Publication of Clinical Trials on Medicinal Products: A Follow-Up Study

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Research

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Abstract

Background: Clinical research should provide reliable evidence to clinicians, health policy makers and researchers, which is only possible once the results are made transparently available. The present research aims to investigate factors influencing publication rates, time and characteristics of clinical trials on medicinal products and to assess the degree of accessibility of trial results on a country level.

Methods: Clinical trials authorized in Hungary in the year of 2012 were followed until publication and/or June 2020. Corresponding scientific publications were searched via clinical trial registries, Pubmed (MEDLINE) and Google.

Results: Out of 330 clinical trials authorized in 2012, a total of 232 trials were completed for more than 1 year in June 2020. The proportion of industry-initiation was high (97%).

Time to publication was 21 (22) months [median (IQR)]. Time to publication was significantly shorter when trials involved both European and non-European countries ($p<0.001$), and when registered in both EU CTR and clinicaltrials.gov ($p<0.001$) based on survival analyses.

A significant amount (24.1%) of unpublished clinical trial results were accessible in a trial register. A total of 70.93% of available publications were published “open access”.

Publications with domestic co-authors contribute to the research output of a country. In our study only 21.5% of the identified publications had a Hungarian author.

Conclusions: We encourage academic researchers to plan, register and conduct trials on medicinal products. Registries should be considered as an important source of information of clinical trials results. Measurable domestic scientific impact of trials on medicinal products need further improvement.

Introduction

Clinical research should provide reliable evidence to clinicians, health policy makers and researchers (1), which is only possible once the results are made publicly available (2). On a national level, published research means that the resources expended are not waisted and the results of the research become part of the international medical knowledge. Published research with a domestic author contributes to the assessment of the scientific performance of a country.

As of 2014, any trial of any medicinal product conducted in a member state of the European Union (EU) is required to be registered in the European Union Clinical Trials Register (EU CTR), which is administered by the European Medicines Agency (EMA). Following the 2012 European Commission guideline 2012/c302/03, sponsors must ensure that all trials registered on EU CTR disclose their results to the EMA within 12 months of trial completion; phase I trials are exempt unless they are part of a pediatric investigation plan (3). Voluntary initiatives (4) and recommendations (5) started to emphasize the importance of registration of clinical trials and subsequent reporting of results. The EU CTR also tries to

increase awareness on mandatory posting of results (6), and recently launched a page with a tutorial to facilitate posting of results on the EU CTR webpage (7).

Beyond mandatory posting in EU CTR, European researchers also often make the decision to register their studies in clinicaltrials.gov, the largest trial register worldwide. However, the extent to which trials conducted in the EU are registered in clinicaltrials.gov and whether this “multiple registration” has benefited the reporting of trial results or scientific quality of publications is not well investigated.

Results posted in registries currently have limited impact and awareness in the scientific community. Advantage of results reported to a registry is undeniably their standardized format (8, 9); however, these results do not undergo rigorous evaluation as do full scientific publications during the peer review process. Besides, publications and scientometrics are – despite international initiatives to change this (10) – currently an integral part of research evaluation and play a crucial role in decision making for national research policies, funding, promotions, and the careers of scientists (7). Therefore, it should be underlined that results posted in registries do not contribute to the total research output of either the participating researchers nor the participating country.

The aim of this methodological cohort study was to investigate how and to what extent does an authorized medical research conducted in a given country become visible and affects the research output of that country. We investigated publication rates, time until publication and the relationship between posting results in trial registers and publishing them as a full scientific publication. Further, we aimed to identify trial characteristics which are associated with timely publication of trial results, measures of scientific impact, authorship and open access publication in a representative sample of clinical trials authorized in Hungary.

Methods

In order to examine the publication rates and time of clinical trials conducted in Hungary, we collected detailed data on the human clinical trials on medicinal products authorized in the country back in 2012.

Search strategy

We used the advanced search function of the EU Clinical Trials Register (www.clinicaltrialsregister.eu) to identify clinical trials registered within the date range of January 1, 2012 to December 31, 2012 with Hungary as a participating research center.

Inclusion and exclusion criteria

Clinical trials were eligible for our study if a) Hungary was a site of the clinical trial; b) they were registered in the database by the National Institute of Pharmacy (Hungary) in the year 2012; c) no restrictions were applied to the trial phase, trial status or participant characteristics (e.g. age, gender, disease group).

