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Reporting of Retrospective Registration in Clinical Trial Publications: a Cross-Sectional Study of German Trials

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3 1 **Reporting of Retrospective Registration in Clinical Trial Publications: a Cross-Sectional Study of**
4 2 **German Trials**

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20 15 **Keywords:** Clinical Trials, Trial Registration, Reporting, Retrospective Registration
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18 Abstract

19 **Objective:** Prospective registration of clinical research has been widely implemented and advocated
20 as it allows for public scrutiny of trials, facilitates the identification of gaps in research, and supports
21 the coordination of efforts by preventing unnecessary duplication. Retrospective registration
22 undermines many of these reasons but is commonly found. We provide an analysis of retrospective
23 registration and the reporting thereof in publications, as well as factors associated with these
24 practices.

25 **Design:** We used a dataset of trials registered on ClinicalTrials.gov or DRKS, with a German University
26 Medical Center as the lead center, completed between 2009 and 2017, and with a corresponding
27 peer-reviewed results publication. We extracted all registration statements from results publications
28 of retrospectively registered trials and assessed whether they mention or justify the retrospective
29 registration. We analyzed associations of retrospective registration and reporting thereof with TRN
30 reporting, ICMJE membership and industry sponsorship.

31 **Results:** In our dataset of 1927 trials with a corresponding results publication, 956 (53.7%) were
32 retrospectively registered. Of those, 2.2% (21) explicitly report the retrospective registration in the
33 abstract and 3.5% (33) in the full text. In 2.1% (20) of publications, authors provide a
34 justification/explanation for the retrospective registration in the full text. Registration numbers were
35 significantly underreported in abstracts of retrospectively registered trials ($p < 0.001$). Publications in
36 ICMJE member journals had higher rates of both prospective registration and disclosure of
37 retrospective registration, although not statistically significant. Publications in journals claiming to
38 follow ICMJE recommendations showed lower rates compared to non-ICMJE-following journals.

39 **Conclusions:** In contrast to ICMJE guidance, retrospective registration is disclosed and explained only
40 in a small number of retrospectively registered studies. Disclosure of the retrospective nature of the
41 registration would require 1-2 additional sentences in the manuscript and could be easily
42 implemented by publishers.

47 Strengths and limitations of this study

- 48 • Although at the core of good registration and reporting practices, the reporting of
49 retrospective registration has been underexplored. Using a high-quality dataset of trial
50 registrations in two main registries and verified results publications, this study aims to
51 explore this topic further.
- 52 • This study only considered trials led by German university medical centers, and therefore
53 reflects German or European registration standards.

55 Introduction

56 Prospective registration of clinical trials (i.e., registration before enrollment of the first participant) is
57 an important practice to reduce biases in their conduct and reporting (1). A number of ethical and
58 legal documents call for prospective registration: The Declaration of Helsinki (2) and the WHO
59 registry standards (3) state that registration and results reporting of clinical trials are an ethical
60 responsibility. In addition, many journals, via the International Committee of Medical Journal Editors
61 (ICMJE), encourage or require prospective registration with an appropriate registry before the first
62 participant is enrolled for all trials they publish, as well as the reporting of trial registration numbers
63 in publications for better findability (4,5). Similarly, reporting guidelines such as CONSORT (6) and
64 GPP3 (7) recommend the reporting of trial registration numbers.

65 Prospective registration has been widely implemented and advocated for many reasons: to detect
66 and mitigate publication bias (i.e., the non-reporting of studies, or aspects of studies, that did not
67 yield a positive result) and selective reporting (i.e., the selective reporting of only statistically
68 significant primary outcomes). Prospective registration allows for public scrutiny of trials,
69 identification of research gaps and to support the coordination of efforts by preventing unnecessary
70 duplication (9). When trials are registered retrospectively, i.e., their registry entry is created after
71 study start, this undermines the many of the reasons for registration. While prospective registration
72 has increased over the past decade, retrospective registration is still widespread (10–14). Some
73 registries, such as DRKS, explicitly mark retrospectively registered entries as such, whereas others,
74 such as ClinicalTrials.gov, do not. While some publishers allow retrospectively registered trials to be
75 published, others do not. Journals following ICMJE guidance should in principle mandate prospective
76 registration, but this principle is not always enforced (12,15,16).

77 Our study aims to investigate the conduct of retrospective registration and its transparent reporting
78 further. In a previous study in a cohort of 1509 trials conducted at German University Medical
79 Centers, registered in DRKS or Clinicaltrials.gov, and reported as complete between 2009–2013, 75%
80 were registered retrospectively (17). This rate dropped to 46% for the 1658 trials completed
81 between 2014–2017 (18). Using the data from these two studies on trials registered in two large
82 registries, led by German University Medical Centers, completed between 2009 and 2017, and with
83 at least one available peer-reviewed results publication (17,18), we investigate whether and how
84 authors report retrospective registration in the results publication. We also explore trends over time
85 and how retrospective registration is associated with other practices such as reporting the trial
86 registration number.

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88 Methods

89 *Data sources and sample.* We based our sample on two related projects that were conducted at our
90 research group (17,18). The projects have drawn a full sample (n = 3113) of registry entries for
91 interventional studies reported as complete between 2009 and 2017, led by a German University
92 Medical Center and registered in one of two registries: The ClinicalTrials.gov platform (CT.gov) and
93 the Deutsches Register Klinischer Studien (DRKS), which is the WHO primary trial registry for
94 Germany. Our dataset also includes the earliest results publications found for 68.4% (2129/3113) of
95 the trials, which were manually identified in different stages until September 1st, 2020. We retrieved
96 the combined data from the two projects from a GitHub repository ([https://github.com/maia-
97 sh/into-value-data](https://github.com/maia-sh/into-value-data), accessed 22.02.2022).

98 *Eligibility criteria.* We included any trial that [1] was registered as an interventional study in either
99 the ClinicalTrials.gov or the DRKS database, [2] was completed between 2009 and 2017, [3] reports a

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German University Medical Center (UMC) listed as the responsible party or lead sponsor, or with a principal investigator from a German UMC, [4] has published results in a peer-reviewed journal. Detailed descriptions of how these variables were derived are provided in the original publications of the dataset (17,18). Retrospective registration was determined based on the registration and study start dates in the registry entries: dates were set to the first of the respective month and studies with a registration date more than one month after start date counted as retrospectively registered. *Data extraction.* For all retrospectively registered trials, we manually searched the abstract and the full text of the publications, including editorial statements, whether they reported

- the fact that the study was registered (binary),
 - a trial registration number (binary),
 - the exact wording used to report the registration, including any provided registration numbers (free text),
 - the date of the retrospective registration (binary), and
 - the fact that the study was retrospectively registered (binary).
- We also assessed whether (binary) and how authors justified or explained the retrospective registration (free text).

One rater (MH) used the keywords “regist”, “nct”, “drks”, “eudra”, “retro”, “delay”, and “after” to search for registration numbers and wording pointing to retrospective registration in all publications. We considered a retrospective registration statement transparent if the authors explicitly mentioned that the registration was retrospective, e.g., “this study was retrospectively registered in [registry], [TRN]”. Reporting of the registration date alone was not considered as transparent reporting of retrospective registration, except if the date of registration was mentioned in combination with the study start date in the same paragraph.

ICMJE journals. We created additional variables for whether journals follow the ICMJE recommendations (list available on <http://www.icmje.org/journals-following-the-icmje-recommendations/>, accessed 07.04.2022).

Cross-registrations. We classified all retrospectively registered studies in our sample that report a registration in EudraCT in the publication as prospective, as registrations on the platform are required prior to the approval of regulatory agencies or research ethics committees (19).

Reliability assessment of ratings. To assess the reliability of the data extraction, another rater (SG) performed three validation steps: first, a sample of 100 publications was screened using the same extraction form, during the main screening to refine category definitions. Second, another sample of 100 publications for which no registration number reporting was noted by MH to check for false negative ratings. Third, all cases with either date, or reporting of retrospective registration or justification were screened, to check for false positives.

Analyses

Associations between prospective registration and other variables

To test the strength of the associations between prospective registration and three variables, we used Pearson’s chi-squared independence test or Fisher’s exact test (for small numbers). These variables are (1) publication in a ICMJE member journal or a journal following ICMJE recommendations, (2) reporting of a registration number, and (3) industry funding.

Associations between reporting of retrospective registration and other variables

To test the strength of the associations between the reporting of retrospective registration and two binary variables, we used Fisher’s exact test. These variables are (1) publication in a ICMJE member journal or a journal following ICMJE recommendations, and (2) industry funding.

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3 145 *Software*

4 146 We used Microsoft Excel for data collection and R (version 4.0.3) for data analysis and visualization.
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7 148 *Reporting*

8 149 We checked our manuscript against the STROBE checklist (supplementary Table 1) (20).
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11 151 *Patient and Public Involvement*

12 152 None
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15 154 **Results**

16 155 *Sample of retrospectively registered trials.* After applying the above-mentioned exclusion criteria,
17 156 1927 (1932 - 5) registered studies with an associated results publication remained. Of these, 1038
18 157 (53.7%) were retrospectively registered according to the information provided in Clinicaltrials.gov
19 158 and DRKS. We screened these 1038 studies for our analysis. 77 (7.8%) of the publications provided a
20 159 EudraCT number, in which case we reclassified the study as prospectively registered. For statistical
21 160 comparisons, we used the prospectively registered studies in the dataset as a control group. A
22 161 flowchart of this study selection is provided in Figure 1. Basic characteristics of included trials are
23 162 available in supplementary Table 2.
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33 166 *Retrospective registration.* Figure 2 shows the extent of retrospective registration over time, which
34 167 has been falling steadily from 100% in 2004 to 25% in 2017.
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170 We describe associations between prospective registration and previously defined binary variables
171 in Table 1: We found no statistically significant association between publications in ICMJE member
172 journals and prospective registration. Trials published in journals reporting to follow ICMJE
173 recommendations were even prospectively registered at a lower rate, compared to non-following
174 journals. It is important to note here that the information on ICMJE-following is based on journals'
175 requests to be included on the ICMJE website, therefore our results suggest that journals requesting
176 to be featured on the site often do not enforce the recommendations strongly. However, there are
177 other journals, such as many PloS journals, that are not featured on the ICMJE site, but implement
178 the recommendations. Retrospectively registered trials, compared to prospectively registered trials
179 significantly underreported registration numbers in the abstract ($p = 0.0007$). Industry sponsorship
180 of trials was associated with prospective registration ($p = 0.002$).
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182 *Table 1: Associations between prospective registration and other variables*

Variable		# (%) prospectively registered	P-value
ICMJE member journal	Y	28 (63.6%)	$p = 0.09$ (Fisher)
	N	943 (50.1%)	
ICMJE member/following	Y	329 (49.2%)	$p = 0.47$ (Chi-sq.)
	N	642 (51.0%)	

journal			
TRN reporting in abstract	Y	404 (55.4%)	p = 0.0007*** (Chi-sq.)
	N	567 (47.3%)	
Industry sponsorship	Y	163 (59.3%)	p = 0.002** (Chi-sq.)
	N	808 (48.9%)	

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184 *Reporting of registration.* Table 2 summarizes the prevalence of reporting of trial registration and
185 the reporting of retrospective registration. In 783 (81.9%) of the remaining 956 results publications
186 of retrospectively registered trials, the registration was explicitly reported in either the abstract or
187 the full text. In all except four of these publications, the registration was mentioned by providing the
188 registration number. In the other cases, the registration was mentioned but without reporting a
189 registration number.

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191 *Table 2: Number of retrospectively registered trials and prevalence of key retrospective registration*
192 *reporting practices.*

193 * "other" includes footnotes, sidebars, etc.

	n	% (of total)
Total: Retrospectively registered trials	956	100.0%
Registration reported	783	81.9%
Registration number reported	779	81.5%
<i>in abstract</i>	325	34.0%
<i>in full-text</i>	535	56.0%
<i>in other*</i>	134	14.0%
Registration date reported	67	7.0%
<i>in abstract</i>	45	4.7%
<i>in full-text</i>	32	3.3%
Retrospective registration addressed	47	4.9%
<i>in abstract</i>	21	2.2%
<i>in full-text</i>	33	3.5%
Retrospective registration justified/explained	20	2.1%
<i>in abstract</i>	0	0.0%
<i>in full-text</i>	20	2.1%

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195 *Reporting of retrospective registration.* The rate of trials for which retrospective registration is
196 reported transparently increased over the last years up to 15.4% in 2020 (Figure 3). Overall, among
197 all 956 retrospectively registered clinical studies, only 47 (4.9%) mention explicitly that this
198 registration was retrospective in the abstract or full text (see Table 2). Among those cases, 20 give
199 some explanation or justification for why registration was retrospective. In 67 (7.0%) cases, the
200 authors reported the registration date alongside the registration statement, but in 35 of those, the
201 date was provided without giving the necessary context that the registration was retrospective.

Publications in ICMJE member or -following journals had a higher rate of reporting of retrospective registration ($p = 0.004$) but we found no association for industry sponsored trials ($p = 0.162$) (Table 3).

Table 3: Associations between transparent reporting of retrospective registration and other variables

Variable		# (%) reporting RR	P-value
ICMJE member journal	Y	2 (12.5%)	$p = 0.184$ (Fisher exact)
	N	45 (4.8%)	
ICMJE member/following journal	Y	7 (2.1%)	$p = 0.004^{**}$ (Fisher exact)
	N	40 (6.5%)	
Industry sponsorship	Y	2 (1.8%)	$p = 0.162$ (Fisher exact)
	N	45 (5.3%)	

Justifications of retrospective registration. In 24 cases in which the retrospective nature of the registration was reported, the authors provided further information explaining or justifying the retrospective registration. Table 4 shows the main themes present in authors' explanations, with text examples.

Table 4. Main themes identified from authors' explanations of retrospective reporting and example statements.

Theme	Example(s)
Unawareness of policy	<p>"At the time when the trial was started, the initiators of this study were unfortunately unaware of the policy of the International Committee of Medical Journal Editors (ICMJE), which requires prospective registration of all interventional clinical trials. As soon as we became aware of this policy, we registered the trial." (PMID: 26812052)</p> <p>"The reason for retrospectively registering the study was that the study authors were not aware of the recommendation to register diagnostic accuracy studies before this date." (PMID: 30011285)</p>
Registry delays	"Registration of the study was applied for in April 2015. All queries from the DRKS were answered until the 31st August 2015 except the planned inclusion date of the first patient (first-patient-in), which was correct in the DRKS registry on 1st December 2015. Confirmation of registration occurred on 4th December 2015. The first patient was recruited and randomized into the study on 20th October 2015. Until 4th December 2015 eight patients were randomized into the trial." (PMID: 32142529)
Not obligatory at the time	<p>"At the time of submission of the study protocol, the Ethics Committee did not require registration for feasibility or proof of concept studies. The study was registered in ClinicalTrials.gov (NCT02196545) in July 2014 in preparation of a manuscript for publication of the data. The authors confirm that all ongoing and related trials for this intervention are registered." (PMID: 25884637)</p> <p>"It was not registered at a clinical trial register, because at the time of setup in 2003, such a registration was not obligatory." (PMID: 23730377)</p>
Not obligatory for the intervention	"According to national laws it is stipulated to inform the respective ethics committee, but it was not necessary to register the study in an official registry or to obtain an ethics committee vote, because it was an expanded access study (Heilversuch). Despite this, we prospectively obtained a vote of the ethics committee. Study design and patient information form were approved by the local ethics committee (ethics committee of the regional medical association; approval no.

