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ORIGINAL RESEARCH

Clinical study report data did not substantially alter point estimates but improved precision in a nephrology systematic review

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Abstract

Objectives: To investigate the effect of adding clinical study report (CSR) data to publication and author data on data completeness and meta-analytical results.

Study Design and Setting: Case report of a systematic review with meta-analysis of randomized controlled trials on icodextrin compared to glucose solutions in peritoneal dialysis including 19 clinical trials. We considered the outcomes mortality, peritoneal dialysis technique failure, quality of life, net peritoneal ultrafiltration (at 3−6 months, and 1−2 years), serious adverse events (SAE), peritonitis, and uncontrolled fluid overload. The results for these outcomes were reanalyzed using (a) publication and author data only, then compared with (b) publication and author data with added CSR data. At outcome level, we compared the number of included trials, pooled point estimates (ie, regarding effect direction), and 95% confidence intervals (CIs; ie, regarding overlap and width) between the two groups of trials (a and b). We illustrated the results of our meta-analyses in forest plots and narratively summarized them.

Results: Except for two of the eight assessed outcomes (quality of life and net peritoneal ultrafiltration [1−2 years]), more complete data was available when adding CSRs to publication and author data. Point estimates were not statistically significantly different for publication and author data, compared to publication, author, and CSR data, for any outcome. For peritonitis, point estimates were on opposite sides of the line of no effect but remained statistically nonsignificant when adding CSR data. For SAE and net peritoneal ultrafiltration (3−6 months), the width of the 95% CI was narrower when adding CSR data and for net peritoneal ultrafiltration (3−6 months), in addition, the point estimate statistically significantly favored icodextrin when adding CSR data.

Conclusion: The fraction of publications reporting results varied substantially by outcome, with SAE most under-reported in publications. While the integration of CSR data did not substantially alter meta-analytical results, it enhanced data completeness and precision in effect estimates. Our findings underscore the importance of accessing CSR data to optimize evidence syntheses and inform clinical decision-making.

Keywords: Clinical study report; Meta-analysis; Outcome reporting bias; Unpublished data; Literature search; Nephrology

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Plain Language Summary

When researchers want to understand how well a treatment works, they often combine results from several clinical studies in a process called a meta-analysis. Usually, these analyses rely on data published in scientific journals. However, published articles don't always include all the important results. Additional information can sometimes be found in clinical study reports (CSRs), which are detailed documents submitted by pharmaceutical companies to regulatory agencies. In this study, we looked at how including CSR data might affect the results of a meta-analysis. We focused on 19 clinical trials that compared two types of interventions used in peritoneal dialysis for patients with kidney disease: solutions based on icodextrin, a sugar polymer, or on a sugar called glucose. We analyzed several health outcomes such as survival, quality of life, peritoneal ultrafiltration, and complications like infections or kidney function, and serious side effects. First, we analyzed the results using only published articles and information provided by study authors. Then we repeated the analysis, this time adding data from CSRs where available. We compared the number of studies included, the size and direction of treatment effects, and the precision of the results. We found that adding CSRs often provided more complete information, especially for outcomes like serious side effects that were not always reported in journal articles. The overall direction of the results—whether icodextrin was better, worse, or the same—did not change much when CSR data was added. However, the results became more precise in two cases (serious side effects and peritoneal ultrafiltration). In one case, adding CSR data made the benefit of icodextrin statistically significant (peritoneal ultrafiltration). In summary, although adding CSR data did not substantially change the main conclusions, it improved the completeness and accuracy of the results. This shows that using CSRs in research summaries can provide a more reliable basis for making clinical decisions.

1. Introduction

Clinical trials are important for evaluating the efficacy and safety of interventions. Systematic reviews play a pivotal role in synthesizing available evidence from primary studies to inform clinical practice and health policy decisions [1]. However, relying solely on published data may lead to incomplete or biased assessments due to publication bias and selective reporting [2−4]. Previous research across various medical fields has consistently highlighted the presence of publication bias and selective reporting in clinical trial publications [5,6]. Meta-research has shown that published trials tend to report favorable outcomes more frequently than negative outcomes, a phenomenon that leads to an overestimation of treatment effects [7].

