



## Regulation 536/2014 and its beneficial impacts on academic clinical research in Italy. Closing the loop

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### ABSTRACT

Regulation (EU) No 536/2014 (Clinical Trial Regulation, CTR) offers two precious tools to academic clinical research in Italy:

- The right to transfer not-for-profit clinical trials data and results for registration purposes, and co-sponsorship.
- The right to transfer data reduces the time needed to make innovative therapeutical agents and therapies accessible to the patient.

Co-sponsorship, on the other hand, allows the establishment of a partnership between entities with different missions, ideals and attitudes, sharing – nevertheless – the same ultimate goal: meeting the patient's medical needs. Co-sponsorship facilitates collaboration among experts, which allows knowledge sharing, thus guaranteeing, to each contributor, recognition for their own contributions to a complex activity such as a clinical trial.

However, the above-mentioned Regulation poses important challenges, especially in terms of infrastructural efficiency, which is demanding, especially for those entities suffering organizational inadequacies: unfortunately, inefficiency is sometimes a structural problem in the academic clinical environment. This publication focuses on the specific innovative aspects introduced by CTR. It also highlights the possible difficulties to be addressed by their implementation.

### 1. The forthcoming present

Regulation (EU) No 536/2014 [1] offers some valuable tools to untie two of the principal knots currently undermining the effectiveness of academic research in Italy.

The transition from an approach based on Sponsor nature and research purposes to a risk-based approach, creates, in fact, a completely different environment for all stakeholders.

In detail, the risk to subject safety in a clinical trial mainly stems from two sources: the investigational medicinal product and the intervention (Fig. 1) [1]. These factors are – in fact – the only key elements in establishing which category a clinical trial belongs to.

Therefore, the Regulation introduces a risk-based classification of clinical trials which allows to overcome – at least partially – the logic of Ministry of Health Decree December 17, 2004, containing “Provisions and conditions of a general nature, concerning the execution of clinical

trials on medicinal products, with particular reference to those for the purpose of improving clinical practice, as an integrated part of health care” [2].

The abovementioned Decree (now repealed, as will be further explained below) distinguished in fact clinical trials according to both sponsor requirements and clinical trial purposes, strictly forbidding the usage of not-for-profit trials data and results for registration purposes.

Following the application of CTR, every clinical trial conducted in the European Union – no matter its purpose – falls instead within its scope, it has to be compliant with its requirements [1], and therefore, given that the regulatory framework is the same, the way of conducting the trial is unequivocal.

As Recital 82 [1] reminds us, the Regulation's aims are the achievement of an internal market as regards clinical trials and medicinal products for human use, taking as a base a high level of protection of health, and to set high standards of quality and safety for medicinal

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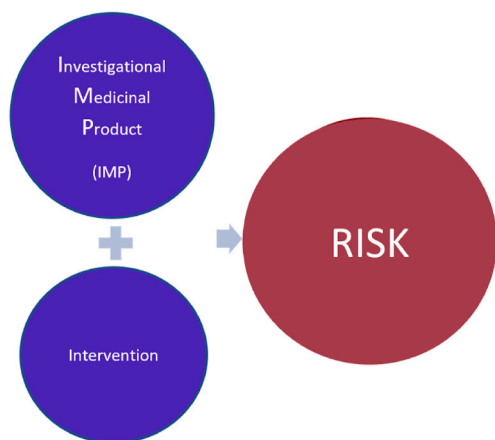
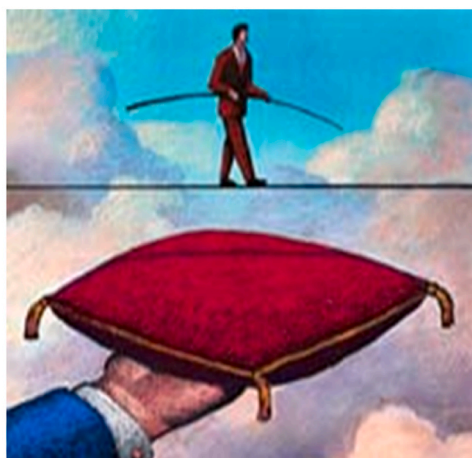


Fig. 1. Sources of risks in clinical trials.

products, in order to meet common safety concerns regarding these products.