Identification of trials in clinicaltrials.gov and data extraction from registries

We tried to identify included trials in the register clinicaltrials.gov by searching the EU CTR identifier or by the use of specific PICO terms.

We extracted pre-defined study characteristics from the study registries: full title of the trial, authorization date, trial start and completion dates, information on participating countries, sponsor, funder, trial scope, trial design, blinding, sample size, study phase, therapeutic area and presence of a data monitoring committee (DMC).

We determined whether or not study results were available in the study registries EU Clinical Trial Register and ClinicalTrials.gov. In this current paper, we aim to distinguish results available in the registries ("results in registries") from results published as full scientific publications ("publication").

Identification of corresponding scientific publications

Full scientific publications were defined as publications which were published in a scientific journal of any type and were reporting study results on pre-defined outcomes. We excluded methods papers and published protocols, and publications which reported results of a secondary analysis.

The availability of scientific publications was first checked in February 2019 and then 16 months later in June 2020. Publications were identified in a step by step process for each trial. First, we checked whether publications were already added to the register. In a second step, we searched for publications in the PubMed database with the following identification data: a) the trial register number, b) the investigators' names, c) keywords describing the intervention or the condition (PICO elements). As a third step, Google was searched with the same search terms.

All identified publications, potentially belonging to the registered study were checked for their content (study design, population characteristics, dates of recruitment, intervention, comparator). Publications which clearly described the results of the originally planned and registered study were included.

Data extraction from scientific publications

We extracted the following data from the scientific publications: the presence of author(s) with a Hungarian affiliation; the number of Hungarian authors or whether Hungarian participation in the study was mentioned in a way other than author affiliation; the journal's name, and date of publication. In cases when there were different forms of publishing (e.g. published electronically ahead of print), we took the first date when the full text of the final manuscript was accessible.

To estimate the time to publication, we counted total months between trial end date available in the EU Clinical Trials Register and the publication date. We expressed publication rate as the percentage of clinical trials with a full scientific publication divided by all clinical trials. The number of all clinical trials

was calculated separately for each month after trial completion, by adding trials without any publication to the number of trials with a publication only until the elapsed time since their completion.

Impact factors for each journal were derived from the Journal Citation Report, Clarivate Analytics via www.webofknowledge.com. Scimago journal rank (Q1-Q4) was derived from www.scimagojr.com.

We also wanted to see the public's degree of accessibility of results from published scientific publications. We therefore investigated whether scientific publications were published openly or with closed access. No distinctions were made between publications published in an open access journal and publications published in a hybrid journal by using the open access option.

Statistical analysis

For binary data, results were summarized as frequencies and proportions, and for continuous data as medians and interquartile ranges. We considered three analysis sets: a dataset based on all trials authorized in 2012 in Hungary, a dataset based on the trials completed for more than one year in June 2020, and a dataset based on corresponding publications. Data was analyzed by descriptive statistics and cross-tabulation. Time to publication was estimated by the nonparametric Kaplan-Meier estimator and the logrank test (by Mantel-Cox) was used to estimate potential effects of investigated factors on time to publication. Hazard ratios and confidence intervals were calculated on the basis of a Cox regression model. We used the statistical program SPSS version 26 (SPSS INC., Chicago, IL, USA) for our analyses.

Results

Included clinical trials

A total of 614 clinical trials were identified in our search. After excluding trials where 2012 did not correspond to the Hungarian registration date, but to the registration date of another participating country of multinational trials, a total of 330 Hungarian national or international clinical trials were eligible to be included in our methodological cohort (see **Additional File 1**). Eight years after trial authorization (in June 2020), a total of 232 clinical trials were "completed" trials for at least 1 year. Baseline characteristics of these trials are presented in Table 1.

Most of the trials were international, initiated and funded by the industry and assessed both efficacy and safety of a therapeutic intervention. Of the investigated clinical trials, 91.8% were registered both in the EU Clinical Trials Register and the clinicaltrials.gov database.

