I would like to start this presentation by referencing a paper that was published by Alessandro Liberati\textsuperscript{1}, who was a great epidemiologist, very much involved in the Cochrane collaboration, wherein he reported his experience as a multiple myeloma patient. When his disease relapsed, he had to make a very difficult decision and decide whether he would get a second transplant. As a methodologist he wanted to base this decision on evidence. He searched for evidence; identifying four completed randomised control trials. However, none of them provided fully published results. Consequently, he was forced to make his decision knowing that information was somewhere but not available and he was unable to make an evidence-based decision.

Access to clinical trial information is essential and is actually an ethical requirement. In the Declaration of Helsinki\textsuperscript{2} which states the ethical principles for medical research involving human subjects, it is clearly stated that every research study must be registered, and that authors have a duty to make publicly available the results of their research and are accountable for the completeness and accuracy of their reports. There is also now some legislation in place. In the United States we have the FDA Amendments Act\textsuperscript{3}, which requires that all trialists who have at least one site in the US in their trials must post the results of their trials, no later than one year after the completion of the study. We have similar requirements in Europe with the need to post the summary results of clinical trials in the EU Clinical Trials Register\textsuperscript{4}.

Do we, however, have access to clinical trial information? A study was done that evaluated the public availability of results of trials assessing cancer drugs in the United States\textsuperscript{5}. All the trials selected were governed by the FDA Amendments Act and were supposed to post their results. However, three years after the study was completed 69\% of the trials had no results posted at the ClinicalTrials.gov register and half of them had no results publicly available, meaning no results that were either posted or published.

We also now have access to data for France thanks to the French Open Science Monitor\textsuperscript{6} whose last edition was made public last week. It shows that only 57\% of the clinical trials with at least one site in France have their results available, with some difference according to the sponsor: 76\% for industry-led trials and 31\% for academic-led trials.
A very important initiative and tools have been developed by Ben Goldacre and his team at Oxford University. They developed the TrialsTracker, which identifies all the studies that have to post their results on ClinicalTrials.gov and on the EU Clinical Trial Register and data mines whether they actually fulfil the law. The number of trials overdue, meaning that they should have posted their results but have not, increases over time. Compliance, meaning posting results one year after the study was completed, has increased slightly, but remains low and currently stable at 40%. When you assess the compliance with the requirement to report on the EU Clinical Trial Register the team evaluated 7,274 completed trials and they found that only 49% actually reported results, 68% for industry-funded trials and only 11% for academic trials.

What are the consequences? Of course, first, we do not have access to the results and cannot make evidence-based decisions. However, we also have some evidence that the fact that results are published depends on the actual results and there is some evidence of publication bias. Erick Turner showed this in a paper published in the New England Journal of Medicine. He identified 74 clinical trials assessing antidepressant treatments that were submitted by the pharmaceutical industry to the FDA to obtain marketing approval. He systematically searched for publications for these trials and found that in one-third of the trials there was no publication. Then he looked at the results and showed that when the trials were positive, showing that the treatment was beneficial, 97% of the trials were published. When the results were questionable, meaning we do not really know whether the treatment is beneficial, half of them were not published and the other half were published but with a conclusion that was not consistent with the FDA decision. When the results were negative, showing that there was no evidence the treatment had any effect, 68% were not published.

Further, the author tried to do a meta-analysis, summarising all the data, using first only the data that were published and compared it to the data including all trials that were published and not published. This showed that meta-analysis of journal dataset, using only data that were published, showed an increase in effect size of 32%, from 11% to 69%, according to the individual drug evaluated.

What could be done? We are meta-researchers and so we always try to find easy low-cost interventions that could improve research. Here we propose to send an email reminding trialists of the legal requirement to post results on ClinicalTrials.gov. We identified 379 trials that met the FDA requirements but did not post their results on the registry one year after the completion of the trials. These trials were randomised. Half of them did not receive any intervention and the other half received an email that was presented like a survey to try to understand why they did not post their results, and in the survey they were reminded that it was a legal requirement and
that there could be a fine of USD 10,000 per day of delay. Our outcomes were the percentage of studies with results posted, which showed, at least at six months, an increase in the percentage of results posted when they received the email. The effect of this intervention is small, an increase of 10%. However, we could imagine that the effect would be larger if the FDA instead of a French research team sent the email.

When results are made available through publication one question is whether the reporting is complete. Do we have enough information to be able to critically appraise the trials and use and interpret the results? We have some reporting guidelines, such as the CONSORT statement\textsuperscript{11}, which consists of a checklist indicating all of the essential information that should systematically be reported in a report of a randomised control trial. These guidelines are widely endorsed by editors who request compliance with the guidelines in their recommendations to authors.

How complete is the reporting of the literature? This was assessed in a very large study evaluating more than 20,000 trials that were included in Cochrane’s Systematic Reviews\textsuperscript{12}. When we do a Cochrane systematic review, we always try to evaluate the methodological quality of the study and we evaluate the risk of bias. In this particular study the evaluation of the risk of bias was impossible in a large percentage of trials because the reporting was incomplete. On the positive side, reporting is improving over time.

