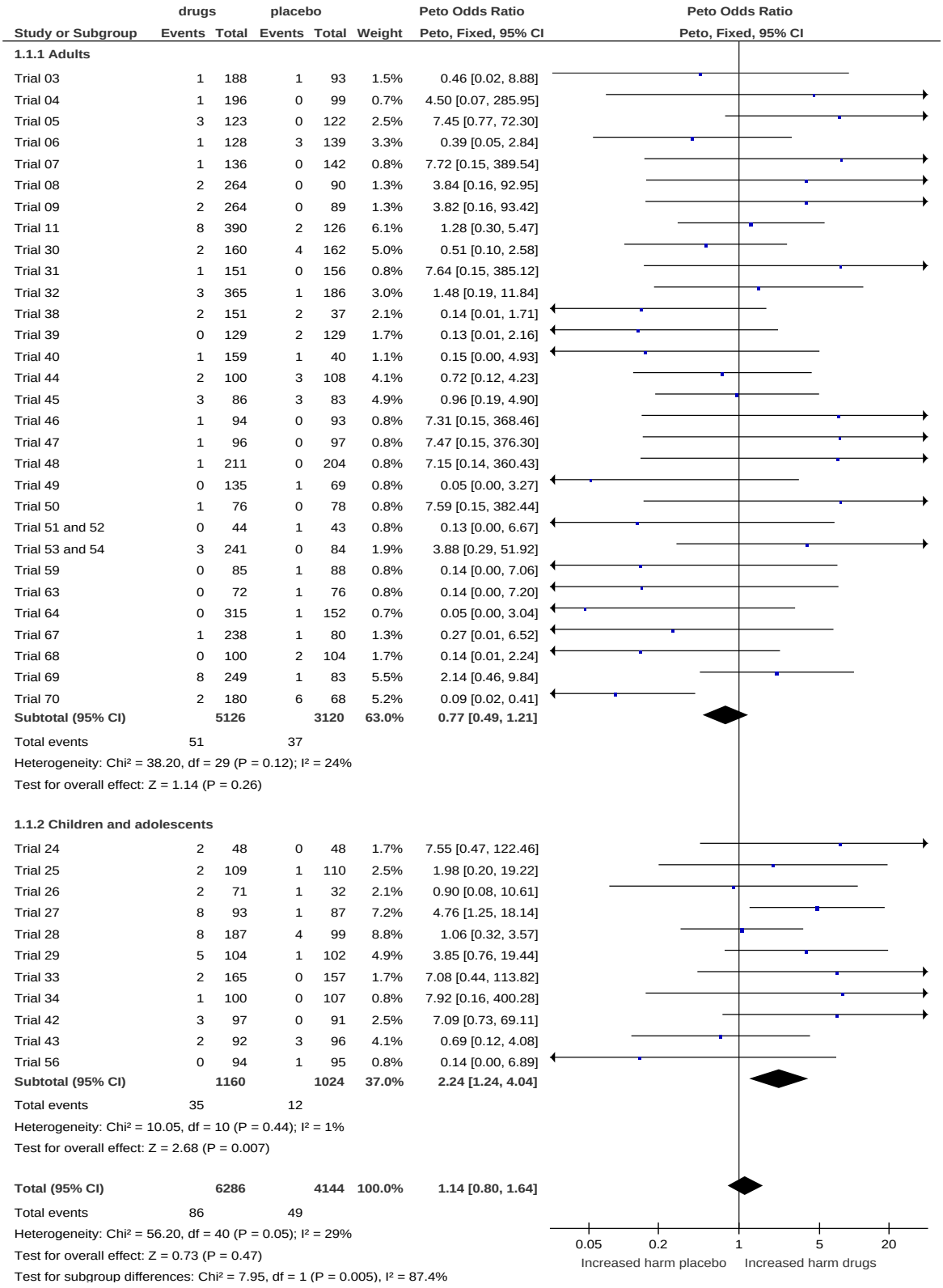
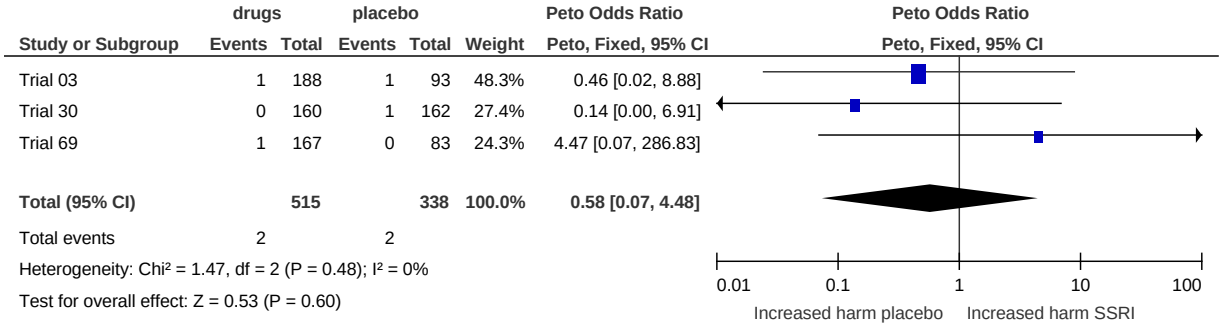
Supplementary Data D: Additional analyses

