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Memorandum

To: Trialists

Fr: Curtis Meinert

Re: Things we should know about trials

An article published in BMJ (2018; 363; 3 October 2018) written by Rasmussen and coworkers entitled "Collaboration between academics and industry in clinical trials" focused on the role of industry in the design, conduct, and analysis of trials. The authors conclude (no surprise) that industry employees and academic authors are involved in the design, conduct, and reporting of most industry funded trials.

The article spurred a writer (Shelley Wood) for the web service tctMD to write a price entitled *The price of knowledge: Industry-sponsored studies in the era of evidence-based medicine* (dated 22 October 2018). She wrote:

> *The vast majority of clinical trials conducted to support regulatory approval of a drug, device, or vaccine—or track its safety after approval—are sponsored by manufacturers. But just how much influence do companies have over the design, conduct, and reporting of trials?*
>
> *This question came up last month when the COAPT and MITRA-FR trials of the MitraClip produced starkly different results. COAPT, which was overwhelmingly positive for device therapy over best medical care, was 100% industry sponsored, with Abbott participating in site selection, site management, and data analysis. MITRA-FR, in contrast, was decidedly negative and conducted and coordinated by an academic research organization.*

When the writer asked the PI of COAPT about the "100% industry sponsorship" of the trial the response was adamant *investigators had full control, with zero influence by the sponsor.*

The writer goes on to note that *Industry-funded trials have, for years, prompted polarized opinions as to whether the sponsor's involvement is healthy and necessary or heavy-handed and damaging.*

The issue of control is not unique to industry. The same issues arise in NIH-funded trials.

Today most NIH multicenter trials are initiated by the NIH and funded by contracts or are investigator-initiated and funded via cooperative agreements with the NIH.

Sponsors, whether they be industry or NIH are not potted plants. Their basic nature is to influence, control, and manage. So the issue is not whether sponsors "influence" but rather whether the influence has a biasing effect on how data are collected, analyzed, and reported.

Industry sponsors have obvious conflicts of interests being invested in the treatment they test and wanting positive results to maintain their marketing pipelines. But the NIH has its own unique conflicts of interest wanting positive results to help their respective directors when arguing for budgets in front of Congress.

As a rule, investigators are in charge in single center trials but responsibilities for trials are usually shared in multicenter trials. That being the case how do you, when reading publications, figure out whether the research and findings are "biased" because of sponsor influence.

The sine qua non of any kind of research is that it be done objectively, by people free of influence or bias.

The supposition, in the case of a multicenter trial, is that it has a data coordinating center to receive, process, and analyze data generated in the trials and that it has a DSMB (data and safety monitoring committee) to review interim results over the course of the trial to decide if it should continue to its appointed end. The key things to know (but hard to devine from publications) when trying to gauge freedom of investigators from control and influence of the sponsor are as represented by the questions below.

					Score
1	Does the trial have a coordinating center that is independent of the sponsor?		Yes (2)	No (-2)	
2	Is the coordinating center part of the sponsoring agency?		Yes (-4)	No (2)	
3	Is the coordinating center funded by the same mechanism as used for clinical centers?		Yes (2)	No (-1)	
4	Does the funding for the coordinating center extend at least one year beyond completion of the trial?		Yes (2)	No (-1)	
5	Who appoints the DSMB?	Both (2)	Investigators (2)	Sponsor (-2)	
6	Who does the DSMB report to?	Both (2)	Investigators (2)	Sponsor (-2)	
7	Does the sponsor have rights of reviews and approvals of publications?		Yes (-2)	No (2)	
8	**Investigator independence score**				**0**

The score ranges from -10 to 12. Great if 12 (unlikely) and not good if -10. The difficulty in tallying the score is that publications rarely contain enough information to permit you to tally the score.

The first four questions relate to coordinating centers. The center should be independent of the sponsor; usually the case for NIH-funded trials but not necessarily so for industry-sponsored trials.

Question 4 relates to funding of the coordinating center relative to other sites in the study. Use of contract mechanisms for funding the coordinating center compared to grant support for clinical centers generally means the sponsor is interested in having more control over the coordinating center than clinics in the trial.

The NIH wants to control DSMBs by appointing them and having them report to the NIH. Industry sponsors are inclined to maintain arms length relationship with DSMBs.