

COMMENTARY**A harmonized and efficient clinical research environment would benefit patients and enhance European competitiveness****Antonino Amato¹, Eugenio Aringhieri², Stefania Boccia³, Filippo Buccella⁴, Barbara Gorini⁵, Donatella Gramaglia⁶, Riccardo Masetti⁷, Paolo Rossi⁸ and Pier Giuseppe Pelicci⁹**¹*Clinical Trial Center, Fondazione Policlinico Universitario A. Gemelli, Rome, Italy*²*Farmindustria-Gruppo Biotecnologico, Rome, Italy*³*Institute of Public Health, Università Cattolica del Sacro Cuore, Fondazione Policlinico Universitario A. Gemelli, Rome, Italy*⁴*EUPATI IT Chairman, Rome, Italy*⁵*Investigator Site Development Lead, Development Operations, Global Clinical Trial Execution-Pfizer Italia, Rome, Italy*⁶*Agenzia Italiana del Farmaco, AIFA, Rome, Italy*⁷*Dipartimento di Chirurgia Senologica, Fondazione Policlinico Universitario A. Gemelli, Rome, Italy*⁸*Dipartimento Pediatrico Universitario-Ospedaliero, Ospedale del Bambino Gesù, Università degli Studi di Roma Tor Vergata, Rome, Italy*⁹*Dipartimento di Oncologia Sperimentale, Istituto Europeo di Oncologia, Milan, Italy***Abstract**

The forthcoming implementation of the European Clinical Trial Regulation (Regulation (EU) No. 536/2014), which is expected to facilitate the conduct of clinical trials across the European Union, will require National Authorities to create the best conditions for the implementation of the new Regulation through national guidelines, so that sponsors may reconsider Europe as a prime location for planning clinical trials. During a meeting titled "Innovation in Clinical Research", an expert panel discussed potential local advances fostering competitiveness of European clinical research with representatives of the pharmaceutical industry, patient organisations and Italian regulatory agency in view of the forthcoming implementation of (EU) No. 536/2014 on clinical trials of medicinal products. In this article we summarise the findings of the meeting, describe features characterising clinical research patterns and offer some suggestions on the possible involvement of all stakeholders in order to foster research innovation and allow the timely access to novel medicines for patients.

Key words

- European Union
- legislation
- clinical research

BACKGROUND

Between 2007 and 2012, overall global biomedical research and development (R&D) expenditures increased by 18.4%, while remaining static or decreasing in North America and Europe [1]. In parallel, between 2004 and 2016, the number of human studies conducted globally increased from 12 018 to 234 321 [2], while the share of clinical trials (CTs) performed in the European Union (EU), including Italy, decreased by 15% between 2009 and 2015 [3, 4]. These trends have

increased demands for regulatory harmonization and improved efficiency of CT research [5]. Cost, speed of approval and shortcomings of the European Clinical Trial Directive [6] are cited in explanation of the declining clinical trial numbers. Dominant factors in trial site selection are investigator-dependent factors and ease of approval. Therefore, fostering competitiveness and bringing more clinical trials to Europe may depend more on harmonization of approval processes, cultivating centers of excellence and reducing "hid-

den” indirect costs rather than additional government investment [7].

An expert panel of investigators with strong expertise in clinical research, together with members of the pharmaceutical industry, patient organizations and the Italian regulatory agency met under the banner of “Innovation in Clinical Research” to identify ways to involve all stakeholders in advancing Italian and European competitiveness in the global “trial market” to foster research innovation and timely access to novel medicines alongside the implementation of the Regulation (EU) No. 536/2014 on CTs for medicinal products [8].

THE EUROPEAN REGULATORY FRAMEWORK: PRESENT AND FUTURE

Europe has consistently expressed the desire to maintain and improve its competitiveness as an attractive place for conducting CTs. Directive 2001/20/EC [6], envisioned to support this goal, has failed, in part because of differences in implementation levels across member states (MSs), excessive bureaucracy, the need for multiple applications, difficulties in handling divergent regulatory decisions and lengthy/uncertain time intervals for authorisations [7, 9].

CTs require the involvement of many/all EU MSs to recruit sufficient patients; new efficient and rapid procedures for CT authorisation are needed. A key innovation of Regulation 536/2014 [8] was a single electronic application for all interventional studies, to be submitted via a EU submission portal once it becomes fully functional.

Regulatory policy makers of all EU MSs should work to create local harmonized conditions and improve local standards of clinical research at all levels, allowing effective implementation of the new Regulation through pilot schemes such as the Voluntary Harmonization Procedure.

PREPARING FOR CHANGE: THE ITALIAN CASE STUDY

The Italian situation is similar to that of several other European MSs. CTs are currently regulated by Legislative Decree no. 211 [10], implementing Directive 2001/20/EC [6]; the Italian Medicines Agency (Agenzia Italiana del Farmaco, AIFA) is the Competent Authority for issuing authorization of all medicinal CTs from Phase I-IV, although AIFA collaborates with the Italian National Institute of Health (Istituto Superiore di Sanità) for the evaluation of phase I and I/II studies.

