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Rate of Asthma Trial Outcomes Reporting on ClinicalTrials.gov and in the Published Literature

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TO THE EDITOR

To improve the transparency and reporting of clinical trials, the U.S. Congress passed the Food and Drug Administration Amendments Act (FDAAA) of 2007, which requires investigators to upload their results of investigational phase 2-4 drug, biologic, and device trials within one year of the trial's completion.¹ Noncompliance may result in the withholding of National Institutes of Health (NIH) grant funding and civil monetary penalties of up to \$10,000.² However, a recent report found that only 22% of qualifying studies had uploaded results within the required timeframe.³

The dissemination of accurate trial results is essential in supporting evidence-based medical decision making. In this study, we sought to evaluate the consistency between registry records and publications of trial results for investigational trials of asthma drugs, biologics, and devices subject to mandatory reporting requirements.

A query of ClinicalTrials.gov was performed using a registry search function with a “conditions” key word of “asthma”. To coincide with the enactment of the FDAAA,² we selected trials registered after September 2007. Additionally, to provide a minimum of at least two years for investigators to analyze their data, write a manuscript, and have their findings published, we identified asthma studies that featured a study completion date before

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January 2012. Publications were identified by reviewing the “publications” field on [ClinicalTrials.gov](https://clinicaltrials.gov) and by manually searching Medline using the study title, the intervention studied, and the name of the principal investigator. Standardized data extraction forms were used to record: the favorability of the primary outcome, the published sample size, and reporting of the National Clinical Trial (NCT) number. For trials that had results reported on [ClinicalTrials.gov](https://clinicaltrials.gov) and a corresponding publication, we compared the primary outcome results reported in both sources. Lastly, we compared the trial registry entry to the publication and evaluated for evidence of discrepancies in the primary outcome(s), secondary outcome(s), and inclusion / exclusion criteria.

The Table displays the characteristics of the 212 completed asthma trials involving drugs, biologics, and devices registered in [ClinicalTrials.gov](https://clinicaltrials.gov); results were reported on the website for 71 (33%). Notably, 39% of industry-sponsored trials had reported results – a rate that was nearly double the rate for trials with any other funding source (17%; $P<0.01$). Additionally, trials that enrolled children (exclusively or in addition to adults) were more likely to have reported results when compared to trials that only enrolled adult subjects ($P<0.001$). The larger the trial, the more likely it was to have results reported ($P=0.01$).

Among the 212 identified asthma trials, 68 (32%) were indexed in Medline (Figure). Of these, 51 (75%) featured favorable primary outcomes. For 29 trials with both results reported on [ClinicalTrials.gov](https://clinicaltrials.gov) and a corresponding publication identified in Medline, 6 (21%) published primary outcome results that differed from the results reported on [ClinicalTrials.gov](https://clinicaltrials.gov).

Discrepancies from the primary outcome described in the [ClinicalTrials.gov](https://clinicaltrials.gov) registry entry were identified in 6/68 (9%) published trials; two trials introduced a new co-primary outcome that was not listed in the trial registry (3%) and another two trials reported primary outcomes in the registry as secondary outcomes in their publications (3%). One trial reported a secondary outcome in the registry as a co-primary outcome in the publication (1%). Lastly, one trial introduced a new composite primary outcome (1%). Discrepancies in secondary outcomes were also frequently noted (46%). Sixty of 68 (88%) trials published different inclusion / exclusion criteria. When compared to the details provided in the [ClinicalTrials.gov](https://clinicaltrials.gov) registry entry, the sample size was lower in twelve (18%) published trials and was higher in nine (13%). Approximately one in five (22%) published trials did not include the [ClinicalTrials.gov](https://clinicaltrials.gov) NCT number associated with the trial’s registry entry.

A primary goal of trial registration and results reporting is to enhance the transparency of research and provide accountability in the planning, conduct, and reporting of clinical trials.⁴ However, the appropriate registration of key trial-specific details only safeguards against the threat of publication bias if reviewers and editors take advantage of the transparency of the trial registration to evaluate for evidence of outcome reporting bias. In our study, 78% of published trials reported their NCT Number, which uniquely identifies the trial’s registry record in [ClinicalTrials.gov](https://clinicaltrials.gov). Although the editors and peer reviewers had access to these identifiers, we found that secondary outcomes and inclusion / exclusion criteria were frequently discrepant between registry entries and corresponding publications. Reassuringly, our assessment found lower rates of primary outcome discrepancies than have been reported

in previous studies among other disease states.^{5, 6} For example, Chan et al. found that 62% of 122 trials conducted in Denmark from 1994–1995 had at least one primary outcome that was changed, added, or omitted.⁵ Registration in [ClinicalTrials.gov](https://clinicaltrials.gov), a pre-requisite for inclusion within this study, may have discouraged selective reporting of results or “data dredging”. This is encouraging, as the purpose of pre-specifying primary outcomes is to define the most clinically-relevant endpoints, which are then used to calculate the trial’s sample size.^{7, 8} We are cautiously optimistic that the adoption of evidence-based reporting guidelines and careful review of registry records may help improve the accurate reporting of clinical trial results.

