Why clinical study reports really matter

Michael Köhler and **Beate Wieseler**
Institute for Quality and Efficiency in Health Care, Cologne, Germany

Correspondence to:
Michael Köhler
Institute for Quality and Efficiency in Health Care (IQWIG)
Im Mediapark 8
50670 Cologne, Germany
+49-221/35685-289
michael.koehler@iqwig.de

Abstract
Clinical study reports (CSRs) have so far served as documents for drug approval, but not as a data source for further use in research and post-regulatory decision-making. Sound post-regulatory decisions also require data other than those available in publications due to reporting bias found in literature. At present, CSRs are the only documents that are comprehensive enough to solve this problem. Developments being carried out by the EMA and journal editors towards data transparency may place CSRs as future core documents.

For many medical writers, preparing clinical study reports (CSRs) is a major part of regulatory medical writing. Most CSRs are conducted or commissioned by pharmaceutical companies and targeted to regulatory agencies (e.g., EMA, FDA), which use CSRs as a basis for their decisions. Until recently, the content of CSRs was classified as commercially confident information (CCI). In consequence, access to CSRs was mainly limited to regulatory bodies, which in turn merely published parts of the data obtained from CSRs in their reports, such as the EMA's European Public Assessment Reports.[1] Thus, one may be tempted to assume that CSRs are written for the archives of pharmaceutical companies and drug authorities and are only sometimes resurrected as data source for selected publications in scientific journals or conference proceedings. However, the need for clinical study data does not end with the approval of a new drug.

Post-approval decisions and the need for complete data
Post-approval decision-making involves far-reaching questions. One is whether a new drug does indeed have an added benefit over the existing standard of care. The task of answering this is usually performed by a country's health technology assessment (HTA) agency, and the answer is required first, to support decisions on reimbursement and pricing, and second, to ensure the development of high-quality clinical guidelines and patient information. If complete information on treatment options is available, then individual patients, together with their physicians, can decide whether they wish to use a certain drug in their specific situation. This ensures patient autonomy, which is in itself a criterion resulting in better treatment and ultimately in high-quality health care.

Regulatory agencies and post-approval decision-makers have different aims, tasks, and concerns. For example, HTA agencies and health policy decision-makers usually place greater emphasis on a new drug's relative effectiveness

(i.e., on added benefit versus harm as well as on cost-effectiveness) than do regulatory bodies. In addition, there are differences in local settings such as the availability and reimbursement policies between countries. Therefore, local HTA agencies and health policy decision-makers often require a different set of data. The same applies to the authors of clinical guidelines, which are largely developed within the context of the conditions of a specific health care system. In spite of these differences, the evidence divide between regulatory bodies and policy makers must be overcome.

As mediators in attaining high-quality health care, HTA agencies, as well as authors of clinical guidelines and patient information, should not have to rely on selective and limited information available in journal publications, but should have access to complete information, i.e., methods and results of all relevant studies.

Criteria for valid decision-making in managing health care

Data from all relevant studies are required to adequately inform all of these stakeholders. They must be available in in a high-quality publication format. A valid interpretation of study results is only possible if the following requirements are met:

1. All study methods as specified in the protocol must be reported, including patient selection, mode of randomisation and blinding, study treatments and comparators, definition of outcomes, data collection, and statistical analysis.
2. Changes to the study protocol must be documented clearly and with sufficient justification.
3. Study results must be presented in an adequately aggregated form as specified in the protocol (and, for specific research questions, as individual patient data).
4. Both study methods and results must be presented in a level of detail that allows critical appraisal of the study.

Unfortunately, these requirements are currently far from being met, as reporting bias is still a common problem.

Reporting bias

Publication bias and outcome reporting bias represent two types of reporting bias and refer to bias caused by missing data at two levels: the study level, i.e., "non-publication due to lack of submission or rejection of study reports", and the outcome level, i.e., "the selective non-reporting of outcomes within published studies".[2] A body of evidence dating back several decades ago[3] demonstrated that reporting bias is a universal problem in medical research. It may not be surprising that study results showing positive results of new drugs are published more rapidly and more often than those with negative or neutral results.[2,4,5] Therefore, published literature may overestimate beneficial effects, while harms are underestimated.

