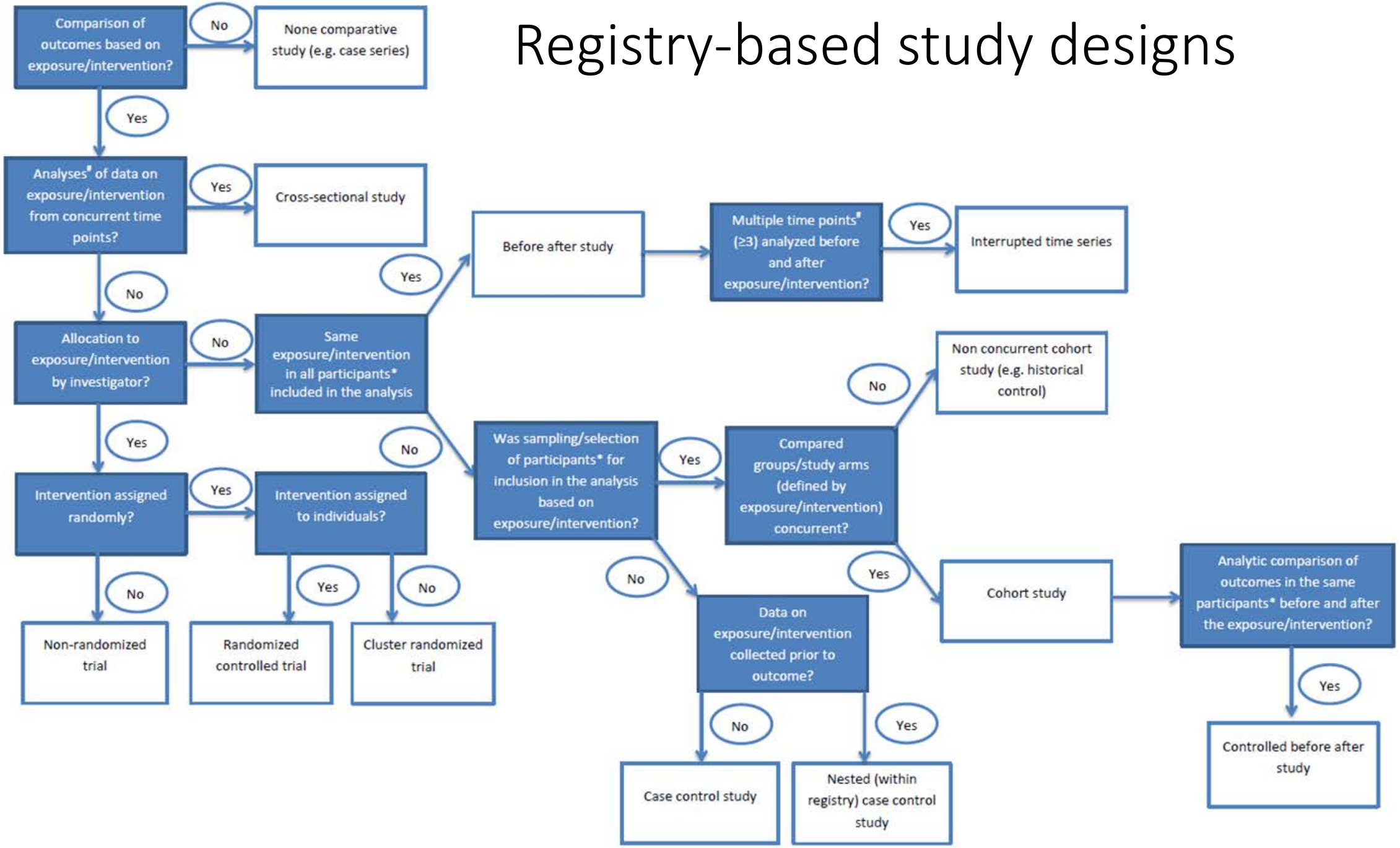
Designs von vergleichenden registerbasierten Interventionsstudien

Tim Mathes
Institut für Medizinische Statistik, Universitätsmedizin Göttingen

Comparative Effectiveness Research

- CER: Generation and synthesis of **causal evidence** that **compares benefits and harms** of Health Technologies (prevention, diagnoses, treatment and monitoring a clinical condition, measures to improve the delivery of care)
- Evidence is generated through research that uses **various study designs**
- Focus on research **under real-world conditions** (e.g. heterogeneous population)

