Funding is associated with increased methodological and statistical reporting in onychomycosis randomised controlled/comparative clinical trials

Dear Editor,

Sample size calculation and primary outcome measure reporting in randomised controlled/comparative trials (RCT) are essential to evaluate and reproduce study methodology and results.[1] General dermatology RCT reporting has improved over time.[2] Our objectives were to characterise onychomycosis RCT reporting and to determine if funding influences trial/manuscript design and quality.

A systematic review was performed by searching PubMed, 1/9/22, for onychomycosis RCTs using the keywords "onychomycosis," "clinical trial" and "randomised controlled trial." Exclusion criteria were non-English language and laser/procedural-based therapies. Eligible trials were assessed for primary outcome specification, including both specific outcome measure and associated timeframe, and full sample size calculation reproducibility, including all α, β, effect size, and variance for continuous outcomes. Partial sample size calculation reproducibility was considered if at least one criterion was met. Trial and manuscript characteristics were assessed by two independent authors who were blinded to each other's assessments ($\kappa = 0.87$; 95% confidence interval: 0.83, 0.90). Univariable analyses were performed to assess associations between funding and manuscript/trial characteristics, and multivariable logistic regression was performed to evaluate independent factors associated with funding status. Studies that received any funding were designated as funded (i.e., no cutoff values). Significance was set at $P < 0.05$.

Initial searches yielded 198 studies, with 102 included for analysis. Seventy-nine (77.5%) studies were conducted in/before 2012 and 23 (22.5%) were conducted after 2012. Overall, 33/102 (32.4%) studies reported both primary outcome and time, with 48/102 (47.1%) reporting outcome measures only. The most common primary outcomes were mycologic (17/65; 26.2%) and complete (16/65; 24.6%) cures. Only 56/102 (5.9%) and 67/102 (65.7%) studies had fully and partially reproducible sample size calculations, respectively. The target sample size was reported in 30/102 (29.4%) studies, with 26/30 (86.7%) achieving target size [Table 1]. Of the studies that reported a target sample size, 22/30 (73.3%) specified a primary outcome, vs. only 11/72 (15.3%) in studies without reported target sample sizes ($P < 0.001$). Sixty out of 102 (58.8%) studies were funded, mostly from pharmaceutical companies (51/60; 85%), followed by institutional grants (4/60; 6.7%), other (4/60; 6.7%) and organisational grants (1/60; 1.7%) ($P < 0.001$). Funded studies vs. non-funded studies more often reported partial sample size calculations [48/60 (80%) vs. 19/42 (45.2%) studies; $P < 0.001$] and primary outcomes [33/60 (55%) vs. 15/42 (35.7%) studies; $P = 0.0548$] were registered more frequently [15/60 (25%) vs. 1/42 (2.4%) studies; $P = 0.0020$], and were more likely to be multicenter [40/59 (67.8%) vs. 19/42 (45.2%) studies; $P = 0.0234$], and published in higher mean impact factor journals (8.2 vs. 5.9; $P = 0.0315$). Median sample sizes were similar in funded [148.0; interquartile range (IQR): 292.0] vs. non-funded (97.5; IQR: 74.0) studies ($P = 0.0714$) [Table 2]. Impact factor [odds ratio (OR): 1.15; $P = 0.033$] and partial reproducibility (OR: 3.61; $P = 0.0151$) were significantly associated with funding using multivariable logistic regression.

Our study showed that few onychomycosis RCTs had full statistical reproducibility and specified both primary efficacy measurements and times. In a previous study analyzing 205 general dermatology RCTs,[2] 49% reported fully reproducible calculation and 67% reported both primary outcome measure and time. Therefore, onychomycosis RCTs appear to be lacking in methodological reporting, as compared to general dermatology RCTs.

Mycologic and complete cure rates were the most common outcome measures; however, there was variability across trials, similar to previous analyses of efficacy measures in onychomycosis trials.[3,4] Primary efficacy endpoints used in RCTs are required by the Food and Drug Administration for drug approvals, but might not be reflective of clinical practice.[5]

How to cite this article: Falotico JM, Desai AD, Lipner SR. Funding is associated with increased methodological and statistical reporting in onychomycosis randomised controlled/comparative clinical trials. Indian J Dermatol Venereol Leprol. 2024;90:121–3. doi: 10.25259/IJDVL_871_2022

Received: September, 2022; **Accepted:** January, 2023 **EPub Ahead of Print:** May, 2023 **Published:** December, 2023

DOI: 10.25259/IJDVL_871_2022 **PMID:** 37317731

Table 1: Inclusion of primary outcome measure, time frame, and sample size calculation in onychomycosis randomised controlled/comparative clinical trials

