Universität Basel

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COVID-19 and Clinical Research – Time to get more efficient

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Bâle

Today's Menu

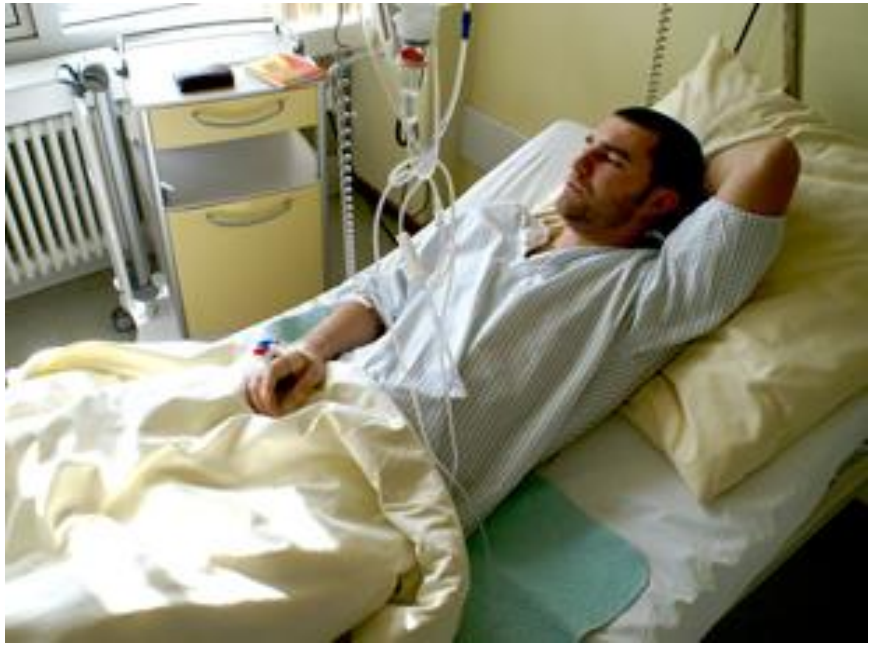
1. Research-on-Research (RoR)
2. Clinical research on & during COVID-19 pandemic
3. COVID-19 pandemic triggers new designs
4. A learning clinical research system
5. Conclusions & Perspective

“There is a peculiar paradox - we perform clinical trials to generate ***evidence to improve patient outcomes****;*
however, we conduct ***clinical trials like anecdotal medicine****.“*

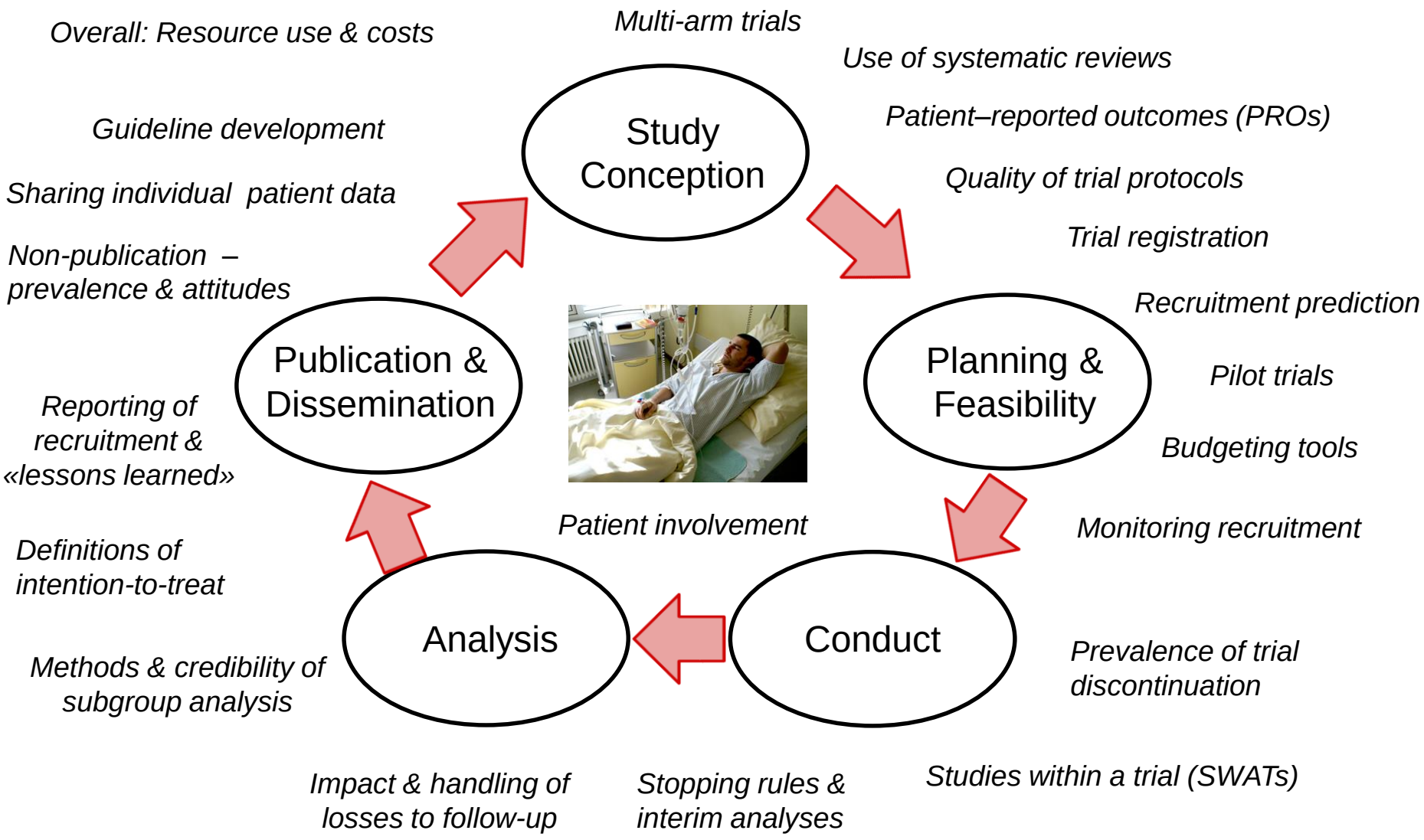
Monica Shah,
National Heart Blood and Lung Institute, Bethesda, USA