Registry-based study designs



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Common pitfalls registry based non-RCT

ORIGINAL ARTICLE

No inexplicable disagreements between real-world data–based nonrandomized controlled studies and randomized controlled trials were found

- Unmeasured confunders, time related biases, and no information on missing data were the most common problems

Target Trial Emulation

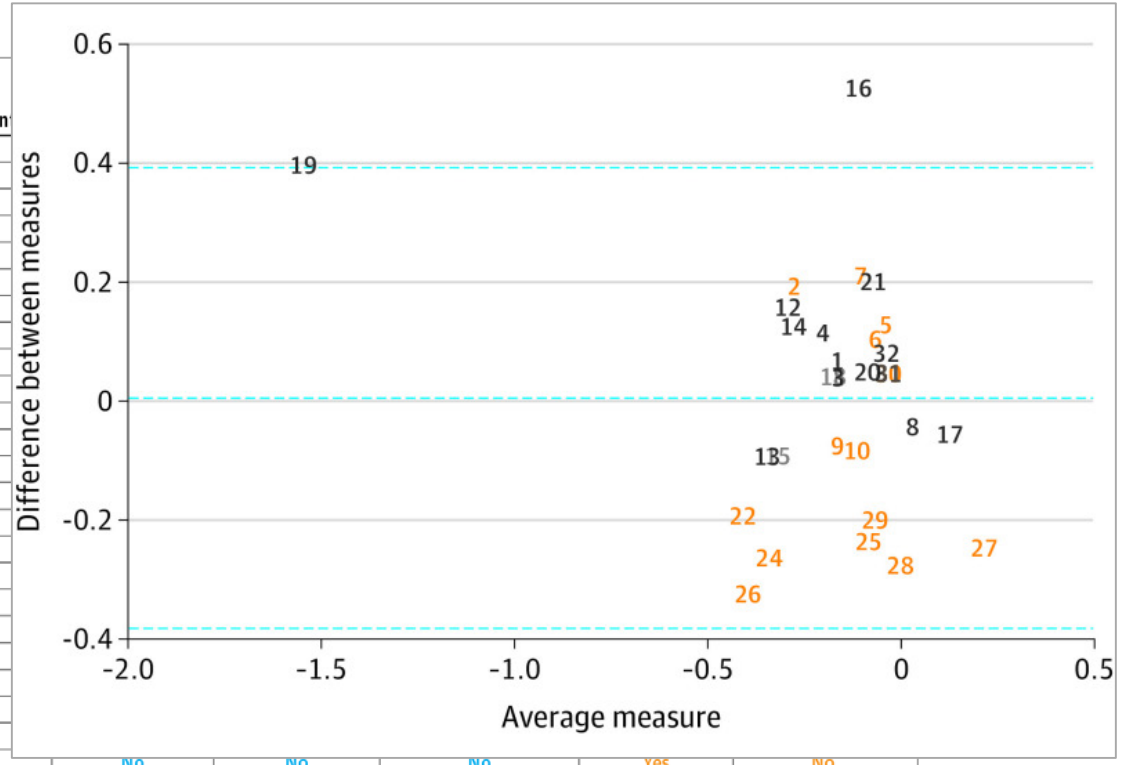
2-steps:

1. Articulating the causal question in the form of the protocol of a hypothetical randomized trial RCT
2. Explicitly emulating the components of that protocol using the observational data

	Target Trial	**Emulation**
Eligibility criteria		
Treatment strategies		
Treatment assignment		
Follow-up period		
Outcomes		
Causal contrast of interest		
Analysis plan		