In recent years, there has been growing recognition of the importance of supplementing data from clinical trial publications for pharmaceutical interventions with information from clinical study reports (CSRs), which can offer a thorough description of trial planning, conduct, analyses, and results [8,9]. While resembling journal articles in content (eg, rationale, objectives, methods, results, discussion/conclusion), CSRs surpass them in detail, featuring extensive tables, figures, and unrestricted datasets due to regulatory reporting requirements and the absence of page limits [9]. These reports can span dozens to tens of thousands of pages for a single trial [10]. CSRs are submitted to regulatory bodies to secure pharmaceutical marketing authorization and approval. They typically include key study documents as appendices, such as the study protocol, statistical analysis plan, any amendments, blank case report forms, patient information sheets, blank informed consent forms, and individual patient listings [11−13].

Research examining the quality of reporting in published trials compared to CSR data has revealed that CSRs often provide more detailed descriptions of outcome measurement and results [14,15]. This suggests that outcome reporting bias may be mitigated by the use of CSRs in evidence syntheses [16]. A few examples have demonstrated the potential benefits of incorporating CSR data into systematic reviews. These benefits include timeliness of data for health care decision-making, increased completeness of data, inclusion of unpublished trials, and more accurate estimation of treatment effects [16,17]. For example, meta-research in diverse medical fields showed that adverse events and patient-relevant outcomes were not reported in sufficient detail or even not at all in public sources (ie, trial registries and journal publications) compared to CSRs [10,18−20]. A systematic review in the field of psychiatry has shown that when considering CSR data, the conclusions of the review changed, not in favor of the antidepressant drug, and that when using published data only, the benefit of the drug was overestimated and harm underestimated [21]. An assessment of the impact of unreported and unpublished data obtained from CSRs on the effect estimation of quality of life in cancer showed that with more complete data from CSRs, effect estimation may change from a clinically important difference to a nonclinically important difference [10]. In Supplementary File 1, we listed relevant evidence identified via preparatory searches for this project on PubMed and Google Scholar.

To add work in this field of research, we conducted a case study based on a previously completed systematic review comparing icodextrin vs glucose solutions in people with kidney failure undergoing peritoneal dialysis [22,23]. Peritoneal dialysis is a widely utilized renal replacement therapy

What is new?

Key findings

- There was no statistically significant difference for point estimates obtained from meta-analysis of publication and author data, compared to publication, author, and CSR data, for any of the assessed outcomes in peritoneal dialysis management.
- Only for one outcome, peritonitis, the direction of effect was changed when adding CSR data.
- While the integration of CSR data did not substantially alter meta-analytical results, it enhanced data completeness and precision of effect estimates, for example in the analysis of serious adverse events.

What this adds to what is known?

- While the overall effect estimates remained largely consistent, adding CSR data may influence the interpretation of certain outcomes.

What is the implication and what should change now?

- Trial sponsors should make full CSRs publicly available without restriction; and researchers and reviewers should actively search for CSRs and consider them in evidence synthesis and meta-analysis; their structured nature facilitates data retrieval.

for patients with end-stage renal disease [24]. Among osmotic agents used in peritoneal dialysis, icodextrin has emerged as a promising alternative to glucose for improving ultrafiltration and fluid management in these patients [22]. In our systematic review, we considered publication, author, and CSR data. Here, we aimed to investigate the effect of adding CSR data to publication and author data on data completeness and meta-analytical results. By systematically comparing the outcomes derived from publication and author data alone vs. those augmented by CSR data, we sought to elucidate the potential methodological implications for evidence synthesis and research practice.

2. Methods

We performed a case study based on our systematic review with meta-analysis [22,23].

