Factsheet: publication of clinical trial results

Network of coordination centres for clinical trials – KKS-Netzwerk e.V. 13. Februar 2020

Over the last months, the media have repeatedly discussed the publication of the results of clinical trials. A debate was triggered by the critical positions voiced by the ALL Trials Initiative (https://www.alltrials.net/), whose supporters include the British Medical Journal (https://www.bmj.com/), the Centre for Evidence-based Medicine (https://www.cebm.net/) and the Cochrane Collaboration (https://www.cochrane.org/). Academic clinical researchers in particular were criticised for not making their data available to the public, or not quickly enough, and thus contributing to bias in the body of evidence. The German Network of coordination centres for clinical trials (KKS-Netzwerk e.V. – KKSN) has long been attending to this problem. Below, you will find a summary of the facts as seen by the KKSN.

Timely publication of the results of clinical trials is both a scientific and an ethical imperative

The publication of the results of clinical trials is a scientific and ethical imperative as noted by leading organisations such as the World Medical Association and the WHO (12, 3). To be able to weigh the benefits and risks of medical procedures or medications, a complete overview as of the current evidence is essential. This does not only apply to new medications and procedures. Such an assessment is always to be seen in the temporal context of the current state of knowledge. It is thus to be reviewed and updated once new data becomes available. If the publication of clinical trials is delayed or does not take place at all, this can bias the basis for such an assessment (publication bias). Furthermore, one has an ethical obligation toward the trial participants, who consent to participate and can expect the results of the trial to be published. Finally, it is a waste of significant human and financial resources if clinical trials are terminated without their results being published. This was discussed in the Lancet's publication series: „Research: increasing value, reducing waste" (https://www.thelancet.com/series/research).

Where are the results from clinical trials being published?

In general, results of clinical trials are published in scientific journals. During the publication process, submitted manuscripts undergo strict scientific evaluation by independent experts (peer review).

Moreover, clinical trial results can be made available in public clinical trials registries. However, in this case, there is no independent peer review. In clinical trials involving medicinal products, there is even a legal obligation to publish clinical trial results in a public registry (1, 2). This applies irrespective of whether the findings are published in a scientific journal or not.

Which study registries are available?

In accordance with the terms of the Declaration of Helsinki (3), the International Committee of Medical Journals Editors (ICMJE) (4) requires that only those trials should be published that were registered in an eligible registry prior to the start of patient recruitment. There are already a considerable number of publicly accessible registries for clinical trials. The World Health Organisation has set up a web portal serving as a meta platform to collect entries from existing registries

throughout the world. All basic data of trials listed in national registries can be retrieved from there (https://www.who.int//ictrp/search/en/.

Publicly accessible registries of particular relevance for Germany are:

German register of clinical trials (DRKS, drks.de)

The DRKS informs in English and German about clinical trials carried out in Germany. All kinds of clinical trials can be registered there (interventional trials with medicinal products, medical devices or other therapeutic procedures, prospective observational studies, trials on diagnostic strategies). Although registration is voluntary, German funding bodies like the DFG and BMBF explicitly mention the DRKS in the context of requesting the public registration of trials. For each trial registered with the DRKS, basic data such as title, short description, inclusion and exclusion criteria, study status and endpoints are retrievable. Results can be uploaded. The DRKS is free and run by the German Institute of Medical Documentation and Information, an agency embedded in the Federal Ministry of Health (BMG). The DRKS is accredited as a register by the WHO.

ClinicalTrials.gov (clinicaltrials.gov)

ClinicalTrials.gov is a registry primarily for clinical trials carried out in the USA, but open for trials from other countries. It is operated by the National Institutes of Health (NIH). As with the DRKS, all kinds of studies can be registered and results can be recorded. Sponsors and investigators of certain trials have been legally bound in the USA since 2008 to register their trials with ClinicalTrials.gov and to post results (5, 6). With more than 300,000 trials from 209 countries ClinicalTrials.gov is the most comprehensive registry acknowledged by the WHO.

EU Clinical Trials Register (clinicaltrialsregister.eu)

The EU Clinical Trials Register (EUCTR) accesses the EudraCT database (European Union Drug Regulating Authorities Clinical Trials Database), a database exclusively for interventional clinical studies with medicinal products within the European Union. The database is operated by the European Medicines Agency (EMA) and used by the competent authorities of the respective member states during approval and for supervision of clinical trials with medicinal products. Clinical trials with medicinal products carried out in the EU must be approved in advance by the competent authorities (7). As part of the authorisation process, registration with the EUCTR is compulsory. The EUCTR also allows sponsors the ability to document clinical study results in a standardised manner. However, the public can only see the results after approval and release by the EMA. Unfortunately, part of the process of data activation is only carried out after considerable delay.

PharmNet.Bund (pharmnet-bund.de)

PharmNet.Bund is the portal for information on medicinal products of the German federal government and the states. The integrated database ‘clinical trials’ contains information about clinical trials that were approved in Germany for medicinal products, including a report of the results. The database is operated exclusively by the responsible competent authorities (Federal Institute for Drugs and Medical Devices (BfArM)), Paul-Ehrlich-Institute (German Federal Agency for Sera and Vaccines, PEI). Reports submitted to the competent authorities by the sponsors of clinical trials are made available to the public with a delay of up to several years. Sponsors of clinical trials have no means of influencing this lengthy process.

Is there a statutory obligation to publish results of clinical trials?

In Germany, the legal requirement to publish results only holds for clinical trials with medicinal products. For all other kinds of clinical trials there is no legal obligation for results to be made available to the public. The current 2013 Declaration of Helsinki (3) states though that “Researchers have a duty to make publicly available the results of their research on human subjects”. According to the (ideal) code of conduct for doctors working in Germany, the Helsinki declaration has to be observed within the framework of research.

