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Benchmarking university medical centres for responsible metrics.

A cross sectional study on timely results dissemination across 36 German centres

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Abstract (347 words)

Background: The results of completed clinical trials build the backbone of evidence-based medicine and inform the design and review of future trials. Many investigations, however, have found that a large proportion of trial results are not disseminated or disseminated with a substantial delay. For most clinical trials, university medical centres (UMCs) take the academic lead. The UMC-specific proportion of timely disseminated trial results thus becomes a "responsible metric" that can inform alternative national and international benchmarking of UMCs. **Methods**: We sampled and tracked all registered trials for all German UMCs that were officially completed between 2009 and 2013. We present our results in several formats, including percentages, Kaplan-Meier graphs and logistic regression modelling. The results, together with an interactive website, benchmark all German UMCs with regard to their performance in results dissemination. **Results**: We identified and tracked 2,132 clinical trials. For 1,509 trials, one of the 36 German UMCs took the academic lead. Of these 1,509 "lead trials", 39% published their results via journal publications or summary results in a timely manner (<24 months after completion date). This publication rate varied from 20% to 64% across all

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36 German UMCs. More than six years after study completion, 26% of all eligible lead trials still had not disseminated results, accounting for an average of more than 8,000 trial participants each year that were included in trials without any knowledge gain. **Conclusion** Despite substantial attention to the topic in the last decade, there is still a delay or even absence of results dissemination of trials, which is unethical, wastes public resources, and negatively affects decision making in medical research and health care. German UMCs have many unique opportunities to improve this situation. The timely dissemination of trial results should become a principle of "Good Scientific Practice" guidelines and play a role in institutional reward and incentive schemes. Funders may consider dissemination practices when reviewing applications for clinical studies. Further research should evaluate whether and how a transparent benchmarking of UMC performance in trial results dissemination and other "responsible metrics" helps to increase value and reduce waste in medical research.

Background

The results of clinical trials build the backbone of evidence-based medicine. They inform clinical decision making [1] and health technology assessment [2, 3]. They also inform decision making within ongoing trials and decision making related to the design, review, and funding of new trials [4]. Because non-dissemination or delayed dissemination of trial results negatively affects all of these decision-making processes, [5-8] it has been investigated and criticized for over three decades [9-11]. In 2013, the revised Declaration of Helsinki included the requirements that every study involving human subjects should be prospectively registered and that all results should be made publicly available – irrespective of the results' direction [12]. The joint statement by the World Health Organization in 2015 defined "timely publication" as "24 months for publication in a peer-reviewed journal (preferably open-access) and 12 months for publication of the key results in the registry's result section" [8].

The current dissemination of clinical trial results looks quite different. Recently, Chen et al. analysed the publication of more than 4,000 interventional clinical trials across all 51 US university medical centres (UMCs) that were completed between October 2007 and September 2010. Only 29% of trials published their results within 24 months after study completion, and only 13% of trials posted their results in the registry. Overall, as of July 2014, 35% of all trials were found to be unpublished. Pica et al. analysed 455 registered paediatric clinical trials completed by December 2012 and found 21% (n=94) to be unreported in September 2015.

In recent years, journals [13], agencies (the Food and Drug Administration (FDA) and European Medicines Agency (EMA)) [14], ethical guidelines [15], and most recently, funding bodies [16] have all explicitly highlighted the need to reduce publication bias and developed policies to proactively achieve this objective. UMCs, however, which function as trial sites and host the responsible principle investigators (PIs), have remained surprisingly silent about this issue [17, 18]. A transparent benchmarking for how complete and timely UMCs are in reporting their trial results could incentivize the implementation of more effective UMC policies in this regard. Such benchmarks could also raise public and media awareness about this issue. The findings from Chen et al. allow such a benchmarking for U.S. UMCs based on nine different data sets presented in their paper (e.g., "overall rate of results reported or published" and "rate of publication <24 months after study completion"). The "TrialsTracker" for the FDA (https://fdaaa.trialstracker.net) and the EU

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(http://eu.trialstracker.net) is another source that provides automatically updated data for benchmarking activities [19]. TrialsTracker increases its public outreach by presenting results via a publicly accessible website and by mentioning the performance of individual centres on Twitter [20]. TrialsTracker, however, has two limitations. First, it focuses on trials that fall under mandatory reporting rules according to the FDA Amendment Act (FDAAA) or the European Commission guideline 2012/c302/03. Second, its method is restricted to the automated search of registry entries and national clinical trial (NCT) identifiers in PubMed.