Heart Fail Review 2012;19: 135-52

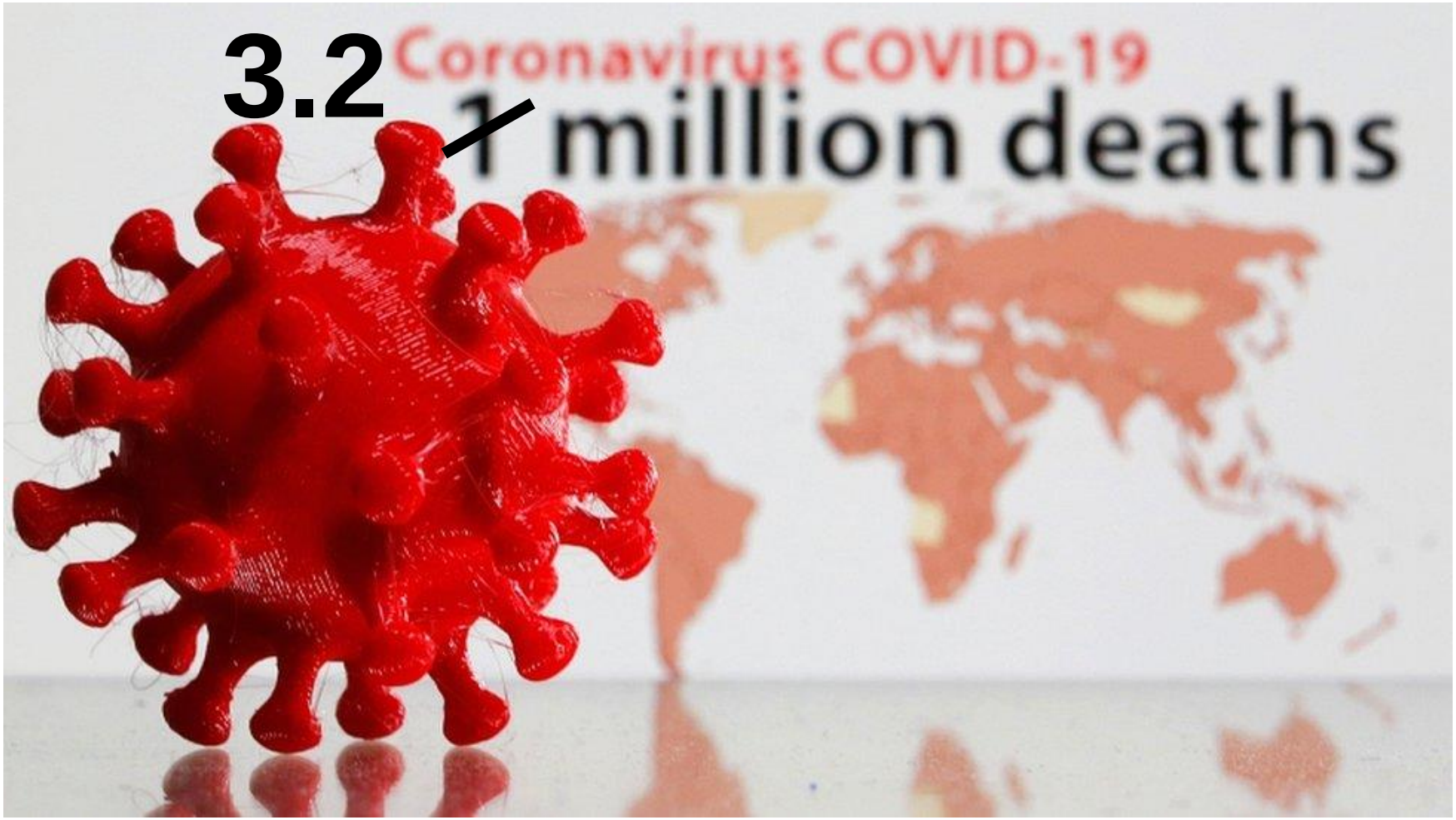
Clinical Research



Research-on-Research (RoR)

