Supplementary Data A: Additional details on methods

Table 1: Glossary of terms from clinical study reports[1-3]

Term	Explanation
Clinical study reports (CSRs)	Clinical study reports (CSRs) are detailed summaries of trial results prepared by the drug industry for submissions to regulatory authorities in order to obtain marketing authorization They can be of any therapeutic, prophylactic, or diagnostic agent conducted in human subjects, in which the clinical and statistical description, presentations, and analyses are fully integrated into a single report.
Adverse events	An adverse event is any undesirable experience associated with the use of a medical product in a patient, which does not necessarily have a causal relationship with this treatment.
Serious adverse event	A serious adverse event as defined by The ICH Guideline on Clinical Safety Data Management, Definitions and Standards for Expedited Reporting is a "any untoward medical occurrence that at any dose: results in death, is life-threatening, requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect."
Adverse event tables	All adverse events occurring after initiation of study treatments are required to be displayed in summary tables. In most cases, it will also be useful to identify in such tables "treatment emergent signs and symptoms" (TESS; those not seen at baseline and those that worsened even if present at baseline). The tables should list each adverse event, the number of patients in each treatment group in whom the event occurred, and the rate of occurrence. Adverse events should be grouped by body system. Each event may then be divided into defined severity categories (e.g., mild, moderate, severe) if these were used. The tables may also divide the adverse events into those considered at least possibly related to drug use and those considered not related, or use some other causality scheme (e.g., unrelated or possibly, probably, or definitely related).
Patient narratives	Patient narratives are brief summaries required by regulatory authorities for certain events such as any deaths, other serious adverse events and other significant events that are of clinical importance (often events that lead to study withdrawal or changes in dose of study medication).
Individual patient listings (IPL)	Individual patient listings (IPL) are lists containing details of events such as patient identifier, the adverse event (preferred term and reported term), duration of the adverse event, severity (for example, mild, moderate, severe), seriousness (serious/non-serious), action taken (none, dose reduced, treatment stopped, etc), and outcome. IPL are also recommended by the authorities for events similar to those for patient narratives, however additionally such lists for all adverse events for all patients are also available (often upon request), and are often placed within appendices.
Appendices	This section is usually at the end of every CSR and should be prefaced by a full list of all appendices available for the study report. The appendices usually should contain the following: protocol and protocol amendments, sample case report form (unique pages only), list of ethics committees, representative written information for patient and sample consent forms, list and description of investigators and other important participants in the study, signatures of principal or coordinating investigator(s) or sponsor's responsible medical officer, listing of patients receiving test drug, randomisation scheme and codes, audit certificates (if available), documentation of statistical and

Term	Explanation
	inter-laboratory standardisation methods, publications based on the study and those referenced in the report, patient listings for efficacy outcomes, adverse events (individual patient listings required), discontinuations, protocol deviations, laboratory measurements, other individual patient listings, case report forms (CRFs) for deaths, other serious adverse events and events leading to withdrawals (required) and any other CRFs submitted.
Case report forms (CRFs)	Case report forms (CRFs) are paper or electronic questionnaires specifically used in clinical trial research to collect data from each participating site, by the sponsor of the clinical trial. All the collected data on each patient participating in the trial are therefore contained and/or documented within the CRF, including individual data on adverse events.

Additional information on methods

The clinical study reports (CSRs) were obtained from the regulatory agencies through the freedom of information request route. We requested the European Medicines Agency (EMA) for all their CSRs for all trials they had for paroxetine, fluoxetine, sertraline, citalopram, escitalopram, mirtazapine, venlafaxine, and duloxetine, from their archives. We were then informed that they did not have any documents for fluoxetine and those were available from the UK's Medicines and Healthcare products Regulatory Agency (MHRA), so we requested the CSRs for fluoxetine from them. However, we could not get access to CSRs for all trials for all the commonly prescribed drugs we had requested. We also did not receive any case report forms (CRFs) for any of the trials.