In this study, we further develop the concept and practice of benchmarking UMCs in three ways. First, with regard to the sample, we sampled and followed up trials that were officially completed between 2009 and 2013 for all German UMCs. Germany is ranked second in the world and first in Europe for the number of active clinical trial sites [21]. Second, with regard to the search strategy, we extended the standard publication search strategies to comprehensive hand searches in Google Scholar to better understand the full picture of available results published outside registry websites and PubMed. Third, with regard to benchmarking, we developed a website, including a Shiny app, that allows the interactive visualization of benchmarking according to the different variables that influence publication measurement, such as time to publication, publication format, sponsor, timing of registration, and completion date.

Methods

The protocol for this project, including all methodological details for sampling and following up clinical trials for data extraction, and statistical analyses were preregistered with the Open Science Framework (OSF) and continuously updated for amendments (https://osf.io/fh426/). In the following sections, we summarize the methods.

Retrieval of trials

We downloaded the AACT dataset, which aggregates information from ClinicalTrials.gov into a relational database, from http://aact.ctti-clinicaltrials.org/ (version date: April 17, 2017). We further downloaded the dataset from the German Clinical Trials Registry (DRKS) from www.drks.de on July 27, 2017. We used an R script to combine all relevant datasets and search criteria needed to retrieve clinical trials from all 36 German UMCs and to extract their study characteristics.

Inclusion and exclusion of studies

R was also used to restrict the resulting dataset to studies with a primary completion date (AACT) or study end date (DRKS) in the years 2009-2013, as well as to exclude observational studies, incomplete entries (missing NCT, affiliation or primary completion date), and duplicates.

For the AACT dataset, a trial was assigned to a UMC if the UMC was either mentioned as a "responsible party" (e.g., lead sponsor or principal investigator) or as a "facility". For the DRKS dataset, the affiliation of the primary sponsor in the "address" and "recruitment location" fields was used. After automatic filtering for the UMC names, the correct assignment of trials to UMCs was verified manually. Only studies with the status "Completed", "Terminated", "Suspended", or "Unknown" (or the equivalent DRKS categories; see detailed methods on OSF) were included. Studies from the DRKS sample that also appeared in the AACT sample were identified by searching for NCT IDs and subsequently removed.

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Publication search

For each of the included studies, a results publication was searched independently by two researchers in a 3-step process between July 2017 and December 2017 (see also Figure 1, search strategy). 1) The clinical trial identifier (NCT ID or DRKS-ID) was entered on ClinicalTrials.gov/DRKS.de, and the earliest result publication linked in the registry was searched. Reviews and other background literature were excluded. 2) The clinical trial identifier was entered on PubMed. 3) Google Scholar and (if no hit was found) Web of Science were searched by subsequently entering the following search terms: clinical trial identifier, official title, brief title (not available for DRKS data), both intervention name and principal investigator (DRKS: name associated with primary sponsor). The first 2 results pages were screened. Publications that did not contain the registry identifier were matched using a list of explicit criteria (i.e., study design, intervention, and outcomes). All criteria needed to be met to be counted as a match.

If, after all three searches, there was still no result, the study was characterized as "no publication found". Additionally, the researchers checked if a summary result was posted on CT.gov.

For further information on interrater reliability, data extraction, R-scripts, and statistics (logistic regression and Kaplan-Meier), see the abovementioned protocol registered with OSF (https://osf.io/fh426/).

Results

Demographic data

We identified 2,132 clinical trials via clinicaltrial.gov (n=1,905) and DRKS (n=227) that i) recruited trial participants from at least one German UMC and ii) had their primary completion date (PCD, last visit of last patient for a primary outcome measure) between 2009 and 2013. These trials included 506,876 anticipated participants.

