

## PROTOCOL

### Prospective protocol registration and selective outcome reporting in recent psychiatry trials: new antidepressants and cognitive-behavior therapies

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#### **Background**

Full reporting of research studies is of paramount importance for the correct interpretations of their results by the patients, clinicians, researchers and policy makers. It is not only a scientific but ethical obligation of the medical profession as stipulated in the Declaration of Helsinki: “Authors have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports.”

Accumulated and accumulating evidence reveals, however, that the reality is far from this ideal. First, studies themselves can remain unpublished, unavailable and unknown. Study publication bias occurs when the publication of research results depends on their nature and direction (Begg et al. (1989), (Dickersin 1990, Song et al. 2010). More than two decades after the problem was first pointed out, 31% of the pre-approval trials of antidepressants were unpublished (Turner et al. 2008), as were 17% of antipsychotic trials (Turner et al. 2012), as were 20% of pharmacological intervention trials for acute stroke (Gibson et al. 2010). Alarming enough, of all FDA-approved drugs in 1998-2000 the probability of the trials being published was less than 50% even more than 5 years post-marketing (Lee et al. 2008). It is not surprising that most of the unpublished trials were negative in contradistinction to the published positive trials (Turner et al. 2008). Second, when studies are published at all, their outcomes can be hidden, changed and/or “spin” to embellish the reports. The influence of selective outcome reporting looks subtle but is arguably more far-reaching and serious than study publication bias per se. In one of the landmark studies of outcome reporting bias, Chan et al. compared protocols of 102 randomized controlled trials (RCTs) with their published reports and showed 62% (51/82) of trials had inconsistencies between primary outcomes in protocols and those in published reports (Chan et al. 2004). Even when studies are identified in systematic

reviews, selective reporting of primary outcomes may magnify the pooled effect size by more than 50% (Furukawa et al. 2007).

Academia has not remained passive and silent against the very biases that seriously undermine its own credibility (Ioannidis 2005, Ioannidis 2008). First, trial registration was proposed and then mandated. In 2000, one of the most common registry web sites, [clinicaltrials.gov](http://clinicaltrials.gov), was opened to the public. In 2004, International Committee of Medical Journal Editors (ICMJE) advocated a policy that they require clinical trials starting after July 2005 to be registered before the enrollment of its first participant (De Angelis et al. 2004). Second, registration of not only the trial itself but also its details, especially its pre-designated primary outcomes, and eventually its results are now recommended. For example, as a result of the Food and Drug Administration Amendments Act of 2007 (FDAAA), not only registration but also submission of basic results is now mandatory for certain trials. Third, guidelines for fuller and more informative reporting of clinical trials have been published, required, updated, and expanded (Begg et al. 1996, Moher et al. 2001, Boutron et al. 2008, Schulz et al. 2010).

Unfortunately the more recent studies reveal that these human efforts have been only partially successful. Despite the advances in trial registration, quality of registered information in terms of timing and completeness is still not adequate. For example, a cross-sectional survey of clinical trial registries revealed that only 36% of trial registries did not provided primary outcome measures in registry entities (Zarin et al. 2011). Another study showed fewer than 50% of trials were registered before study start day (Califf et al. 2012). With regard to reporting of trials, a comprehensive review has concluded that endorsement of the CONSORT statement may have had beneficial influence on the completeness of reporting, which however still remains sub-optimal (Turner et al. 2012). A recent systematic review concluded 40-62% of studies had primary outcome discrepancies between the protocols and published reports (Dwan et al. 2013).

It is now increasingly recognized that the extent and magnitude of publication and related biases may be different for different types of studies and for different clinical disciplines (Nankervis et al. 2012, Hannink et al. 2013). Within psychiatry, two studies have examined trial registration and outcome reporting bias. Tyler et al. (Tyler et al. 2011) assessed the prevalence of multiple outcomes in depression RCTs which were published in six top medical and psychiatry journals in 2007 and 2008. In their study, they showed 76% (42/55) of trials had published protocols, and many trials reported a

greater number of outcomes in the published reports than in the protocols. Milette et al (Milette et al. 2011) examined 63 published articles in four selected psychosomatic and behavioral journals from 2008 to 2009. Although they had planned on assessing outcome reporting bias, they could not do so because they found only one trial which was appropriately registered with enough information to be compared with the published report.

Unfortunately these two studies fall short of characterizing the current state of trial registration and outcome reporting in the field of psychiatry. First and foremost, both studies were conducted only a few years after ICMJE requirement of trial registration, and therefore it may have been too early to detect the influence of ICMJE statement. Second, both of these two studies analyzed trials of a wide range of interventions together (e.g Tyler's included trials of pharmacotherapy, parenting program, dynamic psychotherapy and repetitive transcranial magnetic stimulation, while Milette's included relaxation training, exercise, CBT trials) and can therefore probably be said to represent the average in this respect. However neither had enough statistical power to differentially examine variations within the field. For example, adequate registration has been pointed out to be rare in non-drug trials but it was impossible to examine such differences.(Pinto et al. 2013) Lastly, both studies included only top journals, and thus the prevalence of adequate registration and outcome reporting bias in the field of psychiatry at large remains unknown.