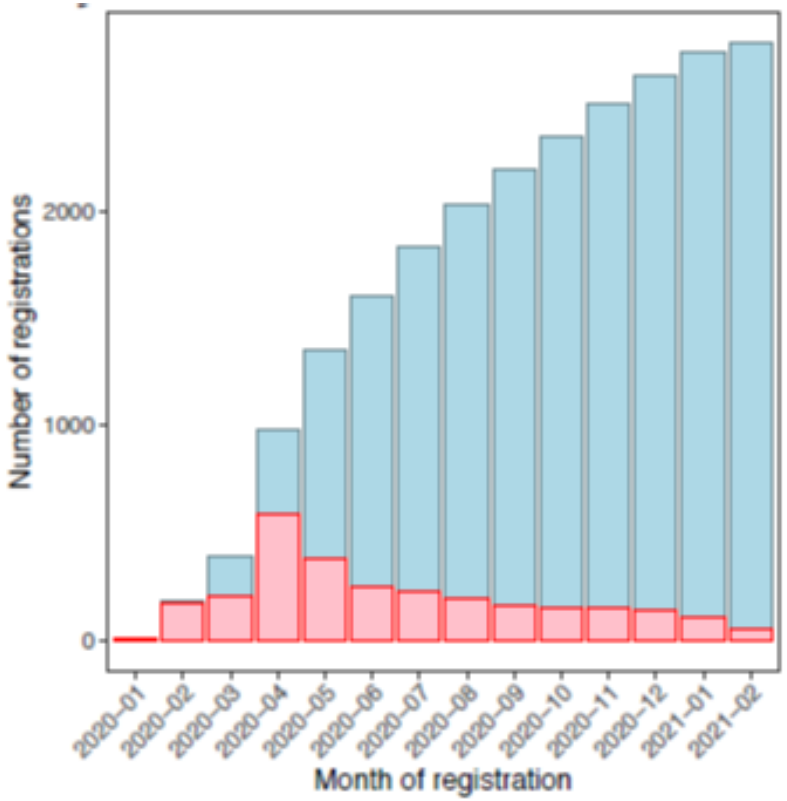


COVID-19 and Clinical Research


3.2
Coronavirus COVID-19
1 million deaths

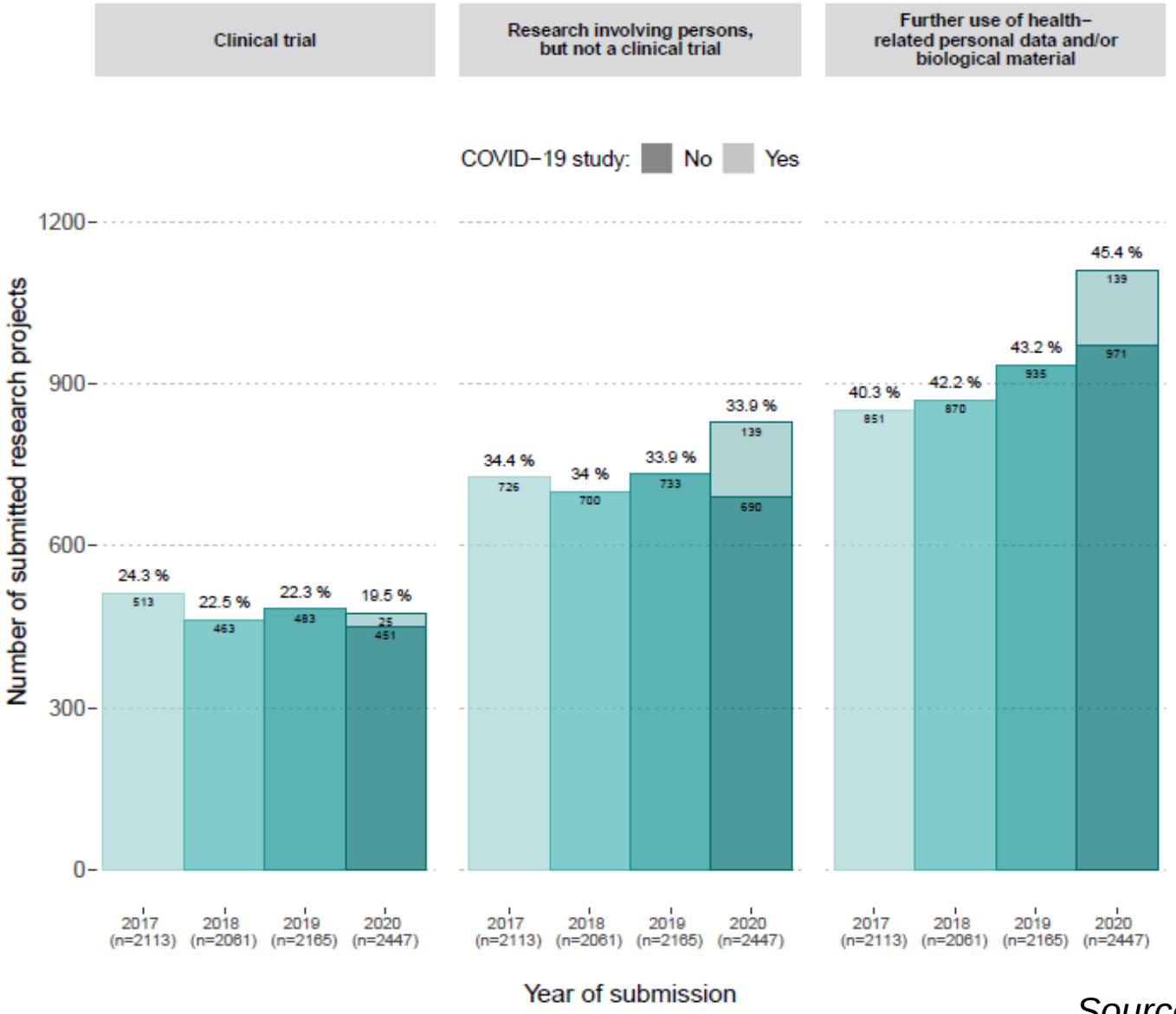
Research Response to COVID-19

- Huge amounts of public money invested
- Huge number of clinical studies initiated (April: 518 RCTs)
- Huge number of researchers & countries involved



