Evaluation of compliance with legal requirements under the FDA Amendments Act 2007 for timely registration of clinical trials, data verification, delayed reporting, and trial document submission

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The US Food and Drug Administration (FDA) Amendments Act of 2007 (FDAAA 2007), as further clarified by regulations effective in 2017 (the Final Rule), requires sponsors of clinical trials covered by the legal requirements to register and report clinical trials to ClinicalTrials.gov.[1] In a prior report,[2] we assessed compliance with the legal requirement to report clinical trial results; 1,722 (40.9%) of 4,209 trials due to report results did so within the 1-year deadline. In this report, we evaluate compliance with additional FDAAA requirements.

Methods

On January 18, 2021, 4 years after the implementation of the Final Rule, we downloaded the ClincialTrials.gov database. Using our prior methods[2] and public data, we identified all trials covered by the Final Rule, that is all trials meeting coverage parameters with primary completion dates after January 17, 2017. ClinicalTrials.gov designates covered trials as "probable applicable clinical trials" or "applicable clinical trials" depending on whether they first enrolled participants before or after implementation of the Final Rule, respectively.

We assessed the proportion of trials in compliance with US regulations for results reporting and in 4 additional areas: trial registration within 21 days of first enrollment of a subject (timely registration); verification of the accuracy of registration data within the last year (annual data verification); requesting delays for results reporting prior to 1 year from the primary completion date (requests for certificates for delayed reporting); and the submission of protocols and statistical analysis plans with results (document submission). Additional methods are in the eTable (Online Supplement). We descriptively assessed factors associated with compliance in each area using univariable and multivariable logistic regression. We set a conservative Bonferonni corrected significance threshold of $p<.001$ and report 99.5% CIs. As the research used publicly available data, the University of Oxford exempted it from ethics review.

Results

We identified 27,645 covered trials. Of the 8,863 trials due to report results, 3,499 (39.5%) did so within the 1-year deadline, and 6,099 (68.8%) reported at any time. After excluding the trials not relevant to a given requirement (eFigure in the Online Supplement), we derived appropriate cohorts for each analysis. The proportion of trials in compliance ranged from 66.0% for on-time requests for delayed reporting to 99.1% for document submission with results (Table 1). Trials registered late were a median of 111 (IQR: 28-354) days late, trials with delayed annual data verification were a median of 275 (IQR: 122-550) days late, and trial with dilatory requests for delayed reporting were a median of 72 (IQR: 22-174) days late. Of the 5,449 due trials with full results posted to the registry (i.e., completed quality control checks), 5,401 (99.1%) accounted for all required documents; only 107 (3.1%) of the 3,414 due trials that had not submitted results had any documents available.

Table 2 shows the unadjusted and adjusted odds ratios for compliance. In the adjusted models, industry sponsors and sponsors with more registered trials were more likely to register trials on time, verify data annually, and request reporting delays within the required timeframes consistent with our prior report.[2] Applicable clinical trials were also more likely to meet registration and verification requirements than probable applicable clinical trials.

Discussion

In a cohort of 27,645 covered clinical trials, 4 years after the effective date of the Final Rule, we found that compliance with legal requirements for timely registration of clinical trials, data verification, delayed reporting, and trial document submission ranged from 66.0 to 99.1%. Our study is not comprehensive of all FDAAA requirements and the publicly available data vary in quality. Some covered trials may not have been identified because of the exclusion of certain

fields from the public data, though this effect is likely small and limited to probable applicable clinical trials. Our findings suggest that the FDA should proactively implement additional measures to improve compliance with the FDAAA[3] such as audits that are made public, notices of non-compliance and the potential imposition of civil monetary penalties. In January, 2021, ClinicalTrials.gov reminded users about the deadline for requesting delays to results reporting.[4] Open dialogue and sharing of best practices for improvement among sponsors may also aid compliance.[5,6]

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Additional Information:

Author Contributions

NJD 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: All Authors

Acquisition, analysis, or interpretation of data: All Authors

Drafting of the manuscript: DeVito

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

Statistical analysis: DeVito

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COI Disclosure

The TrialsTracker project was established under a grant from the Laura and John Arnold Foundation and received additional funding from the Good Thinking Society. BG obtained these grants and NJD was employed on these grants. This work will form part of NJD's doctoral thesis; he recieves a doctoral studentship from the Naji Foundation. Outside the submitted work: NJD has received a grant from the Fetzer Franklin Fund; BG has received research funding from the Wellcome Trust, the NHS National Institute for Health Research, the NHS National Institute for Health Research School of Primary Care Research, the Oxford Biomedical

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Role of the Funder/Sponsor

No funder was involved in the design and conduct of the study; collection, management, analysis, and interpretation of the data; or preparation, review, or approval of the manuscript.

