# R-RCT

# Workshop R-RCT-studiedesign

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R-RCT

UCR

# R-RCT vs. classical RCT

| •RRCT<br>•Evaluation of therapeutic options available/used in routine clinical care | RCT<br>Approval of new pharmaceutical agents and medical devices |
|---|---|
| Simple hypothesis, | Complex |
| Common disease | Rare disease |
| Few or simple subgroup analyses | Many or complex substudies |
| Treatment alternatives available | Treatments not available/ approved |
| Treatment well defined | Treatment complex |
| Open label | Double blind /Double dummy |
| Large sample size | Small sample size |
| Satety profile known | Satety profile unknown |

# Recruitment

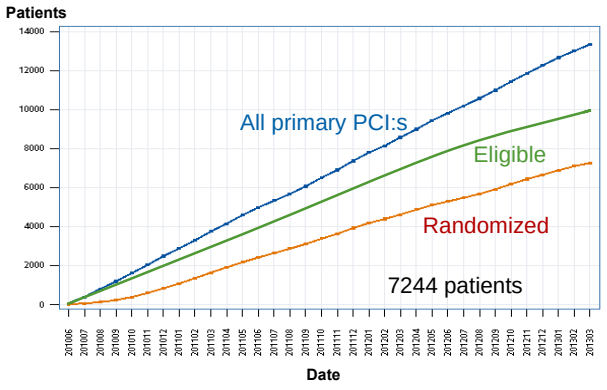
- An RRCT may be more time consuming to plan

# Recruitment

## Device

TASTE

**TASTE inclusion rate**

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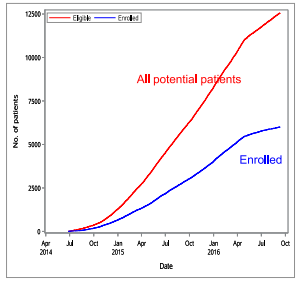
## Pharma- single therapy

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

VALIDATE SWEDEHEART

- 25 PCI centers out of 29 in Sweden participated in the trial
- 47.8% (6006 of 12,561) of all patients in Sweden presenting at enrolling hospitals with an initial diagnosis of STEMI or NSTEMI planned for PCI were randomized.
- Of all patients potentially eligible for enrollment, 70.0% (6006 of 8585) were randomized.

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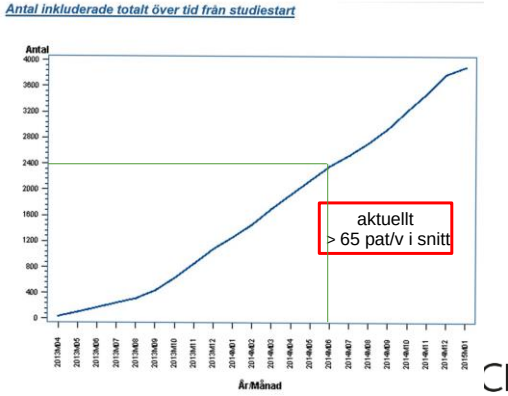
## Pharma- single therapy

DETO2X – AMI

**Inklusionsstatus totalt**

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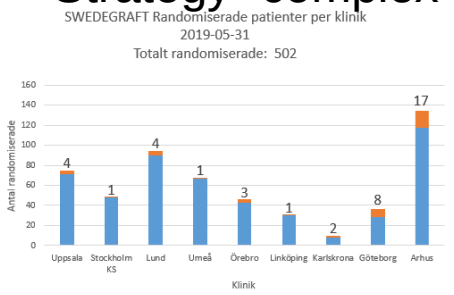
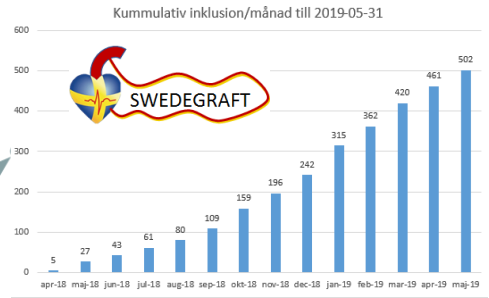
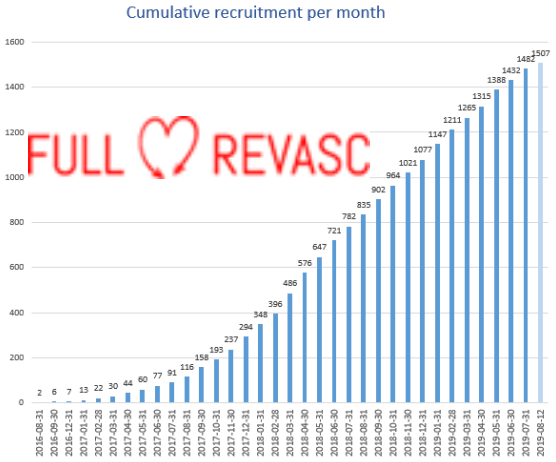
## Strategy- complex



