogate, mechanistic	Clinically important

UCR

The PRECIS-2 tool: designing trials that are fit for purpose

Kirsty Loudon,[1] Shaun Treweek,[1] Frank Sullivan,[2] Peter Donnan,[3] Kevin E Thorpe,[4] Merrick Zwarenstein[5]



UCR

Loudon K, The PRECIS-2 tool. BMJ 2015; 350: h2147.

Definition for pragmatic clinical trial- R. Califf, FDA (2015)

(1) an intent to inform decision-makers (patients, clinicians, administrators, and policymakers), as opposed to elucidating a biological or social mechanism;

(2) an intent to enroll a population relevant to the decision in practice and representative of the patients/populations and clinical settings for whom the decision is relevant; and

(3) either an intent to

- (a) streamline procedures and data collection so that the trial can focus on adequate power for informing the clinical and policy decisions targeted by the trial
- (b) measure a broad range of outcomes

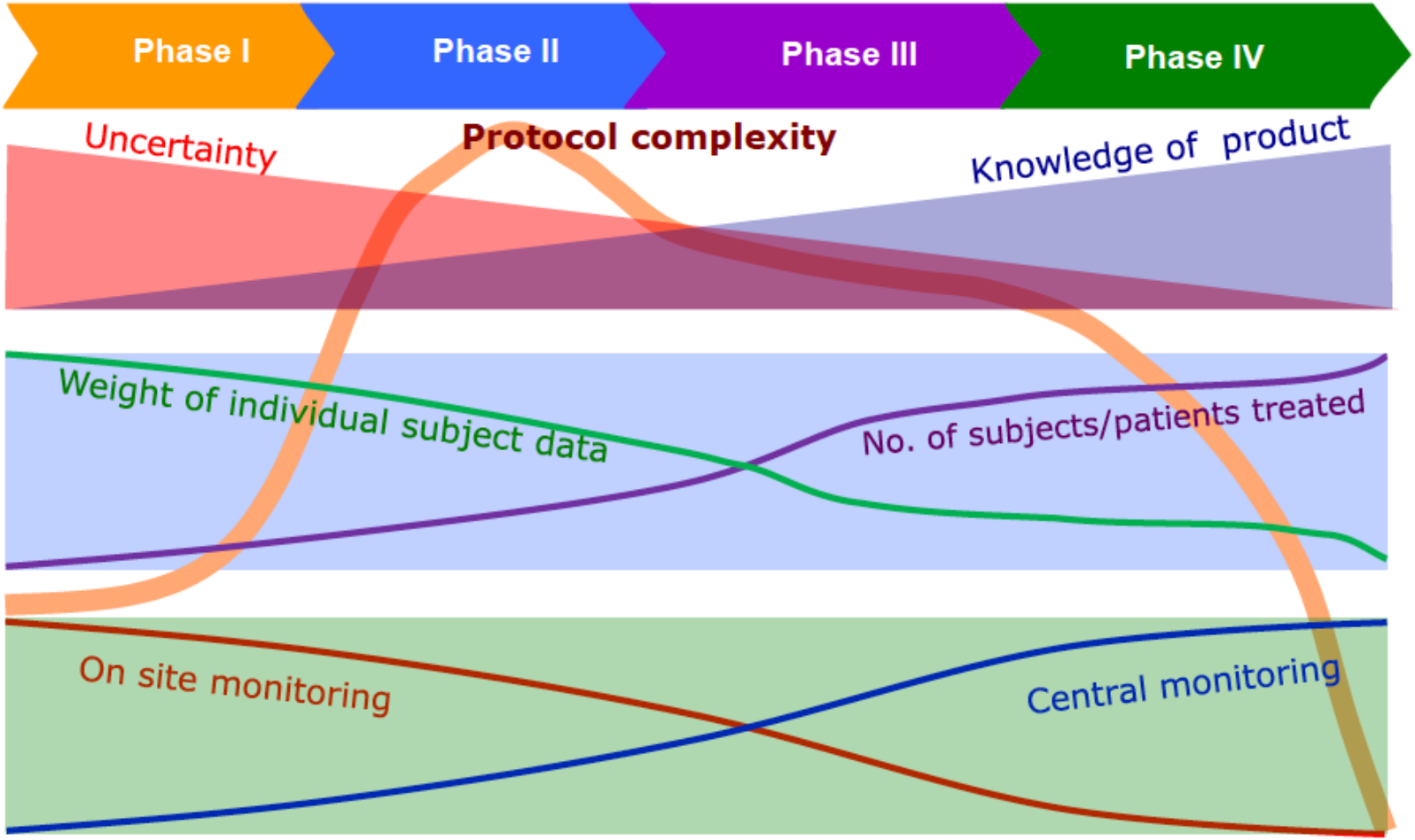
UCR

Study design

Clinical trial – product lifecycle

EUROPEAN MEDICINES AGENCY

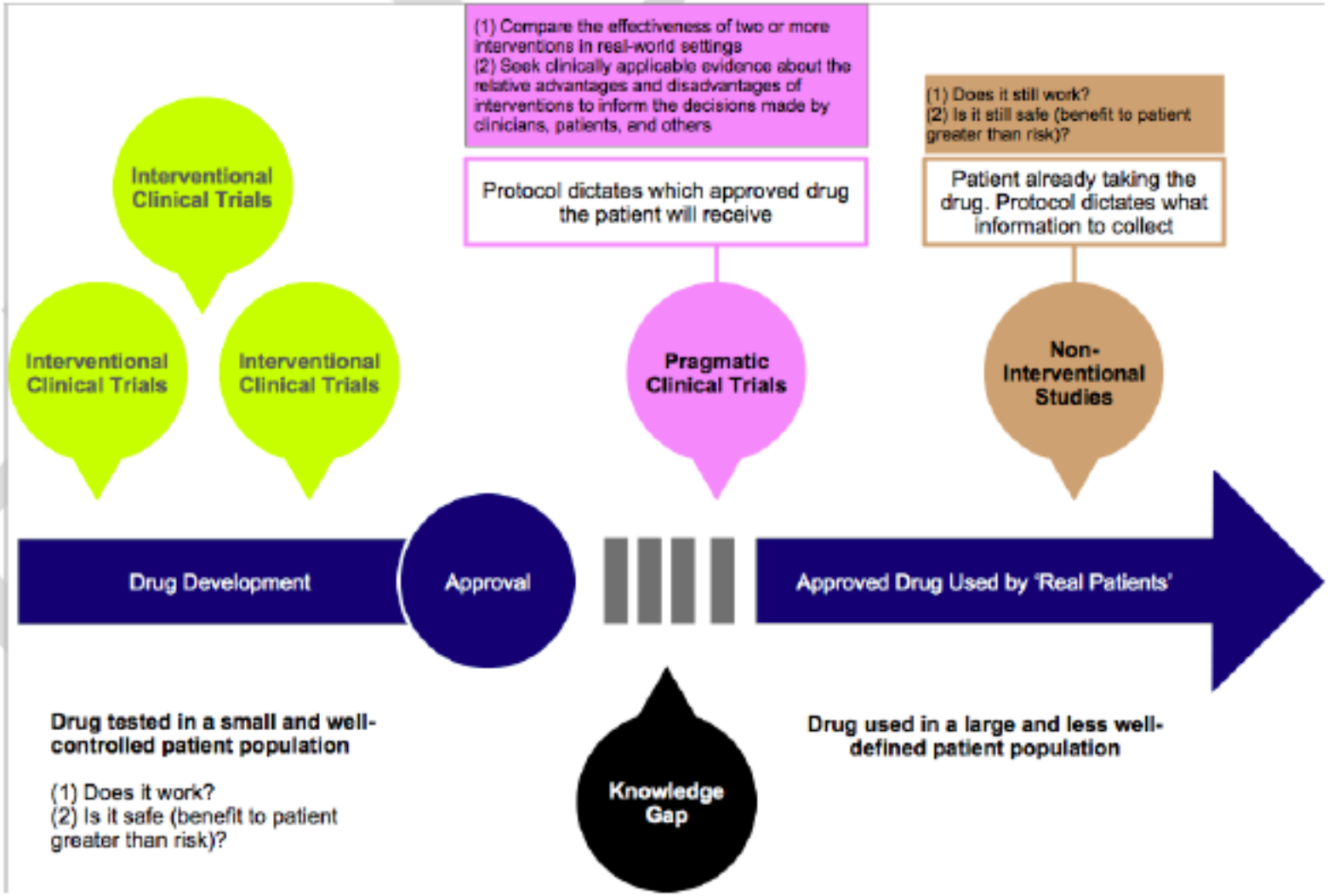
Clinical trial conduct including monitoring and data collection need to be proportionate to the knowledge of the product, protocol complexity and the risks involved to study participants and robustness of data



This representation is conceptual. The actual situation will vary for different medicines, population and trials.

Figure 1 – The Continuum of Product Development and Evidence Generation

This figure illustrates where Pragmatic Clinical Trials (PCTs) fit in the continuum of product development and evidence generation.



Pragmatic Clinical Trial- Califf FDA

Fit for the purpose of informing decision-makers regarding the comparative balance of benefit and risk of a biomedical or behavioral health intervention at the individual or population level

We should be striving for pragmatism in every clinical trial

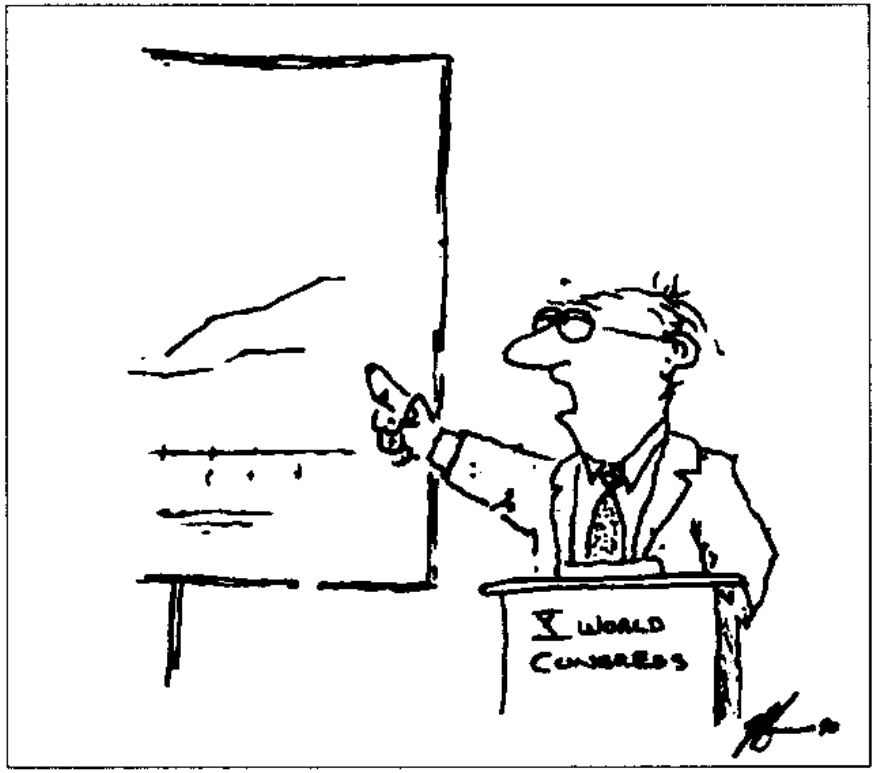
UCR

Usual Clinical Trial after Regulatory/FDA/Academic Interactions

Well planned and conducted pragmatic trial

Poorly planned pragmatic trial

UCR



"This randomized, double-blind trial involving over 20,000 patients was conducted over a 10 year period. Unfortunately we've forgotten why."

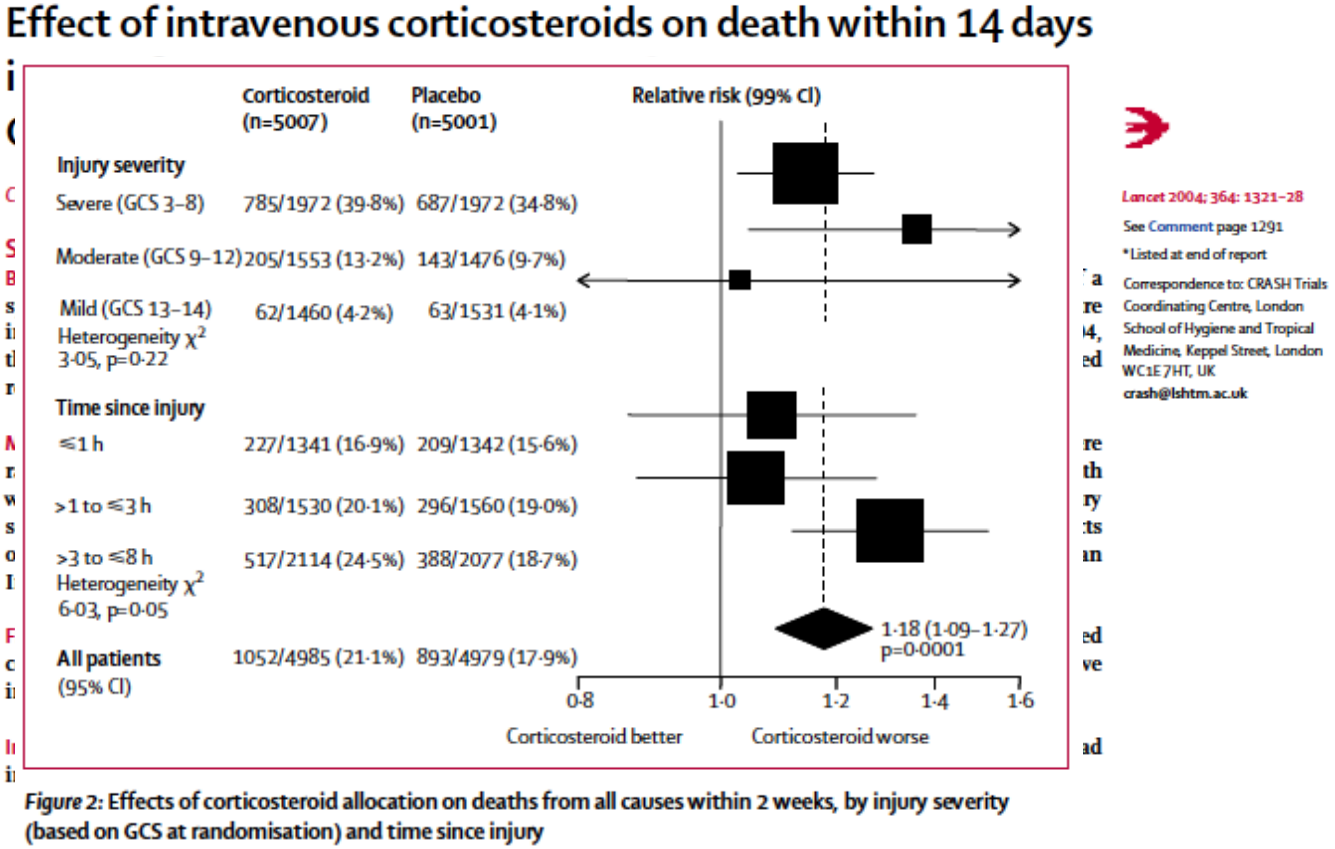


Figure 2: **Effects of corticosteroid allocation on deaths from all causes within 2 weeks, by injury severity (based on GCS at randomisation) and time since injury**