A limitation of this study is that the data quality within [ClinicalTrials.gov](https://clinicaltrials.gov) varies due to sponsor reporting. However, the National Library of Medicine employs an automated evaluation system to alert sponsors when data fields are missing or internally inconsistent.⁹

Previously, Prayle et al. evaluated all trials registered in [ClinicalTrials.gov](https://clinicaltrials.gov) in 2009 that were subject to FDAAA reporting requirements and determined that only 22% had reported their results; however, their analysis aggregated data from all medical specialties and therefore cannot be directly compared with the 33% of asthma trials that reported results in this disease-specific analysis.³ The reasons for the under-reporting of clinical trial results are unclear. It is possible that the user interface and accessibility of [ClinicalTrials.gov](https://clinicaltrials.gov) may be a barrier to results reporting. Discrepancies between the trial registry and associated publications may also occur because investigators and industry sponsors fail to update initial [ClinicalTrials.gov](https://clinicaltrials.gov) registry entries and results following protocol revisions, post-hoc analyses, and alterations in the analytic plan made at the request of peer-reviewers. Additionally, in correspondence with trial sponsors, we were informed that several companies do not want their competitors to have access to the results of their trials, which has led these companies to refrain from uploading the results of their trials. Consequently, additional efforts are needed to promote accountability among investigators and industry sponsors to promote the timely updating of trial protocols and the release of trial results on [ClinicalTrials.gov](https://clinicaltrials.gov).

More than 200 interventional asthma trials registered in [ClinicalTrials.gov](https://clinicaltrials.gov) have been completed over the last six years. Despite a federal mandate requiring the timely reporting of results for late-phase drug and biologic trials, only 33% of completed interventional drug, biologic, and device trials had results available within [ClinicalTrials.gov](https://clinicaltrials.gov) and 32% have been published in peer-reviewed journals. In addition, there were frequent discrepancies between the registration information and publication with respect to primary and secondary outcomes and trial design criteria. In aggregate, these findings reveal evidence of a large gap between current practice and ideal clinical trial reporting, in which accurate results are reported and published in a timely and transparent fashion to inform clinical practice.

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Capsule Summary

Among 212 recently conducted interventional asthma trials subject to the Food and Drug Administration Amendments Act mandatory results reporting requirements, 33% reported results on ClinicalTrials.gov and 32% were published. Results of these trials must be better disseminated to inform clinical practice.

Results reported on ClinicalTrials.gov **Publication indexed on Medline** **Primary outcome results different when ClinicalTrials.gov results were compared to corresponding publication(s) indexed on Medline** **Primary outcome defined differently in the ClinicalTrials.gov registry entry when compared to corresponding publication(s) indexed on Medline** **Secondary outcome defined differently in the ClinicalTrials.gov registry entry when compared to corresponding publication(s) indexed on Medline** **Inclusion / exclusion criteria defined differently in the ClinicalTrials.gov registry entry when compared to corresponding publication(s) indexed on Medline** **Figure.**

An evaluation of the reporting of results for 212 interventional asthma trials of late-phase drugs, biologics, and devices, which were completed more than two years ago and were subject to FDAAA mandatory reporting requirements. The horizontal axis depicts the number of asthma trials and the number and proportions listed next to each bar reflect the number and percent of trials within each group.

Availability of results among phase 2–4 interventional asthma drug, biologic, and device trials registered on ClinicalTrials.gov.

TABLE

Characteristic	Category	Total (n = 212)	Results Available on ClinicalTrials.gov		Publication Indexed in Medline	
			Has Results (n = 71)	No Results Available (n = 141)	Published Results * (n = 68)	No Published Results (n = 144)
Study phase, n (%)	Phase 2	118 (56%)	38 (54%)	80 (57%)	32 (47%)	86 (60%)
	Phase 3	44 (21%)	20 (28%)	24 (17%)	16 (24%)	28 (19%)
	Phase 4	50 (24%)	13 (18%)	37 (26%)	20 (29%)	30 (21%)
Sample size	Median	53	75	46	86	45
	Interquartile range	25 – 198	28 – 339	21 – 160	30 – 295	24 – 116
Age groups, n(%)	Children only	26 (12%)	12 (17%)	14 (10%)	5 (7%)	21 (15%)
	Children and adults	49 (23%)	26 (37%)	23 (16%)	18 (26%)	31 (22%)
	Adults only	137 (65%)	33 (46%)	104 (74%)	45 (66%)	92 (64%)
Lead funding source, n (%)	Industry	160 (75%)	62 (87%)	98 (70%)	48 (71%)	112 (78%)
	Government	1 (<1%)	0 (0%)	1 (1%)	0 (0%)	1 (1%)
	Other	51 (24%)	9 (13%)	42 (30%)	20 (29%)	31 (22%)
Allocation status, n(%)	Randomized	189 (89%)	65 (92%)	124 (88%)	60 (88%)	129 (90%)
	Non-randomized	13 (6%)	4 (6%)	9 (6%)	6 (9%)	7 (5%)
	Not reported	10 (5%)	2 (3%)	8 (6%)	2 (3%)	8 (6%)
Blinding, n(%)	Open	38 (18%)	10 (14%)	28 (20%)	10 (15%)	28 (20%)
	Single blind	5 (2%)	4 (6%)	1 (1%)	2 (3%)	3 (2%)
	Double blind	163 (77%)	57 (80%)	106 (75%)	56 (82%)	107 (78%)
	Not reported	6 (3%)	0 (0%)	6 (4%)	0 (0%)	0 (0%)
Interventional group, n(%)	Single group	22 (10%)	6 (8%)	16 (11%)	8 (12%)	14 (10%)
	Parallel	114 (54%)	37 (52%)	77 (55%)	39 (57%)	75 (52%)
	Cross-over	75 (35%)	28 (39%)	47 (33%)	21 (31%)	54 (38%)
	Not reported	1 (<1%)	0 (0%)	1 (1%)	0 (0%)	1 (1%)

* NOTE: For trials with multiple publications, all publications were reviewed and the publication that most closely mirrored the design described in the trial registry was evaluated.