2.1. Case presentation

The methods used for the previously completed icodextrin systematic review were prespecified [23] and the results are described in full detail elsewhere [22]. In short, we included randomized controlled trials on icodextrin vs glucose solutions as osmotic agents for peritoneal dialysis in people with kidney failure on mortality, peritoneal dialysis technique failure (ie, conversion to another treatment), quality of life, and net peritoneal ultrafiltration (primary outcomes). Secondary outcomes related to safety (serious adverse events (SAE) and peritonitis) and kidney function (uncontrolled fluid overload). We searched MEDLINE, EMBASE, CENTRAL, Ichushi Web, 10 Chinese databases, clinical trial registries, conference proceedings, and citation lists from inception to November 2018 and contacted principal investigators and other experts for additional references. CSRs were requested from trial sponsors Baxter Healthcare and Terumo. Two independent reviewers selected the eligible trials and extracted data using a prespecified extraction instrument. Authors of included studies were contacted for further data when published data was incomplete and if no CSR was available. Two independent reviewers assessed the risk of bias of included trials at the outcome level using the Cochrane risk-of-bias tool for randomized trials (version from 2011 [25]) and the certainty of evidence using the Grading of Recommendations Assessment, Development and Evaluation (GRADE). Nineteen trials that randomized 1693 participants were included in the meta-analysis. Study characteristics of the included trials are shown in Goossen et al [22].

2.2. Design of the case study and data analysis

We prespecified the methods for this case study [26]. From the previously completed icodextrin systematic review, we considered all outcomes from the summary of findings table for analysis: mortality, peritoneal dialysis technique failure, quality of life, net peritoneal ultrafiltration (at 3−6 months and 1−2 years), SAE, peritonitis, and uncontrolled fluid overload [22] (note that the outcome net peritoneal ultrafiltration at $\leq$6 weeks was also part of the summary of findings table in [22], but this outcome was not considered here because data was only available from CSR and could therefore not be compared to publication and author data). The results related to these outcomes were reanalyzed using (a) publication data and data from author request (hereafter also referred to as publication and author data) compared with (b) publication and author data with added CSR data (hereafter also referred to as publication, author, and CSR data). At outcome level, we compared the number of included trials, pooled point estimates (ie, regarding effect direction), and 95% confidence intervals (CIs; ie, regarding overlap and width) between the two comparison groups (a and b) [27]. Data were meta-analyzed using RevMan, version 5.4 [28]. Heterogeneity between trials was quantified using I^2 statistics [29]. Fixed-effect models were used for outcomes in the absence of heterogeneity ($I^2 = 0$), with sensitivity analyses using random-effects models. Otherwise, random effects models were used. Dichotomous

outcomes were analyzed using Mantel-Haenszel risk ratios (RRs) or, when event rates were low, Peto odds ratios (ORs). Continuous outcomes were pooled using the inverse-variance standardized mean difference (SMD). Point estimates were reported along with 95% CIs. A χ^2 test was used to test for significant differences in meta-analytical results. We illustrated the results of our analyses in forest plots and narratively summarized them.

3. Results

We considered 19 trials for our analysis. The data sources for the 19 trials were publication and author data only (9 trials [30−39]), publication, author, and CSR data (9 trials [40−60]), and CSR data only (1 trial [61,62]). One trial included in our previous SR was not used in the meta-analysis for any outcome; and was therefore not included in this case study.

Mortality was reported in 17 of the 19 trials (89%) from publication and author data (a) and in all 19 trials (100%) when CSR data were added (b). SAE were most underreported and only available for two trials (18%) from publication and author data (a) and for 11 trials (58%) when CSR data were added (b; Table 1).

Because point estimates were not estimable from the available data for all trials due to zero events, we finally used less trial data for the meta-analyses of mortality (10 trials for publication and author data vs 11 when adding CSR data), peritoneal dialysis technique failure (8 trials for publication and author data vs 12 when adding CSR data), and peritonitis (8 trials for publication and author data vs 14 when adding CSR data) (Supplementary File 2−9).