Lancet 2004; 364: 1321–28

See Comment page 1291

*Listed at end of report

Correspondence to: CRASH Trials Coordinating Centre, London School of Hygiene and Tropical Medicine, Keppel Street, London WC1E 7HT, UK
crash@lshtm.ac.uk

- No patient consent- only written information
- Simple randomization
- One single-sided outcome form, completed from hospital notes
- Only collection of outcomes though public registries and mailed forms to patients- no extra tests

UCR

VIEWPOINT

Ethics and Regulatory Complexities for Pragmatic Clinical Trials

Jeremy Sugarman, MD, MPH, MA

Robert M. Califf, MD

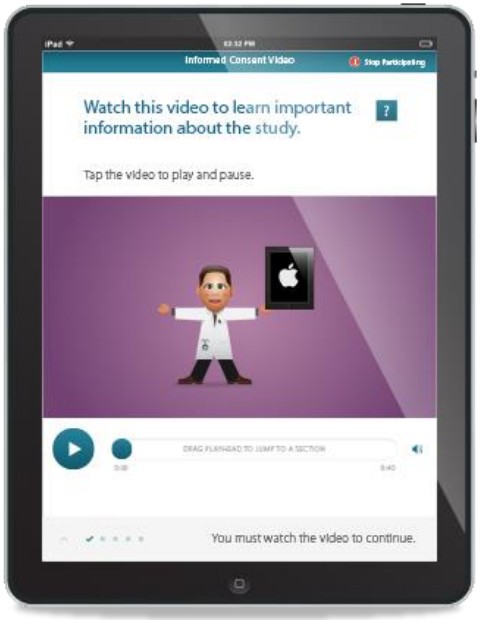
JAMA June 18, 2014 Volume 311, Number 23

HEALTH LAW, ETHICS, AND HUMAN RIGHTS

Informed Consent for Pragmatic Trials — The Integrated Consent Model

Scott Y.H. Kim, M.D., Ph.D., and Franklin G. Miller, Ph.D.

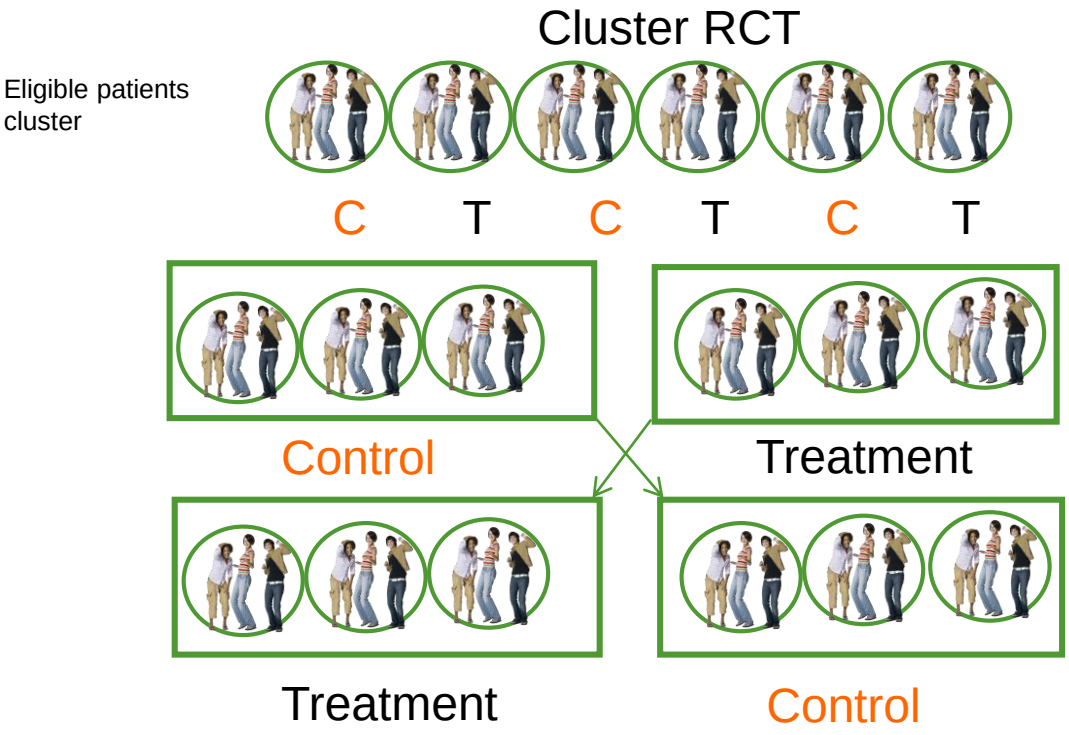
N ENGL J MED 370;8 NEJM.ORG FEBRUARY 20, 2014

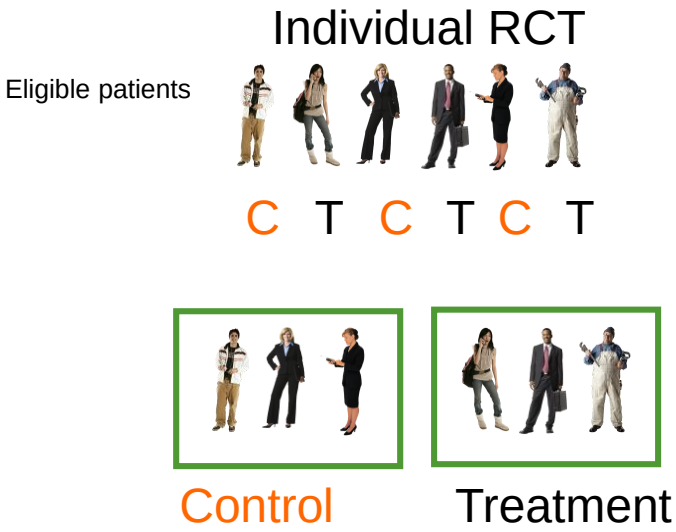


UCR

Cluster randomized trial (CRT)

- A **cluster randomized controlled trial** is a type of trial in which groups of subjects (as opposed to individual subjects) are randomized.
  - different communities, clinics, or cities to either get or not get a particular intervention





The NEW ENGLAND JOURNAL of MEDICINE

SPECIAL ARTICLE

Full Coverage for Preventive Medications after Myocardial Infarction

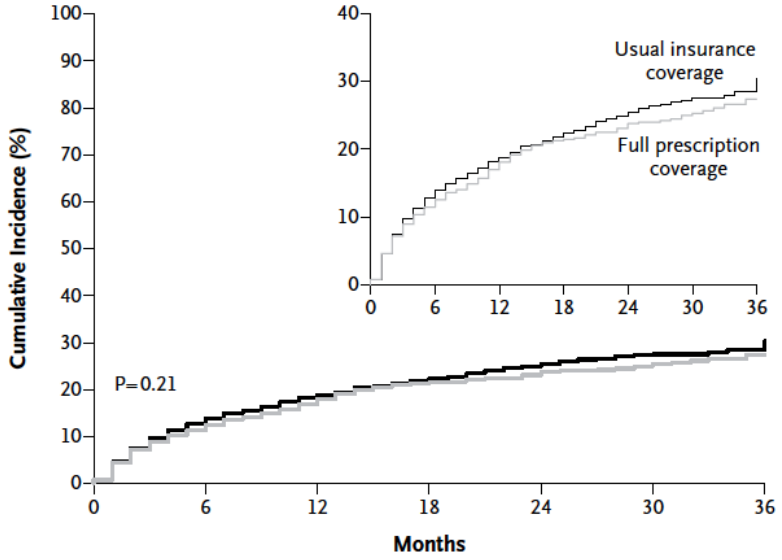
Niteesh K. Choudhry, M.D., Ph.D., Jerry Avorn, M.D., Robert J. Glynn, Sc.D., Ph.D., Elliott M. Antman, M.D., Sebastian Schneeweiss, M.D., Sc.D., Michele Toscano, M.S., Lonny Reisman, M.D., Joaquim Fernandes, M.S., Claire Spettell, Ph.D., Joy L. Lee, M.S., Raisa Levin, M.S., Troyen Brennan, M.D., J.D., M.P.H., and William H. Shrank, M.D., M.S.H.S., for the Post-Myocardial Infarction Free Rx Event and Economic Evaluation (MI FREEE) Trial

- Randomized policy experiment designed to evaluate the comparative effectiveness of two insurance benefit designs
- Potentially eligible patients were identified using administrative discharge claims submitted by hospitals to the insurance company
- Assignment occurred by cluster randomization at the level of the plan sponsor (employer)
- No individual consent
- Outcomes assessed by applying validated diagnostic algorithms to the insurance company health care utilization databases.

UCR

Choudhry N Engl J Med. 2011 Dec 1;365(22):2088-97

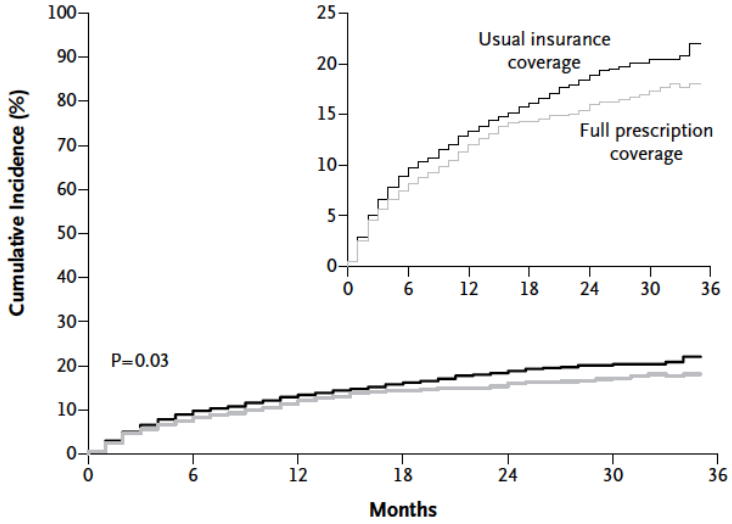
A First Fatal or Nonfatal Vascular Event or Revascularization



No. at Risk

Usual insurance coverage	3010	2251	1544	1012	611	345	119
Full prescription coverage	2845	2184	1465	919	563	304	120

B First Fatal or Nonfatal Vascular Event



No. at Risk

Usual insurance coverage	3010	2361	1652	1099	662	379	131
Full prescription coverage	2845	2295	1572	1013	625	340	135

PERSPECTIVES

OPINION

Registry-based randomized clinical trials—a new clinical trial paradigm

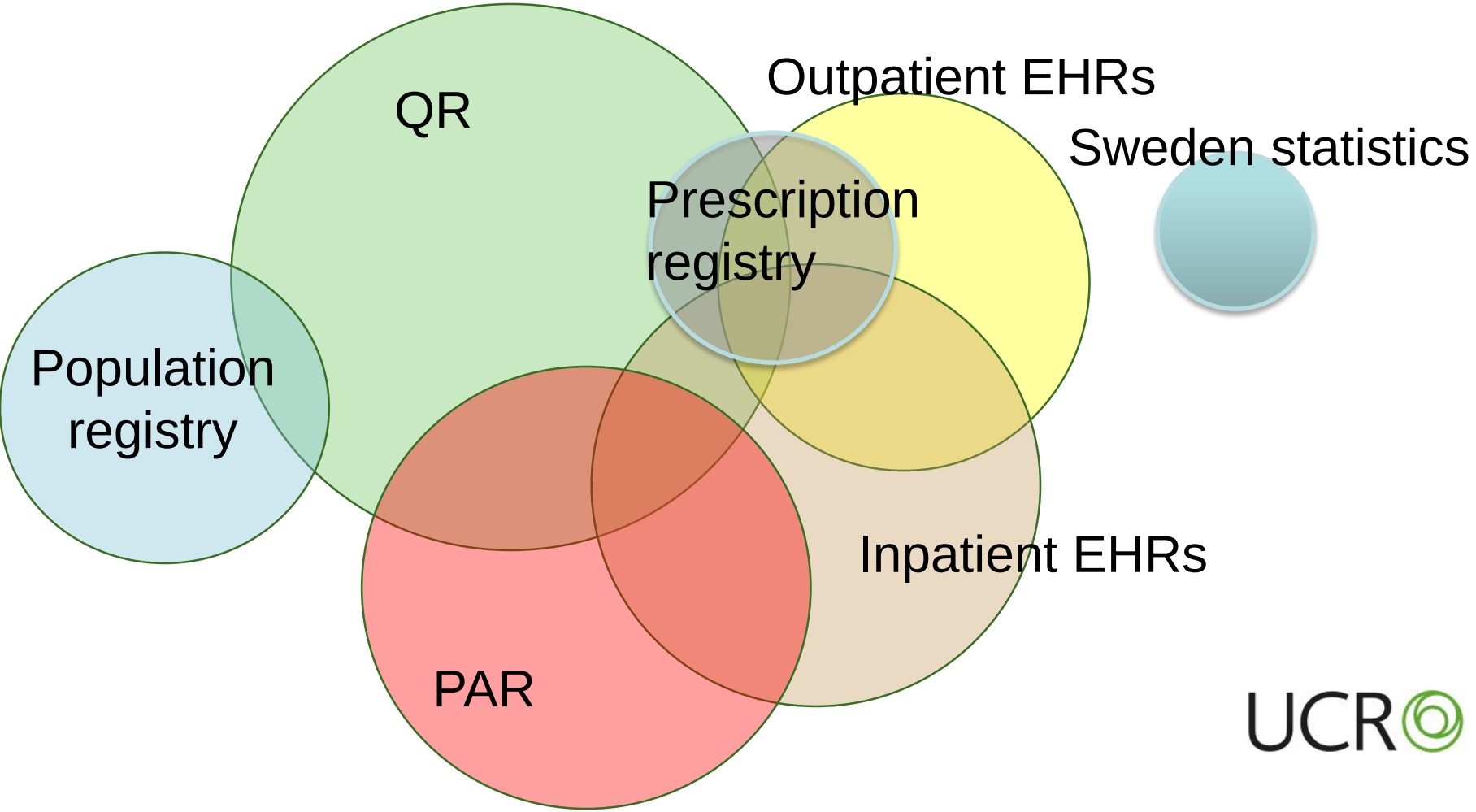
Stefan James, Sunil V. Rao and Christopher B. Granger

Abstract | Randomized clinical trials provide the foundation of clinical evidence to guide physicians in their selection of treatment options. Importantly, randomization is the only reliable method to control for confounding factors when comparing treatment groups. However, randomized trials have limitations, including the increasingly prohibitive costs of conducting adequately powered studies. Local and national regulatory requirements, delays in approval, and unnecessary trial processes have led to increased costs and decreased efficiency. Another limitation is that clinical trials involve selected patients who are treated according to protocols that might not represent real-world practice. A possible solution is registry-based randomized clinical trials. By including a randomization module in a large inclusive clinical registry with unselected consecutive enrolment, the advantages of a prospective randomized trial can be combined with the strengths of a large-scale all-comers clinical registry. We believe that prospective registry-based randomized clinical trials are a powerful tool for conducting studies efficiently and cost-effectively.

