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SHORT REPORT

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Centralised Full Access to Clinical Study Data Can Support Unbiased Guideline Development, Continuing Medical Education, and Patient Information

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Introduction

The existence of publication bias and selective reporting bias ("non-reporting bias" [1]) in clinical research and the related effects, namely, the overestimation of benefits and underestimation of harms, have been extensively studied and repeatedly confirmed [2–5]. Several countermeasures have been introduced in the past decades. Earlier ones included a-priori study registration as a precondition for publication in scientific journals in 2004 [6] and mandatory registration of studies and summaries of study results in the USA in 2007 [7]. However, compliance with legal requirements, especially results registration, is still insufficient, particularly in publicly funded research [8,9]. On the other hand, industry-funded research is associated, among other things, with more positive conclusions [10,11].

Even access to all journal publications and registry reports on all relevant clinical studies on a topic would provide insufficient information for a valid assessment [12,13]. For this purpose, extensive data are required, which are only available in so-called clinical study reports (CSRs).

Full Access to CSR Data for Evidence Syntheses

A CSR is a standardised full report of a clinical study submitted by a pharmaceutical company to a regulatory authority during the drug approval process [14]. This format is generally required for drug studies, but so far not for studies on medical devices or other non-drug interventions. Including appendices, a CSR may consist of up to several thousand pages and often contains (anonymised) individual patient data (IPD) [12]. Consideration of CSR data (with or without IPD) in evidence syntheses may reverse or supplement the conclusions based on evidence retrieved from conventional, publicly available sources such as journal publications [15–19]. Previously, CSRs were only available to regulatory authorities as confidential information. However, in the past 10 years, CSR data have become increasingly publicly available, for instance, due to mandatory submission within the context of health technology assessment (HTA) in Germany since 2011 [20,21] or after an initiative launched in 2014 by the European Medicines Agency to publish clinical study documents [22]. The former measure was implemented by the German Act on the Reform of the Market for Medicinal Products (AMNOG), introducing the mandatory assessment of new drugs at market entry, the "early benefit assessment" [20,21]. The main rationale for the Act was to inform pricing decisions. The assessment process is described in detail in a previous paper [13]. In short, the pharmaceutical company submits a dossier at market entry that must contain all available evidence, including CSRs, and show the added benefit of the new drug over standard care. The Institute for Quality and Efficiency in Health Care (IQWiG) generates a dossier assessment to inform the decision on added benefit and ultimately pricing negotiations. The dossier and dossier assessment, including the relevant CSR data, are published online.

The effect of access to CSR data obtained within the AMNOG process has been shown in a comparison of the data available in dossier assessments and other AMNOG-related documents with conventional publicly available sources. While the former achieve a high degree of reporting completeness and provide

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comprehensive information on the methods and results of clinical studies on new drugs at market entry, conventional sources provide insufficient information, especially with regard to patient-relevant outcomes [13]. Hence, beyond informing pricing decisions, a major advantage of the AMNOG process is the availability of CSR-based evidence syntheses including additional clinically relevant information. For instance, the results of dossier assessments are available online, both in a scientific and in an easily understandable format, for physicians and patients to use.

CSR-based Evidence Syntheses for Further Types of Information Formats

Beyond dossier assessments, CSR data could routinely be used for the production of CSR-based evidence syntheses for further types of information formats such as clinical practice guidelines, continuing medical education (CME) materials, and patient information, which all aim to support informed decision-making by physicians and patients and ultimately improve treatment outcomes. So far, the evidence base used for these formats mainly originates from conventional sources and is thus incomplete and prone to bias, which is increased by industry influence (see below).

Potential Bias in Information for Physicians: Guidelines and CME Materials

Although the quality of clinical practice guidelines has improved, deficits still exist [23–27]. Besides a limited evidence base and a lack of methodological stringency, guidelines are commonly affected by (often undisclosed) conflicts of interest (COI) of guideline authors, which tend to be associated with biased recommendations [28,29]. An extreme example of the potential consequences of such recommendations is their role as a potential contributing factor to the opioid epidemic in the USA. An analysis of the potential risk of bias from COI in guidelines for opioids in chronic non-cancer pain identified 43 red flags in 13 guidelines and concluded that they "were at risk of bias because of pervasive COI with the pharmaceutical industry and a paucity of mechanisms to address bias" [30].

CME materials also traditionally rely on a limited evidence base. Moreover, the medical industry is heavily involved in CME, commonly through indirect funding such as payment of key opinion leaders, provision of non-monetary resources related to CME events, use of medical education and communications companies, and the award of "unrestricted educational grants", which however, may be withdrawn if the company does not agree with the CME content [31]. Although policies are in place to limit industry influence, its involvement is viewed critically [31–33] or, as put in a nutshell by Adriane Fugh-Berman in a recent essay describing several negative examples: "Industry-funded medical education is always promotion" with the aim of "creating diseases, or expanding the market for existing diseases" as well as "the omission or minimization of product harms" [31]. For instance, industry involvement tends to influence prescribing behaviour in favour of the promoted drug and reduce adherence to guidelines [34–36]. With regard to harms, we again refer to the example of the opioid epidemic in the USA: The manufacturer Purdue accompanied the launch of the opioid OxyContin with a massive investment in CME, including the intentional dissemination of misleading information on its alleged lower potential for addiction [31,32,37].