However, until the past decade little was known about the measurable impact of reporting bias on the health care system. This changed in 2006, when The Cochrane Collaboration published a systematic review on the efficacy of the neuraminidase inhibitors (NIs) oseltamivir and zanamivir in the prevention and treatment of influenza. In their original publication, they concluded that NIs were effective in reducing complications of influenza in otherwise healthy adults.[6] In 2009, however, they became aware that their review was based on a single manufacturer-funded study using unpublished data. So in order to update their report, they asked the manufacturer of oseltamivir, Roche, for all data (see Doshi 2009[7] for more details) and found that 60% of patient data from the NI trials had never been published before. In their report update, The Cochrane Collaboration showed that there was insufficient evidence that NIs reduced complications of influenza or hospitalisations.[8,9] This event raised the question as to whether stock-piling NIs for flu epidemics in many countries had been an appropriate use of public money (424 million pounds spent alone in the UK)[8] and prompted to seek measures on aiding decision-making in case of incomplete information in the future.

The case of NIs is probably the most well-known example of reporting bias that led to incorrect conclusions on drug effects.

The next example shows the level of detail that needs to be available to provide a meaningful assessment of a given drug. In 2012, the German HTA agency, the Institute for Quality and Efficiency in Health Care (IQWiG), assessed whether linagliptin had an added benefit over glimepiride, a sulphonylurea, in patients with diabetes.[10] The assessment was based on *Study 1218.20*, published in *The Lancet* in 2012.[11] The study authors stated that in the linagliptin group, hypoglycaemic episodes occurred in fewer patients than in the glimepiride group.[10] This result suggested that linagliptin had an added benefit over glimepiride. Having access to the full CSR of the study, IQWiG was able to peruse the intention-to-treat analysis of the time-course of HbA1c (glycated haemoglobin), which was not available in the publication. They found that there had been a sharp decrease in HbA1c in the glimepiride group (but not in the linagliptin group) in the first 12 weeks of the study. This was probably due to a forced titration of glimepiride as the study aimed for a low blood glucose target. Linagliptin, on the other hand, was given as a fixed-dose treatment without such a target. Examination of the patient data listings of the CSR showed that almost all hypoglycaemic events occurred during this 12-week titration period. Therefore, in contrast to the journal publication, IQWiG concluded that *Study 1218.20* did not provide convincing evidence regarding an added benefit of linagliptin over glimepiride because it could not distinguish between effects of different treatment regimens (fixed dose versus forced titration) or simply, different drugs (linagliptin versus glimepiride, for details see Wieseler 2017).[12] In this case, relying on the publication alone might have led to inappropriate decisions on the use of linagliptin and on its reimbursement price in Germany.

These examples show that the completeness of data available in CSRs is often not adequately reflected in journal publications. In fact, by comparing study results reported in journal publications and study registries with those in CSRs, research showed that the latter provided complete information on a considerably higher proportion of outcomes (86%) than publications and registries combined (39%).[10]

A body of evidence dating back several decades ago demonstrated that reporting bias is a universal problem in medical research.

CSRs need to be made available

The CSR is a comprehensive document that meets all requirements for valid decisions not

only at regulatory but also at policy-making levels (see "Criteria for valid decision-making in managing health care"). It also offers high-quality reporting, as the structure of CSRs follows standard requirements (ICH E3). CSRs should be disclosed to allow scrutiny: readers should be able to see omission of pre-specified data, data dredging, arbitrary changes to data collection, and other sources of bias.

Steps to disclosure

Although lack of transparency in clinical trial reporting has been known for decades, countermeasures are being only slowly implemented.

Study registries

The introduction of study registries was an important step towards the greater goal of full data disclosure of clinical trials. However, recent research has shown that study registration, and perhaps even more so, registration of study results, does not reach the completeness intended by the initiators of these databases. Recent research suggests that a considerable amount of data that should be included in registries is either missing, outdated, or even incorrect. Examples are accuracy of recruitment status and completeness of trial results.[13,14]

Scientific journals

Data transparency has been a topic in scientific journals for quite some time. Major journals such as the *BMJ* and *PLoS Medicine* require authors to submit entire study protocols together with their manuscripts and publish them as online supplements to the final article.[15,16] In addition, many journals only accept study manuscripts that are registered in a publicly available study registry. However, a recent article in the *BMJ* found that improperly registered studies rejected by the *BMJ* were subsequently almost always published in another journal.[17] Stricter requirements among journals may be implemented. A recent statement of the International Committee of Medical Journal Editors (ICMJE) outlined future conditions for the publication of articles on clinical trials in their journals, making the inclusion of a data sharing statement in the manuscript and a data sharing plan in the trial's registration mandatory.[18] This policy may further support the goal of full data disclosure, especially with regard to study results.[19]

Initiatives by regulatory bodies

The fact that comprehensive trial information has been routinely available for regulatory decision-making has led to various initiatives promoting the publication of regulatory data.[20] The EMA was the first regulatory body to make at least part of the information on a clinical trial available. In 2010 the EMA implemented a policy on access to clinical trial information by request and in 2014 on the pro-active routine publication of clinical data from drug trials (policy 0070).[21] Through this policy, clinical data (including CSRs) for all applications for centrally authorised drugs submitted to the EMA from January 1, 2015, and extension line applications submitted from July 1, 2015, are available to the public (see articles on this issue of *Medical Writing*).

