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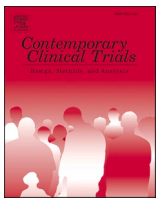
Contemporary Clinical Trials 121 (2022) 106899

Contents lists available at ScienceDirect

Contemporary Clinical Trials

journal homepage: www.elsevier.com/locate/conclintrial



Publication rates in small German trials remained low five years after trial completion

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ARTICLE INFO

Keywords:
Publication rates
Time-to-publication
Small trials
Sample size
Primary outcomes

ABSTRACT

Objective: To investigate publication rates in small trials and to explore which factors are associated with publication rates in small trials, including sample size, the type and number of primary and secondary outcomes.
Study design and setting: We studied a subgroup of 'small' trials from a pre-existing dataset (IntoValue), containing German trials completed between 2009 and 2017. Small trials were defined as phase II-III, III and IV trials with 150 or fewer participants. We performed an updated publication search and collected additional data from online trial records.
Results: Out of 499 trials, 325 (65%) trials published their results in a journal article or dissertation. Median time-to-publication was 3.41 years (95% CI: 3.04–4.10). Planned sample size was not associated with publication rates, but the difference between planned and achieved sample size was (per 10% unsuccessfully recruited participants, HR = 0.95, 95% CI: 0.91–1.00). Phase III vs. II-III trials, studied intervention (device vs. other) and clearly vs. unclearly defined primary outcomes predicted a higher likelihood of earlier publication.
Conclusion: About 35% of small trials in Germany remain unpublished, even after an extensive follow-up period of over 9 years. Publication rates are low and were associated with sample size, trial phase and type of intervention.

1. Introduction

Dissemination of study results is a basic principle of good research practice. Although non-publication is a widely known phenomenon and has received increasing attention over the years, recent evidence shows that about 30–40% of clinical trials still remain unpublished [1–4]. Not only does non-publication add to research waste, it can paint a biased picture of the available evidence, which can potentially lead to wrong conclusions [5,6]. Next to wasting resources, not publishing results also means that the risks and effort of participating in research are in vain as no advancement in knowledge is achieved, and is therefore highly unethical.

Identifying factors that affect the risk of non-publication is important in understanding non-publication and may guide towards possible solutions. Previous research showed that trial characteristics, such as phase, monocentric studies, randomization and funding, are associated with the risk of non-publication [7,8]. However, these findings are not always consistent across the literature, possibly due to heterogeneity in trials investigated (e.g., trials of interest are restricted to certain medical fields, interventions or types of funding).

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https://doi.org/10.1016/j.cct.2022.106899
Received 25 April 2022; Received in revised form 23 August 2022; Accepted 23 August 2022
Available online 28 August 2022

What is new?

- Only 65% of small trials (i.e. phase II-III, III and IV trials with 150 or less participants) in Germany are published, even after an extensive follow-up period of over 9 years
- Median time-to-publication after trial completion in small trials is 3.4 years. Publication rates become stagnant after 5 years.
- Planned sample size was not associated with publication rates in small German trials, but the discrepancy between planned and achieved sample size was. This effect remained after adjustment for terminated trials, although less pronounced.
- Particularly phase III trials in comparison to phase II-III trials, trials with device as intervention in comparison to trials investigating other interventions, and trials with clearly defined primary outcomes on their trial record in comparison to trials with unclearly defined outcomes, seemed to publish their results earlier in time.
- Larger confirmatory studies from other parts of the world investigating reasons for non-publication are needed

Smaller trials are more often investigator initiated, have fewer resources available and are often conducted single-center. Not only are they notorious for being underpowered, they are at risk of being lower quality than large, industry sponsored trials, and may also be more prone to selection bias and other biases. As a result, smaller trials may be scientifically more vulnerable and have a greater risk of non-publication. When looking specifically at sample size, it is indeed reported to be associated with non-publication, with trials having a smaller sample size running a higher risk of non-publication [9–13]. However, sample size is often only analyzed into broad categories without further distinction between planned and achieved sample size. A more detailed look at the association between sample size and risk of non-publication therefore seems warranted, especially in small trials where small absolute differences can have a sizeable impact. Additionally, we wanted to investigate whether variation in primary and secondary outcomes predict non-publication in small trials. The use of multiple primary outcomes, or a very large number of secondary outcomes, could be a sign of researchers being overly optimistic in what is feasible to estimate in small trials. Furthermore, the type of primary outcome, e.g., whether it is continuous or dichotomous, affects the power calculation and the number of participants needed in a trial. Dichotomization of a continuous primary endpoint, resulting in more participants needed to demonstrate a significant effect, may not be a wise choice, particularly not in the context of small trials where resources are scarce. To our knowledge, neither the effect of different primary outcomes types, such as continuous or dichotomous outcomes, nor the number of outcomes on non-publication has been investigated before in relation to non-publication risk.

Therefore, the aims of the current study were to investigate publication rates specifically in small trials and to explore which factors are associated with publication rates in small trials, including sample size, the type and number of primary and secondary outcomes.

2. Methods

2.1. Study design and sampling methods

For the current study, we used the dataset 'IntoValue' from which we sampled a subgroup of small trials [14]. IntoValue contains data from German trials with a primary completion date between 2009–2013 (first cohort, IntoValue 1) [2] and 2014–2017 (second cohort, IntoValue 2) [3] collected from clinicaltrials.gov and DRKS.de. This dataset includes information regarding sample size, phase, randomization, blinding, intervention type, mono vs. multicentric design and sponsor. Automated and hand searches were combined to subsequently find corresponding publications in 2017 (IntoValue 1) and 2020 (IntoValue 2).