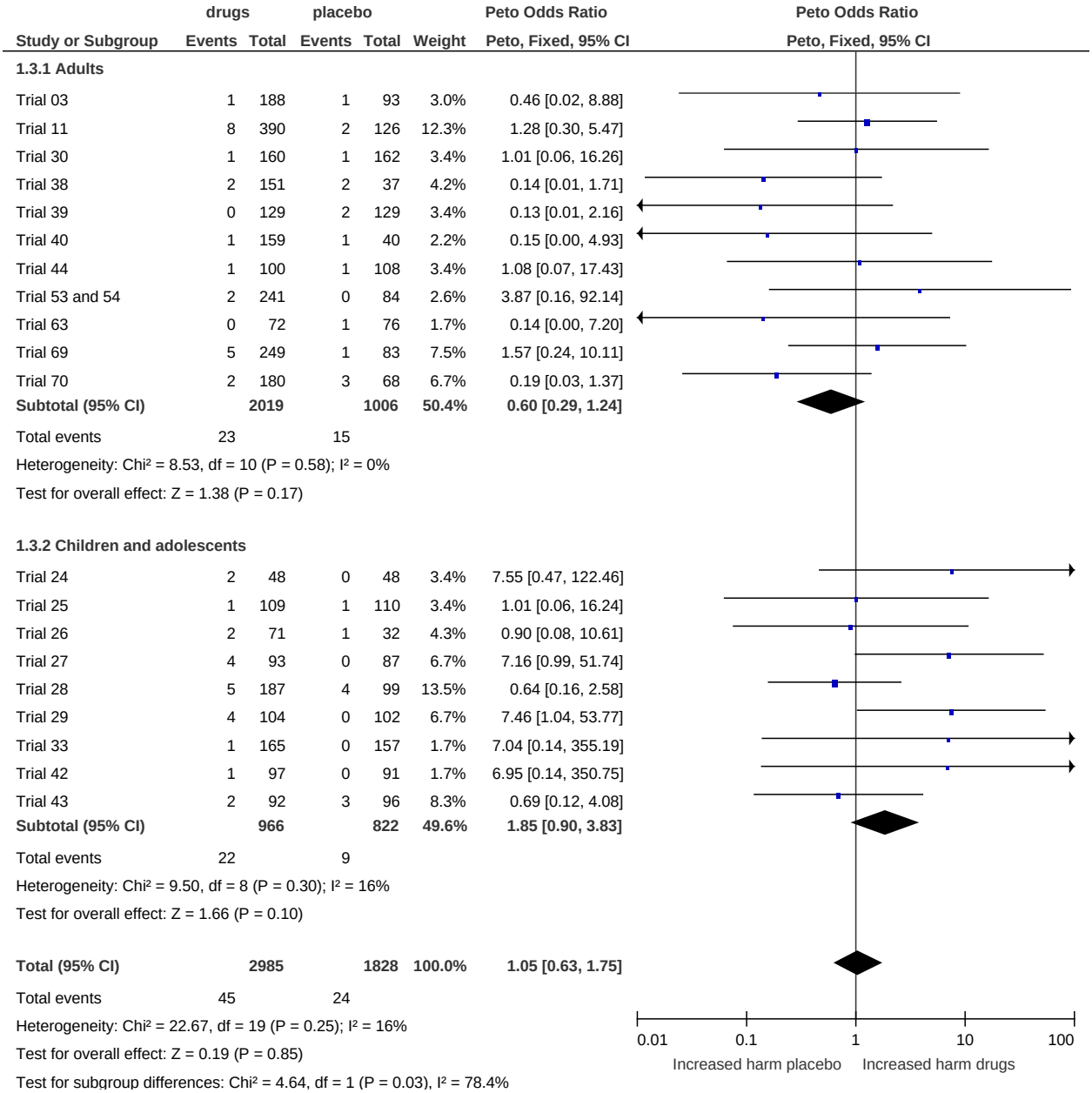
1. Meta-analysis of suicidality events (rather than patients) on SSRIs or SNRIs compared to placebo post randomisation



