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EDITORIAL

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New trends in clinical trials—between complexity and the need for renewal

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Clinical studies are crucial for advancement in the medical field, particularly in onco-hematology, and these studies have enabled the achievement of a significant increase in overall survival and a reduction in patient mortality rates (1). To obtain solid and reproducible results, all studies must comply with very rigorous qualitative and ethical requirements, dictated by good clinical practice (GCP) and by all the rules that, at national and international level, have transformed these guidelines into legislations (2,3). In recent decades, however, clinical research has undergone a deep transformation, and conducting it has become an increasingly challenging endeavor.

The challenges of measuring the safety and efficacy of investigational drugs that target chronic, difficult-to-treat, or rare diseases in more narrowly defined patient subpopulations have made the scope of clinical trials more complex and burdened their conduct in the past 15 years (4).

Over time, clinical trials have had to respond to increasingly stringent quality requirements, often interpreted in an excessively conservative manner by sponsors and institutions (1).

The increase in complexity has affected various fields of research and can be explained by the use of more sophisticated scientific designs, larger global scopes, and greater focus on highly targeted patient subpopulations.

As demonstrated by Getz and Campo (4) comparing the five-year period 2001-2005 and 2011-2015, there is an undeniable boost in the cost of research, in the number of procedures required and in the number of healthy volunteers planned and, above all, in the workload for the study staff, which in Phase 1 studies has increased by about 82%.

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In addition, the group of Getz also found a wide variability in the complexity between therapeutic areas and clinical study phases. Conversely, growth in complexity is at the slowest rate for Phase 3 protocols as companies are focusing on gathering data from early phase trials in an attempt to minimize costs (5).

Bureaucracy, which is mainly linked to the regulatory process, must certainly be considered among the most frequent causes of the growing difficulty in performing studies, both as promoters and as participating centers.

Clinical trials must comply with many regulatory and sponsor-specific requirements that can be inefficient and costly for research programs to implement and often are interpreted conservatively by clinical centers, Clinical Research Organizations (CROs), and sponsors. Although the intent of these requirements is to protect trial participants and manage future patients' risk/benefit ratio, they may also delay research and slow patient access to therapies being developed. This is especially true when the parties involved err on the side of over-reporting, given the perceived risk of penalty (1).

In addition, some authors have argued on how often the presence of a CRO as an intermediary between the promoter and the participating centers is anything but a source of simplification (6).

One cause, albeit indirect, of the complexity at the European level was represented by the vast heterogeneity with which the various Member States have over time implemented Directive 2001/20/EC (2), which has translated in a different power of attractiveness in the pharmaceutical field (7,8). So much so that authorities have decided to repeal it in favor of Regulation 536/2014 (3). The latter, in order to guarantee greater homogeneity in trial management, will impose timelines and requirements that are not easily achievable in all situations, especially for clinical centers and particularly in the field of academic research. Moreover, besides initial intentions, an immediate implementation of the standard has not been possible in all countries, so much so that there are countries still very far from being ready (9). Even the General Data Protection Regulation (GDPR) (10), introduced with the noble intention of protecting the personal data of citizens, has ending up creating numerous obstacles to scientific progress, causing, in some contexts, even interruption of simple studies and with minimal impact on the patient, such as retrospective observational studies (11,12).

To cope with all this complexity, the only way forward is for centers to equip themselves with solid research infrastructures (13-16) and highly trained and qualified multidisciplinary teams to tackle all activities that go beyond clinical management in compliance with the necessary standards. Some of the professional skills required within these teams, among others, seem to account for most of the activities of a research group, namely, clinical research coordinators and research nurses, who deal with more than 30% of the activities foreseen by a trial, compared to clinicians who account for less than 10% (17). The lack of infrastructures is considered one of the main weaknesses of a research system (8) and is connected to a whole series of political/economic controversies deriving from the lack of contractual recognition within centers of many of the necessary professional figures (18,19). One question is obvious: is all this complexity really synonymous of quality? Some doubts about this have often been raised (20). In fact, during the Covid era, the competent authorities themselves allowed us to oversee many of the restrictions that seemed vital to us before the pandemic and many researchers continue to demand for some of the extraordinary operating methods granted in the last 2 years to be maintained (21-24).

The time has come for a thorough reflection by the scientific community regarding the current means of clinical trial management.

Probably the time has come for a serious reflection by the scientific community on the current methods of managing clinical trials and on the possibility of maintaining them in the future. After all, the second major revision of GCP guidelines is approaching and nowadays there is more and more talk on the decentralization of trials (25,26) and the increasingly central role of patients (27).

Are we ready?

I am looking forward to receiving points of view, individual experiences, comments, and opinions from colleagues involved—directly or indirectly—with this complex but fascinating area of research.

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