Table 1
Baseline characteristics of investigated studies

	All trials authorized in 2012 (n = 330)	Trials authorized in 2012 and completed for more than one year in 2020 (n = 232)
	%	%
Number of involved countries (one or more)		
- national trial	3.03	1.72
- international trial	96.96	98.28
Sponsor		
- Industry	96.96	98.7
- Non-Industry	2.72	1,3
Funder		
- Industry	94.24	94.83
- Non-Industry	1.51	0.43
- Not clear	4.24	4.74
Therapeutic Area		
- Infectious diseases	5.45	6.47
- Cancer	22.72	20.26
- Musculoskeletal disorders	10.9	11.64
- Gastrointestinal diseases	8.48	8.62
- Respiratory tract diseases	7.57	8.19
- Nervous system diseases	8.48	7.33
- Cardiovascular diseases	7.87	5.60
- Nutritional and metabolic diseases	7.87	9.05
- Immune system diseases	8.18	8.19
- Other	13.28	14.66
Registration		
- registered in EU-CTR only	10.30	8.19

	All trials authorized in 2012 (n = 330)	Trials authorized in 2012 and completed for more than one year in 2020 (n = 232)
- EU-CTR and clinicaltrials.gov	89.70	91.81

Publication rates

Publication rate over time is shown in Fig. 1.

Twelve months after completion, 19.8% of clinical trials were published as full scientific publication, while 5 years after trial completion 19.4% of studies were not available as full publication. The time between the end of the clinical trial and the publication of the full scientific paper was 21 (22) months [median (IQR)].

At the time of our search, 74.1% of completed clinical trials had an available corresponding scientific publication. A total of 70.7% of trial results were available as both full scientific publications and posted in registries; 3.4 % as publications without posted results in registries, 24.1 % in registries without an available full scientific publication, and 1.7 % of the trials authorized in 2012 and completed for more than one year had no results available in 2020 (see **Additional File 2**).

Factors influencing time to publication

Time to publication was significantly shorter in case of trials involving countries from both inside and outside Europe compared to trials with European sites only (**Additional File 3**; log rank $p < 0.001$); and in case of trials registered in both EU CTR and clinicaltrials.gov compared to trials registered in EU CTR only (**Additional File 4**; $p < 0.001$). Time to publication was not influenced by either being a national or an international trial (**Additional File 5**; $p = 0.45$), an RCT or non-RCT (**Additional File 6**; $p = 0.56$), or by the presence or lack of a DMC (**Additional File 7**; $p = 0.28$) (Table 2).

Table 2
Predictors of time to publication

	HR (95%CI)	p
Trial sites		
only Europe	1	
also from outside Europe	0.38 (0.22–0.66)	0.001
Trial registration		
in EU CTR only	1	
EU CTR and clinicaltrials.gov	0.24 (0.11–0.54)	0.001
Participating countries		
National	1	
International	0.65 (0.21–2.04)	0.46
Trial design		
RCT	1	
non-RCT	1.12 (0.75–1.68)	0.57
DMC		
No	1	
Yes	0.85 (0.63–1.15)	0.29

Scientific results were published earlier, if published in a Q1 as compared to a Q2-Q3 journal (Fig. 2; log rank p = 0.001; HR [95%CI]: 2.14 [1.32–3.48], p = 0.002).

Measures of scientific impact

Hungarian authorship and participation

Hungary was mentioned in 48.0% of the scientific publications (either as an author's affiliation or as a study site listed in the text). Publications had at least one author with a Hungarian affiliation only in 21.5% of cases (16.3% with one Hungarian author, 5.2% with two or more Hungarian authors).

Factors that significantly increased the probability of a scientific publication with a Hungarian author were trials conducted within Europe (RR 2.184 [1.104–4.321]) and initiated by the academy instead of the industry (RR 3.706 [1.953–7.032]) .Other investigated factors, such as studies registered in EU CTR only (0.769 [0.125–0.707), the lack of a DMC (1.071 [0.594–1.933]), non-RCT studies (1.216 [0.588–2.511]), and national trial studies (1.565 [0.308–7.957) had no effect on Hungarian authorship.

Impact factor and Scimago ranking of the journal

No differences were observed between the impact factor of publications with a Hungarian author compared to publications without (IF16.02 [16.59] vs. 19.47 [23.89]; mean [SD]; p = 0.389). The impact factor tended to be higher for international compared to national trials (18.98 [22.63] vs. 4.58 [4.48]; p = 0.171), for trials conducted also outside from Europe as compared to trials within Europe (19.28 [22.77] vs.12.47 [19.09]; p = 0.264), and for trials registered in both the clinicaltrials.gov and the EU CTR as compared to trials registered in EU CTR only (19.08 [22.80] vs.8.92 [8.21]; p = 0.445).

