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From publication bias to lost in information: why we need a central public portal for clinical trial data

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Overview

The availability of clinical trial records has increased markedly. This article outlines the challenges faced in information retrieval for evidence syntheses and provides a proposal for ensuring efficient and complete access to clinical trial records, namely, the establishment of a central, worldwide public portal.

Information retrieval for a health technology assessment (HTA) report

The aim of information retrieval for evidence syntheses is to identify as many relevant studies and study results as possible; detailed requirements exist for the methods to be applied, including the sources to be searched.¹ In 2019, the German HTA agency, the Institute for Quality and Efficiency in Health Care (IQWiG), conducted an HTA on biologicals in rheumatoid arthritis.^{2,3} One hundred and eighteen relevant studies were identified for which 682 relevant documents, which were sometimes difficult to assign to a specific study, were retrieved from various sources (table 1).

Even for a large HTA agency like IQWiG, the task of identifying and processing these numerous documents was challenging. Such an extensive effort for a single HTA is unsustainable, but returning to incomplete and selective study information is not an option.

Reporting clinical trials

This situation represents the result of a long development: the starting point was publication bias in scientific journals,⁴ the traditional form

of reporting clinical trials. The resulting controversies accelerated data transparency initiatives propagating trial registration and the reporting of summary results.⁵ However, even though mandatory implementation in several countries markedly improved reporting, deficits still exist,^{6,7} which triggered calls to release more extensive clinical trial data such as clinical study reports (CSRs). These documents are traditionally used to inform regulatory decision making and were previously always confidential, but public access has increased,^{8,9} and analyses of CSRs have challenged conclusions based on published evidence alone.^{10,11} Furthermore, individual patient data (IPD) have been shown to provide additional, clinically relevant information.^{3,12} Several data-sharing initiatives have been launched and different platforms were established,^{13,14} but various problems exist.¹⁵ There are thus calls for the creation of a single IPD portal, a 'simple one-stop shop for clinical trial data sharing'.¹⁵

Too much and too little

As shown by IQWiG's HTA report, the good intentions behind data transparency measures have resulted in a detrimental side effect: the abundance of retrieved documents results in a waste of resources, and despite this abundance, the publicly available evidence base is still incomplete.

What's the solution? Proposal for a central public information portal

In line with similar proposals by other researchers,^{12,16-18} we call for one central public

Table 1 Summary of relevant studies and documents considered in an HTA report on biologicals in rheumatoid arthritis*

Studies/documents	
Studies	118
Industry sponsored	84 (71%)
Investigator-initiated trials	34 (29%)
Full-text journal article	318 articles for 100/118 studies (85%)
Study registry entry	
Registration	159 records for 96/118 studies (81%)
Results reporting	124 records for 69/118 studies (58%)
Clinical study report provided (not publicly available)	
Overall	81/118 studies (69%)
Industry-sponsored study	80/84 industry-sponsored studies (95%)
Investigator-initiated trials	1/34 investigator-initiated trials (2.9%)
Total number of documents	682

*Extract from IQWiG report A16-70.²

HTA, health technology assessment; IQWiG, Institute for Quality and Efficiency in Health Care.



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information portal. This portal should contain the information required for unbiased and timely assessments, without the hurdle of current on-demand approaches, where sponsors ready the data only on request, resulting in a selective evidence base. Having all information available is also a cost-effective use of data as compared with repeatedly running similar studies.

A starting point could be all clinical trials (including discontinued ones) of all newly approved drugs, which could be extended to include older trials on established drugs and trials on drugs that were never approved. The scope should also be expanded to non-drug interventions.

The main target group of the portal would be researchers conducting evidence syntheses for informed decision making in healthcare, such as the development of guidelines or health policy directives (eg, national HTA agencies, Cochrane and guideline panels). However, drug development in general, including not-for-profit developers and the pharmaceutical industry, would benefit from such a comprehensive information source.

The basic structure of the portal could be as follows:

- ▶ Unique identifier (eg, the National Clinical Trial number given to each clinical trial on registration at ClinicalTrials.gov (CT.gov)).
- ▶ Proactive provision of the CSR (including all results data, the full protocol and statistical analysis plan; excluding IPD).
- ▶ Link to anonymised IPD held at the public organisation running the portal (on request only, for data protection reasons).

As long as the above information is complete, further documents would no longer be required for evidence synthesis. CT.gov's Final Rule¹⁹ already requires deposition of the study protocol and statistical analysis plan, and its requirements could be further expanded; one could thus use the existing CT.gov structure for the portal. For instance, Zarin and Tse¹² previously proposed a comprehensive "information scaffold" using the CT.gov record of a trial to link to various online sources. They also suggested adding journal articles, results registry entries and further sources (eg, news articles) for further target groups. A link to patient information would also be conceivable. If a new portal were established instead, it could be hosted by a global institution such as the WHO, which has promoted public disclosure of clinical trial results and data sharing^{20 21} and already hosts a registration and results database—the WHO International Clinical Trials Registry Platform.

Many of the above-cited proposals to establish a portal are several years old, but unfortunately, legal action to achieve this has been lacking. Following the previous unsatisfactory experiences with voluntary registration and reporting of clinical trials, a mandatory legal framework is indispensable.

Our case study (table 1) showed a striking difference (95% vs 3%) between the provision of CSRs by sponsors of industry trials and investigators conducting investigator-initiated trials (IITs). Similar problems exist with postmarketing trials, which are subject to less scrutiny as they often do not need to be submitted to regulators, and identifying and accessing them may be more difficult. Given the proven superiority of CSRs for the documentation of study methods and results,^{10 11} they should become mandatory for all types of trials (irrespective of whether they were intended for regulatory drug approval or not), that is, for industry trials and IITs, for premarketing and postmarketing trials and for drug and non-drug trials. Redactions should be restricted to a minimum and only be allowed for truly confidential information, such as the composition of a new drug, and not for details on study methods and results.

Clinical trial data are a public good, and data curation should be a legally required component of a clinical trial. As a supranational

law for the mandatory establishment of a central portal, including the mandatory, proactive and routine posting of CSRs, seems unrealistic, harmonised laws in different jurisdictions (individual countries, USA and Europe) might be an alternative. Currently, any trial in humans must be approved by an authority and at least summary results submitted. One could expand this regulation by specifying, for instance, for a multinational trial that the authority responsible for the principal investigator also posts the mandatorily submitted CSR on the central portal. Funding should also be regulated through legislation. Moreover, the portal should be managed by an independent panel. The greatest barrier in the establishment of the portal is that an international consensus is required at the highest political level. A first step could be the creation of a taskforce including representatives of governmental authorities, regulatory agencies and not-for-profit organisations.

Conclusion

Multiple records on a single clinical trial with overlapping information are available in numerous sources, requiring extensive efforts to identify and process these documents. Moreover, despite the abundance of information available, it is often still incomplete. The mandatory publication of all full CSRs, the essential documents on a clinical trial, is therefore required, as well as access to IPD on request. This information should be available in a central, public and worldwide portal. The establishment of such a portal would support the aims of the growing data transparency movement, namely, to improve patient care.

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