



27 October 2015

Memorandum

To: Trialists

Fr: Curtis Meinert

Re: Industry versus NIH trials

How do industry trials compare to NIH trials? Addressing that question before registration of trials would have been impossible. Now we have a tool to address the question.

Key landmarks in the registration process are:

- 1997 Congress passes law requiring trial registration
- 2000 NIH releases ClinicalTrials.gov website (first studies registered 17 September 1999)
- 2005 International Committee of Medical Journal Editors (ICMJE) requires trial registration
- 2006 World Health Organization establishes trial registration policy
- 2007 Congress passes law (FDAAA) expanding ClinicalTrials.gov submission requirements
- 2008 ClinicalTrials.gov releases results database

ClinicalTrials.gov is just one of several sites where trials are registered. The World Health Organization International Clinical Trials Registry Platform (ICTRP) lists 14 registration sites (not including ClinicalTrials.gov).

Registration grew out of the FDA Modernization Act of 1997. The Act required the Department of Health and Human Services, through the NIH (via the National Library of Medicine), to broaden public access to information about clinical trials by establishing a registry for both federally and privately funded trials (Section 113: Information program on clinical trials for serious or life-threatening diseases; Public Law 105-115.)

The first phase of the registration effort was devoted to registering trials funded by or done by the NIH. A news release dated 29 February 2000 indicated that that phase of the effort was well under way and that the next phase was to focus on non-NIH sponsored trials from other Federal agencies and private industry.

The predominant site is ClinicalTrials.gov. It accounts for about 70% of all registrations.

Counts were done using the March 2015 AACT dataset (Aggregate Analysis of ClinicalTrials.gov; downloaded from the Clinical Trials Transformation Initiative website; <http://www.ctti-clinicaltrials.org/>). Counts are limited to trials funded by industry or NIH but not by both industry and NIH (to avoid "double counting"; just 999 trials were logged as involving both industry and NIH support).

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Results

There were 144,248 trials registered through 2014. About 41% (59,472) involved industry funding, but not NIH funding. Just over 10% (14,913) involved NIH funding, but not industry funding.

Table 1 provides counts of trials registered by year. The number of industry-funded trials registered has remained constant since 2005 compared to a 22% drop for NIH trials from 2005-09 to 2010-14.

The fraction of trials that are drug trials has declined for both industry and NIH trials. Eighty-five percent of industry trials were logged as drug trials compared to 62% of NIH trials in 2010-14.

There is a difference in the mix of drug trials (Table 2). There is close to a 50:50 mix of phase 0, 1, or 2 trials versus phase 3 or 4 trials for industry trials. The fraction of phase 0, 1, or 2 trials is much higher for NIH-funded trials.

Registrations a month or more after the start of enrollment has declined, but still accounts for 22% of industry funded trials and 14% for NIH trials in 2010-14 (Table 3).

Industry trials are done faster than NIH trials. Over three-fourths (79%) of industry trials are completed in five years or less from start of enrollment compared to 56% of NIH trials (Table 4).

The median times to completion are given in Table 5. The times to completion for industry-funded trials are about half those for NIH-funded trials.

Industry-funded trials are larger than their NIH-funded counterpart (Table 6). The difference is due to the mix of drug trials as shown in Table 2. There is no material difference in sizes by phase of trials (Table 7).

More industry-funded trials are multicenter than are NIH-funded trials (Table 8); 47% vs 31%.

The percentages of drug trials that are multicenter are higher for both phases 0,1,2 and 3,4 for industry-funded trials (Table 9).

The number of trials logged as terminated, suspended, or withdrawn is about the same for industry and NIH-funded trials (Table 10). The percentage is about 10% of all trials registered for both industry and NIH-funded trials.

The two types of trials differ with regard to gender mix. The percentage of male-only trials was higher for industry-funded trials than for NIH-funded trials (Table 11). The differences are likely due to requirements of investigators applying for NIH funding to ensure inclusion of women and minorities (implemented with the NIH Revitalization Act of 1993).

Table 12 provides counts of drug trials completed 2007-13 with posted results. Only one-third have posted results.

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Table 13 provides counts of completed trials with at least one publication. Only 12% of industry-funded trials and 44% of NIH-funded trials completed in 2005-09 listed publications.

