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REVIEW

The evolution in registration of clinical trials: a chronicle of the historical calls and current initiatives promoting transparency

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Abstract
Purpose Quality of care is strongly influenced by evidence-based medicine, a large part of which is based on results obtained from clinical trials. If trials are conducted in secret, patient safety is at risk. Several mandates—legal, editorial, financial, and ethical—have tried to influence the disclosure of clinical trials, first by encouraging registration in publicly accessible registers and, second, by calling for the publication of results. Not all these initiatives have reached high rates of compliance, but the succession of national and international events over a few years gave an important boost to information disclosure. This article provides a chronicle of the succession of the events, from the historical calls to the recent EMA policy and WHO statement, and public consultations requested by the NIH, and the HHS, which will inevitably change the international panorama. The path of these new policies is moving towards more supervised clinical research. Individual scientific institutions can also contribute, at the local level, to such an ethical endeavor as is improving research transparency, by disclosing information on the trials coordinated by their own researchers.
Results The way is long and complex, but, if everyone contributes there could be a prompt, worldwide diffusion of the findings of clinical trials, and therefore a more possible evidenced-based medicine.

Keywords Clinical trials as topic/legislation and jurisprudence · Government regulation · Publication bias · Registries

Quality of care is strongly influenced by evidence-based medicine (EBM) and shared decision making, both of which are based on information originating from clinical trials. If trials are conducted "secretly", or if their results are not properly shared, publication bias is generated, scientific evidence available can be seriously affected, and medical practice can be steered towards suboptimal, or even dangerous, treatments, negatively affecting patient care [1, 2]. The most common way to disseminate precious trial information is through registration in public registries and through the consequent publication of results in peer reviewed, scientific journals, or scientific congresses [3]. All this information can then feed into the increasingly important scoping reviews and, consequently, into systematic reviews that generate more precise, unbiased evidence [4]. Guidelines aimed to improve quality of reporting, such as the CONSORT statement, are currently endorsed by several editorial groups, including the International Committee of Medical Journal Editors (ICMJE), the Council of Science Editors, and the World Association of Medical Editors (WAME) [5].

The historical calls for registration of studies involving humans date back to the 1970s when Richard Nixon took "the war against cancer" [6] and continued into the 1980s with the American Medical Association (AMA) desire to investigate treatment options for seriously ill patients, for which only a limited number of treatments were available. In that period, Simes RJ first wrote about the importance of making clinical trial data publicly available, raising concerns about difficulties

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in evaluating different therapies, and, consequently, permitting physicians to choose the best therapy available for their patients [7]. This shared desire resulted in the first U.S. federal law focusing on this issue, the Food and Drug Administration Modernization Act of 1997 (FDAMA 113), which established federal requirements for sponsors of trials addressing serious diseases to register the protocol information prior to subject recruitment. The FDAMA 113 also mandated, in 2000, the implementation of the first large clinical trial databank, ClinicalTrials.gov. However, this law had low compliance and, for years, researchers continued to stress how a declaration of the existence of trials and the timely publication of their results are an ethical responsibility with broader connotations [8]. The most evident of which are that fraud and scientific misconduct can be more easily detected, patients are safeguarded [9], a basis for progress in science is created, overtreatment can be limited [10], patients are provided with information that can help them make more informed decisions about their own health [11], and populations neglected by health R&D can be identified more easily [12]. Furthermore, disclosure of trial information allows for a more rational use of healthcare resources [13]. (See Table S1)

The FDAMA 113 opened the way to several other initiatives involving the research industry, public community, academia, and editorial societies (Fig. 1, Table S2). One of the most influential initiatives, however, was made in 2004 by the ICMJE. In a statement, this group announced that registration in a publicly accessible register (e.g., Clinicaltrials.gov) would become a prerequisite for all future publication of the results arising from clinical trials. The amount of information that was to be registered was limited to 20 items that were proposed by the World Health Organization (WHO) advisory group in 2004. In 2005, several national and international calls for registration followed this trend, like the Maine State Law and the Ottawa Statement [14, 15].

