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Memorandum

To: Trialists

Fr: Curtis Meinert

Re: Registration uptake

It has been 20 years since registration of trials became a reality. The requirement came as a result of the Food and Drug Administration Modernization Act of 1997 (FDAMA). Technically, the requirement pertains only to trials done under FDA regulations, but the push has been for registration of all trials, whether or not under FDA control.

The National Library of Medicine (NLM) was tasked with developing a registration system. The NLM launched ClinicalTrials.gov (CT.gov) in early 2000; now with over 244,000 trials (interventional studies) registered.

The World Health Organization (WHO) opened its registration platform (consisting of 16 registries) in 2005. CT.gov remains the predominant registry accounting for about 80% of all registered trials.

The International Committee of Medical Journal Editors (ICMJE) gave registration a push in 2004 with the edict that *member journals will require, as a condition of consideration for publication, registration in a public trials registry. Trials must register at or before the onset of patient enrollment. This policy applies to any clinical trial starting enrollment after July 1, 2005. For trials that began enrollment prior to this date, the ICMJE member journals will require registration by September 13, 2005, before considering the trial for publication. (JAMA 2004; 292:1,363-1,364)*

In 2007 requirements were expanded in the Food and Drug Administration Amendments Act of 2007 (FDAAA). The 2007 Act (for trials under FDA control) required investigators post summary results to registrations within one year of completion of trials with penalties of up to \$10,000 a day for every day late beyond the one year time period.

Trialists have been pushed to register by sponsors, by the FDA, by the public as an ethical obligation, by meta-analysts concerned with publication bias, and by threats of hefty fines for failure to report results on registration sites. So, with those urgings, demands, and threats, what is the impact on the uptake of registration?

You might ask “Who cares?”

If you are a person looking for a trial involving the condition you have, you care.

If you are a health policy person interested in trials done in a particular area, you care.

If you are a meta-analyst interested in trials involving a particular treatment, you care.

If you are a methodologist interested in tracking the nature of trials, you care.

If you are a reader of a results paper and wanting more information about the trial contained in a registry, you care.

There are lots of reasons to want to know about registration uptake, but making those assessments are akin to astronomers looking for color shifts as they gaze into the cosmos trying to determine if the universe is expanding or collapsing.

The tables below provide information on registration uptake but without any way of knowing how many trials should be registered. Alas, we will never know unless registrations are initiated by IRBs when studies are approved and even then we will have no way of knowing until there is some way to merge registries or coalesce them into a single universal registry.

Table 1 is based on 1st posting dates (dates of registration). The 1st posting date can be before or after the start of enrollment. In fact many of the posted dates in first few years of the registry were actually after the start of enrollment.

Basically the uptake of registration proceeded in three stages. Registrations from 2000-03 were predominantly NIH-funded trials; accounting for 63% of all registrations. Industry-funded trials accounted for the majority of registrations in 2004-08. Other funded trials accounted for the majority of 1st postings thereafter.

Table 2 is based on start and completion dates of trials. Results are suggestive of a diminishing pool of unregistered trials. The year to year ratio of trials started to completed decreased to near unity in 2010 and has remained there since.

A related uptake question pertains to editors. The 2004 ICMJE edict precluding publication of trials not registered and required editors to publish registration numbers in abstracts. The ICMJE website lists over 5,000 journals signing onto ICMJE guidelines.

The NLM indexes registration numbers. So how many publications have indexed registration numbers? From Table 3 about 25%, meaning either that most published trials are not registered (unlikely) or that editors are not doing what they signed on to do (likely). If true, the uptake of editors lags considerably behind that of trialists to registration.

