Sizing Up the Gap: Evaluating Sample Size Justification in Prospective Real-World Studies

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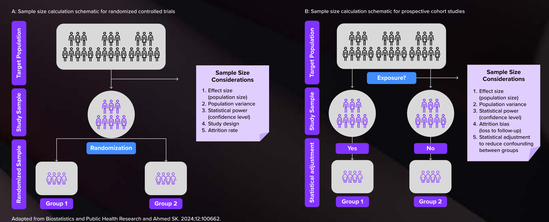
BACKGROUND

Sample size calculation is not only important for clinical trials but also for prospective real-world data (RWD) studies testing hypotheses (**Fig 1**)

Without randomization, RWD studies must adjust for confounding factors using statistical methods (eg, regression). However, the impact on required sample size is not always well understood

While there is not a standard method for calculating sample size to assess health outcomes in prospective RWD studies, suggested methods include estimation based on interim results and applying rules of thumb based on the number of predictors or other sample characteristics[1-7]

Figure 1: Sample size considerations for a clinical trials and prospective cohort studies



Adapted from Biostatistics and Public Health Research and Ahmed SK. 2024;12:100662.

OBJECTIVE

The goal of this study was to review how recent prospective RWD studies published in high-impact journals justified their methods to determine sample size[8,9]

METHODS

We conducted a targeted literature search on PubMed to identify prospective RWD studies in full-text articles that were published in the top 5 highest impact factor general medicine journals (NEJM, Lancet, JAMA, Nature Medicine, Annals of Internal Medicine) and Value in Health between January 1, 2023 and December 31, 2023

Prospective RWD studies included cross-sectional or longitudinal cohort studies and case series in which hypotheses were tested going forward in time[10]

For included studies, we described study characteristics including type of prospective study, disease area, whether studies described sample size calculations, and if sample size was further adjusted based on planned statistical analyses

RESULTS

- A total of 374 publications were identified in this search
- After title/abstract review, 62 were selected for full-text review, and 24 were included (**Fig 2**)

Figure 2: PRISMA diagram

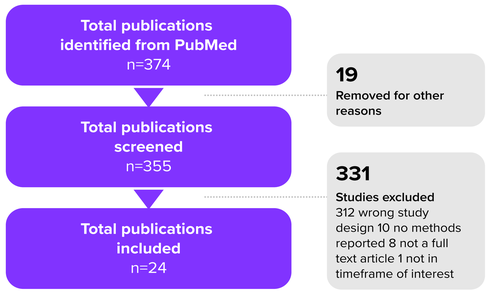


Table 1: Characteristics of included prospective real-world studies in 2023

Study Name	Journal	Location	Longitudinal	Sources of patients	Disease or area of study	Sample size rationale provided
Ahmed et al.	Value in Health	Australia	Y	Community	Respiratory	Y
Allison et al.	Lancet	England, Scotland, Wales	Y	Community	Infections	N
Chen et al.	NEJM	US	Y	Medical centers	Gender affirming care	N
Cheng et al.	Value in Health	Australia	N	Clinics	Substance abuse	N
Emiru et al.	Nature Medicine	Ethiopia	N	Medical centers	Malaria	Y
Fuchs et al.	Annals of Internal Medicine	Denmark	N	Community	Cardio-metabolic	N
Havermans et al.	Value in Health	Netherlands	N	Medical center	Trauma	N
He et al.	Annals of Internal Medicine	US	N	Community	Cardio-metabolic	N
Hinkle et al.	Lancet	US	Y	Medical centers	Cardio-metabolic	N
Lee et al.	Annals of Internal Medicine	South Korea	N	Medical center	Decompression ilness	Y
Maheshwari et al.	Annals ofInternal Medicine	US	N	Community	Cardio-metabolic	N
Maron et al.	JAMA	US	N	Medical centers	Diagnostics	Y
Moreel et al.	Annals of Internal Medicine	Germany	Y	Medical center	Giant cell arteritis	N
Muiru et al.	Annals of Internal Medicine	US	N	Medical centers	Renal	N
Olfson et al.	Annals of Internal Medicine	US	Y	Registry	Substance abuse	N
Pollack et al.	JAMA	US	N	Community	Respiratory	N
Rolfes et al.	JAMA	US	N	Community	Infections	N
Rosas-Salazar et al.	Lancet	US	Y	Clinics	Infections	Y
Schlechte et al.	Nature Medicine	Canada	Y	Medical center	Fecal microbiota	Y
Soni et al.	Annals of Internal Medicine	US	N	Community	Diagnostics	N
Thaweethai et al.	JAMA	US	Y	Registry	Infections	Y
Thieme et al.	Nature Medicine	US	N	Medical center	Diagnostics	Y
Villar et al.	Lancet	Global	N	Medical centers	Infections	Y
Zhao et al.	JAMA	US	Y	Medical centers	Hepatic	N

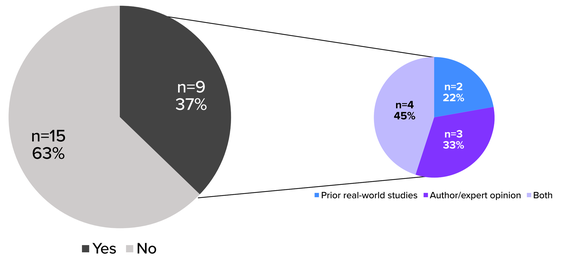
Study Characteristics

- Outcomes from patients were collected from single medical centers (n=5), multiple medical centers (n=7), clinics (n=2), registries (n=2), and the general community (n=8) (**Table 1**)
- Sample sizes for studies ranged from 18 to 1,662,000 patients per group
- Disease or area of study included cardiometabolic diseases, diagnostics, substance abuse, infectious diseases, hepatic disease, renal disease, and others
- A total of 10/24 (42%) studies were longitudinal

Outcomes of interest

- A majority of the studies (15/24 [63%]) did not include a description of methods on sample size calculation (**Fig 3**)
- Of the 9 studies that did, 6 used prior real-world studies and 5 leveraged author/expert opinion (not mutually exclusive) to determine appropriate sample size
- Two (8%) studies increased the number of enrollees after calculations revealed a shortfall in the number required for a well-powered study
- None of the reviewed studies discussed considerations of over fitting issues for future regression adjustment in their sample size calculation

Figure 3: Sample size rationale provided by authors



CONCLUSION & NEXT STEPS

Among recent prospective RWD studies identified in top journals, providing rational for sample size is not common.

Among those that did, consideration of whether or not the observed sample size was robust enough for statistical adjustment of potential confounding variables was rare.

Greater awareness of sample size considerations for RWD studies is needed in order to avoid overconfidence in the findings from prospective cohort studies.

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ABBREVIATIONS IN TABLES AND FIGURES

PRISMA, Preferred Reporting Items for Systematic reviews and Meta-Analyses; RWD, real-world data; US, United States

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Presented at: ISPOR International Conference, May 13-16, 2025, Montreal, Quebec, CA

ACKNOWLEDGEMENT

Kateryna Horblyuk developed the graphics for this poster.

This study was sponsored by AESARA

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