There is no common definition of what is considered a 'small trial'. We selected a subset of trials from the IntoValue dataset, based on the following criteria: (I) total sample size (n) $\leq$ 150, and (II) phase II-III, III or IV. The first criterion ($n \leq 150$) was chosen to cover a broader range of smaller sized trials. This cut-off point allowed us to both include all relatively small trials and still have some variation in sample size. Phase I, I-II, and II trials were excluded from the dataset because they are fundamentally different from phase III/IV trials in many aspects, including research goals, designs, statistical methods, planning and execution, and therefore fall beyond our current scope. Trials with unknown sample size or unknown phase were excluded.

2.2. Data collection

Between August and November 2021, additional data were collected with the aim to update, supplement and extend the IntoValue dataset.

Firstly, we performed an updated publication search for all previously unpublished trials in the dataset, adopting the search strategy from Riedel et al. [3]. Trial records on clinicaltrials.gov and DRKS.de were first checked for linked publications in the publication section. If no matching result was found, a hand search was conducted via Google by entering the trial identification number (NCT or DRKS number), title, brief title (only available for clinicaltrials.gov), intervention and principal investigator (PI). A publication was considered a match if the trial identification number was listed and/or the specific trial characteristics matched the trial record. Only trials with full text articles or dissertations were counted positive for 'publication'. See Appendix B for a detailed description of the search strategy and matching criteria. In addition, all trials were checked if they had posted summary results on clinicaltrials.gov or DRKS.de. We used the broader term 'dissemination' to denote that trials had disseminated their results either via posted summary results, full text article or dissertation. If during our publication search a trial was found to have posted their summary results on EU-CTR, we also counted them as positive for dissemination.

Secondly, a small proportion of the trials had missing information regarding the intervention, randomization, blinding and mono vs. multicentric design of the study. These data were supplemented from trial records or publications where possible.

Thirdly, we extended the dataset by including information on the type and frequency of outcomes, as well as information on both planned and achieved sample sizes (no distinction was made in the original IntoValue dataset). For each trial record, we scored the number of both primary and secondary outcomes. Primary outcomes were categorized as either dichotomous, ordinal, continuous or unclear. In case of multiple primary outcomes, only the first two primary outcomes listed were categorized. (See Appendix C for detailed information.) Planned and achieved sample sizes were also extracted from trial records or via their history of changes. For planned or achieved sample sizes that were missing from trial records, we checked the corresponding publication if available. If a planned sample size was still missing, or if the achieved sample size was unclearly defined (e.g., publications presenting aggregate data from multiple trials, without further specification of individual trial sample sizes), we marked them as missing in the dataset.

Finally, we sent out questionnaires inquiring reasons for study termination and non-publication to the PIs of all trials that were terminated or remained unpublished after our updated publication search. See Appendix D for both questionnaires. If the results of the questionnaires led to newly matched publications, they were added to the database and included in the analysis.

2.3. Outcome and covariate definitions

Publication rate (time-to-publication) was the main outcome in the present study. The completion date of a trial was considered as start of follow-up. Follow-up ended when a trial was published or if the end of study was reached (1st of December 2021), whichever came first.

Other outcomes of interest were (I) timely publication and (II) dissemination. Timely publication was defined as published trial results <24 months after the completion date (adopted from WHO statement 2017) [15]. We considered results disseminated if a trial either had a publication (full text article or dissertation) or posted their summary results (see section 2.2).

The dataset included 3 sample size variables; (I) sample size from IntoValue, (II) planned sample size and (III) achieved sample size. The latter two were extracted from trial records and/or publications (see section 2.2). The sample size variable from the IntoValue dataset did not distinguish between planned or achieved sample sizes. Instead, it consisted of the most recent sample size from the trial record. In practice, this means most sample sizes were achieved sample sizes, but could also include planned sample sizes if the achieved sample size was not available. This resulted in the inclusion of some trials ($n = 53$) in our dataset that had initially planned to recruit >150 participants.

2.4. Statistical analysis

Trial characteristics, overall proportion of publication and dissemination, trial outcomes and the results of the questionnaires were reported without formal statistical testing.

Kaplan-Meier estimation and Cox proportional hazards regression analysis were used for the time-to-event analysis (i.e. time-to-publication). Trials with a negative follow-up time (i.e., publication date was before the trial completion date) were excluded from these analyses (20 trials in total). We calculated median follow-up time using the reverse Kaplan-Meier method [16]. Cox regression was used to explore possible associations between a set of candidate variables on time-to-publication. After modeling each variable separately, their predictive value was further explored in a multivariable model including all covariates. The set of covariates included sample size, phase, sponsor, mono vs. multicentric design, intervention, allocation, masking, time of trial registration, number of primary outcomes, number of secondary outcomes and primary outcome type. Because not all trials had the planned and achieved sample size available, we used the IntoValue sample size variable (i.e., most recent sample size listed on the trial record) for our main analysis. As a sensitivity analysis, we repeated the analysis in a subgroup for which the planned sample size was available and $n \leq 150$. Furthermore, we performed a complete case analysis in trials that had all sample size information available and had a planned sample size of $n \leq 150$. Planned sample size, achieved sample size and the difference between planned and achieved sample size were included as covariates for the univariable and multivariable models.