Table 1. CT.gov registrations by funding source

1 st yr posted	No registered	NIH funded	Industry funded	Other funded	% NIH funded	% Industry funded	% Other funded	% sum
2000	1,103	992	27	82	89.94%	2.45%	7.43%	99.82%
2001	1,470	767	692	56	52.18%	47.07%	3.81%	103.06%
2002	1,062	407	573	62	38.32%	53.95%	5.84%	98.12%
2003	3,330	2,193	601	579	65.86%	18.05%	17.39%	101.29%
	6,965	4,359	1,893	779	62.58%	27.18%	11.18%	100.95%
2004	2,955	1,635	908	456	55.33%	30.73%	15.43%	101.49%
2005	11,167	1,566	5,440	3,841	14.02%	48.72%	34.40%	97.13%
2006	9,301	1,357	4,614	3,213	14.59%	49.61%	34.54%	98.74%
2007	10,467	1,184	5,229	3,945	11.31%	49.96%	37.69%	98.96%
2008	14,350	1,417	7,263	5,489	9.87%	50.61%	38.25%	98.74%
	48,240	7,159	23,454	16,944	14.84%	48.62%	35.12%	98.58%
2009	13,589	1,202	6,390	5,816	8.85%	47.02%	42.80%	98.67%
2010	13,527	1,103	5,893	6,356	8.15%	43.56%	46.99%	98.71%
2011	13,864	1,079	5,841	6,773	7.78%	42.13%	48.85%	98.77%
2012	15,364	1,084	5,835	8,247	7.06%	37.98%	53.68%	98.71%
2013	16,258	1,147	5,517	9,395	7.06%	33.93%	57.79%	98.78%
	72,602	5,615	29,476	36,587	7.73%	40.60%	50.39%	98.73%
2014	18,465	1,155	6,698	10,426	6.26%	36.27%	56.46%	98.99%
2015	19,247	1,062	6,061	11,873	5.52%	31.49%	61.69%	98.70%
2016	21,574	1,093	6,313	13,960	5.07%	29.26%	64.71%	99.04%
2017	22,100	1,329	6,014	14,555	6.01%	27.21%	65.86%	99.09%
2018	23,502	1,322	6,379	15,554	5.63%	27.14%	66.18%	98.95%
	104,888	5,961	31,465	66,368	5.68%	30.00%	63.28%	98.96%
Total	232,695	23,094	86,288	120,678	9.92%	37.08%	51.86%	98.87%

Table 2. CT.gov registrations by year when started and when completed

Year	No. started	% change: Current yr vs previous yr.	No. completed	% change: Current yr vs previous yr
2000	1,856		371	
2001	2,389	128.72%	542	146.09%
2002	3,479	145.63%	814	150.18%
2003	4,757	136.73%	1,234	151.60%
2004	6,308	132.60%	1,691	137.03%
2005	7,721	122.40%	2,510	148.43%
2006	9,283	120.23%	3,683	146.73%
2007	10,379	111.81%	5,679	154.19%
2008	11,832	114.00%	8,659	152.47%
2009	12,788	108.08%	10,073	116.33%
2010	13,320	104.16%	10,880	108.01%
2011	14,088	105.77%	11,870	109.10%
2012	14,854	105.44%	12,928	108.91%
2013	15,671	105.50%	13,439	103.95%
2014	17,181	109.64%	14,719	109.52%
2015	18,389	107.03%	16,146	109.70%
2016	19,360	105.28%	17,600	109.01%
2017	19,442	100.42%	18,670	106.08%
2018	19,859	102.14%	20,303	108.75%

Table 3. Publications indexed [CT] and having indexed registration numbers

Yr of pub	No. pubs. indexed [CT]	No. with NCT reg. no.	% of pubs. with NCT reg. no.	No. with any other reg. no.	% with any other reg. no.	No. with any reg. no.	% pubs. with any reg. no.
2005	14,749	38	0.26%	73	0.49%	111	0.75%
2006	15,510	309	1.99%	119	0.77%	428	2.76%
2007	17,044	749	4.39%	230	1.35%	979	5.74%
2008	17,769	1,362	7.67%	354	1.99%	1,716	9.66%
2009	18,776	1,928	10.27%	426	2.27%	2,354	12.54%
2010	20,543	2,670	13.00%	532	2.59%	3,202	15.59%
2011	23,183	3,438	14.83%	633	2.73%	4,071	17.56%
2012	25,061	3,979	15.88%	618	2.47%	4,597	18.34%
2013	27,341	4,794	17.53%	898	3.28%	5,692	20.82%
2014	27,770	5,439	19.59%	1,491	5.37%	6,930	24.96%
2015	27,511	5,971	21.70%	1,856	6.75%	7,827	28.45%
2016	26,576	5,331	20.06%	1,417	5.33%	6,748	25.39%
2017	25,391	5,326	20.98%	971	3.82%	6,297	24.80%
2018	16,438	3,267	19.87%	625	3.80%	3,892	23.68%
Total	303,662	44,601	14.69%	10,243	3.37%	54,844	18.06%