

## Systematic Review of The Assessment of Publication Bias in Early Casgevy Intervention in Randomized Controlled Trials

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**ABSTRACT** The increased use of meta-analysis in systematic reviews of healthcare interventions has highlighted several types of bias that can arise during the completion of a randomized controlled trial. Study publication bias has been recognized as a potential threat to the validity of meta-analysis and can make the readily available evidence unreliable for decision making. Until recently, outcome reporting bias has received less attention. We review and summarize the evidence from a series of cohort studies that have assessed study publication bias and outcome reporting bias in randomized controlled trials. Nineteen studies were eligible all the way through from protocol approval to information regarding publication of outcomes. Eight of the studies investigated study publication bias and ten studies have found that statistically significant outcomes had a higher risk of being fully reported compared to non-significant outcomes (range of risk ratios: 1.9 to 3.4). In comparing trial publications to protocols, we found that 40–65% of studies had at least one primary outcome that was changed, introduced, or omitted. We decided not to undertake meta-analysis due to the differences between studies. Recent work provides direct empirical evidence for the existence of study publication bias and outcome reporting bias. There is strong evidence of an association between significant results and publication; studies that report positive or significant results are more likely to be published and outcomes that are statistically significant have higher risk of being fully reported. Publications have been found to be inconsistent with their protocols. Researchers need to be aware of the problems of both types of bias and efforts should be concentrated on improving the reporting of trials.

**KEYWORDS:** Casgevy Intervention; RCTs; Potential Bias; Begg's and Egger's tests

### I. INTRODUCTION

Study publication bias arises when studies are published or not depending on their results, it has received much attention (Rothstein et al., 2005). Empirical research consistently suggests that published work is more likely to be positive or statistically significant ( $P, 0.05$ ) than unpublished research (Dickersin et al., 1993). Study publication bias will lead to overestimation of treatment effects; it has been recognized as a threat to the validity of meta-analysis and can make the readily available evidence unreliable for decision making. There is additional evidence that research without statistically significant results takes longer to achieve publication than research with significant results, further biasing evidence over time (Scherer et al., 2007). In meta-analysis, publication bias is a particularly thorny issue because meta-analysis has been put forward as providing a more accurate appraisal of a research than the traditional narrative review. If the sample of studies retrieved for review is biased, then the validity of the results of a meta-

analysis review, no matter how systematic and thorough it might be is threatened. Within-study selective reporting bias relates to studies that have been published. It has been defined as the selection on the basis of the results of a subset of the original variables recorded for inclusion in a publication (Hutton et al., 2000). Researchers have considered selective outcome reporting to be a major problem, and deserving of substantially more attention than it currently receives (Tannock et al., 1996). Recent work (Von Elm et al., 2008) has provided direct empirical evidence for the existence of outcome reporting bias. Studies have found that statistically significant results had a higher risk of being fully reported compared to non-significant results for both efficacy and harm outcomes. Studies comparing trial publications to protocols are accumulating evidence on the proportion of studies in which at least one primary outcome was changed, introduced, or omitted. The aim of this paper was to review and summarize the evidence from empirical cohort studies that have assessed study publication bias and/or outcome reporting bias in RCTs approved by a inception cohorts of RCTs. The percentage of the studies lost in the file drawer according to Jeffrey and Scargle (2000) can result in a significant bias. Publication bias has much effect on meta-analysis as studies may not be truly representative of all valid studies undertaken and hence may distort the results of the meta-analysis and systematic review of large number of studies.

