

# Registerbasierte randomisierte kontrollierte Studien: ein innovativer Ansatz

Registertage 2023

- Definition: randomisierte kontrollierte Studien (RCT) die Daten aus einem Register Nutzen (rRCT)

### Register



### eCRF

Rapid Case Management Form, Ebola Virus Disease, 28 May 2018.  
Based on WHO VHF/SARI\_Case\_Record\_Form 2016.

World Health Organization

**ADMISSION FORM**

**I. CASE IDENTIFICATION/ DEMOGRAPHIC DETAILS**

Patient Name:		ETU Number:	
<b>EPI ID:</b>			
<input type="checkbox"/> Male <input type="checkbox"/> Female		Patient occupation	
		<input type="checkbox"/> Healthcare worker. Please specify: _____	
		<input type="checkbox"/> Non-Healthcare worker. Please specify: _____	
Date of birth: (dd/mm/yyyy)		If date of birth unavailable, please indicate age in month or years (mark an X by one):	
		Age: <input type="checkbox"/> Years <input type="checkbox"/> Months	
Date of admission: (dd/mm/yyyy)		Was patient transferred from another facility?	
		<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unknown. If yes, name of facility: _____	

**II. VITALS AT TRIAGE:**

Heart rate (bpm):	Respiratory Rate (1/min):	Temperature (°C):
BP (mmHg): (systolic) (diastolic)	O <sub>2</sub> saturation room air (%):	Mental status: A / V / P / U
Capillary refill > 3 sec? <input type="checkbox"/> Yes <input type="checkbox"/> No	Weight (kg):	Mid-upper arm circumference (MUAC) (mm) _____
	Self-reported height (cm):	

**III. CLINICAL DETAILS (on admission)**

Date onset first symptoms (dd/mm/yyyy): / /	If female patient, is she pregnant? <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> ND
Date of admission to isolation unit (dd/mm/yyyy): / /	Admitted to what type of bed?
	<input type="checkbox"/> Ward <input type="checkbox"/> ICU

<b>Comorbid conditions</b>	<b>Malignancy/Chemotherapy</b>
Tuberculosis <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unknown	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unknown
Asplenia <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unknown	Chronic heart failure <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unknown
Hepatitis <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unknown	including congenital disease <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unknown
Diabetes <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unknown	Chronic pulmonary disease <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unknown
HIV <input type="checkbox"/> Yes and on ART <input type="checkbox"/> Yes and not on ART <input type="checkbox"/> No <input type="checkbox"/> Unknown	Chronic kidney disease <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unknown
Chronic liver disease <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unknown	Chronic neurologic condition <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unknown
	Other, specify: _____

<b>Symptoms (on presentation)</b>	<b>Headache</b>	<b>Chest pain</b>
Fever <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unknown	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unknown	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unknown
Unknown <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unknown	Nausea <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unknown	Difficulty breathing <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unknown
Fatigue <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unknown	Chest pain <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unknown	Difficulty swallowing <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unknown
Unknown <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unknown	Joint Pain <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unknown	Abdominal pain <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unknown
Weakness <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unknown	Hiccups <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unknown	Diarrhoea <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unknown
Unknown <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unknown	Cough <input type="checkbox"/> Yes and productive <input type="checkbox"/> Yes and not productive <input type="checkbox"/> No <input type="checkbox"/> Unknown	Vomiting <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unknown
Malaise <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unknown		Intubity / Confusion <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unknown
Unknown <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unknown		
Myalgia <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unknown		
Unknown <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unknown		
Anorexia <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unknown		
Unknown <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unknown		
(i.e. loss of appetite)		
Sore throat? <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unknown		

<b>Signs (on presentation)</b>	<b>Enlarged lymph nodes</b>
Pharyngeal erythema <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unknown	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unknown
Pharyngeal exudate <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unknown	Lower extremity oedema <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unknown
Conjunctival injection/bleeding <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unknown	Bleeding <input type="checkbox"/> No <input type="checkbox"/> Unknown
Oedema of face/neck <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unknown	<input type="checkbox"/> Nose
Tender abdomen <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unknown	<input type="checkbox"/> Mouth
Sunken eyes or fontanelle <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unknown	<input type="checkbox"/> Vagina
Tenting on skin pinch <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unknown	<input type="checkbox"/> Rectum
Palpable liver <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unknown	<input type="checkbox"/> Spum
Palpable spleen <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unknown	<input type="checkbox"/> Urine
Rash <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unknown	<input type="checkbox"/> IV site
Jaundice <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unknown	<input type="checkbox"/> Other, specify: _____