Point estimates were not statistically significantly different for publication and author data (a), compared to publication, author, and CSR data (b), for any outcome (Fig 1; Fig 2; Supplementary File 2−9). For peritonitis, point estimates were on opposite sides of the line of no effect but remained statistically nonsignificant (Mantel-Haenszel RR 0.91 [95% CI 0.75−1.10] for publication and author data [a] vs 1.07 [95% CI 0.88−1.31] when adding CSR data [b]). For SAE, the 95% CI was narrower when adding CSR data (Mantel-Haenszel RR 0.89 [95% CI 0.51−1.54] for publication and author data [a] vs 0.91 [95% CI 0.76−1.10] when adding CSRs [b]). For net peritoneal ultrafiltration (3−6 months), the 95% CI was narrower when adding CSR data and statistically significantly favored icodextrin (inverse variance SMD 0.70 [95% CI −0.35 to 1.74] for publication and author data [a] vs 0.82 [95% CI 0.17−1.47] when adding CSRs [b]).

4. Discussion

The results of our case study showed that the fraction of publications reporting results varied substantially by outcome, that SAE were most under-reported in publications, that the conclusions of the meta-analysis remained unchanged when adding unpublished CSR data. Contrary to our expectations based on previous research, the integration of CSR data did not yield statistically significant differences in point estimates for any outcome when compared to publication and author data alone. It is noteworthy that the direction of effect for peritonitis was altered with the inclusion of CSR data, though this was not statistically significant either with or without integrated CSR data. The results of two endpoints became more precise (SAE) or statistically significant (peritoneal ultrafiltration) when adding CSR data to publication and author data. This suggests that, while the overall effect estimates remained largely consistent, the additional information from CSR data might influence the interpretation of some outcomes. However, in our case analysis it is very unlikely that the slight differences would have an impact on practice recommendations (eg, in clinical guidelines).

Evidence on the impact of using CSR data into meta-analyses and comparisons between meta-analysis with and without CSR data is rare. An analysis of quality of life in cancer patients showed that when using more complete data from CSRs, pooled effect estimation may change from a clinically important difference to a nonclinically important difference [10]. For an assessment of a drug to treat depression, the inclusion of CSR data changed the conclusions of the review, not in favor of the drug compared with placebo and active comparators, and that when using published data only, the benefit of the drug was overestimated and harm underestimated [21]. In contrast to these studies, the conclusions of the meta-analysis in our case study remained unchanged when adding unpublished data. Even if the results did not differ statistically significantly, this does not diminish the potential of CSRs. In our case, adding CSR data changed the precision two out of the eight assessed outcomes and therefore had the potential to generate more precise and trustworthy meta-analytical results.

The reporting of outcome data did not clearly differ between publications and CSRs in either benefit or harms outcomes, however, the analysis of SAE has shown that this outcome is most under-reported in publications, and that adding CSR data can lead to more accurate results. This is consistent with other analyses that showed that SAE or harm endpoints were also reported less extensively or even not at all [14,18,19,63]. CSRs may therefore play an important role in the consideration of the full body of evidence, particularly regarding potential harms of drug assessments.

Meta-research and systematic reviews that assessed the utility of CSR data in evidence synthesis highlighted barriers such as access to CSR data and standardization of data extraction methods [63−65]. In a survey study, Hodkinson et al investigated the main barriers to the use of regulatory data such as CSRs, stratifying their respondents into three groups: respondents who had requested/used regulatory data, who had considered regulatory data, or who had not

Table 1. Assessed outcomes with number of trials and participants per comparison groups a (publication and author data) and b (publication, author, and clinical study report data)

Outcome	a: Publication and author data (*n* trials)	b: Publication, author, and CSR data (*n* trials)	a: Publication and author data (*n* patients)	b: Publication, author, and CSR data (*n* participants)
Mortality	17 (10[a])	19 (11[a])	1605	1688
Peritoneal dialysis technique failure	14 (8[a])	18 (12[a])	1079	1401
Quality of life	2	2	143	116[b]
Net peritoneal ultrafiltration (3–6 mo)	4	6	162	363
Net peritoneal ultrafiltration (1–2 y)	3	3	104	104
Serious adverse events	2	11	160	1303
Peritonitis	9 (8[a])	15 (14[a])	896	1348
Uncontrolled fluid overload	5	8	301	602

CSR, clinical study reports; *n*, number.