The increased demand for transparency was not just limited in the USA. The WHO, during the Mexico summit on Health Research in 2004 and the 58th World Assembly (2005), called for the worldwide scientific community, international partners, the private sector, society in general, and other interested parties to document their findings in an internationally accessible register. They also announced their intention "to establish a voluntary platform" that would work as a meta-register, collecting data only from the WHO accepted register, in order

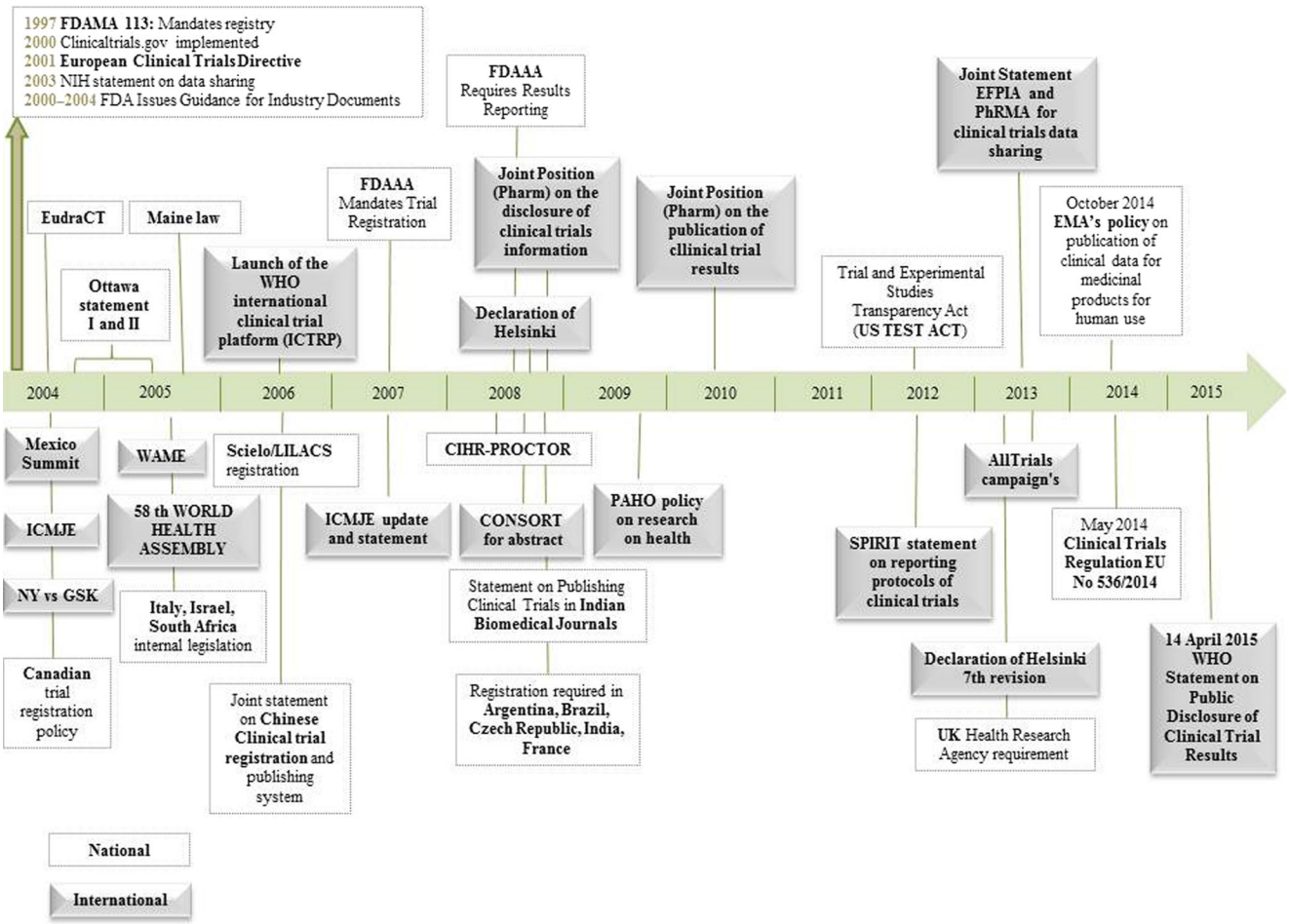

Fig. 1 Global view of initiatives promoting trial registration and release of results