2. Meta-analysis of suicides on SSRIs or SNRIs compared to placebo post randomisation



3. Meta-analysis of suicides and suicide attempts only (no ideation) on SSRIs or SNRIs compared to placebo post randomisation



4. Fraudulent behaviour:

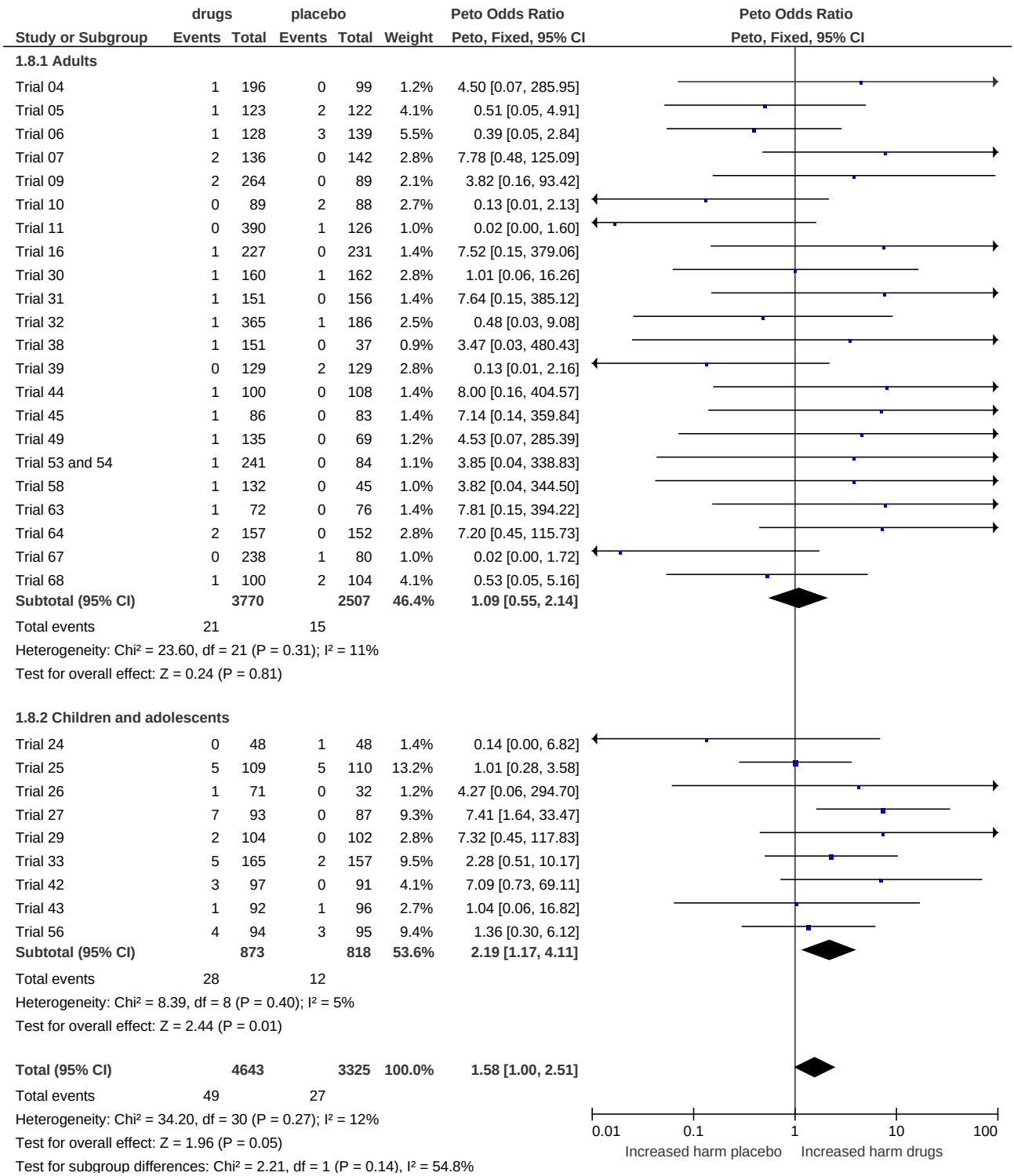
The drug companies had concerns about the validity of the data or fraudulent behaviour in some centres, in 3 trials:

