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Memorandum

To: Trialists

Fr: Curtis Meinert

Re: NIH-funded phase 4 trials

A phase 4 trial is a trial of a drug done after FDA approval; not to be confused with post-marketing surveillance (usually observational and devoid of concurrent comparison groups).

The NIH is the best hope for comparative phase 4 trials. Drug companies are not disposed to doing trials involving comparison of their product with competing products.

To the extent to which many of the drugs approved by the FDA are for chronic health conditions, the expectation is that phase 4 trials will be larger and longer term than phase 3 trials, but one would be wrong. One of the surprises in a paper we published earlier this year (Gillian Gresham, Stephan Ehrhardt, Jill Meinert, Lawrence Appel and myself; "Characteristics and trends of clinical trials funded by the National Institutes of Health between 2005 and 2015"; Clinical Trials 2018, Vol. 15; 65–74e) was that phase 4 trials represent less than 7% of all drug trials funded by the NIH and that the median sample size is 1/3rd that for phase 3 trials (306 versus 108).

NIH-funded phase 4 trials by year of registration, planned or achieved sample size (median and interquartile range) and planned or actual times to completion (median and interquartile ranges)

Year	No. reg	Mdn SS	IQ SS range	Mdn time	IQ time range
2000	17	144	106-186	1,827	943-3,652
2001	20	270	44-582	1,341	884-2,161
2002	29	73	40-140	1,385	959-2,039
2003	30	130	58-300	1,492	912-1,993
2004	6	168	130-307	701	395-1,796
2005	103	94	47-211	1,582	1,188-2,101
2006	56	153	50-500	1,614	1,157-2,010
2007	48	120	45-214	1,764	943-2,343
2008	75	80	27-181	1,583	1,005-2,068
2009	71	66	32-206	1,279	822-1,857
2010	52	74	33-315	1,188	670-1,765

Year	No. reg	Mdn SS	IQ SS range	Mdn time	IQ time range
2011	38	51	20-250	1,416	762-1,857
2012	50	137	44-300	1,537	1,004-2,070
2013	39	113	54-290	1,673	808-2,160
2014	30	77	40-150	1,490	534-1,856
2015	34	120	50-300	1,430	883-1,735
2016	36	140	80-350	1,308	883-1,645
2017	64	80	30-190	91	61-289

The table above makes me wonder what passes for phase 4 trials. One has to hope that hidden among them are the trials that Donald Fredrickson (NIH Director: Jul 1975 - 30 Jun 1981) spoke of in his address to the New York Academy of Science in 1968.

> *Field trials are indispensable. They will continue to be an ordeal. They lack glamor, they strain our resources and patience, and they protract the moment of truth to excruciating limits. Still, they are among the most challenging tests of our skills. I have no doubt that when the problem is well chosen, the study is appropriately designed, and that when all the populations concerned are made aware of the route and the goal, the reward can be commensurate with the effort. If, in major medical dilemmas, the alternative is to pay the cost of perpetual uncertainty, have we really any choice?*

Fredrickson's field trials are long-term treatment and prevention trials. The expectation with both types is that they are long-term and large enough to find differences if they exist. If a treatment is used long-term in general practice, the expectation is that trials done to assess treatment efficacy also have to be long-term. Prevention trials have to have outcome measures that are the condition aimed for prevention or reoccurrence of the condition in secondary prevention trials. If treatment is given in the belief that it prevents MIs the outcome has to be MI or death related to occurrence of MI.