Access to Data and Data Analysis

NJD had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Additional Information

Full data and code for this analysis is available at:
https://github.com/ebmdatalab/fdaaa_requirements

Table 1: FDAAA Compliance and Characteristics in Assessment Areas

		Compliant Results Reporting		Timely Registration[a]		Annual Data Verification		Certificate of Delay Requests		Document Submission[b]	
Cohort Size		8,863		27,645		16,709		1,354		5,449	
Trials in Compliance (%)		3,499 (39.5%)		24,429 (88.4%)		12,632 (75.6%)		893 (66.0%)		5401 (99.1%)	
Detailed Compliance Data											
		Total (%)	n compliant (%)	Total (%)	n compliant (%)	Total (%)	n compliant (%)	Total (%)	n compliant (%)	Total (%)	n compliant (%)
Covered Status	**Is a Probable Applicable Clinical Trial**	5,484 (61.9%)	2,249 (41.0%)	9,282 (33.6%)	7,818 (84.2%)	5,180 (31.0%)	3,586 (69.2%)	770 (56.9%)	505 (65.6%)	3,812 (70.0%)	3.764 (98.7%)
	Is an Applicable Clinical Trial[c]	3,379 (38.1%)	1,250 (37.0%)	18,363 (66.4%)	16,611 (90.5%)	11,529 (69.0%)	9,046 (78.5%)	584 (43.1%)	388 (66.4%)	1,637 (30.0%)	1647 (100%)
Industry Sponsor		3,951 (44.6%)	1784 (45.2%)	11,444 (41.4%)	10,516 (91.9%)	6,603 (39.5%)	5,001 (75.7%)	1,204 (88.9%)	814 (67.6%)	2,522 (46.3%)	2509 (99.5%)
Trial Contains a Drug		6,069 (68.5%)	2,632 (43.2%)	19,074 (69.0%)	17,358 (91.0%)	11,492 (68.8%)	9,004 (78.4%)	1,061 (78.4%)	713 (67.2%)	4,008 (73.6%)	3969 (99.0%)
Phase[d]	**Early Phase**	3,487 (39.3%)	1,456 (41.8%)	12,415 (44.9%)	11,533 (92.9%)	7,802 (46.7%)	6,297 (80.7%)	649 (47.9%)	418 (64.4%)	2,276 (41.8%)	2,254 (99.0%)
	Late Phase	1,770 (20.0%)	869 (49.1%)	5,513 (19.9%)	5,102 (92.5%)	3,247 (19.4%)	2,611 (80.4%)	510 (37.7%)	357 (70.0%)	1,266 (23.2%)	1,257 (9.3%)
	N/A	3,606 (40.7%)	1174 (32.6%)	9,717 (35.1%)	7,794 (80.2%)	5,660 (3.9%)	3,724 (65.8%)	195 (14.4%)	118 (60.5%)	1,907 (35.0%)	1,890 (99.1%)
Number of Trials Registered[e]	**Quartile 1 (1-11)**	2,357 (26.6%)	458 (19.4%)	7,128 (25.8%)	6,135 (86.1%)	4,526 (27.1%)	2,788 (61.6%)	315 (23.3%)	162 (51.4%)	830 (15.2%)	821 (98.9%)
	Quartile 2 (12-220)	2,390 (27.0%)	709 (29.7%)	6,710 (24.3%)	5,759 (85.8%)	4,095 (24.5%)	2,747 (67.1%)	613 (45.3%)	374 (61.0%)	1,278 (23.5%)	1,268 (99.2%)
	Quartile 3 (221-987)	2,102 (23.7%)	993 (47.2%)	6,955 (25.2%)	6,153 (88.5%)	4,128 (24.7%)	3,464 (83.9%)	196 (14.5%)	157 (80.1%)	1,577 (28.9%)	1,563 (99.1%)
	Quartile 4 (988-3341)	2,014 (22.7%)	1,339 (66.5%)	6,852 (24.8%)	6,382 (93.1%)	3,960 (23.7%)	3,633 (91.7%)	230 (17.0%)	200 (87.0%)	1,764 (32.4%)	1749 (99.2%)

a: All trials in the cohort were included in this analysis. b: This includes trials that proactively declared having no statistical analysis plan. c: Applicable Clinical Trials are covered trials that began after 17 Jan 2017, Probably applicable clinical trials began before but ended after 17 Jan 2017. d: Early Phase = Phase 1/2 & 2, Late Phase = Phase 2/3, 3, & 4, N/A typically indicates a device trial e: The range of the number of registered trials on ClinicalTrials.gov in each quartile is provided below each quartile name.