	EK-BR-50/10-1, date of approval December 10th, 2010). In addition, the study was registered at www.clinicaltrials.gov (ID no. NCT02168790)." (PMID: 25955359)
Miscommunication between investigators	<p>"The time of first registration was June 17, 2013, and final approved trial registration was July 1, 2013. First patient inclusion was in July 2012 at the Heart Center Leipzig University Hospital, Leipzig, Germany. Thus, there was a delay between first patient inclusion and trial registration that was the result of a misunderstanding between the principal investigator of the trial, Dr Thiele, and the first author, Dr Fuernau, who was responsible for clinical project coordination at the investigator's site at the Heart Center Leipzig University of Leipzig. According to initial communication, registration had to be performed by Dr Fuernau. When the study principal investigator recognized that it had not been performed, we immediately registered the trial at http://www.ClinicalTrials.gov. At this time, only 7 patients at the Heart Center Leipzig University Hospital had been included in the trial." (PMID: 30026282)</p> <p>„[...] there was a delay of trial registration before first patient inclusion which was induced by a misunderstanding between the project coordination for the EU grant (at this time gabo:mi, later on ARTTIC) and the clinical project coordination at the investigator's site at the Heart Center Leipzig - University of Leipzig. According to initial communication registration should be performed by gabo:mi. When the study coordinator recognized that it has not been performed we immediately registered it at clinicaltrials.gov. At this time only 13 patients at the Heart Center Leipzig University Hospital (and no other study site) have been included into the trial.“ (PMID: 29083953)</p>
Publication	"Registration was done after the study has been conducted and the results suggested a publication and further continuation of this research." (PMID: 27485732)
Confidentiality	"The principal investigator (N.H.) delayed the registration of the study until data acquisition was completed for confidentiality reasons concerning the study methods, especially the magnetic resonance with the related morphometric measurements." (PMID: 26305790)
Logistic/ Administrative issues	<p>"Because of administrative problems, release of registration occurred about six months after study start. The authors confirm that all ongoing and related trials for this intervention are registered. Relevant de-identified data can be downloaded from https://osf.io/426pd." (PMID: 31465443)</p> <p>"Due to organisational changes in the research project shortly before the start of the recruitment we put great efforts into avoiding a delayed start of the data collection in the cooperating inpatient units, which resulted in retrospective study registration and a delayed publication of our study protocol." (PMID: 29077724)</p> <p>„Registration of the trial was delayed after the enrollment of the first patient due to an administrative error. The authors confirm that all ongoing and related trials for this intervention are registered.“ (PMID: 26501562)</p>

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Discussion

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In this study we show that in a sample of 956 results publications from retrospectively registered clinical studies led by German UMCs and completed between 2009 and 2017, only a small number of publications (4.9%) make the retrospective nature of the registration transparent, and even fewer (2.1%) explain the reasons for retrospective registration. To our knowledge, only two studies have previously addressed the reporting of retrospective registration: Al-Durra et al. (21) found in a sample of 286 publications in ICMJE member journals and published in 2018 that only 2.8% (n=8) of papers of retrospectively registered trials in their sample include justifications or explanations for delayed registration. Loder et al. (22), in their analysis of 70 papers submitted to the BMJ from 2012-2015 and rejected for registration issues, found that 2.9% (n=2) disclosed the registration problem when published in another journal. Our study finds a slightly lower percentage of 2.1% for explanations of the reasons for retrospective registration, but a higher percentage of 4.9% for disclosure in a larger sample representing a more diverse selection of journals and broader time frame.

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3 234 There were diverse reasons for retrospective registration brought forth by authors, many of which
4 235 have been published previously (21,22). In some cases, authors raise points that lie outside their
5 236 direct responsibility, such as delays caused by the registry or research not being legally required to
6 237 be preregistered. Several other reasons provided were within authors' control, such as logistic and
7 238 administrative issues, miscommunication between researchers or unawareness of registration
8 239 policies. In some cases, authors report registering a study to meet journal editorial policies even
9 240 though registration would not be required for the kind of research otherwise. Another identified
10 241 theme revolves around the confidentiality of methods – however, in this case many other data
11 242 about the trial could have been preregistered.
12 243

16 244 *Limitations*

17 245 For feasibility and data quality reasons, our study was based on an existing validated dataset,
18 246 containing only trials led by German UMCs, which might limit its generalizability to other regions. For
19 247 example, in Germany, unlike many other countries, there is no legal mandate to register all clinical
20 248 studies, but the largest funding institutions in Germany (e.g., DFG, BMBF) require the registration of
21 249 studies as prerequisite for funding. However, the sample also contained multi-center trials with
22 250 other countries involved and is much larger and from a wider variety of journals than in previous
23 251 studies (21,22). In addition, due to Germany's high research output (23) our results in any case
24 252 highlight a key transparency issue in a major research environment.
25 253 Our analysis of retrospective registration is based on trial start dates and registration dates as
26 254 provided by the two registries used for sampling: Clinicaltrials.gov and DRKS. It is possible that
27 255 authors did not update their registry entries when delays to the start date occurred. For example,
28 256 we did not specifically follow up cases in which authors wrote that a trial was registered
29 257 prospectively, but the registry dates did not reflect that statement. In our analyses involving the
30 258 classification into ICMJE-following and non-following journals, we relied on the data provided on the
31 259 ICMJE website (icmje.org), which are self-reported by journals, i.e., a journal must write to the ICMJE
32 260 that they want to be included in the list. Thus, there are some journals missing in the ICMJE data and
33 261 therefore in our dataset. For ICMJE member journals (n=16) on the other hand, there is a complete
34 262 listing available.
35 263

41 264 *Conclusion*

42 265 The Declaration of Helsinki and many other guidelines for responsible clinical research unanimously
43 266 recommend prospective registration of all clinical studies. For highly regulated clinical trials this was
44 267 even codified into law. A major aim of prospective registration is to minimize the risk of undisclosed
45 268 changes in the protocol after the study started and first results are analyzed. When registration
46 269 happens retrospectively, this major goal is not addressed. The reporting of study registration is
47 270 generally considered a best practice to make a study more trustworthy. In the case of retrospective
48 271 registration, in contrast, reporting registration without transparency on the retrospective nature
49 272 should rather raise concerns as readers might wrongly interpret the mentioning of registration as a
50 273 quality criterion. This could be considered "performative reproducibility", i.e., the "pretence of
51 274 reproducibility without the reality" (24). Journals could enforce explicit reporting and explanation of
52 275 retrospective registration, but we found that this rarely happens. A simple note in the registration
53 276 statement of the paper would suffice, such as: "This study was retrospectively registered at
54 277 [Registry], [X] days after the trial started because [Reason]".
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280 **Ethics approval**

281 Not applicable

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283 **Contributorship statement**

284 Martin Haslberger – Conceptualization, methodology, investigation, analysis, writing - original draft,
285 project management

286 Stefanie Gestrich – Methodology, investigation

287 Daniel Strech – Conceptualization, methodology, supervision, writing – review and editing, funding
288 acquisition

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291 **Competing interests**

292 The authors declare no competing interests.

293

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298 manuscript, or the decision to submit for publication.

299

300 **Data sharing statement**

301 All code and the data for this study are available at <https://github.com/mhaslberger/retrospective->
302 registration.

303

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BMJ Open
 Registered (DRKS, CT.gov)
 clinical studies with results
 publications in Germany
 completed 2009-2017
 n = 1932

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Prospectively registered
 n = 894

Retrospectively registered
 n = 1038

Reclassified publications:
 registration in EudraCT reported
 in the publication (n=77)

Excluded publications:
 - incorrect publication in dataset
 (n=5)

Prospectively registered
 n = 971

Retrospectively registered
 n = 956

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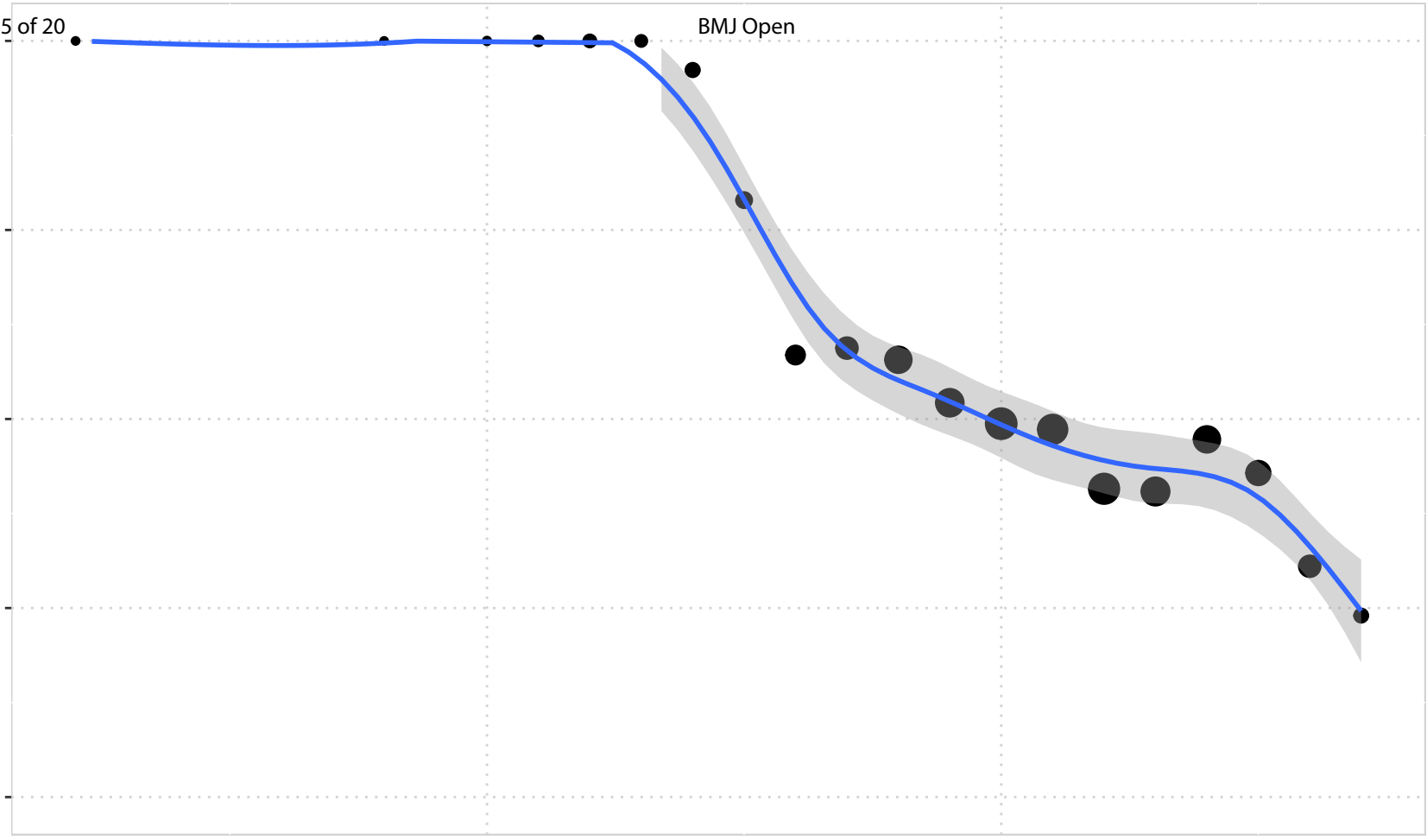
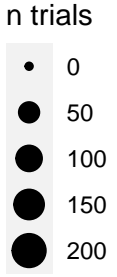
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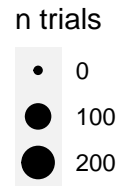
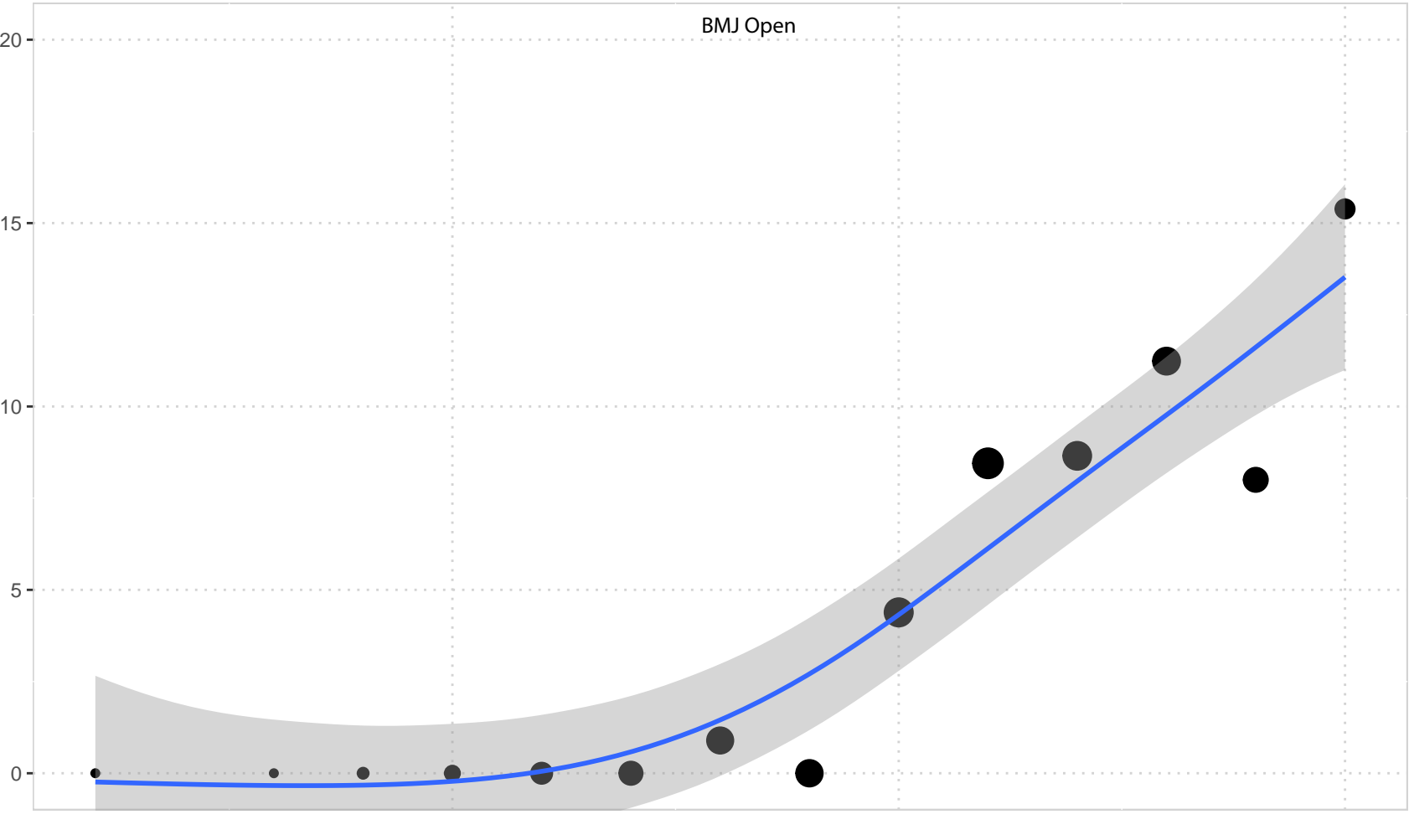
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Year (Pub.)	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020
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%RRR	0		0	0	0	0	0	0.9	0	4.4	8.5	8.7	11.2	8	15.4

