# A Systematic Review of the Use of Registry-Based Randomized Controlled Trials (R-RCTs) for Regulatory Approval and Access

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## Introduction

Registry-based randomized controlled trials (R-RCTs) are prospective, randomized trials that use patient registries for 1 or more major trial functions, including screening, recruitment, randomization, data collection, and follow-up.[1,2]

Unlike traditional RCTs (which typically use highly selected patient populations in ideal settings), R-RCTs usually have pragmatic designs, use broad inclusion criteria, and focus on real-world environments.[2]

There is increasing interest in R-RCTs for both real-world effectiveness research and for complementing RCTs in regulatory decision making.[3,4]

The aim of this systematic review was to investigate the use of R-RCTs for regulatory approval and access.

## Methods

A systematic literature search of ongoing and completed R-RCTs was performed. R-RCTs were identified from 3 recent systematic reviews,[4-6] through a search of ClinicalTrials.gov and Citeline's Trialtrove (all citations included until the search on January 12, 2023), and through a manual search. Trial details were extracted from study protocols and indexed publications; if critical details were missing, a manual search was performed.

Trials were cross-referenced with reimbursement decisions in the UK (NICE: The National Institute for Health and Care Excellence), France (HAS: Haute Autorité de santé), Germany (G-BA: Gemeinsamer Bundesausschuss), and Sweden (TLV: Tandvårds-och läkemedelsförmånsverket), as well as with regulatory decisions by the European Medicines Agency and the US Food and Drug Administration.

### *Inclusion and exclusion criteria*

All trials using a clinical or administrative registry were included from ClinicalTrials.gov and Citeline's Trialtrove, whereas trials from systematic reviews were only included if they also had a pharmaceutical or surgical/medical device intervention. Trials were excluded if they had been prematurely terminated, or if they used registries only for long-term, post-trial follow-up.

## Results

In total, 554 trials were identified. After manual qualification, **112 R-RCTs** were eligible for inclusion, of which 68 trials (60.7%) involved a clinical patient registry. The earliest R-RCT identified was from 1982 (NCT02719678).

### *Type of intervention*

Among the 112 R-RCTs, approximately one third (n=37; 33.0%) were for pharmaceutical interventions (Table 1). Both the number of R-RCTs and the proportion with a pharmaceutical intervention increased up to 2017, but then remained relatively stable (Figure 1).

| Intervention type | Number of trials, n (%)* |
|---|---|
| Pharmaceutical | 37 (33.0%) |
| Surgery/devices | 33 (29.5%) |
| Screening | 7 (6.3%) |
| Vaccine | 6 (5.4%) |
| Other† | 29 (25.9%) |