- Trial 28 (paroxetine protocol 377) - The centre identified for fraudulent behaviour was 7. There were no deaths in this trial and none of the 8 patients with suicidality events on paroxetine (centres 9, 11, 30, 42(3), 49, and 53), nor the 4 on placebo (centres 5, 10, 29, 41), were from that centre. This trial also had 3 aggressive behaviour events on paroxetine, but as we did not have the individual data, could not identify which centres they were from.

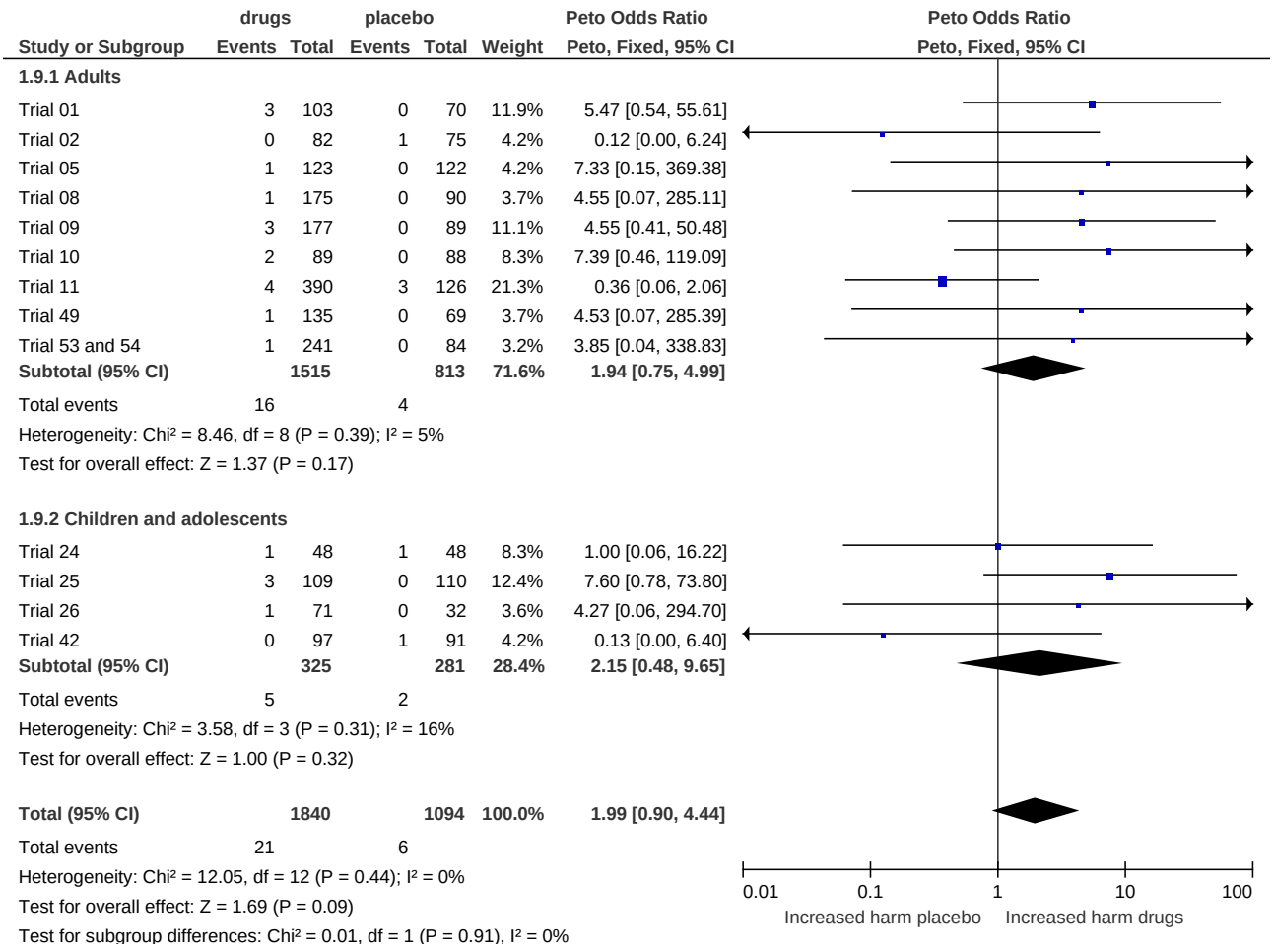
- Trial 34 (paroxetine protocol 704) - The centre identified for fraudulent behaviour was 5. There were no deaths in this trial and the one suicidal ideation event on paroxetine was a patient from centre 33. This trial also had 10 aggressive behaviour events on paroxetine and one on placebo, but as we did not have the individual data, could not identify which centres they were from.

- Trial 70 (venlaflaxine extended release 0600B 1-384-US/EU/CA) - The centres identified for fraudulent behaviour were 33, 34, 35 and 36 and for centres 33, 34, 35 no adverse event data was included: "*Since all source documentation and CRF case books were impounded before patient data could be reviewed, it was determined that only the available adverse event records from these sites would be reviewed for safety. The medical monitor determined that no unexpected adverse events or serious adverse events were identified.*" For centre 36, only efficacy data was not included. Two deaths were noted for this trial but were from centres 66 (imipramine) and 52 (venlaflaxine extended release). There were 6 patients on placebo (centres 20, 23, 25, 37, 46 and 52) and 2 on venlaflaxine extended release (centres 20 and 66) that had suicidality events, so once again not from centres with concerns.This trial also had one akathisia event on venlaflaxine extended release but as we did not have the individual data, could not identify which centre that was from.

4a. Meta-analysis of aggressive behaviour events excluding trials (28 and 34) with fraudulent behaviour



4b. Meta-analysis of akathisia events excluding trial (70) with fraudulent behaviour