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Supplementary Table 1: STROBE checklist

	Item No.	Recommendation	Page No.	Relevant text from manuscript
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	2	Cross-sectional study
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2	See abstract
Introduction				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3	When trials are registered retrospectively, i.e., their registry entry is created after study start, this undermines the many of the reasons for registration. While prospective registration has increased over the past decade, retrospective registration is still widespread (10–14). Some registries, such as DRKS, explicitly mark retrospectively registered entries as such, whereas others, such as ClinicalTrials.gov, do not. While some publishers allow retrospectively registered trials to be published, others do not. Journals following ICMJE guidance should in principle mandate prospective registration, but this principle is not always enforced (12,15,16).
Objectives	3	State specific objectives, including any prespecified hypotheses	3	Our study aims to investigate the conduct of retrospective registration and its transparent reporting
Methods				
Study design	4	Present key elements of study design early in the paper	3	We based our sample on two related projects that were conducted at our research group (17,18). The projects have drawn a full sample (n = 3113) of registry entries for interventional studies reported as complete between 2009 and 2017, led by a German University Medical Center and registered in one of two registries: The ClinicalTrials.gov platform (CT.gov) and the Deutsches Register Klinischer Studien (DRKS)
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	3-4	See above

Participants	6	<i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants	3-4	We included any trial that [1] was registered as an interventional study in either the ClinicalTrials.gov or the DRKS database, [2] was completed between 2009 and 2017, [3] reports a German University Medical Center (UMC) listed as the responsible party or lead sponsor, or with a principal investigator from a German UMC, [4] has published results in a peer-reviewed journal.
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	3	we investigate whether and how authors report retrospective registration in the results publication. We also explore trends over time and how retrospective registration is associated with other practices such as reporting the trial registration number.
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	3-4	Data sources and sample. We based our sample on two related projects that were conducted at our research group (17,18). The projects have drawn a full sample (n = 3113) of registry entries for interventional studies reported as complete between 2009 and 2017, led by a German University Medical Center and registered in one of two registries: The ClinicalTrials.gov platform (CT.gov) and the Deutsches Register Klinischer Studien (DRKS), which is the WHO primary trial registry for Germany. Our dataset also includes the earliest results publications found for 68.4% (2129/3113) of the trials, which were manually identified in different stages until September 1st, 2020. We retrieved the combined data from the two projects from a GitHub repository (https://github.com/maia-sh/into-value-data , accessed 22.02.2022).
Bias	9	Describe any efforts to address potential sources of bias	4	<i>Reliability assessment of ratings.</i> To assess the reliability of the data extraction, another rater (SG) performed three validation steps: first, a sample of 100 publications was screened using the same extraction form, during the main screening to refine category definitions. Second, another sample of 100 publications for which no registration number reporting was noted by MH to check for false negative ratings. Third, all cases with either date, or reporting of retrospective registration or justification were screened, to check for false positives.

Study size	10	Explain how the study size was arrived at	3	We based our sample on two related projects that were conducted at our research group
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	-	Not applicable
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	4	See Methods
		(b) Describe any methods used to examine subgroups and interactions	4	See Methods
		(c) Explain how missing data were addressed	-	Not applicable
		(d) <i>Cross-sectional study</i> —If applicable, describe analytical methods taking account of sampling strategy	-	Not applicable
		(e) Describe any sensitivity analyses	-	Not applicable
Results				
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	5	First paragraph of Results
		(b) Give reasons for non-participation at each stage	5	First paragraph of Results
		(c) Consider use of a flow diagram	5	Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	5	Supplementary table 1
		(b) Indicate number of participants with missing data for each variable of interest	-	Complete case analysis
		(c) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)	3	The projects have drawn a full sample (n = 3113) of registry entries for interventional studies reported as complete between 2009 and 2017, led by a German University Medical Center and registered in one of two registries: The ClinicalTrials.gov platform (CT.gov) and the Deutsches Register Klinischer Studien (DRKS), which is the WHO primary trial registry for Germany. Our dataset also includes the earliest results publications found for 68.4% (2129/3113) of the trials, which were manually identified in different stages until September 1st, 2020
Outcome data	15*	<i>Cross-sectional study</i> —Report numbers of outcome events or summary measures	5-7	See results, e.g. Table 2, Figures 2,3
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and	-	Not applicable

		their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included		
		(b) Report category boundaries when continuous variables were categorized	-	Not applicable
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	-	Not applicable
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	6-9	See results
Discussion				
Key results	18	Summarise key results with reference to study objectives	9-10	See 1 st paragraph of discussion
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	10	See Limitations section
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	9-10	See first paragraph of discussion
Generalisability	21	Discuss the generalisability (external validity) of the study results	10	For feasibility and data quality reasons, our study was based on an existing validated dataset, containing only trials led by German UMCs, which might limit its generalizability to other regions. [...]
Other information				
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	1	This work was partly funded under a grant from the Federal Ministry of Education and Research of Germany (Bundesministerium fuer Bildung und Forschung - BMBF) [01PW18012]. The funder was not involved in the study design, data collection, analysis, or interpretation, writing of the manuscript, or the decision to submit for publication.

Supplementary Table 2: Basic characteristics of included trials

	Retrospectively registered trials (n = 956)	Prospectively registered trials (n = 971)
Registry		
ClinicalTrials.gov	713	766
DRKS	243	205
Sponsorship		
Industry	112	163
Other	844	808
Phase		
Phase 1	33	71
Phase 2	122	206
Phase 3	91	134
Phase 4	78	99
No phase	632	461
Intervention type		
Behavioral	94	72
Biological	18	32
Device	199	138
Dietary Supplement	40	30
Drug	186	340
Genetic	1	1
Procedure	96	70
Radiation	6	9
Other	73	74
Not given	243	205

BMJ Open

Reporting of Retrospective Registration in Clinical Trial Publications: a Cross-Sectional Study of German Trials

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2022-069553.R1
Article Type:	Original research
Date Submitted by the Author:	28-Feb-2023
Complete List of Authors:	Haslberger, Martin; Berlin Institute of Health at Charité, QUEST Center for Responsible Research Gestrich, Stefanie; Berlin Institute of Health at Charité, QUEST Center for Responsible Research Strech, Daniel; Berlin Institute of Health at Charité, QUEST Center for Responsible Research
Primary Subject Heading:	Medical publishing and peer review
Secondary Subject Heading:	Research methods, Ethics
Keywords:	MEDICAL ETHICS, STATISTICS & RESEARCH METHODS, Clinical trials < THERAPEUTICS

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3 1 **Reporting of Retrospective Registration in Clinical Trial Publications: a Cross-Sectional Study of**
4 2 **German Trials**

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21 15 **Keywords:** Clinical Trials, Trial Registration, Reporting, Retrospective Registration
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18 Abstract

19 **Objective:** Prospective registration has been widely implemented and accepted as a best practice in
20 clinical research, but retrospective registration is still commonly found. We assessed to what extent
21 retrospective registration is reported transparently in journal publications, and investigated factors
22 associated with transparent reporting.

23 **Design:** We used a dataset of trials registered in ClinicalTrials.gov or Deutsches Register Klinischer
24 Studien, with a German University Medical Center as the lead center, completed 2009–2017, and
25 with a corresponding peer-reviewed results publication. We extracted all registration statements
26 from results publications of retrospectively registered trials and assessed whether they mention or
27 justify the retrospective registration. We analyzed associations of retrospective registration and
28 reporting thereof with registration number reporting, International Committee of Medical Journal
29 Editors (ICMJE) membership/-following and industry sponsorship using chi-squared or Fisher exact
30 test.

31 **Results:** In the dataset of 1927 trials with a corresponding results publication, 956 (53.7%) were
32 retrospectively registered. Of those, 2.2% (21) explicitly report the retrospective registration in the
33 abstract and 3.5% (33) in the full text. In 2.1% (20) of publications, authors provide an explanation
34 for the retrospective registration in the full text. Registration numbers were significantly
35 underreported in abstracts of retrospectively registered trials compared to prospectively registered
36 trials. Publications in ICMJE member journals did not have statistically significantly higher rates of
37 both prospective registration and disclosure of retrospective registration, and publications in
38 journals claiming to follow ICMJE recommendations showed statistically significantly lower rates
39 compared to non-ICMJE-following journals. Industry sponsorship of trials was significantly associated
40 with higher rates of prospective registration, but not with transparent registration reporting.

41 **Conclusions:** Contrary to ICMJE guidance, retrospective registration is disclosed and explained only
42 in a small number of retrospectively registered studies. Disclosure of the retrospective nature of the
43 registration would require a brief statement in the manuscript and could be easily implemented by
44 journals.

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49 Strengths and limitations of this study

- 50 • We use a large, high-quality dataset of all trials conducted at German university medical
51 centers and registered in two registries, with results publications determined by an
52 extensive manual screening process.
- 53 • We consider a period of nine years (2009 – 2017) and describe the development of reporting
54 practices over time
- 55 • This study only includes trials led by German university medical centers, reflecting German
56 regulatory standards.

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58 Introduction

59 Prospective registration of clinical trials (i.e., registration before enrollment of the first participant) is
60 an important practice to reduce biases in their conduct and reporting (1). A number of ethical and
61 legal documents call for prospective registration: The Declaration of Helsinki (2) and the World
62 Health Organization registry standards (3) state that prospective registration and results reporting of
63 clinical trials are an ethical responsibility. European law, for example, explicitly mandates
64 prospective registration of pharmaceutical trials (4). In addition, many journals, via the International
65 Committee of Medical Journal Editors (ICMJE), encourage or require prospective registration with an
66 appropriate registry before the first participant is enrolled for all trials they publish, as well as the
67 reporting of trial registration numbers (TRNs) in publications for better findability (5,6). Similarly,
68 reporting guidelines such as Consolidated Standards of Reporting Trials (CONSORT) (7) and Good
69 Publication Practice 3 (GPP3) (8) recommend the reporting of trial registration numbers.

70 Prospective registration has been widely implemented and advocated for many reasons: to detect
71 and mitigate publication bias (i.e., the non-reporting of studies, or aspects of studies, that did not
72 yield a positive result) and selective reporting (i.e., the selective reporting of only statistically
73 significant primary outcomes). Prospective registration allows for public scrutiny of trials,
74 identification of research gaps and to support the coordination of efforts by preventing unnecessary
75 duplication (9). When trials are registered retrospectively, i.e., their registry entry is created after
76 study start, this undermines the many of the reasons for registration. While prospective registration
77 has increased over the past decade, retrospective registration is still widespread (10–14). Some
78 registries, such as Deutsches Register Klinischer Studien (DRKS) or the WHO's International Clinical
79 Trials Registry Platform, explicitly mark retrospectively registered entries as such, whereas others,
80 such as ClinicalTrials.gov, do not. While some journal editors allow retrospectively registered trials to
81 be published, others do not. Journals following ICMJE guidance should in principle mandate
82 prospective registration, but this principle is not always enforced (12,15,16). According to ICMJE
83 guidance, journals should publish retrospectively registered studies only in exceptional cases, noting
84 that "authors should indicate in the publication when registration was completed and why it was
85 delayed. Editors should publish a statement indicating why an exception was allowed." (5) This was
86 investigated by previous studies which found that such reporting rarely happens (17,18).

87 Our study aims to investigate the conduct of retrospective registration and its transparent reporting
88 in a larger sample. In a previous study in a cohort of 1509 trials conducted at German University
89 Medical Centers (UMC), registered in DRKS or ClinicalTrials.gov, and reported as complete between
90 2009-2013, 75% were registered retrospectively (19). This rate dropped to 46% for the 1658 trials
91 completed between 2014-2017 (20). Using the data from these two studies on trials registered in
92 two large registries, led by German UMCs, completed between 2009 and 2017, and with at least one
93 available peer-reviewed results publication (19,20), we investigate whether and how authors report
94 retrospective registration in the results publication. We also explore how retrospective registration
95 is associated with other practices such as TRN reporting.

96

97 Methods

98 *Data sources and sample.* We based our sample on two related projects that were conducted at our
99 research group (19,20). The projects have drawn a full sample (n = 3113) of registry entries for
100 interventional studies reported as complete between 2009 and 2017, led by a German UMC and
101 registered in one of two registries: DRKS, which is the WHO primary trial registry for Germany, and
102 ClinicalTrials.gov, which is also routinely used in Germany to register clinical research and accepted

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103 by the ICMJE. Our dataset also includes the earliest results publications found for 68.4% (2129/3113)
104 of the trials, which were manually identified in different stages until September 1st, 2020. We
105 retrieved the combined data from the two projects from a GitHub repository
106 (<https://github.com/maia-sh/intoalvalue-data>, accessed 22.02.2022). The final dataset is publicly
107 available (21).

108 *Eligibility criteria.* We included any trial that [1] was registered as an interventional study in either
109 the ClinicalTrials.gov or the DRKS database, [2] was completed between 2009 and 2017, [3] reports a
110 German UMC listed as the responsible party or lead sponsor, or with a principal investigator from a
111 German UMC, [4] has published results in a peer-reviewed journal. Detailed descriptions of how
112 these variables were derived are provided in the original publications of the dataset (19,20).

113 Retrospective registration was determined based on the registration and study start dates in the
114 registry entries: dates were set to the first of the respective month and studies with a registration
115 date more than one month after start date counted as retrospectively registered. For trials that were
116 registered in both registries, we kept the entry that was created earlier.

117 *Data extraction.* For all retrospectively registered trials, we manually searched the abstract and the
118 full text of the publications, including editorial statements, whether they reported

- 119 • the fact that the study was registered (binary),
- 120 • a trial registration number (binary),
- 121 • the exact wording used to report the registration, including any provided registration
122 numbers (free text),
- 123 • the date of the retrospective registration (binary), and
- 124 • the fact that the study was retrospectively registered (binary).
- 125 • We also assessed whether (binary) and how authors justified or explained the retrospective
126 registration (free text).

127 One rater (MH) used the keywords “regist”, “nct”, “drks”, “eudra”, “retro”, “delay”, and “after” to
128 search for registration numbers and wording pointing to retrospective registration in all publications.
129 We considered a retrospective registration statement transparent if the authors explicitly mentioned
130 that the registration was retrospective, e.g., “this study was retrospectively registered in [registry],
131 [TRN]”. Reporting of the registration date alone was not considered as transparent reporting of
132 retrospective registration, except if the date of registration was mentioned in combination with the
133 study start date in the same paragraph.

134 *ICMJE journals.* We created additional variables for whether journals are ICMJE members or follow
135 the ICMJE recommendations (22).