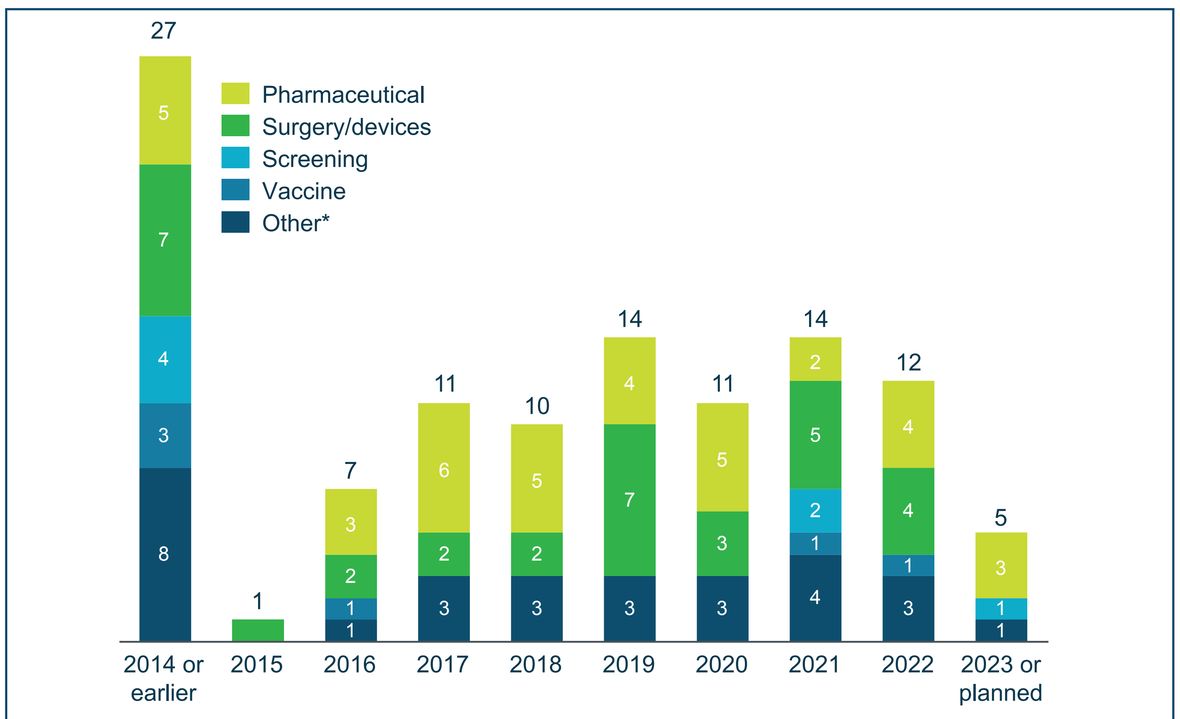
*Please note, % may add up to >100% due to rounding. †Advertising/outreach, complex healthcare interventions, oxygen therapy, patient education, etc.

**Table 1: Number of R-RCTs by intervention type**

### *R-RCTs with pharmaceutical interventions*

All 37 R-RCTs for pharmaceutical interventions used approved drugs, and only 1 (DAPA-MI, NCT04564742) was industry-initiated and indication-seeking.

None of the identified R-RCTs with pharmaceutical interventions were used as primary evidence for regulatory or reimbursement decisions.




*Advertising/outreach, complex healthcare interventions, oxygen therapy, patient education, etc.

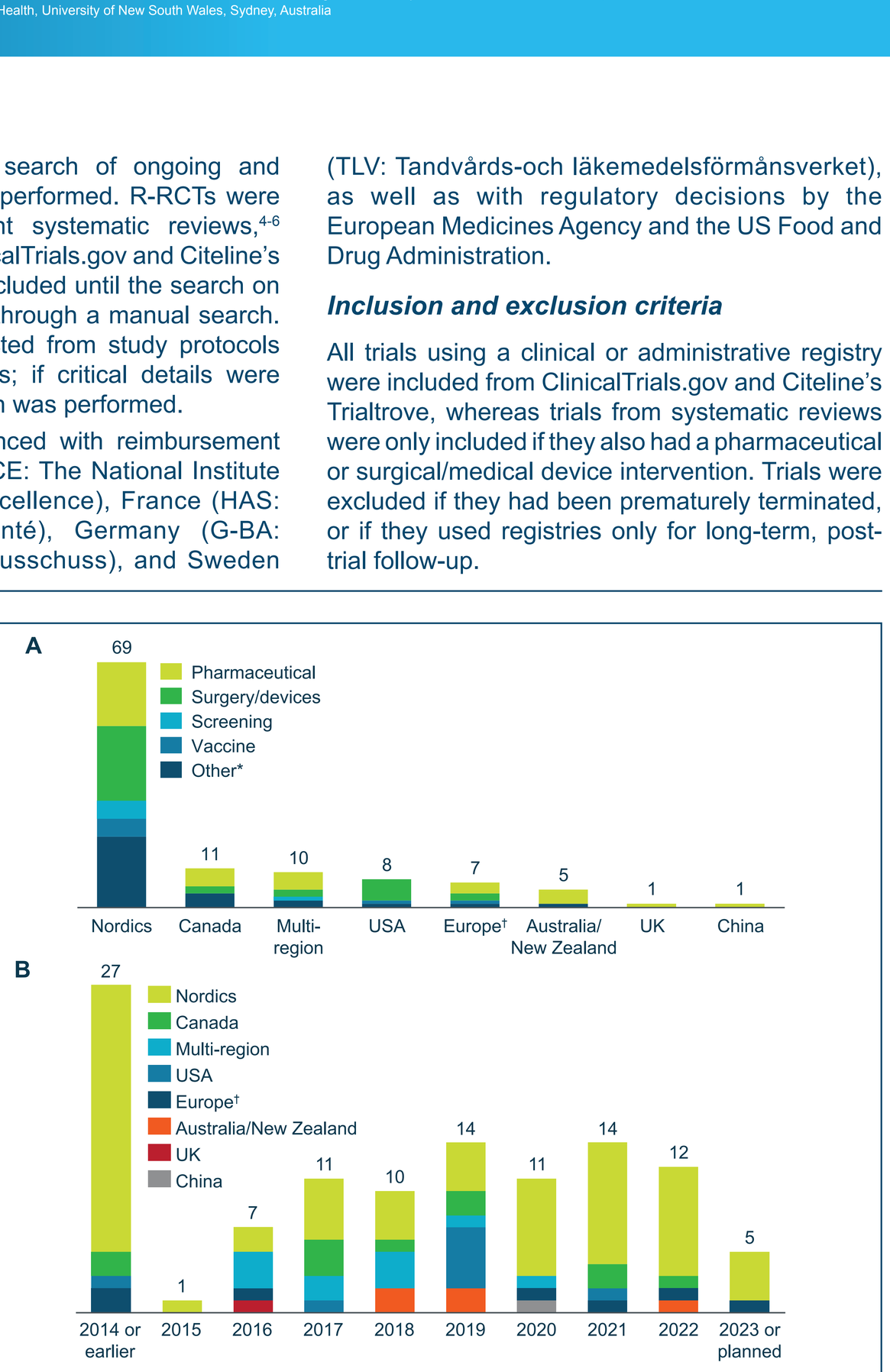
**Figure 1: R-RCTs by year and intervention type**