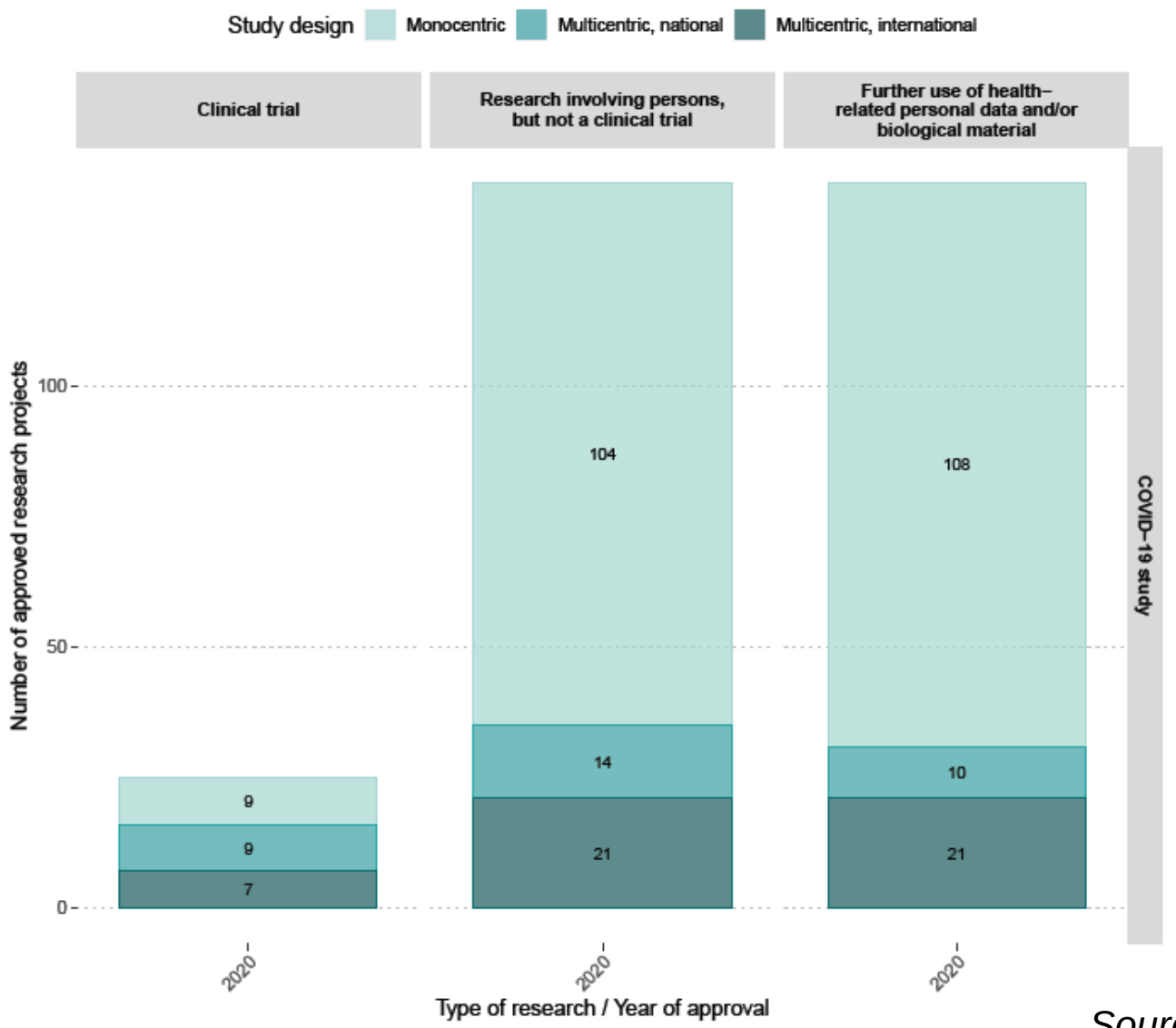
https://covid-evidence.org/

Research in Switzerland during COVID-19



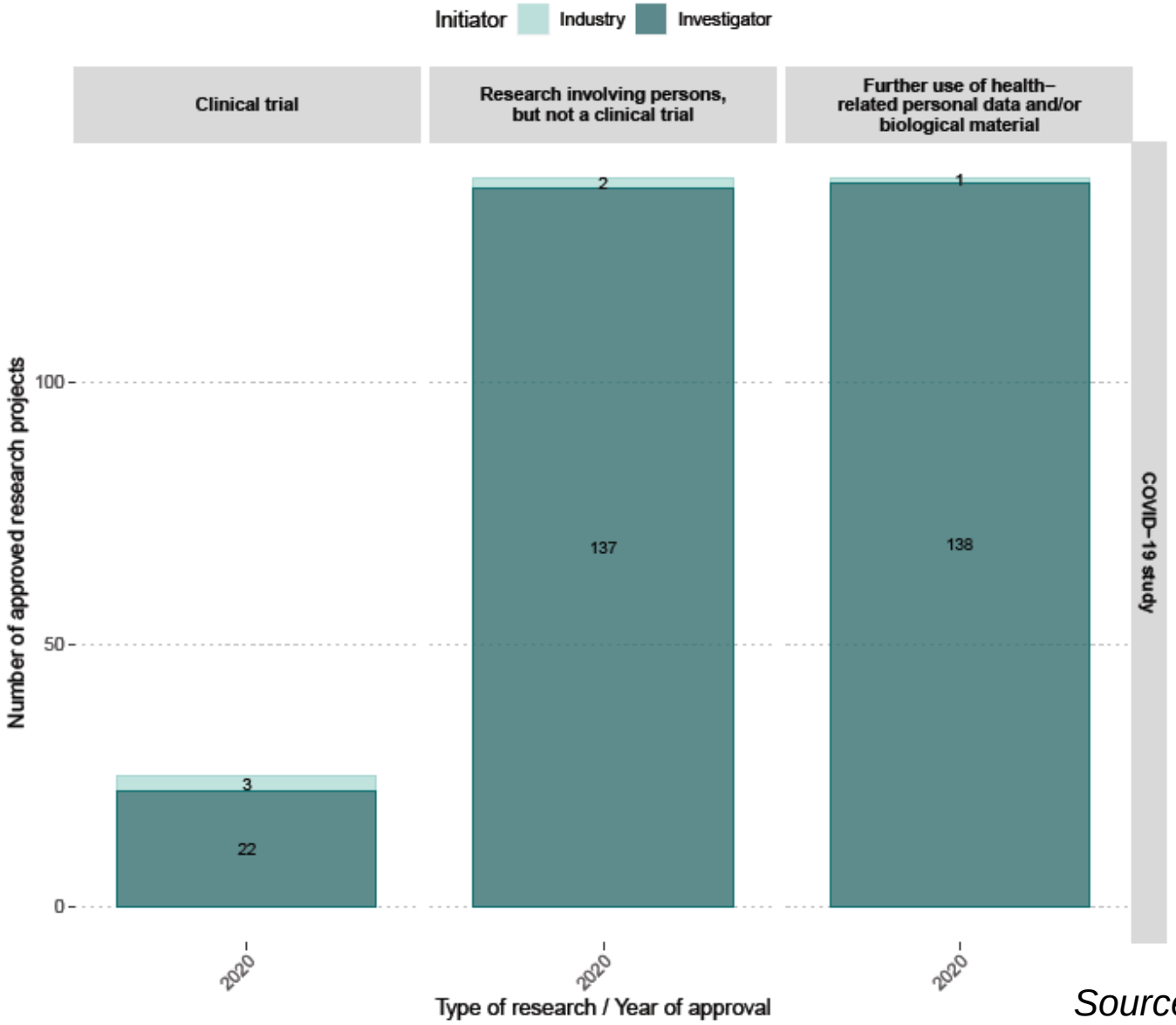
Source: BASEC

COVID-19 Research in Switzerland



Source: BASEC

COVID-19 Research in Switzerland

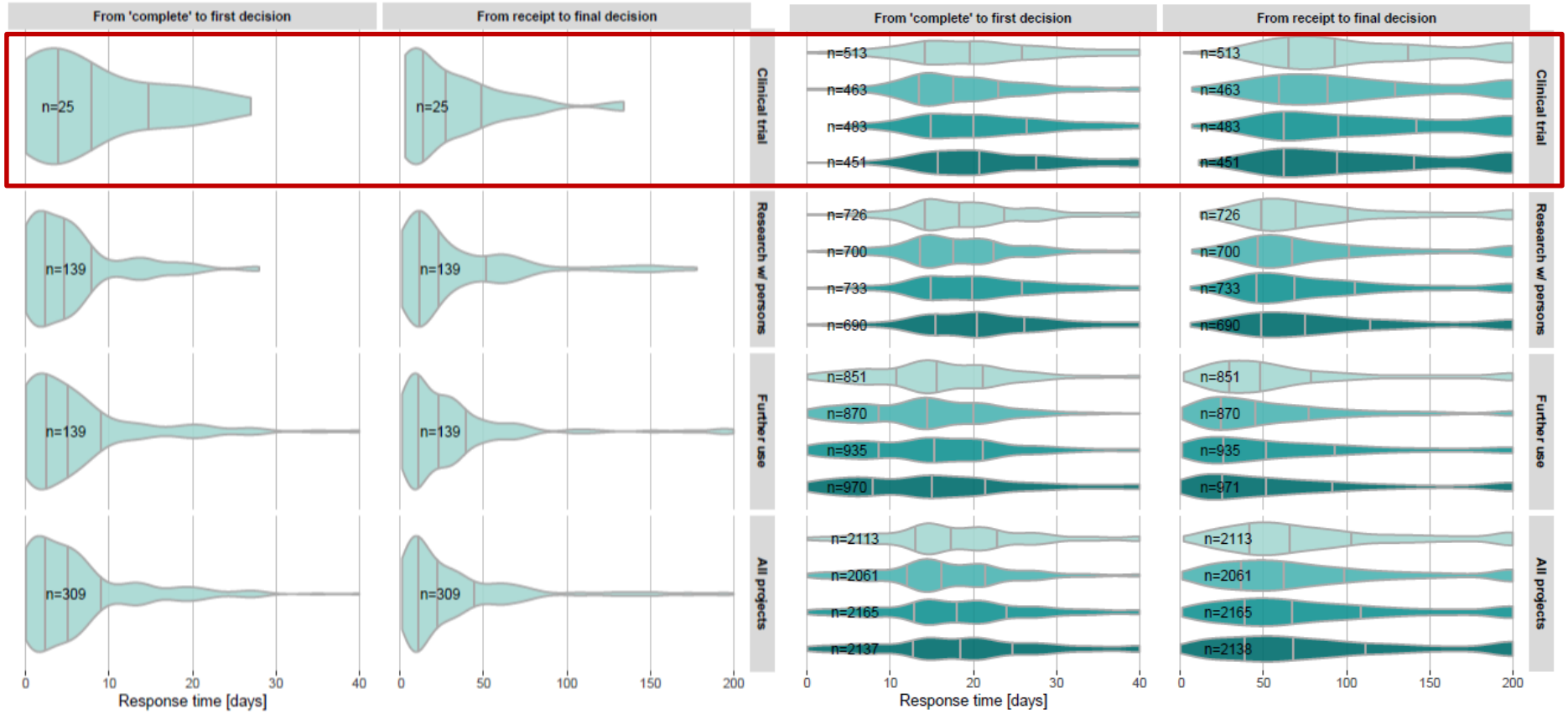


Source: BASEC

Time for ethics review

COVID-19 Studies

Non-COVID-19 Studies



Source: BASEC

Return on Investment ?

- Most initiated trials were small (82% < 500 pats)
- Few non-drug interventions (e.g. mask use, social distance, school closures)
- Many duplications (1/6 of trials on hydroxychloroquine in first 100 days)
- Many poorly designed (non-randomized, no protocol, outcome switching)
- 30% of trials did not recruit any patient (small trials, China)
- Of those started 6 months later: 1/3 of trials discontinued (too few COVID-19 pats), 1/3 completed; 1/3 ongoing (many delayed)
- Many non-COVID trials suspended

INEFFICIENT

Positive:

- Expedited governance/ethics approvals, more open access/preprint use
- Solidarity, RECOVERY, REMAP-CAP with timely & reliable results

Glasziou et al. BMJ 2020
Janiaud et al. JAMANetwOpen 2021
Park et al. Lancet Glob Health 2021

COVID-19 pandemic triggers new designs –

platform trials & trials using routine data

COVID-19 Pandemic

→ **Novel research methodology**

to address **pressing clinical questions**

Desired trial characteristics:

- **fast** & **efficient**
- **embedded in routine** clinical care
- rapidly **adaptable** to new research questions
- **affordable**