Altogether, in 71% (n=1,509) of all trials, the corresponding German UMC either was the lead sponsor or hosted the PI and was thus legally determined to be the "responsible party". Of these 1,509 "lead trials", 516 (34%) investigated drugs, and 276 (18%) investigated devices; the rest were "behavioural", "procedure" or "other" interventions. Only a minority of these lead trials (n=371; 25%) were registered prospectively, and 909 (60%) were registered more than 21 days after the given start date of the study, with 258 (17%) registered after the completion date (CD). 118 lead trials (8%) included more than 500 anticipated participants. A total of 1,095 trials (73%) were completed, and 138 (10%) were either terminated early or suspended; for 276 trials (18%), the status was unknown. For additional demographic data, see Table 1.

Overall results reporting and the Shiny app website

In the following sections, we report the most essential findings of our study. Our fine-grained analysis, however, allows the combination of different measurement variables in different ways, e.g., i) the proportion of summary results reported after 12, 24, or 60 months, ii) the proportion of result publications in peer-reviewed journals after 24 months for all non-drug trials, or iii) the proportion of results reported after more than 6 years for all trials with industry as sponsor. Because our paper cannot report on all different combinations, we developed an interactive website (based on a Shiny app) that allows users to select and combine the measurement variables in which they are most

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interested and develop a corresponding benchmark for all 36 German UMCs. The website is http://s-quest.bihealth.org/intovalue/

Of all 1,509 lead trials, we could follow up 1,490 for a minimum of 24 months after the CD. Of those trials, 39% published their results via journal publications or summary results within 24 months after the CD. At the level of German UMCs, this publication rate varied from 20% to 64% (Table 2). Across "high-volume" centres (>50 completed trials), the publication rate varied from 29% to 49%. Figure 2 presents the percentage of unpublished trials over time. By April 2017, summary results were reported in the registry for 94 (7%) of 1,295 lead trials registered with clinicaltrials.gov.

Of the 1,509 lead trials, there was a subgroup of 666 trials that we could follow up for more than six years after the CD. For this subgroup, we found an overall publication rate of 74%, with a variation across universities of 56% to 100%. Altogether, 18,345 participants were planned to be included in the 173 trials that have not published their results. Extrapolated to the full sample of lead trials (18,345 × 1,509 ÷ 666 ÷ 5 years) an average of 8,313 planned participants per year were included in trials from German UMCs that did not disseminate their results after more than six years.

All the results presented above were generated by time-intensive searches, including searches in Google Scholar and Web of Science (see Methods), that were performed independently by two researchers with training in literature searching. When restricting our search efforts to more convenient standards (registry and PubMed; see Methods), we could identify results for only 26% of trials within 24 months after CD (vs. 39% with our extensive search) and for 45% of trials followed up for more than six years (vs. 74% with our extensive search). Thus, we could identify 33% of all timely publications and 39% of all publications with a six-year follow-up period only via the additional search strategies.

Subgroup analyses

The overall publication rates (for more than six years after CD) differed substantially (more than 10%) according to the following factors:

- sample size (72% for trials with 1-100 participants but 92% for trials with >500 participants),
- timing of registration (72% for prospectively registered trials but 85% for trials registered after the CD), and
- trial status (49% for trials with terminated/suspended/unknown status but 84% for completed trials).

The timely publication rates (within 24 months after CD) differed substantially according to the following factors:

- the completion year (37% for trials completed in 2009 up to 51% for trials competed in 2013)
- the lead sponsor (52% for trials with industry as the lead sponsor and 39% for trials with academia as the lead sponsor).

The logistic regression analysis yielded consistent results and identified similar variables with a strong effect on timely publication (see the supplementary file on OSF), although the associations were too weak to predict which studies will be reported in time with great confidence.

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Discussion

In this study, we demonstrate that only 39% of all registered clinical trials conducted at one of the 36 German UMCs published their results in a timely manner within 24 months after the trial's completion date (CD). This rate further decreases when applying standard search strategies: only 26% of trials published results in both a "timely" and "easily accessible" manner. Even more than six years after the CD and with the most extensive search strategies, 26% of all trials remain unpublished and do not report summary results in the registry.

