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### **Clinical Trial Registration Patterns and Changes in Primary Outcomes of Randomized Clinical Trials from 2002 to 2017**

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# Letters

## RESEARCH LETTER

### HEALTH CARE POLICY AND LAW

#### Clinical Trial Registration Patterns and Changes in Primary Outcomes of Randomized Clinical Trials From 2002 to 2017

Trial registration ensures accountability of randomized clinical trials (RCTs). In the US, registration of certain trials was mandated in 2001. Subsequently, the International Committee of Medical Journal Editors announced that its member journals would consider trials beginning on or after July 1, 2005, only if they were prospectively registered. Correct registration of study methods and outcomes before trial data are collected or analyzed enables detection of hypotheses that were formulated after the results are known,<sup>1</sup> selective reporting of results, and other questionable research practices.<sup>2</sup> In this cross-sectional study, which is part of a larger project<sup>3</sup> and for which data-acquisition scripts are available,<sup>4</sup> we assessed changes in trial registration practices over time for published RCTs.

**Methods** | This study did not undergo ethical review because it analyzed published literature and did not involve human participants. We followed the [STROBE](#) reporting guideline.

Using PubMed, we identified RCTs published between January 1, 2002, and November 8, 2017. We downloaded the full text, metadata, and abstracts of all RCTs available through an institutional access subscription. We screened these materials for National Clinical Trial identification numbers for ClinicalTrials.gov and registration numbers from 15 World Health Organization International Clinical Trials Registry Platform registries. For studies registered in ClinicalTrials.gov, we extracted study dates, registration date of the primary outcomes, and any subsequent changes in the registration.

We analyzed the temporal patterns of the proportion of RCTs with a registration number, registration before the study started (including the first 21 days), and substantial changes to the primary outcome in the registry during or after recruitment. Data were analyzed from August 1, 2021, to March 20, 2022.

**Results** | From the 326 398 published RCTs identified, we extracted 146 462 full-text publications. Of these, 46 868 (32.0%) reported a trial registration number (**Table**). The percentage of trials with a registration number increased from 0.2% (11 of 4662) in 2002 to 61.1% (4973 of 8138) in 2017 (**Figure, A**). There were fewer trials in 2017 than 2016 because only partial data

Table. Published RCTs With Registration in ClinicalTrials.gov, International Clinical Trials Registry Platform, or Both

Year of publication	Published RCTs, No.	Registration, No. (%)		
		ClinicalTrials.gov	ICTRP <sup>a</sup>	Any registry <sup>b</sup>
2002	4662	0	11 (0.2)	11 (0.2)
2003	5286	0	21 (0.4)	21 (0.4)
2004	6608	1 (0)	61 (0.9)	62 (0.9)
2005	7398	36 (0.5)	90 (1.2)	125 (1.7)
2006	7548	213 (2.8)	151 (2.0)	361 (4.8)
2007	8333	634 (7.6)	296 (3.6)	914 (11.0)
2008	8436	1109 (13.2)	454 (5.4)	1543 (18.3)
2009	9020	1637 (18.2)	632 (7.0)	2232 (24.7)
2010	9363	2183 (23.3)	809 (8.6)	2923 (31.2)
2011	10 244	2738 (26.7)	1003 (9.8)	3646 (35.6)
2012	11 439	3387 (29.6)	1300 (11.4)	4559 (39.9)
2013	12 002	3907 (32.6)	1586 (13.2)	5333 (44.4)
2014	12 954	4704 (36.3)	1870 (14.4)	6352 (49.0)
2015	12 817	5116 (39.9)	2125 (16.6)	6948 (54.2)
2016	12 214	5018 (41.1)	2160 (17.7)	6865 (56.2)
2017 <sup>c</sup>	8138	3726 (45.8)	1478 (18.2)	4973 (61.1)
Total	146 462	34 409 (23.5)	14 047 (9.6)	46 868 (32.0)