For a secondary analysis, we used multiple logistic regression to explore possible associations between the same set of covariates on timely publication (i.e., publication <24 months after trial completion).

For both Cox regression and logistic regression, we converted the number of primary outcomes and number of secondary outcomes into categories. This was done to account for non-linearity of right skewed data (number of primary outcomes) and to be able to include 'no mention of secondary outcomes' as a separate category. The cut-off points for the primary outcomes variable were chosen in a way to keep them meaningfully interpretable (1, 2 or ≥ 3 outcomes). The cut-off points for the secondary outcomes variable were based on quintiles.

Statistical analyses were performed using R 4.0.5 (R studio version 2021.09.1).

2.5. Data and code availability

The original IntoValue dataset can be accessed here: https://doi.org/10.5281/zenodo.5141342. Our extended 'small trials' dataset, including code and protocol, can be accessed here: https://osf.io/496dm/. Questionnaire responses are not included in the dataset, for we have not asked permission from respondents to share their data in an open online data repository in order to improve response rates.

3. Results

A total of 511 trials with phase II-III, III or IV and a sample size $n \leq 150$ were available from the IntoValue 1 and 2 datasets. After the removal of duplicates 499 trials were included.

3.1. Trial characteristics, sample size and distribution of primary outcomes

Table 1 summarizes characteristics of the included trials. The median sample size (IntoValue) of trials in the dataset was 56 (IQR: 30–92). For 466 trials (93.4%) the planned sample size was available from the trial record or corresponding publication. Achieved sample size was available for 445 trials (89.2%). The median planned sample size was 70 (40–120), while the median achieved sample size was 53 (30–88). Terminated trials ($n = 64$) often did not reach their planned sample size (Fig. 1). Most completed trials ($n = 264$) had an achieved sample size close to their planned sample size. The distribution of primary and secondary outcomes is shown in Table 2.

3.2. Publication and dissemination

Our updated publication search revealed 27 new publications. Three more publications were identified via the questionnaire responses. After scrutinizing the data, we reclassified 9 trials from 'published' to 'non-published' according to our definition in use. Three-hundred-twenty-five trials (65.1%) published their results in a journal article (322 trials, 64.5%) or dissertation (3 trials, 0.6%). When also considering summary reports in trial registries (found for 93 trials, 18.6%), 357 trials (71.5%) disseminated their results.

3.2.1. Time-to-publication

Four-hundred-ninety-nine trials were followed for a median of 9.25 years (95% CI: 8.67–9.59) since trial completion. The median time-to-publication was 3.41 years (95% CI: 3.04–4.10). Time-to-publication differed significantly between sample size groups (log-rank test, $\chi^2 = 14.3$, $p < 0.014$) (Fig. 2).

Table 3 shows univariable and multivariable hazard ratios on time-to-publication. Trials with a larger sample size (per 10 participants, HR = 1.05, 95% CI: 1.02–1.08) and phase III trials (phase III vs. II-III, HR = 1.47, 95% CI: 1.00–2.18) published their results earlier after trial completion. Although non-significant, trials that investigate a device (device vs. other, HR = 1.40, 95% CI: 0.97–2.01), and trials with continuous and dichotomous primary outcomes (continuous vs. unclear, HR = 1.51, 95% CI: 0.99–2.31; dichotomous vs. unclear, HR = 1.47, 95% CI: 0.92–2.33) also seemed to predict a higher likelihood of earlier publication. Additionally, a small advantage in time-to-publication was observed for retrospectively registered trials (retrospective vs. prospective, HR = 1.17, 95% CI: 0.92–1.48). On the other hand, although again non-significant, trials with ≥10 secondary outcomes seemed to predict a lower likelihood of publication earlier in time in comparison to trials that did not fill in any secondary outcomes (HR = 0.65, 95% CI: 0.41–1.03). The number of primary outcomes, sponsor, mono vs. multicentric design, allocation, and masking appeared unrelated to time-to-publication.

3.2.2. Timely publication (publication <24 months after completion date)

In total, 139 trials (27.9%) published their trial results <24 months after trial completion. Table 4 shows univariable and multivariable odds ratios for each covariate on timely publication. Trials with device as an intervention (device vs. other, OR = 2.43, 95% CI: 1.28–4.68) had a higher likelihood of timely publication. Similar patterns were observed for trials with a larger sample size (per 10 participants, OR = 1.05, 95% CI: 0.99–1.11), multicentric trials (multi- vs. monocentric, OR = 1.46, 95% CI: 0.90–2.37) and trials with multiple primary outcomes (≥3 vs. 1 outcome, OR = 1.81, 95% CI: 0.97–3.34), although not statistically

Table 1
Trial characteristics stratified by sample size.