For the following reasons, this high proportion of delayed or omitted result dissemination is unethical and a substantial waste of important research resources. First, the fact that 26% of all clinical trials withhold the knowledge they gained or delay its dissemination negatively impacts i) the design of future, non-redundant translational research and ii) patient-oriented, evidence-based medical decision making. Second, every year, more than 8,000 participants on average were included in lead trials from German UMCs that did not generate any knowledge gain and thus no social value. Social value, however, is the basic ethical principle justifying research that adds burdens and risks to participants. Moreover, most trial participants are patients who already suffer from a disease. Third, administrative efforts to report summary results in the tabular format required by ClinicalTrials.gov are minimal, and this type of results reporting does not prevent more detailed and contextualized result publications in peer-reviewed journals [22]. Despite the ethical rationale and the low administrative burden, only 7% (n=94) of clinical trials conducted at German UMCs ("lead trials") reported their summary results in clinicaltrials.gov. The recently published EU TrialsTracker that evaluated the compliance with summary results reporting in the EU Clinical Trials Registry (EUCTR) confirmed these low reporting rates [19].

In contrast to most other trial tracking activities our search strategy included additional hand searches in Google Scholar that identified many publications that were not indexed at clinicaltrials.gov or PubMed. To increase the value of clinical trials, authors of peer-reviewed publications should proactively link their publications at the trial's registry entry.

German UMCs have many unique possibilities to improve the current situation. A minimally time-consuming option would be to develop policies highlighting the ethical duty of PIs to publish on time. In Germany, all UMCs put much emphasis on the so-called "Good Scientific Practice" guideline ("Gute Wissenschaftliche Praxis"), which was published by the German Research Foundation (DFG). Timely and unbiased reporting of research results is not but should become a core principle of guidelines defining good scientific practice or research integrity. A second option would be to reward those PIs who manage to publish their results in a timely manner and/or report summary results in the registry. At German UMCs, the performance-oriented allocation of funds ("LOM/Leistungsorientierte Mittelvergabe") currently only rewards aggregated impact factors and third-party funding. A third and harsher option would be to sanction those PIs who do not manage to report at least summary results in the registry within 24 months after CD.

The timely publication rates (within 24 months after CD) for German UMCs (39%) and US UMCs (36%) [23] are similar. However, the U.S. study by Chen et al. defined "study completion" as the PCD. In contrast, our study referred to the CD, which is 7 months later on average than the PCD. When following the German trials from the PCD, the timely publication rate decreases to 31%. Further

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differences in results between the U.S. and the German sample highlight the importance of developing default measures for assessing publication rates. We will publish a more detailed commentary on how different measurement variables influence the assessment of publication rates elsewhere.

Even though some study characteristics were related to an increased probability of timely publication (i.e., industry sponsored, large sample size and completion year), this information cannot be used to reliably distinguish studies that will be published in a timely manner and those that will not. This finding suggests that a plethora of causal factors determine timely publication; thus, the solution to this issue is probably multifaceted, with changes needed at several levels.

Our study, however, has several limitations. Our results might underestimate the true publication rates because we did not search in scientific databases other than PubMed and Web of Science, and we did not contact the responsible parties. However, our study included additional hand searches in the broad search engine of Google Scholar, and we identified higher publication rates than all former tracking studies. Our results might also overestimate the true publications rates for several reasons. First, most included trials were retrospectively registered. These trials had substantially higher publication rates, which might reflect a registration and reporting bias. Furthermore, we did not include observational clinical studies in our sample. Former tracking studies that sampled at the level of German institutional review boards (IRBs) reported substantially lower publication rates for observational studies [24].

Finally, but importantly, the substantial improvement in timely publication (within 24 months after CD) over time, with 70% for trials completed in 2015 or later, is very promising. In contrast, the very low proportion of trials (7%) that report summary results in the registry is alarming, as most trials thus forego an important opportunity to increase their scientific and social value. Additionally, more recent trials might get published in a timely manner, but old trials still have relevant information that remains unavailable and unused. These results, which are both promising and alarming, should encourage German UMCs and other stakeholders, such as patient and funding organizations, to further improve their efforts and develop policies for the timely publication of trial results for future trials, as well as already finished yet unpublished trials. The publicly available Shiny app (http://s-quest.bihealth.org/intovalue/) might further be used to raise awareness about this element of good scientific practice in the scientific community and in the public.

