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Memorandum

To: Trialists

Fr: Curtis Meinert

Re: Impact of the 1993 NIH Revitalization Act on trials

There is no metric as to how research dollars are to be apportioned between the sexes. In trials the issues of who and what is studied has been driven largely by those doing the trials. That started to change in the 1980s from growing concern that women and their diseases and conditions were being shortchanged relative to those of men.

The prevailing belief was that trials were done predominately in white men. The belief was highlighted by a few high profile male-only heart trials, principally the

Multiple Risk Factor Intervention Trial (MRFIT),
Physicians Health Study (PHS),
and
Coronary Drug Project (CDP).

The concern was enough to cause Congress, in the NIH Revitalization Act of 1993 (enacted by the 103rd Congress and signed into law by William Clinton 10 June 1993), to specify that:

> *In the case of any clinical trial in which women or members of minority groups will be included as subjects, the Director of NIH shall ensure that the trial is designed and carried out in a manner sufficient to provide for valid analysis of whether the variables being studied in the trial affect women or members of minority groups, as the case may be, differently than other subjects in the trial*.

The "valid analysis requirement", taken literally, meant that trials involving men and women would have to be designed to provide the same power for treatment comparisons in women as in men. That requirement would lead to sizeable increases in sample sizes, but the interpretation instead was an "unbiased assessment" of the treatment differences (Controlled Clinical Trials 16: 277-285; 1995).

One change brought about by attention to who is studied is on publications, as seen in the table below. The percentage of publications indexable to gender increased from 71% for 1970 publications to 93% for 2015 publications.

The table also provides counts of randomized controlled trials [RCT] publications indexed as involving both males and females, males-only, and females-only. The ratio of female-only to male-only RCTs is given in column G. The ratio has increased from 0.81 for 1970 publications to 1.70 for 2015 publications, signaling a sizable shift in published single gender trials from male to female over the time period covered in the table.

Publications indexed as [randomized controlled trial] (Col A), % of publications where authors reported gender composition (Col C), and ratio of F-only to M-only publications (Col G)

Yr pub	A [RCT]	B M/F Indexed	C (B/A)%	D M&F	E M-only	F F-only	G F/M
1970	302	213	70.53%	128	47	38	0.81
1975	797	564	70.77%	365	107	92	0.86
1980	1,735	1,244	71.70%	812	223	209	0.94
1985	3,102	2,519	81.21%	1,744	394	381	0.97
1990	5,784	4,457	77.06%	3,078	680	699	1.03
1995	9,204	7,785	84.58%	5,578	1,151	1,056	0.92
2000	9,999	8,626	86.27%	6,466	898	1,262	1.41
2005	14,724	12,977	88.14%	9,905	1,119	1,953	1.75
2010	20,519	18,435	89.84%	14,347	1,582	2,506	1.58
2015	27,441	25,392	92.53%	20,433	1,836	3,123	1.70

The impact of the legislation is also apparent in the table below using data in ClinicalTrials.gov. The ratio of female-only to male-only trials is approaching 3 to 1 for NIH-funded trials, compared to a modest excess of male-only industry-funded trials.

Trials registered on ClinicalTrials.gov and number completed by year of registration and by gender composition

A: NIH-funded trials

Yr registered	A No. completed	B M and F	C M-only	D F-only	E F-only/ M-only
2000-04	3,066	2,581	146	339	2.32
2005-09	3,445	2,930	144	371	2.58
2010-14	1,431	1,252	47	132	2.81
2015-17	112	95	7	10	1.43
Total[#]	8,054	6,858	344	852	2.48

B: Industry-funded trials

Yr registered	A No. completed	B M and F	C M-only	D F-only	E F-only/ M-only
2000-04	7,761	6,639	509	613	1.20
2005-09	21,642	18,809	1,423	1,410	0.99
2010-14	15,431	13,185	1,529	717	0.47
2015-17	3,603	2,963	509	131	0.26
Total[#]	48,437	41,596	3,970	2,871	0.72

[#] Excluding 12 NIH-funded trials and 49 industry-funded trials not providing gender composition