to ensure a single point of access and the unambiguous identification of trials through the use of a Universal Trial Number (UTN). This platform, known as the International Clinical Trial Registry Platform (ICTRP), was formally launched in 2007. At the 11th World Congress in Public Health in 2006, a commitment was made to "make research results publicly available and incorporate them into the formulation of public policies and health interventions".

The pharmaceutical industry, initially reticent about sharing its research due to financial interests [16], also recognized, through a Joint Position, enforced in 2009, the importance of disclosure of clinical trial information and committed member companies to post the results of certain clinical trials in results registries, such as those on company websites or in other web-based industry registries such as ClinicalStudyResults.org [17, 18].

Another important milestone, called the Food and Drug Administration Act (FDAAA), set up in 2007, mandates the registration of trials on a widespread range of diseases (except for phase I drug trials) and requires the disclosure, within 1 year, of results for all completed studies. The non-compliance for federally funded trials results in monetary penalties of up to $10,000/day. The FDAAA also expanded the scope of Clinicaltrials.gov, which was provided with a new section in which results must be added.

As a whole, these initiatives seem to have positively influenced trial registration worldwide, and this evidence came from the continuous increase in the rate of new registrations occurring in the ClinicalTrials.gov register. However, the quality and timing of registration were found to need improvement [19, 20], and publication rates among completed trials registered within Clinicaltrials.gov were found to be low [21–23].

Despite the progress made in clinical trial registration, several challenges and areas of improvement remain. The US Trial and Experimental Studies Transparency (TEST) Act, drawn up in 2012 as a consequence of the underreporting of clinical trial results, expands the reporting requirements to include interventional studies conducted outside the USA and post marketing surveillance studies of class II or class III devices that involve data collection from human subjects. The act warrants companies to submit a trial's summary of results to the registry in which the trial was registered, including information on the primary and secondary outcomes and statistical analyses conducted, within 1 year of completion of the trial [24].

The World Medical Association's Declaration of Helsinki (DoH), later, required that any clinical study involving humans be registered in a public clinical trial register before recruitment of the first participant, emphasizing the need for registration of all clinical trials conducted worldwide (Article 19). In a 2013 revision, it also called for the disclosure of all results, including negative or inconclusive ones (Article 30), outlining the principles for research involving human subjects, and underscored the ethical obligation to publish all results in a complete and accurate manner.

In Europe, under a growing demand for transparency, the European Medicines Agency (EMA) announced, in 2012, a new policy on publication of clinical data for medicinal products for human use. After a long public consultation process, which was the participation of industry representatives, patients, healthcare professionals, and academia, the final law was published in June 2014. This version was, however, criticized and considered a step back by a large part of the scientific world [25] due to a series of limitations that accompanied it. In this context, an important global movement called the AllTrials campaign came to light, placing itself on the forefront in the battle against these restrictions. This shared discontent resulted, in October 2014, in the EMA's final version of the new policy on the Publication of Clinical Data for Medicinal Products for Human Use concerning EU clinical trials, which partly overlaps with the US FDAAA of 2007 [26–28]. The final version of the new policy will also serve as a complementary tool in the implementation of the EU Clinical Trials Regulation published on 27 May 2014 (EU No 536/2014), which requires the expansion of the European Clinical Trials database (EudraCT) (that currently covers only phase II to IV drug trials) to align it to that of ClinicalTrials.gov, with its results section. This regulation requires the public disclosure of the most complete final report of studies conducted, called the clinical study report (CSR), within a year of a commercial trial's completion. This policy, that will make trial data in Europe more transparent than anywhere else in the world, even the USA [29], will officially come into force in January 2015, requiring submission of CSRs for all applications for centralized marketing authorization submitted after this date. The EMA will provide public access to the core content of CSRs and will allow researchers to download and use the reports for further analyses. Two levels of access will be available: the first level will be accessible through a simple registration process and will be viewable in screen only mode, while the second level (for academic and research use only) will also require proof of identity and will allow users to be able to download and save parts of the CSRs. However, these users are encouraged to provide the EMA with a copy of their secondary analyses before publishing any research results. The EMA is also currently attempting [30] to find the most appropriate way to make individual patient data (IPD) available in compliance with the current law on raw data sharing of the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) [31].