	Sample size groups[a]												Total dataset	
	n = 1–25		n = 26–50		*n* = 51–75		*n* = 76–100		*n* = 101–125		*n* = 126–150			
All	98		137		102		61		51		50		499	
Phase														
II-III	13	13%	17	12%	13	13%	10	16%	6	12%	5	10%	64	13%
III	41	42%	51	37%	41	40%	31	51%	23	45%	28	56%	215	43%
IV	44	45%	69	50%	48	47%	20	33%	22	43%	17	34%	220	44%
Sponsor														
Industry	16	16%	32	23%	29	28%	17	28%	19	37%	26	52%	139	28%
Other	82	84%	105	77%	73	72%	44	72%	32	63%	24	48%	360	72%
Intervention														
Drug	66	67%	84	61%	61	60%	29	48%	20	39%	24	48%	284	57%
Device	15	15%	27	20%	20	20%	9	15%	18	35%	10	20%	99	20%
Procedure	8	8.2%	12	8.8%	3	2.9%	6	9.8%	5	9.8%	7	14%	41	8.2%
Behavioral	4	4.1%	2	1.5%	6	5.9%	6	9.8%	4	7.8%	1	2%	23	4.6%
Biological	2	2%	5	3.6%	1	1%	4	6.6%	2	3.9%	5	10%	19	3.8%
Dietary supplement	0	0%	2	1.5%	2	2%	3	4.9%	1	2%	0	0%	8	1.6%
Radiation	1	1%	1	0.7%	1	1%	0	0%	0	0%	0	0%	3	0.6%
Other	2	2%	4	2.9%	8	7.8%	4	6.6%	1	2.0%	3	6.0%	22	4.4%
Mono vs. multicentric														
Monocentric	71	72%	85	62%	54	53%	31	51%	30	59%	13	26%	284	57%
Multicentric	27	28%	52	38%	48	47%	30	49%	21	41%	37	74%	215	43%
Allocation														
Randomized	66	67%	106	77%	84	82%	49	80%	41	80%	39	78%	385	77%
Non-randomized	32	33%	31	23%	18	18%	12	20%	10	20%	11	22%	114	23%
Masking														
Blinded	38	39%	68	50%	62	61%	36	59%	25	49%	20	40%	249	50%
Open	60	61%	69	50%	40	39%	25	41%	26	51%	30	60%	250	50%
Trial registration														
Prospective	56	57%	75	55%	65	64%	37	61%	26	51%	29	58%	288	58%
Retrospective	42	43%	62	45%	37	36%	24	39%	25	49%	21	42%	211	42%
Recruitment status														
Completed	47	48%	92	67%	73	72%	43	70%	42	82%	37	74%	334	67%
Terminated	40	41%	27	20%	6	5.9%	10	16%	3	5.9%	9	18%	95	19%
Unknown	11	11%	14	10%	20	20%	8	13%	5	9.8%	4	8%	62	12%
Other [b]	0	0%	4	2.9%	3	2.9%	0	0%	1	2%	0	0%	8	1.6%

[a] Sample size groups are based on the IntoValue sample size variable.
[b] Consists of withdrawn, suspended (clinicaltrials.gov) and 'recruiting stopped after recruiting started' (DRKS.de).

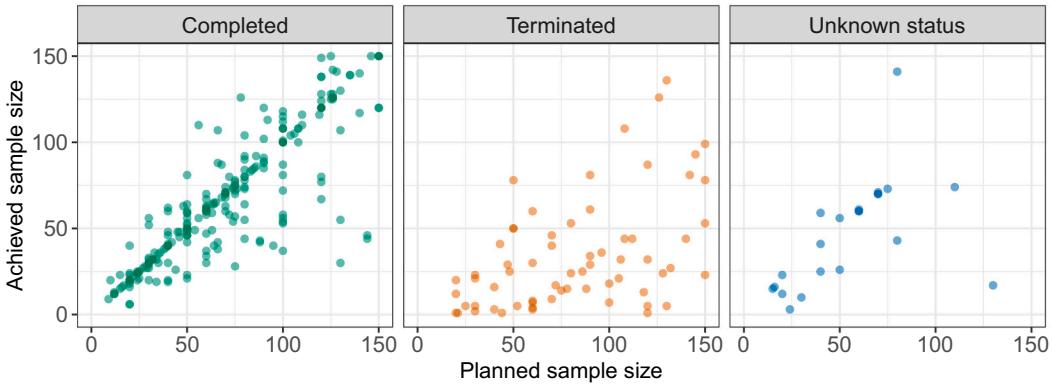

Fig. 1. Scatterplots illustrating planned vs. achieved sample size, stratified by recruitment status (in trials with planned sample size $n \leq 150$).
A total of 412 trials had data available for both the planned and achieved sample size. Of these, 359 trials had a planned sample size of n ≤ 150. The planned vs. achieved sample size for this subgroup is plotted above, separated into facets based on recruitment status. Most of the completed trials (n = 263) had an achieved sample size close to their planned sample size, while terminated trials (n = 64) often did not reach their planned sample size.

significant. Trials that had a larger number of secondary outcomes listed on their trial record, particular those with ≥10 outcomes, predicted a lower likelihood of timely publication in comparison to trials that did not mention any secondary outcomes on their trial record (OR = 0.29, 95% CI: 0.09–0.52).

3.2.3. *Sensitivity analysis and complete case analysis*

Results of the sensitivity analyses (Table 5) were in line with the main analysis, except for planned sample size which appeared not to be associated with publication rates (per 10 participants, HR = 0.99, 95% CI: 0.95–1.02). Trials that were not able to achieve their planned sample size (and thus had a discrepancy between their planned and achieved sample size) had a lower likelihood of publishing results earlier in time (relative difference planned vs. achieved sample size, per increment of 10% unsuccessfully recruited participants, HR = 0.89, 95% CI: 0.86–0.92) (complete case analysis, results are shown in Table A.2, Appendix A). After adjustment for recruitment status (and thus taking terminated trials into account), the association persisted (relative

Table 2
Distribution of primary and secondary outcomes.

