Possible Positions to Avoid Conflict of Interest

CASE COMMENTARY

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As principal investigator, my loyalty of course must be to uphold the integrity of the research, which means that I should follow the protocol diligently and faithfully, including the proper recruitment of participants, and reporting of all serious adverse events (SAEs). Equally important should be to advise the sponsor of any doubts or discomfort on my part regarding these SAEs. The monetary compensation should never be a factor for decisions at this point.

Hence, I will not even consider recruiting my patient who had viral hepatitis because this violates the recruitment policy. The trial is just a month from completion and the results will be out soon enough for me to make a proper judgment on whether to give her the treatment or not later. Meanwhile, if she has been suffering from this condition for the past seven years and has never had any of the SAEs mentioned in this case, I will not be remiss if I continue just treating her with thus far approved regimen.

This decision regarding my patient (Mrs L) is also reached upon realisation that seven patients out of 37 thus recruited and participating in the trial had adverse reactions which I may consider alarming. Not only are the reactions (myocardial infarction, cardiac rhythm abnormality, acute liver dysfunction) relatively rare in cases of irritable bowel syndrome and constipation which may not even be under active treatment; but also because, presuming that one of the exclusion criteria was heart disease, it is easy to deduce that these could not be due to the placebo. However, I will have to go over the history and clinical presentation of the participants who manifested these adverse effects and find out if there is a chance that the side effects could not be drug related. If my thorough review of these cases convince me that they are indeed drug related, then I will request the sponsors to stop the recruitment now, especially

if the recruited number so far can lead to statistically significant results. If the recruitment could be possibly stopped now, I will recommend decoding the side arms (investigational drug and placebo) for the 37 patients so that I could continue treating them accordingly, like using standard care for the condition. If I find that the SAEs were indeed drug related, but that the reactions are more due to dosage, administration, and not with the active ingredient itself (an ingredient which in the literature and in previous animal studies and phase 1 trials may have been shown to be effective in treating the condition it purported to treat), then I can suggest a modification of dose and administration, and make stricter inclusion/exclusion criteria and suggest, as the data safety monitoring board (DSMB) suggested, stricter surveillance, and an altogether new if not amended protocol. I am just wondering why the Ethics Review Committee (ERC), which is supposed to be receiving SAE reports and protecting participants, has not stepped in to suspend recruitment!

In summary, these are my possible positions:

- *Position 1.* I will stop the recruitment. If I am an ethical investigator, I will not even think of the $7,400 I stand to lose (I have been paid or stand to be paid almost $30,000 anyway!) as a condition to continue looking for the last three participants. This is because I am alarmed by the SAEs, although honestly, I think they are either drug- or placebo-related. Having treated several patients suffering from constipation in my practice, I think the SAEs could not all be drug-related as long as the patients are being given standard care. Maybe, I could go back to my literature research on constipation and irritable bowel syndrome and find out what, even without treatment, are the most alarming conditions that patients can complain of. Offhand, I know that if one strains so much to move his bowels, he can suffer a myocardial infarction, especially in the elderly, but what is really the incidence of such among cases of constipation associated with irritable bowel syndrome? And there is also the question about liver dysfunction, which is one of the SAEs. What is the incidence rate of liver dysfunction in untreated irritable bowel syndrome? If I have been careful in my literature research and I am really qualified to undertake this research (meaning, I am a good gastroenterologist and realised that many of my patients with the said condition were not being helped by standard care, and might indeed benefit from this drug) then I should think that the drug may not be any better than standard care at all. Thus I will stop the recruitment while we are a step ahead, meaning, no deaths yet.
- *Position 2.* I will continue with the recruitment if, at this point, meaningful statistical analysis and validation will require it, but will request for extension of

the recruitment period if it is really impossible to get the last three participants within a month. But I will be stricter in the recruitment by delving into the history and condition of those being recruited (especially their heart and liver history) without sacrificing the integrity of the research. I will also be stricter with the surveillance and be on top of SAEs that might occur. Because of the increase in the degree of risk in participating (as shown by the SAEs), I will ask for a bigger compensation for the last three participants. I will also request for an increase in compensation for those who had the SAEs because of possible need of longer treatment for their SAEs. I will not however change the recruitment criteria, so I will not recruit my patient. I will also request that the compensation to the principal investigator stands.

- *Position 3.* I will amend the protocol after consultation with the sponsors. I will submit the amended protocol to the ERC for approval. In the amended protocol I will reduce the dose and/or modify the administration if previous studies (borne by phase 2 trials and the literature) on the active ingredient of the drug showed its efficacy in treating constipation due to irritable bowel syndrome. I will not change recruitment criteria but will improve on surveillance for serious adverse events.

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