Electronic submission of data and supporting documents are submitted through AIFA’s portal, the National Monitoring Centre on Clinical Trials of Drugs (Osservatorio nazionale sulla Sperimentazione Clinica dei medicinali). Many challenges face the Italian Regulatory Authorities and Ethics Committees (ECs) in fully complying with the new Regulations: strict time frames for assessments, need for internal consistency for opinions, difficulties in identifying experts in specific areas, and adequate internal resources.

Reorganization of the operations of ECs to reduce their excessive numbers and simplify the complex regulatory framework while boosting operating standards

and training is needed, with the goal of a few regional/national ECs.

“Hidden” costs related to bureaucracy, slow recruitment or poor overall site performance relative are perceived to be factors influencing the selection of Italy as a site for CTs [7]; carefully crafted harmonization of approvals, greater visibility of centers of excellence and reduction in “hidden” costs are needed to reach the goals of an attractive European “trial market”, thus saving time and reducing costs of drug development.

CLINICAL EXCELLENCE AND CLINICAL TRIAL CENTERS

Italian academic institutions such as Fondazione Policlinico Gemelli in Rome have created their own Clinical Trial Center (CTC) to foster excellence in running CTs, providing investigators with tools for planning, starting-up, managing and conducting high quality CTs, allowing early exposure of patients to innovative treatments.

CTCs act as a single interface with industry, guaranteeing a homogeneous and efficient process at different levels throughout the study process, and can provide training for the CT personnel. Funds thus generated could primarily be used to finance full-time positions of clinical research-dedicated personnel, who will be instrumental in running qualitative CTs, ultimately attracting additional clinical research to Europe.

Oncology and pediatrics are examples where such cooperation can play a relevant role of benefit to all stakeholders.

Oncology

Oncology is currently undergoing a transformation triggered by new insights in genomics and cellular biology, characterized by rapid improvement in the understanding of underlying disease mechanisms and the development of targeted drugs. The European Institute of Oncology (Istituto Europeo di Oncologia) in Milan, an oncology-focused hospital translating basic research into an innovative and successful drug discovery program, is an example of how investment in basic and clinical research through National Health System hospitals can accelerate the discovery of new cancer therapies and improve access to innovation.

Pediatrics

Drug development programs in adults do not automatically translate to the pediatric setting. Ethical concerns, methodological issues, lack of awareness of the need for validated pediatric-specific outcome measures, and economic reasons are obstacles in performing pediatric CTs and increasing the relatively low number of pediatric marketing authorizations. Strengthening the application of the new EU regulation in the light of specific pediatric considerations, including establishing a network of pediatric CTCs, such as the partnership between Bambino Gesù Children’s Hospital (Ospedale Pediatrico Bambino Gesù) in Rome and GRiP, would be valuable.

PUBLIC-PRIVATE PARTNERSHIPS

Available public sector funding is decreasing as medical needs and scientific complexity increase, and tight

collaboration among the private sector, academia and government is vital for advancement, fostering the translation from basic science to clinical treatment through advances in study design and drug development [11, 12]. Academicians should guide study design and selection of investigator sites, with the industry providing expertise in study monitoring and reporting.

Success in drug development derives not only from the critical mass of a single company, but from its ability to enter into an international network of excellence. The “Investigator Networks, Site Partnerships and Infrastructure for Research Excellence” (INSPIRE) program, started in 2012 by Pfizer is an innovative model for private-public partnerships in R&D that focuses on global sites where the most successful clinical research is conducted.

THE CENTRAL ROLE OF THE PATIENT

Traditionally, the prescriber (influenced by the payer/healthcare system) has been the true counterpart for the pharmaceutical companies, with the patient (the consumer) accepting what the healthcare professional thought best, with little understanding of therapeutic options. This era of doctors deciding what is best for a patient is coming to an end, as patients are becoming more informed and involved in their health.

Active participation of patient organizations in clinical research is welcome, potentially leading to better study designs, higher patient enrollment and retention rates, improved credibility of study results and better applicability to patients in the real world [13]. We encourage further cooperation between patient organizations, industry, academia and regulatory agencies in furthering patient-relevant research to streamline study design, improve the economics of research, and provide greater generalizability of study results that will improve industry chances of having profitable drugs approved. The new EU Regulation also requires that CT data are made accessible to laypersons, an important step towards growing awareness and involvement of pa-

tients, and a driver for a better healthcare landscape in the EU.

This concept of “Partnerships in medicines development = value for all” has been adopted by the European Patients’ Academy on Therapeutic Innovation (EU-PATI), a pan-European project led by the European Patients’ Forum and 32 other partners from patient organizations, universities, non-profit organizations and European pharmaceutical companies. It aims to help patients become better educated and involved in R&D through reliable, objective, comprehensive, lay-friendly information and training [14].