**ORIGINAL ARTICLE**

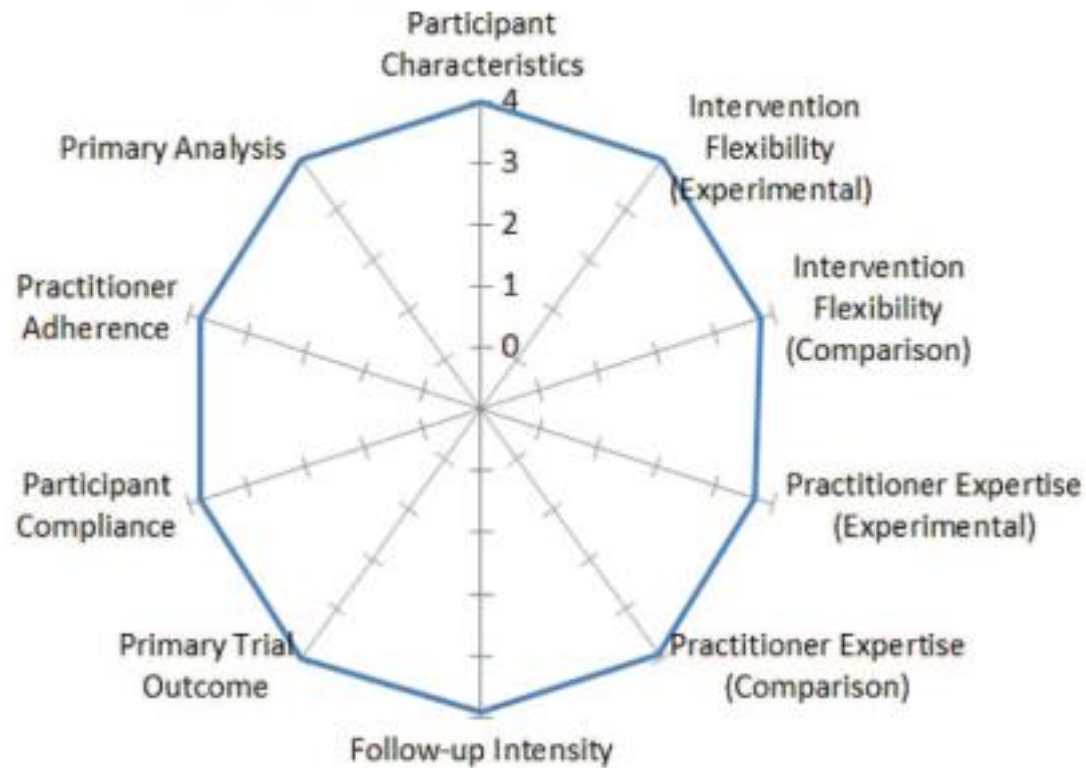
Registry-based randomized controlled trials merged the strength of randomized controlled trials and observational studies and give rise to more pragmatic trials

- Meisten Studien aus Skandinavien und den USA
- Meisten Studien in Bereich Onkologie und Kardiologie
- 45% der Studien Prävention, insbesondere Screening und Organisation/Koordination der Versorgung
- 28% Arzneimittel

