The Unfinished Story: Analyzing Publication Rates in Diabetic Retinopathy and Diabetic Macular Edema Trials Before the COVID-19 Era (1972–2018)

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ABSTRACT

Clinical trials are essential to evidence-based ophthalmology, yet publication bias and discontinued studies threaten data transparency. For diabetic retinopathy (DR) and diabetic macular edema (DME), the extent of unpublished or terminated trials remains unclear. This study evaluates publication trends in DR and DME trials conducted prior to the COVID-19 pandemic. We performed a retrospective cross-sectional analysis of interventional DR and DME trials registered in ClinicalTrials.gov from 1972–2018. Collected variables included funding source, intervention type, trial phase, publication and discontinuation status, and sample size. Chi-square tests assessed associations between trial characteristics and publication outcomes using Stata/SE 18.0. Among 333 included trials, 284 were non-terminated. Of these, 70.1% (n=199) were unpublished, representing 26,251 participants, while 29.9% (n=85) were published, accounting for 45,747 participants. Trials with fewer than 50 participants were over three times more likely to remain unpublished (P <0.0001). Industry-funded trials comprised 48.6% of the cohort but were not significantly more likely to publish than academic-funded trials (P = 0.874). Phase 2 trials were the most common (31.2%), and 18.3% of trials lacked phase designation. This is the first study to comprehensively assess publication patterns in DR and DME trials. The high rate of non-publication, particularly among smaller trials, contributes to a substantial loss of participant data and raises ethical concerns. Greater accountability and complete dissemination of trial outcomes are necessary to uphold the integrity of ophthalmic research and ensure that patient contributions meaningfully inform clinical care.

KEYWORDS: publication bias; clinical trial; research ethics; diabetic retinopathy; macular edema.

INTRODUCTION

Clinical trials serve as the cornerstone of evidence-based medicine, guiding treatment decisions across all medical specialties, including ophthalmology. For diabetic retinopathy (DR) and diabetic macular edema (DME), clinicians rely on landmark trials to inform management strategies. However, the quality of available evidence is undermined by publication bias, trial discontinuation, and unpublished results. While the COVID-19 pandemic disrupted approximately 80% of clinical trials,[1] this study focuses on trials conducted from 1972 to 2018 to avoid confounding factors. Our aim is to identify and analyze publication patterns in DR and DME interventional trials, addressing a critical gap in the current literature.

METHODS

We conducted a retrospective, cross-sectional analysis of DR and DME trials registered in ClinicalTrials.gov from 1972 to 2018. Data collected included funding source, intervention type, publication status, trial phase, discontinuation status, and sample size. Chi-square tests explored associations between trial characteristics and publication outcomes, using Stata/SE 18.0.

RESULTS

As shown in **Table 1**, among the 333 analyzed trials, 78.7% investigated drug/biological interventions, 16.2% device/procedural, and 5.1% other types. Funding was evenly split between academic institutions (51.4%) and industry (48.6%). Most trials (93.4%) were conducted from 2003-2018, with 9.3% terminated and 5.4% withdrawn. Phase distribution varied considerably, with Phase 2 trials comprising 31.2% of all studies, followed by Phase 3 (26.4%) and Phase 4 (15.0%), while 18.3% did not specify their phase.

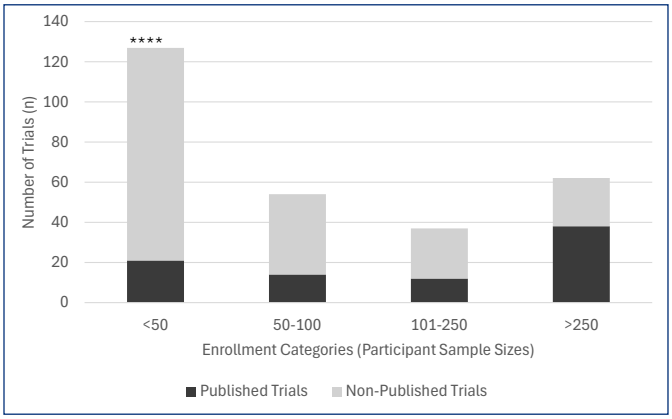
Of the 284 non-terminated trials, 70.1% (n=199) remain unpublished, representing 26,251 participants. In contrast, 29.9% (n=85) were published, contributing data from 45,747 participants. Among discontinued trials, 1.5% (n=5) were published and 7.8% (n=26) unpublished. As illustrated in **Figure 1**, non-terminated trials with fewer than 50 participants were over three times more likely to remain unpublished compared to larger trials (P <0.0001). Funding source did not significantly influence publication status (P = 0.874 for non-terminated trials; P = 0.56 for terminated trials).