[a] Because point estimates were not estimable from the available data for all trials, we finally used less trial data for the meta-analyses of mortality (10 trials for publication and author data vs 11 when adding CSR data), peritoneal dialysis technique failure (8 trials for publication and author data vs 12 when adding CSR data), and peritonitis (8 trials for publication and author data vs 14 when adding CSR data).

[b] The total number participant data is lower when adding CSR data because for one study, the publication reported data at 12 weeks [60], the CSR at 52 wk [41]. The total number of participants at 52 wks was smaller due to withdrawals over the course of the study (follow-up).

considered regulatory data [15]. Actual or potential users of regulatory data (the first two groups) cited ''restricted and limited sharing of data'' and ''time constraints'' as the main barriers. In contrast, ''effort/resources required'' was cited as a barrier exclusively by the third group, who had not considered using regulatory data in their review. Our own experience confirms that the additional workload associated with working with CSRs is small because their structured nature facilitates data retrieval. For studies where CSRs were available, we found that they eliminated the need to extract publication data and reduced the amount of time spent resolving ambiguities.

We did not plan to systematically compare the GRADE certainty of evidence ratings with and without the addition of CSR data. However, we suspect that the addition of CSR data may have slightly affected the GRADE evidence profiles in our underlying systematic review [22] in the domains of risk of bias and imprecision due to more comprehensive study information, less selective reporting and more precise CIs, with a trend toward more certainty and a higher level of evidence. Further research is needed to assess the impact of adding CSR data to publication data on GRADE certainty ratings, but this should be prospectively planned and rigorously embedded in the review process.

