Journal of Clinical Trials
ISSN: 2167-0870

Leibowitz-Amit, J Clin Trials 2017, 7:1
DOI: 10.4172/2167-0870.1000295

Commentary Open Access

# Being Principal Investigators on Pharma-initiated Clinical Trials: Have we Sold Ourselves Too Cheap?

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**Received date:** June 30, 2016; **Accepted date:** January 5, 2017; **Published date:** January 20, 2017



**Abstract**

The other day in clinic I was going through one of those good-clinical-practice (GCP) modules, as requested by one of the pharma companies in order for me to participate as an investigator in one of their clinical trial. As I repetitively wasn't able to correctly answer the minimum 80% of the questions needed for me to pass the final test of the module, my morning hours just flew by, and with my increasing level of anxiety, it suddenly dawned on me-we, physician-investigators participating in pharma-initiated clinical trials, have sold ourselves too cheap.

**Keywords:** Clinical trial; Case report; Good clinical practice; Monitoring

## Commentary

I am a senior medical oncologist in a large tertiary centre. I graduated from medical school, finished the demanding 5-year residency in medical oncology, completed the 2-year fellowship, successfully completed the 4-day GCP training course almost a decade ago, and I am running a small research group which studies micro-RNAs in solid tumours. I have been an investigator on clinical trials for a good few years now, first as a sub-investigator and recently as a principal investigator, and yet I must oblige, like the rest of my colleague investigators, with an ever-growing list of bureaucratic chores and requests, that sometimes seems almost arbitrary, and all on of which I have absolutely no say.

The dynamics are simple–as we are all very eager to open clinical trials in our centre in order to allow our patients many treatment opportunities and maximal exposure to investigational drugs, we find ourselves forced to comply with a growing administrative task list, almost none of which have anything to do with actual medicine. It is not only the web-based trainings and modules; it is the document signing, becoming ever-so fragmented, or the growing list of queries needed to be addressed, or the meticulous reporting of the tiniest events, such as dispensing a single tab of Tylenol to a painful patient in clinic or documenting an isolated occurrence of blood pressure elevation. This growing demand naturally takes up huge amounts of time, time that otherwise would have been spent treating patients.

Moreover, this tedious effort sometimes prevents separating the wheat from the chaff. The patient's chart and case report form (CRF) can become so cramped with details that it becomes hard to extract the big clinical picture. For example, when a patient uses synonyms to describe the same clinical condition (such as 'fatigue', 'tiredness', lack of energy'), current-day reporting standards usually mandate describing these as three different adverse events, rather than clustering them all to one single event that captures the exact same clinical essence. This can eventually hamper patient management and evidently impede on the trial. This is especially true in light of the fact that there is no formal evidence supporting the extent or frequency of current clinical trial monitoring [1].

Last and most concerning-it sometimes feels that this enormous clinical trial machinery undermines our ability to act in the best interest of our patient or forces us to act in an insensible or insensitive manner with our patients. The latter can be exemplified by the currently pressing demand to discuss the use of contraception in each and every patient visit (and document it in the chart every single time), even when impregnation is clearly of no concern due to abstinence of the patient or merely due to his/her age or performance status.

Whereas it is clear to me why adherence to protocol is cardinal, from both the medical and the procedural perspective, I find that there is a constant drift in what is defined as a major protocol deviation. It is not uncommon to find, in current-day trials, that clinically meaningless events are defined as major deviations; this can be exemplified, for instance, by a two-day postponement in the initiation of an oral drug course being defined as a 'major deviation'. It is not uncommon to have to perform a clinically unnecessary stop or change in treatment merely to satisfy the protocol, without any underlying medical logic.

It should have been the case that in all such circumstances, the medical judgment of the principal investigator would take precedence over technical protocol adherence (following discussion with the sponsor). Yet this is hardly the case; in the vast majority of these collisions between common clinical sense and protocol, the latter wins alas. The fear of protocol deviation has been rooted so deep in us that the majority of us would not dare violate protocol under no circumstances, thus ultimately, at times, compromising patient care or wasting huge resources.

Many of the issues raised here were brought up in the past as barriers to the conduct of randomized trials [2], yet in recent years clinical trial methodology and conduct have in fact become even more complex and more cumbersome, making the need to address these issues, in my opinion, more burning. There already is growing awareness of the need to relax inclusion criteria in order to increase accrual rates to trials [3] and the recent initiative to modernize eligibility criteria for clinical trials, coming from the American Society

of Clinical Oncology and Friends of Cancer Research, is a welcome progress in this direction [4]. Still, not enough is said on the cost (financial and other) of the burdensome management of patients once they are accrued and treated.

I believe that many physicians share my sentiment on this matter, but there are no means for us to convey our frustration or to suggest other options. Choosing not to participate in a clinical trial would negatively affect our patients. We therefore clench our teeth and continue. In contrast to factory workers or teachers, we–principal investigators on pharma-initiated clinical trials–do not have a 'union', and our opinions–on protocol, on trial management, on procedure–are hardly ever heard.

What, then, are potential solutions to this problem? First, the pharmaceutical industry, on its part, must realize that no physician should be pushed to act against his best clinical judgment, and must allow more flexibility and sovereignty in our day-to-day management of clinical-trial patients. The extent of monitoring should be re-assessed, the excessive demand for documentation should be revised to include only clinically-meaningful events or clinic discussions, and the definition of what constitutes protocol deviations and violations should be re-appraised to consist of significantly less, and more clinically-relevant events. The regulatory agencies on their part, should somewhat relax their requirements on trial reporting and should redefine protocol violations. Such simple steps would not affect the completeness of data capture on trial, nor would they hamper safety or ethical conduct; they will surely not affect the integrity of the trial or its conduct according to the principles of GCP.

Last, I think that principal investigators on pharma-initiated clinical trials should set a stronger foot as it relates to these following issues: better use of our time, less cumbersome documentation and more independence in our decision-making. It is time we realize that, despite being 'one of many' (especially on the large phase III registrational trials), our professional opinions on trial protocol and conduct are cardinal and must be stated without fear. When an investigator on a trial is faced with requests to act in an insensible or insensitive manner (such as discussing contraception with a dying patient who is clearly not sexually active), he or she should simply say 'no' without hesitation. I think it's time to turn the tables and reclaim our role as the patients' primary caretakers and advocates, even when the patients are participants in a pharma-sponsored clinical trial, and perhaps even more during that time than ever.

I claim that such steps, from both the pharma sponsors, the regulators and the clinical investigators, would increase accrual and patient adherence to the trial, and would increase patients' and doctors' satisfaction from the clinical trial, ultimately allowing this important machinery to continue and prosper, for the benefit of our patients and for the advancement of science.

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