136 *Cross-registrations.* We classified all retrospectively registered studies in our sample that also report
137 a registration in EudraCT in the publication as prospective, as registrations on the platform are
138 required prior to the approval of regulatory agencies or research ethics committees (4).

139 *Reliability assessment of ratings.* To assess the reliability of the data extraction, another rater (SG)
140 performed three validation steps: first, a sample of 100 publications was screened using the same
141 extraction form, during the main screening to refine category definitions. Second, another sample of
142 100 publications for which no registration number reporting was noted by MH to check for false
143 negative ratings. Third, all cases with either date, or reporting of retrospective registration or
144 justification were screened, to check for false positives.

145 *Analyses*

146 *Associations between prospective registration and other variables.* To test the strength of the
147 associations between prospective registration and three variables, we used Pearson’s chi-squared

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3 148 independence test. These variables were (1) publication in a ICMJE member journal or a journal
4 149 following ICMJE recommendations, (2) reporting of a registration number, and (3) industry funding.
5 150 *Associations between reporting of retrospective registration and other variables.* To test the strength
6 151 of the associations between the reporting of retrospective registration and two binary variables, we
7 152 used Fisher's exact test, as case numbers were low. These variables are (1) publication in a ICMJE
8 153 member journal or a journal following ICMJE recommendations, and (2) industry funding.

11 154 *Software*

12 155 We used Microsoft Excel for data collection and R (version 4.0.3) for data analysis and visualization.

13 156

15 157 *Reporting*

16 158 We checked our manuscript against the STROBE checklist (supplementary Table 1) (23).

17 159

18 160 *Patient and Public Involvement*

19 161 No patient involved.

20 162

22 163 **Results**

23 164 *Sample of retrospectively registered trials.* After applying the above-mentioned exclusion criteria,
24 165 1932 registered studies with an associated results publication remained. Of these, 1038 (54%) were
25 166 retrospectively registered according to the information provided in ClinicalTrials.gov and DRKS. We
26 167 screened these 1038 studies for our analysis. Five of the publications were excluded as they were
27 168 mislabeled as results publications in the dataset. Another 77 (8%) of the publications provided a
28 169 EudraCT number, in which case we reclassified the study as prospectively registered, leaving 956
29 170 studies. For statistical comparisons, we used the studies classified as prospectively registered
30 171 (n=971) in the dataset as a control group. A flowchart of this study selection is provided in Figure 1.
31 172 Basic characteristics of included trials are available in supplementary Table 2.

32 173

33 174 *Retrospective registration.* Figure 2 shows the extent of retrospective registration over time, which
34 175 has been falling steadily from 100% in 2004 to 25% in 2017.

35 176 We describe associations between prospective registration and previously defined binary variables
36 177 in Table 1: We found no statistically significant association between publication in ICMJE member
37 178 journals and prospective registration ($p=0.10$). Similarly, we found no statistically significant
38 179 association with prospective registration when also including publication in journals reporting to
39 180 follow ICMJE recommendations ($p=0.47$). It is important to note here that the information on ICMJE-
40 181 following is based on journals' requests to be included on the ICMJE website as a journal following
41 182 the ICMJE's recommendations (22), therefore our results suggest that journals requesting to be
42 183 listed on the site often do not enforce the recommendations strongly. However, there are other
43 184 journals, such as many PLOS journals, that are not featured on the ICMJE site, but implement the
44 185 recommendations. Retrospectively registered trials, compared to prospectively registered trials
45 186 significantly underreported registration numbers in the abstract ($p = 0.0007$). Industry sponsorship
46 187 of trials was associated with prospective registration ($p = 0.002$). In 31% (294/956) of trials,
47 188 registration occurred between study completion and publication (median 370 days before
48 189 publication). Another 3% (25/956) of trials were registered after publication (median 249 days after
49 190 publication).

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192 *Table 1: Associations between prospective registration and other variables*

Variable (Yes/No)		n (%) prospectively registered	P-value (Chi-sq.)
ICMJE member journal	Y	28 (63.6%)	p = 0.10
	N	943 (50.1%)	
ICMJE member/following journal	Y	329 (49.2%)	p = 0.47
	N	642 (51.0%)	
TRN reporting in abstract	Y	404 (55.4%)	p = 0.0007
	N	567 (47.3%)	
Industry sponsorship	Y	163 (59.3%)	p = 0.002
	N	808 (48.9%)	

193
194 *Reporting of registration.* Table 2 summarizes the prevalence of reporting of trial registration and
195 the reporting of retrospective registration. In 82% (783/956) of the remaining results publications of
196 retrospectively registered trials, the registration was explicitly reported in either the abstract or the
197 full text. In all except four of these publications, the registration was mentioned by providing the
198 registration number. In the other cases, the registration was mentioned but without reporting a
199 registration number.

200
201 *Table 2: Number of retrospectively registered trials and prevalence of key retrospective registration*
202 *reporting practices.*

203 * "other" includes footnotes, sidebars, etc.

	n	% (of total)
Total: Retrospectively registered trials	956	100.0%
Registration reported	783	81.9%
Registration number reported	779	81.5%
<i>in abstract</i>	325	34.0%
<i>in full-text</i>	535	56.0%
<i>in other*</i>	134	14.0%
Registration date reported	67	7.0%
<i>in abstract</i>	45	4.7%
<i>in full-text</i>	32	3.3%
Retrospective registration addressed	47	4.9%
<i>in abstract</i>	21	2.2%
<i>in full-text</i>	33	3.5%
Retrospective registration justified/explained	20	2.1%
<i>in abstract</i>	0	0.0%
<i>in full-text</i>	20	2.1%

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205 *Reporting of retrospective registration.* The rate of trials for which retrospective registration is
206 reported transparently increased over the last years up to 15% in 2020 (Figure 3). Overall, among all
207 956 retrospectively registered clinical studies, five percent (47) mention explicitly that this
208 registration was retrospective in the abstract or full text (see Table 2). Among those cases, 20 give

209 some explanation or justification for why registration was retrospective. In seven percent (67) of
 210 cases, the authors reported the registration date alongside the registration statement, but in 35 of
 211 those, the date was provided without giving the necessary context that the registration was
 212 retrospective.

213 Publications in ICMJE member journals did not have a statistically significantly higher rate of
 214 reporting of retrospective registration (13% vs. 5%, $p = 0.18$), whereas publications in ICMJE member
 215 or -following journals had a significantly lower rate (2% vs. 7%, $p = 0.004$). We found no association
 216 with transparent reporting of retrospective registration for industry sponsored trials (2% vs. 5%, $p =$
 217 0.16) (Table 3).

218
 219 *Table 3: Associations between transparent reporting of retrospective registration and other variables*

Variable (Yes/No)		n (%) reporting RR	P-value (Fisher test)
ICMJE member journal	Y	2 (12.5%)	$p = 0.18$
	N	45 (4.8%)	
ICMJE member/following journal	Y	7 (2.1%)	$p = 0.004$
	N	40 (6.5%)	
Industry sponsorship	Y	2 (1.8%)	$p = 0.16$
	N	45 (5.3%)	

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 221 *Justifications of retrospective registration.* In 20 cases in which the retrospective nature of the
 222 registration was reported, the authors provided further information explaining or justifying the
 223 retrospective registration. Notably, 14 of the 20 studies (70%) that justified the retrospective
 224 registration were published in a single journal, PLOS ONE. Table 4 shows the main themes present in
 225 authors' explanations, with text examples.

226
 227 *Table 4. Main themes identified from authors' explanations of retrospective reporting and example*
 228 *statements.*

Theme	Example(s)
Unawareness of registration policy	<p>"At the time when the trial was started, the initiators of this study were unfortunately unaware of the policy of the International Committee of Medical Journal Editors (ICMJE), which requires prospective registration of all interventional clinical trials. As soon as we became aware of this policy, we registered the trial." (doi: 10.1371/journal.pone.0146678)</p> <p>"The reason for retrospectively registering the study was that the study authors were not aware of the recommendation to register diagnostic accuracy studies before this date." (doi: 10.1371/journal.pone.0199345)</p>
Delays by the registry	"Registration of the study was applied for in April 2015. All queries from the DRKS were answered until the 31st August 2015 except the planned inclusion date of the first patient (first-patient-in), which was correct in the DRKS registry on 1st December 2015. Confirmation of registration occurred on 4th December 2015. The first patient was recruited and randomized into the study on 20th October 2015. Until 4th December 2015 eight patients were randomized into the trial." (doi: 10.1371/journal.pone.0229898)
Not obligatory at the time	"At the time of submission of the study protocol, the Ethics Committee did not require registration for feasibility or proof of concept studies. The study was registered in ClinicalTrials.gov (NCT02196545) in July 2014 in preparation of a manuscript for publication of the data. The authors confirm that all ongoing and related trials for this intervention are registered." (doi: 10.1371/journal.pone.0121478)

	„It was not registered at a clinical trial register, because at the time of setup in 2003, such a registration was not obligatory.“ (doi: 10.2174/1874325001307010133)
Not obligatory for the intervention	“According to national laws it is stipulated to inform the respective ethics committee, but it was not necessary to register the study in an official registry or to obtain an ethics committee vote, because it was an expanded access study (Heilver such). Despite this, we prospectively obtained a vote of the ethics committee. Study design and patient information form were approved by the local ethics committee (ethics committee of the regional medical association; approval no. EK-BR-50/10-1, date of approval December 10th, 2010). In addition, the study was registered at www.clinicaltrials.gov (ID no. NCT02168790).“ (doi: 10.1371/journal.pone.0125035)
Miscommunication between investigators	<p>“The time of first registration was June 17, 2013, and final approved trial registration was July 1, 2013. First patient inclusion was in July 2012 at the Heart Center Leipzig University Hospital, Leipzig, Germany. Thus, there was a delay between first patient inclusion and trial registration that was the result of a misunderstanding between the principal investigator of the trial, Dr Thiele, and the first author, Dr Fuernau, who was responsible for clinical project coordination at the investigator’s site at the Heart Center Leipzig University of Leipzig. According to initial communication, registration had to be performed by Dr Fuernau. When the study principal investigator recognized that it had not been performed, we immediately registered the trial at http://www.ClinicalTrials.gov. At this time, only 7 patients at the Heart Center Leipzig University Hospital had been included in the trial.” (doi: 10.1161/CIRCULATIONAHA.117.032722)</p> <p>„[...] there was a delay of trial registration before first patient inclusion which was induced by a misunderstanding between the project coordination for the EU grant (at this time gabo:mi, later on ARTTIC) and the clinical project coordination at the investigator's site at the Heart Center Leipzig - University of Leipzig. According to initial communication registration should be performed by gabo:mi. When the study coordinator recognized that it has not been performed we immediately registered it at clinicaltrials.gov. At this time only 13 patients at the Heart Center Leipzig University Hospital (and no other study site) have been included into the trial.“ (doi: 10.1056/NEJMoa1710261)</p>
Publication	“Registration was done after the study has been conducted and the results suggested a publication and further continuation of this research.“ (doi: 10.1186/s12903-016-0264-2)
Confidentiality	“The principal investigator (N.H.) delayed the registration of the study until data acquisition was completed for confidentiality reasons concerning the study methods, especially the magnetic resonance with the related morphometric measurements.“ (doi: 10.1371/journal.pone.0136375)
Logistic/ Administrative issues	<p>“Because of administrative problems, release of registration occurred about six months after study start. The authors confirm that all ongoing and related trials for this intervention are registered.“ (doi: 10.1371/journal.pone.0220436)</p> <p>“Due to organisational changes in the research project shortly before the start of the recruitment we put great efforts into avoiding a delayed start of the data collection in the cooperating inpatient units, which resulted in retrospective study registration and a delayed publication of our study protocol.“ (doi: 10.1371/journal.pone.0186967)</p> <p>„Registration of the trial was delayed after the enrollment of the first patient due to an administrative error. The authors confirm that all ongoing and related trials for this intervention are registered.“ (doi: 10.1371/journal.pone.0140584)</p>

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Discussion

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In this study we show that in a sample of 956 results publications from retrospectively registered clinical studies led by German UMCs and completed between 2009 and 2017, only a small number of publications (5%) make the retrospective nature of the registration transparent, and even fewer (2%) explain the reasons for retrospective registration. To our knowledge, two studies have previously quantified the reporting of retrospective registration: Al-Durra et al. (17) found in a sample of 286 publications in ICMJE member journals and published in 2018 that only three percent (8/286) of papers of retrospectively registered trials in their sample include justifications or

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239 explanations for delayed registration. Similarly, Loder et al. (18), in their analysis of 70 papers
240 submitted to the British Medical Journal from 2012-2015 and rejected for registration issues, found
241 that three percent (2/70) disclosed the registration problem when published in another journal. Our
242 study finds a slightly lower percentage of two percent for explanations of the reasons for
243 retrospective registration, but a higher percentage of five percent for disclosure in a larger sample
244 representing a broader selection of journals and extended time frame.
245 We found that publications were not significantly more often prospectively registered when they
246 were published in ICMJE member journals or in journals following ICMJE recommendations, but
247 showed a significantly higher rate of TRN reporting. A similar result was found by Al-Durra et al. (17).
248 Further, we found that transparent reporting of retrospective registration does not happen
249 significantly more often in publications in ICMJE member journals, and is even happening at a
250 significantly lower rate in journals listed as following ICMJE recommendations.

251 There were different reasons for retrospective registration brought forth by authors, many of which
252 have been described previously (15,17,18,24). In some cases, authors raise points that lie outside
253 their direct responsibility, such as delays caused by the registry or research not being legally
254 required to be preregistered. Several other reasons provided were within authors' control, such as
255 logistic and administrative issues, miscommunication between researchers or unawareness of
256 registration policies. In some cases, authors report registering a study to meet journal editorial
257 policies even though registration would not be required for the kind of research otherwise. This is
258 also possibly reflected in the fact that almost a third (31%) of retrospectively registered studies in
259 our sample have been registered between study completion and publication. In one publication, the
260 authors transparently describe that the registration occurred only when "results suggested a
261 publication and further continuation of this research", which has been previously described as
262 "selective registration bias" (17) and is explicitly called out in ICMJE guidance as it "meets none of
263 the purposes of preregistration" (5). Another identified theme revolves around the confidentiality of
264 methods – however, in this case many other details about the trial could have been preregistered.