Tables and figures

Table 1: Demographic data for "all trials"

	All trials		Lead trials	
Total	2132	100.0 %	1509	100%
Type of intervention				
Behavioural	125	6%	125	8%
Biological	97	5%	40	3%
Device	422	20%	276	18%
Dietary supplement	65	3%	64	4%
Drug	894	42%	516	34%
Genetic	2	0%	1	0%
Other	121	6%	114	8%
Procedure	162	8%	143	9%
Radiation	17	1%	16	1%
Lead sponsor				
Industry	774	36%	252	17%
Academia	1358	64%	1257	83%
Phase				

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I	101	5%	79	5%
I-II	92	4%	64	4%
II	429	20%	271	18%
II-III	80	4%	47	3%
III	414	19%	184	12%
IV	250	12%	185	12%
Not given	766	36%	679	45%
Mono-/Multicentric				
Multicentric	1056	50%	466	31%
Monocentric	1003	47%	970	64%
Not given	73	3%	73	5%
Number of participants				
1-99	1139	53%	929	62%
100-500	745	35%	452	30%
>500	238	11%	118	8%
Not given	10	0%	10	1%
Time of registration				
Before trial start	603	28%	371	25%
After trial start	1528	72%	1137	75%

21 days after trial start	1192	56%	909	60%
60 days after trial start	918	43%	744	49%
After trial completion (CD)	280	13%	258	17%
After publication	26	1%	20	1%
Start date not given	1	0%	1	0%
Trial end (CD)				
2009	226	11%	164	11%
2010	335	16%	241	16%
2011	417	20%	303	20%
2012	456	21%	339	22%
2013	476	22%	330	22%
2014	132	6%	83	6%
2015	55	3%	31	2%
>2015	35	1%	18	1%
Trial status				
Completed	1595	75%	1095	73%
Terminated	221	10%	130	9%
Suspended	10	0%	8	1%
Unknown status	306	14%	276	18%

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Table 2: Publication rates at the level of individual German university medical centres (UMCs)
→ More variations of this table are available on the interactive website http://bit.ly/intovalue.

Cities	# of Trials	Published <24 m after CD	%	# of Lead trials	Published <24 m after CD	%	High-volume[1] German UMC (numbers indicate top 5)
Aachen	80	31	39%	34	12	35%	
Berlin/Charité	422	183	43%	163	55	34%	x
Bochum	76	32	42%	34	11	32%	
Bonn	129	64	50%	42	15	36%	
Dresden	166	88	53%	59	26	44%	4
Duisburg	147	70	48%	41	18	44%	
Düsseldorf	92	43	47%	33	15	45%	
Erlangen	134	62	46%	56	16	29%	x
Frankfurt	186	86	46%	55	20	36%	x
Freiburg	194	88	45%	81	27	33%	x
Giessen	77	28	36%	28	7	25%	
Göttingen	89	43	48%	33	12	36%	
Greifswald	58	20	34%	30	6	20%	
Halle	82	22	27%	29	9	31%	
Hamburg	180	89	49%	56	23	41%	x
Hannover	189	87	46%	72	26	36%	x
Heidelberg	267	127	48%	134	50	37%	x
Homburg	86	53	62%	22	14	64%	
Jena	89	39	44%	38	11	29%	
Kiel	99	41	41%	23	9	39%	
Köln	128	68	53%	52	24	46%	3
Leipzig	154	83	54%	60	25	42%	5
Lübeck	75	32	43%	19	5	26%	
Magdeburg	66	28	42%	22	5	23%	
Mainz	147	67	46%	33	8	24%	
Mannheim	102	46	45%	33	12	36%	
Marburg	86	37	43%	25	8	32%	
München LMU	156	83	53%	60	26	43%	2
München TU	161	80	50%	92	39	42%	x
Münster	111	49	44%	32	10	31%	
Regensburg	66	37	56%	22	11	50%	
Rostock	53	25	47%	12	6	50%	
Tübingen	178	93	52%	65	32	49%	1
Ulm	133	78	59%	42	21	50%	
Würzburg	79	42	53%	26	11	42%	
Witten-Herdecke	21	7	33%	18	5	28%	
TOTAL			**44%**			**39%**	