Studies that were initiated by the industry were less likely to have their results published in a Q1 journal (0.875 [0.826–0.926]), while trials with a data monitoring committee (DMC; i.e. a group of experts external to the study monitoring safety during study conduct) were more likely (1.131 [1.008–1.270]). Other investigated factors, such as registration in two or only one registry (1.055 [0.735–1.516]), international versus national trial (2.663 [0.537–13.204]), trials conducted outside of versus within Europe (1.249 [0.893–1.748]), or study design (1.020 [0.871–1.195]) did not affect the Scimago journal ranking of the subsequent publication.

Study results available for all, as part of an open access publication

A total of 70.93% of scientific publications were openly accessible, making the results accessible to the public. None of the investigated factors increased the probability for open access publication (see **Additional File 8**).

Influence of the industry on transparency and scientific impact of a trial

The number of authorized clinical trials initiated by the academy was extremely low (2.7% of all authorized trials). Clinical trials initiated by the industry or the academy are shown and compared in Table 3.

Table 3
Role of industry in trial conduct: comparison between industry-initiated and academy-initiated clinical trials (n = 329; no information for 1 trial)

	Industry-initiated clinical trials (n = 320) %	Investigator-initiated clinical trials (n = 9) %
Financial background		
Founded by the industry	96.88	11.11
Founded by non-industry	0	55.55
No information available	3.13	33.33
Trial design		
RCT	79.69	88.88
Non-RCT	16.88	11.11
No information available	2.81	0
Blinding		
Double-blind	62.19	44.44
Single-blind	1.25	0
Open-label	21.88	44.44
Not clear	14.69	11.11
Collaboration		
National	1.88	44.44
International (only EEA)	88.75	33.33
International (within and outside the EEA)	9.375	22.22
Trial scope		
Safety and efficacy	93.75	55.55
Safety	5	0
Efficacy	1.25	33.33
None	0	11.11
Trial phase		

	Industry-initiated clinical trials (n = 320) %	Investigator-initiated clinical trials (n = 9) %
Phase I	1.5625	0
Phase II	38.75	0
Phase III	52.8125	55.55
Phase IV	4.0625	22.22
Not mentioned/ More phases	2.8125	22.22
Data monitoring committee		
Yes	55.31	33.33
No	44.69	66.66
Availability of study results		
Results posted in EU CTR	73.125	11.11
Results published as full scientific publication	62.8125	55.55
Time to publication (months; mean [SD])	21.70 [16,82]	18.33 [3,77]
Impact on the scientific reputation of the authorizing country		
Publication with at least one Hungarian author	12.1875	33.33
Publication mentioning Hungarian participant(s)	27.5	44.44

All industry-initiated trials with accessible information regarding funding were funded by the industry. Investigator-initiated clinical trials were also partly funded by the industry. For one third of investigator-initiated trials information on funding was unavailable.

A DMC was available to a much larger extent in trials initiated by the industry.

Results for investigator-initiated trials were significantly less likely to be posted in a clinical trial register (73.1% vs. 11.1%) and also slightly less likely to be published as a full scientific publication (62.8% vs. 55.6%).

Both the rate of publications with at least one Hungarian author (33.3% vs. 12.2%), and the rate of publications mentioning Hungarian participation in any form (44.4% vs. 27.5) was higher among investigator-initiated as compared to industry-initiated trials.

Discussion

Summary of findings

Our study provides empirical evidence about the publication tendencies of authorized clinical trials in Hungary, the impact of authorized clinical trials on the scientific reputation of the authorizing country, and the role of multiple registrations in increasing transparency.

A total of 97.3% of authorized and EU CTR -registered clinical trials were initiated by the industry. About 20% of clinical trials were published within one year after trial completion. Trials conducted only within Europe and registered only in the EU CTR register were published significantly later.

Universality is a fundamental principle of science (11); open access publications have therefore the largest impact on the scientific community. In this study, 70.93% of publications were found to be openly accessible to the public. However, we were not able to identify trial characteristics which might influence the access to scientific publications.