265 *Limitations*

266 For feasibility and data quality reasons, our study was based on an existing validated dataset,
267 containing only trials led by German UMCs, which might limit its generalizability to other regions.
268 However, the sample also contained multi-center trials with other countries involved and is larger
269 and from a wider variety of journals compared to previous studies (17,18). Our analysis of
270 retrospective registration is based on trial start dates and registration dates as provided by the two
271 registries used for sampling: Clinicaltrials.gov and DRKS. It is possible that authors did not update
272 their registry entries when delays to the start date occurred. For example, we did not specifically
273 follow up cases in which authors wrote that a trial was registered prospectively, but the registry
274 dates did not reflect that statement. In order not to reduce the sample size, we also did not correct
275 for varying follow-up in the identification of result publications, e.g., by limiting our analysis to
276 publications published within 2 years of trial completion. However, this means that the newer trials
277 in the sample (i.e., years 2016, 2017) might not reflect the complete research output of those years
278 as some trials may not have been published by the end of follow-up in 2020 and were therefore
279 excluded from the analysis. The numbers presented in Figures 2 and 3 may overestimate the
280 improvements in prospective registration as trials reporting results on time might likely generally

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3 281 show a higher quality of registration conduct and might therefore be registered prospectively at a
4 282 higher rate.
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6 283 In our analyses involving the classification into ICMJE-following and non-following journals, we relied
7 284 on the data provided on the ICMJE website (icmje.org), which are self-reported by journals, i.e., a
8 285 journal must write to the ICMJE that they want to be included in the list. Thus, there are some
9 286 journals missing in the ICMJE data and therefore in our dataset. For ICMJE member journals (n=12)
10 287 on the other hand, there is a complete listing available.
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12 288

13 289 *Conclusion*

14 290 The Declaration of Helsinki and other guidelines for responsible clinical research unanimously
15 291 recommend prospective registration of all clinical research (2). For clinical trials regulated by drug
16 292 and device regulatory authorities, this was codified into law (4). A major aim of prospective
17 293 registration is to minimize the risk of undisclosed changes to the protocol after the study started and
18 294 first results are analyzed. When registration happens retrospectively, this major goal is not
19 295 addressed. The reporting of study registration is generally considered a best practice to make a
20 296 study more trustworthy. In the case of retrospective registration, in contrast, reporting registration
21 297 without transparency on the retrospective nature should rather raise concerns as readers might
22 298 wrongly interpret the mentioning of registration as a quality criterion. This could be considered
23 299 “performative reproducibility”, i.e., the “pretence of reproducibility without the reality” (25). Journal
24 300 editors and reviewers could enforce explicit reporting and explanation of retrospective registration,
25 301 but we found that this rarely happens. To fulfill the ICMJE requirements on reporting retrospective
26 302 registration, a simple note in the registration statement of the paper would suffice, such as: “This
27 303 study was retrospectively registered as [TRN] at [Registry], [X] days after the trial started because
28 304 [Reason]”.
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307 **Ethics approval**

308 Not applicable

310 **Contributorship statement**

311 Martin Haslberger – Conceptualization, methodology, investigation, analysis, writing - original draft,
312 project management

313 Stefanie Gestrich – Methodology, investigation

314 Daniel Strech – Conceptualization, methodology, supervision, writing – review and editing, funding
315 acquisition

318 **Competing interests**

319 The authors declare no competing interests.

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325 manuscript, or the decision to submit for publication.

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4 327 **Data sharing statement**

5 328 All code and the data for this study are available at <https://github.com/mhaslberger/retrospective->
6 329 registration. Data are also available in an OSF repository (<https://osf.io/8g5cf/>).
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3 407 Figure 1: Flowchart of in-/exclusion of studies. From the 1038 trials that were retrospectively
4 408 registered in Clincialtrials.gov or DRKS, we excluded 5 publications that clearly did not report clinical
5 409 study results (e.g., secondary analyses of CT data) and another 77 that reported EudraCT entries in
6 410 the publications, resulting in 956 retrospectively registered studies from a total dataset of 1927 (971
7 411 + 956) studies.
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14 414 Figure 2: Percentage of retrospectively registered (RR) trials over time (per study start year). GAM
15 415 (generalized additive model) smoother laid over (blue) with 95% confidence interval. Bubble sizes
16 416 indicate the number of trials per year included in the dataset.
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22 419 Figure 3: Percentage of retrospectively registered trials reporting retrospective registration
23 420 transparently in the publication over time (per study publication year). GAM (generalized additive
24 421 model) smoother laid over (blue) with 95% confidence interval. Bubble sizes indicate the number of
25 422 trials per year included in the dataset. Starting in 2013, some authors begin to report retrospective
26 423 registration. 15% of publications of retrospectively registered trials from 2020 transparently report
27 424 retrospective registration. Four trials were published before 2009 – in all those cases the study
28 425 completion dates provided in the registry were after 2009. Study start dates were before 2005 and
29 426 studies were registered in 2005 (3/4) or later (1/4).
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BMJ Open
Registered (DRKS, CT.gov)
clinical studies with results
publications in Germany
completed 2009-2017
n = 1932

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Prospectively registered
n = 894

Retrospectively registered
n = 1038

Reclassified publications:
registration in EudraCT reported
in the publication (n=77)

Excluded publications:
- incorrect publication in dataset
(n=5)

Prospectively registered
n = 971

Retrospectively registered
n = 956

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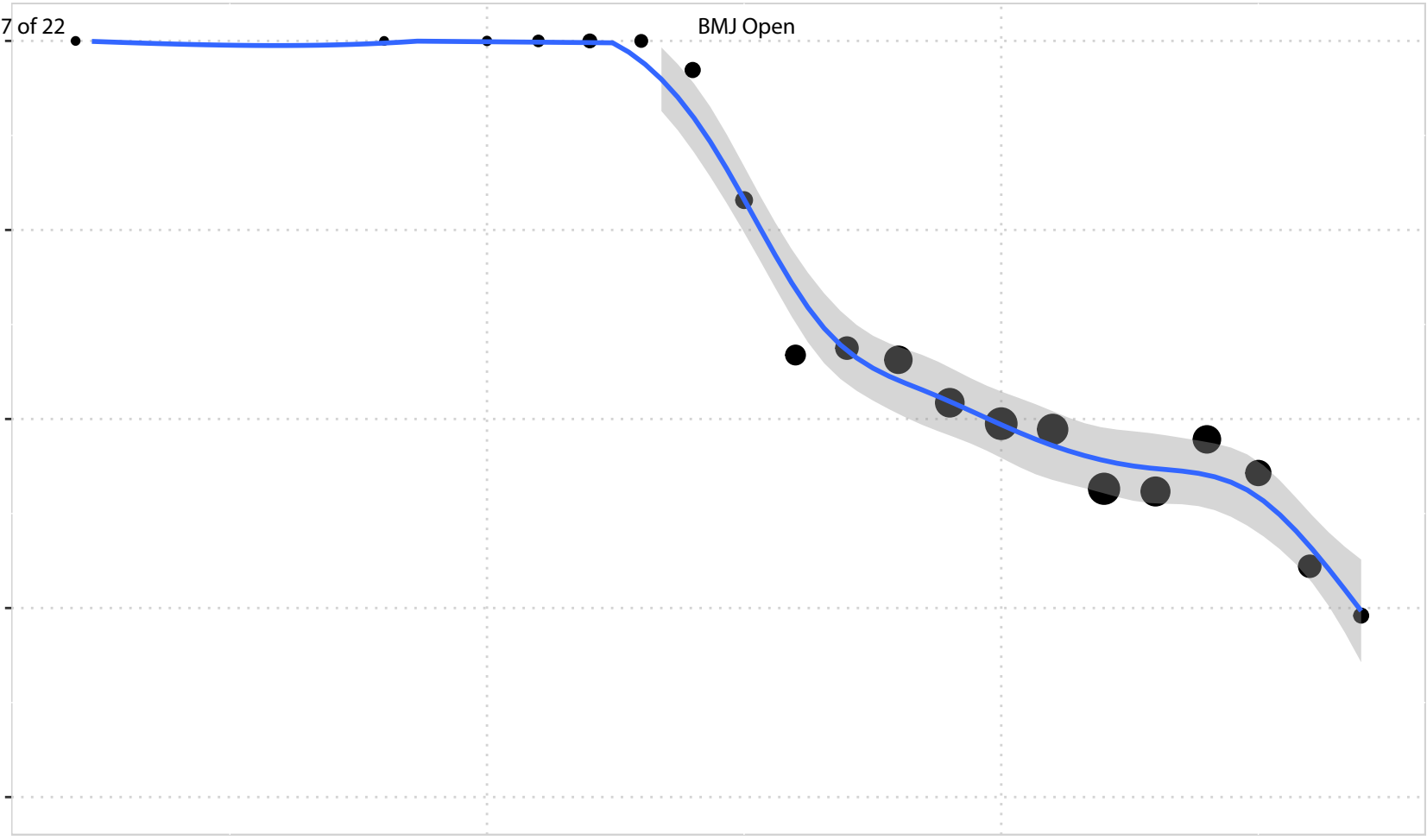
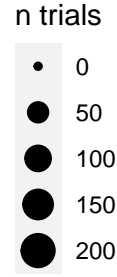
Year(Start)

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n 1 0 0 0 0 0 1 0 2 8 18 13 26 38 65 96 166 186 243 218 233 193 167 133 95 25

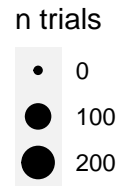
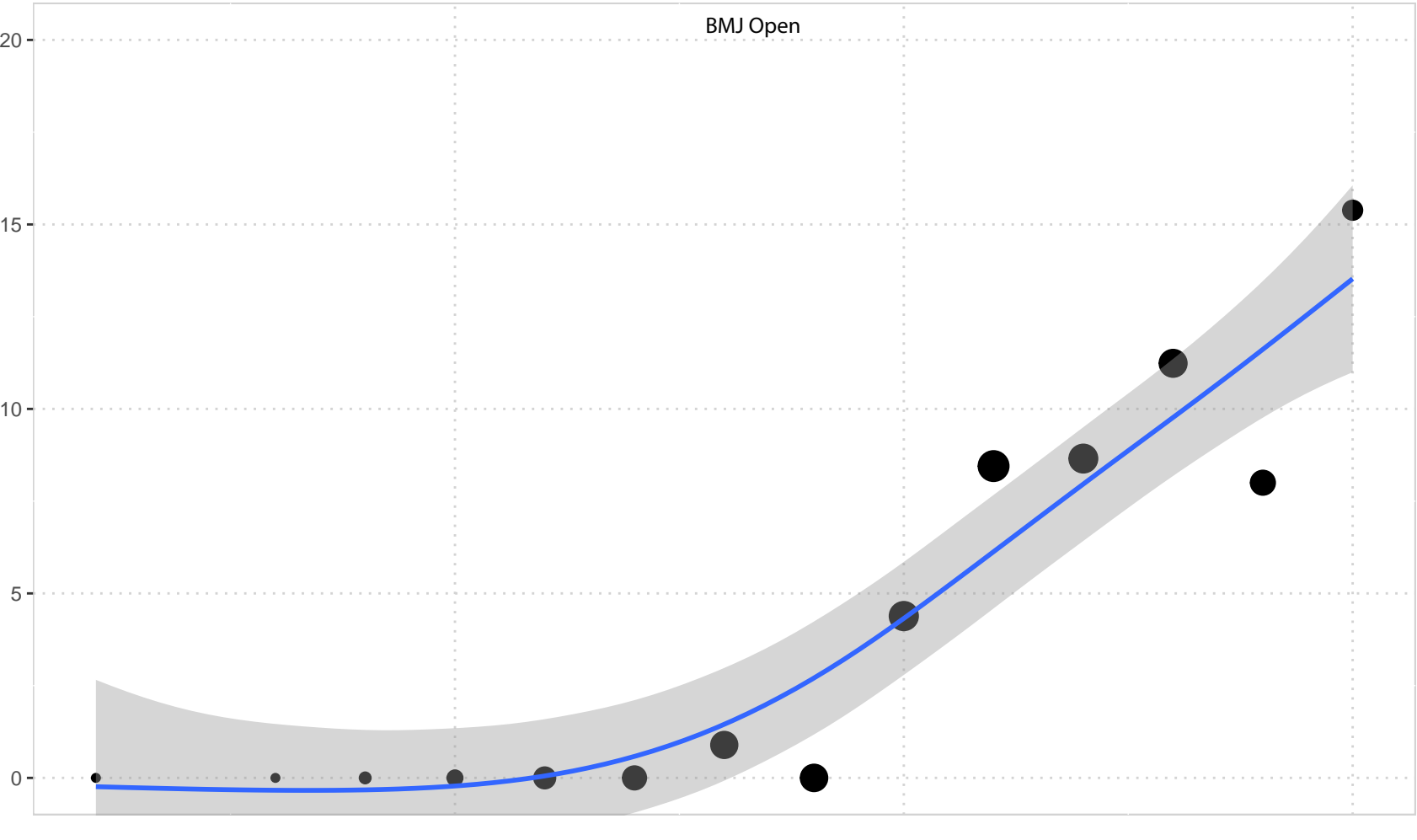
RR 1 0 0 0 0 0 1 0 2 8 18 13 25 30 38 57 96 97 120 106 95 78 79 57 29 6

% RR 100 100 100 100 100 100 96.2 78.9 58.5 59.4 57.8 52.2 49.4 48.6 40.8 40.4 47.3 42.9 30.5 24



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Year (Pub.)	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020
n	2	0	2	12	40	111	144	199	205	240	278	234	215	160	85
RRR	0	0	0	0	0	0	0	1	0	5	12	9	10	4	6
%RRR	0		0	0	0	0	0	0.9	0	4.4	8.5	8.7	11.2	8	15.4

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Supplementary Table 1: STROBE checklist

	Item No.	Recommendation	Page No.	Relevant text from manuscript
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	2	Cross-sectional study
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2	See abstract
Introduction				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3	When trials are registered retrospectively, i.e., their registry entry is created after study start, this undermines the many of the reasons for registration. While prospective registration has increased over the past decade, retrospective registration is still widespread (10–14). Some registries, such as DRKS, explicitly mark retrospectively registered entries as such, whereas others, such as ClinicalTrials.gov, do not. While some publishers allow retrospectively registered trials to be published, others do not. Journals following ICMJE guidance should in principle mandate prospective registration, but this principle is not always enforced (12,15,16).
Objectives	3	State specific objectives, including any prespecified hypotheses	3	Our study aims to investigate the conduct of retrospective registration and its transparent reporting
Methods				
Study design	4	Present key elements of study design early in the paper	3	We based our sample on two related projects that were conducted at our research group (17,18). The projects have drawn a full sample (n = 3113) of registry entries for interventional studies reported as complete between 2009 and 2017, led by a German University Medical Center and registered in one of two registries: The ClinicalTrials.gov platform (CT.gov) and the Deutsches Register Klinischer Studien (DRKS)
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	3-4	See above

Participants	6	<i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants	3-4	We included any trial that [1] was registered as an interventional study in either the ClinicalTrials.gov or the DRKS database, [2] was completed between 2009 and 2017, [3] reports a German University Medical Center (UMC) listed as the responsible party or lead sponsor, or with a principal investigator from a German UMC, [4] has published results in a peer-reviewed journal.
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	3	we investigate whether and how authors report retrospective registration in the results publication. We also explore trends over time and how retrospective registration is associated with other practices such as reporting the trial registration number.
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	3-4	Data sources and sample. We based our sample on two related projects that were conducted at our research group (17,18). The projects have drawn a full sample (n = 3113) of registry entries for interventional studies reported as complete between 2009 and 2017, led by a German University Medical Center and registered in one of two registries: The ClinicalTrials.gov platform (CT.gov) and the Deutsches Register Klinischer Studien (DRKS), which is the WHO primary trial registry for Germany. Our dataset also includes the earliest results publications found for 68.4% (2129/3113) of the trials, which were manually identified in different stages until September 1st, 2020. We retrieved the combined data from the two projects from a GitHub repository (https://github.com/maia-sh/into-value-data , accessed 22.02.2022).
Bias	9	Describe any efforts to address potential sources of bias	4	<i>Reliability assessment of ratings.</i> To assess the reliability of the data extraction, another rater (SG) performed three validation steps: first, a sample of 100 publications was screened using the same extraction form, during the main screening to refine category definitions. Second, another sample of 100 publications for which no registration number reporting was noted by MH to check for false negative ratings. Third, all cases with either date, or reporting of retrospective registration or justification were screened, to check for false positives.