	$n = 499$ (100%)	
Primary outcome type in trials with 1 outcome		
Continuous	207	(56%)
Dichotomous	116	(31%)
Ordinal	9	(2%)
Unclear	39	(11%)
Primary outcome type in trials with 2 outcomes		
Continuous	76	(57%)
Dichotomous	38	(28%)
Ordinal	6	(4%)
Unclear	14	(10%)
Number of primary outcomes		
1	371	(74%)
2	67	(13%)
≥3	61	(12%)
Number of secondary outcomes [a]	5	(2–7)
Trial records that did not mention secondary outcomes	67	(13%)

[a] median (IQR).

difference planned vs. achieved sample size, per 10% unsuccessfully recruited participants, HR = 0.95, 95% CI: 0.91–1.00).

3.3. Reasons for non-publication and trial termination

Questionnaires were sent out to principal investigators of the 171 registered trials for which no publication was found. Of these, 22 (13%) researchers returned the questionnaire. Eighteen (82%) respondents confirmed that the trial results were unpublished, while 4 (18%) respondents mentioned they had already published their trial results. Main reasons for non-publication are given in Table 6. The most common response (6 respondents; 33%) was that there was insufficient time, resources or funding to analyze the results and write a manuscript. Four (22%) respondents indicated that they planned to disclose the trial results in the future.

A total of 95 questionnaires were sent inquiring reasons for trial termination, of which 15 (16%) researchers responded. Most respondents (6; 40%) gave recruitment failure as the main reason for trial termination. See Table 6 for other main reasons. Thirteen (87%) respondents indicated that trial termination was not foreseeable.

4. Discussion

In the present study, we aimed to investigate publication rates of results of small trials, and its determinants.

In our sample of small German trials, we found that only 65% of the trials published their results in journal articles or dissertations, even

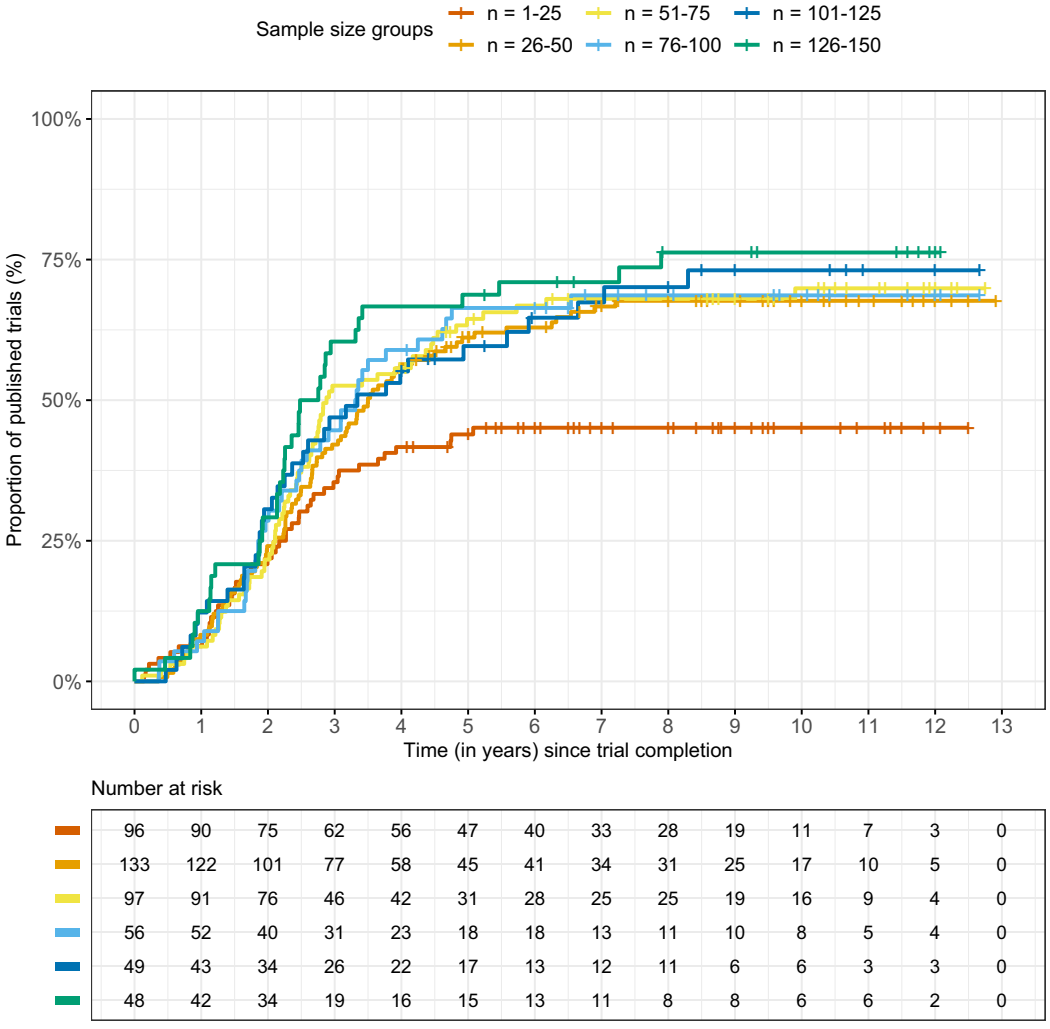

Fig. 2. Kaplan-Meier curves for time-to-publication stratified by sample size. The sample size groups are based on the IntoValue sample size variable.