## **II. METHODOLOGY**

### **A. Study inclusion criteria and exclusion Criteria**

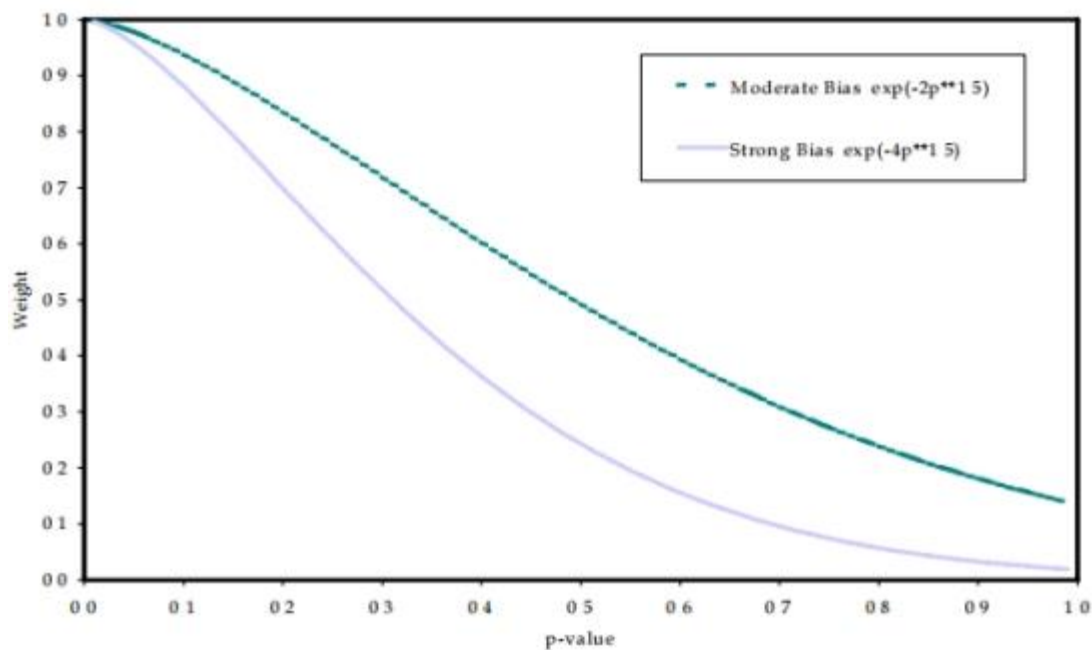
The methodology developed from the preferred reporting items for systematic reviews and meta-analysis statement (Liberati et al., 2009). Eligible studies included full articles and abstracts of randomized controlled trials. We included research that assessed an inception cohort of RCTs for study publication bias and/or outcome reporting bias. We focused on inception cohorts with study protocols being registered before start of the study as this type of prospective design were deemed more reliable. We excluded cohorts based on prevalence archives, in which a protocol is registered after a study is launched or completed, since such cohorts can already be affected by publication and selection bias. Both cohorts containing exclusively RCTs or containing a mix of RCTs and non-RCTs were eligible. For those studies where it was not possible to identify the study type (i.e. whether any included studies were RCTs), we attempted to contact the authors to try to resolve this. In cases where it could not be resolved, studies were excluded. Those studies containing exclusively non RCTs were excluded. The assessment of RCTs in the included studies had to involve comparison of the protocol against all publications (for outcome reporting bias) or information from trialists (for study publication bias).

### **B. Search strategy**

The sample size was made up of 19 validity studies. No masking was used during the screening of abstracts. PUBMED, SCOPUS and MEDLINE (2016 to 2024). SCOPUS is a much larger database than EMBASE, it offers more coverage of scientific, technical, medical and social science literature than any other database. Over 90% of the sources indexed by EMBASE are also indexed by SCOPUS plus many other indexed sources as well. Additional steps were taken to complement electronic database searches: First, the references given in the empirical evidence section of the HTA report of (Song et al 2000) were checked for relevance. Second, the lead reviewer of the protocol on the Cochrane library entitled 'Publication bias in clinical trials' (Olsen et al., 2001).

### C. Selection of Primary Studies: Magnitude of Publication Bias

The magnitude of the publication bias had three levels: no bias, moderate bias, and strong bias. The publication bias in the meta-analyses was manipulated by generating a weight function to establish the probability of a simulated study being included in the meta-analysis, with the probability of inclusion being inversely related to the  $p$ -value obtained in the simulated study (Begg & Mazumdar, 1994). That is, samples that yield statistically significant results are more likely to be published than those that do not yield statistically significant results (Sutton et al., 2000). The weight functions are illustrated in the diagram.



**Figure 1.** Weight functions to establish probability of inclusion in a meta-analysis as a function of the  $p$ -value.