Table 1. Characteristics of Diabetic Retinopathy and Diabetic Macular Edema Clinical Trials (1972–2018) by Trial Status and Outcome

	All Trials (n = 333)	Non-terminated Published Trials (n = 85)	Non-terminated Unpublished Trials (n = 199)	Terminated Published Trials (n = 5)	Terminated Unpublished Trials (n = 26)	Withdrawn Trials (n = 18)
Primary Funding Source [n (%)]						
Academic Institution	171 (51.4)	47 (55.9)	108 (54.3)	2 (40)	7 (26.9)	7 (38.9)
Industry	162 (48.6)	38 (44.7)	91 (45.7)	3 (60)	19 (73.1)	11 (61.1)
Study Date [n (%)]						
Before 2003	22 (6.6)	16 (18.8)	6 (3)	0	0	0
2003-2018	311 (93.4)	69 (81.2)	193 (97.0)	5 (100)	26 (100)	18 (100)
Intervention [n (%)]						
Drug/Biologic	262 (78.7.)	62 (72.9)	158 (79.4)	4 (80)	21 (80.8)	17 (94.4)
Device/Procedure	54 (16.2)	15 (17.6)	34 (17.1)	1 (20)	3 (11.5)	1 (5.6)
Other	17 (5.1)	8 (9.5)	7 (3.5)	0	2 (7.7)	0
Trial Phase* [n (%)]						
Phase 1	30 (9)	2 (2.4)	20 (10.1)	0	4 (15.4)	4 (22.2)
Phase 2	104 (31.2)	21 (24.7)	69 (34.7)	2 (40)	6 (23.1)	6 (33.3)
Phase 3	88 (26.4)	39 (45.9)	38 (19.1)	2 (40)	7 (26.9)	2 (11.1)
Phase 4	50 (15.0)	9 (10.6)	33 (16.6)	0	3 (11.5)	5 (27.8)
Unknown	61 (18.3)	14 (16.4)	39 (19.6)	1 (20)	6 (23.1)	1 (5.6)
Enrollment [n (%)]						
<50	163 (49.0)	21 (24.7)	106 (53.3)	2 (40)	16 (61.5)	18 (100)
50–100	55 (16.5)	14 (16.5)	40 (20.1)	0	1 (3.8)	0
101–250	45 (13.5)	12 (14.1)	25 (12.6)	3 (60)	5 (19.3)	0
>250	64 (19.2)	38 (44.7)	24 (12.0)	0	2 (7.7)	0
Unknown	6 (1.8)	0	4 (2)	0	2 (7.7)	0
Total Number of Participants [n]	74,252	45,747	26,251	606	1,648	N/A

* Trials described as Phase 1/2 (n = 16) were categorized as Phase 2 and trials described as Phase 2/3 (n = 6) were categorized as Phase 3.

Figure 1. Publication Status by Sample Size in Non-Terminated Diabetic Retinopathy and Diabetic Macular Edema Clinical Trials



Chi-square test was used to compare publication status by sample size. Trials with fewer than 50 participants were over three times as likely to remain unpublished ($p < 0.0001$). Statistical significance is indicated by four asterisks (****).

DISCUSSION

This study presents the first comprehensive analysis of publication patterns in DR and DME trials, revealing concerning trends. Non-publication threatens evidence-based medicine. Small sample sizes (n<50) were significantly associated with non-publication, potentially due to limited result generalizability. The lack of phase designation in 18.3% of trials complicates interpretation of progress and outcomes.[2] Consistent with previous research,[3] funding source did not impact publication likelihood. Notably, 36.5% of non-terminated trial participants did not contribute to the literature due to non-publication, representing not only a loss of valuable data but also a disservice to those who gave their time and effort to advance scientific knowledge.

While ClinicalTrials.gov may not include all trials and reported data are not always independently verified,[4] it captures at least 70% of globally registered trials,[5] and is supposed to capture 100% of American trials, thus providing a robust sample.

The high rate of non-publication in DR and DME trials results in a substantial loss of evidence and raises significant

ethical concerns regarding the appropriate use of participant data and the responsible conduct of research. Greater transparency and more consistent reporting of outcomes, regardless of findings, are needed to uphold the integrity of the scientific process and honor the contributions of study participants. Future research should explore factors contributing to non-publication and develop strategies to enhance the complete dissemination of trial results. Our findings highlight a similar theme that span clinical medical trials across various specialties. Clinical trial publication rates and individual study characteristics have been examined across neurology, oncology, rheumatology, and gynecology.[6-9] Addressing this critical issue is essential to advancing evidence-based medicine and improving patient care across healthcare.

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Disclosures

The authors report no conflicts of interest relevant to this work. The views expressed herein are those of the authors and do not necessarily reflect the views of their affiliated institutions. This study is based on a retrospective analysis of publicly available, de-identified data from ClinicalTrials.gov. As the data does not involve human subjects or require interaction with participants, the Brown University Institutional Review Board (IRB) Human Research Protection Program deemed this study exempt from IRB review.

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