Table 3
Univariable and multivariable hazard ratios (HR) with 95% CI on time-to-publication ($n = 479$ trials).

	Univariable HR (95% CI)		Multivariable[a] HR (95% CI)	
Sample size [b, c]	1.05	(1.02–1.08)	1.05	(1.02–1.08)
Phase				
II-III	ref		ref	
III	1.33	(0.92–1.94)	1.47	(1.00–2.18)
IV	1.19	(0.82–1.74)	1.23	(0.83–1.83)
Sponsor				
Other	ref		ref	
Industry	1.08	(0.84–1.38)	0.89	(0.66–1.21)
Intervention				
Other [d]	ref		ref	
Drug	0.99	(0.75–1.30)	1.07	(0.80–1.44)
Device	1.31	(0.93–1.85)	1.40	(0.97–2.01)
Mono vs. multicentric				
Monocentric	ref		ref	
Multicentric	1.11	(0.89–1.39)	1.05	(0.80–1.38)
Allocation				
Non-randomized	ref		ref	
Randomized	1.05	(0.80–1.73)	1.05	(0.76–1.47)
Masking				
Open	ref		ref	
Blinded	1.04	(0.83–1.30)	1.05	(0.79–1.39)
Trial registration				
Prospective	ref		ref	
Retrospective	1.19	(0.95–1.50)	1.17	(0.92–1.48)
Primary outcome				
Unclear	ref		ref	
Continuous	1.46	(0.96–2.20)	1.51	(0.99–2.31)
Dichotomous	1.47	(0.95–2.27)	1.47	(0.92–2.33)
Ordinal	1.05	(0.47–2.32)	0.89	(0.40–2.00)
Number of primary outcomes				
1	ref		ref	
2	1.10	(0.79–1.52)	1.14	(0.81–1.61)
≥ 3	0.89	(0.61–1.29)	0.86	(0.59–1.27)
Number of secondary outcomes				
Not available	ref		ref	
0–2	1.02	(0.69–1.52)	1.00	(0.67–1.50)
3–4	1.07	(0.72–1.59)	1.00	(0.66–1.52)
5–6	1.06	(0.71–1.58)	0.99	(0.66–1.50)
7–9	1.02	(0.66–1.59)	0.88	(0.55–1.39)
≥ 10	0.74	(0.48–1.16)	0.65	(0.41–1.03)

[a] Multivariable HRs are adjusted for all other variables in the table
[b] IntoValue sample size
[c] Analyzed per increase of 10 participants
[d] Other included 'behavioral', 'biological', 'dietary supplement', 'procedure', 'radiation' and 'other' interventions as given on the trial record

Table 4
Univariable and multivariable odds ratios (OR) with 95% CI on timely publication (<24 months after trial completion) (n = 499 trials).

	Univariable OR (95% CI)		Multivariable[a] OR (95% CI)	
Sample size [b, c]	1.04	(0.99–1.10)	1.05	(0.99–1.11)
Phase				
II-III	ref		ref	
III	1.17	(0.64–2.24)	1.37	(0.70–2.77)
IV	0.99	(0.53–1.90)	0.92	(0.47–1.87)
Sponsor				
Other	ref		ref	
Industry	1.07	(0.69–1.64)	0.65	(0.37–1.11)
Intervention				
Other [d]	ref		ref	
Drug	1.05	(0.64–1.75)	1.17	(0.69–2.03)
Device	2.13	(1.19–3.85)	2.43	(1.28–4.68)
Mono vs. multicentric				
Monocentric	ref		ref	
Multicentric	1.39	(0.94–2.06)	1.46	(0.90–2.37)
Allocation				
Non-randomized	ref		ref	
Randomized	1.04	(0.66–1.69)	1.44	(0.81–2.61)
Masking				
Open	ref		ref	
Blinded	0.81	(0.54–1.19)	0.77	(0.47–1.28)
Trial registration				
Prospective	ref		ref	
Retrospective	1.09	(0.74–1.62)	0.98	(0.64–1.49)
Primary outcome				
Unclear	ref		ref	
Continuous	1.18	(0.61–2.41)	1.20	(0.60–2.51)
Dichotomous	1.36	(0.68–2.86)	1.34	(0.62–3.01)
Ordinal	0.47	(0.07–2.02)	0.32	(0.04–1.47)
Number of primary outcomes				
1	ref		ref	
2	1.31	(0.73–2.28)	1.32	(0.71–2.42)
≥ 3	1.62	(0.90–2.84)	1.81	(0.97–3.34)
Number of secondary outcomes				
Not available	ref		ref	
0–2	0.68	(0.36–1.30)	0.72	(0.37–1.41)
3–4	0.71	(0.37–1.36)	0.70	(0.35–1.40)
5–6	0.58	(0.29–1.15)	0.53	(0.26–1.07)
7–9	0.51	(0.24–1.09)	0.47	(0.21–1.05)
≥ 10	0.25	(0.11–0.56)	0.23	(0.09–0.52)