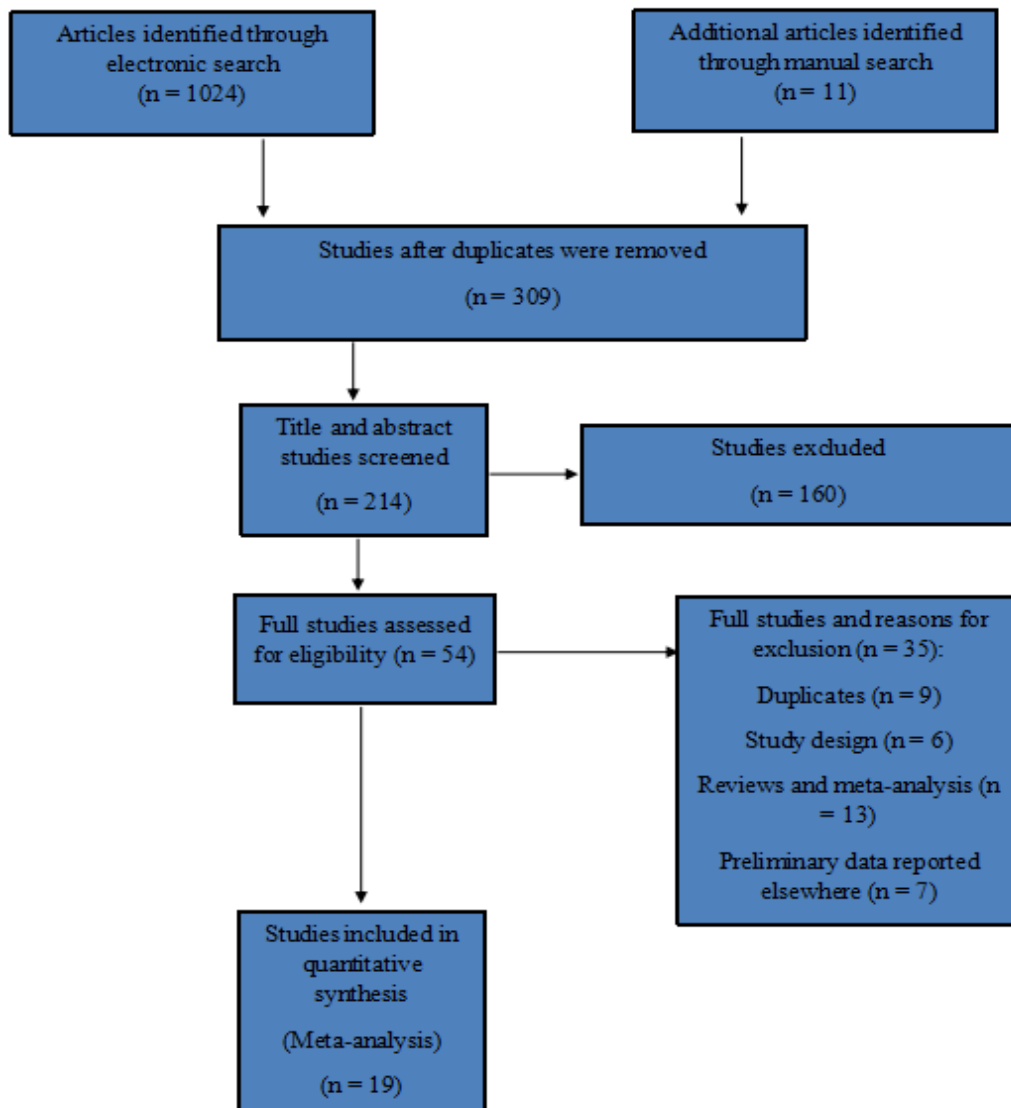
In a similar study to the one being proposed, Rendina-Gobioff and Kromrey (2004) implemented the same method for selection of studies to be included in meta-analyses. The average proportion of studies selected when the imposed publication bias was moderate was .66 (min=.49 and max=.97). When the imposed publication bias was strong the average proportion reported was .54 (min=.31 and max=.95). The following primary study data were the product of stage 1: total sample sizes, effect sizes, and  $p$ -values.

### D. Publication Bias Tests Applied

The next step in stage 2 of the analysis was the application of the statistical methods to detect publication bias. In each simulated meta-analysis, publication bias was assessed using the Begg Rank Correlation method (using both the estimated variance and the sample size), the Egger Regression method, the Funnel Plot Regression method suggested by Macaskill, Walter and Irwig (2001) and the Trim and Fill method suggested by Duval and Tweedie (2000a, 2000b). For the Egger Regression, OLS estimation was employed because preliminary analyses suggested that WLS estimates were substantially biased (Rendina-Gobioff & Kromrey, 2004).

### E. PRISMA Diagram

This review provides a descriptive summary of the included empirical studies. We refrained from statistically combining results from the different cohorts due to the differences in their design.

