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Association between prospective and retrospective protocol registration and reporting quality and methodological rigor of systematic reviews: a protocol for a meta-research study

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ADMINISTRATIVE INFORMATION

Support - None.

Review Stage at time of this submission - Preliminary searches.

Conflicts of interest - João Vitor dos Santos Canellas is a founder and Editor-in-Chief of INPLASY, the registry used as the data source for this study. This relationship will be transparently disclosed in all resulting publications. The competing-interest declarations of all remaining authors will be confirmed before submission of the final manuscript.

INPLASY registration number: INPLASY202640087

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 24 April 2026 and was last updated on 9 September 2026. The present amendment, performed before the main data extraction and statistical analyses, clarifies the eligibility criteria and finalizes the operational definitions of the reporting, methodological-rigor, and retrospective-registration transparency instruments. A summary and justification of these changes are provided under "Other relevant information."

INTRODUCTION

Study aim To evaluate whether the timing of protocol registration (prospective versus retrospective) is associated with the reporting quality and methodological rigor of systematic reviews with conventional pairwise meta-analysis of healthcare interventions exclusively including randomized controlled trials (RCTs). Additionally, among retrospectively registered reviews, we will evaluate the transparency of retrospective registration practices and examine whether these practices are associated with reporting quality and methodological rigor.

Background Prospective protocol registration is widely recommended as a core methodological standard for systematic reviews because it promotes transparency, reduces the risk of selective reporting, and supports the prespecification of review methods before study conduct. Despite these well-recognized benefits, a substantial proportion of systematic reviews continue to be registered retrospectively. Although retrospective registration may improve transparency compared with the absence of protocol registration, its ability to preserve methodological rigor and reduce the risk of bias remains uncertain, particularly when registration occurs after key stages of the review process have already been completed. Consequently, it is unclear whether the timing of protocol registration

is associated with differences in the reporting quality and methodological rigor of published systematic reviews.

Rationale Previous meta-epidemiological studies have suggested that protocol registration is associated with improved reporting quality and methodological rigor in systematic reviews. However, the interpretation of these findings remains challenging because widely used reporting and methodological assessment tools often include protocol registration as one of their evaluation domains. Consequently, comparisons between registered and non-registered reviews may be affected by methodological circularity, potentially inflating the observed association between registration and study quality.

Furthermore, the distinction between prospectively and retrospectively registered reviews has received limited empirical attention. Although prospective registration is intended to promote transparency and reduce bias through the prespecification of review methods, retrospective registration may occur after key stages of the review process have already been completed. Consequently, retrospective registration cannot provide the same assurance that methodological decisions were established before review conduct.

Recent conceptual work has proposed that retrospectively registered protocols should not be interpreted solely according to the timing of registration but also according to the transparency with which retrospective registration is reported, including clear disclosure of its retrospective nature, justification for delayed registration, and transparent reporting of methodological changes. Although this transparency-oriented framework provides a conceptual basis for interpreting retrospectively registered protocols, it has not yet been empirically evaluated.

Existing meta-epidemiological studies have rarely compared prospectively and retrospectively registered systematic reviews while simultaneously minimizing methodological circularity and evaluating transparency practices among retrospectively registered reviews. Consequently, it remains unclear whether differences in reporting quality and methodological rigor are primarily associated with the timing of registration itself or with the extent to which retrospective registration is transparently reported.

To address these gaps, this study will compare prospectively and retrospectively registered systematic reviews using assessment instruments specifically designed to avoid circularity. In addition, among retrospectively registered reviews, we will evaluate the transparency of retrospective registration practices and examine whether greater

transparency is associated with higher reporting quality and methodological rigor. By empirically testing this recently proposed transparency-oriented framework, this study aims to provide evidence to inform the interpretation of retrospectively registered protocols in evidence synthesis.

METHODS

Search strategy A comprehensive dataset will be constructed from systematic reviews registered in the INPLASY registry and subsequently published in peer-reviewed journals. The analytical sample will be restricted to systematic reviews with conventional pairwise meta-analysis evaluating healthcare interventions and exclusively including randomized controlled trials (RCTs). Network meta-analyses will not be included in the analytical sample.

INPLASY was selected as the data source because it permits both prospective and retrospective protocol registration and systematically records information on the stage of the review at the time of registration. In addition, the registry includes optional fields describing the reasons for retrospective registration, allowing the evaluation of transparency-related practices that are central to the objectives of this study.