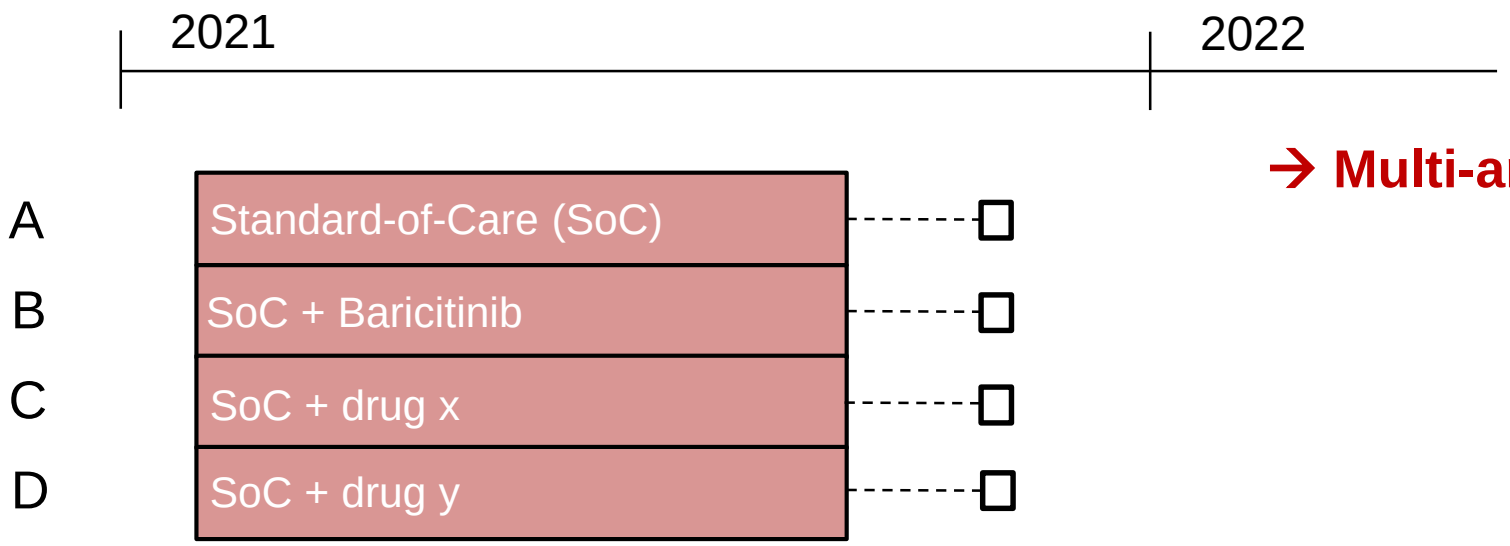
Platform Trials - features

- Address **multiple research questions** in **one administrative trial structure**
- Combination of
  - **Multi-arm** (one common control)
  - **Multi-stage** (stop for lack-of-benefit)
  - **Addition of new questions/arms** (adaptable)
- **More efficient** than traditional trials (organisation & recruitment)

Example: **SolidAct Trial**

- New treatments vs standard; hospitalized pats with SARS-CoV2 on disease progression/mortality; >100 centres in Europe

Spring 2021 – Planned Recruitment Start

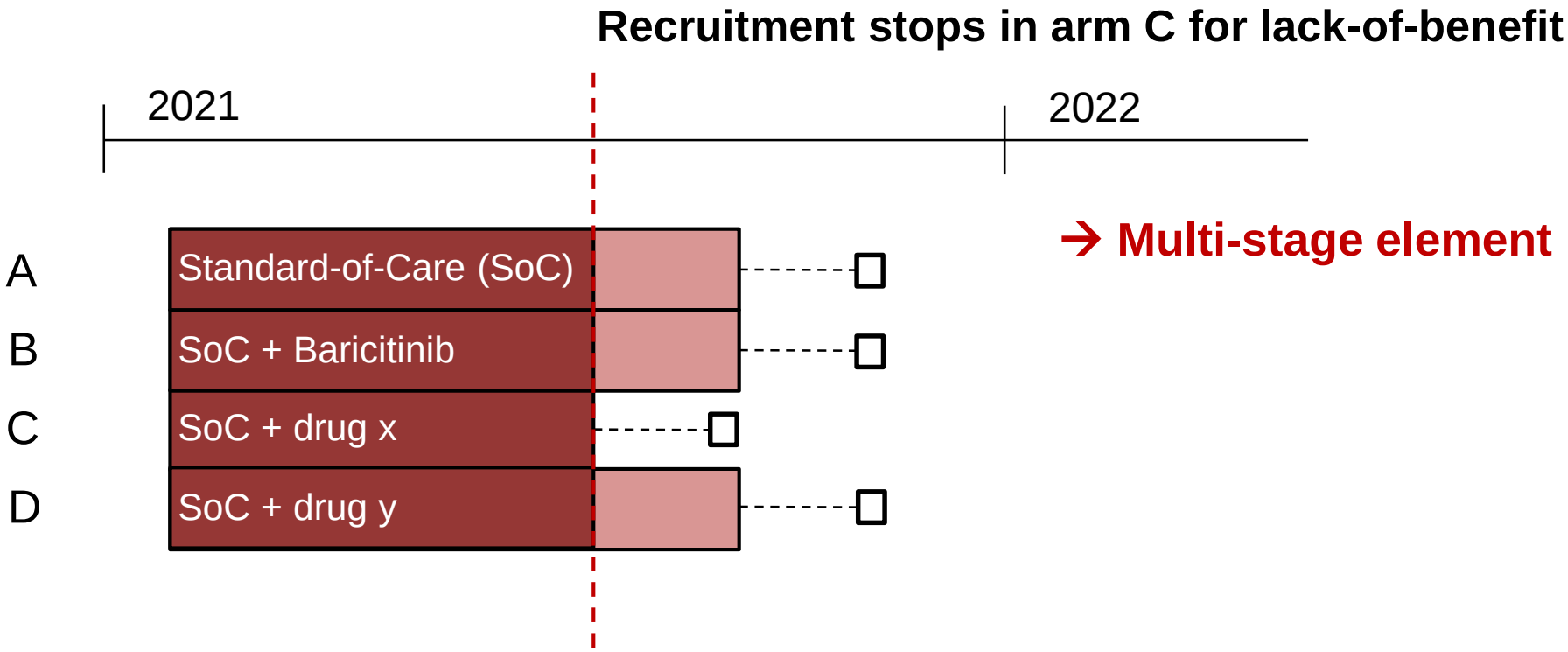


→ **Multi-arm element**

EU-RESPONSE (European Research and Preparedness Network for Pandemics and Emerging Infectious Diseases)

Example: **SolidAct Trial**

- Hospitalized pats with SARS-COV2 new treatment vs standard on disease progress/mortality; >100 centres in Europe