5. Comparison of our data with the online summary trial reports on Eli Lilly's website

Drug: duloxetine				
Trial No.	**Trial Name**	**Relevant Outcomes**	**From clinical study report (CSRs)**	**From Lilly website online summary reports**
1.	HMAQa	akathisia	3 events on duloxetine	Missing
2.	HMAQb	akathisia	1 event on placebo	Missing
3.	HMAYa	mortality	2 deaths on duloxetine and 1 on placebo	2 deaths on duloxetine and 1 on placebo also noted
		suicidality	1 suicide on duloxetine and 1 on placebo	1 suicide on duloxetine and 1 on placebo also noted
4.	HMAYb	suicidality	1 suicidal ideation on duloxetine	Missing
		aggressive behaviour	1 event on duloxetine	Missing
5.	HMBHa	suicidality	3 suicidal ideation events on duloxetine	Missing
		aggressive behaviour	1 event on duloxetine and 2 events on placebo	Missing
		akathisia	1 event on duloxetine	Missing
6.	HMBHb	suicidality	1 suicidal ideation event on duloxetine and 3 suicidal ideation events on placebo	Missing

Drug: duloxetine				
Trial No.	**Trial Name**	**Relevant Outcomes**	**From clinical study report (CSRs)**	**From Lilly website online summary reports**
		aggressive behaviour	1 event on duloxetine and 3 events on placebo	Missing
7.	HMBC	mortality	1 death on duloxetine (prior to randomisation)	Missing (report only available from randomisation phase not the 12 week open label treatment with duloxetine)
		suicidality	1 suicide (prior to randomisation) and 1 suicidal ideation event both on duloxetine	Missing (report only available from randomisation phase not the 12 week open label treatment with duloxetine)
		aggressive behaviour	2 events on duloxetine	Missing
8.	HMATa	mortality	1 death on duloxetine	1 death on duloxetine also noted
		suicidality	1 suicidal ideation event on duloxetine and 1 on paroxetine	Missing
		akathisia	1 event on duloxetine	Missing
9.	HMATb	suicidality	1 suicidal ideation event on duloxetine and 1 on paroxetine	Missing
		aggressive behaviour	2 events on duloxetine	Missing
		akathisia	3 events on duloxetine	Missing
10.	HMAH	suicidality	No suicidality outcomes detected. No events noted, as accidental overdoses were not included in our study. From the CSRs we can see that though there were 9 patients with overdoses on duloxetine (5 in the main phase of the trial and 4 additional cases in the extension phase) and 8 on placebo (4 in each phase), they were all accidental *(*e.g. on day 12 a 30 year old female on duloxetine *"took two doses on same day; patient accidently dosed twice in the same day. The first dose was at 19:15 and the second dose was at 21:08. No AE's reported as result)".*	9 patients on duloxetine and 8 patients on placebo took overdoses. The report does not distinguish between accidental overdoses and intentional overdoses. We took the conservative approach and did not include any accidental overdoses in our study.
		aggressive behaviour	2 events on the same placebo patient noted.	2 events on placebo also noted.
		akathisia	2 events on duloxetine	Missing
11.	HMAI	suicidality	8 suicide attempts in 7 patients on duloxetine and 2 on placebo From the CSR we can see that 5 patients on duloxetine had 'suicide attempts' and 2 patients had intentional overdoses listed (with one patient having 2 events). There was 1 intentional injury on placebo and 1 suicide attempt.	Only 2 events of intentional overdose and 4 suicide attempts on duloxetine listed. No events on placebo listed.
		aggressive behaviour	1 event on placebo	Missing
		akathisia	4 events on duloxetine and 3 on placebo	Missing
12.	HMAG	none	No primary nor secondary outcomes detected	2 patients on placebo took overdoses. The report does not distinguish