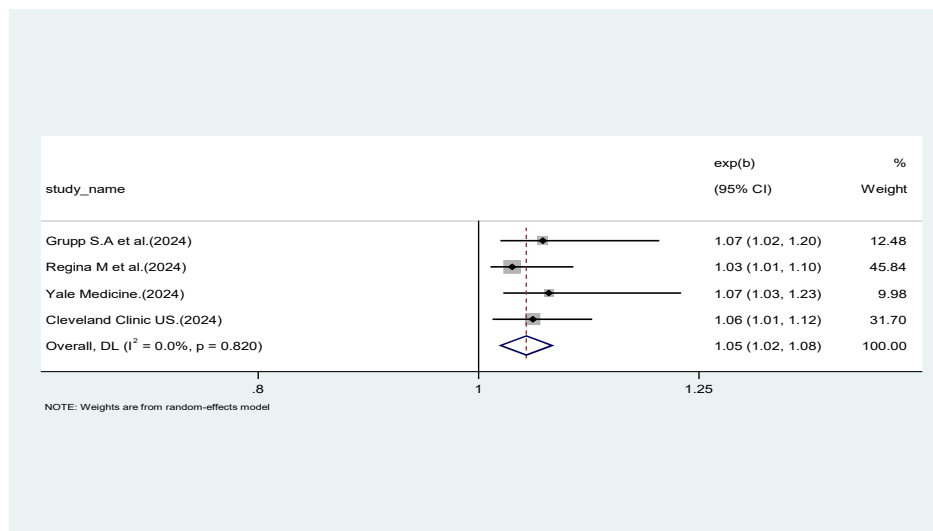


**Figure 2:** Flow diagram of included and excluded studies.

### III. RESULTS AND DISCUSSION

#### A. Results of Meta-analysis on the summary effect on the Casgevy intervention in sickle cell patients.

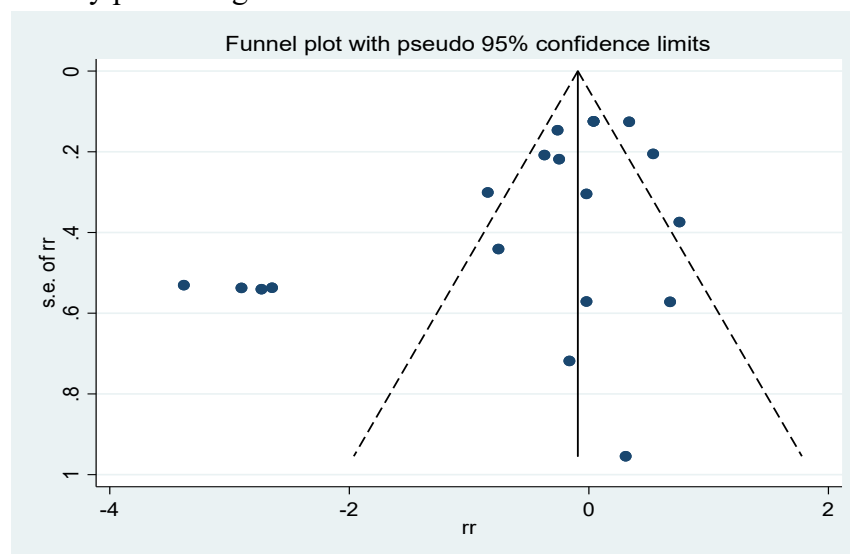
Figure 3 is an illustration of the literature search in electronic databases, Pubmed, Science Direct, Medline, Rechargegate, and relevant medical journals to obtain the nineteen (19) studies that we used for the meta-analysis, in which four centered on casgevy intervention to ascertain the effectiveness compared to previous interventions. This result shows randomized controlled trials of interventions in the treatment of sickle cell confirmed in the random effects model illustrated in Figure 4.1 with a summary result of 1.05 with a 95% confidence interval of 0.02 – 1.08.



**Figure 3:** Showing Meta-Analysis Results

### B. Result of Funnel Plot in the Early Assessment of the Casgevy Intervention.

Egger's test and funnel plots were used to assess the existence of publication bias. Egger's test ( $p = 0.04$ ) supported the funnel plot's (Figure 4) suggestion of some asymmetry, suggesting possible bias in study publishing.



**Figure 4:** Flow: Funnel Plot

Each included study is represented as a dot. The y-axis represents a measure of study precision, with standard error being commonly used. Larger studies with greater precision are displayed at the top and studies with lower precision at the bottom. Other measures such as the reciprocal of the standard error, the reciprocal of the sample size, or variance of the estimated effect can also be used as the y-axis. The x-axis displays the study estimated effect size for an outcome. The scale for the x-axis can include risk ratios which should be plotted on a logarithmic scale, or continuous measures such as mean difference or standardized mean difference. In the absence of both bias and heterogeneity, 95% of studies would be expected to lie within the diagonal dotted '95% Confidence Interval' lines.

A funnel plot, plotting the unadjusted log rr vs. its standard error for each study, is presented. This figure demonstrates an asymmetrical shape, with most studies having relatively low

standard errors (i.e. a narrow spread on the vertical axis), with a few exceptions, and relatively wide range (on the horizontal axis) of effect sizes among those with low standard errors. Funnel plots, and tests for funnel plot asymmetry, have been widely used to examine bias in the results of meta-analyses. A funnel plot is a simple scatter plot of the intervention effect estimates from individual studies plotted on the horizontal axis, against the standard error of the estimated effect on the vertical axis (Fernández-San-Martín et al., 2014). A sufficient number of studies ( $n > 10$ ) were identified to allow use of formal statistical tests for detecting funnel plot asymmetry (Fernández-San-Martín et al., 2014).