Study size	10	Explain how the study size was arrived at	3	We based our sample on two related projects that were conducted at our research group
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	-	Not applicable
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	4	See Methods
		(b) Describe any methods used to examine subgroups and interactions	4	See Methods
		(c) Explain how missing data were addressed	-	Not applicable
		(d) <i>Cross-sectional study</i> —If applicable, describe analytical methods taking account of sampling strategy	-	Not applicable
		(e) Describe any sensitivity analyses	-	Not applicable
Results				
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	5	First paragraph of Results
		(b) Give reasons for non-participation at each stage	5	First paragraph of Results
		(c) Consider use of a flow diagram	5	Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	5	Supplementary table 1
		(b) Indicate number of participants with missing data for each variable of interest	-	Complete case analysis
		(c) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)	3	The projects have drawn a full sample (n = 3113) of registry entries for interventional studies reported as complete between 2009 and 2017, led by a German University Medical Center and registered in one of two registries: The ClinicalTrials.gov platform (CT.gov) and the Deutsches Register Klinischer Studien (DRKS), which is the WHO primary trial registry for Germany. Our dataset also includes the earliest results publications found for 68.4% (2129/3113) of the trials, which were manually identified in different stages until September 1st, 2020
Outcome data	15*	<i>Cross-sectional study</i> —Report numbers of outcome events or summary measures	5-7	See results, e.g. Table 2, Figures 2,3
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and	-	Not applicable

		their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included		
		(b) Report category boundaries when continuous variables were categorized	-	Not applicable
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	-	Not applicable
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	6-9	See results
Discussion				
Key results	18	Summarise key results with reference to study objectives	9-10	See 1 st paragraph of discussion
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	10	See Limitations section
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	9-10	See first paragraph of discussion
Generalisability	21	Discuss the generalisability (external validity) of the study results	10	For feasibility and data quality reasons, our study was based on an existing validated dataset, containing only trials led by German UMCs, which might limit its generalizability to other regions. [...]
Other information				
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	1	This work was partly funded under a grant from the Federal Ministry of Education and Research of Germany (Bundesministerium fuer Bildung und Forschung - BMBF) [01PW18012]. The funder was not involved in the study design, data collection, analysis, or interpretation, writing of the manuscript, or the decision to submit for publication.

Supplementary Table 2: Basic characteristics of included trials

	Retrospectively registered trials (n = 956)	Prospectively registered trials (n = 971)
Registry		
ClinicalTrials.gov	713	766
DRKS	243	205
Sponsorship		
Industry	112	163
Other	844	808
Phase		
Phase 1	33	71
Phase 2	122	206
Phase 3	91	134
Phase 4	78	99
No phase	632	461
Intervention type		
Behavioral	94	72
Biological	18	32
Device	199	138
Dietary Supplement	40	30
Drug	186	340
Genetic	1	1
Procedure	96	70
Radiation	6	9
Other	73	74
Not given	243	205

BMJ Open

Reporting of Retrospective Registration in Clinical Trial Publications: a Cross-Sectional Study of German Trials

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2022-069553.R2
Article Type:	Original research
Date Submitted by the Author:	27-Mar-2023
Complete List of Authors:	Haslberger, Martin; Berlin Institute of Health at Charité, QUEST Center for Responsible Research Gestrich, Stefanie; Berlin Institute of Health at Charité, QUEST Center for Responsible Research Strech, Daniel; Berlin Institute of Health at Charité, QUEST Center for Responsible Research
Primary Subject Heading:	Medical publishing and peer review
Secondary Subject Heading:	Research methods, Ethics
Keywords:	MEDICAL ETHICS, STATISTICS & RESEARCH METHODS, Clinical trials < THERAPEUTICS

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3 1 **Reporting of Retrospective Registration in Clinical Trial Publications: a Cross-Sectional Study of**
4 2 **German Trials**

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21 15 **Keywords:** Clinical Trials, Trial Registration, Reporting, Retrospective Registration
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18 Abstract

19 **Objective:** Prospective registration has been widely implemented and accepted as a best practice in
20 clinical research, but retrospective registration is still commonly found. We assessed to what extent
21 retrospective registration is reported transparently in journal publications, and investigated factors
22 associated with transparent reporting.

23 **Design:** We used a dataset of trials registered in ClinicalTrials.gov or Deutsches Register Klinischer
24 Studien, with a German University Medical Center as the lead center, completed 2009–2017, and
25 with a corresponding peer-reviewed results publication. We extracted all registration statements
26 from results publications of retrospectively registered trials and assessed whether they mention or
27 justify the retrospective registration. We analyzed associations of retrospective registration and
28 reporting thereof with registration number reporting, International Committee of Medical Journal
29 Editors (ICMJE) membership/-following and industry sponsorship using chi-squared or Fisher exact
30 test.

31 **Results:** In the dataset of 1927 trials with a corresponding results publication, 956 (53.7%) were
32 retrospectively registered. Of those, 2.2% (21) explicitly report the retrospective registration in the
33 abstract and 3.5% (33) in the full text. In 2.1% (20) of publications, authors provide an explanation
34 for the retrospective registration in the full text. Registration numbers were significantly
35 underreported in abstracts of retrospectively registered trials compared to prospectively registered
36 trials. Publications in ICMJE member journals did not have statistically significantly higher rates of
37 both prospective registration and disclosure of retrospective registration, and publications in
38 journals claiming to follow ICMJE recommendations showed statistically significantly lower rates
39 compared to non-ICMJE-following journals. Industry sponsorship of trials was significantly associated
40 with higher rates of prospective registration, but not with transparent registration reporting.

41 **Conclusions:** Contrary to ICMJE guidance, retrospective registration is disclosed and explained only
42 in a small number of retrospectively registered studies. Disclosure of the retrospective nature of the
43 registration would require a brief statement in the manuscript and could be easily implemented by
44 journals.

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49 Strengths and limitations of this study

- 50 • We use a large, high-quality dataset of all trials conducted at German university medical
51 centers over a period of nine years (2009 – 2017) and registered in two registries, with
52 results publications determined by an extensive manual screening process.
- 53 • This study only includes trials led by German university medical centers, which might limit its
54 generalizability to other regions. Follow-up for trial publications ends uniformly in 2020,
55 meaning that older trials had longer follow-up for publication than newer trials in the
56 dataset.

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57 Introduction

58 Prospective registration of clinical trials (i.e., registration before enrollment of the first participant) is
59 an important practice to reduce biases in their conduct and reporting (1). A number of ethical and
60 legal documents call for prospective registration: The Declaration of Helsinki (2) and the World
61 Health Organization registry standards (3) state that prospective registration and results reporting of
62 clinical trials are an ethical responsibility. European law, for example, explicitly mandates
63 prospective registration of pharmaceutical trials (4). In addition, many journals, via the International
64 Committee of Medical Journal Editors (ICMJE), encourage or require prospective registration with an
65 appropriate registry before the first participant is enrolled for all trials they publish, as well as the
66 reporting of trial registration numbers (TRNs) in publications for better findability (5,6). Similarly,
67 reporting guidelines such as Consolidated Standards of Reporting Trials (CONSORT) (7) and Good
68 Publication Practice 3 (GPP3) (8) recommend the reporting of trial registration numbers.

69 Prospective registration has been widely implemented and advocated for many reasons: to detect
70 and mitigate publication bias (i.e., the non-reporting of studies, or aspects of studies, that did not
71 yield a positive result) and selective reporting (i.e., the selective reporting of only statistically
72 significant primary outcomes). Prospective registration allows for public scrutiny of trials,
73 identification of research gaps and to support the coordination of efforts by preventing unnecessary
74 duplication (9). When trials are registered retrospectively, i.e., their registry entry is created after
75 study start, this undermines the many of the reasons for registration. While prospective registration
76 has increased over the past decade, retrospective registration is still widespread (10–14). Some
77 registries, such as Deutsches Register Klinischer Studien (DRKS) or the WHO's International Clinical
78 Trials Registry Platform, explicitly mark retrospectively registered entries as such, whereas others,
79 such as ClinicalTrials.gov, do not. While some journal editors allow retrospectively registered trials to
80 be published, others do not. Journals following ICMJE guidance should in principle mandate
81 prospective registration, but this principle is not always enforced (12,15,16). According to ICMJE
82 guidance, journals should publish retrospectively registered studies only in exceptional cases, noting
83 that "authors should indicate in the publication when registration was completed and why it was
84 delayed. Editors should publish a statement indicating why an exception was allowed." (5) This was
85 investigated by previous studies which found that such reporting rarely happens (17,18).

86 Our study aims to investigate the conduct of retrospective registration and its transparent reporting
87 in a larger sample. In a previous study in a cohort of 1509 trials conducted at German University
88 Medical Centers (UMC), registered in DRKS or ClinicalTrials.gov, and reported as complete between
89 2009-2013, 75% were registered retrospectively (19). This rate dropped to 46% for the 1658 trials
90 completed between 2014-2017 (20). Using the data from these two studies on trials registered in
91 two large registries, led by German UMCs, completed between 2009 and 2017, and with at least one
92 available peer-reviewed results publication (19,20), we investigate whether and how authors report
93 retrospective registration in the results publication. We also explore how retrospective registration
94 is associated with other practices such as TRN reporting.

95

96 Methods

97 *Data sources and sample.* We based our sample on two related projects that were conducted at our
98 research group (19,20). The projects have drawn a full sample (n = 3113) of registry entries for
99 interventional studies reported as complete between 2009 and 2017, led by a German UMC and
100 registered in one of two registries: DRKS, which is the WHO primary trial registry for Germany, and
101 ClinicalTrials.gov, which is also routinely used in Germany to register clinical research and accepted

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102 by the ICMJE. Our dataset also includes the earliest results publications found for 68.4% (2129/3113)
103 of the trials, which were manually identified in different stages until September 1st, 2020. We
104 retrieved the combined data from the two projects from a GitHub repository
105 (<https://github.com/maia-sh/intoalvalue-data>, accessed 22.02.2022). The final dataset is publicly
106 available (21).

107 *Eligibility criteria.* We included any trial that [1] was registered as an interventional study in either
108 the ClinicalTrials.gov or the DRKS database, [2] was completed between 2009 and 2017, [3] reports a
109 German UMC listed as the responsible party or lead sponsor, or with a principal investigator from a
110 German UMC, [4] has published results in a peer-reviewed journal. Detailed descriptions of how
111 these variables were derived are provided in the original publications of the dataset (19,20).

112 Retrospective registration was determined based on the registration and study start dates in the
113 registry entries: dates were set to the first of the respective month and studies with a registration
114 date more than one month after start date counted as retrospectively registered. For trials that were
115 registered in both registries, we kept the entry that was created earlier.

116 *Data extraction.* For all retrospectively registered trials, we manually searched the abstract and the
117 full text of the publications, including editorial statements, whether they reported

- 118 • the fact that the study was registered (binary),
- 119 • a trial registration number (binary),
- 120 • the exact wording used to report the registration, including any provided registration
121 numbers (free text),
- 122 • the date of the retrospective registration (binary), and
- 123 • the fact that the study was retrospectively registered (binary).
- 124 • We also assessed whether (binary) and how authors justified or explained the retrospective
125 registration (free text).

126 One rater (MH) used the keywords “regist”, “nct”, “drks”, “eudra”, “retro”, “delay”, and “after” to
127 search for registration numbers and wording pointing to retrospective registration in all publications.
128 We considered a retrospective registration statement transparent if the authors explicitly mentioned
129 that the registration was retrospective, e.g., “this study was retrospectively registered in [registry],
130 [TRN]”. Reporting of the registration date alone was not considered as transparent reporting of
131 retrospective registration, except if the date of registration was mentioned in combination with the
132 study start date in the same paragraph.

133 *ICMJE journals.* We created additional variables for whether journals are ICMJE members or follow
134 the ICMJE recommendations (22).

135 *Cross-registrations.* We classified all retrospectively registered studies in our sample that also report
136 a registration in EudraCT in the publication as prospective, as registrations on the platform are
137 required prior to the approval of regulatory agencies or research ethics committees (4).

138 *Reliability assessment of ratings.* To assess the reliability of the data extraction, another rater (SG)
139 performed three validation steps: first, a sample of 100 publications was screened using the same
140 extraction form, during the main screening to refine category definitions. Second, another sample of
141 100 publications for which no registration number reporting was noted by MH to check for false
142 negative ratings. Third, all cases with either date, or reporting of retrospective registration or
143 justification were screened, to check for false positives.

144 *Analyses*

145 *Associations between prospective registration and other variables.* To test the strength of the
146 associations between prospective registration and three variables, we used Pearson’s chi-squared

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3 147 independence test. These variables were (1) publication in a ICMJE member journal or a journal
4 148 following ICMJE recommendations, (2) reporting of a registration number, and (3) industry funding.
5 149 *Associations between reporting of retrospective registration and other variables.* To test the strength
6 150 of the associations between the reporting of retrospective registration and two binary variables, we
7 151 used Fisher's exact test, as case numbers were low. These variables are (1) publication in a ICMJE
8 152 member journal or a journal following ICMJE recommendations, and (2) industry funding.

11 153 *Software*

12 154 We used Microsoft Excel for data collection and R (version 4.0.3) for data analysis and visualization.

15 156 *Reporting*

16 157 We checked our manuscript against the STROBE checklist (supplementary Table 1) (23).

19 159 *Patient and Public Involvement*

20 160 No patient involved.

22 162 **Results**

23 163 *Sample of retrospectively registered trials.* After applying the above-mentioned exclusion criteria,
24 164 1932 registered studies with an associated results publication remained. Of these, 1038 (54%) were
25 165 retrospectively registered according to the information provided in ClinicalTrials.gov and DRKS. We
26 166 screened these 1038 studies for our analysis. Five of the publications were excluded as they were
27 167 mislabeled as results publications in the dataset. Another 77 (8%) of the publications provided a
28 168 EudraCT number, in which case we reclassified the study as prospectively registered, leaving 956
29 169 studies. For statistical comparisons, we used the studies classified as prospectively registered
30 170 (n=971) in the dataset as a control group. A flowchart of this study selection is provided in Figure 1.
31 171 Basic characteristics of included trials are available in supplementary Table 2.

32 172
33 173 *Retrospective registration.* Figure 2 shows the extent of retrospective registration over time, which
34 174 has been falling steadily from 100% in 2004 to 25% in 2017.