We received in total 198 CSRs but these included a number of open-label studies, healthy volunteer studies and cross-over studies. We only included double-blind placebo controlled trials and then further excluded CSRs of trials where we had no detailed information (patient narratives nor individual patient listings) at all, even for serious events or events leading to discontinuation or change of dose of medication. We excluded these trials as we felt that they would not give us any added benefit of using CSRs, because there would be no additional information regarding our outcomes of interest.

The CSRs were first obtained as scanned PDF documents, but once converted to a readable format using the 'optical character recognition (OCR)' function of Adobe Acrobat XI Professional they could be searched electronically. As a pilot, one report for each drug was randomly chosen and read in its entirety to help understand the different formats of the CSRs and to refine the data extraction form. We had planned that the second observer would extract the data blindly, with the treatment groups masked, but the pilot showed that the format and the language used within the CSRs made blinding impossible.

Search terms

The search terms we used for the primary outcomes of all cause mortality and suicidality were informed by the search strategy developed and used by the FDA[4,5]. The terms for suicidality were quite broad and all search results were verified manually and only confirmed as relevant when the full context and case was read.

For the secondary outcomes the terms for aggressive behaviour were informed by the pilot study and for akathisia we only used the term "akathisia". This was because our pilot showed that unless akathisia was a serious adverse event or one that led to discontinuation, we would not have any patient narrative or the verbatim terms. So if we had only the coded terms (which we expected would be the case for most of the trials), akathisia could be coded as 'hyperkinesia' or other activation terms but not all hyperkinesia events or activation events would necessarily have been akathisia. We felt that we would take the conservative approach and only consider terms where "akathisia" was noted as such. This would of course mean that our

numbers would be under-estimates but we would not have wrongly attributed some events as akathisia, if they were not.

Moreover, the pilot showed that electronically searching alone could not always be trusted (sometimes a space was inserted within a word or an additional letter was registered by the recognition software incorrectly) and relevant synonyms could also be missed. We therefore started with the electronic searches using the defined search terms but then also went through the documents manually to ensure we did not miss any relevant outcomes (except for akathisia as no synonyms were considered) or had picked up irrelevant cases by mistake. It was incredibly laborious but after our pilot we felt this extra step was needed.

Table 2: Terms used for identifying relevant data for the primary and secondary outcomes from CSRs for extraction; the terms were searched through the search function on Adobe Acrobat XI Pro and then any synonyms were identified manually

Primary outcomes	**Search terms**
All cause mortality	death; died
Suicidality	accident; attempt; burn; cut; drown; gas; gun; hang; hung; immolation; injury; jump; monoxide; mutilation; overdose; poison; self damage; self harm; self inflict; self injury; self mutilation; shoot; suicide; suicidal ideation; suicidal thoughts; thoughts of killing one's self; asphyxiation; suffocation; firearm
Secondary outcomes	**Search terms**
Aggressive behaviour	aggression; aggressive behavior; assault; criminal behaviour; damage to property; homicide; homicidal threat; homicidal ideation; hostility; increased anger; increased rage; physical abuse; physically threatening behaviour
Akathisia	akathisia

References:

(1) Wieseler B, Wolfram N, McGauran N, Kerekes MF, Vervolgyi V, Kohlepp P et al. Completeness of Reporting of Patient-Relevant Clinical Trial Outcomes: Comparison of Unpublished Clinical Study Reports with Publicly Available Data. PLoS Med 2013; 10(10):e1001526.

(2) Maund E, Tendal B, Hróbjartsson A, Jørgensen KJ, Lundh A, Schroll J et al. Benefits and harms in clinical trials of duloxetine for treatment of major depressive disorder: comparison of clinical study reports, trial registries, and publications. *BMJ* 2014; 348:g3555.

(3) Structure and content of clinical study reports: E3. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, 1995. Available from www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E3/E3_Guideline.pdf [Accessed 10 August 2015].

(4) 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].

(5) Stone M, Laughren T, Jones ML, Levenson M, Holland PC, Hughes A et al. Risk of suicidality in clinical trials of antidepressants in adults: analysis of proprietary data submitted to US Food and Drug Administration. *BMJ* 2009; 339.