At present, the EMA's aim to publish all clinical data on new drug applications rapidly has not been fully achieved. The availability of data in the EMA's database lags behind the rate of new applications. This is probably due to redaction before publication of the data. Manufacturers have the right to redact certain passages in the submitted documents that they classify as CCI. In general, the EMA does not consider CSRs to be CCI and redaction is intended to be limited. It remains to be seen whether and in what way redactions may hinder the scientific usability of CSRs, and whether clinical trial data will be published more swiftly after drug approval.

The FDA is lagging behind its European counterpart. But in a recent press release, the FDA announced a pilot programme, which

started in January 2018, through which CSRs will be released on a new section of the FDA website.[22] Posted information will also include protocols, protocol amendments, and statistical analysis plans. The pilot project will contain up to nine drug applications. If successful, this may lead to the routine release of CSR data on the FDA website for future drug applications.

Outlook

In light of these developments, one might think that the problems surrounding transparency of clinical trial data are largely solved or are close to being solved. Indeed, there is reason for optimism. Compared with the previous situation, we have seen relevant improvements. Since the case of NIs became public, both the discussion and the measures taken seem to have been accelerated. However, it is still a long way to go. The current initiatives of EMA, FDA, and ICMJE cover only data on new studies of drugs submitted for approval. So far, there is no concept for publishing the CSRs of studies that were conducted before these measures were initiated, even though these CSRs refer to the vast majority of drugs currently used. For non-pharmaceutical interventions (e.g., medical devices, in vitro diagnostics, etc.), the situation is even more unsatisfactory. Standards for study reporting are less detailed, and clinical trials for all high-risk devices have only recently become mandatory in the EU.[23,24]

Meanwhile, the discussion about data sharing has progressed. The focus has begun to shift from aggregated data (bodies of CSRs and supplementary tables) to the sharing of individual patient data (IPD).[25,26] In its *policy 0070*, the EMA has taken a first step in this direction. The policy plans to make IPD available; however, the discussion on how to achieve this without compromising data protection of study participants has only just started.

Whatever direction further measures will take, CSRs are at the centre of the current development and will remain so. CSRs really matter because they provide a ready-to-use complete representation of a study in the required level of detail and represent the most comprehensive format available for the reporting of the methods and results of clinical trials. CSRs will therefore be the core element of clinical data sharing for the foreseeable future.

In conclusion, the times when writing CSRs was referred to as purely "regulatory medical writing" are over. CSRs will remain the core documents for drug approval, but their use is extending beyond regulatory activities and beyond being a data source for heavily condensed publications reporting selected data. In the near future, CSRs will be available as information sources for independent researchers and post-approval decision-makers. Therefore, for all medical writers who write CSRs and wonder who they are writing for, good news is coming: Your reports have gained in importance and will continue to do so, your audience is constantly growing, and your work may be relevant and sought after for years to come.

In light of these developments, one might think that the problems surrounding transparency of clinical trial data are largely solved or are close to being solved.

Acknowledgements

The authors would like to thank Natalie McGauran for reviewing the manuscript.

Conflicts of interest

The authors are employed by the Institute for Quality and Efficiency in Health Care (IQWiG), Cologne, Germany. To produce unbiased HTA reports, the Institute depends on access to all of the relevant data on the topic under investigation. The authors support public access to clinical study reports.

References

1. European Medicines Agency. European public assessment reports. [cited 2018 Jan 19]. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/epar_search.jsp&mid=WC0b01ac058001d124.
2. Dwan K, Gamble C, Williamson PR, Kirkham JJ. Systematic review of the empirical evidence of study publication bias and outcome reporting bias: an updated review. PLoS One. 2013;8(7):e66844.
3. Hemminki E. Study of information submitted by drug companies to licensing authorities. Br Med J. 1980;280(6217):833–6.
4. Ioannidis JP. Effect of the statistical significance of results on the time to completion and publication of randomized efficacy trials. JAMA. 1998;279(4):281–6.
5. Song F, Parekh S, Hooper L, Loke YK, Ryder J, Sutton AJ, et al. Dissemination and publication of research findings: an updated review of related biases. Health Technol Assess. 2010;14(8):iii, ix-xi, 1–193.
6. Jefferson TO, Demicheli V, Di Pietrantonj C, Jones M, Rivetti D. Neuraminidase inhibitors for preventing and treating influenza in healthy adults. Cochrane Database Syst Rev. 2006(3):CD001265.
7. Doshi P. Neuraminidase inhibitors: the story behind the Cochrane review. BMJ. 2009;339:b5164.
8. Torjesen I. Cochrane review questions effectiveness of neuraminidase inhibitors. BMJ. 2014;348:g2675.
9. Jefferson T, Jones M, Doshi P, Del Mar C, Dooley L, Foxlee R. Neuraminidase inhibitors for preventing and treating influenza in healthy adults. Cochrane Database Syst Rev. 2010(2):CD001265.
10. Institute for Quality and Efficiency in Health Care. Linagliptin: re-assessment of benefit according to § 35a, Para. 5b, Social Code Book V (dossier assessment). 2012 [cited 2018 Feb 28]. Available from: https://www.iqwig.de/en/projects-results/projects/drug-assessment/a12–11-linagliptin-re-assessment-of-benefit-according-to-35a-para-5b-social-code-book-v-dossier-assessment.2694.html.
11. Gallwitz B, Rosenstock J, Rauch T, Bhattacharya S, Patel S, Von Eynatten M, et al. 2-year efficacy and safety of linagliptin