The contrast between pharmacological and psychological interventions may be particularly pertinent to our field. In drug trials publication bias was often discussed in association with funding sponsors (Turner et al. 2008, Eyding et al. 2010). On the other hand, in psychotherapy trials the existence of publication bias was also reported, (Watanabe et al. 2007, Cuijpers et al. 2010), but researchers' interest and allegiance appear to play a major role (Cuijpers et al. 2010). Additionally, quality of trials and quality of their reporting may be a bigger problem in psychotherapy trials than in pharmacotherapy trials (Cuijpers et al. 2010, Thoma et al. 2012).

To the best of our knowledge, no study to date has investigated trial registration and outcome reporting bias among drug and psychotherapy trials. Given the potential influences of the target clinical conditions on the quality of trials in the area, it would be also very important to focus on the same mental illness in order to appreciate the possible differences between two interventions. Our study therefore aims to evaluate registration

and outcome reporting bias in trials of depression treatments by examining reports of RCTs that used cognitive behavioral therapy (CBT) or new generation antidepressants published in any journal.

We chose depression because it is one of the common mental illnesses and many trial reports have been published. In this study, we decided to focus on the two treatments because we want to exclude effects caused by trials of other non-standard intervention, (e.g. repetitive transcranial stimulation on one hand or complementary and alternative medicine on the other). We chose CBT and new generation antidepressants because both have been widely used since 1980's, have almost the same length of research and clinical history, and constitute well-established commonly used treatments recommended by national guidelines (NICE 2009, APA 2010). The objectives of the current study are therefore:

1. To evaluate what proportion of trials which examined efficacy/effectiveness of CBT or new generation antidepressants for depression were appropriately registered, i.e. before patient enrollment with specified primary outcomes.
2. To evaluate what proportion of trials which examined efficacy/effectiveness of CBT or new generation antidepressants for depression reported primary outcomes in trial reports as specified in the protocols or registry entities.
3. To examine predictors of outcome reporting bias, including the difference between CBT and antidepressants

## **Methods**

### **Inclusion and exclusion criteria of trial reports**

- Types of study design

We will include all RCTs (parallel or cross-over design) which used CBT or new generation antidepressants as treatment for depression. We will exclude secondary analyses, duplications. If several trials reports were published from the same trial data set, we will only include the trial report that reported on the efficacy of the treatment for depressive symptoms at the end of the treatment.

Meta-analysis, unpublished reports, conference abstracts and dissertations will be excluded. Trials that had started before July 1, 2005 when ICMJE required trial registry prior to patient enrollment will be excluded.

- Types of participants

We will include trials targeting people with clinically diagnosed depression. Diagnosis

should be made using research diagnostic criteria or validated depression symptom questionnaire such as Hamilton depression scale (HAM-D).(Hamilton 1960) Trials focused on anxiety and depressive disorder will not be included. For example, trial recruited patients with either depressive or anxiety symptoms will be excluded.

Trials aimed to improve specific symptom related to depression (e.g. insomnia in depression) or comorbidity with depression (abstinence in depressive alcoholic people) will also be included. Trials of relapse prevention will also be included. However, trials in which it took more than two years from patient enrollment to assessment of primary outcomes will be excluded because those studies need longer time for implementation than other types of studies, and five years from ICMJE statement may be short to assess those studies.

- **Types of intervention**

We will include trails of CBT if the authors described they used intervention based on the cognitive-behavioral model. As new antidepressants we will include: agomelatine, bupropion, citalopram, desvenlafaxine, duloxetine, escitalopram, fluoxetine, fluvoxamine, milnacipran, mirtazapine, paroxetine, reboxetine, sertraline, venlafaxine or vilazodone.

In addition to trials that compared CBT or new antidepressants with other intervention, we will also include trials of combination therapies using them. However, when we compare CBT trials with antidepressants trials, we will exclude trials that are difficult to classify as CBT or antidepressants trial. For example, trials included head-to-head comparison of CBT with antidepressants or examined efficacy of a combination therapy of CBT with antidepressants will be excluded in this analysis. We will exclude trials that used CBT or antidepressants arm only as a control.

### **Searching for trials**

We will search CENTRAL (Cochrane Central Register of Controlled Trials) in January 2014 to identify all published reports of randomized controlled trials (RCTs) published from 2011 to 2013 that examined the efficacy of CBT or new generation antidepressants for depression.