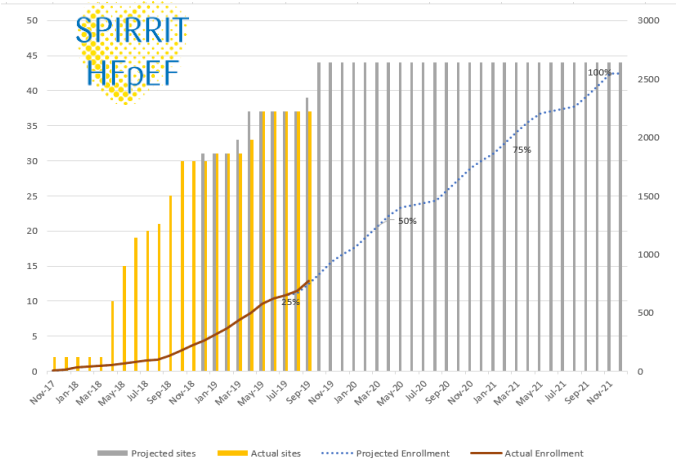

## Strategy- complex




## Pharma chronic therapy

Sverige: **772 patienter**

USA: **54 patienter** (36 öppna sites)

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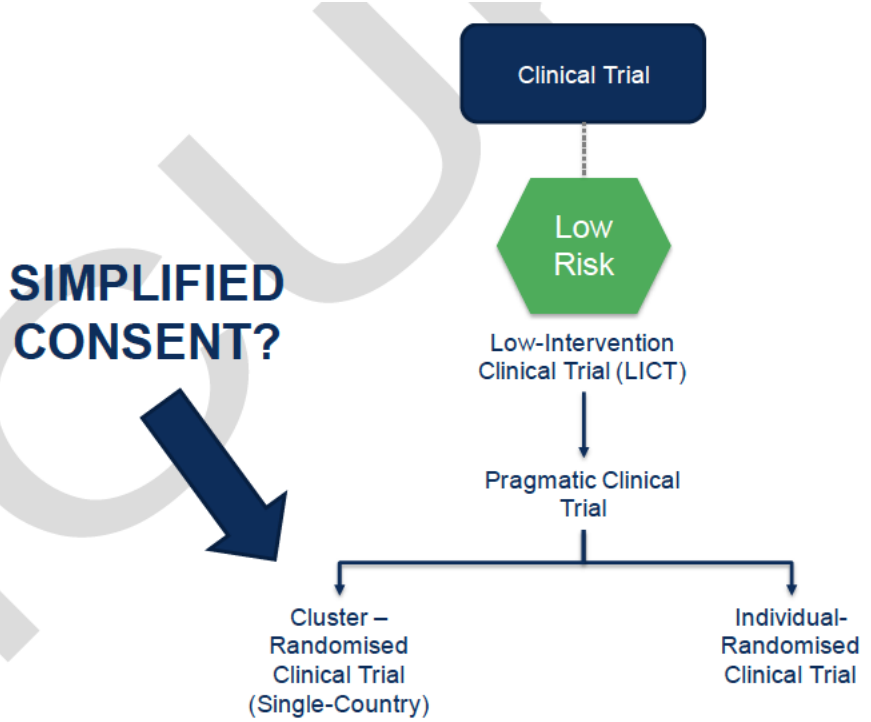
# Safety – and additional variables

- Extra sampling, tests, -demands on patients, requirements from authorities
- The more safety data to collect the more similar to classical RCT Safety surveillance (AE, SAE, SUSAR)

# Informed consent, IC

- According law and ethics approval
- Not different as classic RCT but try to streamline



ELSEVIER

Journal of Clinical Epidemiology 114 (2019) 60–71

Journal of Clinical Epidemiology

ORIGINAL ARTICLE

# A limited number of medicines pragmatic trials had potential for waived informed consent following the 2016 CIOMS ethical guidelines

Rafael Dal-Ré[a,*], Cristina Avendaño-Solà[b], Anthonius de Boer[c], Stephan K. James[d], Frits R. Rosendaal[e], Richard Stephens[f], John P.A. Ioannidis[g]