35 175 We describe associations between prospective registration and previously defined binary variables
36 176 in Table 1: We found no statistically significant association between publication in ICMJE member
37 177 journals and prospective registration ($p=0.10$). Similarly, we found no statistically significant
38 178 association with prospective registration when also including publication in journals reporting to
39 179 follow ICMJE recommendations ($p=0.47$). It is important to note here that the information on ICMJE-
40 180 following is based on journals' requests to be included on the ICMJE website as a journal following
41 181 the ICMJE's recommendations (22), therefore our results suggest that journals requesting to be
42 182 listed on the site often do not enforce the recommendations strongly. However, there are other
43 183 journals, such as many PLOS journals, that are not featured on the ICMJE site, but implement the
44 184 recommendations. Retrospectively registered trials, compared to prospectively registered trials
45 185 significantly underreported registration numbers in the abstract ($p = 0.0007$). Industry sponsorship
46 186 of trials was associated with prospective registration ($p = 0.002$). In 31% (294/956) of trials,
47 187 registration occurred between study completion and publication (median 370 days before
48 188 publication). Another 3% (25/956) of trials were registered after publication (median 249 days after
49 189 publication).

191 *Table 1: Associations between prospective registration and other variables*

Variable (Yes/No)		n (%) prospectively registered	P-value (Chi-sq.)
ICMJE member journal	Y	28 (63.6%)	p = 0.10
	N	943 (50.1%)	
ICMJE member/following journal	Y	329 (49.2%)	p = 0.47
	N	642 (51.0%)	
TRN reporting in abstract	Y	404 (55.4%)	p = 0.0007
	N	567 (47.3%)	
Industry sponsorship	Y	163 (59.3%)	p = 0.002
	N	808 (48.9%)	

192
193 *Reporting of registration.* Table 2 summarizes the prevalence of reporting of trial registration and
194 the reporting of retrospective registration. In 82% (783/956) of the remaining results publications of
195 retrospectively registered trials, the registration was explicitly reported in either the abstract or the
196 full text. In all except four of these publications, the registration was mentioned by providing the
197 registration number. In the other cases, the registration was mentioned but without reporting a
198 registration number.

199
200 *Table 2: Number of retrospectively registered trials and prevalence of key retrospective registration*
201 *reporting practices.*

202 * "other" includes footnotes, sidebars, etc.

	n	% (of total)
Total: Retrospectively registered trials	956	100.0%
Registration reported	783	81.9%
Registration number reported	779	81.5%
<i>in abstract</i>	325	34.0%
<i>in full-text</i>	535	56.0%
<i>in other*</i>	134	14.0%
Registration date reported	67	7.0%
<i>in abstract</i>	45	4.7%
<i>in full-text</i>	32	3.3%
Retrospective registration addressed	47	4.9%
<i>in abstract</i>	21	2.2%
<i>in full-text</i>	33	3.5%
Retrospective registration justified/explained	20	2.1%
<i>in abstract</i>	0	0.0%
<i>in full-text</i>	20	2.1%

203
204 *Reporting of retrospective registration.* The rate of trials for which retrospective registration is
205 reported transparently increased over the last years up to 15% in 2020 (Figure 3). Overall, among all
206 956 retrospectively registered clinical studies, five percent (47) mention explicitly that this
207 registration was retrospective in the abstract or full text (see Table 2). Among those cases, 20 give

208 some explanation or justification for why registration was retrospective. In seven percent (67) of
 209 cases, the authors reported the registration date alongside the registration statement, but in 35 of
 210 those, the date was provided without giving the necessary context that the registration was
 211 retrospective.

212 Publications in ICMJE member journals did not have a statistically significantly higher rate of
 213 reporting of retrospective registration (13% vs. 5%, $p = 0.18$), whereas publications in ICMJE member
 214 or -following journals had a significantly lower rate (2% vs. 7%, $p = 0.004$). We found no association
 215 with transparent reporting of retrospective registration for industry sponsored trials (2% vs. 5%, $p =$
 216 0.16) (Table 3).

217
 218 *Table 3: Associations between transparent reporting of retrospective registration and other variables*

Variable (Yes/No)		n (%) reporting RR	P-value (Fisher test)
ICMJE member journal	Y	2 (12.5%)	$p = 0.18$
	N	45 (4.8%)	
ICMJE member/following journal	Y	7 (2.1%)	$p = 0.004$
	N	40 (6.5%)	
Industry sponsorship	Y	2 (1.8%)	$p = 0.16$
	N	45 (5.3%)	

219
 220 *Justifications of retrospective registration.* In 20 cases in which the retrospective nature of the
 221 registration was reported, the authors provided further information explaining or justifying the
 222 retrospective registration. Notably, 14 of the 20 studies (70%) that justified the retrospective
 223 registration were published in a single journal, PLOS ONE. Table 4 shows the main themes present in
 224 authors' explanations, with text examples.

225
 226 *Table 4. Main themes identified from authors' explanations of retrospective reporting and example
 227 statements.*

Theme	Example(s)
Unawareness of registration policy	<p>"At the time when the trial was started, the initiators of this study were unfortunately unaware of the policy of the International Committee of Medical Journal Editors (ICMJE), which requires prospective registration of all interventional clinical trials. As soon as we became aware of this policy, we registered the trial." (doi: 10.1371/journal.pone.0146678)</p> <p>"The reason for retrospectively registering the study was that the study authors were not aware of the recommendation to register diagnostic accuracy studies before this date." (doi: 10.1371/journal.pone.0199345)</p>
Delays by the registry	"Registration of the study was applied for in April 2015. All queries from the DRKS were answered until the 31st August 2015 except the planned inclusion date of the first patient (first-patient-in), which was correct in the DRKS registry on 1st December 2015. Confirmation of registration occurred on 4th December 2015. The first patient was recruited and randomized into the study on 20th October 2015. Until 4th December 2015 eight patients were randomized into the trial." (doi: 10.1371/journal.pone.0229898)
Not obligatory at the time	"At the time of submission of the study protocol, the Ethics Committee did not require registration for feasibility or proof of concept studies. The study was registered in ClinicalTrials.gov (NCT02196545) in July 2014 in preparation of a manuscript for publication of the data. The authors confirm that all ongoing and related trials for this intervention are registered." (doi: 10.1371/journal.pone.0121478)

	„It was not registered at a clinical trial register, because at the time of setup in 2003, such a registration was not obligatory.“ (doi: 10.2174/1874325001307010133)
Not obligatory for the intervention	“According to national laws it is stipulated to inform the respective ethics committee, but it was not necessary to register the study in an official registry or to obtain an ethics committee vote, because it was an expanded access study (Heilver such). Despite this, we prospectively obtained a vote of the ethics committee. Study design and patient information form were approved by the local ethics committee (ethics committee of the regional medical association; approval no. EK-BR-50/10-1, date of approval December 10th, 2010). In addition, the study was registered at www.clinicaltrials.gov (ID no. NCT02168790).“ (doi: 10.1371/journal.pone.0125035)
Miscommunication between investigators	<p>“The time of first registration was June 17, 2013, and final approved trial registration was July 1, 2013. First patient inclusion was in July 2012 at the Heart Center Leipzig University Hospital, Leipzig, Germany. Thus, there was a delay between first patient inclusion and trial registration that was the result of a misunderstanding between the principal investigator of the trial, Dr Thiele, and the first author, Dr Fuernau, who was responsible for clinical project coordination at the investigator’s site at the Heart Center Leipzig University of Leipzig. According to initial communication, registration had to be performed by Dr Fuernau. When the study principal investigator recognized that it had not been performed, we immediately registered the trial at http://www.ClinicalTrials.gov. At this time, only 7 patients at the Heart Center Leipzig University Hospital had been included in the trial.” (doi: 10.1161/CIRCULATIONAHA.117.032722)</p> <p>„[...] there was a delay of trial registration before first patient inclusion which was induced by a misunderstanding between the project coordination for the EU grant (at this time gabo:mi, later on ARTTIC) and the clinical project coordination at the investigator's site at the Heart Center Leipzig - University of Leipzig. According to initial communication registration should be performed by gabo:mi. When the study coordinator recognized that it has not been performed we immediately registered it at clinicaltrials.gov. At this time only 13 patients at the Heart Center Leipzig University Hospital (and no other study site) have been included into the trial.“ (doi: 10.1056/NEJMoa1710261)</p>
Publication	“Registration was done after the study has been conducted and the results suggested a publication and further continuation of this research.“ (doi: 10.1186/s12903-016-0264-2)
Confidentiality	“The principal investigator (N.H.) delayed the registration of the study until data acquisition was completed for confidentiality reasons concerning the study methods, especially the magnetic resonance with the related morphometric measurements.“ (doi: 10.1371/journal.pone.0136375)
Logistic/ Administrative issues	<p>“Because of administrative problems, release of registration occurred about six months after study start. The authors confirm that all ongoing and related trials for this intervention are registered.“ (doi: 10.1371/journal.pone.0220436)</p> <p>“Due to organisational changes in the research project shortly before the start of the recruitment we put great efforts into avoiding a delayed start of the data collection in the cooperating inpatient units, which resulted in retrospective study registration and a delayed publication of our study protocol.“ (doi: 10.1371/journal.pone.0186967)</p> <p>„Registration of the trial was delayed after the enrollment of the first patient due to an administrative error. The authors confirm that all ongoing and related trials for this intervention are registered.“ (doi: 10.1371/journal.pone.0140584)</p>

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Discussion

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In this study we show that in a sample of 956 results publications from retrospectively registered clinical studies led by German UMCs and completed between 2009 and 2017, only a small number of publications (5%) make the retrospective nature of the registration transparent, and even fewer (2%) explain the reasons for retrospective registration. To our knowledge, two studies have previously quantified the transparent reporting of retrospective registration in journal publications: Al-Durra et al. (17) found in a sample of 286 publications in ICMJE member journals and published in 2018 that only three percent (8/286) of papers of retrospectively registered trials in their sample

238 include justifications or explanations for delayed registration. Similarly, Loder et al. (18), in their
239 analysis of 70 papers submitted to the British Medical Journal from 2012-2015 and rejected for
240 registration issues, found that three percent (2/70) disclosed the registration problem when
241 published in another journal. Our study finds a slightly lower percentage of two percent for
242 explanations of the reasons for retrospective registration, but a higher percentage of five percent for
243 disclosure in a larger sample representing a broader selection of journals and extended time frame.
244 We found that publications were not significantly more often prospectively registered when they
245 were published in ICMJE member journals or in journals following ICMJE recommendations, but
246 showed a significantly higher rate of TRN reporting. A similar result was found by Al-Durra et al. (17).
247 Further, we found that transparent reporting of retrospective registration does not happen
248 significantly more often in publications in ICMJE member journals, and is even happening at a
249 significantly lower rate in journals listed as following ICMJE recommendations.

250 There were different reasons for retrospective registration brought forth by authors, many of which
251 have been described previously (15,17,18,24). In some cases, authors raise points that lie outside
252 their direct responsibility, such as delays caused by the registry or research not being legally
253 required to be preregistered. Several other reasons provided were within authors' control, such as
254 logistic and administrative issues, miscommunication between researchers or unawareness of
255 registration policies. In some cases, authors report registering a study to meet journal editorial
256 policies even though registration would not be required for the kind of research otherwise. This is
257 also possibly reflected in the fact that almost a third (31%) of retrospectively registered studies in
258 our sample have been registered between study completion and publication. In one publication, the
259 authors transparently describe that the registration occurred only when "results suggested a
260 publication and further continuation of this research", which has been previously described as
261 "selective registration bias" (17) and is explicitly called out in ICMJE guidance as it "meets none of
262 the purposes of preregistration" (5). Another identified theme revolves around the confidentiality of
263 methods – however, in this case many other details about the trial could have been preregistered.

264 *Limitations*

265 For feasibility and data quality reasons, our study was based on an existing validated dataset,
266 containing only trials led by German UMCs, which might limit its generalizability to other regions.
267 However, the sample also contained multi-center trials with other countries involved and is larger
268 and from a wider variety of journals compared to previous studies (17,18). Our analysis of
269 retrospective registration is based on trial start dates and registration dates as provided by the two
270 registries used for sampling: Clinicaltrials.gov and DRKS. It is possible that authors did not update
271 their registry entries when delays to the start date occurred. For example, we did not specifically
272 follow up cases in which authors wrote that a trial was registered prospectively, but the registry
273 dates did not reflect that statement. In order not to reduce the sample size, we also did not correct
274 for varying follow-up in the identification of result publications, e.g., by limiting our analysis to
275 publications published within 2 years of trial completion. However, this means that the newer trials
276 in the sample (i.e., years 2016, 2017) might not reflect the complete research output of those years
277 as some trials may not have been published by the end of follow-up in 2020 and were therefore
278 excluded from the analysis. The numbers presented in Figures 2 and 3 may overestimate the
279 improvements in prospective registration as trials reporting results on time might likely generally

280 show a higher quality of registration conduct and might therefore be registered prospectively at a
281 higher rate.
282 In our analyses involving the classification into ICMJE-following and non-following journals, we relied
283 on the data provided on the ICMJE website (icmje.org), which are self-reported by journals, i.e., a
284 journal must write to the ICMJE that they want to be included in the list. Thus, there are some
285 journals missing in the ICMJE data and therefore in our dataset. For ICMJE member journals (n=12)
286 on the other hand, there is a complete listing available.

288 *Conclusion*

289 The Declaration of Helsinki and other guidelines for responsible clinical research unanimously
290 recommend prospective registration of all clinical research (2). For clinical trials regulated by drug
291 and device regulatory authorities, this was codified into law (4). A major aim of prospective
292 registration is to minimize the risk of undisclosed changes to the protocol after the study started and
293 first results are analyzed. When registration happens retrospectively, this major goal is not
294 addressed. The reporting of study registration is generally considered a best practice to make a
295 study more trustworthy. In the case of retrospective registration, in contrast, reporting registration
296 without transparency on the retrospective nature should rather raise concerns as readers might
297 wrongly interpret the mentioning of registration as a quality criterion. This could be considered
298 “performative reproducibility”, i.e., the “pretence of reproducibility without the reality” (25). Journal
299 editors and reviewers could enforce explicit reporting and explanation of retrospective registration,
300 but we found that this rarely happens. To fulfill the ICMJE requirements on reporting retrospective
301 registration, a simple note in the registration statement of the paper would suffice, such as: “This
302 study was retrospectively registered as [TRN] at [Registry], [X] days after the trial started because
303 [Reason]”.

306 **Ethics approval**

307 Not applicable

309 **Contributorship statement**

310 Martin Haslberger: Conceptualization, methodology, investigation, analysis, writing - original draft,
311 project management; Stefanie Gestrich: Methodology, investigation; Daniel Strech:
312 Conceptualization, methodology, supervision, writing – review and editing, funding acquisition.

315 **Competing interests**

316 The authors declare no competing interests.

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322 manuscript, or the decision to submit for publication.

