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Dear Dr Shannon

Re: Responding to serious adverse events in Study 329

Thank you for your letter of 20 January.

1. You state that GSK was not in a position to recognise that Paxil carried a substantial risk of suicide related adverse events until 'adverse event data was interrogated further and data from individual trials were pooled together'. Yet even a scan of the patient narratives in study 329 immediately raises concerns about the level of suicidal behaviour in the Paxil group. Any responsible scientist should have raised an alarm in response to these narratives. Instead GSK and your ghostwriters attempted to bury this information, as my co-authors and I spelt out in our 2008 paper[1]:

> Although suicidal thoughts and behaviour were grouped under the euphemism of 'emotional lability', Table 48 of SKB's internal final report [14, p. 109] clearly shows that five of the six occurrences of emotional lability were rated 'severe' and that all five had self-harmed or reported emergent suicidal ideas. Just a few minutes' reading of the serious adverse events narratives in this final report (pp. 276–307) would have revealed three more cases of suicidal ideas or self-harm that had not been classified as emotional lability. So the authors should have known that at least eight adolescents in the paroxetine group had self-harmed or reported emergent suicidal ideas compared to only one in the placebo group. Relatively small numbers and brief follow up in RCTs lessen the likelihood of detecting serious adverse events (SAEs), so any signal should be highlighted. Yet early drafts of the paper prepared for *JAMA* did not discuss SAEs at all [15]. Subsequently SKB senior scientist McCafferty composed a paragraph on SAEs that appeared for the first time in the draft of July, 1999. It disclosed that 11 patients on paroxetine, compared to two on placebo, had SAEs, but did not mention the statistical significance of these figures. Subsequently McCafferty's disclosures of overdose and mania were edited out, and SAEs

[1] International Journal of Risk & Safety in Medicine 20:73–81

on paroxetine were attributed to other causes. Where McCafferty's draft reads:

> worsening depression, emotional lability, headache, and hostility were considered related or possibly related to treatment [20],

the published *JAACAP* paper states:

> only headache (1 patient) was considered by the treating investigator to be related to paroxetine treatment.

2. With regard to the follow-up of patients in clinical trials, it is true that physicians are most familiar with patient's medical histories but individual physicians are not in a position to spot emerging patterns of serious adverse events. Do you agree that if a sponsor is able to identify the emergence of a significant adverse event that is possibly related to the experimental drug, it is the duty of the sponsor to inform patients, through physician investigators, of the potential risks?

3. You will have seen the Institute of Medicine's (IoM) Draft *Discussion Framework for Clinical Trial Data Sharing: Guiding Principles, Elements, and Activities.*[2] On page 6 (PDF p.21), we note IoM's query:

> Under what circumstances are identifiable data needed to fulfill articulated purposes of a data sharing activity? Under what circumstances might re-identification of trial participants be beneficial (for the participants or the public)? *Have there been there examples of instances of re-identification of trial participants (e.g., for safety reasons to warn a patient of a potential risk*, or for questionable and potentially unethical reasons) and what were the impacts? (My emphasis)

GSK and its investigators know about the injury to the patients in 329. Would you comment on your responsibility to pursue their current well-being?

We intend to raise this issue in response to the IoM's invitation to offer comments on their paper. If it stimulates debate and the consensus is that in a case like this there is an ongoing duty to inform, who do you think should do so - GSK, or the investigators prompted by GSK?

If GSK were not to take on this responsibility, what is your view about third parties, such as our RIAT team, taking on the duty to inform?

Yours sincerely

Jon Jureidini

On behalf of the Study 329 RIAT team

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[2] http://www.iom.edu/Reports/2014/Discussion-Framework-for-Clinical-Trial-Data-Sharing.aspx