ThinkWell and WHO Statement on RCT Disclosure

Response: ThinkWell and WHO Statement on Public Disclosure of Clinical Trial Results
Thank you, representatives of the World Health Organization (WHO), for highlighting the important areas of concern in Trials registration and reporting. ThinkWell welcomes the opportunity to provide public comments on this draft. All the trustees of the ThinkWell charity are willing to discuss this further, electronically or face to face and do whatever we can to promote this important step towards transparency and improving international public health.

ThinkWell is an organization that helps the public engage in all aspects of research from identifying and prioritizing questions, to designing, participating in and analysing research studies designed to address genuine uncertainties, including running online randomized controlled trials. ThinkWell currently focuses on self-management of health. All data from studies is de-identified and the public owns their own data and can choose where to share it. Participants learn about what makes health research trustworthy by doing and actively engaging in all aspects of the research process.
WHO Suggested Draft Edits

Most information about clinical trials sites contains advice for patients to make sure the trials they choose to be a part of are registered. The WHO’s decision to adopt a statement on clinical trial reporting reflects the Declaration of Helsinki which states that “every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject” and that “researchers have a duty to make publicly available the results of their research.” The trial registration process has come to be seen by members of the public, patients and many medical practitioners as a stamp of legitimacy.

ThinkWell agrees with All Trials that the statement needs to call for the disclosure of the results of past trials. The vast majority of medicines we use every day were approved by regulators a decade or more ago and so were tested in clinical trials over the past decades. As an example, this includes all of the drugs that are currently on the WHO essential medicines
list and the Package of Essential Non-communicable (PEN) Disease Interventions for Primary Health Care in Low Resource settings. It is these past trials that have not fully been reported; extensive documentation will still exist, and it should be shared. Multiple tragedies could be averted and black box warnings can be minimized when all results of trials are on record and freely available in a standardized format. The best available evidence [1] is that around half of all clinical trials have not reported results. Doctors, patients, regulators, academics and potential funders of health services cannot make informed decisions about which treatment is best, if half of all the trial results on that treatment are withheld. The WHO has the opportunity to state unequivocally that the era of secrecy must end and that there is a moral imperative to report the results of all trials that have occurred, on all treatments currently being used.

ThinkWell recognizes that standards for planning, conducting, and reporting trials have changed as they have for collecting, analyzing, curating, and storing data. Research teams may have changed leaving geographically fragmented, incomplete and lost data behind. These data sets are still better than nothing and we do not suggest groups be penalized for past actions, however the WHO might instead make it clear that getting old results into the public domain no matter what the condition is preferable to hidden trials data.

We suggest that WHO adopt the widely advocated timeline of twelve months from completion of a study to the reporting of results. The current period of thirty months deprives decision makers, is they patients of health professionals, of information and could permit unsafe materials, devices and interventions to continue to be used or prevent people from being able to choose the best available treatment. A deadline of 12 months to report results (or to offer a public reason for any delay) has precedents which demonstrate that is feasible: the USA’s FDA Amendment Act 2007 require results to
be reported within 12 months of the completion of the clinical trial as does the recent EU Clinical Trials Regulation. In the UK the Health Research Authority is consulting with academic and industry stakeholders on adopting a 12-month deadline for reporting results of clinical trials. Pharmaceutical company Glaxo Smith Kline’s approach is to publish summary results from pharmaceutical clinical trials within 8 – 12 months of completion of the study [2]. Pharmaceutical company LEO Pharma publishes summary results of all its clinical trials within 12 months of the completion of the study [3]

ThinkWell is aware that publication in peer-reviewed journals can take time; however, results can be reported on clinical trial registers sooner. After results are reported in these registers, researchers can go on to publish in academic journals (even if that may take longer than 12 months). Publication of results in a clinical trial register does not prejudice subsequent publication of a peer reviewed paper based on the results, for example the International Committee of Medical Journal Editors 2013 statement: “The ICMJE does not consider results posted in clinical trial registries as previous publication if the results are presented in the same, ICMJE accepted registry in which initial registration of trial methods occurred and if the results are posted in the form of brief structured abstracts or tables.” [4]

The WHO statement suggests that results should be reported both in a peer reviewed journal paper and on a publicly available register. We agree, however, it is important to bear in mind that publication in a peer reviewed journal within 18 months may not always be possible, particularly for new investigators and for unfunded trials, and outcomes where compliance is not necessarily within the control of researchers should not be made mandatory. Publishing on registers should therefore be the primary responsibility.
Academic journals do not always provide complete and objective reporting of results (permitting, for example, primary outcomes to be switched and substituted) registers can offer more standardized and objective formats than journal publications. A 2013 review in PLOS Medicine of results of the same trial published on ClinicalTrials.gov and in a journal paper found that “trial results, especially serious adverse events, are more completely reported at ClinicalTrials.gov than in the published article.” [5] The researchers found that the summary results contained more efficacy results than the published article (79% vs. 69%), adverse events (73% vs. 45%), serious adverse events (99% vs. 63%) and the flow of participants (64% vs. 48%). Standardized reporting on registers is the only way to ensure that vital important information about outcomes measured and adverse events are made available.