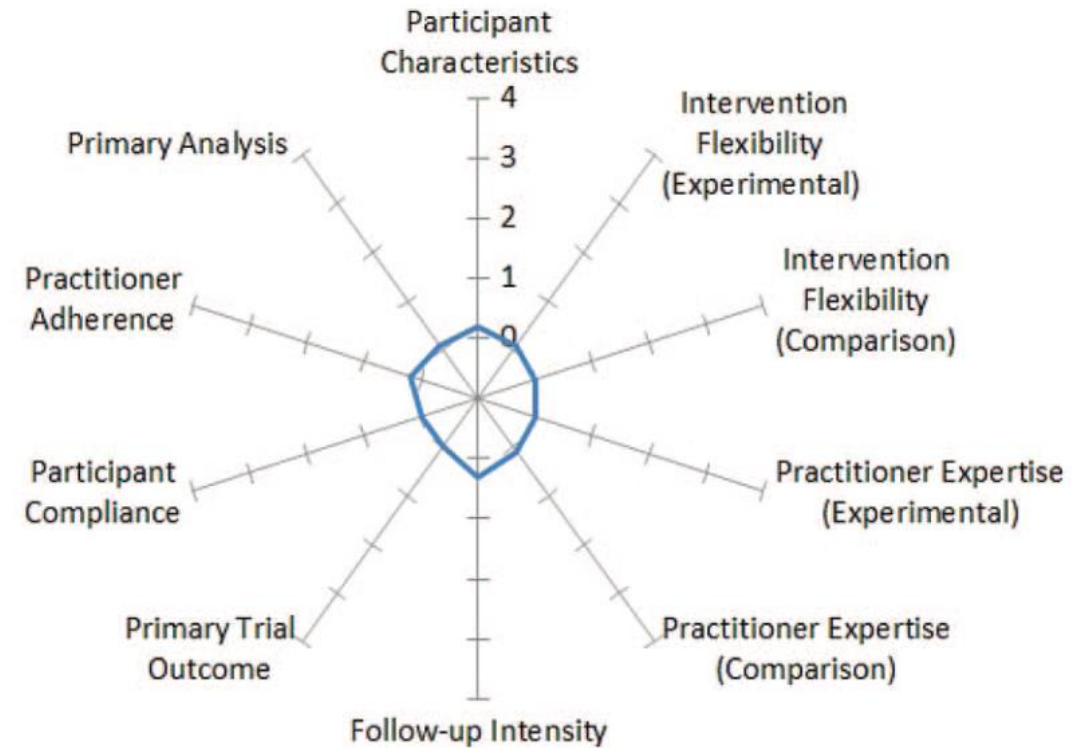
Cluster rRCT ( $n = 71$ )	8 (11.3%)
Blinded <sup>a</sup> ( $n = 71$ )	6 (8.5%)
Included patients ( $n = 65$ , median, interquartile range, range)	2,000 (533–17,793; 69–273,620)
Same number of patients analyzed as randomized ( $n = 56$ )	46 (82%)
Exclude from analysis ( $n = 12$ ; mean, range)	5.5% (<1%–21%)
More than one registry utilized ( $n = 71$ )	36 (50.7%)
Number of outcomes ( $n = 71$ , median, interquartile range, range)	2 (1–3; 1–9)
Only one outcome from registry ( $n = 71$ )	34 (47.9%)
Primary outcome from registry ( $n = 71$ )	58 (81.7%)
Mortality ( $n = 71$ )	43 (60.6%)
Composite outcome ( $n = 71$ )	14 (19.7%)
Information on data quality provided ( $n = 71$ )	8 (11.3%)
Type of registry (patient registry; $n = 124^b$ )	46 (37.1%)
Duration follow-up ( $n = 65$ , median, interquartile range, range)	5.3 yr (1.0–11.1; 0.1–27.0)
Record linkage (unique identifier; $n = 27$ )	19 (70.4%)

# Grad des „Pragmatismus“

A) PRECIS wheel illustrating a more pragmatic approach.



B) PRECIS wheel illustrating a more explanatory approach.