The recent EU initiatives will open up a new era in the European landscape, although even greater endeavors are needed. The vagueness concerning precisely which parts of the CSRs, and which kind of information submitted by pharmaceutical companies could be considered as "commercially confidential",

however, is still worrying [32]. Furthermore, the new EU regulation should be expanded to include older, marketed drugs, which are the ones most commonly used today.

Similar measures are currently under evaluation in the USA. In November 2014, the US department of Health and Human services (HHS) proposed new rules to clarify and expand the requirements of the FDAAA to include submission of summary results of trials involving unapproved, unlicensed, and unclear products [33]. In conjunction, the National Institute of Health (NIH) proposed a new policy on registration and results reporting for all clinical trials they funded. The same proposal announced that timely reporting of clinical trials will be taken into consideration during the review process of subsequent funding applications [34]. Once again, however, there is no mention of a mandatory requirement for public access to CSRs. Both proposed rules were open for public consultation until mid-February/end of March 2015.

Giving full access to a trial protocol and to the main trial results is an attempt to safeguard the integrity of the study and is considered the gold standard for minimizing the effects of reporting bias [35]. Examples of suppressed evidence, including the link between some SSRI antidepressants and increased suicidal thinking and behavior in some children and adolescents [36], as well as the link between COX2 inhibitors and cardiac failure, better known as the "Vioxx story", show how dangerous such omissions can be [37]. The recent "Tamiflu saga" [38], which ended in the large Cochrane meta-analysis on neuraminidase inhibitors (oseltamivir and zanamivir) [39], shows that when bias is introduced due to the inaccessibility of complete information, billions of dollars, including those from public funds, are lost [13]. Several doubts exist, however, on giving full access to a trial protocol and to the main trial results. Access to such data could give rise to unfounded health scares [40], since independent reviews of data are "vulnerable to distortion" and can lead to important cases such as that of the fraudulent research findings linking the measles, mumps, and rubella (MMR) vaccine to autism [41].

Researchers have reported several examples of discrepancies between protocols and published reports[42] and reported that these changes are often linked to the safety and efficacy outcomes originally mentioned in the trial protocol [43, 44], and that industry funded trials are more often associated with significant primary outcome changes [45]. The industry, criticized for a long time [22], to maintain the commercial information confidential, has recently been shown to have become more responsive to the FDAAA legal mandate [46]. However, reports of trials are often difficult to find and, in some cases, do not even exist, as many trials are abandoned or not published due to negative or ambiguous results. It was estimated that journal editors publish about 73 % of positive studies [47], and that these appear in journals more often, and about 1 year earlier, than do those with negative results [48, 49]. Legislation must also evolve on the international level to ensure that regulation and data requirements are aligned within countries and addressed to poorer nations that have inadequate systems available for keeping up with the continuing evolution of legal requirements. The WHO is endorsing the idea that only a global system of obligations can effectively ensure global trial registration and data transparency and, in April 2015, launched a statement [50] on the public disclosure of trial results calling for every trial present or past, positive or negative to come to light. Among other resolutions, it also recommends that protocols for clinical trials be written in accordance with the SPIRIT reporting statement and that ethics committees and ethical review boards be encouraged to review the publication of results from trials they approved [51, 52].