Results of attempts to systematically emulate RCTs

No.	Trial name	Comparator emulation[a]	Outcome emulation[b]	Age distribution, mean difference, y	Sex distribution, difference in % female	Run-in window[c]	Placebo con					
1	LEADER	Moderate	Good	-3.4	-17.8	Yes, placebo	Yes					
2	DECLARE	Moderate	Moderate	1.4	-4.9	Yes, placebo	Yes					
3	EMPA-REG	Moderate	Good	1.2	-11.9	Yes, placebo	Yes					
4	CANVAS	Moderate	Good	-2.0	-10.5	Yes, placebo	Yes					
5	CARMELINA	Poor	Good	-6.4	-16.2	No	Yes					
6	TECOS	Poor	Moderate	-6.8	-18.1	No	Yes					
7	SAVOR-TIMI	Poor	Good	-3.8	-13.7	No	Yes					
8	LEAD-2	Good	Moderate	-2.0	-6.0	Yes, both groups	No					
9	TRITON-TIMI 38	Good	Good	3.4[f]	4.9	No	No					
10	PLATO	Good	Good	-3.3[f]	-4.1	No	No					
11	ISAR-REACT 5	Good	Good	5.6	0.9	No	No					
12	ARISTOTLE	Good	Good	-6.1	-16.7	No	No					
13	RE-LY	Good	Good	-4.7	-5.9	No	No					
14	ROCKET-AF	Good	Good	-4.5	-14.9	No	No					
15	EINSTEIN DVT	Good	Moderate	-14.7	-17.0	No	No					
16	EINSTEIN PE	Good	Moderate	-8.2	-4.9	No	No					
17	RE-COVER II	Good	Moderate	-13.5	-16.4	No	No					
18	AMPLIFY	Good	Moderate	-0.6	-10.1	No	No					
19	RECORD1	Good	Good	1.0	1.6	No	No					
20	TRANSCEND	Moderate	Good	-4.0	-14.1	Yes, both groups	Yes					
21	ON TARGET	Good	Good	-2.4	-27.2	Yes, both groups	No					
22	HORIZON PFT	Moderate	Good	-1.0	0	No	Yes					
23	VERO	Good	Moderate	1.1	0	No	No					
24	DAPA-CKD	Moderate	Moderate	-5.5	-11.4	No	Yes	No	No	No	Yes	No
25	PARADIGM-HF	Moderate	Moderate	-4.7	-6.2	Yes, both groups	No	No	No	Yes	No	No
26	P04334	Good	Good	-11.2	1.9	Yes, 1 class	No	No	No	Yes	No	No
27	D5896	Good	Good	-3.3	-1.8	No	No	No	No	Yes	No	No
28	IMPACT	Good	Good	-4.0	-25.5	Yes, baseline prescription	No	No	No	Yes	No	No
29	POET-COPD	Good	Good	-7.5	-28.3	Yes, mixed	No	No	No	Yes	No	No
30	INSPIRE[h]	Good	Moderate	-1.5	-44.6	Yes, 1 class	No	No	No	Yes	No	No
31	CAROLINA[i]	Good	Good	-6.3	-12.3	Yes, placebo	No	No	Yes	No	No	Yes
32	PRONOUNCE1[i]	Good	Good	-3.0	0	No	No	No	Yes	No	No	Yes



Requirements on data for TTE to avoid bias


Propensity Scores

OPEN ACCESS

Übersichtsarbeit

Anforderung an die Daten für die Target-Trial-Emulation: Eine Diskussion unter Betrachtung von Patientenregistern

- Information on patients, intervention, comparison, outcomes
- Confounding: all important confounders available or data allow high-dimensional matching
- Time related biases: detailed information of study start, time of fulfilling inclusion criteria, start of follow-up
- In certain circumstances data for calculating a specific estimand of interest (e.g. per protocol effect)
- Sufficient data quality, particularly regarding missing data and measurement error

Registry-based RCT (rRCT)

ORIGINAL ARTICLE

Registry-based randomized controlled trials merged the strength of randomized controlled trails and observational studies and give rise to more pragmatic trials