Publications with Hungarian co-authors occurred in 21.5% of cases only. Clinical trials with study sites within Europe and trials initiated by the academy resulted more often in scientific publications with Hungarian authors.

Trials registered not only in the EU Clinical Trials Register, but also in the clinicaltrials.gov database were more likely to be identified as full publications. The results of clinical trials available as full scientific papers but absent in registries were in low numbers. However, we found that almost one quarter of results of the investigated clinical trials were available in registries, but not as a full scientific publication.

Strength and limitations of this methodological research study

Our study analyzed a representative sample of trials authorized in Hungary, the results can therefore be generalized to the country. All trials were registered in study registries, thus basic study information was available for all the trials included in our study. All data extractors were trained and the main outcome data were double-checked and double-extracted.

Our study has limitations. The cohort was composed of trials that were authorized and included in the study registry EU Clinical Trials Register by the national authority. Due to the low number of investigator-initiated trials it is difficult to draw firm conclusions on their publication tendencies. Nevertheless, our results may indicate a publication trend also for investigator-initiated trials.

Another limitation is, that the information provided for researchers in the EU Clinical Trials Register on trials defined as completed (when it „has been completed in accordance with the full requirements of the protocol”) might be interpreted in different ways by researchers and may have impacted our results. We

searched for scientific publications in 2020 and trials completed within one year before the search date were excluded.

Comparison with other studies

To our knowledge, this is the first study investigating how and to what extent research authorized and conducted in a given country becomes visible and affects the scientific performance of that country.

Authorship issues were already discussed is several papers, dealing mainly with gender distribution of authorship (12, 13); association between sponsorship and authorship (14, 15); under-representation of researchers from specific regions in papers published from research done in these regions (16, 17); and difficulties and possibilities in determining authorship in multicenter clinical trials (18, 19). These studies were mainly based on publication data sets. The approach to prospectively follow trials authorized in a given country until publication and investigate authorship in such a cohort of studies is novel.

There was one large cohort study investigating compliance with requirement to report results on the EU Clinical Trials Register up to December 2016 (8). This study found that trials with a commercial sponsor tend to be substantially more likely to post results on the EU CTR than those with a non-commercial sponsor (68.1% v 11.0%)(8). This is in line with the results of the present study: a significantly higher posting of results in the EU CTR for industry-initiated trials were found (73.1%) than for investigator-initiated trials (11.1%). Besides the need for standardized procedures (20), periodic quality control assessments during trial implementation (21), improved reporting about funding (22), improvement of reporting (23), mandatory trial registration and trial result posting are additional requirements which still are not optimal in case of investigator-initiated trials.

Implications of findings for practice, policy and future research

All interventional clinical trials on medicinal products authorized in the European Union and, without any distinction by type of sponsor, should be registered in the EU Clinical Trials Register. To get a valid picture about research activity on a country level, the EU Clinical Trial Register for trials conducted in Europe should be the first step to register a trial. Trial registration in the clinicaltrials.gov register can further increase the visibility of registered European trials.

The present research shows that a surprisingly low number of clinical trials initiated by the academy are registered in the EU Clinical Trial Register in Hungary. Academic clinical trials have an important place on the map of clinical research. These studies focus on specific questions that arise during clinical care and are extremely important in everyday medical practice; these include but are not limited to facilitating the optimization of a therapy, or the discovery of potential new clinical areas where a therapeutic intervention can be used. Increased transparency and use of results of academic clinical trials is essential for evidence-based medical decision-making and optimal patient management.

Posting trial results in study registries might be the first step to make study results become openly available for the public; however, study results should be published also as a scientific publication as soon as possible after trial completion. Systematic reviewers and guideline developers are advised to search clinical trial registers in addition to electronic databases to identify study results, which have not been published as full text publications at the time of the search.

The present study also showed that the participation of Hungarian researchers in industry-initiated studies on medicinal products has only partial measurable scientific benefits, as Hungarian researchers appear as authors in only a fraction of scientific publication derived from these trials. Several publications not even contain the list of countries of trial participants. In line with the Lancet journals, which strongly support the inclusion of authors from local countries on papers reporting studies from those countries, we also would like to "encourage authors to include researchers who originally collected the data, where possible, and to share expertise in analysis and other skills, so that the research capacity of the country from which the data were obtained is strengthened" (24); i.e. to enable local researchers to fulfil the criteria for authorship developed by the International Committee for Medical Journal Editors.