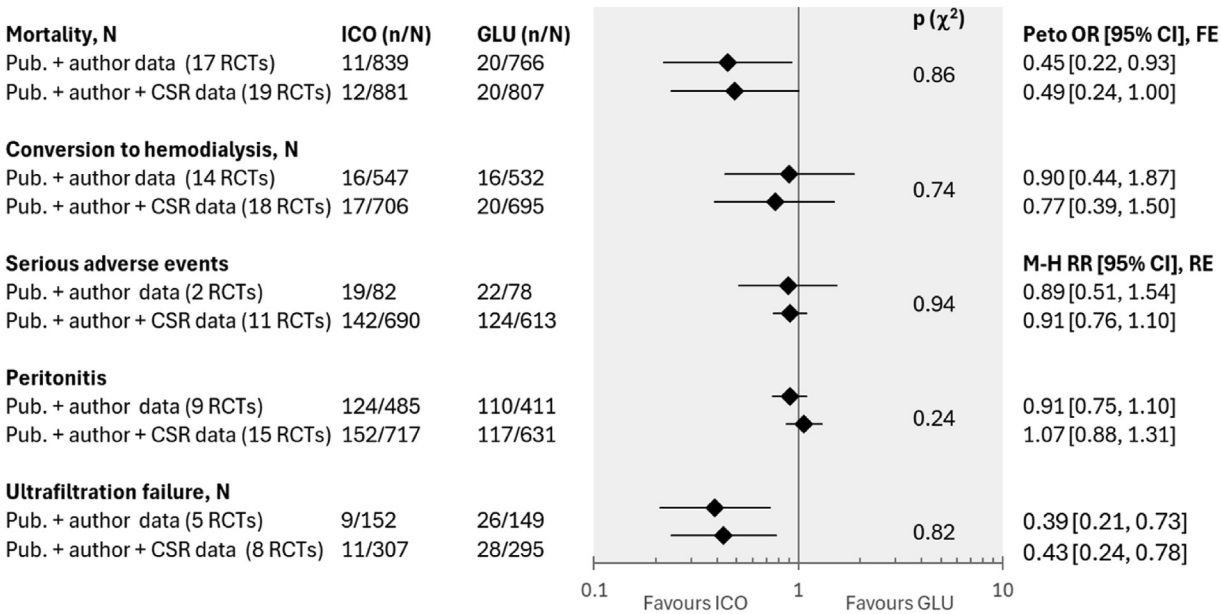

Figure 1. Comparison of pooled point estimates of binary results for publication and author data vs publication, author, and CSR data. CI, confidence interval; CSR, clinical study report; FE, fixed effect; GLU, glucose; ICO, icodextrin; M-H RR, Mantel-Haenszel risk ratio; *n*, number of events; N, number of participants; OR, odds ratio; *P*, *P* value; Pub, publication; RCT, randomized controlled trial; RE, random effect.

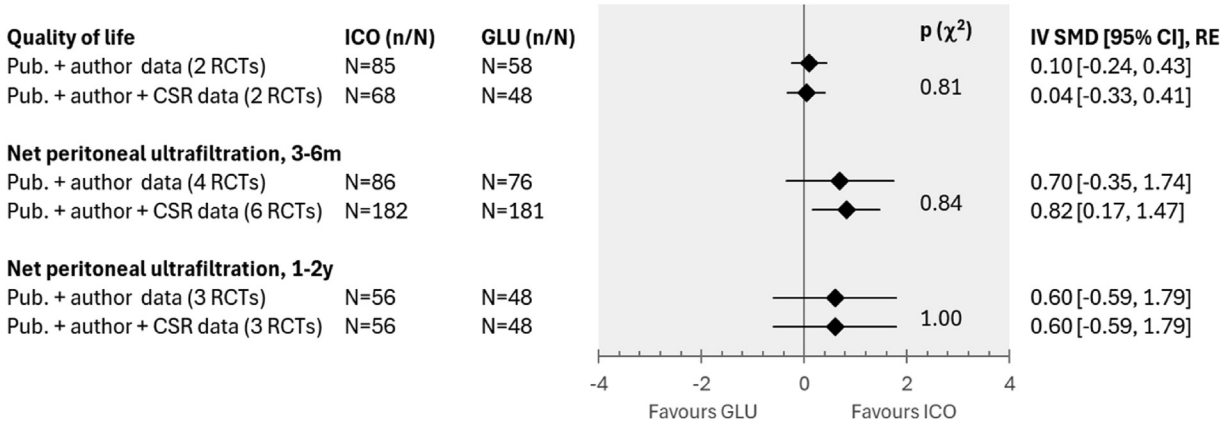

Figure 2. Comparison of pooled point estimates of metric results for publication and author data vs publication, author, and CSR data. CI, confidence interval; CSR, clinical study report; GLU, glucose; ICO, icodextrin; IV, inverse variance; m, month; N, number of participants; *P*, *P* value; Pub, publication; RCT, randomized controlled trial; RE, random effect; SMD, standardized mean difference; y, year.

Addressing the challenge of timely access to CSRs is crucial for ensuring the validity and reliability of meta-analytical findings. Although the CSRs have been published by the European Medicines Agency (EMA) since 2016 [66], a recent study showed that there are significant delays in the provision of such data [65] and that access is hampered by cumbersome registration or separate requests [64,66]. Hence, the availability and accessibility of CSRs still seems to be limited despite efforts by the EMA, partly because some restrictions to public access are still in place. Limited search and retrieval options in the databases of approval document may add another challenge for the use of CSRs in evidence synthesis [13,67]. At this point, we can reiterate the call for the ''establishment of a worldwide, public, central, and digitized clinical study portal containing all CSRs'' [68] to promote resource-efficient production of unbiased evidence syntheses. Examples exist from Vivli, an independent and nonprofit organization that has developed a global data-sharing and analytics platform with a focus on individual patient data, or ClinicalStudyDataRequest.com, a data sharing consortium of clinical study sponsors [69–71]. We believe that trial sponsors have an obligation to make full CSRs publicly available without restriction or delay. In return, we believe that researchers and reviewers ought to actively search for CSRs and include them in evidence syntheses and meta-analyses, as this is time well spent to improve the quality of systematic reviews. However, and to inform time- and cost-benefit planning about the integration of CSR data in the future, systematic review teams may consider tracking the time and efforts made to search and include CSR into evidence syntheses.