Characteristics

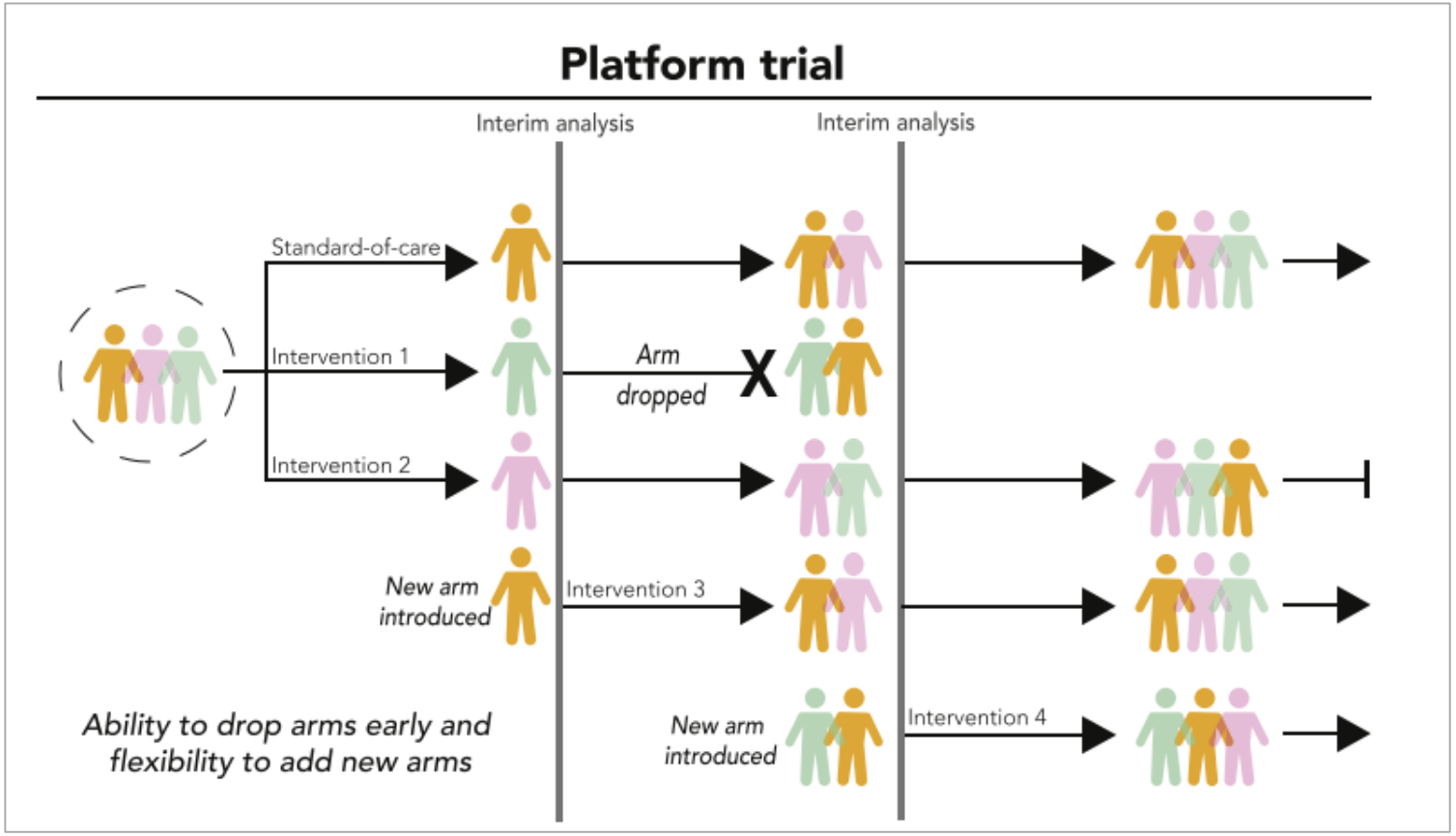
- Number of included patients (median; IQR): 2000 (533; 17793)
- Mean follow-up (median; IQR): 5,3Y (1,0; 11,1)

Risk of Bias

- Time related biases avoided by design
- Missing data and outcome measurement error will be often balanced because of randomization
- Can often be considered blinded