Drug: duloxetine				
Trial No.	**Trial Name**	**Relevant Outcomes**	**From clinical study report (CSRs)**	**From Lilly website online summary reports**
			No events noted, as accidental overdoses were not included in our study. From the CSRs we can see that the two patients on placebo (64 year old man and 45 year old woman) had accidental overdoses, they both took two tablets instead of one at 12 weeks and 11 weeks respectively.	between accidental overdoses and intentional overdoses. We took the conservative approach and did not include any accidental overdoses in our study.
13.	SBAT	none	No primary nor secondary outcomes detected	None
14.	SAAW	none	No primary nor secondary outcomes detected	None
15.	SAAB	none	No primary nor secondary outcomes detected	None
16.	SBAX	mortality	1 death on duloxetine	1 death on duloxetine also noted
17.	SBAV	none	No primary nor secondary outcomes detected	None
18.	SBAM	none	No primary nor secondary outcomes detected	None
19.	SAAA	none	No primary nor secondary outcomes detected	No summary report available
20.	SAAH	none	No primary nor secondary outcomes detected	No summary report available
21.	SAAI	none	No primary nor secondary outcomes detected	No summary report available
22.	HMBOa	none	No primary nor secondary outcomes detected	No summary report available
23.	HMAW	mortality	1 death on placebo (2 deaths on duloxetine occurred in the extension phase of this trial, for which we did not have a CSR)	2 deaths on duloxetine and 1 on placebo also noted

Drug: fluoxetine				
Trial No.	**Trial Name**	**Relevant Outcomes**	**From clinical study report (CSRs)**	**From Lilly website online summary reports**
24.	X065	suicidality	2 suicide attempts on fluoxetine	2 suicide attempts on fluoxetine also noted
		aggressive behaviour	1 event on placebo	Missing*
		akathisia	1 event on fluoxetine and 1 on placebo	Missing*
25.	HCJE	suicidality	1 suicide attempt and 1 suicidal ideation on fluoxetine and 1 suicide attempt on placebo	Missing
		aggressive behaviour	5 events on fluoxetine and 5 on placebo	Only 2 events on fluoxetine and 5 on placebo listed
		akathisia	3 events on fluoxetine	Only 2 events on fluoxetine listed
26.	HCJW	suicidality	2 suicide attempts on fluoxetine and 1 on placebo	2 suicide attempts on fluoxetine and 1 on placebo also noted
		aggressive behaviour	1 event on fluoxetine	1 event on fluoxetine also noted
		akathisia	1 event on fluoxetine	1 event on fluoxetine also noted

* The online summary report only had a table of solicited adverse events (from a pre-defined checklist) and not unsolicited adverse events.

6. Additional analyses done using Laughren 2006 FDA report[1], Table 30 and Vanderburg 2009[2] study for sertraline

Data source	No of trials	Active sertraline arm		Placebo arm		Crude Relative Risk [95% confidence intervals (CI)]
		Number of episodes	Number of subjects	Number of episodes	Number of subjects	
FDA data from Table 30 Laughren 2006[1], Suicides, Self harm or suicide attempt	66	7	6950	7	6047	0.87 [0.31, 2.48]
Vanderburg 2009[2] Table 2, short-term studies Suicidality codes 1 and 2 (suicides and suicide attempts)	95	5	6561	8	5480	0.52 [0.17, 1.59]
Vanderburg 2009[2] Table 3, all duration studies Suicidality codes 1 and 2 (suicides and suicide attempts)	Not stated	25	10917	14	9006	1.47 [0.77, 2.83]
Gunnell 2005[3] study data as stated in Table 30 Laughren 2006[1] Suicides and non-fatal self-harm	156	24	7169	8	5108	2.14 [0.96, 4.75]

References:

1. Laughren TP. Overview for December 13 Meeting of Psychopharmacologic Drugs Advisory Committee (PDAC). 2006. Available online from: http://www.fda.gov/ohrms/dockets/ac/06/briefing/2006-4272b1-01-fda.pdf [Accessed 22 October 2013]. (Reference 7 in manuscript).
2. Vanderburg DG, Batzar E, Fogel I, et al. A pooled analysis of suicidality in double-blind, placebo-controlled studies of sertraline in adults. *J Clin Psychiatry* 2009;70:674-83. (Reference 39 in manuscript).
3. Gunnell D, Saperia J, Ashby D. Selective serotonin reuptake inhibitors (SSRIs) and suicide in adults: meta-analysis of drug company data from placebo controlled, randomised controlled trials submitted to the MHRA's safety review. *BMJ* 2005;330:385. (Reference 8 in manuscript).