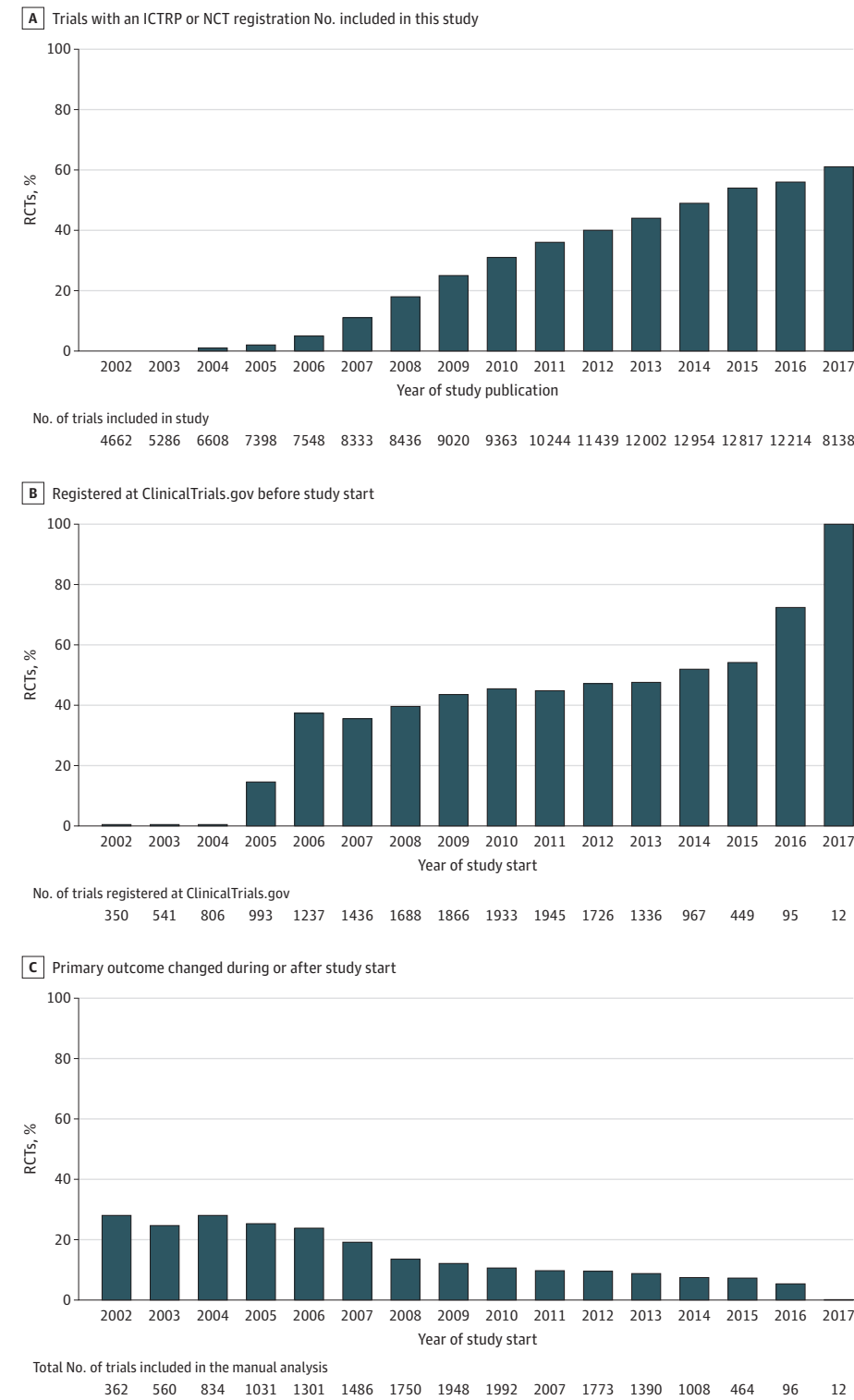
Abbreviations: ICTRP, International Clinical Trials Registry Platform; RCT, randomized clinical trial.

<sup>a</sup> The World Health Organization ICTRP registries include Australian New Zealand Clinical Trials Registry (ANZCTR), Brazilian Clinical Trials Registry (ReBec), Chinese Clinical Trial Registry (ChiCTR), Clinical Research Information Service (CRIS) of Republic of Korea, Clinical Trials Registry-India (CTRI), Cuban Public Registry of Clinical Trials (RPCEC), EU Clinical Trials Register (EU-CTR), German Clinical Trials Register (DRKS), International Standard Randomized Controlled Trial Number (ISRCTN), Iranian Registry of Clinical Trials (IRCT), Japan Registry of Clinical Trials (jRCT), Pan African Clinical Trial Registry (PACTR), Sri Lanka Clinical Trials Registry (SLCTR), Thai Clinical Trials Registry (TCTR), and The Netherlands National Trial Register (NTR).

<sup>b</sup> Any registry is not the sum of the ClinicalTrials.gov and ICTRP registration numbers because some trials were registered in multiple registries.

<sup>c</sup> Fewer trials were included because trials were identified in fall 2017 and subsequently downloaded through early 2018.

**Figure. Patterns of Randomized Clinical Trial (RCT) Registration Practices Over Time**



were included for 2017. Even in 2016 and 2017, however, approximately 40% of published RCTs did not include a trial registration number in the abstract, full text, or PubMed.

We identified registration numbers in ClinicalTrials.gov for 34 409 RCTs, of which 17 380 (50.5%) had available study

dates and 18 158 (52.8%) were available for textual analysis of the primary outcome. Of these 17 380 RCTs, 6817 (39.2%) were registered within 21 days of first-patient enrollment; 7378 (42.5%), during recruitment; and 3185 (18.3%), after trial completion. The proportion of RCTs registered before

study start increased from 0% (0 of 1697) in 2002 to 2004 to 72.6% (69 of 95) in 2016 (Figure, B).

Of the 18 158 trials with available data, 5679 (31.3%) had entered textual changes to the primary outcome during the trial or after trial completion. Independent assessors classified 2622 textual changes (46.2%) as substantive. Primary outcomes had been added for 1193 trials and removed for 474. For 1334 trials, substantive changes to the measurement or timing of the primary outcome had been made to the registry information. The percentage of changed primary outcomes decreased from 25.4% (92 of 362) in 2002 to 5.2% (5 of 96) in 2016 (Figure, C).

**Discussion** | Late registration and lack of registration of RCTs and changes to primary outcomes during a trial or after trial completion are concerning.<sup>5,6</sup> Between 2002 and 2017, the proportions of trials registered and registered before study start substantially increased and the percentage of registered trials with changes to the primary outcome during or after the trial substantially decreased.

One study limitation is that we may have underreported the number of registered RCTs. When a trial registration number was not mentioned in the publication, we reported the trial as unregistered. Another limitation is that we reviewed only changes to primary outcomes that were made in the registry and did not review them in the published articles. Although trial registration practices advanced over time, further improvements are possible and necessary.

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**Author Contributions:** Dr Lamberink had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

*Concept and design:* Lamberink, Vinkers, Bouter, Otte, Tjink.

*Acquisition, analysis, or interpretation of data:* Lamberink, Lancee, Damen, Otte, Tjink.

*Drafting of the manuscript:* Lamberink, Otte, Tjink.

*Critical revision of the manuscript for important intellectual content:* All authors.

*Statistical analysis:* Lamberink, Lancee, Tjink.

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