The search terms will include (depress\* or dysthymi\* or "adjustment disorder\*" or "mood disorder\*" or "affective disorder\*"), and (therap\* or psychotherap\*) or (Antidepressive Agents or agomelatine or bupropion or citalopram or desvenlafaxine or duloxetine or escitalopram or fluoxetine or fluvoxamine or milnacipran or mirtazapine or paroxetine

or reboxetine or sertraline or venlafaxine or vilazodone) in title abstract keywords. (See Appendix1)

### **Trial selection**

One investigator (KS) will examine titles and abstracts of all publications and select eligible trial reports. Other authors will reassess the excluded trial reports to make sure no candidate report is excluded. Any disagreement will be resolved through discussion or consulting a third author. We will apply no language restrictions.

### **Finding registry or protocol**

If trial report provided information of protocol or registry like registration number, we will use it to retrieve the protocols or the registry entities. When there was no such information in trial report, we will send e-mail to the corresponding author at least two times after an interval of two weeks. In case that we receive no response from the author, we will search clinical trials registries on the World Health Organization Registry Search Portal : International Clinical Trials Registry Platform (ICTRP) web site

If no protocol or registry entity is found after this procedure, the trial will be classified as “not registered” trial.

### **Data extraction from trial reports**

From published reports, we will extract all primary outcomes and secondary outcomes (including efficacy and harm outcomes). We will not set a limit on the number of primary outcomes, but we will conduct a sensitivity analysis excluding trials with multiple primary outcomes. If the primary outcomes were not explicitly declared in publication, we will define outcomes used for sample size calculation as their primary outcomes. When the study neither identified their primary outcome nor provided sample size estimation, the trials will be considered as “trials reporting no primary outcome in publication” and it will be included “not reporting as pre-specified trial” category even if the trial was registered. Also we will extract the results of primary outcomes in trial reports and classify them as “statistically significant results” or “non-significant results” according to the authors’ judgment. If they showed more than one primary outcomes in trial report, we will choose the one which came first in the text. In addition to those items, total sample sizes, funding sources, journal names, number of arms will be extracted. All data extraction will be conducted by two authors independently.

### **Data extraction from registry**

From trial registration we will extract timing of registry, the study start day, all primary outcomes, secondary outcomes, study sponsors and collaborators. If trials were registered after commencement of patient enrollment, we will not conduct further assessment about them.

We will define trials as “properly registered” trials if they were registered before patient enrollment with specified primary outcome. We decided registry entities should have information of how they measure primary outcomes (e.g. HAM-D, dropout rate) to considered having specified primary outcome. In other words, we will not require time-point of assessment because treatment effect is generally assessed at the end of treatment in depression trials. Therefore, if registry entity did not state time-point of assessment of primary outcome, we will assume they had planned to measure the outcome at the end of the treatment.

In “properly registered trials”, we will check whether they reported primary outcomes in published reports as specified at registry. If the primary outcomes in published reports were the same as registry entities, we will classify them as “reporting as pre-specified” trials. When trial had any primary outcome discrepancy meeting the pre-specified criteria (See table 1) (6), we will classify them as “not reporting primary outcome as pre-specified” trials.

We will calculate proportion of registered trial and “properly registered” trials in all included trials, CBT trials, and antidepressants trials. Also odds ratio for “reporting primary outcomes as pre-specified” will be calculated about all “properly registered” trials, “properly registered” CBT trials, “properly registered” antidepressants trials. In addition, odds ratio for “reporting as pre-specified” will be calculated about trials with “statistically significant results” and those with “non-significant results”.

### **Outcomes (See table2)**

#### Primary outcomes

1. Trials which reported primary outcomes in publication as pre-specified at registry.
  - 1-1. Proportion of trials which reported primary outcome as pre-specified in all included trials
  - 1-2. Proportion of CBT trials which reported primary outcome as pre-specified in included CBT trials

1-3. Proportion of antidepressants trials which reported primary outcome as pre-specified in included antidepressants trials

#### Secondary outcomes

2. Trials registered before patient enrollment with specified primary outcomes: “properly registered” trials

2-1. Proportion of “properly registered” trials in all included trials

2-2. Proportion of “properly registered” CBT trials in included CBT trials

2-3. Proportion of “properly registered” antidepressants trials in included antidepressants trials

3. Trial registry

3-1. Proportion of registered trials in all included trials

3-2. Proportion of registered CBT trials in included CBT trials

3-3. Proportion of registered antidepressants trials in included antidepressants trials

4. Association between statistically significant results and “reporting outcomes as pre-specified” (We will calculate this in efficacy outcomes and harm outcomes separately)

4-1. Odds ratio for “reporting outcomes as pre-specified” between trials with statistically significant outcomes and that with non-significant outcomes in all properly registered trials (See table3)

4-2. Odds ratio for “reporting outcomes as pre-specified” between trials with statistically significant outcomes and that with non-significant outcomes in all properly registered CBT trials

4-3. Odds ratio for “reporting outcomes as pre-specified” between trials with statistically significant outcomes and that with non-significant outcomes in all properly registered antidepressants trials

5. Trials which were registered before patient enrolment with fully specified primary outcomes enough to prevent post hoc choice of specific metric or method of aggregation(Zarin et al. 2011): including specific measurement, specific metric, and method of aggregation and time point (e.g. proportion of participants with 50% or greater reduction on HAM-D at three months).