With the involvement of ethics committees and of the funding agencies, which are increasingly implicated in this aspect of trial conduction, the "disappearance" of data to the public knowledge base can certainly be limited. In this context, in 2011, a German act asked sponsors to submit a standardized dossier, subsequently reviewed and made public by the German Institute for Quality and Efficiency in Health Care (IQWiG), including evidence of a drug's added benefit over already available drugs, without, however, including the CSR. Major limitations exist with this system, however, since most of the documents are in German, limiting readership and accessibility. The initiative of the UK Health Research Authority (2013) [53], requiring the registration of all clinical trials in the UK as a condition for a favorable ethics approval, is another important step and should be taken in all countries.

With all these laudable efforts aimed at increasing transparency through trial registration, one cannot forget that a huge responsibility falls on researchers to find, grasp, and assess the resulting data in a complete and competent manner. This responsibility involves both individual researchers, for their publications, and those compiling and assessing data for systematic reviews. Quality checks of new records, performed by those who manage the registries, along with the more recent concept of rendering CSRs public, have some positive effects, at least in terms of data completeness [54]. Initiatives like the Enhancing the Quality and Transparency Of health Research (EQUATOR) network (http://www.equator-network.org/) being made to increase the quality of results reporting.

Before a foolproof system will be put into place, however, the hazy "incubator" formed by the progressive input of results into registries by (well-meaning) individuals represents a tremendous potential, both in positive and in negative, and should not be underestimated. Given the well-documented delay in publication of results, data often remains unemployed for an indeterminate period of time [55]. Scoping reviews can rummage around in this "incubator" to gather information on research that has not yet been exposed, in order to better orient patient care without delay, but they can also guide the

investment of resources based on gaps in research. However, scoping reviews, which have the potential to "instantly" capture data from these free and easily available sources, are not yet regulated by a standard methodology and process of results reporting that can guarantee their integrity and comprehensiveness, unlike CSRs and journal publications, which are covered by the ICH E3 guideline [56] and the Consolidated Standards of Reporting Trials (CONSORT) statement [57], respectively.

Data sharing is, at the moment, the new gold standard for the scientific community. The latest set of recommendations in this context, proposing standards for sharing clinical trial data, comes from the Institute of Medicine (IOM) [58]. A number of pharmaceutical manufacturers and research institute, increasingly oriented toward data transparency, have developing platform to provide access to data from clinical trials and to promote its use [33]. Researchers could request, through these specific platform, access to anonymised patient level data and other supporting documentation to conduct further research and generate new knowledge. Several successful initiatives have launched data sharing platforms such as the YODA Project (http://medicine.yale.edu/core/projects/yodap/), Project Data Sphere® (https://www.projectdatasphere.org/projectdatasphere/html/home.html), the Immune Tolerance Network (http://www.immunetolerance.org/), and the ClinicalStudyDataRequest.com (https://www.clinicalstudydatarequest.com/). With these emerging data sharing platforms, both in the private and the public sector, researchers will be able to speed up research and provide the basis for advances in medicine.

Worldwide initiatives so far have strengthened EBM. The new health policy proposals launched by some of the most important institutions worldwide (NIH, EMA, and WHO) will surely improve the situation. Individual scientific institutions can also contribute, at the local level, to such an ethical endeavor as is improving research transparency by disclosing information on the trials coordinated by their own researchers [59].

The way is long and complex, but if everyone contributes there could be a prompt, worldwide diffusion of the findings of clinical trials that will benefit not only scientists but also several groups of people (physicians, research participants, regulators trials sponsors, and funding organisations). This would be in the interest of everyone, but firstly the patients.

Conflict of interest The authors declare that they have no competing interests.

Author's contribution Claudia Pansieri drafted the initial manuscript, reviewed and revised the manuscript, and approved the final manuscript as submitted.

Chiara Pandolfini supervised, reviewed and revised the manuscript, and approved the final manuscript as submitted.

Maurizio Bonati conceptualized, reviewed and revised the manuscript, and approved the final manuscript as submitted.

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