Editorial

Is there any hope that we can reduce research wastage and prevent publication bias?

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In order to fulfil the ethical contract between researchers and the participants of research, trial results need to be disseminated. Patients and carers have identified publication and dissemination as one of the key areas of research wastage that they are concerned about (1). Research wastage is also of concern to public funders with an analysis looking at 9 years of EU-funded health projects with a resultant wastage of 570.2 million euros resulting in no detectable academic output (2).

One of the most concerning consequences of research wastage is the impact on the available evidence base. We have been aware for a long time that research is more likely to be published if reporting favourable results (3-5). If the evidence base only consists of favourable trials, whilst those trials that have reported inconclusive or even unfavourable results remain unpublished, then bias is possible, and this is known as publication or reporting bias (6).

In response to the concerns about publication bias, researchers, publishers, funders and ethics committees have tried through various means some regulatory and others self-regulatory to address this problem. The most widely recognized of these strategies is the requirement that all clinical trials are prospectively registered in order to be published. In 2004 a statement of intent was published by the International Committee of Medical Journal Editors (ICMJE) (7), the journals belonging to this group agreed to require trial registration as mandatory for any trial conducted after July 1, 2005. Trials had to be registered on any of the primary registries of the World Health Organizations International Clinical trials Registry Platform (WHO-ICTRP, https://www.who.int/ictrp/en/). The purpose of trial registration is to have a publically accessible record of all clinical trials. This allows patients and researchers alike to be aware of all the trials that are being or have been conducted within research areas.

A recent systematic review published in *BMC Medicine* by Trinquart *et al.* (8) has looked at the success of registration as a means of tracking clinical trials. Unfortunately, this review was not able to show that clinical trial registration to date has been successful. The review included 40 studies that had examined the rate of trial registration in randomised controlled trials (RCTs) across various clinical areas. Overall 8,773 RCTs were included within these 40 studies with an overall proportion of only 53% (CI: 44–58%) having being registered (8). On a more positive note, trial registration is actually increasing with the rate of registration increasing from 25% in 2005 to 52% in 2015 (8,9). But we are a long way from fulfilling the requirements mandated by the ICMJE in 2004. The picture becomes even bleaker if you look at the rates of prospective trial registration which was the original intent. Prospective trial registration requires that trials are registered prior to the enrolment of participants. When this rule was applied only 20% (CI: 15–25%) of trials had been prospectively registered (8).

The reality is although guidance has been provided by the ICMJE, journals are not willing to follow through and reject articles that have not been prospectively registered. Possible reasons for this lack of adherence to the ICMJE guidance include fear of losing a publication to competing journals, the paucity of clinical trial papers, concern about increasing publication bias by rejecting papers and finally,

the concern that the research from developing countries may be unfairly affected by this requirement because of poor access to trial registries (10).

In addition to the registration requirement by the ICMJE there are also legal avenues that have been introduced to reduce research wastage. The Food and Drug Administration (FDA) Amendment Act of 2007 (FDAAA) was signed into law on September 27, 2007. This act requires all clinical trials in the United States (US) to be registered with ClinicalTrials.gov (one of the primary registries on WHO-ICTRP) soon after the trials inception. In addition, the FDAAA requires a summary of the trial's results to be submitted to the same repository within 12 months of the trial's primary completion date. Although, trial registration increased following the FDAAA, data from the trials was not as forthcoming with only 10% of trials adhering (11). The FDA as a result of this low compliance has since issued the Final Rule which is an amendment which clarifies what clinical trials these rules relate too and which has expanded the information that is required to include more specifics about methods and outcome measures (11). The European Union (EU) has also introduced legal requirements for registration and result publication of clinical trials. The Clinical Trials Regulation (CTR) came into force on June 16, 2014 (12). However, once again it would appear only half of the trials registered are reporting their results within the 12 month timeframe (13).

Although these legal recourses are being introduced researchers still express concerns about forced trial registration increasing their research workload, adding restrictions to how they conduct research as well as the possibility of "intellectual theft" (14).

So where to from here, thanks to the systematic review by Trinquart and others we know that mandatory trial registration to this point has failed to make an impact. We do not appear to be able to rely on researchers or journals to enforce the registration of clinical trials or publication of their results. The next obvious target is the funders. The AllTrials campaign is an initiative that began in 2013 and calls for all past and present clinical trials to be registered and full methods and summary results reported http://www.alltrials.net/. AllTrials are now targeting non-commercial funders of clinical research on May 18, 2017 a joint statement was issued with 21 signatories from public funders of clinical trials (15). This statement asks that funders of clinical research to mandate time frames for prospective registration and public disclosure of clinical trial results which abide by the current Declaration of Helsinki. Items 35 and 36 of this declaration require that all studies involving human subjects must be registered before recruitment commences and that all resulting trial results will be made publically available (16). But once again during follow up with the funders an audit showing to date only 50% of the signatories have added policies to their webpages and are trying to enact the promises made (17).

We can only hope that through the continued efforts of all those involved in clinical research including patients, carers, funders and researchers we will eventually embrace the necessity of trial registration and resultant result publication.

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