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Reporting of Non-inferiority Trials in ClinicalTrials.gov and Corresponding Publications

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Non-inferiority clinical trials are designed to determine whether an intervention is not ‘unacceptably worse’ than a comparator by more than a prespecified difference, known as the non-inferiority margin. Selection of an appropriate margin is fundamental to non-inferiority trial validity, yet a point of frequent ambiguity.^{1,2} Given the increasing use of non-inferiority trial designs, maintaining high standards for conduct and reporting is a priority.^{3,4} Publicly-accessible trial registries and results databases promote transparency and accountability by requiring specification of research designs and endpoints and disclosure of summary results.^{1,5} To better understand reporting of non-inferiority trials, we examined registration records and results posted on ClinicalTrials.gov, as well as their corresponding publications, for information about the non-inferiority margin and statistical analyses, and determined their association with trial and journal characteristics.

Methods

Because ClinicalTrials.gov does not currently require registration of non-inferiority-specific information, we searched Ovid MEDLINE for non-inferiority trials published between January 2012 and June 2014 using keywords pertaining to “non-inferior” and “equivalence,” limited to English-language publications. We then selected publications reporting primary analyses of non-inferiority trials indexed with a ClinicalTrials.gov identifier, excluding publications without trial registration (n=163) or registered in other registries (n=97). For each trial, we abstracted details on trial design, including specification and justification of the non-inferiority margin, and results, including reporting of non-inferiority statistical analyses, from both ClinicalTrials.gov (July/August 2014) and corresponding publications. We used Chi-Square tests to compare reporting by study sponsor, condition, location, intervention, trial design characteristics, and journal impact factor (Table), with a two-sided type 1 error level of 0.006 to account for multiple comparisons. Analyses were performed using JMP (version 10.0.0, SAS Institute).

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Results

We identified and characterized 344 unique trials registered on ClinicalTrials.gov, published in 338 articles (6 described multiple trials) that reported primary results of non-inferiority trials (Table). Consistent with our search strategy, all publications described non-inferiority designs and nearly all (n=340 trials; 98.8%) provided non-inferiority margins. However, rationales for choosing margins were provided for only 95 (27.6%); the most commonly cited reasons were previous research (including historical data and meta-analyses) (n=46) and reliance on expert opinion/clinical judgment (n=43). In contrast, on ClinicalTrials.gov, approximately one-quarter (n=99; 28.8%) described non-inferiority designs, among which 15 (4.4% of total) specified non-inferiority margins, 9 of which (2.6% of total) were prespecified at initial registration. The ClinicalTrials.gov and published margin values were concordant for all 15.

Nearly all publications reported non-inferiority analyses and results (n=342, 99.4%). On ClinicalTrials.gov, 129 (37.5%) had posted summary results, among which 76 (22.1% of total) reported that non-inferiority analyses were performed and provided appropriate confidence intervals (CI) or p-values to interpret results. On ClinicalTrials.gov, industry-sponsored trials were less likely to register non-inferiority designs when compared with non-industry-sponsored trials (22.9%, 95% CI, 17.7%–29.0%, vs. 38.1%, 95% CI, 30.3%–46.5%; $p=0.002$), but were more likely to provide results with appropriate details of non-inferiority analyses (33.3%, 95% CI, 27.3%–40.0%, vs. 4.5%, 95% CI, 2.1%–9.4%; $p<0.001$). Location, intervention, masking, and enrollment were also associated with providing results with appropriate details (Table).

Discussion

Our cross-sectional analysis of non-inferiority trials published between 2012 and 2014 demonstrated near-universal reporting of non-inferiority designs and margins within our sample of publications, although not rationales. However, voluntary reporting of non-inferiority designs and margins in corresponding ClinicalTrials.gov records was suboptimal, consistent with prior research.⁶ Moreover, among trials with results reported on ClinicalTrials.gov, more than one-third provided insufficient information to interpret non-inferiority analyses.