324 **Data sharing statement**

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3 325 All code and the data for this study are available at <https://github.com/mhaslberger/retrospective->
4 326 registration. Data are also available in an OSF repository (<https://osf.io/8g5cf/>).
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9 330 Holst and Dr. Delwen Franzen for feedback on the manuscript.
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3 404 Figure 1: Flowchart of in-/exclusion of studies. From the 1038 trials that were retrospectively
4 405 registered in Clincialtrials.gov or DRKS, we excluded 5 publications that clearly did not report clinical
5 406 study results (e.g., secondary analyses of CT data) and another 77 that reported EudraCT entries in
6 407 the publications, resulting in 956 retrospectively registered studies from a total dataset of 1927 (971
7 408 + 956) studies.
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14 411 Figure 2: Percentage of retrospectively registered (RR) trials over time (per study start year). GAM
15 412 (generalized additive model) smoother laid over (blue) with 95% confidence interval. Bubble sizes
16 413 indicate the number of trials per year included in the dataset.
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22 416 Figure 3: Percentage of retrospectively registered trials reporting retrospective registration
23 417 transparently in the publication over time (per study publication year). GAM (generalized additive
24 418 model) smoother laid over (blue) with 95% confidence interval. Bubble sizes indicate the number of
25 419 trials per year included in the dataset. Starting in 2013, some authors begin to report retrospective
26 420 registration. 15% of publications of retrospectively registered trials from 2020 transparently report
27 421 retrospective registration. Four trials were published before 2009 – in all those cases the study
28 422 completion dates provided in the registry were after 2009. Study start dates were before 2005 and
29 423 studies were registered in 2005 (3/4) or later (1/4).
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BMJ Open
Registered (DRKS, CT.gov)
clinical studies with results
publications in Germany
completed 2009-2017
n = 1932

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Prospectively registered
n = 894

Retrospectively registered
n = 1038

Reclassified publications:
registration in EudraCT reported
in the publication (n=77)

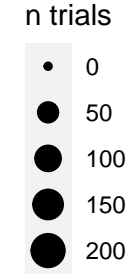
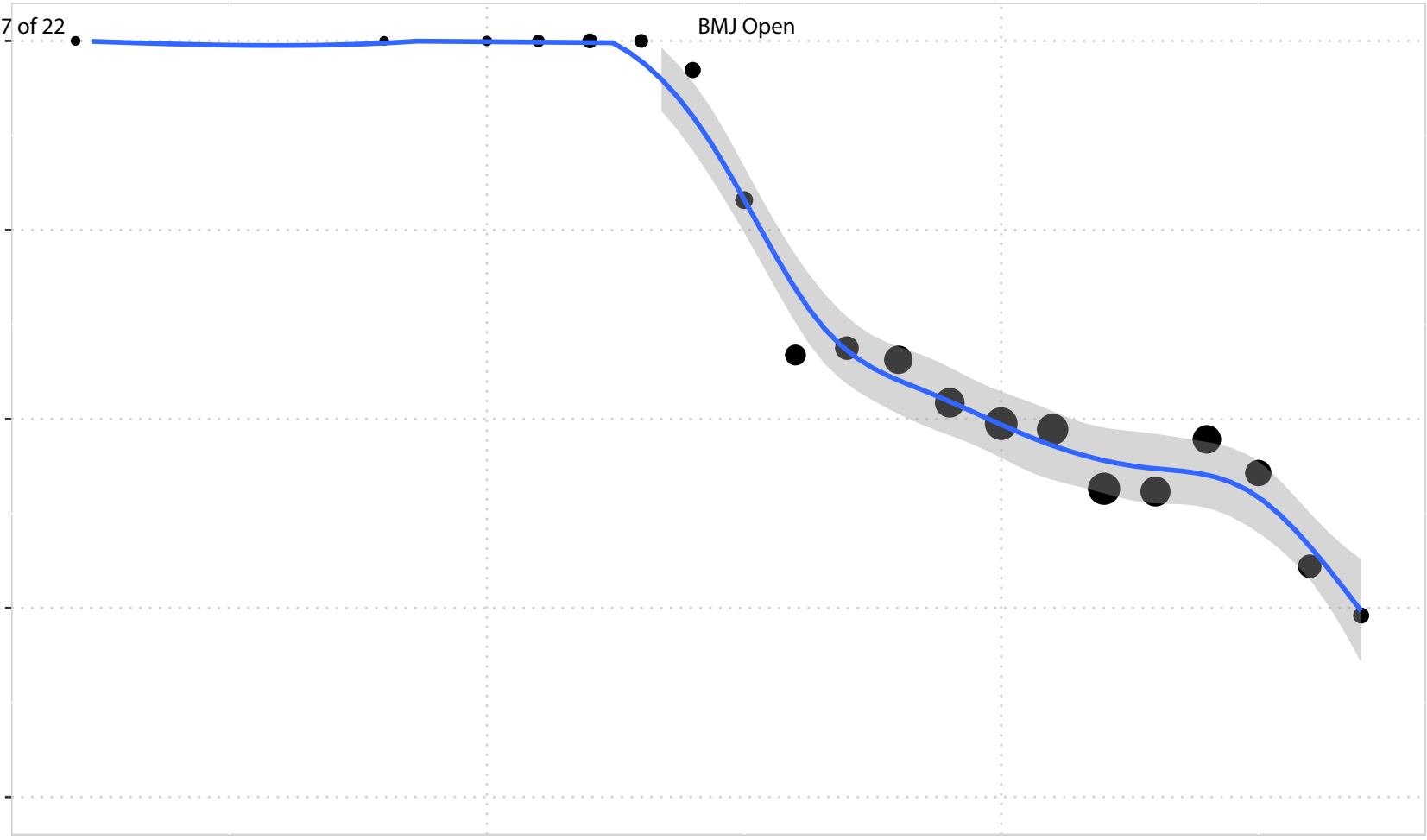
Excluded publications:
- incorrect publication in dataset
(n=5)

Prospectively registered
n = 971

Retrospectively registered
n = 956

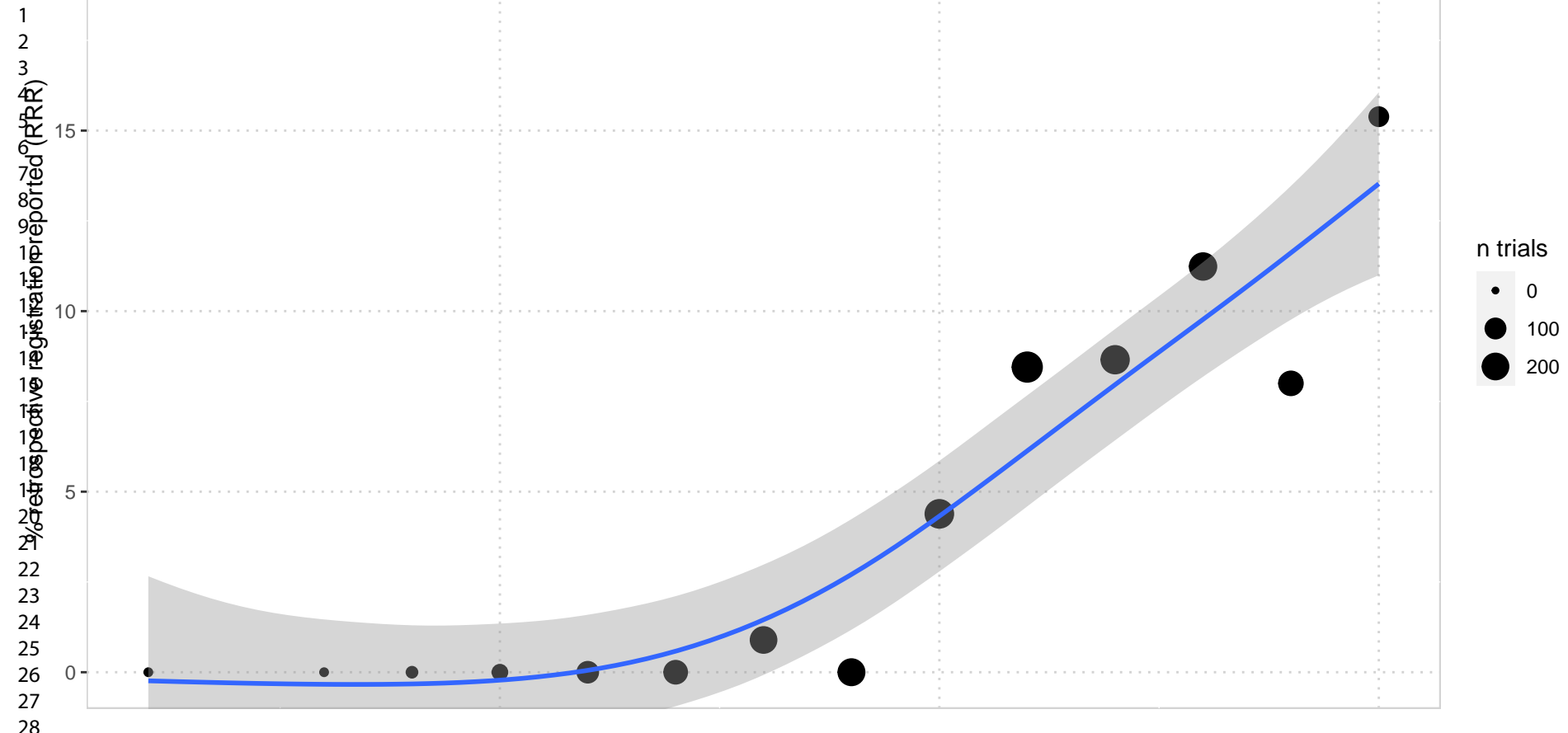
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1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017
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100						100		100	100	100	100	96.2	78.9	58.5	59.4	57.8	52.2	49.4	48.6	40.8	40.4	47.3	42.9	30.5	24



Year (Pub.)	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020
n	2	0	2	12	40	111	144	199	205	240	278	234	215	160	85
RRR	0	0	0	0	0	0	0	1	0	5	12	9	10	4	6
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Supplementary Table 1: STROBE checklist

	Item No.	Recommendation	Page No.	Relevant text from manuscript
Title and abstract	1	(a) Indicate the study’s design with a commonly used term in the title or the abstract	2	Cross-sectional study
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2	See abstract
Introduction				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3	When trials are registered retrospectively, i.e., their registry entry is created after study start, this undermines the many of the reasons for registration. While prospective registration has increased over the past decade, retrospective registration is still widespread (10–14). Some registries, such as DRKS, explicitly mark retrospectively registered entries as such, whereas others, such as ClinicalTrials.gov, do not. While some publishers allow retrospectively registered trials to be published, others do not. Journals following ICMJE guidance should in principle mandate prospective registration, but this principle is not always enforced (12,15,16).
Objectives	3	State specific objectives, including any prespecified hypotheses	3	Our study aims to investigate the conduct of retrospective registration and its transparent reporting
Methods				
Study design	4	Present key elements of study design early in the paper	3	We based our sample on two related projects that were conducted at our research group (17,18). The projects have drawn a full sample (n = 3113) of registry entries for interventional studies reported as complete between 2009 and 2017, led by a German University Medical Center and registered in one of two registries: The ClinicalTrials.gov platform (CT.gov) and the Deutsches Register Klinischer Studien (DRKS)
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	3-4	See above

Participants	6	<i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants	3-4	We included any trial that [1] was registered as an interventional study in either the ClinicalTrials.gov or the DRKS database, [2] was completed between 2009 and 2017, [3] reports a German University Medical Center (UMC) listed as the responsible party or lead sponsor, or with a principal investigator from a German UMC, [4] has published results in a peer-reviewed journal.
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	3	we investigate whether and how authors report retrospective registration in the results publication. We also explore trends over time and how retrospective registration is associated with other practices such as reporting the trial registration number.
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	3-4	Data sources and sample. We based our sample on two related projects that were conducted at our research group (17,18). The projects have drawn a full sample (n = 3113) of registry entries for interventional studies reported as complete between 2009 and 2017, led by a German University Medical Center and registered in one of two registries: The ClinicalTrials.gov platform (CT.gov) and the Deutsches Register Klinischer Studien (DRKS), which is the WHO primary trial registry for Germany. Our dataset also includes the earliest results publications found for 68.4% (2129/3113) of the trials, which were manually identified in different stages until September 1st, 2020. We retrieved the combined data from the two projects from a GitHub repository (https://github.com/maia-sh/into-value-data , accessed 22.02.2022).
Bias	9	Describe any efforts to address potential sources of bias	4	<i>Reliability assessment of ratings.</i> To assess the reliability of the data extraction, another rater (SG) performed three validation steps: first, a sample of 100 publications was screened using the same extraction form, during the main screening to refine category definitions. Second, another sample of 100 publications for which no registration number reporting was noted by MH to check for false negative ratings. Third, all cases with either date, or reporting of retrospective registration or justification were screened, to check for false positives.

Study size	10	Explain how the study size was arrived at	3	We based our sample on two related projects that were conducted at our research group
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	-	Not applicable
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	4	See Methods
		(b) Describe any methods used to examine subgroups and interactions	4	See Methods
		(c) Explain how missing data were addressed	-	Not applicable
		(d) <i>Cross-sectional study</i> —If applicable, describe analytical methods taking account of sampling strategy	-	Not applicable
		(e) Describe any sensitivity analyses	-	Not applicable
Results				
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	5	First paragraph of Results
		(b) Give reasons for non-participation at each stage	5	First paragraph of Results
		(c) Consider use of a flow diagram	5	Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	5	Supplementary table 1
		(b) Indicate number of participants with missing data for each variable of interest	-	Complete case analysis
		(c) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)	3	The projects have drawn a full sample (n = 3113) of registry entries for interventional studies reported as complete between 2009 and 2017, led by a German University Medical Center and registered in one of two registries: The ClinicalTrials.gov platform (CT.gov) and the Deutsches Register Klinischer Studien (DRKS), which is the WHO primary trial registry for Germany. Our dataset also includes the earliest results publications found for 68.4% (2129/3113) of the trials, which were manually identified in different stages until September 1st, 2020
Outcome data	15*	<i>Cross-sectional study</i> —Report numbers of outcome events or summary measures	5-7	See results, e.g. Table 2, Figures 2,3
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and	-	Not applicable

		their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included		
		(b) Report category boundaries when continuous variables were categorized	-	Not applicable
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	-	Not applicable
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	6-9	See results
Discussion				
Key results	18	Summarise key results with reference to study objectives	9-10	See 1 st paragraph of discussion
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	10	See Limitations section
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	9-10	See first paragraph of discussion
Generalisability	21	Discuss the generalisability (external validity) of the study results	10	For feasibility and data quality reasons, our study was based on an existing validated dataset, containing only trials led by German UMCs, which might limit its generalizability to other regions. [...]
Other information				
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	1	This work was partly funded under a grant from the Federal Ministry of Education and Research of Germany (Bundesministerium fuer Bildung und Forschung - BMBF) [01PW18012]. The funder was not involved in the study design, data collection, analysis, or interpretation, writing of the manuscript, or the decision to submit for publication.

Supplementary Table 2: Basic characteristics of included trials

	Retrospectively registered trials (n = 956)	Prospectively registered trials (n = 971)
Registry		
ClinicalTrials.gov	713	766
DRKS	243	205
Sponsorship		
Industry	112	163
Other	844	808
Phase		
Phase 1	33	71
Phase 2	122	206
Phase 3	91	134
Phase 4	78	99
No phase	632	461
Intervention type		
Behavioral	94	72
Biological	18	32
Device	199	138
Dietary Supplement	40	30
Drug	186	340
Genetic	1	1
Procedure	96	70
Radiation	6	9
Other	73	74
Not given	243	205