Clinical trials: registration and transparency

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Today, scientific evidence drives medical practice. Translational, clinical and operational research provide, day after day, new information to clinicians, public health specialists, policymakers and health officials, improving their management of single patients and of the general population. However, it is not easy to identify the best sources of information within a growing number of journals and scientific articles.

The scientific evidence can be hierarchically ranked as follows: systematic reviews and meta-analyses at the top and case series and case reports at the bottom. In the middle of the scientific evidence pyramid, clinical trials and observational studies represent an important milestone for medical practice. In particular, clinical trials can show the role played by interventions (*e.g.* drugs vaccines) in modifying the natural history of diseases and health status.

An interesting scientific debate on the role and importance of clinical trial design and registration [1, 2] was generated by the study conducted by Tang *et al.* [3] in the People's Republic of China and published in a previous issue of the *European Respiratory Journal*. The aim of the study was to assess the efficacy, safety and tolerability profile of linezolid-containing regimens in patients with difficult-to-treat extensively drug-resistant (XDR) tuberculosis (TB). The authors carried out a randomised controlled trial, in which XDR-TB patients were randomly assigned to the experimental drug-containing regimen or to a control regimen. In the recent past the *ERJ* has published several articles describing the findings of observational and experimental studies focused on therapeutic alternative options for multidrug-resistant TB and XDR-TB [4–8].

Results of clinical trials, which are considered one of the main sources of scientific evidence, can be confirmed by the findings of well-designed and adequately conducted epidemiological observational studies [6]. However, observational studies carried out in order to assess the effectiveness and safety of drugs suffer from some methodological biases, which can significantly affect inference and reliability of the findings. Epidemiological observational studies do not provide any interventions by definition. They can be prospective or retrospective; however, the principal investigator or the sub-investigators cannot actively control the intervention and can only observe the "natural history" of a routine activity (including the daily administration of a drug). Frequently, the studies describe a clinical experience of a prospective or retrospective cohort of patients, consecutively recruited by a single clinical centre, without a control arm. The sample size is usually not computed *a priori* and not based on scientific assumptions, with the consequent highest risk of performing an underpowered study, which is unable to adequately assess the magnitude of the effect of the experimental drug. Furthermore, the role played by noncontrolled demographic, epidemiological or clinical variables on the drug effect could be relevant, heightening the background noise around the primary and secondary objectives of the study and rendering the interpretation of the findings very

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complicated. Some methodological biases (*e.g.* the effect of covariates) can be reduced but not eliminated during the statistical analysis, by stratifying or adjusting for the main confounding variables.

On the other side, clinical trials are studies where the investigators assign an experimental or a control drug following a pre-defined procedure, usually randomly in order to reduce the influence of subjective factors (*e.g.* disease severity) and to provide patients the same probability of being included in the experimental arm. They are frequently controlled (as, for instance, phase IIb or IIIa and IIIb trials) in order to assess the efficacy of the experimental approach. Interventional studies are designed following strict methodological rules, driven by a specific research question, linked to one or more statistical hypotheses representing the basis for the computation of the experimental and control arm size. The selection (inclusion/exclusion) criteria favour the establishment of homogeneous groups for the main confounding variables (*e.g.* age, sex, comorbidity, *etc.*).

In the recent past, in particular, scientific experts highlighted the risk of publication bias, which is defined, in simple words, as a disproportionately higher frequency of published experimental studies with "positive" findings. Publication bias could result in a distorted picture of a drug's efficacy, safety and tolerability, with obvious clinical, scientific and ethical consequences.

On this basis, in 2004 the Canadian Institutes for Health Research hosted an international meeting to sustain the clinical trial registration [9, 10] and to develop the rationale behind it. In particular, the meeting stated the crucial importance of providing a unique identification code and sharing publicly both the research protocol and the main findings at the end of the study. Ethical and scientific principles support what, at first glance, seems to be a simple bureaucratic activity.

From an ethical point of view, registering the trials offers the following advantages: 1) ensuring global access to scientific data; 2) offering to all patients the possibility of being recruited in an experimental study (with increased probability of clinical recovery if compared with the exposure to the standard of care); 3) reduction of redundant studies based on the same aim (preserving the concept of scientific reproducibility) to save public financial resources for other studies; and 4) the evaluation of the adherence to internationally agreed-upon ethical standards.

From a scientific perspective, trial registration allows investigators to increase the quality of research design and reliability of the scientific evidence (by peer-reviewed analysis of methods and results), supports international scientific cooperation and reduces the likelihood of negative findings being under-reported.

The decisions of policymakers, regulatory agencies and other relevant stakeholders are based on interventional studies, as a consequence of the methodological advantages mentioned above.

The transparency achieved by registering the trials allows prevention (to some extent) of inappropriate or ambiguous studies, including the modification of primary end-points during the interim analyses according to the results.

TABLE 1 Primary clinical trial registries in the World Health Organization Registry Network (available at www.who.int/ictrp/network/primary/en/)

Registries	Website
Australian New Zealand Clinical Trials Registry (ANZCTR)	www.anzctr.org.au
Brazilian Clinical Trials Registry (ReBec)	www.ensaiosclinicos.gov.br
Chinese Clinical Trial Registry (ChiCTR)	www.chictr.org.cn
Clinical Research Information Service (CRiS), Republic of Korea	http://cris.nih.go.kr/cris/en/use_guide/cris_introduce.jsp
Clinical Trials Registry – India (CTRI)	http://ctri.nic.in
Cuban Public Registry of Clinical Trials (RPCEC)	http://registroclinico.sld.cu/en/home
EU Clinical Trials Register (EU-CTR)	www.clinicaltrialsregister.eu
German Clinical Trials Register (DRKS)	www.germanctr.de
Iranian Registry of Clinical Trials (IRCT)	www.irct.ir
ISRCTN.org	www.isrctn.org
Japan Primary Registries Network (JPRN)	http://rctportal.niph.go.jp
UMIN CTR	www.umin.ac.jp/ctr
JapicCTI	www.japic.or.jp
JMACCT CTR	www.jmacct.med.or.jp/en
Thai Clinical Trials Registry (TCTR)	www.clinicaltrials.in.th
The Netherlands National Trial Register (NTR)	www.trialregister.nl
Pan-African Clinical Trial Registry (PACTR)	www.pactr.org
Sri Lanka Clinical Trials Registry (SLCTR)	www.slctr.lk

All clinical trials should be recorded in one of the international registries available worldwide (table 1). Observational studies, which are hierarchically at a lower level in the scale of the scientific evidence, may be approved by an institutional review board but also deserve the public advertisement requested for clinical trials in order to improve the transparency of their epidemiological design.

The Chinese study mentioned above [3], although not recorded in any of the international registries available, was duly approved by national authorities. While this approach might be deemed acceptable, this cannot be considered as an ideal one as the same rules should be applied to all investigators worldwide irrespective of the country where the study has been carried out.

On this basis, while exceptionally accepting to publish the study reported by Tang *et al.* [3], the *ERJ* strongly requests all investigators to register their clinical trials as per the current recommendations of the International Committee of Medical Journal Editors (table 1) [11, 12]. Today, more than ever, the *ERJ* is committed to improving the understanding of both the research community and the national scientific boards on the advantages of achieving a systematic public registration of clinical trials.

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