James, S. *et al. Nat. Rev. Cardiol.* **12**, 312–316 (2015); published online 17 March 2015;
doi:10.1038/nrcadio.2015.33

UCR

Data bases for baseline characteristics and outcomes in Sweden



Register based Randomized Clinical trials- R-RCT

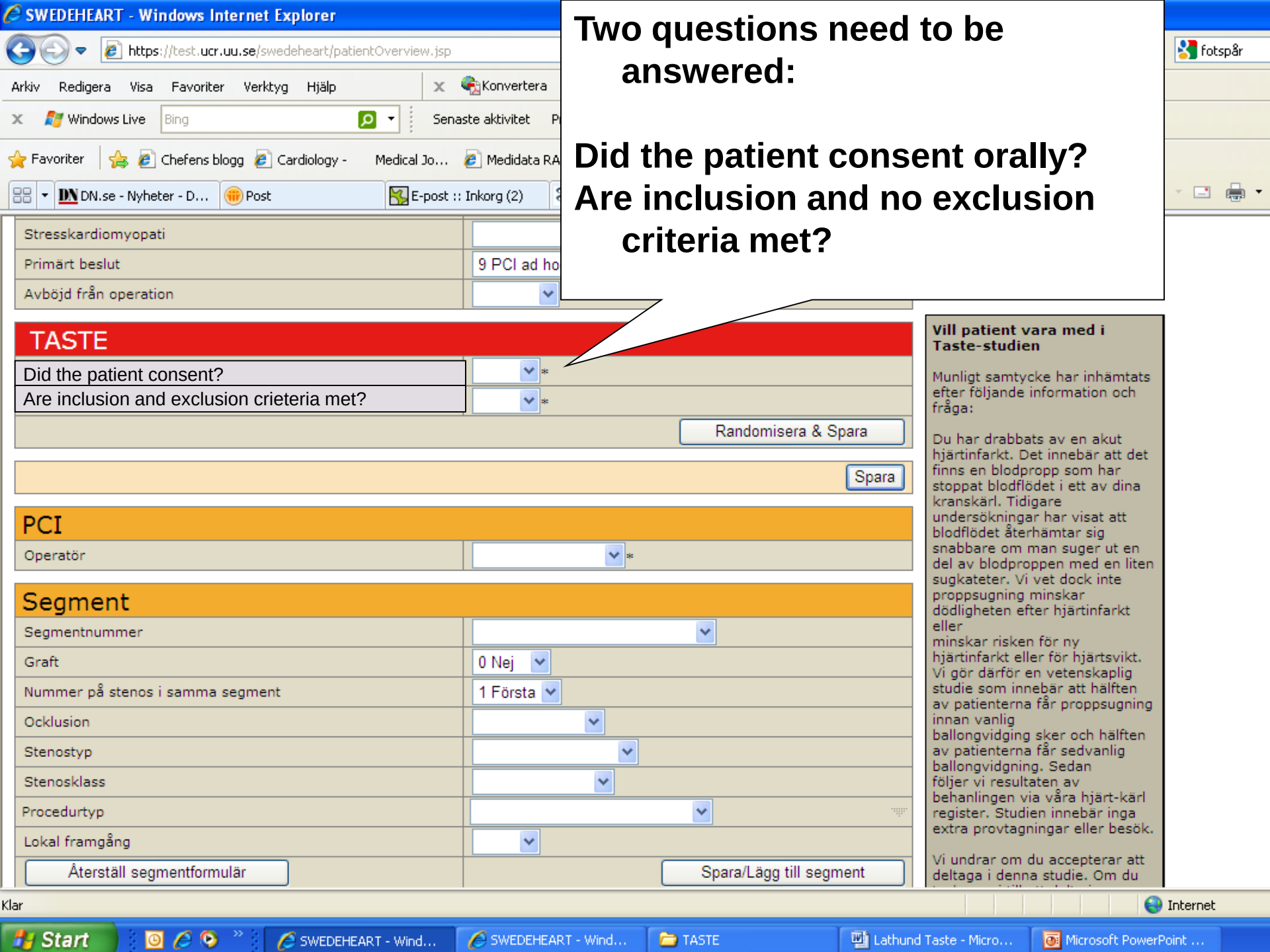
Prosective randomized trial that uses a clinical registry for one or several major functions for trial conduct and outcomes reporting.

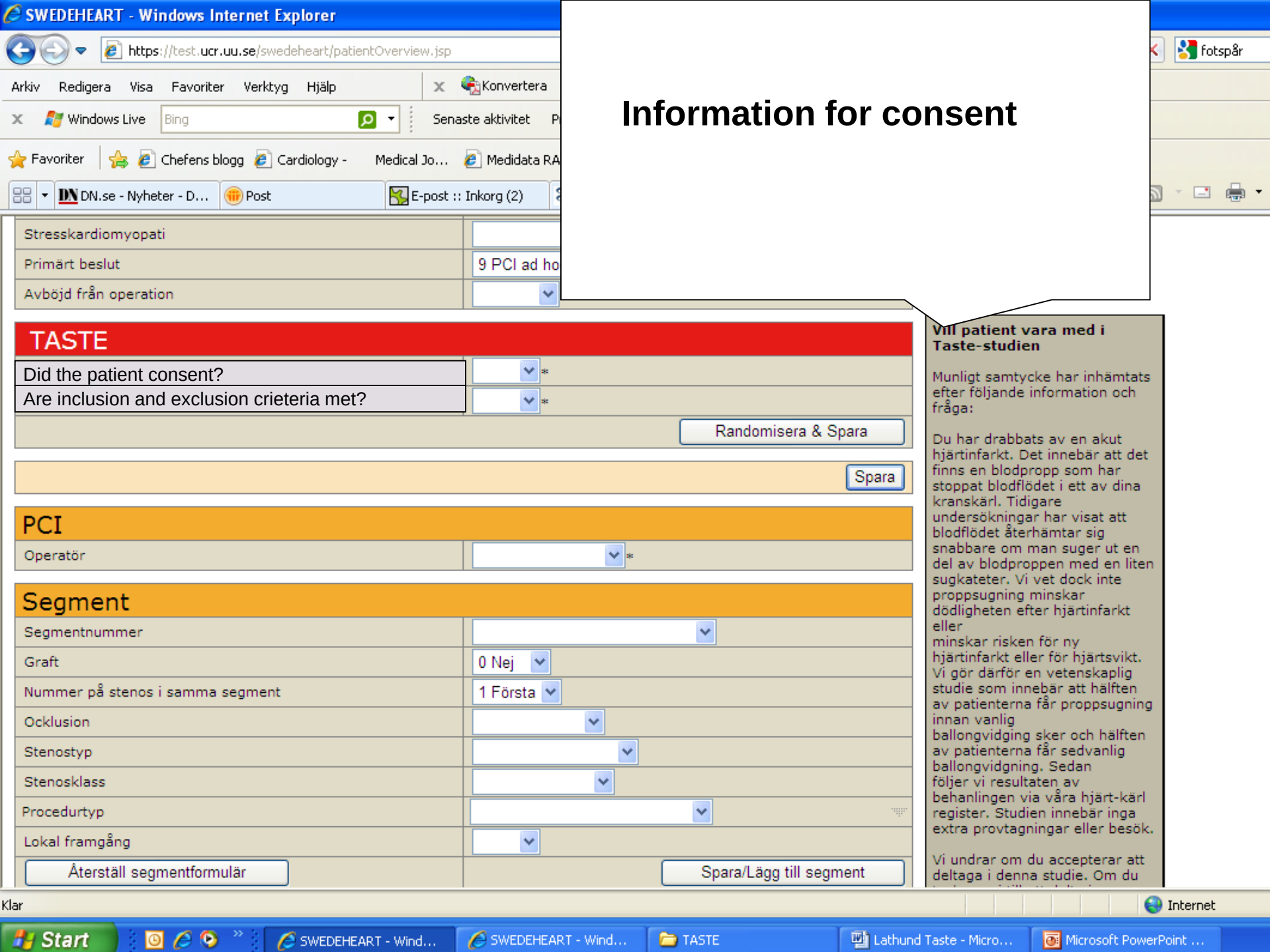
What can a registry do?

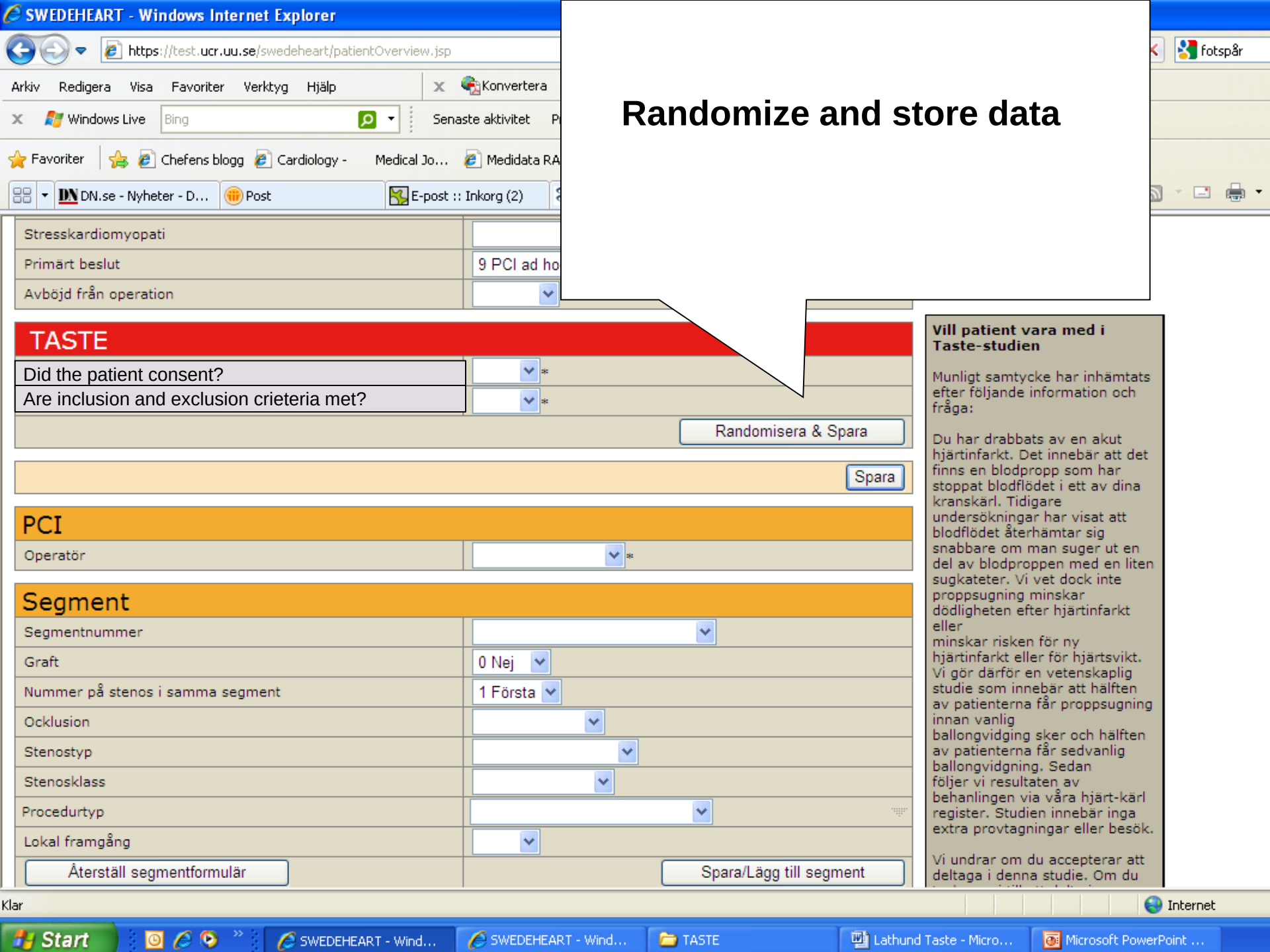
Some or all parts of trial

- Identify patients
- Randomize
- Collect baseline and procedure characteristics (CRF)
- Assist with and collect consent forms
- Identify clinical endpoints (endpoint detection)
- Control clinical outcome events (adjudication, CEC)

