# WHAT'S IN OUR FILE DRAWERS?

## Trial pre-registration and reporting consistency in eMental health: preliminary results

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## BACKGROUND

In the wake of many failed replications of well-known studies, the field of psychology is undergoing a transformation. To reduce and prevent 'sloppy science', researchers increasingly focus on transparency and methodological rigour to increase the reproducibility and trustworthiness of the literature.

For randomised controlled trials (RCTs) specifically, pre-registration of RCTs is recommended or demanded by many academic journals. Failure to do so leaves the door open to all sorts of bias, from unintended failure to report outcome measures to questionable research practices (QRPs) to research misconduct. For example, pre-specification of outcome measures aims to prevent selective outcome reporting, in which a researcher could claim to have found significant effect X, but in fact was looking for Y. If researchers give a short description of the study, specify the general hypotheses of the study, its primary and secondary outcomes, the anticipated number of participants and a general timeline, it is difficult to change hypothesis or outcomes if these did not show the results the researcher was looking for.

In 2005, the ICMJE issued a guideline in that recommends, among other things, prospective pre-specification of primary and secondary outcome measures in trial registries. Full compliance with these guidelines is reported by the Journal of Medical Internet Research and the Journal of Telemedicine and Telecare. Internet Interventions does not explicitly state compliance to ICMJE standards with regards to trial registration; but refers to its parent company Elsevier who states a noncommittal 'authors are expected to conform to industry best standards in clinical trial registration and presentation'. At the time of writing, Telemedicine and e-Health had no statement on ICMJE compliance.

As eHealth publications find their way in a large variety of generic, biomedical or psychology journals; with differing expectations, guidelines and standards, investigating trial registration and outcome reporting in eMental Health studies is easier in a "bottom-up" approach, starting from trial protocols and finding registration and reporting compliance from there.

The aim of this study was therefore to investigate trial pre-registration and subsequent outcome reporting in Internet-based interventions for diagnosed anxiety and depression. These results are part of a larger, ongoing project to track registration and subsequent publication of registered trials for Internet-based interventions for anxiety and depression.

## METHODS

We searched publicly accessible databases (e.g., WHO-ICTRP, ClinicalTrials.gov) and included protocols evaluating eHealth interventions focusing on mood and/or anxiety disorders. Inclusion criteria were; (i) tested the efficacy of an Internet-based psychological; (ii) for a diagnosed mood/anxiety disorder; (iii) the trial was registered before Jan 2016 (to prevent retrieving too many unfinished trials).

We extracted the number and nature of primary and secondary outcomes, anticipated and reported sample sizes and means and effect sizes, and compared these to the peer-reviewed, published journal articles for those study protocols.

The following information was independently extracted and coded:

- Switching of outcomes: prespecified primary outcome measures demoted to secondary outcome measures in the published paper or vice versa;
- Outcome insertion: new primary outcome measures not prespecified in the trial registration were inserted in the published paper;
- Outcome removal: a prespecified outcome measure was not reported in the published paper;

Additionally, the following information was coded:

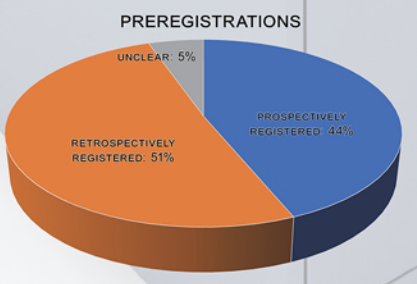
- Whether the trial was prospectively registered or retrospectively registered (if a trial was registered before the first participant entered the trial, it is deemed to be prospectively registered according to ICMJE criteria);
- The anticipated sample size and actual randomised sample size reported in the published paper;
- The number and nature of primary and secondary outcomes.

## RESULTS

### PREREGISTRATION

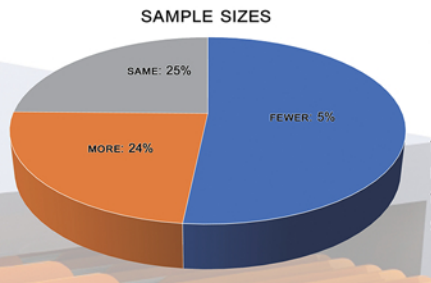
Of the 112 trial registrations processed so far, 89 had been published, and 23 were either still recruiting, awaiting follow-up, or completed but unpublished. Of these 23 registry entries, 13 had a published study protocol.