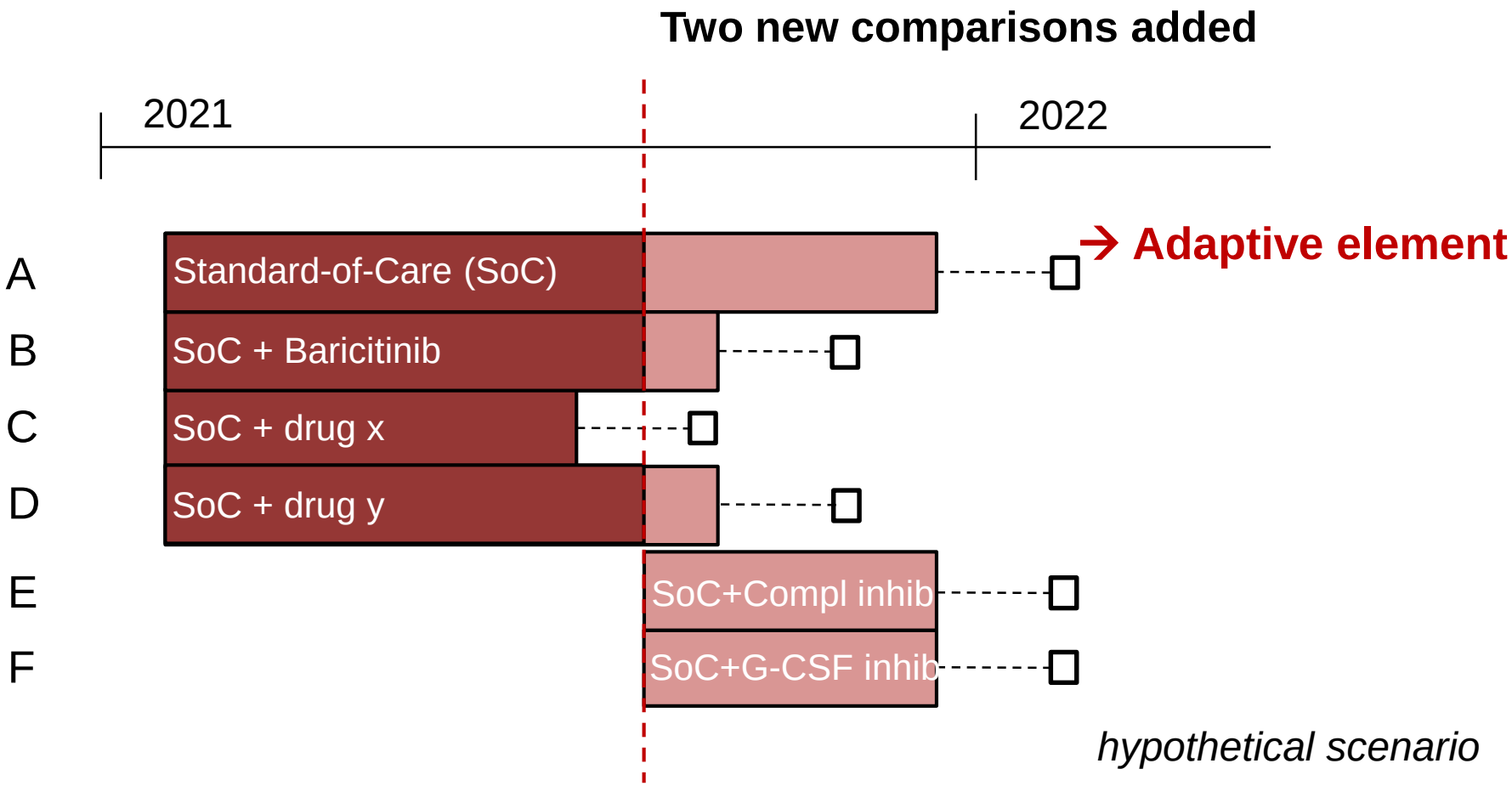


→ **Multi-stage element**

hypothetical scenario

Example: **SolidAct Trial**

- Hospitalized pats with SARS-COV2 new treatment vs standard on disease progress/mortality; >100 centres in Europe



Empirical Evaluation of Platform Trials

- Platform trials more popular, but **experience** still **limited**
- **Relevant questions:**
  - How «successful» are they on average? Output?
  - What are important barriers and facilitators?
  - How are they typically funded?
  - What are the preferred fields?
  - What are platform-specific quality features?

Project:

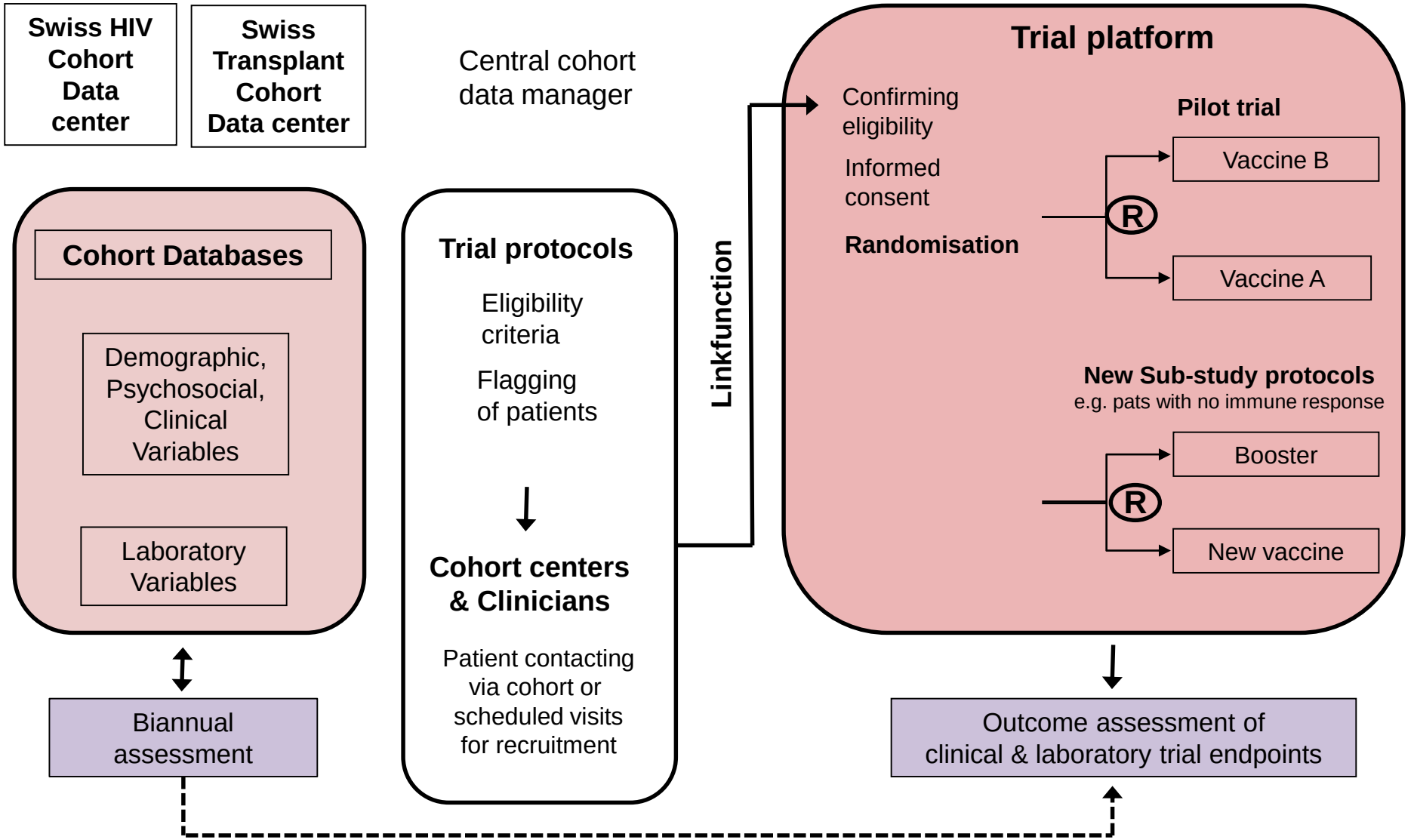
Systemat search for **all platform trials** (published or registered)