Table 2: Unadjusted and Adjusted[a] Odds Ratios for Factors Associated with Compliance

		Timely Registration		Annual Data Verification		Certificate of Delay Requests		Document Submission	
Odds Ratios (99.5% CI, p-value)		**Crude OR**	**Adj OR**	**Crude OR**	**Adj OR**	**Crude OR**	**Adj OR**	**Crude OR**	**Adj OR**
Is an Applicable Clinical Trial[c]		1.78 (1.57-2.01, p<.001)	2.14 (1.87-2.44, p<.001)	1.62 (1.43-1.83, p<.001)	1.99 (1.74-2.28, p<.001)	1.04 (0.71-1.52, p=.743)	1.17 (0.78-1.76, p=.202)	DNC[b]	N/A
Industry Sponsor		1.86 (1.63-2.13, p<.001)	2.03 (1.74-2.37, p<.001)	1.01 (0.9-1.14, p=.736)	1.52 (1.31-.76, p<.001)	1.88 (1.06-3.33, p<.001)	4.71 (2.19-10.15, p<.001)	2.34 (0.8-6.83, p=.009)	2.54 (0.76-8.54, p=.011)
Trial Contains a Drug		2.15 (1.89-.43, p<.001)	1.35 (1.16-1.57, p<.001)	1.59 (1.4-1.79, p<.001)	0.94 (0.8-1.1, p=.205)	1.29 (0.82-2.02, p=.066)	1.08 (0.6-1.94, p=.666)	0.64 (0.19-2.17, p=.228)	0.62 (0.16-2.44, p=.251)
Phase[c]	**Early Phase**	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
	Late Phase	0.95 (0.77-1.16, p=.402)	0.8 (0.65-0.99, p<.001)	0.98 (0.82-1.17, p=.719)	0.92 (0.77-1.11, p=.158)	1.29 (0.85-1.96, p=.045)	1.14 (0.73-1.79, p=.322)	1.36 (0.37-5.04, p=.435)	0.96 (0.24-3.83, p=.922)
	N/A	0.31 (0.27-0.36, p<.001)	0.38 (0.23-0.44, p<.001)	0.46 (0.40-0.52, p<.001)	0.46 (0.39-0.54, p<.001)	0.85 (0.49-1.47, p=.322)	0.97 (0.47-2, p=.896)	1.09 (0.37-3.16, p=.801)	0.95 (0.29-3.09, p=.876)
Number of Trials Registered[d]	**Quartile 1 (1-11)**	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
	Quartile 2 (12-220)	0.98 (0.83-0.15, p=.682)	1.04 (0.88-1.23, p = .48)	1.27 (1.09-1.47, p<.001)	1.36 (1.17-1.59, p<.001)	1.48 (0.93-2.34, p=.005)	1.42 (0.89-2.28, p=.014)	1.39 (0.3-6.35, p=.476)	1.19 (0.26-5.57, p=.707)
	Quartile 3 (221-987)	1.24 (1.05-1.47, p<.001)	1.76 (1.47 - 2.11, p<.001)	3.25 (2.74-3.86, p<.001)	4.35 (3.6-5.25, p<.001)	3.8 (1.9-7.62, p<.001)	6.07 (2.77-13.32, p<.001)	1.22 (0.3-5.03, p=.638)	1.57 (0.37-6.58, p=.301)
	Quartile 4 (988-3341)	2.20 (1.81-2.67, p<.001)	2.74 (2.23 - 3.36, p<.001)	6.93 (5.59-8.59, p<.001)	8.7 (6.92-10.93, p<.001)	6.3 (2.99-13.24, p<.001)	10.58 (4.53-24.7, p<.001)	1.28 (0.32-5.15, p=.562)	1.58 (0.39-6.44, p=.287)

a: Each adjusted model included all listed covariates b: Applicable Clinical Trial status perfectly predicted compliance with the document reporting rule and therefore the regression did not converge (DNC). This covariate was therefore dropped from the adjusted regression. c: Early Phase = Phase 1/2 & 2, Late Phase = Phase 2/3, 3, & 4, N/A typically indicates a device trial d: The range of the number of registered trials on ClinicalTrials.gov in each quartile is provided below each quartile name.