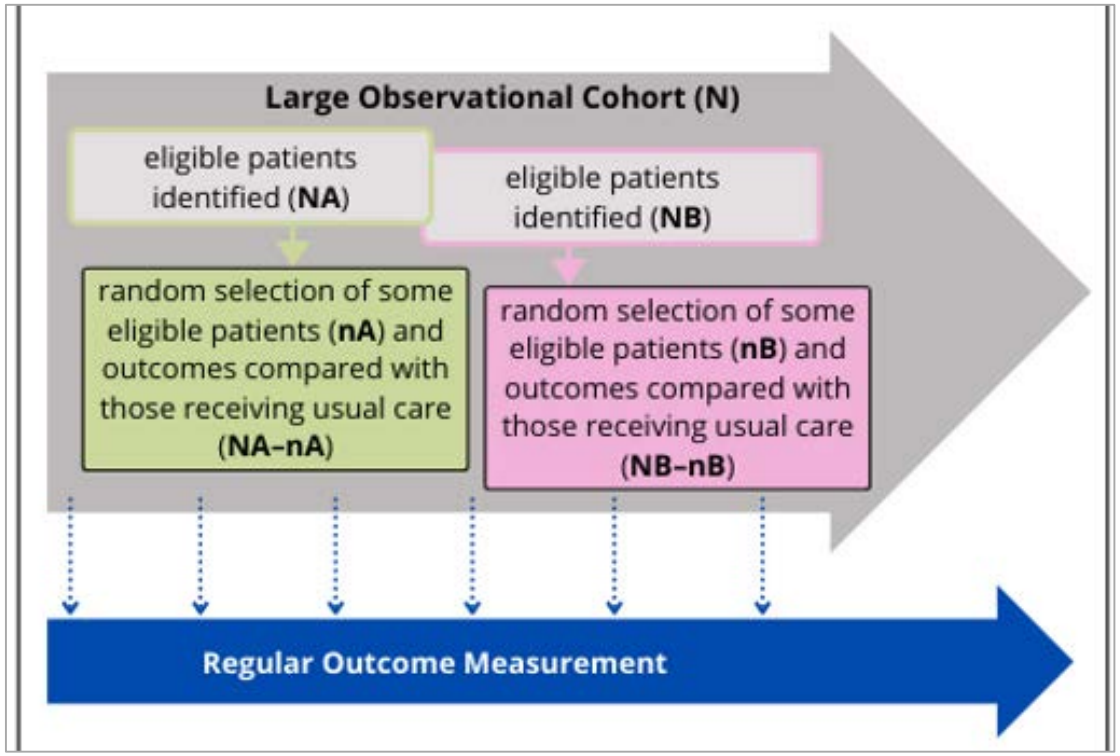
The future?: Plattform Trials

Evaluation of multiple Interventions to a common control

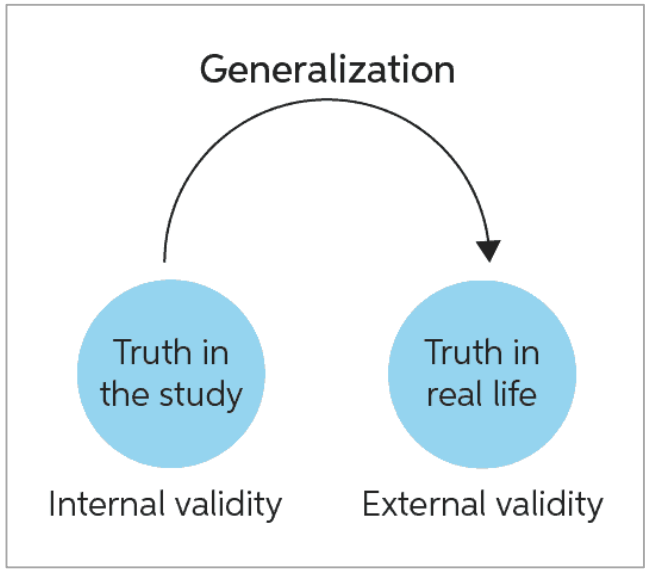


The future?: Trials within registry cohorts

Trial within Cohort (TwiCs)



Quelle: https://www.twics.global/



Combining data from rRCTs and observational data

Originalarbeit

Präv Gesundheitsf
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Tim Friede · Christian Röver · Tim Mathes
Institut für Medizinische Statistik, Universitätsmedizin Göttingen, Göttingen, Deutschland

Verknüpfung von randomisierten kontrollierten Studien und Real World Data

- Hierarchical models for evidence synthesizes
- Extrapolation of RCTs to real-world
- Bias adjustment of non-randomized studies

Conclusion

- If all necessary data are available (and self-inflected bias is avoided), RCT-effects can be emulated using registry data. However some uncertainty always remains
- rRCTs usually require less data, and data quality and thus maybe associated with less effort than adapting a registry for a trial
- Combing registry-based non-RCTs and RCTs using advanced synthesizes methods will usually give the highest information and evidence level

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