compared with glimepiride in patients with type 2 diabetes inadequately controlled on metformin: a randomised, double-blind, non-inferiority trial. Lancet. 2012;380(9840):475–83.
12. Wieseler B. Beyond journal publications: a new format for the publication of clinical trials. Z Evid Fortbild Qual Gesundhwes. 2017;120:3–8.
13. Jones CW, Safferman MR, Adams AC, Platts-Mills TF. Discrepancies between ClinicalTrials.gov recruitment status and actual trial status: a cross-sectional analysis. BMJ Open. 2017;7(10):e017719.
14. Riveros C, Dechartres A, Perrodeau E, Haneef R, Boutron I, Ravaud P. Timing and completeness of trial results posted at ClinicalTrials.gov and published in journals. PLoS Med. 2013;10(12): e1001566; discussion e1001566.
15. BMJ. Article types and preparation. [cited 2018 Feb 28]. Available from: http://www.bmj.com/about-bmj/resources-authors/article-types.
16. PLOS Medicine. Submission guidelines: guidelines for specific study types; clinical trials. [cited 2018 Feb 28]. Available from: http://journals.plos.org/plosmedicine/s/submission-guidelines#loc-clinical-trials.
17. Loder E, Loder S, Cook S. Characteristics and publication fate of unregistered and retrospectively registered clinical trials submitted to The BMJ over 4 years. BMJ Open. 2018;8(2):e020037.
18. Taichman DB, Sahni P, Pinborg A, Peiperl L, Laine C, James A, et al. Data sharing statements for clinical trials: a requirement of the international committee of medical journal editors. PLoS Med. 2017;14(6):e1002315.
19. Naudet F, Sakarovitch C, Janiaud P, Cristea I, Fanelli D, Moher D, et al. Data sharing and reanalysis of randomized controlled trials in leading biomedical journals with a full data sharing policy: survey of studies published in The BMJ and PLOS Medicine. BMJ. 2018;360:k400.
20. Gøtzsche PC, Jorgensen AW. Opening up data at the European Medicines Agency. BMJ. 2011;342:d2686.
21. European Medicines Agency. European Medicines Agency policy on publication of clinical data for medicinal products for human use. 2014 [cited 2018 Jan 19]. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2014/10/ WC500174796.pdf.
22. U. S. Food and Drug Administration. FDA Commissioner Scott Gottlieb, M.D., on new steps FDA is taking to enhance transparency of clinical trial information to support innovation and scientific inquiry related to new drugs. 2018 [cited 2018 Jan 19]. Available from: https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm592566.htm?utm_campaign=01162018_Statement_Transparency%20of%20clinical%20trial%20information&utm_medium=email&utm_source=Eloqua.
23. Cohen D. Medical devices face tougher premarket testing under new EU laws. [cited 13.03.2018]. Available from: http://www.bmj.com/content/357/bmj.j1870.
24. Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices, amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC, (2017).
25. Institute of Medicine. Sharing clinical trial data: maximizing benefits, minimizing risk. Washington, DC: National Academies Press; 2015.
26. Zarin DA, Tse T. Sharing Individual Participant Data (IPD) within the context of the Trial Reporting System (TRS). PLoS Med. 2016;13(1):e1001946.

Author information

Michael Köhler was previously a medical writer at a contract research organisation and is currently a Research Associate in the Drug Assessment Department at the Institute for Quality and Efficiency in Health Care (IQWiG).

Beate Wieseler was previously a medical writer at a contract research organisation and is currently the Head of the Drug Assessment Department at IQWiG. Their main responsibility is the production of health technology assessments on the added benefit of new drugs in Germany. They both have a special interest in the issue of data transparency.