UCR

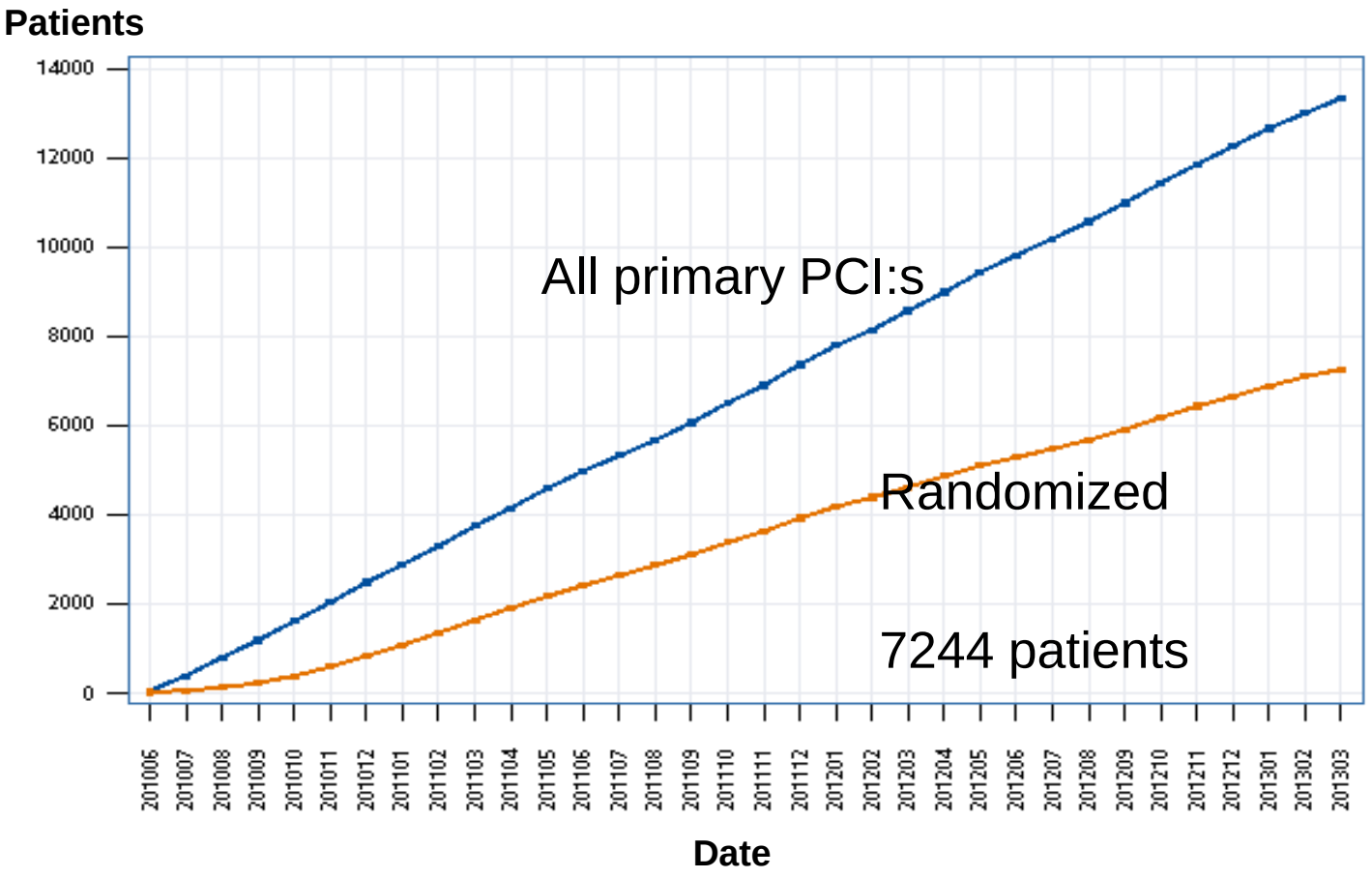

Two questions need to be answered:
Did the patient consent orally?
Are inclusion and no exclusion criteria met?
SWEDEHEART - Windows Internet Explorer
https://test.ucr.uu.se/swedeheart/patientOverview.jsp
Stresskardiomyopati
Primärt beslut
9 PCI ad ho
Avböjd från operation
TASTE
Did the patient consent?
Are inclusion and exclusion crieteria met?
Randomisera & Spara
Spara
PCI
Operatör
Segment
Segmentnummer
Graft
0 Nej
Nummer på stenos i samma segment
1 Första
Ocklusion
Stenostyp
Stenosklass
Procedurtyp
Lokal framgång
Återställ segmentformulär
Spara/Lägg till segment
Vill patient vara med i Taste-studien
Munligt samtycke har inhämtats efter följande information och fråga:
Du har drabbats av en akut hjärtinfarkt. Det innebär att det finns en blodpropp som har stoppat blodflödet i ett av dina kranskärl. Tidigare undersökningar har visat att blodflödet återhämtar sig snabbare om man suger ut en del av blodproppen med en liten sugkateter. Vi vet dock inte proppsugning minskar dödligheten efter hjärtinfarkt eller
minskar risken för ny hjärtinfarkt eller för hjärtsvikt. Vi gör därför en vetenskaplig studie som innebär att hälften av patienterna får proppsugning innan vanlig
ballongvidging sker och hälften av patienterna får sedvanlig ballongvidgning. Sedan följer vi resultaten av behanlingen via våra hjärt-kärl register. Studien innebär inga extra provtagningar eller besök.
Vi undrar om du accepterar att deltaga i denna studie. Om du
Klar
Internet
Start
SWEDEHEART - Wind...
SWEDEHEART - Wind...
TASTE
Lathund Taste - Micro...
Microsoft PowerPoint ...


SWEDEHEART - Windows Internet Explorer
https://test.ucr.uu.se/swedeheart/patientOverview.jsp
Arkiv Redigera Visa Favoriter Verktyg Hjälp
Konvertera
Windows Live
Bing
Senaste aktivitet
Favoriter
Chefens blogg
Cardiology -
Medical Jo...
Medidata RA
DN.se - Nyheter - D...
Post
E-post :: Inkorg (2)
Information for consent
Stresskardiomyopati
Primärt beslut
9 PCI ad ho
Avböjd från operation
TASTE
Did the patient consent?
Are inclusion and exclusion crieteria met?
Randomisera & Spara
Spara
PCI
Operatör
Segment
Segmentnummer
Graft
0 Nej
Nummer på stenos i samma segment
1 Första
Ocklusion
Stenostyp
Stenosklass
Procedurtyp
Lokal framgång
Återställ segmentformulär
Spara/Lägg till segment
Vill patient vara med i Taste-studien
Munligt samtycke har inhämtats efter följande information och fråga:
Du har drabbats av en akut hjärtinfarkt. Det innebär att det finns en blodpropp som har stoppat blodflödet i ett av dina kranskärl. Tidigare undersökningar har visat att blodflödet återhämtar sig snabbare om man suger ut en del av blodproppen med en liten sugkateter. Vi vet dock inte proppsugning minskar dödligheten efter hjärtinfarkt eller
minskar risken för ny hjärtinfarkt eller för hjärtsvikt. Vi gör därför en vetenskaplig studie som innebär att hälften av patienterna får proppsugning innan vanlig
ballongvidging sker och hälften av patienterna får sedvanlig ballongvidgning. Sedan följer vi resultaten av behanlingen via våra hjärt-kärl register. Studien innebär inga extra provtagningar eller besök.
Vi undrar om du accepterar att deltaga i denna studie. Om du
Klar
Internet
Start
SWEDEHEART - Wind...
SWEDEHEART - Wind...
TASTE
Lathund Taste - Micro...
Microsoft PowerPoint ...


SWEDEHEART - Windows Internet Explorer
https://test.ucr.uu.se/swedeheart/patientOverview.jsp
Arkiv Redigera Visa Favoriter Verktyg Hjälp
Konvertera
Windows Live
Bing
Senaste aktivitet
Favoriter
Chefens blogg
Cardiology -
Medical Jo...
Medidata RA
DN.se - Nyheter - D...
Post
E-post :: Inkorg (2)
fotspår
Randomize and store data
Stresskardiomyopati
Primärt beslut
9 PCI ad ho
Avböjd från operation
TASTE
Did the patient consent?
Are inclusion and exclusion crieteria met?
Randomisera & Spara
Spara
PCI
Operatör
Segment
Segmentnummer
Graft
0 Nej
Nummer på stenos i samma segment
1 Första
Ocklusion
Stenostyp
Stenosklass
Procedurtyp
Lokal framgång
Återställ segmentformulär
Spara/Lägg till segment
Vill patient vara med i Taste-studien
Munligt samtycke har inhämtats efter följande information och fråga:
Du har drabbats av en akut hjärtinfarkt. Det innebär att det finns en blodpropp som har stoppat blodflödet i ett av dina kranskärl. Tidigare undersökningar har visat att blodflödet återhämtar sig snabbare om man suger ut en del av blodproppen med en liten sugkateter. Vi vet dock inte proppsugning minskar dödligheten efter hjärtinfarkt eller
minskar risken för ny hjärtinfarkt eller för hjärtsvikt. Vi gör därför en vetenskaplig studie som innebär att hälften av patienterna får proppsugning innan vanlig
ballongvidging sker och hälften av patienterna får sedvanlig ballongvidgning. Sedan följer vi resultaten av behanlingen via våra hjärt-kärl register. Studien innebär inga extra provtagningar eller besök.
Vi undrar om du accepterar att deltaga i denna studie. Om du
Klar
Internet
Start
SWEDEHEART - Wind...
SWEDEHEART - Wind...
TASTE
Lathund Taste - Micro...
Microsoft PowerPoint ...

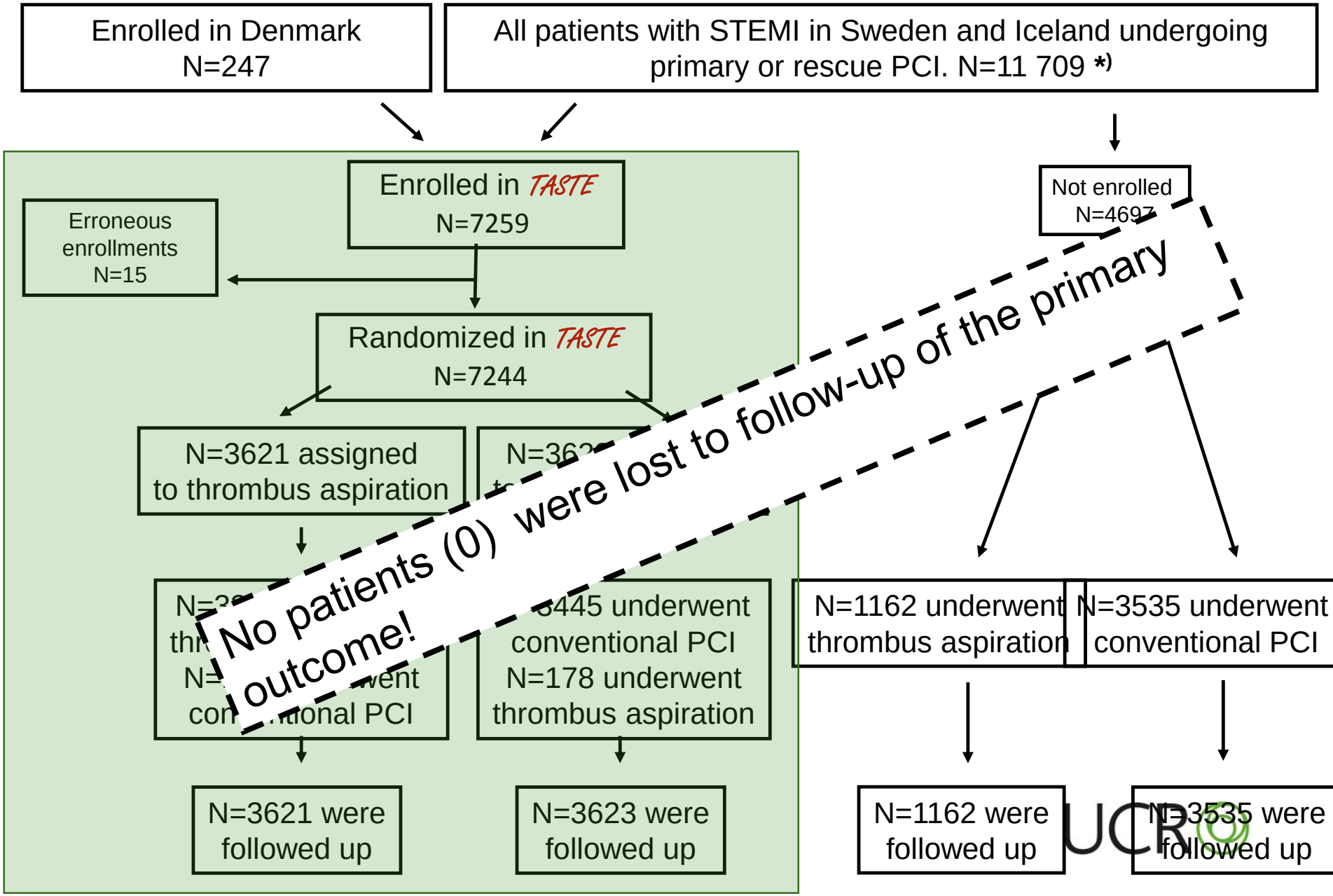
TASTE

TASTE inclusion rate



UCR

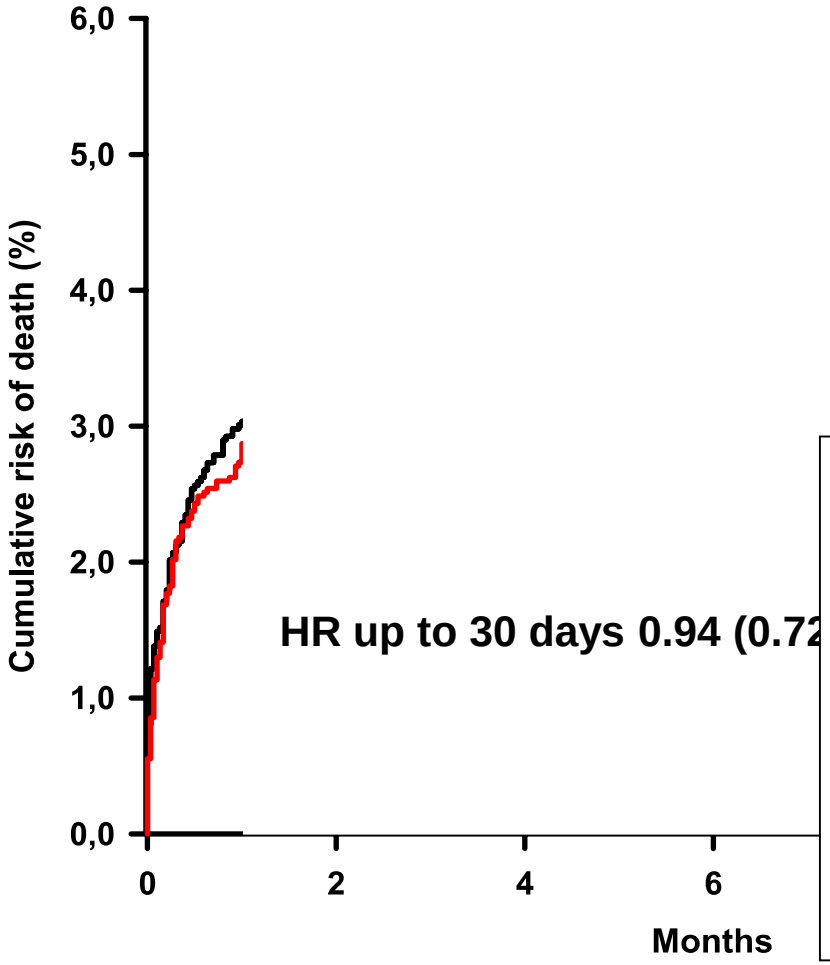
TASTE trial enrollment flow chart



TASTE

All-cause mortality up to 1 year

SWEDE HEART



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Thrombus Aspiration during ST-Segment Elevation Myocardial Infarction

Ole Fröbert, M.D., Ph.D., Bo Lagerqvist, M.D., Ph.D., Göran K. Olivecrona, M.D., Ph.D., Elmir Omerovic, M.D., Ph.D., Thorarinn Gudnason, M.D., Ph.D., Michael Maeng, M.D., Ph.D., Mikael Aasa, M.D., Ph.D., Oskar Angerås, M.D., Fredrik Calais, M.D., Mikael Danielewicz, M.D., David Erlinge, M.D., Ph.D.,

The NEW ENGLAND JOURNAL of MEDICINE Perspective

The Randomized Registry Trial — The Next Disruptive Technology in Clinical Research?