Potential Bias in Patient Information

The importance of considering the patient perspective in drug research, health policy and clinical decision-making ("shared decision making") is widely accepted and the provision of easily understandable, independent and unbiased information is essential to enable informed participation by patients. However, in addition to being based on a limited evidence base, patient information is often funded directly or indirectly by industry, for example, through sponsored websites or via patient groups that have disclosed or undisclosed industry relations, which tend to result in positions favourable to the sponsor [38,39].

One Database for All

Although a complete evidence base as the basis for independent evidence syntheses does not alone solve the problem of industry influence, it is the precondition for the development of unbiased treatment recommendations. However, even if all evidence on an intervention were fully available, it would be scattered in different information sources such as journal publications, public and industry study registries, as well as regulatory and HTA agency websites, resulting in extensive resources required for retrieving and screening the evidence. For example, in a recent HTA report on biologics published by IQWiG, 118 relevant studies with 682 related study documents were identified in multiple sources [40]. To enable the production of CSR-based evidence syntheses for various information formats with an efficient use of resources, a central, public and worldwide portal for CSRs is required [40]. Similar demands have previously been voiced by other researchers [19,41–43]. Figure 1

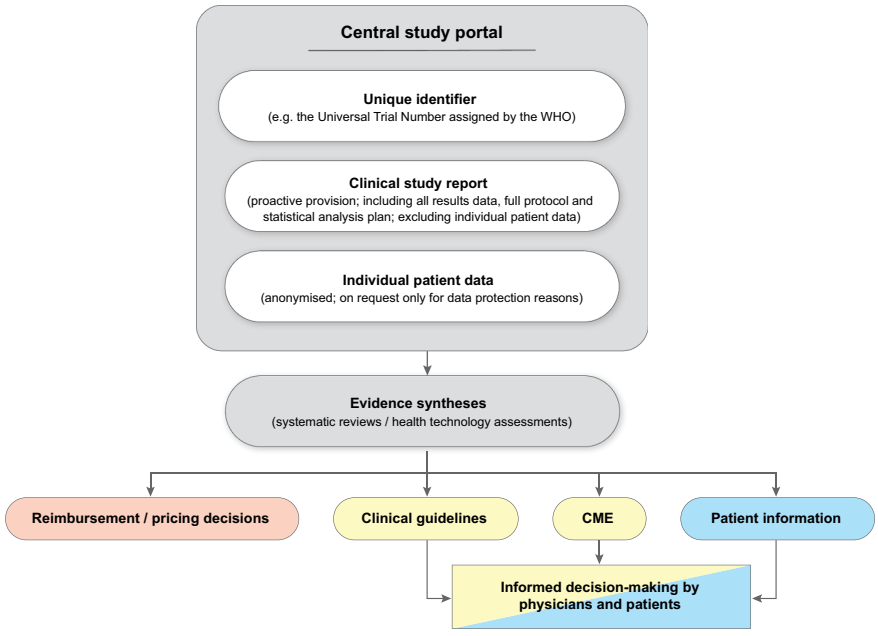

Figure 1. Structure of a central study portal for generating CSR-based evidence syntheses for various types of information formats.

shows a proposal for the basic structure of the portal for each clinical study, including a unique identifier as well as the corresponding CSR (provided proactively) and anonymised IPD (provided on request). To enable efficient data processing (i.e. easily searchable, copyable and downloadable content) and to minimise errors, a digitised format of the portal is needed. The scope of the portal could also be expanded to studies on medical devices and other non-drug interventions, with prior development of requirements for standardised study reports in these areas.

With regard to legal requirements, the International Coalition of Medicines Regulatory Authorities (ICMRA) and the World Health Organization (WHO) have recently demanded that CSRs "should be published without redaction of confidential information for reasons of overriding public health interest" and "call on the pharmaceutical industry to commit, within short timelines, and without waiting for legal changes, to provide voluntary unrestricted access to trial results data for the benefit of public health" [44]. However, based on previous experience, it is unlikely that voluntary measures will suffice. Legislation for establishment of the portal, including mandatory posting of all CSRs, is therefore essential [40].

Conclusion

Access to clinical study data is still incomplete. The establishment of a worldwide, public, central, and digitised clinical study portal containing all CSRs would enable the resource-efficient production of unbiased evidence syntheses, not only to inform health policy decisions, but also for use in other information formats such as clinical guidelines, CME materials, and patient information, and could thus ultimately improve treatment outcomes.

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