### C. Discussion of Findings

On the use of funnel plot in the early assessment of the casgevy intervention, this section describes using funnel plot in intervention assessment, with the outcome of the funnel plot via visual inspection, egger's test and the sensitivity analysis, in which all these three indicators show a positive results.

**Visual Inspection:** The plot shows a noticeable asymmetry, with several small studies on the right side of the plot indicating positive results and few studies on the left side indicating negative results.

**Sensitivity Analysis:** we conduct a sensitivity analysis to assess the robustness of the results. Leave-one-out analysis, the results remain relatively stable. Statistical test: we conduct statistical tests to qualify the asymmetry, the egger's test with  $p\text{-value} = 0.04$ , indicating significant asymmetry. Our assessment suggests that publication bias may be present, but the adjusted meta-analysis results still indicate a statistically significant positive effect of the therapy. However, we must interpret the results with caution, considering the potential impact of publication bias and other limitations. By following these steps, we can assess the impact of potential biases and provide a more nuanced understanding of the meta-analysis results. In the absence of publication bias, the funnel plot should resemble a symmetrical funnel (Fernández-San-Martín et al., 2014). The results show a correlation between interventions and effect estimate. These findings support earlier research that found comparable patterns.

### Possible reasons for asymmetry in a funnel plot and its impact on the overall estimate of the treatment effect.

#### (a). Heterogeneity

Heterogeneity will lead to funnel plot asymmetry if it induces a correlation between study sizes and intervention effects (Terrin et al., 2005). For example, substantial benefit may be seen only in high risk patients, and these may be preferentially included in early, small studies (Davey et al., 1994). Or the intervention may have been implemented less thoroughly in larger studies, resulting in smaller effect estimates compared with smaller studies (Stuck et., 1993).

#### (b). Reporting Bias

Reporting biases arise when the dissemination of research findings is influenced by the nature and direction of results. Statistically significant "positive" results are more likely to be published, published rapidly, published in English, published more than once, published in high impact journals, and cited by others (Song et al., 2010). Data that would lead to negative results may be filtered, manipulated, or presented in such a way that they become positive (Song et al., 2010).

#### (c). Chance

The role of chance is critical for interpretation of funnel plots because most meta-analyses of randomised trials in healthcare contain few studies (Sterne et al., 2000). Investigations of relations across studies in a meta-analysis are seriously prone to false positive findings when



there is a small number of studies and heterogeneity across studies, (Higgins et al., 2004) and this may affect funnel plot symmetry.

Decision makers rely on meta-analytic estimates to trade off benefits and harms. If such estimates were erroneous because of publication bias, “Evidence to Decision” frameworks (Alonso-Coello et al., 2016) can be misled by skewed balance of benefits and harms and the resulting recommendations may be erroneous or detrimental to patient care. Because the agreement among most publication bias tests is weak or moderate, researchers need to carefully interpret the result produced by a single test. As publication bias tests usually have low statistical power, (Macaskill et al., 2001) a single test that has a non-significant P value may lead to a false-negative conclusion. Instead of relying on the conclusion from a single test, researchers should assess publication bias using a variety of methods because different tests make different assumptions on the association between the treatment effects and precision measures. Lastly, considering the importance of publication bias and the challenges in statistically ascertaining its presence, systematic reviewers should resort to non-statistical approaches. These approaches include comparing published evidence to data available in clinical trials registries, records of drug or device approving agencies such as the Food and Drug Administration, and scientific conference proceedings.

#### IV. CONCLUSION

Very few empirical studies examined both study publication bias and outcome reporting bias in the same cohort. However, nineteen of the included empirical studies demonstrate consistent evidence of an association between positive or statistically significant results and publication. They suggest that studies reporting positive/ statistically significant results are more likely to be published and that statistically significant outcomes have higher risk of being fully reported.

In this review we focused on empirical studies that included RCTs since they provide the best evidence of the efficacy of medical interventions (Egger et al., 2001). RCTs are prone to study publication bias, but it has been shown that other types of studies are more prone to study publication bias (Easterbrook et al., 1991). The main limitation of this review was that for eight of the 19 included cohorts, information on RCTs could not be separated from information on other studies. Due to this barrier, and variability across empirical studies in the time lapse between when the protocol was approved and when the data were censored for analysis,

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