CONCLUSIONS

We are in broad agreement that consistency of standards in the development of medical products improves the efficiency and transparency of the drug evaluation process, promoting medication quality and public health. Implementation of Regulation (EU) No. 536/2014 should facilitate a more efficient approval and execution process for CTs, and we encourage engagement of all stakeholders to carefully implement the legislative, administrative and academic adjustments required, so that Europe and Italy become a prime location for CTs.

Acknowledgments

Medical writing assistance was provided by HPS – Health Publishing and Services Srl with support from Pfizer Global Clinical Trial Execution.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflict of interest statement

The authors declare no conflicts of interest.

Accepted on 7 March 2017.

REFERENCES

1. Chakma J, Sun GH, Steinberg JD, Sammut SM, Jagsi R. Asia’s Ascent – Global Trends in Biomedical R&D Expenditures. *N Engl J Med* 2014;370(1):3-6. DOI: 10.1056/NEJMp1311068
2. *ClinicalTrials.gov*. A service of the US National Institutes of Health. Trends, Charts, and Maps. Available from: <https://clinicaltrials.gov/ct2/resources/trends#RegisteredStudiesOverTime>.
3. Agenzia Italiana del Farmaco. *15° Rapporto nazionale sulla Sperimentazione Clinica dei medicinali in Italia*. Roma: AIFA; 2016. Available from: www.aifa.gov.it/sites/default/files/15_Rapporto_OsSC_2016.pdf.
4. Agenzia Italiana del Farmaco. *13° Rapporto nazionale sulla Sperimentazione Clinica dei medicinali in Italia*. Roma: AIFA; 2014. Available from: [www.agenziafarmaco.gov.it/ricclin/sites/default/files/files_wysiwyg/files/Pubblicazioni_OsSC/13_Rapporto_OsSC_2014%20\(2\).pdf](http://www.agenziafarmaco.gov.it/ricclin/sites/default/files/files_wysiwyg/files/Pubblicazioni_OsSC/13_Rapporto_OsSC_2014%20(2).pdf).
5. Forum on Drug Discovery, Development, and Translation; Board on Health Sciences Policy; Institute of Medicine (IOM). Weisfeld V, Lustig TA (Eds). *International regulatory harmonization amid globalization of drug development. Workshop Summary*. Washington (DC): National Academies Press (US); 2013. Available from: www.ncbi.nlm.nih.gov/books/NBK153504/.
6. European Parliament and Council of the European Union. Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use. *Official Journal of the European Union* 2001;L21:34-54.
7. Gehring M, Taylor RS, Melody M, Casteels B, Piazza A, Gensini G, Ambrosio G. Factors influencing clinical trial site selection in Europe: the Survey of Attitudes towards Trial sites in Europe (the SAT-EU Study). *BMJ Open* 2013;3(11):e002957. DOI: 10.1136/bmjopen-2013-002957

8. European Parliament, Council of the European Union. Regulation (EU) 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC. *Official Journal of the European Union* 2014;L158:1-76.
9. Petrini C. Regulation (EU) No 536/2014 on clinical trials on medicinal products for human use: an overview. *Ann Ist Super Sanità* 2014;50(4):317-21. DOI: 10.4415/ANN_14_04_04
10. Italia. Decreto Legislativo 24 giugno 2003, n. 211 Attuazione della direttiva 2001/20/CE relativa all'applicazione della buona pratica clinica nell'esecuzione delle sperimentazioni cliniche di medicinali per uso clinico. *Gazzetta Ufficiale* n. 184, 9 agosto 2003 (Suppl. Ord. n. 130).
11. Laterre PF, François B. Strengths and limitations of industry vs. academic randomised controlled trials. *Clin Microbiol Infect* 2015;21(10):906-9. DOI: 10.1016/j.cmi.2015.07.004
12. Chakravarthy R, Cotter K, DiMasi J, Milne CP, Wendel N. *Public and private sector contributions to the research & development of the most transformational drugs of the last 25 years*. Boston: Tufts Center for the Study of Drug Development; 2015. Available from: <http://csdd.tufts.edu/files/uploads/PubPrivPaper2015.pdf>.
13. Domecq JP, Prutsky G, Elraiyah T, Wang Z, Nabhan M, Shippee N, Brito JP, Boehmer K, Hasan R, Firwana B, Erwin P, Eton D, Sloan J, Montori V, Asi N, Dabrh AM, Murad MH. Patient engagement in research: a systematic review. *BMC Health Serv Res* 2014;14:89. DOI: 10.1186/1472-6963-14-89
14. *European Patients' Academy on Therapeutic Innovation*. Available from: www.patientsacademy.eu/index.php/en/about-eupati.