Transparency in registering and reporting all trials with easy and standardized access to the data could reduce confusion. For example in the retraction of the 2012 Heart article, “Low sodium versus normal sodium diets in systolic heart failure: systematic review and meta-analysis,” a low sodium diet was
thought to lead to increased morbidity. The meta analysis paper was retracted due to duplicated and then missing data. The problems point to indirectness as the patients had too high a dose to represent clinical practice. Unfortunately this level of detail was not readily available in the original systematic review, however original studies if available could have provided useful evidence when consistency with clinical practice for population, intervention, comparison and outcomes was examined [6]

In summary we suggest that the WHO propose that publication of standardized results on a clinical trial register be mandatory, with subsequent publication of a journal paper or papers desirable but not mandatory.

We suggest the WHO should require that registries provide study protocols (with version number and any amendments clearly reported) or, at least, linkage to protocols elsewhere on the web. This is presently done on PROSPERO an open access portal where protocols for Systematic Reviews are published followed by a link to the study result.

ThinkWell requests the WHO use its considerable influence to:

- Recommend that protocols for clinical trials be written in accordance with the SPIRIT reporting statement. [7]
• Ensure that registers give guidance on the date by which results are required, and when results have been posted, and where with documentation of the correspondence explaining why the results have been withheld, wherever there are delays.

• Ensure that trial funders are required to routinely audit publication records, to identify where results are missing on specific trials, and explain where and why a delay has been granted and WHO could suggest that any trials registration set aside resource funding for this purpose to avoid undue delays in access to information.

• Advise journals to check registration and reporting of trial results of trials submitted to them for publication and to report on compliance.

• Encourage ethics committees and ethical review boards to review publication of results from trials approved by them, and request new applicants to disclose whether they or their sponsor are currently withholding results on any previous trials more than 12 months after completion.

• Since methodological shortcomings in trials are often only apparent in the Clinical Study Report on a trial, the WHO should advise sponsors and regulators to disclose these documents publicly, with appropriate controls to protect patient confidentiality where necessary, within 12 months of trial completion, wherever such a CSR has been produced.

Additional Draft Concerns

There are additional areas of concern that we urge the World Health Organization to consider. A federal standard for IRBs and the mandatory training of the IRB members would increase trial quality and decrease reported and unreported adverse events. Most people are not aware that applying for a license for an IRB is not standardized or rigorous in all nations. A worldwide agreed on standard for training and operations such
as that adopted by the Collaborative Institutional Training Initiative (CITI) [8] would be indicated. If we are going to advise patients/participants that the trial needs IRB approval and clinical trials registration is seen as a step in validation we need to make sure this means something.

The public is in need of ways to validate the research methods through an oversight organization as many questionable trials are offered with MDs as medical directors. There is a conflict as the patients have been taught to respect an MD’s authority, which translates to if an MD has his/her name on it, the trial is registered, the inventor has published papers and the trial was submitted to an IRB this must be good research. Sadly this is not always true.

As for trial expenses, compensation for adverse events and costs for pre and post trial testing as well as inclusion/exclusion criteria should be clearly laid out upfront and the terms standardized. For example if a patient in a trial is expected to pay pre-testing and costs of the medical device or the intervention or biological materials but the trial itself is “free” how can the public differentiate appropriate from inappropriate research when they are asked by an ethics challenged, non compliant group to pay upfront and be included as part of a trial?

**Problem Solving Suggestions:**

- Competing interest declaration. At the very least, if a company is directly profiting from a trial itself then that competing interest should be prominently displayed in the listing or be disallowed. The public and potential trial participants have a right to know.
- No use of clinical trials listings as a marketing tool.
If patients are convinced to pay for the trial participation or intervention via website promotional material indicating that they are legitimate because their trial is listed the listing should be deleted.

- Keeping the food and drug administration or national equivalent regulatory agency informed about new trials as they are listed. In this way the regulatory agencies can examine whether they need to investigate these new trials for compliance and they would have all information about investigators, intervention and geography on hand. This would save time, resources and money in the event of complaints or questionable practice.

- That it be suggested that governmental or academic funding be conditional on trial registration, institutional review board approvals and that investigators maintain a track record of registering all trials and reporting trial results within 12 months.

- We maintain that registration be enabled on a free database and that the reporting of the trial results takes place within this trial registration site.

- Ensure that lack of funds cannot be a reason for researchers failing to transparently report results. The nature of scientific publishing is of course changing rapidly, so the issue of open access is really important, although the predominance of gold over green policies could have a detrimental effect on access to published trials given the vagaries of ‘pay for publication’ and some predatory publishing tactics. One solution could be to set up a fund to cover the cost of open publication if this is necessary [9].

**Conclusion**

ThinkWell applauds the WHO for recognizing that it is unethical to have patients participate in trials and then not have the results contribute to future decision making or be
facing a, potentially critical, health decision and be deprived of access to relevant evidence to inform the decision [10]. We thank the WHO for the opportunity to provide comment on this valuable draft. WHO action on this important area has the capacity to change medical and research practice.

Signed

Respondents as ThinkWell Directors

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References