[1]high-volume centres: >50 completed trials

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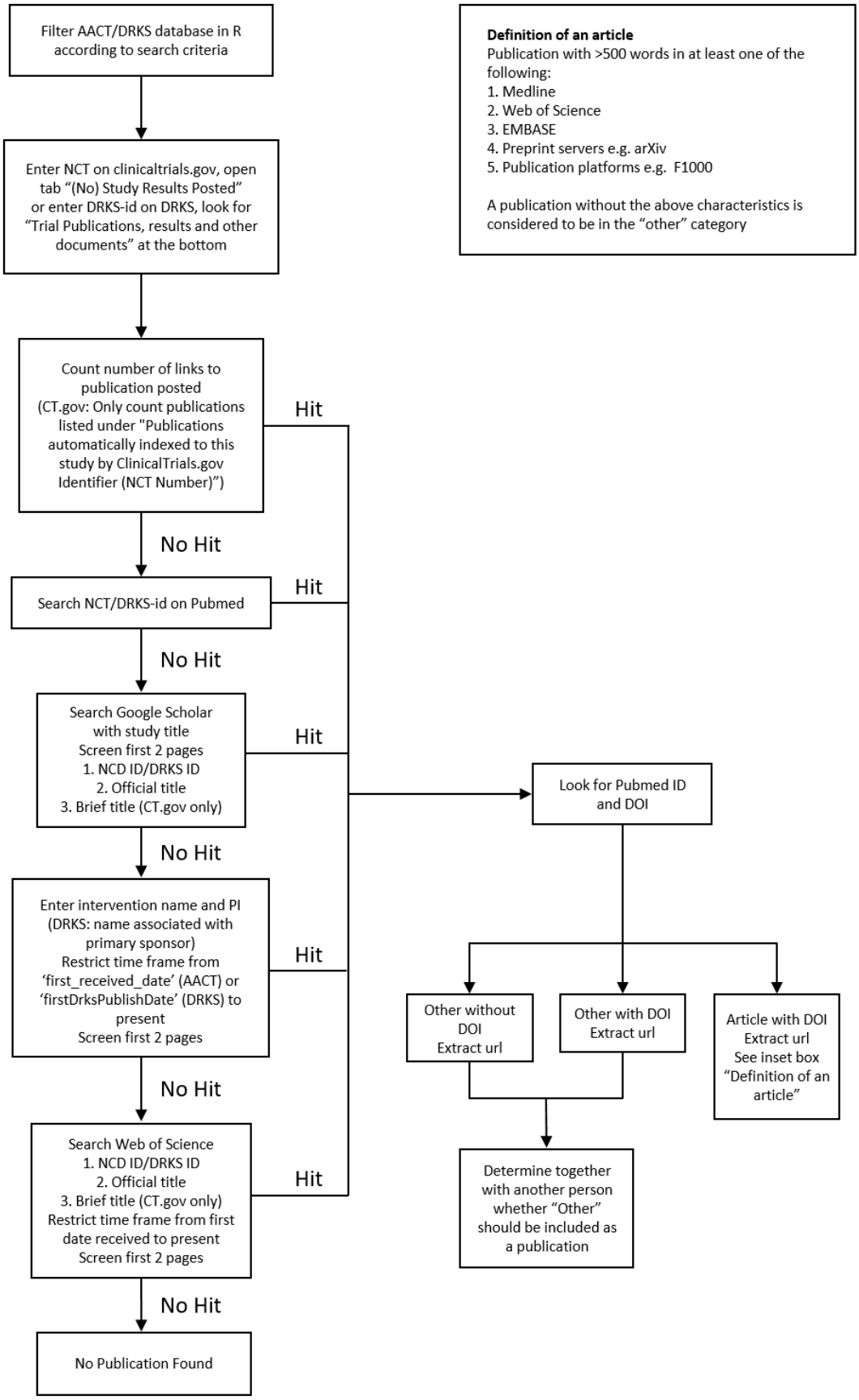
Figure 1: Search strategy