### *R-RCTs by region*

The number of R-RCTs by geographical region and intervention type is shown in Figure 2A.

Most R-RCTs (n=69; 61.6%) were conducted in the Nordic countries, which have excellent registry infrastructure (Figures 2A and 2B).

Only 12 (10.7%) R-RCTs were conducted in multiple countries. Of these, 5 (4.5%) used an R-RCT design only among Nordic sites, and 4 (3.6%) did not report the registry used.




*Advertising/outreach, complex healthcare interventions, oxygen therapy, patient education, etc.
†Excluding Nordic countries and the UK.

**Figure 2: R-RCTs by (A) region and intervention type; (B) region and year**

## Conclusions

Up to January 12, 2023, all R-RCTs for pharmaceutical interventions have been conducted with approved drugs. No drug has used R-RCTs as key evidence for a regulatory filing and reimbursement decisions.

R-RCTs have predominantly been conducted in the Nordic countries, which have high-quality patient registries with excellent infrastructure.

Multi-country R-RCTs were rare, highlighting the practical challenges likely due to a scarcity of appropriate or compatible registries.

R-RCT is a promising study design that, so far, has not been frequently utilized by the pharmaceutical industry for the development of novel drugs, warranting further exploration of the prospects of this tool, particularly in the field of multi-country R-RCTs.

## References

1. Uppsala Clinical Research Center. Available at: https://www.ucr.uu.se/en/services/r-rct. Accessed September 12, 2023.
2. National Recommendations for R-RCTs, Sweden (2018). Available at: https://www.r-rct.se/. Accessed September 12, 2023.
3. Guowei L, et al. *J Clin Epidemiol*. 2016;80:16-24.
4. Karanatsios B, et al. *Trials*. 2020;21:552.
5. Mathes T, et al. *J Clin Epidemiol*. 2018;93:120-127.
6. Shea NO, et al. 2022. Available at: https://assets.researchsquare.com/files/rs-1485391/v1/7f88b82a-d6b2-4d88-8f30-e725ab72be11.pdf?c=1655225065 (preprint). Accessed September 19, 2023.

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