Our study was limited to a sample of recently published non-inferiority trials registered on ClinicalTrials.gov. While ClinicalTrials.gov does not currently provide specific registration data elements for specifying non-inferiority trial designs, it provides specific elements for reporting non-inferiority results. Nevertheless, modifications may improve reporting and temper the possibility of *post hoc* distortion of design and margins, facilitating transparency and accountability for non-inferiority trial conduct. Our findings raise concerns about the adequacy of non-inferiority trial registration and results reporting within publicly-accessible trial registries and highlight the need for continued efforts to improve its quality.

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Conflicts of interest: Dr. Tse is an employee of the U.S. National Institutes of Health and a program analyst for ClinicalTrials.gov. Dr. Ross receives support from Medtronic, Inc. and Johnson & Johnson to develop methods of clinical trial data sharing, from the Centers of Medicare and Medicaid Services (CMS) to develop and maintain performance measures that are used for public reporting, and from the Food and Drug Administration (FDA) to develop methods for post-market surveillance of medical devices.

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References

1. Gotzsche PC. Lessons from and cautions about noninferiority and equivalence randomized trials. *JAMA*. Mar 8; 2006 295(10):1172–1174. [PubMed: 16522840]
2. Schumi J, Wittes JT. Through the looking glass: understanding non-inferiority. *Trials*. May 3.2011 12:106.doi: 10.1186/1745-6215-1112-1106 [PubMed: 21539749]
3. Piaggio G, Elbourne DR, Pocock SJ, Evans SJ, Altman DG. Reporting of noninferiority and equivalence randomized trials: extension of the CONSORT 2010 statement. *JAMA*. Dec 26; 2012 308(24):2594–2604. doi:2510.1001/jama.2012.87802. [PubMed: 23268518]
4. Le Henanff A, Giraudeau B, Baron G, Ravaud P. Quality of reporting of noninferiority and equivalence randomized trials. *JAMA*. Mar 8; 2006 295(10):1147–1151. [PubMed: 16522835]
5. Zarin DA, Tse T, Williams RJ, Califf RM, Ide NC. The ClinicalTrials.gov results database—update and key issues. *N Engl J Med*. Mar 3; 2011 364(9):852–860. doi:810.1056/NEJMsa1012065. [PubMed: 21366476]
6. Dekkers OM, Soonawala D, Vandenbroucke JP, Egger M. Reporting of noninferiority trials was incomplete in trial registries. *J Clin Epidemiol*. Sep; 2011 64(9):1034–1038. doi:1010.1016/j.jclinepi.2010.1012.1008. [PubMed: 21444195]

Table

Reporting of trial design and results for non-inferiority trials registered on ClinicalTrials.gov and published between January 2012 and June 2014, stratified by trial and journal characteristics (n=344).