Mixed methods study with investigator survey, interviews, and tailored internet searches

Speich B, Griessbach A, et al. (work in progress)

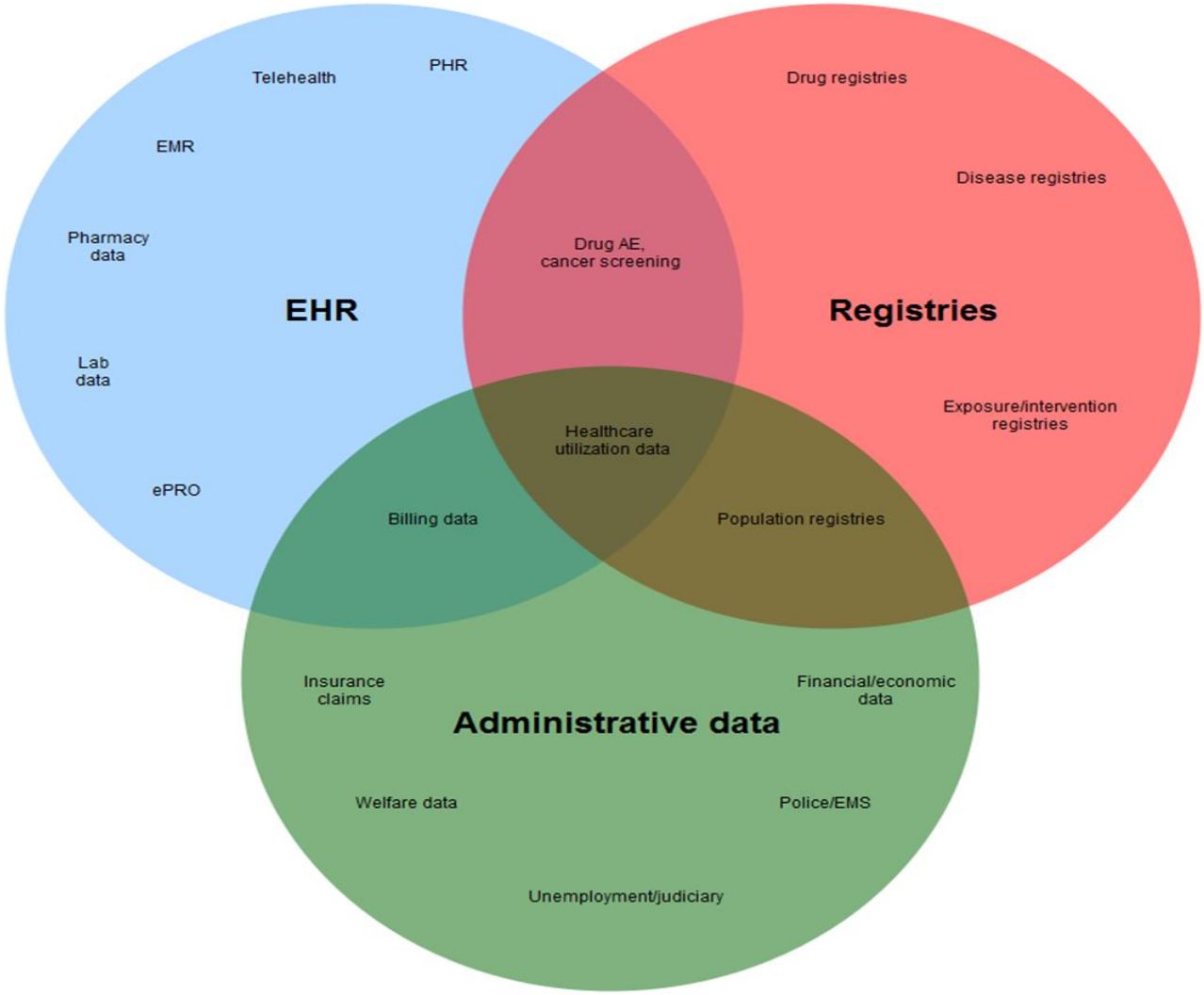
Platform trial within cohorts: COVERALL

(COrona VaccinE tRiAL pLatform)



Routinely Collected Data

…data that are not collected for the pupose of research
…data from **existing data infrastructures**



Non-Randomized | Randomized

VS.

Routinely collected | Active

Routinely Collected Data for clinical trials

TASTE

Thrombus aspiration during ST-segment elevation myocardial infarction

Abstract

Background: The clinical effect of routine intracoronary thrombus aspiration before primary percutaneous coronary intervention (PCI) in patients with ST-segment elevation myocardial infarction (STEMI) is uncertain. We aimed to evaluate whether thrombus aspiration reduces mortality.

Methods: We conducted a multicenter, prospective, randomized, controlled, open-label clinical trial, with enrollment of patients from the national comprehensive Swedish Coronary Angiography and Angioplasty Registry (SCAAR) and end points evaluated through national registries. A total of 7244 patients with STEMI undergoing PCI were randomly assigned to manual thrombus aspiration followed by PCI or to PCI only. The primary end point was all-cause mortality at 30 days.

Results: No patients were lost to follow-up. Death from any cause occurred in 2.8% of the patients in the thrombus-aspiration group (103 of 3621), as compared with 3.0% in the PCI-only group (110 of 3623) (hazard ratio, 0.94; 95% confidence interval [CI], 0.72 to 1.22; P=0.63). The rates of hospitalization for recurrent myocardial infarction at 30 days were 0.5% and 0.9% in the two groups, respectively (hazard ratio, 0.61; 95% CI, 0.34 to 1.07; P=0.09), and the rates of stent thrombosis were 0.2% and 0.5%, respectively (hazard ratio, 0.47; 95% CI, 0.20 to 1.02; P=0.06). There were no significant differences between the groups with respect to the rate of stroke or neurologic complications at the time of discharge (P=0.87). The results were consistent across all major prespecified subgroups, including subgroups defined according to thrombus burden and coronary flow before PCI.

Conclusions: Routine thrombus aspiration before PCI as compared with PCI alone did not reduce 30-day mortality among patients with STEMI. (Funded by the Swedish Research Council and others; ClinicalTrials.gov number, NCT01093404.).

Fröbert et al. N Engl J Med 2013; 369;17:1587

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Research

JAMA Internal Medicine | Original Investigation

Personalized Prescription Feedback Using Routinely Collected Data to Reduce Antibiotic Use in Primary Care
A Randomized Clinical Trial

Lars G. Hemkens, MD, MPH; Ramon Saccilotto, MD; Selene Leon Reyes, PhD; Dominik Glinz, PhD, MSc; Thomas Zumbrunn, PhD; Oliver Grolimund; Viktoria Gloy, PhD; Heike Raatz, MD, MSc; Andreas Widmer, MD, MSc; Andreas Zeller, MD, MSc; Heiner C. Bucher, MD, MPH

IMPORTANCE Feedback interventions using routinely collected health data might reduce antibiotic use nationwide without requiring the substantial resources and structural efforts of other antibiotic stewardship programs.

OBJECTIVE To determine if quarterly antibiotic prescription feedback over 2 years reduces antibiotic use when implemented in a complex health care system.