The registry also maintains an active follow-up process to identify completed reviews and link registered protocols to their corresponding peer-reviewed publications, including cases in which authors do not subsequently update the registry. This process improves the completeness of protocol-publication linkage and facilitates the construction of a comprehensive analytical dataset.

These registry characteristics enable the identification of prospectively and retrospectively registered reviews using standardized registry information and provide the data required to evaluate transparency practices associated with retrospective registration.

Eligible studies will be identified through a structured process consisting of: (1) extraction of records from the INPLASY registry that are classified as completed and linked to a peer-reviewed publication; and (2) linkage of registered protocols to their corresponding publications using Digital Object Identifiers (DOIs) and registry identification numbers.

For the analytical sample, eligibility will be restricted to systematic reviews with conventional pairwise meta-analysis evaluating healthcare interventions that exclusively include randomized controlled trials (RCTs). Eligibility will be determined using information from the full-text

publication rather than title terminology alone. Therefore, absence of the terms “meta-analysis” or “meta-analyses” from the article title will not constitute a reason for exclusion when quantitative pooling is demonstrated in the full text.

Eligibility criteria Initially, all evidence syntheses registered in the INPLASY registry and subsequently published in peer-reviewed journals, with full-text availability, will be identified to characterize the overall study sample.

The analytical sample will be restricted to systematic reviews with conventional pairwise meta-analysis evaluating healthcare interventions that exclusively include randomized controlled trials (RCTs). Reviews employing network meta-analysis as their primary quantitative synthesis will be excluded to improve methodological comparability across the analytical sample, particularly regarding synthesis methods, effect estimation, and the reporting and methodological domains under evaluation.

This restriction is intended to enhance methodological comparability across studies and reduce heterogeneity arising from differences in review design, methodological approaches, and underlying evidence.

Protocol-only publications, narrative reviews, scoping reviews, umbrella reviews, diagnostic test accuracy reviews, qualitative evidence syntheses, and other forms of evidence synthesis that do not meet the eligibility criteria will be excluded.

Reviews combining randomized and non-randomized study designs will be excluded from the analytical sample, even when results for RCTs are reported separately, because eligibility requires the body of included evidence to consist exclusively of RCTs.

Reviews in which participant characteristics or prognostic/exposure variables are evaluated as potential effect modifiers will remain eligible when the underlying quantitative estimates represent randomized comparisons of healthcare interventions versus an eligible comparator.

Studies will not be excluded based on reporting quality or methodological rigor. Information that is not reported will be coded as “not reported” according to predefined operational definitions.

When eligibility cannot be established from the title or abstract, the full-text article will be assessed. Studies will only be excluded for insufficient information when eligibility cannot be determined after examination of the available full-text publication.

Data extraction Data extraction will be conducted using a structured and standardized data collection form developed specifically for this

meta-research study. Reviews that have not resulted in a full-text peer-reviewed publication will be excluded, as assessment of reporting quality, methodological rigor, and transparency requires access to the complete published manuscript.

Data will be primarily extracted from INPLASY registry records and supplemented with information from the corresponding peer-reviewed publications. Registry-derived variables will be obtained preferentially from the INPLASY record, whereas variables concerning reporting and methodological characteristics will be assessed from the full-text publication.

Before initiation of the main data extraction phase, all reviewers will undergo a structured calibration process. Reviewers will independently assess a common set of eligible systematic reviews using the complete extraction instrument and predefined operational definitions. Item-level agreement will be examined, discrepancies and ambiguous cases will be discussed, and operational guidance will be refined when necessary. Additional calibration rounds may be conducted for items showing lower agreement before reviewers proceed to the main analytical sample.

For the main extraction, each included review will initially be assessed by one trained human reviewer using the standardized extraction form and the predefined operational criteria. Reviewers will be instructed to base their judgments exclusively on information explicitly reported in the source documents and not to infer unreported methodological procedures.

To independently evaluate the reliability of the human extraction process, a randomly selected 20% sample of included reviews will undergo complete duplicate extraction by a second trained human reviewer. Sampling will be stratified according to prospective versus retrospective registration status to ensure representation of both exposure groups. The second reviewer will perform the extraction independently and without access to the primary reviewer’s classifications. Disagreements between the two human reviewers will subsequently be resolved through discussion or, when necessary, adjudication by an experienced investigator.

Agreement in the independently duplicated sample will be quantified at the item level using appropriate agreement statistics according to the measurement scale of each variable. Percentage agreement will be reported, together with chance-corrected agreement measures when applicable. Weighted agreement methods will be used for ordinal items with 0, 0.5, and 1 response categories.