A minority of trials (N=49, 44%) were prospectively registered (i.e., registered before first patient enrolment), and 51% of trials were retrospectively registered. Six trials (5%) were recorded as 'prospectively registered', but information on recruitment in the published paper showed that these had probably been retrospectively registered, and were therefore marked as 'unclear'.




### SAMPLE SIZES

Sample size is an important parameter in trials, and it is usually informed by a power calculation based on an expected effect size on a prespecified primary outcome measure. Recruiting too few (or losing too many) participants can mean a trial is underpowered to detect the expected effect. Only one prospectively registered trial randomised the anticipated number of participants.

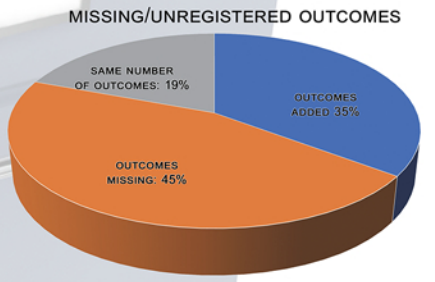



83% of registered trials showed a discrepancy between the anticipated sample size and actual randomised (not enrolled) participants. On average, prospectively registered trials randomised 33% fewer participants than anticipated, retrospectively registered trials were 52% off. On top of this, many trials have high drop-out rates, effectively lowering statistical power even more.

### OUTCOME DISCREPANCIES

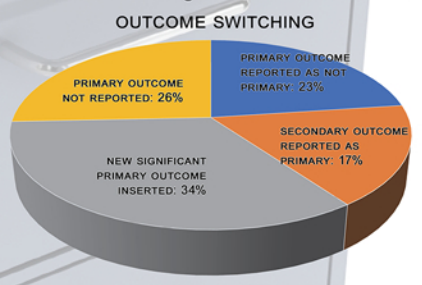
Outcome measures of clinical trials are not set in stone. However, to prevent the "Texas Sharpshooter" fallacy, or p-hacking, all prespecified outcomes should be reported; usually one or more primary outcomes and a number of secondary outcomes are prespecified. Although a deviation from these prespecified outcomes is not always avoidable, this can be problematic, especially if many (primary) outcomes are omitted or inserted.

Of all trials assessed up to now, 37 (42%) showed a discrepancy in the number of prespecified outcomes vs. the number of reported outcomes, meaning that outcomes were either added or removed. For retrospectively registered trials the numbers were more favourable: possibly because they were registered with hindsight after the trial had been concluded.




### OUTCOME SWITCHING

Apart from an absolute difference in number of outcomes, we also looked at outcome switching. This is perhaps the most serious issue with trials, as a researcher can essentially pick and choose a favourable result as being '*the* primary outcome measure' from any range of measured outcomes (prespecified or not). Cherry-picking of outcomes leads to inflated effect sizes and therefore biased estimates of treatment effects. Despite preregistration, outcome switching was common in the trials assessed so far.




46 out of 88 trials (46%) showed evidence of some kind of outcome switching. Of these 46 trials, 34% reported one or more new, statistically significant primary outcome measure(s) that had not been prespecified in the trial protocol. 26% omitted one or more prespecified primary outcome measures, and 27 out of these 46 trials (59%) showed more than one discrepancy in outcomes.

## IMPLICATIONS

### CONCLUSION

Despite best intentions and editorial guidelines (e.g., ICMJE guidelines, CONSORT-eHealth, trial registration and reporting in eMental Health is suboptimal. Given the relatively low proportion of truly prospectively registered trials and the high prevalence of missing, inserted, or switched outcomes; it seems that the importance or relevance of trial preregistration has not been fully appreciated by authors, reviewers and editors.

*Limitations:* the data presented here are an incomplete representation of the entire dataset. Since a number of trial protocols could not be traced using the trial protocol number, or trial protocol numbers for registered trials were not mentioned in published papers; matching published papers with on protocol numbers is a time-consuming task, often relying on help from the original authors (that might be you!).

### PRACTICAL IMPLICATIONS

To improve the literature and evidence base of eMental Health, a number of recommendations can be made:

- Retrospective registration of RCTs - especially after patient enrolment is completed - is next to useless and should be discouraged.
- Risk of bias assessments in meta-analyses and systematic reviews underestimate the risk of selective outcome reporting if trial protocols are not searched in detail, as per Cochrane recommendations.
- Reviewers should routinely ask for, and cross-reference, trial protocols when reviewing outcome papers of RCTs. Deviations from protocol happen – but they should be described in the interest of full disclosure.
- Journal editors should either adopt preregistration guidelines, or enforce existing standards in collaboration with reviewers.

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