The scientific performance of universities and countries is evaluated and ranked – despite valuable initiatives for change – based on research productivity (i.e. the number of scientific publications), research impact and research excellence (i.e. the number of scientific papers in high impact journals). Considering that slightly over a fifth of authorized Hungarian trials result in scientific publications with a Hungarian co-authorship, we can conclude that the authorized, mainly industry-initiated clinical trials on medicinal products currently result in limited measurable scientific benefits to the participating researchers and their countries.

Conclusions

We call researchers of investigator-initiated clinical trials, to register their trials in an openly available clinical trial register. Trial registers have to be considered as an important source of information of clinical trial results, as they may contain results from unpublished trials or trials published with closed access. Domestic scientific impact of trials on medicinal products has to be further improved; an increase in the number and role of investigator-initiated trials might help to achieve this goal.

Declarations

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Consent for publication: Not applicable.

Availability of data and material: The data supporting the conclusions of this article is included within the article (and its additional files).

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Figures

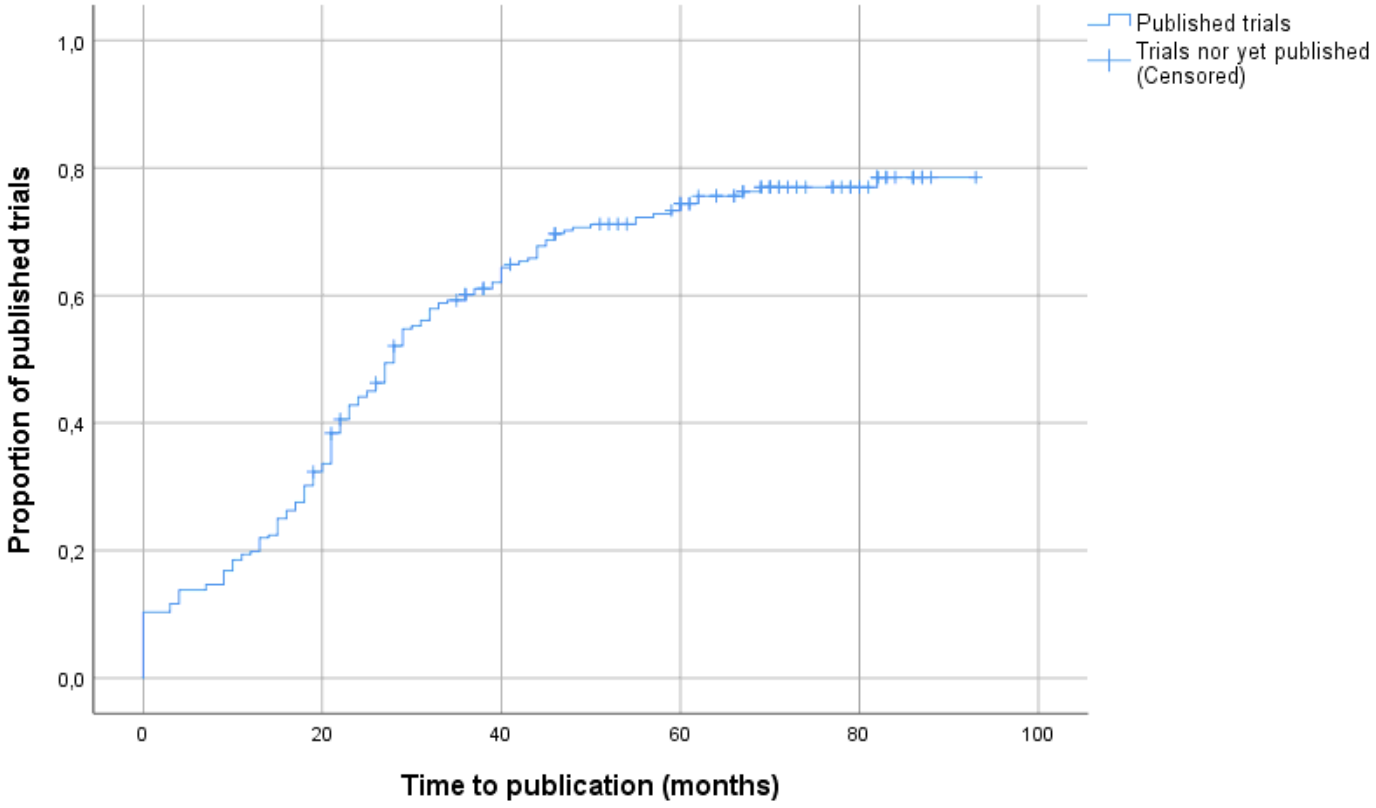

Figure 1

Publication rates over time in a cohort of trials authorized in 2012 in Hungary (n=232)