	Overall (column %, 95% CI)	NI design reported on CTgov (row %, 95% CI)	P Value	Trial results with NI analysis posted on CTgov (row %, 95% CI) ^e	P Value
Overall	344 (100)	99 (28.8, 24.2–33.8)		76 (22.1, 18.0–26.8)	
Trial sponsor ^a			0.002		<0.001
Industry	210 (61.0, 55.8–66.1)	48 (22.9, 17.7–29.0)		70 (33.3, 27.3–40.0)	
Non-industry	134 (39.0, 33.9–44.2)	51 (38.1, 30.3–46.5)		6 (4.5, 2.1–9.4)	
Condition ^a			0.09		0.05
Heart and blood diseases	63 (18.3, 14.6–22.7)	24 (38.1, 27.1–50.4)		10 (15.9, 8.9–26.8)	
Nutritional and metabolic disorders	43 (12.5, 9.4–16.4)	7 (16.3, 8.1–30.0)		17 (39.5, 26.4–54.4)	
Cancers and other neoplasms	42 (12.2, 9.2–16.1)	11 (26.2, 15.3–41.1)		6 (14.3, 6.7–27.8)	
Bacterial, fungal, and parasitic diseases	39 (11.3, 8.4–15.1)	16 (41.0, 27.1–56.6)		7 (17.9, 9.0–32.7)	
Viral diseases	38 (11.0, 8.2–14.8)	10 (26.3, 15.0–42.0)		9 (23.7, 13.0–39.2)	
Other	119 (34.6, 29.8–39.8)	31 (26.1, 19.0–34.6)		27 (22.7, 16.1–31.0)	
Location ^{a,d}			0.64		<0.001
International only	166 (50.2, 44.8–55.5)	51 (30.7, 24.2–38.1)		19 (11.4, 7.5–17.2)	
US/Canada only	107 (32.3, 27.5–37.5)	31 (29.0, 21.2–38.2)		31 (29.0, 21.2–38.2)	
US/Canada and international	58 (17.5, 13.8–22.0)	14 (24.1, 15.0, 36.5)		24 (41.4, 29.6–54.2)	
Intervention ^b			0.35		<0.001
Pharmacologic	179 (52.0, 46.8–57.3)	50 (27.9, 21.9–34.9)		53 (29.6, 23.4–36.7)	
Vaccine or biologic	79 (23.0, 18.8–27.7)	19 (24.1, 16.0–34.5)		17 (21.5, 13.9–31.8)	
Medical device	32 (9.3, 6.7–12.8)	13 (40.6, 25.5–57.7)		2 (6.3, 1.7–20.1)	
Other	54 (15.7, 12.2–19.9)	17 (31.5, 20.7–44.7)		4 (7.4, 2.9–17.6)	
Randomized ^b			0.54		0.04
Yes	330 (95.9, 93.3–97.6)	96 (29.1, 24.5–34.2)		76 (23.0, 18.8–27.9)	
No	14 (4.1, 2.4–6.7)	3 (21.4, 7.6–47.6)		0 (0, 0–0)	
Masking ^b			0.03		<0.001

	Overall (column %, 95% CI)	NI design reported on CTgov (row %, 95% CI)	P Value	Trial results with NI analysis posted on CTgov (row %, 95% CI) ^e	P Value
Open-label	168 (48.8, 43.6–54.1)	49 (29.2, 22.8–36.4)		31 (18.5, 13.3–25.0)	
Double-blind	121 (35.2, 30.3–40.4)	26 (21.5, 15.1–29.6)		42 (34.7, 26.8–43.5)	
Single blind	44 (12.8, 9.7–16.7)	19 (43.2, 29.7–57.8)		3 (6.8, 2.3–18.2)	
Not reported	11 (3.2, 1.8–5.6)	5 (45.5, 21.3–72.0)		0 (0, 0–0)	
Enrollment ^b			0.25		0.004
500 patients	150 (43.6, 38.5–48.9)	48 (32.0, 25.1–39.8)		44 (29.3, 22.6–37.1)	
< 500 patients	194 (56.4, 51.1–61.5)	51 (26.3, 20.6–32.9)		32 (16.5, 11.9–22.4)	
Journal impact factor ^c			0.34		0.24
10	112 (32.6, 27.8–37.7)	36 (32.1, 24.2–41.3)		29 (25.9, 18.7–34.7)	
< 10	232 (67.4, 62.3–72.2)	63 (27.2, 21.8–33.3)		47 (20.3, 15.6–25.9)	

Notes: NI=Non-inferiority; CTgov=ClinicalTrials.gov; CI=Confidence Interval.

^aData abstracted from ClinicalTrials.gov.

^bData abstracted from journal publication.

^cData abstracted from Journal Citation Reports (Thomson Reuters).

^dTotal n=331 as study location information was missing for 13.

^eA total of 129 trial records posted summary results, of which 76 reported that non-inferiority analyses were performed and provided appropriate confidence intervals or p-values to interpret results.