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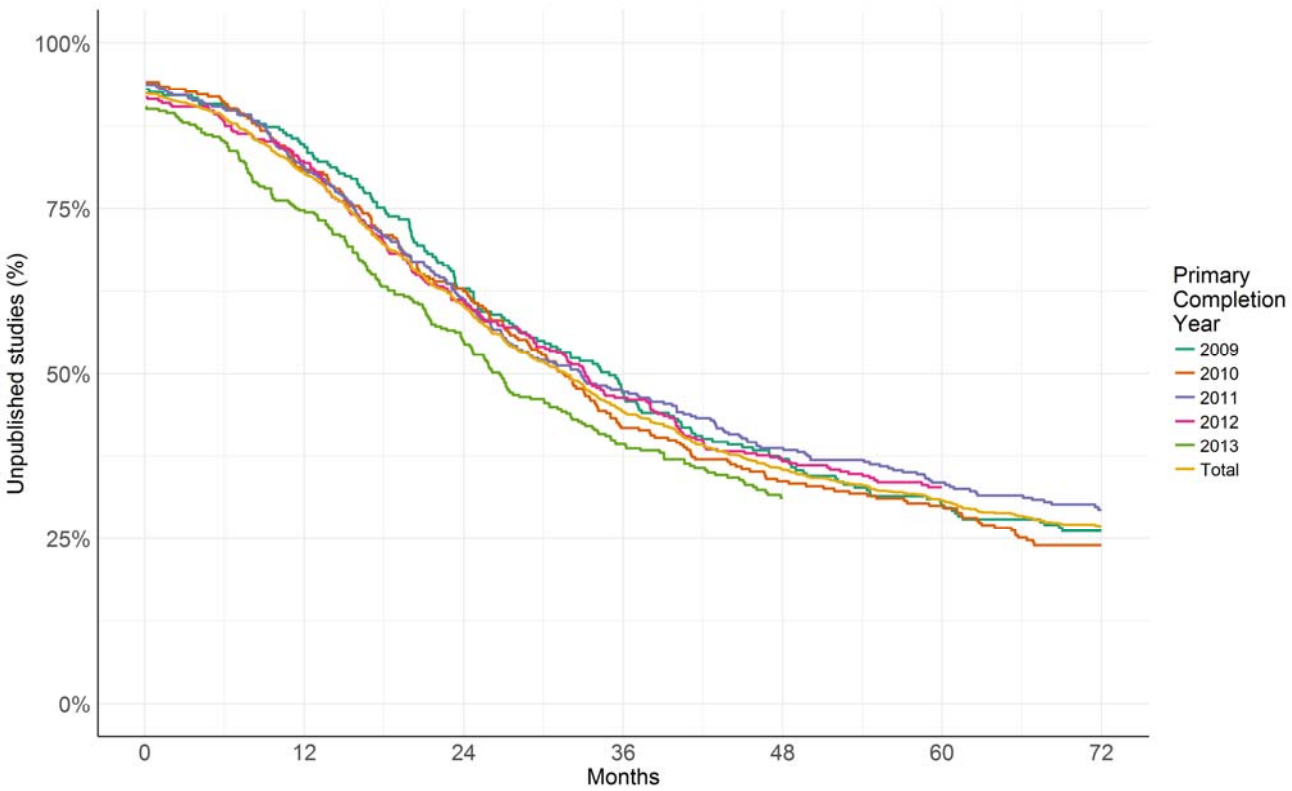

Figure 2: Kaplan-Meier curve showing the percentage of unpublished lead studies over time grouped by primary completion year.

More variations of this graph are available on the interactive website http://s-quest.bihealth.org/intovalue/

Competing interest statement

All authors are affiliated with a German UMC in Berlin, Hannover or Freiburg. No further conflicts of interest exist.

Contributorship statement

DS, JM and UD designed the study. SW, NR, KW, HK, SO, CS, SK, UK and BS performed the search. NR, SK and BS performed the statistical analysis. All authors were involved in writing and editing the manuscript.

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Data sharing

All data can be viewed at http://s-quest.bihealth.org/intovalue/. The protocol and the data code can be accessed at https://osf.io/fh426/.

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