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Viewpoint

Rebuttal

Lorraine E. Ferris, C. David Naylor

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We are encouraged (but not surprised) that an investigator of Salim Yusuf's stature and considerable experience in leading large multicentre international randomized controlled trials (RCTs) has not seen financial conflicts of interest in his dealings with industry.[1] These trials, as Yusuf notes, are robust enough to make added regulatory protections unnecessary (and wasteful). Such large-scale trials comparing approved drugs or exploring new indications for an established compound often do involve industry as a sponsor (or cosponsor), but they are initiated largely by investigators. As such, the researchers have a major role in trial design, control of the trial databases, oversight of the analysis and interpretation of the data, and reporting of the results, with little or no interference from industry.

However, a large number of RCTs and nonrandomized studies are done by pharmaceutical companies with the sole purpose of obtaining regulatory approval for a new drug. These studies, focused on meeting regulatory requirements, are usually funded exclusively by industrial sponsors (usually a single company with a considerable vested interest) and managed by the sponsors or by nonacademic contract research organizations. Each year, such studies involve thousands of physicians whose main role, within the regulatory framework, is to provide clinical care to patients participating in the clinical study. Our commentary on the need for standardized clinical trial budgets[2] is directed largely at this thriving sector of premarket therapeutic studies and was a response to concerns about conflicts of interest in industry-sponsored clinical trials and perceived or real effects on the integrity of these studies.[3,4]

Preapproval studies are susceptible to business imperatives precisely because the stakes are high: sponsors have already invested a great deal of money into research and development of the drug and will be investing heavily in the required preapproval trials. Ensuring public confidence is particularly important[5-8] given the increasingly powerful technologies now being marshalled in these studies.

We agree with Yusuf that the drug approval process should be streamlined or improved. But that does not mean that one should not try to shed more light on the finances of clinical research. We argued, after all, for nothing radical: a consensus on appropriate physician remuneration in clinical studies; clear, detailed and standardized budget templates; and greater transparency for all involved.

Yusuf argues that companies already have standardized budget formats in multicentre trials and cites inevitable variations among companies and countries as major problems. However, extant standardized budgets do not always have sufficient detail to indicate what services are being offered and the amount of remuneration for each service. Aware of these potential variations, we called for guidelines, templates, standardized categories, and a regional or

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national consensus on appropriate compensation levels — not legalistic homogenization.

Yusuf also takes issue with our proposal to require research ethics boards (REBs) to approve not only the protocol, but also the study budgets. Yet because REBs are mandated to provide the necessary oversight to protect the health and well-being of the institution's research subjects, it is imperative that they review trial budgets. Officials at institutions (e.g., research administration) may review more detailed trial budgets, but they are arguably conflicted in some cases, and in any event review by such officials is not a replacement for REB review.

As to disclosure to patients about financial remuneration, we view Yusuf's position as paternalistic. If our proposal were followed, disclosure to research subjects would be straightforward: "The institution and the health care professionals involved in this clinical trial are being reimbursed for their services by the company that is funding the study (name of the sponsor), at the usual rates suggested by national guidelines for industry-sponsored clinical research."

In sum, we have great respect for Yusuf's global leadership in late-stage, academically driven multicentre trials and share his concerns about overregulation and bureaucracy. The hard fact, however, is that these big studies are the tip of the iceberg, focused largely on defining indications and market segmentation. Beneath the waterline is a very large volume of industry-sponsored trials of preapproval therapies, being performed in diverse clinical environments. Bringing the finances of these studies to light is in everyone's interest.

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