DESIGN, SETTING, AND PARTICIPANTS Pragmatic randomized trial using routinely collected claims data on 2900 primary care physicians with the highest antibiotic prescription rates in Switzerland.

INTERVENTIONS Physicians were randomized to quarterly updated personalized antibiotic prescription feedback over 2 years (n = 1450) or usual care (n = 1450). Feedback was provided both by mail and online from October 2013 to October 2015 and was supported by an initial 1-time provision of evidence-based guidelines.

MAIN OUTCOMES AND MEASURES The primary outcome was the prescribed defined daily doses (DDD) of any antibiotic to any patient per 100 consultations in the first year analyzed by intention-to
and sex for the

Editorial
Related article
Supplemental content

Hemkens et al. JAMA Int Med 2017;177(2):176-183.

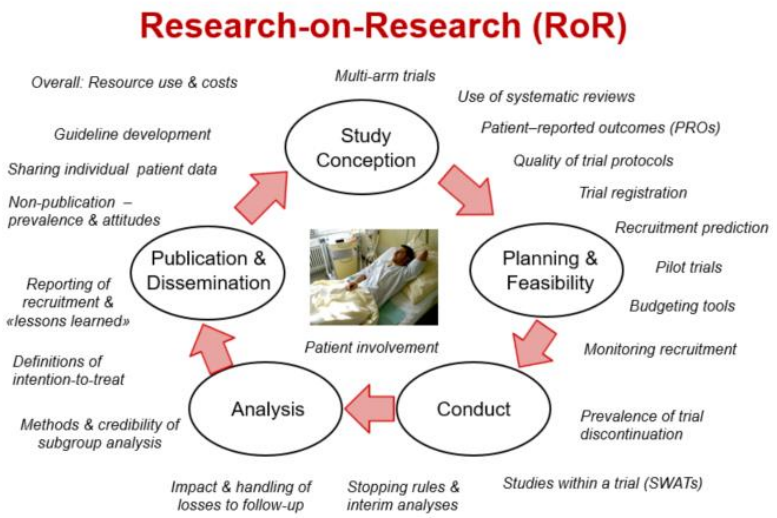
Towards a learning research system

- **Teaching & training**
  (under-/postgraduate)
- **Consulting** & **collaboration**
  with researchers across disciplines and stakeholders
  (checklists, online tools, new designs)

feeds into

- **Swiss** methods network
  (STEAM Working Group)
- **International** initiatives
  (e.g. Swiss branch Trial Forge)
- Concerted **EU** efforts
  (EU COST Action on «Evidence-based research»)

triggers

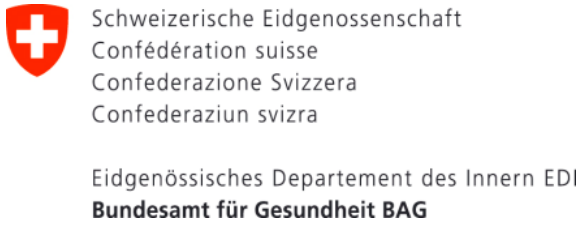


triggers

Conclusions & Perspective on Clin Research

- Existing **inefficiencies aggravated** with COVID-19
- **Too little collaboration & coordination**
- Empirical evidence as a **prerequisite for improvement**
- **Efficiency can be improved through**
  - leveraging **new designs** & **new technologies** for research
  - making **use of available data infrastructures**
  - building of **research networks** (collaborat & coordination!)
  - increasing **value of research** (e.g. building in more ‘Studies Within A Trial (**SWATs**); training of trialists & study staff)
  - building and entertaining **learning research system**
  - better **knowledge translation** of research methodology

Collaborators & Support



Thank you!

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Dmitry Gryaznov (PhD Clin Res)
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Tobias Jakob (Mmed)
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Jakub Surina (MSc Epi)
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Shanil Ebrahim
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Per Olav Vandvik
John You
Elie Akl
Gordon Guyatt

Sherbrook
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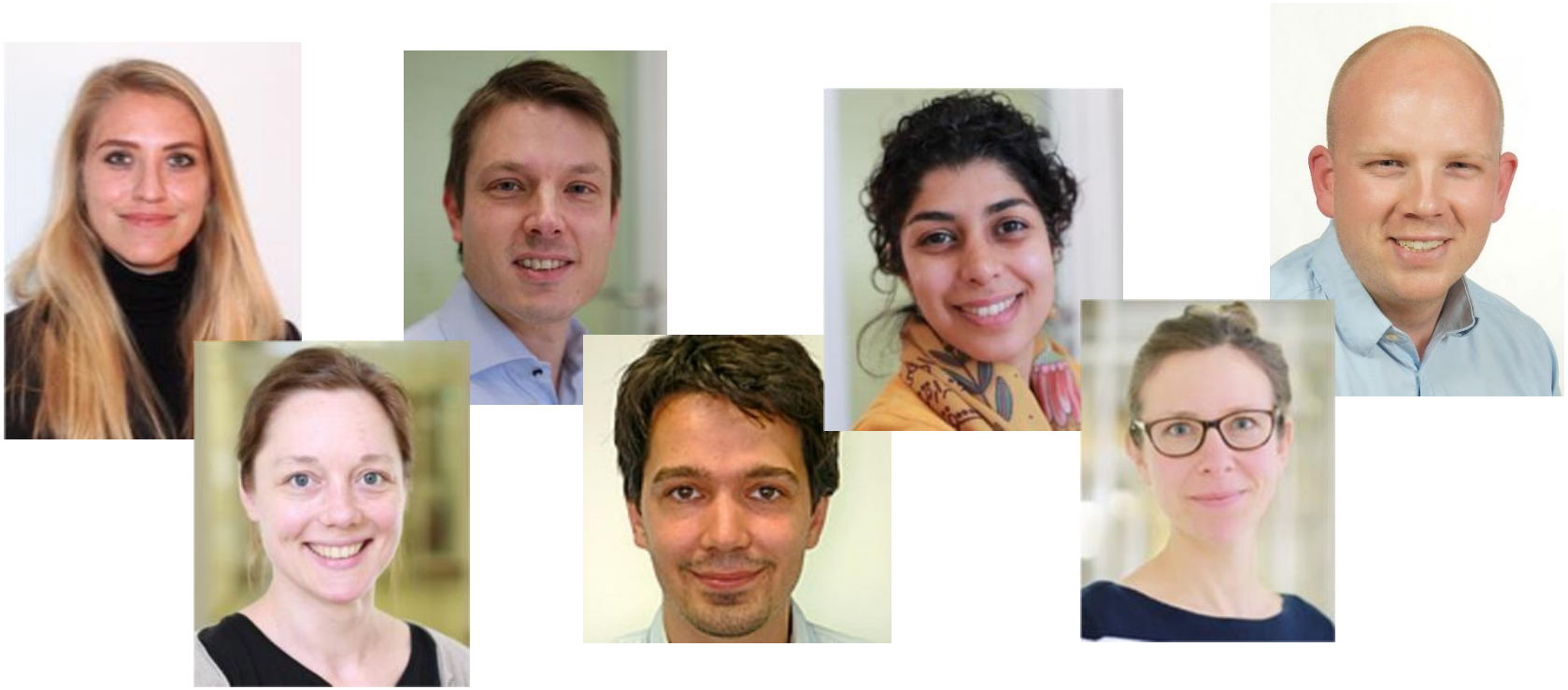
Thank you for your attention!



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