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

The randomized trial is one of the most powerful tools clinical researchers possess, a tool that enables them to evaluate the effectiveness of new (or established) therapies while accounting for

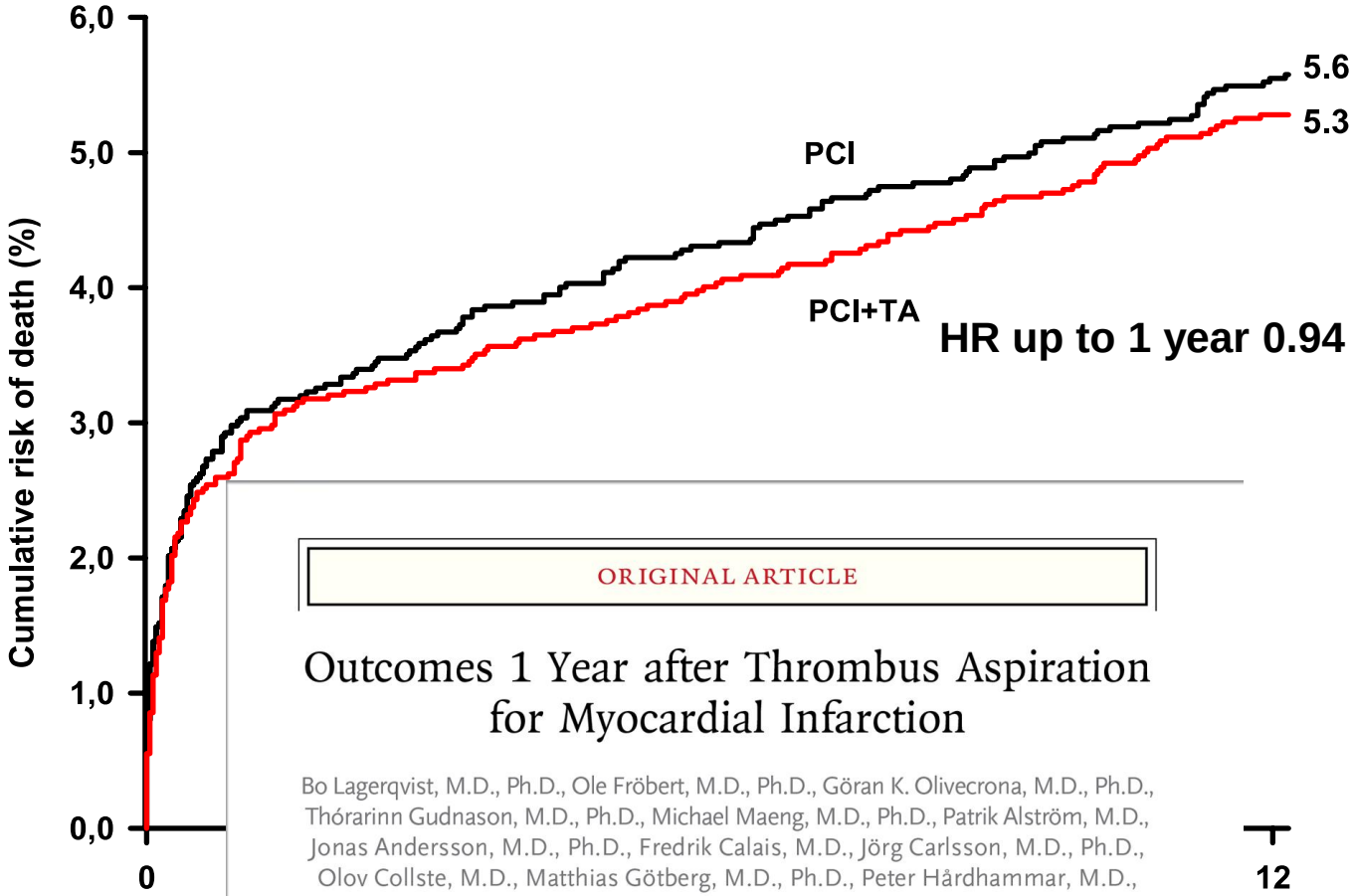
United States and abroad have collected vast amounts of data from patients with acute coronary syndromes, stable coronary disease, and heart failure, as well as

UCR

TASTE

All-cause mortality up to 1 year

SWEDE HEART



HR up to 1 year 0.94 (0.78 – 1.15), P=0.57

ORIGINAL ARTICLE

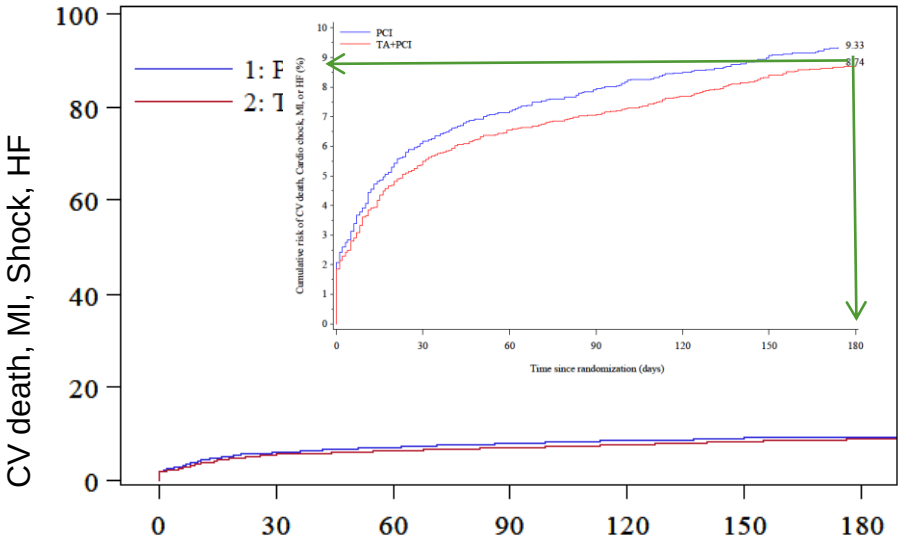
Outcomes 1 Year after Thrombus Aspiration for Myocardial Infarction

Bo Lagerqvist, M.D., Ph.D., Ole Fröbert, M.D., Ph.D., Göran K. Olivecrona, M.D., Ph.D., Thórarinn Gudnason, M.D., Ph.D., Michael Maeng, M.D., Ph.D., Patrik Alström, M.D., Jonas Andersson, M.D., Ph.D., Fredrik Calais, M.D., Jörg Carlsson, M.D., Ph.D., Olov Collste, M.D., Matthias Götberg, M.D., Ph.D., Peter Hårdhammar, M.D., Dan Ioanes, M.D., Anders Kallryd, M.D., Rickard Linder, M.D., Ph.D., Anders Lundin, M.D., Jacob Odenstedt, M.D., Elmir Omerovic, M.D., Ph.D., Verner Puskar, M.D., Tim Tödt, M.D., Ph.D., Eva Zelleroth, M.D., Ollie Östlund, Ph.D., and Stefan K. James, M.D., Ph.D.

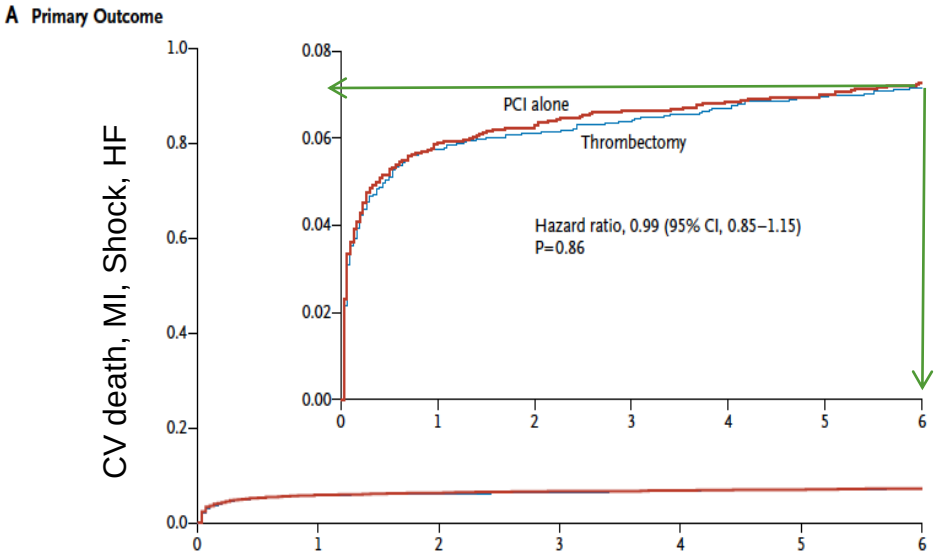
UCR

Same composite clinical endpoint at 180 days

Registry-based Follow-up



Site-based Follow-up



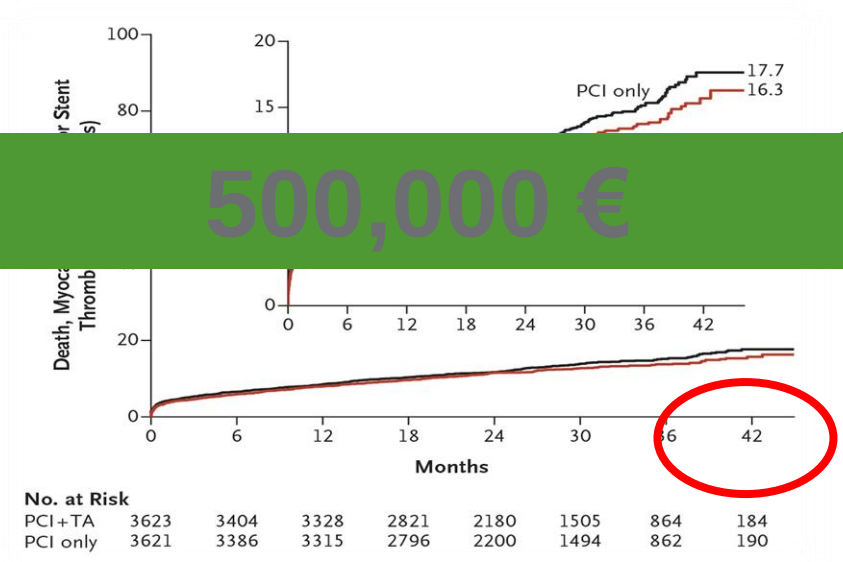
Lagerqvist B et al. N Engl J Med 2014;371:1111-1120