For all included studies, the following variables will be extracted:

Registration characteristics

- 1.1 Registration type (prospective or retrospective)
- 1.2 Review stage at the time of submission
- 1.3 Number of protocol versions
- 1.4 Registration ID
- 1.5 Protocol status in the registry
- 1.6 Registration date
- 1.7 Presence of a hyperlink to the full registration record

Publication characteristics

- 2.1 DOI
- 2.2 Title of the manuscript
- 2.3 Journal name
- 2.4 Open access status
- 2.5 Year of publication
- 2.6 Time from protocol registration to publication, in days

Journal and bibliometric characteristics

- 3.1 Journal Citation Reports year
- 3.2 Journal Impact Factor
- 3.3 Journal category
- 3.4 Publisher

Study characteristics

- 4.1 Type of evidence synthesis
- 4.2 Country of the corresponding author
- 4.3 Source of funding

Protocol-related characteristics

- 5.1 Presence of a published peer-reviewed protocol

5.2 If applicable, journal of protocol publication

For the analytical sample, additional item-level data required to calculate the Protocol-related Reporting Transparency Score (PRTS), the adapted methodological-rigor score, and, among retrospectively registered reviews, the Retrospective Registration Transparency Index (RRTI) will be extracted according to their predefined operational definitions.

In cases where discrepancies exist between registry records and published articles, registry data will be considered the primary source for registry-specific characteristics, whereas the publication will be used as the primary source for reporting and methodological assessments. Publication data may also be used to complement missing or unclear registry information where appropriate.

Missing information will not lead to study exclusion when eligibility has already been established. Variables that cannot be determined from the relevant source documents will be coded as “not reported” according to predefined operational definitions.

Derived variables, such as time intervals between registration and publication, will be calculated from the extracted dates. All variables will be coded

according to predefined operational definitions to ensure consistency across reviewers.

Study Outcomes The primary outcomes of this study are reporting quality and methodological rigor of systematic reviews with meta-analysis.

Reporting quality will be defined as the completeness and transparency with which essential methodological aspects of a systematic review are reported. It will be assessed using the 12-item PRTS. Item-level scores will be summed to generate a continuous overall score ranging from 0 to 12, with higher values indicating greater reporting transparency.

Methodological rigor will be defined as the extent to which fundamental methodological standards for the conduct of systematic reviews are fulfilled. It will be assessed using the four-domain adapted AMSTAR-2 framework comprising comprehensive literature search, duplicate study selection, duplicate data extraction, and appropriate risk-of-bias assessment for RCTs. Domain scores will be summed to generate a continuous overall score ranging from 0 to 4, with higher values indicating greater methodological rigor.

The secondary outcomes concern transparency practices among retrospectively registered reviews. These will be assessed using the Retrospective Registration Transparency Index (RRTI), which evaluates three domains: (1) transparency of registration timing, (2) justification for delayed registration, and (3) transparency regarding methodological changes during review conduct.

Initially, the frequency of each transparency domain will be described. Subsequently, each domain and the overall RRTI score will be analyzed as explanatory variables to investigate their association with reporting quality and methodological rigor.

Strategy of data synthesis / Statistical analysis

Descriptive analyses will be conducted to summarize the characteristics of the included studies overall and according to protocol registration timing (prospective versus retrospective). Categorical variables will be presented as frequencies and percentages, whereas continuous variables will be summarized as means and standard deviations or medians and interquartile ranges, as appropriate. The distribution of continuous variables will be assessed using graphical methods and the Shapiro–Wilk test.

Primary analysis

The primary objective is to evaluate the association between protocol registration timing (prospective versus retrospective) and reporting quality and methodological rigor.

Initially, unadjusted comparisons between prospectively and retrospectively registered reviews will be performed using appropriate parametric or non-parametric statistical tests according to the distribution of the outcome variables. However, the primary inference will be based on multivariable regression models.

Reporting quality, measured using the PRIS, and methodological rigor, measured using the four-domain adapted AMSTAR-2 score, will be analyzed as continuous outcomes using multivariable linear regression models. Generalized linear models will be considered if assumptions for ordinary least-squares regression are not satisfied. Covariates will be selected a priori based on methodological relevance rather than statistical significance. All multivariable models will be adjusted for potential confounding factors, including publication year, journal impact factor (or an equivalent bibliometric indicator when unavailable), journal category, publisher, country of the corresponding author, source of funding, and the presence of a peer-reviewed protocol publication.