Clinical Trials with medicinal products

Status quo: For clinical trials with medicinal products conducted in the EU, there is a legal obligation to publish trial results, which is based on the European Regulations 726/2004 (8) and 1901/2006 (9). These provide the legal basis for the establishment of the public clinical trials database on PharmNet.Bund, a database containing information on medicinal products, provided by the German federal government and the states. The German medicines law and the subordinate regulation on the application of Good Clinical Practice for the conduct of clinical trials with medicinal products (1, 2) oblige sponsors of clinical trials to submit a report to the competent authority within one year of terminating the trial. This holds for all clinical trials that were started in Germany since 2004. After revision by the responsible authority, the report is published on the publicly accessible portal PharmNet.Bund.

In 2012, the EU published guideline 2012/c302/03 (10), complementing the previous regulations 726/2004 (8) and 1901/2006 (9) with regard to the disclosure of results from clinical trials. In particular, the guideline requires that results from clinical trials have to be submitted to the EudraCT database (and therewith on EUCTR) in a standardised manner. This extension of the EudraCT database was completed on 21.07.2014. Since then, sponsors can submit results directly to the EudraCT database.

However, a European guideline is not legally binding in the same way as a regulation. In Germany, the German medicines law continues to be the authoritative source for sponsors of clinical trials. Already in 2014, the KKSN raised the topic with the EU-commission in a detailed letter. Receipt of the letter was acknowledged.

Future status: On 16 June 2014 the new EU-regulation 536/2014 (11) on clinical trials on medicinal products came into effect. This regulation only becomes valid, however, after completion and full functionality of an EU-portal and an associated database for the transmission of data and information on clinical trials. Its completion was scheduled for 2016 but has been postponed repeatedly since. Even now, six years after the regulation came into effect, it is not yet possible to forecast when the database will be executable and hence the regulation becoming valid. Upon validity of the EU-regulation 536/2014, article 37 stipulates that reporting of results from clinical trials via the EU portal becomes legally binding within the entire EU (Joint Letter by the European Commission, EMA and HMA, June 2019).

To summarise, in Germany it is currently legally required that results from clinical trials with medicinal products are made public. This takes place through submission of the final report to the competent authorities. For other kinds of clinical trials, for instance those with medical devices, there are currently no such legal requirements. With the creation of the EU regulations 536/2014 (medicinal products) and 2017/745 (medical devices – legally binding from May 2020 (12)), the legal basis was set up for the reporting of results from clinical trials to the respective register. Concerning clinical trials with medicinal products, this reporting obligation is linked to a corresponding European

database structure, the completion of which has already been postponed for several years. Notwithstanding the above, the publication of results from clinical trials should be an ethical imperative to all researchers.

What about the rate of publication of clinical trials conducted at university medical centres?

In recent years, public disclosure of results from clinical trials has increasingly been spotlighted by both methodological research and public debate. Reliable statements with regard to the rate of publication, however, are methodologically difficult. This is because, as outlined above, there are different ways in which the results from clinical trials can be published.

All analyses carried out to date show, however, that a substantial proportion of clinical trials remains unpublished. Depending on methodological and temporal aspects, publication rates in scientific journals and study registries of 54% have been reported (clinical trials with medicinal products phases II-IV, with completion 2006 - 2015) (13), 71% (for randomised trials with a large number of participants, completion before 2009) (14), 66% (for academic studies in the USA, with completion of studies 2007 - 2010) (15) und 74% (for interventional academic trials in Germany (16).

If one looks at the rate of promptly reported clinical trial results (that is within 24 months following study completion as required by the WHO (17)), numbers are much lower. In interventional academic trials from Germany, a positive trend in publication rate can be seen: in trials completed in 2009/2010, 35% were disclosed within 24 months compared to 42% for trials from 2013 (16).

Two further publications that attracted public attention analysed the disclosure of results from clinical trials in public registries, with the objective of assessing compliance with the relevant laws: Goldacre et al. (18) for the EU, and De Vito et al (19) for the USA. In the analysis by Goldacre et al., however, compliance of German sponsors is considerably underestimated since according to German legislation, results from clinical trials have to be reported to the competent authorities, who in turn disclose those reports to the public via the PharmNet.Bund portal and not on EUCTR.

The overall conclusion is that results from a number of clinical trials are still not being published – neither in journals nor on registries.

How could the rate of publication be enhanced in the future?

The KKSN believes that the following measures could contribute to the improvement of the situation:

- Definition of a harmonised basic data set for reporting of results approved by all registries – in extension to the information belonging to the core data set requested by the WHO
- Extension of the WHO portal, via which trial data from all registries can be retrieved, to information on study results. This would have the benefit that one central portal could provide an overview on results from all kinds of clinical studies.
- The establishment of the legal framework by which scientific publications that have undergone peer review and are available to the public as ‘Open Access’ can be considered sufficient trial reporting. The corresponding register could provide a link to the publication.
- Improve the possibility for timely public disclosure also of trials with negative results, discontinued trials or trials lacking fundamental gain of insight.
- Timely processing and posting of reports submitted to the competent authorities (for PharmNet.Bund portal) and the EMA (for the EUCTR).

- Establishing a publication ethic at universities that encourages timely disclosure of studies, irrespective of results and thus of the impact of the publication medium. This would constitute a major step toward increased transparency. This could be realised for example by considering such aspects when allocating performance-oriented funds.

The members of the KKSN are committed to contributing to the improvement of the situation and therefore endorse the appeal of the WHO (17).

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