[a] Multivariable ORs are adjusted for all other variables in the table
[b] IntoValue sample size
[c] Analyzed per increase of 10 participants
[d] Other included 'behavioral', 'biological', 'dietary supplement', 'procedure', 'radiation' and 'other' interventions as given on the trial record

after an extensive follow-up period of over 9 years. The overall percentage of disseminated results, which included summary reports on trial registries, was slightly higher (71%). These findings are in line with publication proportions reported in recent literature, although most studies have shorter follow up durations [1–4]. We found that 5 years after trial completion, only a few additional publications were found. This explains why we observed publication rates similar to those reported previously, despite a longer follow-up time. The median time-to-publication was 3.4 years, which is considerably higher than what is defined as timely publication (publication <24 months after trial completion) by the WHO [15]. In fact, only 28% of the trials in our sample were able to publish their results within 2 years. Although the proportion of timely published trials is similar to what has been reported previously [1–3,7], the median time-to-publication in our sample seems longer than other studies [9,10,17–19]. This difference can be partly explained by inclusion of terminated trials and trials with unknown completion statuses in our sample, and by different definitions of median time-to-publication (i.e., calculating median time-to-publication for published trials only, not accounting for censored trials and differing follow-up lengths), but may additionally be the result of small trials taking a longer time to publish their results.

Our analyses suggest several potential factors to be associated with publication rates in small trials. A smaller sample size is related to lower publication rates. Specifically, the difference between planned and achieved sample size, but not planned sample size in itself, seemed to be associated with the time-to-publication even after adjustment for terminated trials. Trials that were not able to recruit their planned number of participants may have become underpowered and consequently were unable to detect the effect of interest, potentially complicating further publication of the results. Phase III trials in comparison to phase II-III trials, appeared to have a higher likelihood of publishing their results earlier in time. This is in line with what has been previously reported [7]. We observed a similar, although non-significant effect for trials with device as an intervention vs. trials with other interventions, and trials with clearly defined continuous or dichotomous outcomes vs. trials that had unclear outcomes. The use of continuous vs. dichotomous outcomes however, did not seem to be particularly associated with publication rate. Funding, randomization, blinding, mono- vs. multicentric design and the number of primary outcomes did not predict time-to-publication in our sample of small trials. However, when strictly looking at publication within 2 years after trial completion, in addition to a larger sample size, phase III and device as the studied intervention,

Table 5
Univariable and multivariable hazard ratios (HR) on time-to-publication in trials with planned sample size n ≤ 150 (sensitivity analysis, $n = 394$ trials).

	Univariable HR (95% CI)		Multivariable[a] HR (95% CI)	
Sample size [b, c]	1.05	(1.02–1.08)	–	
Planned sample size [c]	1.00	(0.97–1.04)	0.99	(0.95–1.03)
Phase				
II-III	ref		ref	
III	1.37	(0.90–2.06)	1.71	(1.11–2.65)
IV	1.23	(0.81–1.86)	1.36	(0.87–2.12)
Sponsor				
Other	ref		ref	
Industry	1.11	(0.85–1.46)	0.98	(0.71–1.36)
Intervention				
Other [d]	ref		ref	
Drug	1.04	(0.77–1.40)	1.08	(0.78–1.50)
Device	1.37	(0.95–1.99)	1.55	(1.04–2.31)
Mono vs. multicentric				
Monocentric	ref		ref	
Multicentric	1.13	(0.88–1.45)	1.04	(0.77–1.40)
Allocation				
Non-randomized	ref		ref	
Randomized	1.10	(0.82–1.47)	1.25	(0.86–1.83)
Masking				
Open	ref		ref	
Blinded	1.07	(0.84–1.37)	1.14	(0.83–1.56)
Trial registration				
Prospective	ref		ref	
Retrospective	1.26	(0.98–1.62)	1.24	(0.96–1.61)
Primary outcome				
Unclear	ref		ref	
Continuous	1.41	(0.90–2.20)	1.45	(0.91–2.30)
Dichotomous	1.72	(1.07–2.76)	2.04	(1.23–3.38)
Ordinal	1.02	(0.43–2.38)	0.95	(0.40–2.25)
Number of primary outcomes				
1	ref		ref	
2	1.08	(0.75–1.54)	1.09	(0.75–1.58)
≥ 3	0.88	(0.59–1.32)	0.85	(0.56–1.29)
Number of secondary outcomes				
Not available	ref		ref	
0–2	1.09	(0.72–1.66)	1.08	(0.70–1.67)
3–4	1.07	(0.69–1.65)	1.05	(0.66–1.66)
5–6	1.19	(0.76–1.85)	1.20	(0.76–1.91)
7–9	1.12	(0.68–1.85)	1.06	(0.63–1.78)
≥ 10	0.82	(0.51–1.32)	0.77	(0.47–1.27)

[a] Multivariable HRs are adjusted for all other variables in the table (except sample size)
[b] IntoValue sample size
[c] Analyzed per increase of 10 participants
[d] Other included 'behavioral', 'biological', 'dietary supplement', 'procedure', 'radiation' and 'other' interventions as given on the trial record

Table 6
Main reasons for non-publication and trial termination.

Reason	No (%) of respondents	
Non-publication	$n = 18$	(100%)
No time / resources / funding to analyze results or write a manuscript	6	(33%)
Manuscript is written, but difficulty to get this accepted for publication	4	(22%)
The study was terminated or never started	5	(28%)
The results are not interesting	1	(6%)
Other	2	(11%)
Trial termination	$n = 15$	(100%)
Recruitment failure	6	(40%)
Sponsor decision / lack of funding	2	(13%)
Safety concerns	2	(13%)
Results of interim analysis: futility	1	(7%)
Other	4	(27%)

the use of ≥3 primary outcomes vs. 1 outcome and multicentric vs. monocentric design did appear to predict a higher probability of timely publication, although not all of these associations were statistically significant, potentially due to our limited sample size. A large number of secondary outcomes listed on the trial record in comparison to none specified, predicted a lower probability of timely publication.