Given the potential non-independence of observations arising from multiple reviews conducted by the same research groups or published in the same journals, mixed-effects regression models will be fitted when supported by the data structure. Random intercepts for journal and corresponding author will be considered to account for clustering. As a sensitivity analysis, regression models with cluster-robust standard errors will also be evaluated.

Model assumptions, including linearity, homoscedasticity, and normality of residuals, will be examined using graphical diagnostics and formal statistical procedures where appropriate. Influential observations will be assessed using leverage statistics and Cook's distance. Robust standard errors or alternative modeling approaches will be considered when necessary.

Because reporting standards and protocol registration practices have evolved over time, publication year will be included in all multivariable models. Potential effect modification by publication year will be explored by incorporating interaction terms between registration timing and publication year.

Methodological rigor analyses will be conducted across the full analytical sample rather than in a separate predefined subsample.

Secondary analyses: transparency practices in retrospectively registered reviews

Among retrospectively registered reviews, descriptive analyses will summarize the frequency and distribution of the three transparency domains evaluated by the Retrospective Registration

Transparency Index (RRTI): transparency of registration timing, justification for delayed registration, and transparency regarding methodological changes during review conduct.

Each transparency domain will first be evaluated individually as an explanatory variable in relation to reporting quality and methodological rigor using univariable and multivariable regression models.

Subsequently, the overall RRTI score (range 0–3, with 0.5-point increments) will be analyzed as a continuous explanatory variable to investigate whether increasing levels of transparency are associated with improved reporting quality and methodological rigor. These analyses will be considered exploratory and interpreted as hypothesis-generating.

Sensitivity analyses

Prespecified sensitivity analyses will be performed to evaluate the robustness of the findings. These analyses may include adjustment for the presence of a peer-reviewed protocol publication, exclusion of influential observations, alternative approaches for handling clustered data, and restriction of the analytical sample according to publication period when appropriate.

Handling of missing data

Missing data will not result in study exclusion. Primary analyses will be based on complete-case analysis. The extent and pattern of missing data will be summarized for all variables. If missing data exceed a prespecified threshold (e.g., 5%) for variables included in multivariable analyses, sensitivity analyses will be conducted to evaluate the robustness of the findings under alternative assumptions regarding missingness.

Statistical significance

All statistical tests will be two-sided, and a P value <0.05 will be considered statistically significant. Effect estimates will be reported with corresponding 95% confidence intervals. Standardized regression coefficients will also be presented, where appropriate, to facilitate comparison of effect sizes across models.

All statistical analyses will be performed using R (R Foundation for Statistical Computing, Vienna, Austria), using the most recent version available at the time of analysis. The R version and all packages used will be reported in the final manuscript to ensure full reproducibility.

Results will be interpreted primarily based on the magnitude and precision of effect estimates, considering confidence intervals and clinical or methodological relevance, rather than statistical significance alone.

Country(ies) involved Brazil and United States.

Keywords Systematic review; protocol registration; prospective registration; retrospective registration; meta-research; reporting quality; methodological rigor; research transparency.

Other relevant information This amendment was introduced before the main data extraction and statistical analyses and was not informed by study outcomes. The eligibility criteria were clarified to restrict the analytical sample to conventional pairwise meta-analyses of healthcare interventions exclusively including RCTs, with network meta-analyses excluded to improve methodological comparability. It was also clarified that eligibility will be determined from the full-text publication rather than title terminology alone.

The reporting assessment was harmonized into a 12-item Protocol-related Reporting Transparency Score (PRTS), the methodological-rigor assessment into four predefined domains, and the three-domain RRTI scoring was clarified. A formal reviewer-calibration phase was also incorporated before the main extraction. Each study will be assessed by one trained reviewer, while a randomly selected 20% of the sample, stratified by prospective versus retrospective registration status, will undergo independent duplicate extraction by a second human reviewer. These updates represent methodological clarifications and quality-control refinements introduced to improve consistency, reproducibility, and reliability of the study.

Dissemination plans The findings of this study will be submitted for publication in a peer-reviewed, high-impact journal and presented at national and international scientific conferences. Reporting will follow relevant methodological reporting guidelines to ensure transparency and reproducibility. Where appropriate, supplementary materials, including data extraction forms and analytical code, will be made publicly available to facilitate reproducibility and future meta-research.

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