We are currently doing a large living systematic review the evaluation of which includes all randomised control trials involving potential treatments for COVID-19\textsuperscript{13}. This is an open review where we put all the results online. Here we are trying to evaluate transparency indicators and the completeness of reporting of the first trials that were included in the review in the first 17 months of the pandemic. The results show that transparency indicators are not well fulfilled. Only 55% of the trials were prospectively registered. Protocol and statistical analysis plans were available in only 39% and 29% of the trials respectively. Nevertheless, 68% reported a data-sharing statement. In terms of completeness of reporting, results were also very disappointing. Only one-third completely reported the primary outcome. 58% provided essential information related to the conduct of the study. Half reported the results adequately and only 15% adequately reported harm in terms of the safety of the treatment.

One question is: what is the role of the peer review process? Is the peer review process able to improve transparency? This was assessed in a study on 93 published randomised control trials\textsuperscript{14} where it was possible to have access to the first papers submitted, to the peer review documents and to the published articles and to compare completeness reporting before and after the peer review process. There is
some improvement for some domains related to the methodology, such as sequence generation, allocation concealment and blinding, but other domains did not improve at all after the peer review process and overall the reporting remains very poor with information available for these important items in less than 60% of the trials.

What can be done? We tried to provide some tools. First, we developed an online writing aid tool entitled COBWEB\textsuperscript{15}. This tool aims to guide authors when they are writing the first draft of their manuscript by providing the CONSORT items, explanations about the CONSORT items and examples of adequate reporting. We showed in randomised control trials that when authors were using the writing aid tool, they produced a more complete manuscript than when they did not have access to the tool. We also developed an online peer review tool that is dedicated to early-career researchers and associated with a training programme. We showed that when early-career researchers were using this tool they were more likely to detect inadequate reporting during the peer review process than the usual peer review process.

Completeness of reporting is important, but the reporting also needs to be accurate. In the protocols in particular, investigators have to specify primary and secondary data that will be assessed and analysed in their trials. We expect that these results are consistently reported in the published reports. However, there is some evidence of selective reporting of outcomes\textsuperscript{16}. For example, in the studies that systematically compared the outcomes reported in the registry, which are the outcomes that are planned in the protocol, to the outcomes that were reported in the manuscript there was some discrepancy in one-third of the randomised control trials, and these discrepancies favoured statistically significant results.

Finally, there is some evidence of spin in publications\textsuperscript{17}. Spin is a specific way of reporting that might distort the interpretation of the study results. For example, the authors will present the results to convince the reader that the treatment is more beneficial than is actually shown by the results. There is evidence of spin and quite a prevalence of it in published manuscripts in clinical trials, observational studies and systematic review, whatever the study design. This is problematic because there is some evidence showing that spin can impact readers’ interpretation. This was assessed in randomised control trials where we randomised readers to read an abstract with spin or the same abstract reported without spin\textsuperscript{18}. We found that readers were more likely to believe that a treatment would be beneficial when they read the abstract with spin.

Another important topic is access to individual patient data, mainly to be able to reproduce the results, to reproduce the analysis and to check whether we can trust the
results. It is also very important to develop other types of research and to synthesis the trial’s research in individual patient data meta-analysis. These types of analysis are very useful, particularly to identify the patients who are more likely to benefit from the treatment.

Some journals, such as *The BMJ* and *PLOS Medicine*, have a very strong policy in that they require data sharing as a condition for publication of clinical trials in their journals. A study led by Florian Naudet published in *The BMJ* in 2018 evaluated whether we actually had access to this data. He selected 37 published randomised control trials, requested the individual patient data from all of the authors, but could access the data in only half of the trials.

I would like to finish this presentation with a quote from Professor Doug Altman, who was a Professor of Statistics at the University of Oxford, founder of the Equator Network and one of the great leaders in the field of transparency and meta-research. He wrote that the scientific community and the public at large deserve an accurate and complete record of research. We need to make changes to ensure that we will get one.

**To go a step further**

“Particularly when we look at compliance with the law, pharmaceutical companies are doing better than academic researchers because I think it is more in their process – there is a law, and they need to follow it – and they probably have more support internally to be able to do it. On the other side, for academic trialists there is definitely a lack of incentive to comply with this requirement of posting results. This is linked to the fact they are not as interested and some of them feel that it is additional administrative requirements. They are going to publish their results, so why should they also post them? There needs to be better understanding in the community and, all the more, more incentives and greater recognition of people who actually fulfil this requirement.”

“All of the stakeholders have an important role. Institutions have a huge role in decision-making in terms of the criteria they will use to promote their researchers, and currently transparency and good research are not among the criteria they use. They also need to set up strong support for sharing individual patient data because this is currently not at all well organised. The funders have an essential role. Some try to implement some actions. For example, the NIH I think requests that access is given
to all individual patient data, and in the UK that is also the case, but we need more recognition and support from the funders.”

“An important point to remember is that researchers want to do good research. Then there are some incentives that will make them go in some directions more than others, and perhaps we need to play with these incentives. We definitely need to be very careful in the way we want to change the system and to be very careful in the way we are going to implement these changes. The way things are implemented, and how well understood the reasons are, is going to be very important to achieve a successful outcome.”

References

10. Annabel Maruani et al., « Impact of Sending Email Reminders of the Legal Requirement for Posting Results on ClinicalTrials.Gov: Cohort Embedded Pragmatic Randomized Controlled Trial », BMJ 349 (19 septembre 2014): g5579, https://doi.org/10.1136/bmj.g5579