Table 1 Trials registered

Year registered	Industry-funded			NIH-funded		
	All trials	Drug trials*		All trials	Drug trials*	
		No.	% of all		No.	% of all
2000-04	1,986	1,964	98.9	3,787	3,361	88.8
2005-09	28,502	26,019	91.3	6,245	4,583	73.4
2010-14	28,984	24,656	85.1	4,881	3,003	61.5
2000-14	59,472	52,639	88.5	14,913	10,947	73.4

* Phase 0, 1, 2, 3, or 4 trials; can include device trials

Table 2 Drug trials by phase and year of enrollment start

Year enrollment started	Industry-funded			NIH-funded		
	Number	% phase 0, 1, or 2	% phase 3 or 4	Number	% phase 0, 1, or 2	% phase 3 or 4
		2000-04	7,581		44.0	56.0
2005-09	21,284	56.6	43.4	3,716	77.4	22.6
2010-14	21,864	62.6	37.4	2,760	80.0	20.0
2000-14	50,729	57.3	42.7	9,978	78.4	21.6

Table 3 Registration > 30 days after enrollment start*

Year registered	Industry-funded			NIH-funded		
	Number registered	Reg > 30 days after start enrollment		Number registered	Reg > 30 days after start enrollment	
		registered	% registered late		registered	% registered late
2005-09	28,075	13,215	47.1	6,161	2,580	41.9
2010-14	28,776	6,362	22.1	4,850	680	14.0
2005-14	56,851	19,577	34.4	11,011	3,260	29.6

* Limited to studies where start date for enrollment is reported

Studies counted as registered after start of enrollment if date of registration is a month or more after the start of enrollment

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Table 4 Trials completed \leq 5 years from start of enrollment

Year enrollment started	Industry-funded			NIH-funded		
	Number started	Completed \leq 5 yrs	%	Number started	Completed \leq 5 yrs	%
2000-04	5,454	4,477	82.1	1,154	666	57.7
2005-09	16,252	12,655	77.9	1,048	575	54.9
2000-09	21,706	17,132	78.9	2,202	1,241	56.4

Completed defined on ClinicalTrials.gov as a study no longer recruiting and ending normally; participants no longer being examined or treated.

Table 5 Median time (yrs) to completion from start of enrollment

Year enrollment started	Industry-funded			NIH-funded		
	Number started	Number completed	Mdn yrs to completion	Number started	Number completed	Mdn yrs to completion
2000-04	6,990	6,212	2.08	3,096	2,598	4.59
2005-09	21,391	16,517	1.58	4,084	2,839	3.83
2010-14	23,853	12,211	0.91	3,221	910	2.08

Table 6 Sample sizes of completed trials by year of enrollment start

Year enrollment started	Industry-funded				NIH-funded			
	Number completed	Mean SS	Mdn SS	IQ range	Number completed	Mean SS	Mdn SS	IQ range
2000-04	6,754	454	116	312	2,730	424	61	139
2005-09	17,923	297	75	208	3,144	246	61	148
2010-14	12,708	198	56	139	950	300	60	171

Table 7 Median sample sizes for drug trials by year of enrollment start

Year enrollment started	Industry-funded				NIH-funded			
	No. completed		Mdn SS		No. completed		Mdn SS	
	Phase 0,1,2	Phase 3,4	Phase 0,1,2	Phase 3,4	Phase 0,1,2	Phase 3,4	Phase 0,1,2	Phase 3,4
2000-04	2,748	3,595	50	254	1,695	533	45	200
2005-09	9,200	7,168	46	220	1,748	497	42	196
2010-14	7,302	3,731	40	200	458	112	36	233

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Table 8 Multicenter (MC) versus single center (SC) or center not specified (NS) trials by year of completion

Year enrollment started	Industry-funded				NIH-funded			
	Number completed	MC	SC or NS	% MC	Number completed	MC	SC or NS	% MC
2000-04	7,066	2,884	4,182	40.8	3,353	1,040	2,313	31.0
2005-09	18,073	9,059	9,014	50.1	3,155	1,006	2,149	31.9
2010-14	12,740	5,750	6,990	45.1	950	273	677	28.7
2000-14	37,879	17,693	20,186	46.7	7,458	2,319	5,139	31.1

Multicenter if number of study sites listed >1

Table 9 Percentage of drug trials that are multicenter (MC) by year completed

Year enrollment started	Industry-funded				NIH-funded			
	Phase 0,1,2		Phase 3,4		Phase 0,1,2		Phase 3,4	
	Number completed	% MC	Number completed	% MC	Number completed	% MC	Number completed	% MC
2000-04	2,886	38.6	3,755	44.6	2,194	30.4	592	42.4
2005-09	9,282	47.6	7,212	58.5	1,756	33.9	498	46.6
2010-14	7,317	39.2	3,740	64.9	458	34.1	112	41.1
2000-14	19,485	43.1	14,707	56.6	4,408	32.2	1,202	44.0

Multicenter if number of study sites listed >1

Table 10 Number of trials terminated (T), suspended (S), or withdrawn (W) by year of registration

Year registered	Industry-funded			NIH-funded		
	Number registered	Number T, S, or W	%	Number registered	Number T, S, or W	%
2000-04	1,986	202	10.2	3,787	365	9.6
2005-09	28,502	3,683	12.9	6,245	643	10.3
2010-14	28,984	2,347	8.1	4,881	374	7.7
2000-14	59,472	6,232	10.5	14,913	1,382	9.3

As defined in the glossary of terms on ClinicalTrials.gov

Terminated: The clinical study has stopped recruiting or enrolling participants early and will not start again. Participants are no longer being examined or treated.

