



JOHNS HOPKINS
BLOOMBERG
SCHOOL of PUBLIC HEALTH

Department of Epidemiology
Johns Hopkins Bloomberg School of Public Health
415 N. Washington Street, 2nd Floor
Baltimore, Maryland 21231

21 January 2020

Memorandum

To: Trialists

Fr: Curtis Meinert

Re: NIH prevention trials

A recent article (8 Nov 2019) in JAMA OPEN by Ashley J. Vargas and coworkers entitled *Assessment of Prevention Research Measuring Leading Risk Factors and Causes of Mortality and Disability Supported by the US National Institutes of Health* touches on an important issue concerning efforts of the NIH research community devoted to prevention trials.
(<https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2754251>)

The authors looked at a sample of grant and cooperative agreements funded by the NIH in fiscal years 2012 through 2017. They concluded:

the leading risk factors and causes of death and disability were underrepresented in the NIH prevention research portfolio.

Given the disease and disability burden in the United States associated with the leading risk factors and causes of death and disability, the findings reported herein suggest that the nation may benefit from directing more of the prevention research portfolio supported by NIH grants and cooperative agreements to studies that focus on those risk factors and causes, to studies that address multiple risk factors and causes, and to studies that develop and evaluate preventive interventions to address those risk factors and causes.

Broadly, prevention trials are “primary” or “secondary”. “Primary” if the aim is prevention of a disease or adverse health condition. “Secondary” if the aim is delaying the progression or worsening of a disease or adverse health condition. The defining features of prevention trials is the outcome measure, basically, a clinical event like death, onset of a disease, or recurrence or worsening of a disease or health condition.

A crude indication of how the clinical trials enterprise apportions its effort relative to mortality is displayed in the table below.

The table gives counts of trials registered on CT.gov indexed to the indicated cause of mortality. Counts are of trials registered on CT.gov since inception. Counts in Column C are for NIH-funded trials. Counts in Column E are for trials regardless of funding source. Counts were generated by entering the condition in the “Condition or disease” search field on CT.gov. Counts are as of November 2019.

Heart disease is the leading cause of mortality followed closely by cancer deaths. The two causes together account for 45% of all U.S. mortality. If trials track mortality, counts of trials for the two conditions would be about equal, but cancer trials outnumber heart trials 14 to 1 for NIH-funded trials and 5 to 1 for all trials.

US 2017 leading causes of death* by counts of trials registered on CT.gov

	Col A	Col B	Col C	Col D	Col E	Col F
	Cause of death	% of all deaths	NIH-funded trials	% NIH-funded trials	All registered trials	% all registered trials
1	Heart disease	23.0%	724	2.96%	11,541	4.58%
2	Cancer	21.3%	10,490	42.85%	58,377	23.14%
3	Accidents (Search term: Injuries)	6.0%	589	2.41%	11,790	4.67%
4	Chronic lower respiratory disease (Search term: Respiratory disease)	5.7%	1,940	7.92%	2,529	1.00%
5	Stroke and CV disorders	5.2%				
	Stroke		264	1.08%	3,689	1.46%
	CV disorders		2,092	8.55%	27,658	10.96%
6	Alzheimer's disease	4.3%	225	0.92%	1,826	0.72%
7	Diabetes	3.0%	851	3.48%	12,095	4.79%
8	Influenza and pneumonia	2.0%				
	Influenza		246	1.00%	1,921	0.76%
	Pneumonia		114	0.47%	1,253	0.50%
9	Kidney disease	1.8%	645	2.63%	6,317	2.50%
10	Suicide	1.7%	74	0.30%	386	0.15%
	Sum	74.00%	18,254	74.57%	139,382	55.26%
			24,480 NIH reg trials		252,248 all reg trials	

* National Vital Statistics Report, Vol. 68, No. 9, June 24, 2019

Trials completed 2004 to present where NCI or NHLBI is lead sponsor as registered on CT.gov

Institute	# trials completed	Phase 0 - 3	Phase 4	Other (non drug)	% phase 0 - 3	% phase 4	% other (non drug)
NCI	830	814	0	16	98.07%	0.00%	1.93%
NHLBI	147	120	2	25	81.63%	1.36%	17.01%

Almost all NCI-funded trials are developmental trials, phase 0 - 3 (98%). There were no post approval phase 4 trials.

The picture for NHLBI is about the same except many fewer trials. As with the NCI, most of the effort goes to drug development with just two phase 4 trials. A difference is in effort devoted to trials other than drug trials; 17% of NHLBI trials versus 2% for NCI.

The fact is that most trials are too small to answer even basic questions, let alone questions regarding effectiveness as preventative treatments. The median sample size of registered NIH-funded trials is 60. That translates to an N of 30 per treatment group assuming designs with one test and one control treatment.

As seen from the work of Vargas and coworkers trials are difficult to classify vis-à-vis purpose. There is no bright line separating treatment trials from prevention trials, but the expectation is that prevention trials will usually be larger than the typical treatment trial.

There were 3,468 trials registered on CT.gov listed as NIH or other U.S. government funded and completed in 2018. Of those 135 were listed as having sample sizes of 1,000 or more. About half (62) were drug development trials; phase 0 - 3. Only ten were listed as phase 4. Over half (68) were listed as funded by the CDC or VA. Twenty-three were funded by NIAID. Only eight were funded by the NCI and only four were funded by the NHLBI reinforcing Vargas and coworkers observation that:

the leading risk factors and causes of death and disability were underrepresented in the NIH prevention research portfolio.