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Memorandum

To: Trialists

Fr: Curtis Meinert

Re: What drives the clinical trials enterprise?

What drives the clinical trials enterprise? Who knows but forces are likely to be admixtures of money, opportunity, curiosity, pursuit of knowledge, and desires to improve health and well-being.

If you are the Big Exchequer in the sky, responsible for directing the clinical trials enterprise, how would you do it? How much effort would you devote to treatment versus prevention? How would you allocate effort across the age spectrum and gender groups? Which health conditions would you give priority to? Would you pay attention to previous performance of groups seeking funding and whether they published? Would your primary focus be on the mortality impact of health conditions or would it be on the misery and disability caused by health conditions?

Alas (and perhaps fortunately) there is no Big Exchequer in the sky. To be sure, trials are heavily regulated, but the forces driving the enterprise are diverse and disjointed, consisting of public pressures, policy makers, regulators, activists, funders, and investigators, buttressed by a supporting and accepting public.

The first reports of AIDs deaths appeared June 5th, 1981 in MMWR (Morbidity and Mortality Weekly Report). The illness then was a mysterious condition seen mostly in gay men. When it became clear later that the virus was spread person to person by bodily fluids, including breast milk from infected mothers, the world took note.

Being HIV positive went from a kiss of death in the 1980s to a manageable chronic condition 20 years later. That would not have happened without major efforts by researchers around the world funded by governmental agencies, industry, and foundations to facilitate searches for drugs to treat the condition.

Activist groups, notably ACT UP (AIDS Coalition to Unleash Power; formed 1987), lobbied for funding for HIV/AIDs research. NIH Funding increased from \$3.4 million in fiscal year 1982 to \$804.6 million for FY 1991. Counts of HIV/AIDs trials registered on CT.gov (24 Oct 2019) by funding source are:

1,912	NIH
187	Other US gov't
2,017	Industry
1,862	Other funders

US 2017 leading causes of mortality (source CDC)

Rank	Cause of death	% of all deaths	Trials registered on CT.gov	% of registered trials
1	Heart disease	23.5%	11,541	4.58%
2	Cancer	21.3%	58,377	23.14%
3	Unintentional injuries	6.0%	2	0.00%
4	Chronic lower respiratory disease	5.7%	2,529	1.00%
5	Stroke and CV disorders	5.2%		
	Stroke		3,689	1.46%
	CV disorders		27,658	10.96%
6	Alzheimer's disease	4.3%	1,826	0.72%
7	Diabetes	3.0%	12,095	4.79%
8	Influenza and pneumonia	2.0%		
	Influenza		1,921	0.76%
	Pneumonia		1,253	0.50%
9	Kidney disease	1.8%	6,317	2.50%
10	Suicide	1.7%	386	0.15%
	Totals	74.50%	127,594	50.58%
			252,248 Total # trials reg CT.gov	

Just about 75% of all US deaths are accounted for by the ten causes listed above.

The third column in the table gives counts of trials registered on CT.gov (20 October 2019) indexed to the indicated condition. The fourth column gives those counts as percentages of registered trials.

There is only a loose relationship between mortality and trials undertaken. Indeed, if there was a one-to-one relationship, trials involving heart disease would outnumber cancer trials, but in fact they outnumber heart disease trials 5 to 1.

Why the disparity? You have to ask the Exchequer, but if you ask me I would say part of the reason has to do with our anxieties concerning cancer versus heart disease.

Survey 100 people and ask what they fear more, cancer or heart disease, odds are most will say cancer (though they are more likely to die of heart disease). The word alone strikes fear. Cancer is not a respecter of age striking the very young, children, adolescents, and adults of any age.

Heart disease, for the most part spares the young. It is largely a disease of mid-life and beyond. It scares us, but not as much as cancer.

Worldwide, breast cancer is the most common cancer affecting women. Concerns about breast cancer here and lobbying led to creation of a grants program by the Department of Defense. Funding from the Department through FY 2019 has been in excess of 3.6 billion dollars.

It also pays to be first. The Cancer Institute, established 1937, was the first NIH institute. The Heart Institute (now the National Heart, Lung, and Blood; NHLBI) was established eleven years later.

The budget for the cancer institute is roughly twice that of the heart institute. Its research efforts have been enhanced by standing cancer cooperative groups (currently five: Alliance for Clinical Trials in Oncology, ECOG-ACRIN Cancer Research Group, SWOG, and Children's Oncology Group (COG)).

Another difference has to with the nature of trials done. Almost 80% of cancer trials registered on CT.gov are drug trials compared to 50% for heart disease trials:

Cancer trials: 58,411

Drug trials: 46,118 (78.9%)

Heart disease trials: 11,348

Drug trials: 5,638 (49.6%)

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So what drives the clinical trials enterprise?

Every time I confront the question I come away with the same answer: I have no idea.

Obviously, the forces are diverse and disjointed. The wonder is that the enterprise covers the waterfront as well as it does.

I am not sure the Big Exchequer in the sky could do any better.