Variable	N	%
Primary outcome specification	48/102	47.1
All components present*	33/102	32.4
Pre-defined primary outcome measure	48/102	47.1
Timeframe of primary outcome measure	33/102	32.4
Primary outcome classification	48/102	47.1
Mycologic cure	17/65	26.2
Complete cure	16/65	24.6
Clinical improvement/efficacy/response	7/65	10.8
Effective cure	3/65	4.6
Clinical cure	3/65	4.6
Mycologic examination	3/65	4.6
Effective treatment	2/65	3.1
Other	14/65	21.5
Formal sample size calculation performed		
Full reproducibility†	6/102	5.9
Partial reproducibility‡	67/102	65.7
Components		
Alpha value	56/102	54.9
Beta value	26/102	25.5
Effect size	14/102	13.7
Variance (for continuous outcomes)	23/30	76.7
Target sample size reported	30/102	29.4
Target sample size achieved	26/30	86.7

*Complete primary outcome measure specification requires both a clearly defined primary outcome measure and an associated timeframe, †Requires alpha value, beta value, effect size, and standard deviations for continuous outcomes, ‡Requires at least one measure (alpha value, beta value, effect size, or standard deviations for continuous outcomes)

Table 2: Associations between funding status and trial/manuscript characteristics

Variable	Funded studies, *n* (%)	Non-funded studies, *n* (%)	*P*-value*
Trial characteristics			
Funder			**<0.0001**
Pharmaceutical	51 (85)	N/A	
Other	9 (15)	N/A	
Setting†			**0.0234**
Multicenter	40 (67.8)	19 (45.2)	
Single center	19 (32.2)	23 (54.8)	
Registered trial/published protocol			**0.0020**
Yes	15 (25)	1 (2.4)	
No	45 (75)	41 (97.6)	
Intervention (oral vs. topical)			**0.0248**
Oral	36 (60)	34 (81.0)	
Topical	24 (40)	8 (19.1)	
Blinding‡			0.0971
Yes	51 (85)	27 (64.3)	
No	9 (15)	15 (35.7)	
Median final achieved sample size (IQR)§	148.0 (292.0)	97.5 (74.0)	0.0714
Manuscript characteristics			
Word count			0.1011
>3000	15 (25)	5 (11.9)	
≤3000	45 (75)	37 (88.1)	
Primary outcome measure specification			0.0548
Yes	33 (55)	15 (35.7)	
No	27 (45)	27 (64.3)	
Fully reproducible sample size calculation			0.2086
Yes	5 (8.3)	1 (2.34)	
No	55 (91.7)	41 (97.6)	
Partially reproducible sample size calculation			**0.0003**
Yes	48 (80)	19 (45.2)	
No	12 (20)	23 (54.8)	
Description of randomisation methods			**0.0004**
Yes	29 (48.3)	6 (14.3)	
No	31 (51.7)	36 (85.7)	
Journal impact factor (average, SD)	8.12 (6.0)	5.94 (3.2)	**0.0315**

IQR: interquartile range, N/A: not applicable, SD: standard deviation, Chi-square and Fisher's Exact tests were used to compare categories for categorical variables and *t*-tests were used to compare continuous variables, *Bolded *P*-values are statistically significant, †Setting information (multi vs. single center) was unavailable for one funded study, ‡Single or double blinded, §Wilcoxon rank sums test used for non-parametric comparison for skewed sample size data

Therefore, although consensus in outcome measures is necessary to compare therapies, it is uncertain whether standardised measurements will translate into improved clinical outcomes.

We found that funded studies had better statistical and outcome measure reporting than non-funded studies and were also more robustly designed. Therefore, funding likely plays an important role in trial design, recruitment of participants, and hiring research coordinators and statisticians, resulting in high-quality trials that are likely to be published in high-impact journals.

Our study is limited by the inclusion of oral and topical onychomycosis studies only. We did not screen journals for Consolidated Standards of Reporting Trials (CONSORT) guideline status, and it is possible that studies published in these journals may have better reporting. Allocation concealment, which can indicate an assessment of bias in RCTs, was not collected.

Overall, our study shows that many onychomycosis RCTs lack appropriate methodological and statistical reporting, without reproducibility across trials. Funding may thus be influential in increasing RCT quality and the likelihood of publishing in journals with a wide readership, positively impacting outcomes for onychomycosis patients.

Declaration of patient consent

Patient's consent not required as there are no patients in this study.

Financial support and sponsorship

Nil.

Conflicts of interest

Ms. Falotico and Mr. Desai have no conflicts of interest. Dr. Lipner has served as a consultant for Ortho Dermatologics, Hoth Therapeutics, and BelleTorus Corporation.

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