Our analysis revealed a disparity between data reported in trial publications and CSRs. The outcome ''peritonitis'' may be defined as ''number of patients with peritonitis'' and ''number of peritonitis events''. While CSRs generally reported both types of data, the outcome definition was not always clear in the publications and may lead to misinterpretation of the published data. The consideration and inclusion of CSRs therefore also requires a careful review of the quality, accuracy and consistency between and within the various clinical trial sources. So far, reviewers have been left on their own to deal with such discrepancies between trial publications and CSRs, as already noted by others [19]. It is therefore necessary to develop methodological guidelines for the correct and efficient handling of CSRs, for example, also for dealing with differences in the results data of clinical trials.

4.1. Limitations

Our study had the following limitations. Our analysis was based on a limited number of trials for a single intervention, which may restrict the generalizability of our findings. Additionally, the inclusion of CSR data may introduce biases inherent to industry-sponsored trials, warranting careful consideration in data interpretation. Future research should aim to replicate our findings in larger and more diverse samples (ie, other populations, interventions, and outcomes). We did not follow a reporting guideline as we were unable to identify one.

5. Conclusion

Our case study provides valuable insights into the effect of adding CSR data to publication data in systematic reviews of icodextrin trials in peritoneal dialysis. The fraction of publications reporting results varied substantially by outcome with SAE most under-reported in publications. While the integration of CSR data did not substantially alter meta-analytical results, it enhanced data completeness and precision in effect estimates, for example, evident in the analysis of SAE. These findings underscore the importance

of accessing CSR data to optimize evidence syntheses (ie, more comprehensive understanding of trial outcomes and ensure data completeness) and inform clinical decision-making in peritoneal dialysis management. As access to CSRs has become easier in some cases in recent years, reviewers may consider including CSR data in meta-analysis of drug trials. Future research should systematically analyze to what extent unpublished data influence outcome assessment in meta-analyses, for example by conducting a scoping review or systematic review on the topic, including case studies such as ours.

Declaration of generative AI and AI-assisted technologies in the writing process

We used the free version of ChatGPT on 16 April 2025 to draft the plain language summary that we manually refined. We prompted ChatGPT using our scientific abstract.

CRediT authorship contribution statement

Julian Hirt: Investigation, Visualization, Methodology, Writing − original draft, Software, Formal analysis, Writing − review & editing, Validation. **Dawid Pieper:** Supervision, Writing − review & editing, Investigation, Conceptualization, Validation, Project administration, Formal analysis, Resources, Methodology. **Monika Becker:** Writing − review & editing, Methodology, Validation. **Jessica Breuing:** Methodology, Writing − review & editing, Validation. **Mark R. Marshall:** Methodology, Validation, Writing − review & editing. **Käthe Goossen:** Software, Data curation, Writing − original draft, Resources, Formal analysis, Writing − review & editing, Validation, Project administration, Investigation, Visualization, Supervision, Methodology.

Declaration of competing interest

K.G., M.B., J.B., M.R.M., and D.P. received funding from Baxter International for the conduct of a systematic review comparing icodextrin vs glucose in peritoneal dialysis. At that time, MRM was an employee of Baxter International. D.P. is an associate editor with the Journal of Clinical Epidemiology but had no role in the editorial process. There are no competing interests for any other author.

Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.jclinepi.2025.111890.

Data availability

All data that we generated or analyzed in this study is provided in this publication.

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