# Endpunktbezogene Verzerrung/Datenqualität

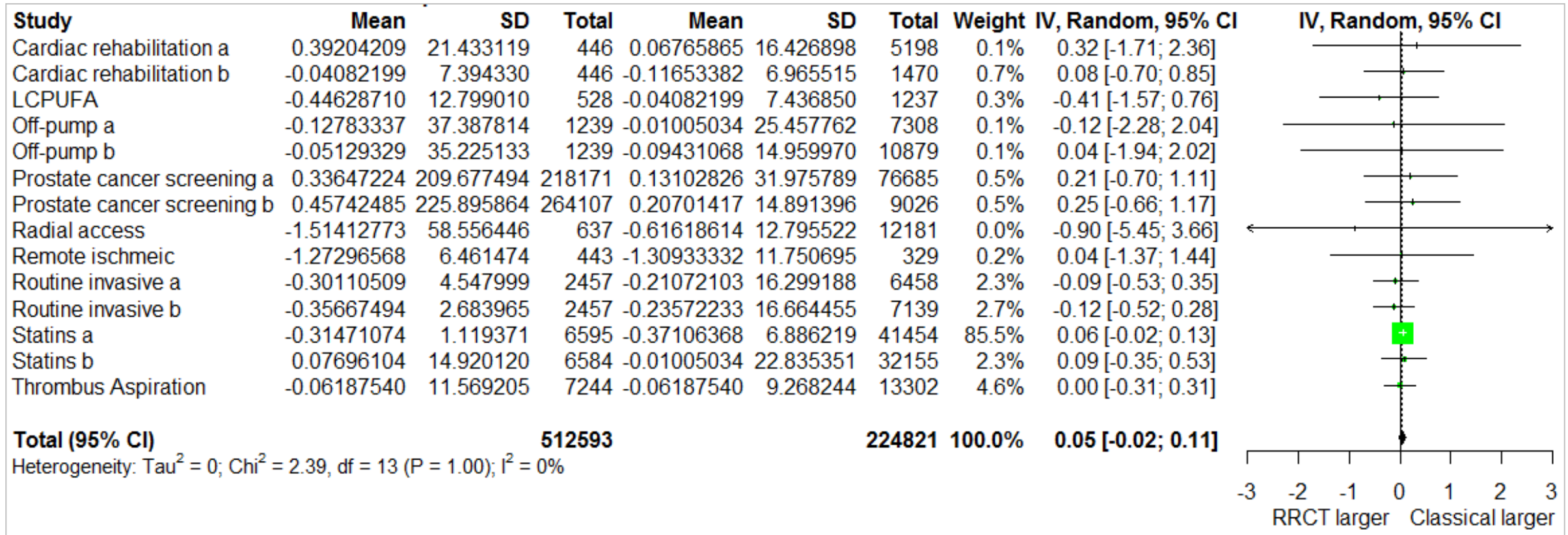
## Unveröffentlichte Daten

- Daten Erfassung innerhalb der Register wird in der Regel nicht (stark) zum Zweck der Studie verändert
- Anteil an fehlenden Werten kann häufig nicht bestimmt werden
- Validität der Endpunkterfassung häufig unklar
  - Aber kann als verblindet angesehen werden, da Endpunkterheber\*innen nicht in Studie involviert (?)
- (Gründe) für fehlende Werte und Qualitätsmängel (z.B. inkorrekte Einträge) vermutlich gleich verteilt zwischen den Gruppen, da randomisiert



## ORIGINAL ARTICLE

No differences were found between effect estimates from conventional and registry-based randomized controlled trials



Paper II:

Thematic framework analysis of registry-based randomized controlled trials provided insights for designing trial ready registries

Karolin R Krause<sup>3\*</sup>, Joanne Tay<sup>b\*</sup>, William A Douglas<sup>b</sup>, Adrian Sammy<sup>b</sup>, Ami Baba<sup>b</sup>, Katherine

- Stärken

1. Vergleich von in rRCT eingeschlossenen Probanden mit nicht-eingeschlossenen Probanden
2. Große Fallzahlen
3. Höhere Effizienz
4. Höhere Generalisierbarkeit

- Schwächen

1. Unvollständige unzureichende Registerdaten
2. Uneinheitliche Registerdaten
3. Beschränkte Nutzbarkeit der Registerdaten aufgrund von Datenschutz
4. Unzureichende Generalisierbarkeit



# Zusammenfassung

- Scheinen (aktuell) ein geeigneter Ansatz, insbesondere für die Durchführung von pragmatic Trials (Public-Health-Interventionen, HTA, post-Marketing)
- Derzeit Nutzung für explanatory Trials (Zulassung) fraglich, da Erfüllung der Anforderung an die Daten häufig unklar (z. B. Source Data Verification)
- Können aber als Ergänzung verwendet werden (z. B. Langzeit-Follow-up).
- Register sollten bei ihrer (weiter) Entwicklung die Einbettung von rRCTs und deren potentiellen Verwendungszweck (z.B. Zulassungsstudien) berücksichtigen

# References

1. Karolin R. et al. (2023). Paper II: Thematic framework analysis of registry-based randomized controlled trials provided insights for designing trial ready registries, *Journal of Clinical Epidemiology*
2. Loudon, K., et al. (2015). The PRECIS-2 tool: designing trials that are fit for purpose. *bmj*, 350.
3. Mathes, T., et al. (2018). Registry-based randomized controlled trials merged the strength of randomized controlled trails and observational studies and give rise to more pragmatic trials. *Journal of clinical epidemiology*, 93, 120-127.
4. Mathes, T., et al. (2019). No differences were found between effect estimates from conventional and registry-based randomized controlled trials. *Journal of clinical epidemiology*, 105, 80-91.