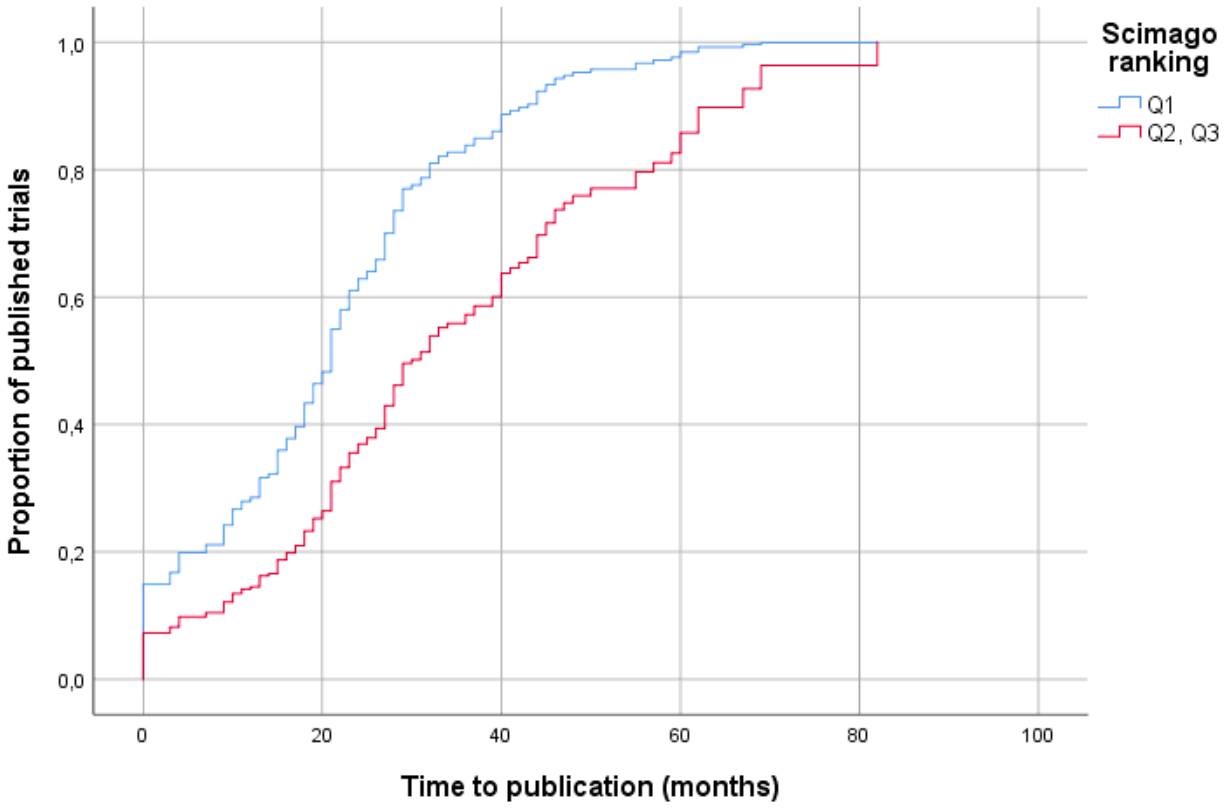

Figure 2

Publication rates over time in Q1 (n=151), and Q2-Q3 (n=21) journals* *the Q2-Q3 group contains 19 Q2 and two Q3 publications

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- CONSORT2010ChecklistPublpraxisinHungarymanuscript.doc
- Additionalfile1.tif
- Additionalfile2.tif
- Additionalfile3.tif
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- Additionalfile6.tif
- Additionalfile7.tif
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