**Table 2.** PRECIS-2 tool 9 domains self-assessments by trials' investigators (contact persons) and self-declared ongoing status (as of October to November 2018)

| | Pragmatic approach of the trial with regards to the following domains | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Trial name | Eligibility | Recruitment | Setting | Organization | Flexibility (delivery) | Flexibility (adherence) | Follow-up | Primary outcome | Primary analysis | No. (%) of domains with pragmatic features | Ongoing status[a] |
| DiDo | Yes | Yes | Yes | Yes | Partially | Yes | Yes | Yes | Yes | 8 (89) | Active, not recruiting |
| HOT-ICU | Partially | Yes | Yes | Yes | Yes | NA[b] | Partially | Yes | Yes | 6 (75) | Recruiting |
| iPROVE-O2 | Partially | Yes | Yes | Yes | Yes | NA[b] | Yes | Yes | Yes | 7 (88) | Active, not recruiting |
| LIBERAL | Partially | Yes | Yes | Yes | Yes | NA[b] | Partially | Yes | Yes | 6 (75) | Recruiting |
| LQD Study | Yes | Partially | Yes | Yes | Yes | Yes | Yes | Partially | Yes | 7 (78) | Recruiting |
| PROGRESS | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | 9 (100) | Recruiting |
| PRO-SWAP | Yes | Yes | Yes | Partially | Yes | Partially | Yes | Yes | Yes | 7 (78) | Recruiting |
| REBOOT-CNIC | Yes | Yes | Yes | Partially | Yes | Partially | Partially | Yes | Yes | 6 (67) | Not yet recruiting |
| RECOVER Study | Partially | Yes | Yes | Partially | Yes | NA[b] | Yes | Yes | Yes | 6 (75) | Not yet recruiting |
| REDUCe SWEDE-HEART | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | 9 (100) | Recruiting |
| REMINDRA | Yes | Yes | Yes | Partially | Yes | Yes | Yes | Yes | Yes | 8 (89) | Recruiting |
| SUNSTAR | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Partially | Yes | 8 (89) | Recruiting |
| SYMTRI | Yes | Yes | Yes | Yes | No[c] | Yes | Yes | Yes | Yes | 8 (89) | Not yet recruiting |
| TACSI | Yes | Yes | Yes | Yes | Yes | Partially | Partially | Yes | Yes | 7 (78) | Recruiting |
| The Eczema Study | No | No | Yes | Yes | Yes | Partially | No | Partially | Yes | 4 (44) | Recruiting |

**Table 4.** CIOMS provisions for modification or waiver of participants' informed consent: assessment by members of research ethics committees ($n$ = 11) and patients ($n$ = 7)

| | Assessment by research ethics committees' members | | | | | | Patients' assessment ($n$=7) | | |
|---|---|---|---|---|---|---|---|---|---|
| | Art. 10—provision 2: This trial has important social value | | | Art. 10—provision 3: This trial poses no more than minimal risks to participants | | | Art. 10—provision 2: This trial has important social value | | |
| Clinical trial (# of RECs assessing the trial) | Yes | Not sure | No | Yes | Not sure | No | Yes | Not sure | No |
| DiDo (5) | 2 | 3 | 0 | 3 | 2 | 0 | 1 | 5 | 1 |
| PROGRESS (5) | 5 | 0 | 0 | 4 | 1 | 0 | 6 | 1 | 0 |
| REBOOT-CNIC (5) | 4 | 1 | 0 | 2 | 1 | 2 | 2 | 3 | 2 |
| RECOVER study (5) | 2 | 2 | 1 | 1 | 3 | 1 | 3 | 4 | 0 |
| REDUCe SWEDE HEART (6) | 6 | 0 | 0 | 3 | 3 | 0 | 5 | 1 | 1 |
| REMINDRA (6) | 6 | 0 | 0 | 6 | 0 | 0 | 4 | 3 | 0 |
| SUNSTAR (6) | 4 | 2 | 0 | 5 | 1 | 0 | 4 | 3 | 0 |
| SYMTRI (6) | 5 | 1 | 0 | 4 | 2 | 0 | 0 | 4 | 3 |

*Abbreviation:* CIOMS, Council for International Organizations of Medical Sciences.

# R-RCT vs. classical RCT

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# Randomization

- Continuously on-line or link to an external platform
- Registry identifies patients and propose randomization
- Few pre-randomization variables
- Lock all pre randomization variables

# Data quality

- High requirements for all registry variables
- Monitoring of key variables may be recommended
- Store study specific study variables in a separate data base
- The registry needs to be kept unchanged