#### Sensitivity analysis

1. Excluding trials that did not use operationalized diagnostic criteria: We assume that

trials of CBT are more likely to target subthreshold depression than those of antidepressants, and it will influence the results.

2. Including only trials focused on the treatments for acute phase of major depression
3. Excluding trials with multiple primary outcomes. In this analysis, we will exclude trials with more than one efficacy primary outcomes and more than one harm primary outcomes. In other words, we will include trials if they had one efficacy primary outcome or one harm primary outcome or “one efficacy primary outcome and one primary harm outcome”.

### **Subgroup analysis**

We will conduct subgroup analyses about the following factors because previous studies suggested association between those factors and proper registration and selective reporting of outcomes. (Mathieu et al. 2009, Milette et al. 2011, Tyler et al. 2011, Pinto et al. 2013)

1. Funding source: Industry/ all other sources (NIH, individual, University etc.) / unknown
2. Center: Multi centers/ single center
3. Sample size: (50<, 50-100, 100-400, 400<)

We will use almost the same categories used in the previous survey of depression trials, (Tyler et al. 2011) but add a category of less than 50 patients because CBT studies seem to have smaller sample size than antidepressant trials.

4. Impact factor: High impact factors journals /other journals

We will select journals with the top ten highest impact factors in general medicine and similar impact factors in psychiatry and psychology based on Journal Citation Report in 2012. (the New England Journal of Medicine, Lancet, Journal of the American Medical Association, British Medical Journal, PLOS Medicine, Annals of Internal Medicine, Archives of Internal Medicine, BMC Medicine, Canadian Medical Association journal, Journal of Internal Medicine, Molecular Psychiatry, American Journal of Psychiatry, Archives of General Psychiatry, Biological Psychiatry, World Psychiatry, Neuropsychopharmacology, Schizophrenia Bulletin, Psychotherapy and Psychosomatics, Journal of the American Academy of Child and Adolescent Psychiatry, the British Journal of Psychiatry, the Journal of Psychiatry and Neuroscience, Psychological Bulletin, the Annual Review of Psychology, Annual Review of Clinical Psychology, Psychological Review )

In addition to them, we will search for other factors that may contribute to proper

registration or outcome reporting bias.

5. Country / Continent where the trial took place
6. Number of arms: We expect if trial compared more arms, it is easier to introduce favorable primary outcome in publication which was not specified at registry.
7. Focusing on comorbidity or not: We hypothesize that trials focusing on physical or mental comorbidities with depression (e.g. depression among people with Parkinson's disease) were different from those targeted general depressive patients in terms of research background.
8. Protocol or registry entities: We expect that trials properly registered with published protocols will be more adhere to their protocols than trials properly registered without published protocol. In this subgroup analysis, we will only compare proportion of “reporting outcomes as pre-specified” in “properly registered” trials.
9. Endorsement of ICMJE by the journal

### **Statistical analysis**

Fisher's exact test will be used to test association between types of studies (CBT or antidepressants) and proportion of proper registry trials or trials “reporting as pre-specified” in publication. Statistical tests will be performed using SPSS statistics 22. The level of significance is set at conventional  $p < 0.05$  (two-tailed).

If there is a statistically significant difference between CBT and antidepressants trials in terms of proper registration and full reporting, we will conduct further analysis to assure the existence of difference after adjusting for other possible cofounders.

### **Appendix1**

#1 'therap\* or psychotherap\* in title abstract keywords and (depress\* or dysthymi\* or "adjustment disorder\*" or "mood disorder\*" or "affective disorder\*") in title abstract keywords from 2011 to 2013 in Trials'

#2 Antidepressive Agents or agomelatine or bupropion or citalopram or desvenlafaxine or duloxetine or escitalopram or fluoxetine or fluvoxamine or milnacipran or mirtazapine or paroxetine or reboxetine or sertraline or venlafaxine or vilazodone in title abstract keywords and (depress\* or dysthymi\* or "adjustment disorder\*" or "mood disorder\*" or "affective disorder\*") in title abstract keywords from 2011 to 2013 in Trials'

#1 or #2

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