Jolly SS et al. N Engl J Med 2015;372:1389-1398

Claims-based Patient Follow-up

STEMI Thrombectomy Story

Registry-based Follow-up

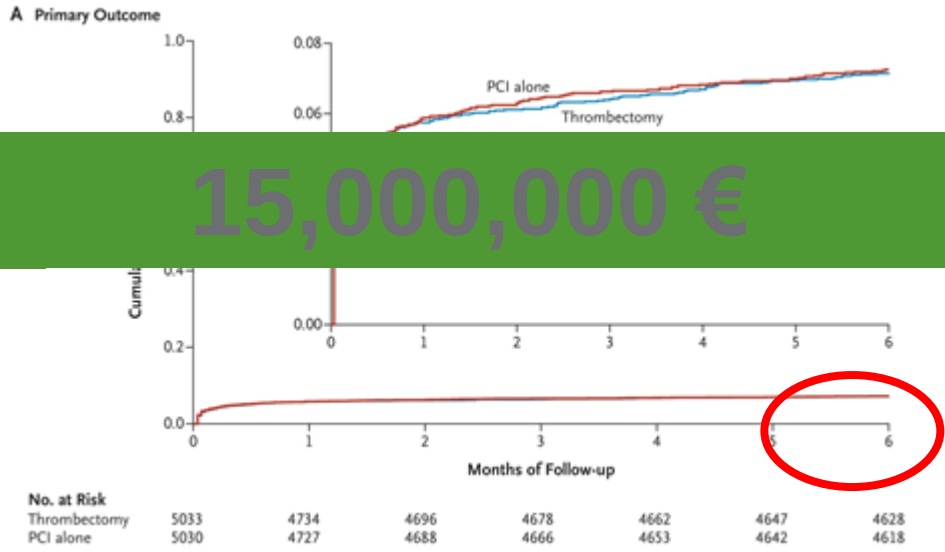


500,000 €

1st patient: June 2010
30 centers
33 months to full enrollment
7,244 patients

Lagerqvist B et al. N Engl J Med 2014;371:1111-1120

Site-based Follow-up



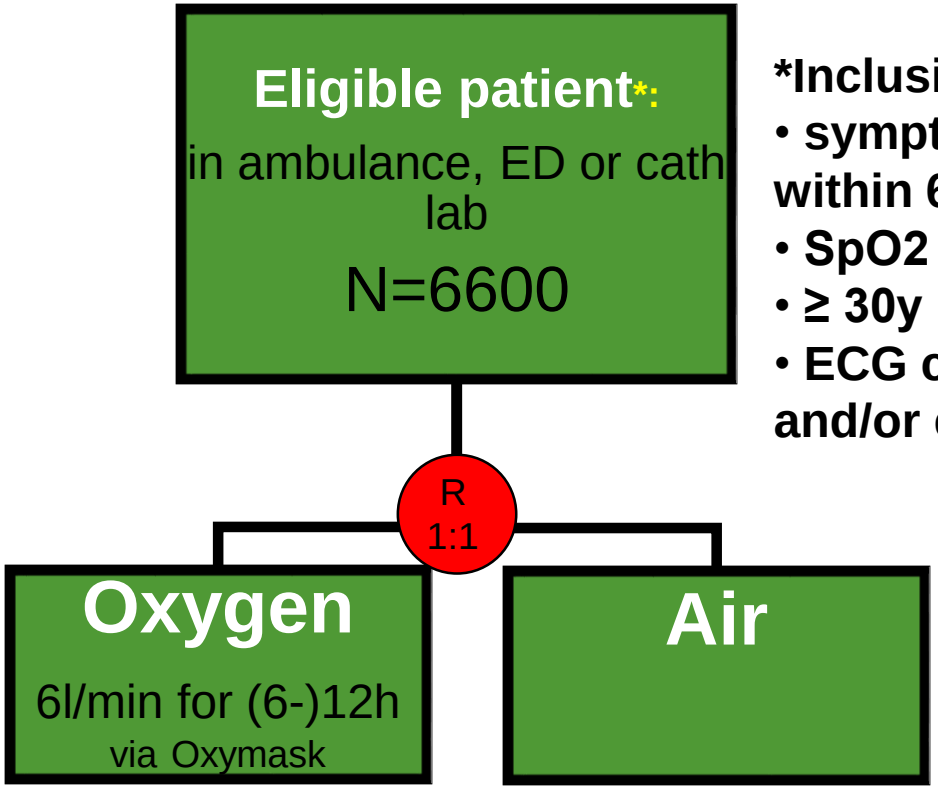
15,000,000 €

1st patient: August 2010
87 centers
48 months to full enrollment
10,732 patients

Jolly SS et al. N Engl J Med 2015;372:1389-1398

UCR

DETO2X – AMI



***Inclusion criteria:**

- **symptoms suggestive of AMI within 6h**
- **SpO2 ≥ 90%**
- **≥ 30y**
- **ECG changes indicating ischemia and/or elevated troponin levels**

Primary Endpoint: 1-year total mortality

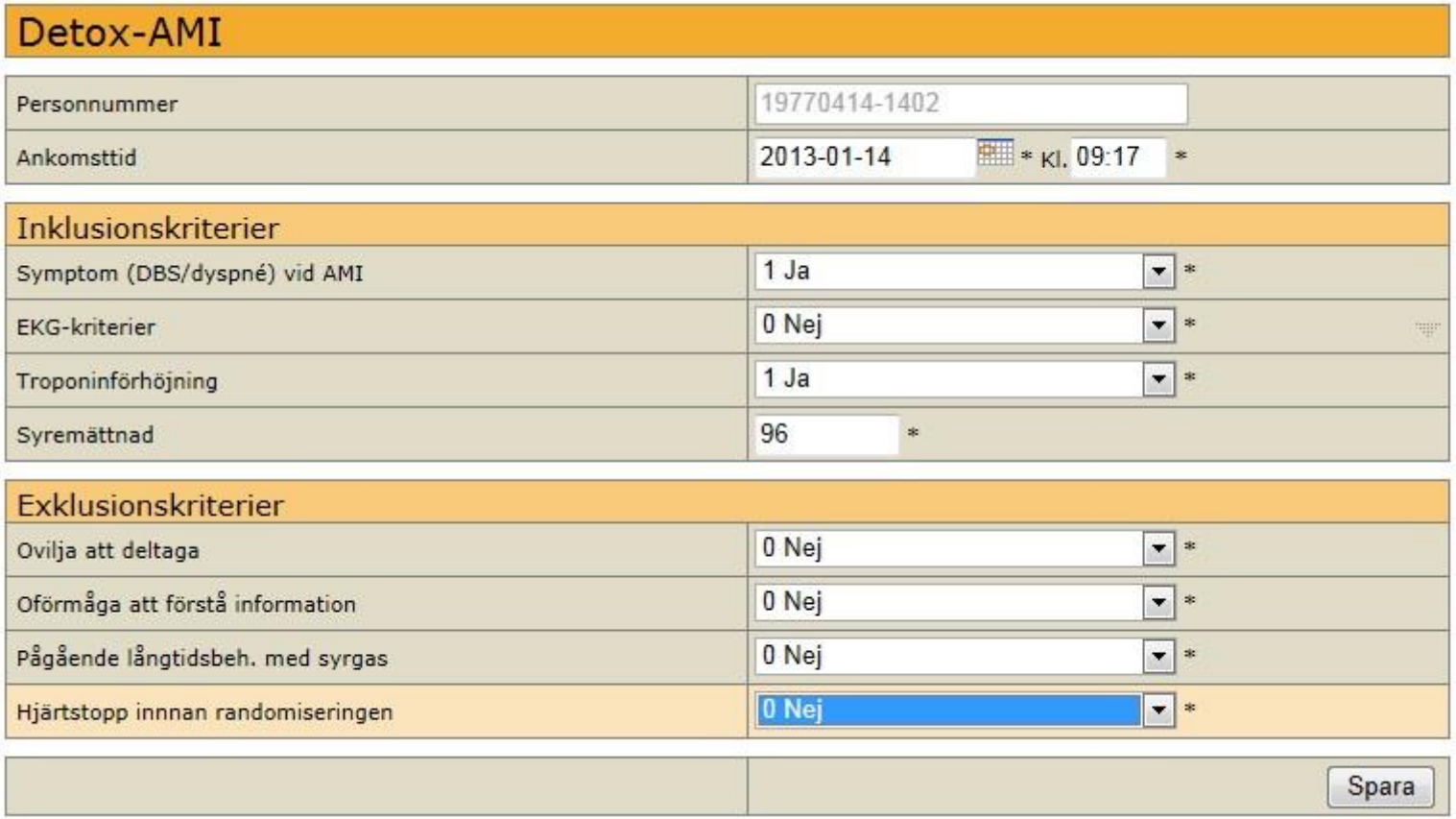
Additional secondary endpoint and sub studies

Data analysis through **SWEDEHEART** registry and **national mortality registry**

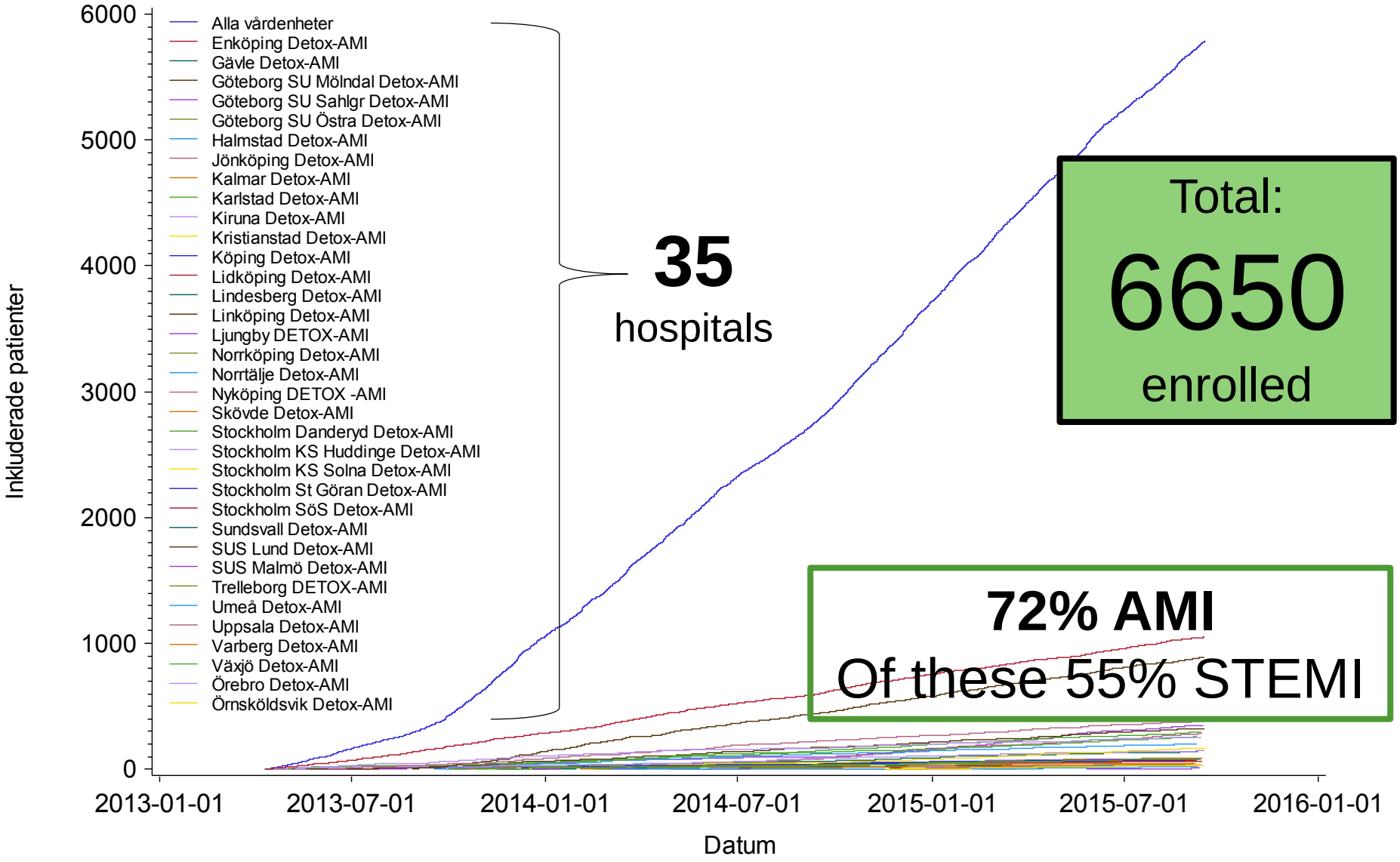
UCR

Funding: Swedish Research council (VR)

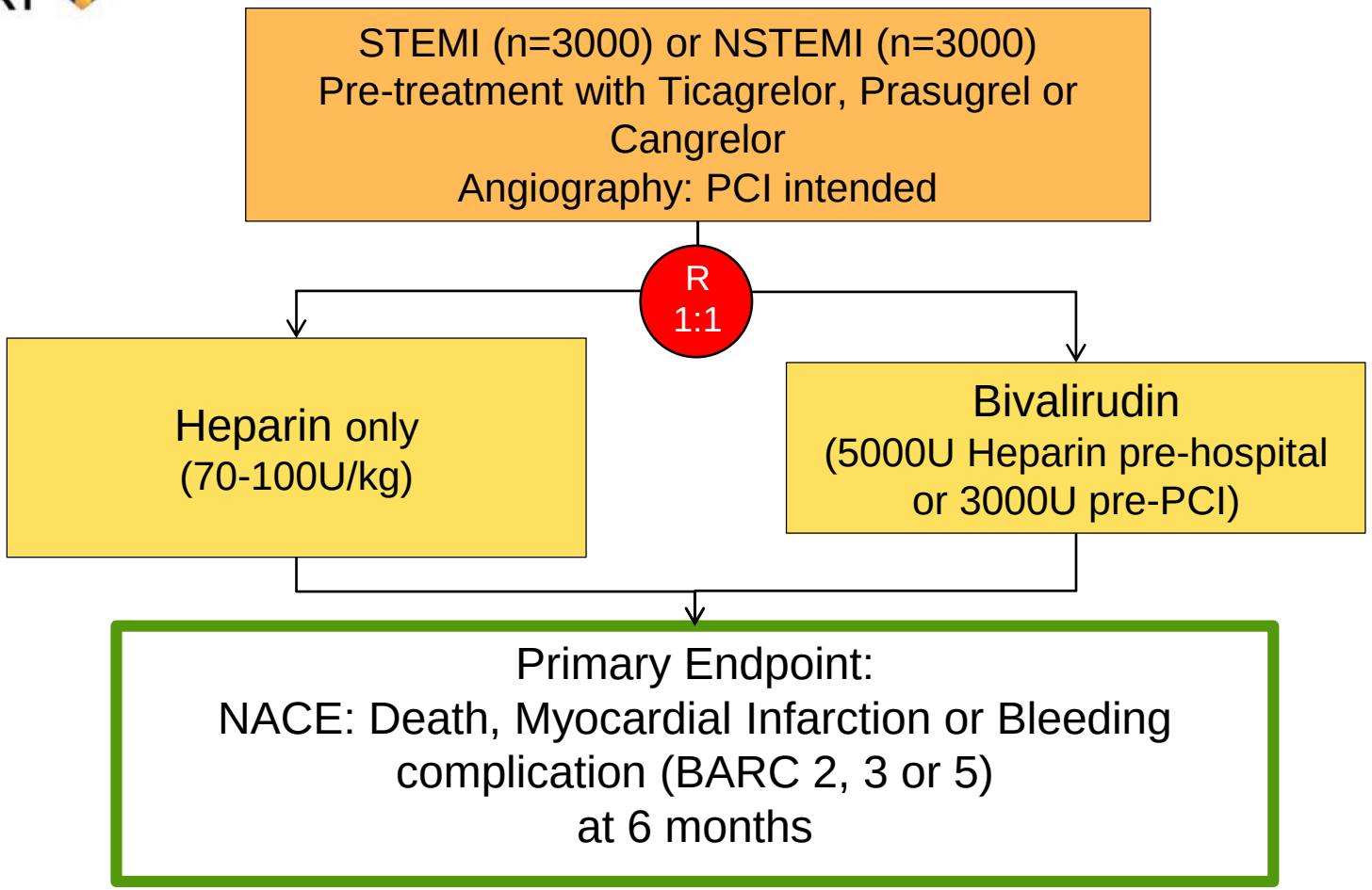
Randomization in ambulance, ED, cath lab or CCU