Suspended: The clinical study has stopped recruiting or enrolling participants early, but it may start again.

Withdrawn: The clinical study stopped before enrolling its first participant.

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Table 11 Gender composition of completed trials by year of enrollment start

Year enrollment started	Industry-funded				NIH-funded			
	Number completed	% Both	% F only	% M only	Number completed	% Both	% F only	% M only
2000-04	7,040	85.9	7.8	6.3	3,339	84.0	11.8	4.2
2005-09	18,058	86.7	6.4	6.8	3,154	84.0	11.8	4.3
2010-14	12,735	84.9	4.6	10.5	949	85.7	10.2	4.1
2000-14	37,833	85.9	6.1	8.0	7,452	84.1	11.6	4.2

Dataset limited to studies where gender composition reported

Table 12 Tabular results postings for drug trials by year of completion

Year completed	Industry-funded			NIH-funded		
	Number completed	No. with results postings	%	Number completed	No. with results postings	%
2007-09	9,052	3,045	33.6	1,439	304	21.1
2010-13	13,019	4,194	32.2	1,933	729	37.7
2007-13	22,071	7,239	32.8	3,372	1,033	30.6

Table 13 Publication listings

Year completed	Industry-funded			NIH-funded		
	Number completed	≥ 1 pub listed	%	Number completed	≥ 1 pub listed	%
2005-09	13,649	1,654	12.1	2,942	1,293	43.9
2010-14	18,248	1,383	7.6	3,367	1,205	35.8
2005-14	31,897	3,037	9.5	6,309	2,498	39.6

Discussion

It is safe to assume that virtually all NIH-funded trials are registered on ClinicalTrials.gov, but not so for industry-funded trials. For comparisons to be valid it is necessary to assume that industry trials registered elsewhere are not materially different from those registered on ClinicalTrials.gov.

A difference is the mix of trials. A much higher fraction of industry-funded trials are drug trials than is the case for NIH-funded trials. Also different is the mix of drug trials. The NIH does more phase 0, 1, or 2 trials than industry. The difference in time to completion is largely due to the mix differential since there is no marked difference in time to completions by phase (Table 7).

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You cannot be in a hurry and do trials. Usually, the time before and after completion of a trial is more than the time for doing the trial.

It will take upwards of two years (if not more) to get the trial funded and at least another year after funding before start of enrollment. After the trial is finished it will take several months to finish data cleaning and editing and at least another year or two thereafter to get the results published. The only time under investigator control is the time for doing the trial. The time before and after is largely fixed.

There is no way, with information on ClinicalTrials.gov, to know front and back times. On average, it is likely that the funding process is more efficient for industry-funded than NIH-funded trials, but industry has its own bureaucracies to slow implementation.

Start a trial and the patients disappear.

Recruitment is always a problem. The only "fix", other than extending the time needed to complete the trial, is to increase potentials for recruitment by having multiple study sites. More industry-funded trials are multicenter than NIH-funded trials. One can only speculate as to the reasons for the difference, but it is probably due to the role of industry in initiating trials.

There is nothing in ClinicalTrials.gov to indicate how trials are initiated, but it is likely that the fraction of trials that are investigator-initiated is higher for NIH-funded trials than for industry-funded trials. It takes a lot of resolve and perseverance on the part of investigators to fund multicenter trials via the NIH on their own.

Drug and device trials are subject to the Food and Drug Administration Amendments Act of 2007. The regulation requires results of eligible trials to be posted within one year of completion unless exemptions are granted for later postings. Basically, the requirement applies to any trial completed after 2007. Without details as to specifics of trials, it is difficult to know how many trials are subject to the FDAAA posting requirement, but counts reported indicate less than stellar compliance.

The requirement of registration before the start of enrollment as a condition for publication was announced by the ICMJE in the fall of 2004 and became applicable to trials starting after 1 July 2005. It is obvious that the requirement is not yet in the DNA of trialists with 22% of industry-funded trials and 14% of NIH-funded trials being registered a month or more after the start of enrollment; trials registered 2010-14 (Table 3). The interquartile range for late registrations for trials registered in that time period is 16 to 298 days for industry-funded trials and 23 to 411 days for NIH-funded trials.

It is hard to believe all papers containing results of trials published in ICMJE journals meet the registration requirement. One surmises editors subscribing to the policy have "workarounds" for papers from trials not registered before the start of enrollment.

In an ideal world, every completed trial would be published regardless of the nature or direction of results. Judging from results in Table 13 we are far from that ideal.

One cannot, without reading the papers listed, know how many actually contain results, but even if every trial listing publications for 2005-09 were of results, it would mean that less than 20% of completed trials are published (16,591 completed trials and 2,947 with publications

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listed). But even at that, the likelihood is that the 20% is an overestimate, since publications listed may not have anything to do with the trial in question.

Thanks to Jill Meinert for doing the numerous counts and analyses in this memo.

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