Overall, the results show that many small trials in our sample had great difficulty with publishing their results in a timely manner. Possibly, researchers may have been too optimistic when designing these small trials and may have had unrealistic expectations regarding recruitment (as shown by the discrepancy between planned and achieved sample sizes), and perhaps also regarding the resources needed for the data collection, analyses and manuscript writing. Small trials often have fewer resources available compared to larger trials, and low publication rates may simply be an expression of this general feasibility problem. Another possibility is that the overall quality of the trials was low, as many trials in our sample were not able to recruit their planned sample size, implying poor trial operation. However, poor recruitment in trials, potentially indicating lower quality, appears relatively often [20], and we consider the publication of these trials important.

To our knowledge, the present study was the first study to investigate publication rates in small trials. We were able to follow up trials for a median of 9.25 years, with an absolute minimum follow-up length of 47 months. This is substantially longer than most studies investigating publication rates. Furthermore, we were able to investigate sample size in more detail – using sample size both as a continuous variable and distinguishing between planned and achieved sample sizes. We also explored the effect of primary and secondary outcomes on publication rates for the first time. Finally, our study was not restricted to one particular medical field, making the results more generalizable to other small trials.

Our study has several limitations. Firstly, the analyses were exploratory in nature and the number of trials investigated was limited. The results should therefore be interpreted cautiously. A future confirmatory study investigating a larger sample of trials in a different dataset is needed.

Secondly, our sample of trials only included registered trials from Germany. Our results may not be representative for trials that were performed in other countries, or trials that were not registered. Although most research institutions and journals require trials to be registered in order to be eligible for funding and publication, there is no legal requirement in Germany to register clinical trials [21]. It is possible that some trials were only registered because there was a wish to publish the results (in fact, some trials were registered after recruitment had already ended). This may have led to an overestimation of publication rates, and it could explain why our results showed a small benefit on time-to-publication for retrospectively registered trials.

Thirdly, we did not consider significance, nor the scientific strength of trial outcomes as a factor on time-to-publication. The significance of trial outcomes plays an important role in the publication process, and has been demonstrated several times in the past [7]. However, in the current study we did not have access to the significance of trial results for trials that were not published, as these were often not reported on trial records. As a result, our study may have been vulnerable to identify associations that could in part be explained by trial outcome significance. A study investigating a cohort of completed trials approved by RECs (where trial results are typically reported to the REC at the end of a trial, regardless of publication status) would be useful to investigate various factors on time-to-publication, adjusted for trial outcome significance, in the future.

Fourthly, a limitation of our study concerns the quality of the data entered in clinical trial records. Trial records were not always updated after trial completion and could therefore contain outdated information. Additionally, not all fields of a trial record are mandatory to fill in, which leads to missing information. Finally, information filled in was sometimes very poorly described or could be inconsistent between

different parts of the trial record (e.g., some primary outcomes were omitted in the 'outcome' section of a trial record in comparison to the primary outcomes listed in the 'detailed description' section – or vice versa). For about 10% of the trial records, we were unable to score the exact number and type of primary outcomes and for nearly half of the trial records, we were unable to precisely score the number of secondary outcomes (details in Table A.4, Appendix A). Furthermore, about 10% of the trial records had at least 1 unclearly described primary outcome (see Appendix C for several examples of unclear primary outcomes). Another related issue is that some trials had a double registration across two trial registries (clinicaltrials.gov and EU-CTR), but only reported summary results on one of these. All summary reports we found as result of our search strategy were added as "disseminated results", but we did not systematically check EU-CTR (unlike clinicaltrials.gov and DRKS.de) for each trial in our dataset. The actual number of disseminated trial results could therefore be slightly higher than what we found in our study.

A final limitation is that we may have missed some publications in our search. We tried to mitigate any missed publications by contacting principal investigators, while simultaneously investigating reasons for non-publication and trial termination – but response rates were very low.

5. Conclusion

About 35% of small trials in Germany remain unpublished, even after an extensive follow-up period of over 9 years. Publication rates in small trials are low, with a median time-to-publication of 3.4 years. Possible associated factors are sample size (particularly the difference between planned and achieved sample size), phase and intervention type.

Funding

There was no external funding for this project.

CRediT authorship contribution statement

M.S. Jansen: Conceptualization, Methodology, Investigation, Formal analysis, Data curation, Writing – original draft. **O.M. Dekkers:** Conceptualization, Methodology, Writing – review & editing. **R.H.H. Groenwold:** Conceptualization, Methodology, Formal analysis, Writing – review & editing. **B. Siegerink:** Conceptualization, Methodology, Resources, Writing – review & editing.

Declaration of Competing Interest

The authors declare no competing interests.

Acknowledgments

We would like to thank Nico Riedel and colleagues for making their data publicly available and enabling us to use it for our research.

Appendix A. Supplementary data

Supplementary data to this article (including Appendix A, B, C and D) can be found online at https://doi.org/10.1016/j.cct.2022.106899.

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