DETOX – AMI

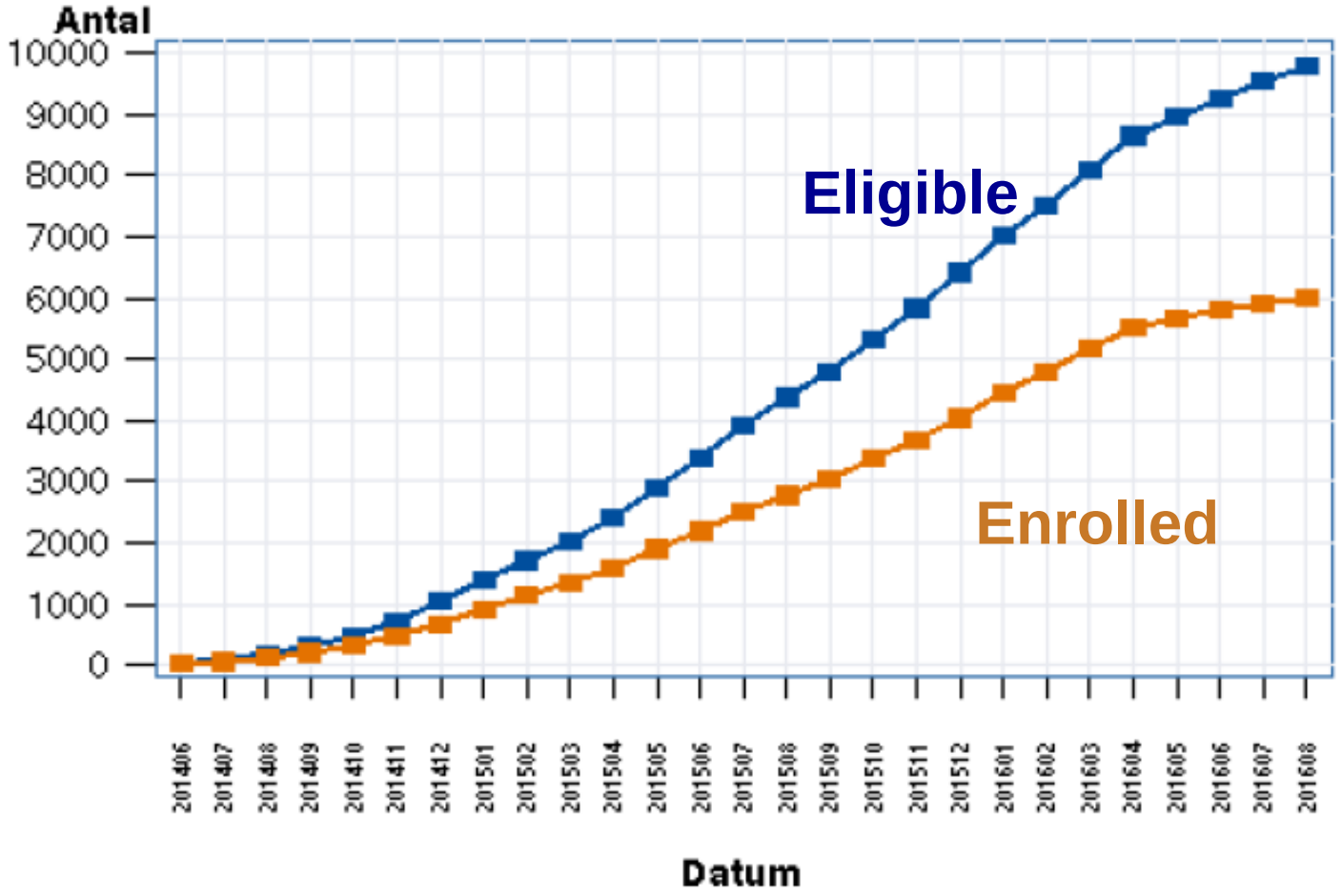

Inkluderade patienter
6000
5000
4000
3000
2000
1000
0
2013-01-01
2013-07-01
2014-01-01
2014-07-01
2015-01-01
2015-07-01
2016-01-01
Datum
Alla vårdenheter
Enköping Detox-AMI
Gävle Detox-AMI
Göteborg SU Mölndal Detox-AMI
Göteborg SU Sahlgr Detox-AMI
Göteborg SU Östra Detox-AMI
Halmstad Detox-AMI
Jönköping Detox-AMI
Kalmar Detox-AMI
Karlstad Detox-AMI
Kiruna Detox-AMI
Kristianstad Detox-AMI
Köping Detox-AMI
Lidköping Detox-AMI
Lindesberg Detox-AMI
Linköping Detox-AMI
Ljungby DETOX-AMI
Norrköping Detox-AMI
Norrtälje Detox-AMI
Nyköping DETOX -AMI
Skövde Detox-AMI
Stockholm Danderyd Detox-AMI
Stockholm KS Huddinge Detox-AMI
Stockholm KS Solna Detox-AMI
Stockholm St Göran Detox-AMI
Stockholm SöS Detox-AMI
Sundsvall Detox-AMI
SUS Lund Detox-AMI
SUS Malmö Detox-AMI
Trelleborg DETOX-AMI
Umeå Detox-AMI
Uppsala Detox-AMI
Varberg Detox-AMI
Växjö Detox-AMI
Örebro Detox-AMI
Örnsköldsvik Detox-AMI
35
hospitals
Total:
6650
enrolled
72% AMI
Of these 55% STEMI

VALIDATE (R-RCT)



- Hybrid R-RCT: Register data, register randomisation combined with phone call endpoint follow up and CEC
- Funding: Heart-lung foundation. Astra Zeneca, The Medicines company.
- Total cost: <2 million dollar

Included NSTEMI/STEMI in relation to possible eligible patients in Sweden

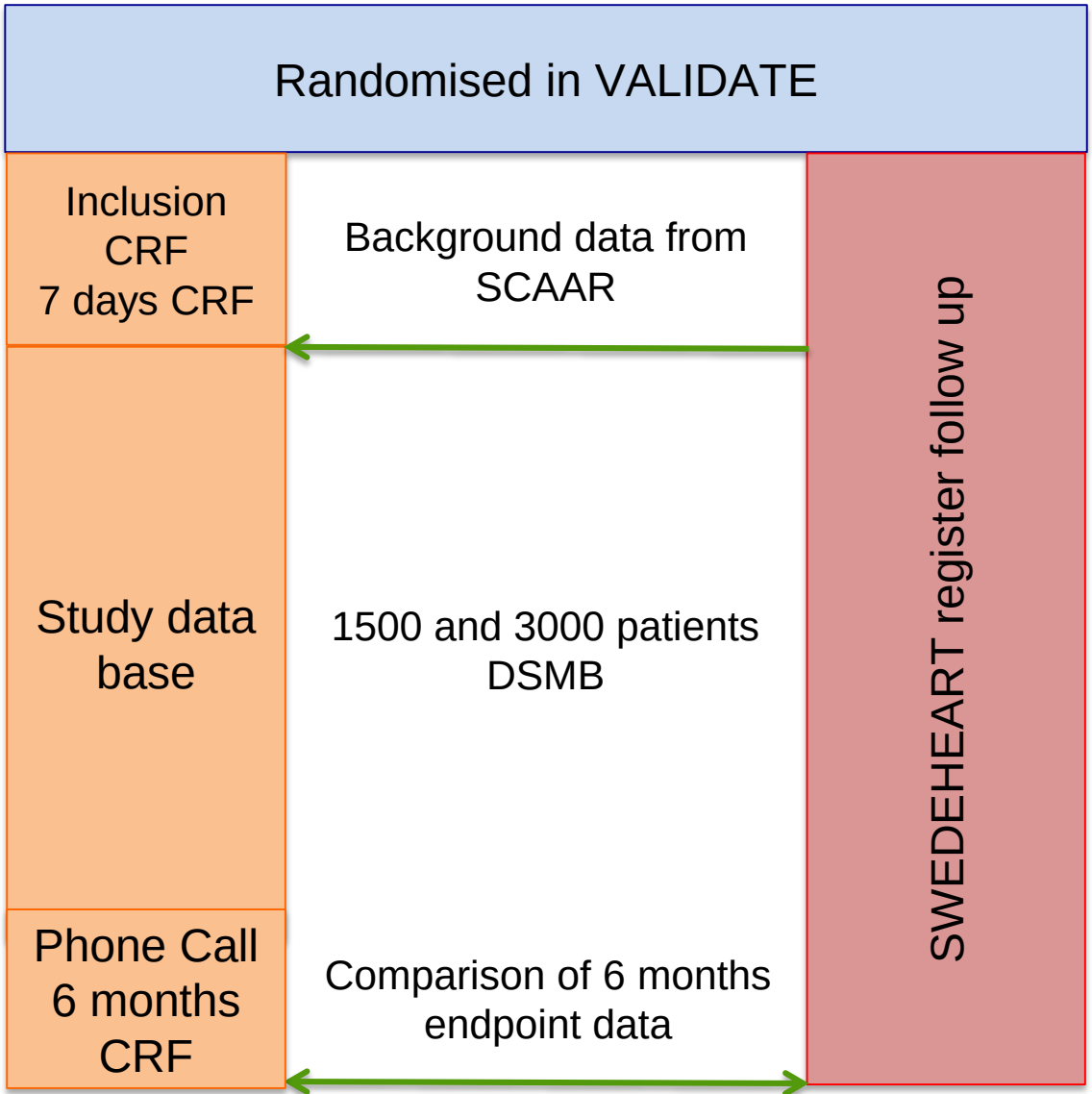


>60% of all eligible patients in a whole country is enrolled

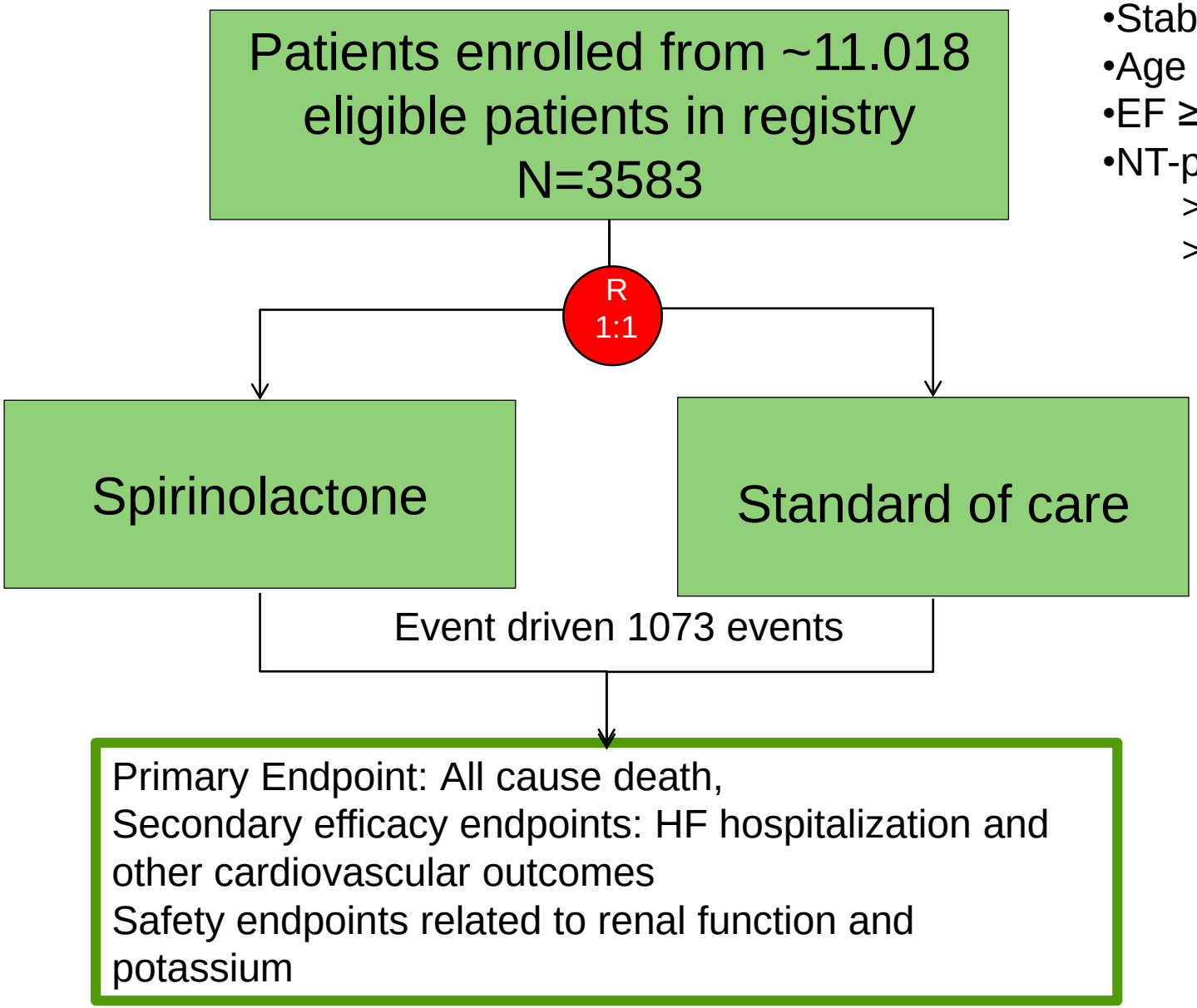
UCR

VALIDATE R-RCT

A substudy to prove the validity of pharmaceutical R-RCT, by comparing a Hybrid R-RCT (phone follow up, CEC) with a pure R-RCT

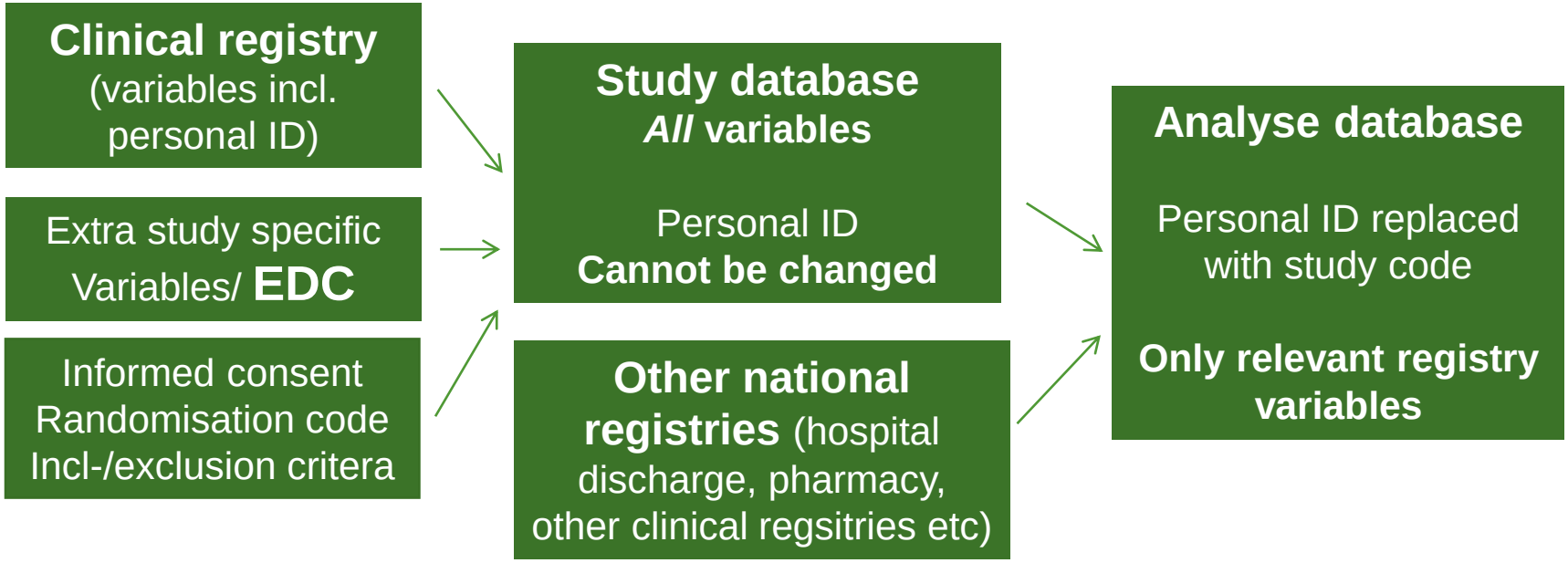


SPIRRIT- HFPEF



- Stable chronic HF
- Age ≥ 50 years
- EF ≥ 40%
- NT-proBNP
  - > 300 (sinus rhythm);
  - > 750 (AF)

Data base



Open database

Available for investigators

Possibility to remove patients from registry

Available for registry staff/ for registry staff/trialists

Not possible to remove patients from a trial

Audit trail

Available for trialists, sponsor

Data checks

All patients

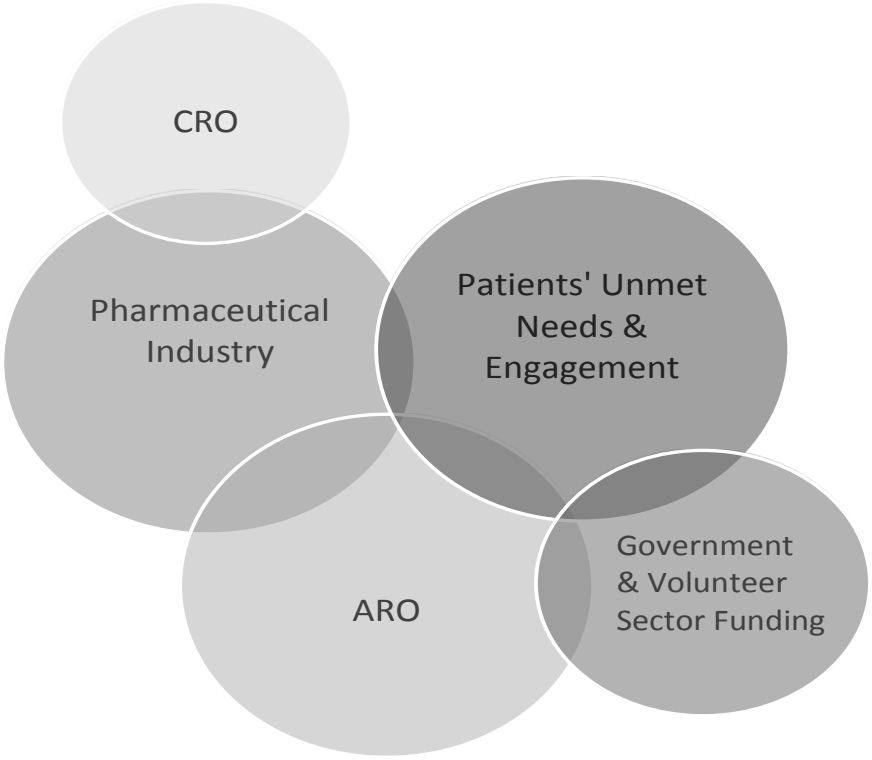
UCR

The future of cardiovascular clinical research in North America and beyond—addressing challenges and leveraging opportunities through unique academic and grassroots collaborations

Matthew T. Roe, MD, MHS,[a] Kenneth W. Mahaffey, MD,[b] Justin A. Ezekowitz, MBBCh, MSc,[c] John H. Alexander, MD, MHS,[a] Shaun G. Goodman, MD, MSc,[c,d] Adrian Hernandez, MD, MHS,[a] Tracy Temple, BScN, RN,[c] Lisa Berdan, PA, MHS,[a] Robert M. Califf, MD,[c] Robert A. Harrington, MD,[b] Eric D. Peterson, MD, MPH,[a] and Paul W. Armstrong, MD[c] *Durham, NC; Stanford, CA; Alberta, and Ontario, Canada*

Threats	Opportunities
• Limited pool of experienced investigators	• Expansion of clinical and site-based research training programs • Building strong and durable site networks • Supporting more academic recognition of site-based researchers
• Increased site costs and complexities of trial participation	• Supporting regulatory reforms such as quality by design • Registry-based trials • Leveraging large health systems and Electronic Health Records (EHRs) for pragmatic trials
• Increasing enrollment competition from developing countries	• Simplifying trial participation • Incentivizing investigators by incorporating trial participation into the cardiovascular board recertification process
• Strong concerns about patient privacy issues	• Advocating for new ethics and regulatory policies • Increasing dialogue with patient-disease advocacy groups to support the value of research
• Increasing regulatory burden for site investigators	• Leveraging academic-regulatory relationships to streamline safety reporting requirements and secure upfront commitments for approval pathways for pragmatic pivotal trials

Paradigm for Collaboration



Roe MT et al. Am Heart J; 2015

UCR

PCORnet:
Integrated Research Network in the U.S.

1. Highly **engaged** patients, clinicians, health systems, researchers and other partners
2. A **collaborative community** supported by robust governance
3. Analysis-ready **standardized data** with strong privacy protections
4. Oversight that **protects patients**, supports the timely conduct of research, and builds trust in the research enterprise
5. Research that is **sustainably integrated** into care settings and with communities of patients

ADAPTABLE Study Design

Patients with known ASCVD + ≥1 "Enrichment Factor"

Identified through EHR screening and electronic patient contact by CDRNs/PPRNs
(PPRN patients would need to connect through a CDRN to participate)

Patients contacted electronically with trial information and e-consent via web portal
Treatment assignment will be provided directly to patient

***Enrichment Factors**

- Age > 65 years
- Creatinine > 1.5 mg/dL
- Diabetes mellitus (type 1 or 2)
- Known 3-vessel CAD
- Current CVD or PAD
- Known EF<50% by echo, cath, nuclear study
- Current smoker

ASA 81 mg QD

ASA 325 mg QD

Randomized Electronic Follow-Up: 3 vs 6 months
Supplemented with EHR/CDM Data Queries

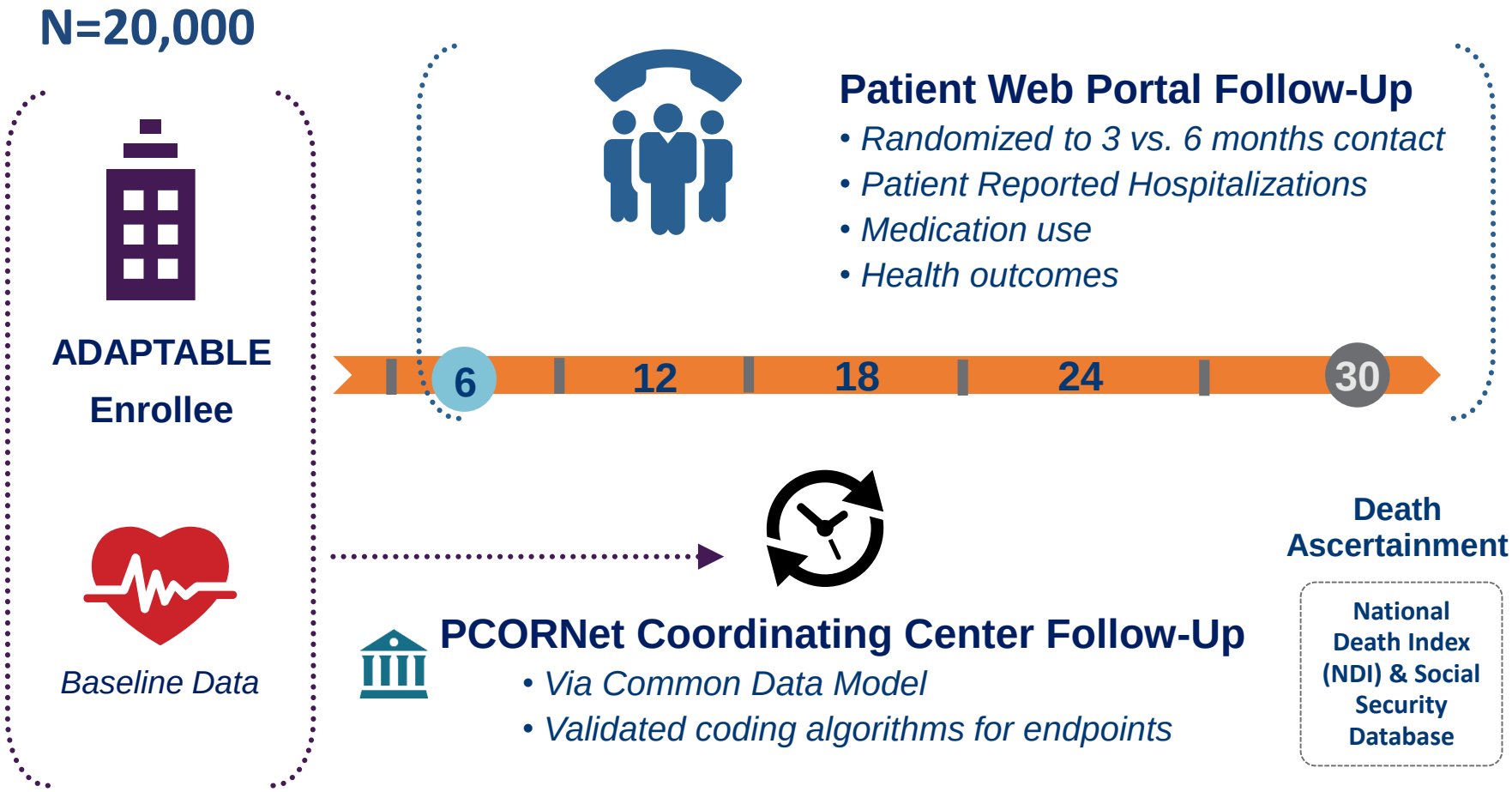
Duration: Enrollment over 24 months;
maximum follow up of 30 months

Primary Endpoint: Composite of all-cause mortality, hospitalization for MI, or hospitalization for stroke

Primary Safety Endpoint: Hospitalization for major bleeding

UCR

Enabling and Testing Pragmatic Research: e-Data Collection and e-Follow-Up



UCR

Web-Based, Electronic Informed Consent

- Text and video review of the consent is completed on the web portal
- Simplified common consent form with selected local adaptations
- Focused questions to confirm patient comprehension for informed consent and eligibility for randomization after consent is obtained
- Direct patient feedback and user testing for the development of the consent form and process as well as the comprehension questions

UCR

ClinicalTrials.gov: NCT02697916

Adaptable
The Aspirin Study

TEXT SIZE A

There are 5 steps to join the study!

The time on each card is an estimate of
how long it will take you to complete each section.
There are no time limits, so please go at your own pace.

Watch
the ADAPTABLE short video

5 min

Read
more details about participating in ADAPTABLE

15 min

Answer
a few questions about the study

5 min

Join
the ADAPTABLE study

3 min

Inform
us about your current health

5 min

LET'S GET STARTED

ClinicalTrials.gov: NCT02697916

Disrupting the Norm
Traditional Trials vs. ADAPTABLE

	Traditional	ADAPTABLE
I/E Criteria Reviewed	Sample via CRA Visit	CDM
Representative Cohort	Narrow	Broad
Consent	Facilitated	Patient Directed
Comprehension Tested	No	Yes
Format	Paper	e-consent
Data Collection	Patient Reported	Patient Reported
	Site Recorded	CDM
Source Documents	Only seen by Site	Received via CDM
Endpoint Adjudication	Yes	CDM, EHR data
Patient Involvement	Participants Only	Protocol design, Committee, Analyses, Dissemination
Costs	+	+++++

Conclusions

- Large need for randomized trials (RCT) particularly for the evaluation of strategies, devices, pharmacological therapies
- Classical (explantory) RCTs are often not performed in broad representative patient populations. They are expensive and has slow enrollment.
- All trials should strive for pragmatism
- Sweden has opportunities to lead the development of more pragmatic trials with strong track record in clinical trials, strong AROs, good collaboration, and complete national public registries
- The national clinical registries are strong networks for collaboration and enroll complete patient populations
- Prospective Registry based Randomized Clinical Trials (RRCT) is a unique opportunity for clinical research in Sweden

UCR

Uppsala Clinical Research Center

Part of Uppsala University and Uppsala University Hospital.

Assessing the Level of Pragmatism in a Trial, the Pragmatic–Explanatory Continuum Indicator Summary 2 (PRECIS-

PRECIS-2

Dimension	Assessment of Pragmatism
Recruitment of investigators and participants	
Eligibility	To what extent are the participants in the trial similar to patients who would receive this intervention if it was part of usual care?
Recruitment	How much extra effort is made to recruit participants over and above what would be used in the usual care setting to engage with patients?
Setting	How different are the settings of the trial from the usual care setting?
The intervention and its delivery within the trial	
Organization	How different are the resources, provider expertise, and organization of care delivery in the intervention group of the trial from those available in usual care?
Flexibility in delivery	How different is the flexibility in how the intervention is delivered from the flexibility anticipated in usual care?
Flexibility in adherence	How different is the flexibility in how participants are monitored and encouraged to adhere to the intervention from the flexibility anticipated in usual care?
The nature of follow-up	
Follow-up	How different is the intensity of measurement and the follow-up of participants in the trial from the typical follow-up in usual care?
The nature, determination, and analysis of outcomes	
Primary outcome	To what extent is the primary outcome of the trial directly relevant to participants?
Primary analysis	To what extent are all data included in the analysis of the primary outcome?

Loudon K, The PRECIS-2 tool. BMJ 2015; 350: h2147.