Setting common standards of quality and safety means to make all data generated from every clinical trial throughout the Union, performed in compliance with CTR, acceptable for the request of authorization of a medicinal product. The same standards lend equal value to the data, thus opening the way to not commercial trial's data usage for registration purposes. This supposes a direct benefit, namely for the patient, as the time needed for the patient to gain access to new therapies is reduced: the impact of such a benefit is potentially enormous, given that, unfortunately, sometimes the innovative therapeutic option is the only possible cure.

Another positive consequence of the Regulation is the prompt use of the therapeutic agent, outside of trials, which allows the collecting of important information about real-life effectiveness. This information allows the widening of knowledge, affecting the safety of a less homogeneous patient population than that of a clinical trial, and it provides crucial indicators for pharmaceutical governance [3].

## 2. A look at the past

As briefly mentioned above, in Italy, art.1 paragraph 2 letter *d* of repealed Ministerial Decree of December 17, 2004 [2] (i.e. that the clinical trial is not aimed at industrial development or therefore at commercial purposes), restricted significantly the possibility to use not-for-profit trials data and results, making sometimes difficult to confirm the social utility of the clinical trial and preventing that improvement of clinical practice it was meant to pursue.



Fig. 2. The rational transfer creates a virtuous cycle of funds that goes in favour of patients.

In fact, only when the data were in the general domain of the scientific community, they could be inserted into a registration dossier only as support, meaning that another trial should have been conducted by the patent or marketing authorization holder.

The application of the Ministerial Decree of December 17, 2004 [2] turned out to be, ultimately, a dead-end, an incomplete process, regardless of the pathways for early access to a drug (off-label use).

## 3. The future

The Regulation (EU) No 536/2014 and country-level regulatory reorganization turn towards the rational transfer of data and royalties.

That more rational approach foresees that a pharmaceutical company, to which the data is transferred, refunds the direct and indirect costs connected with the clinical trial, as well as the foregone revenue as a consequence of not-for-profit clinical trial classification, which involved some facilitations.

The effects of the rational transfer are aimed at the protection and benefit of each stakeholder:

- first of all, the patients will gain access to treatment much earlier, with already demonstrated results;
- the National Health System and the Sponsor, which are the subjects taking more risks and obligations (such as financial obligations); the clinical sites and the Ethics Committees also benefit, as they can receive unexpected income to be reinvested in research and assistance.

Through rational transfer we ultimately create a virtuous cycle, as more funds will be available to invest in new research activities solely for the benefit of the patient. Therefore, there are two advantages: early access to innovative cures throughout conventional paths and new research to discover other cures (Fig. 2).

The regulatory reorganization started, in Italy, through Law No 3 of January 11, 2018 "Delegation to the Government for clinical trials of medicinal products as well as provisions for the reorganization of the health professions and the health management of the Ministry of Health" [4] foreseeing the reorganization of the legislation referred to in the decree of the Minister of Health December 17, 2004, in the sense of providing for the possibility of transferring the clinical trial's data and results to the pharmaceutical company and their use for registration purposes, to enhance the social and ethical use of the research, and to establish that the pharmaceutical company reimburses the direct and indirect costs connected to the clinical trial as well as the missed income consequent to the qualification of the study as a non-profit activity.

Subsequently, Legislative Decree No 52 of May 14, 2019 [5] and, lastly, Ministerial Decree of November 30, 2021, “Measures aimed at facilitating and supporting the implementation of clinical trials of non-profit medicines and observational studies and to regulate the transfer of data and results of non-profit trials for registration purposes, according to art. 1, paragraph 1, letter c), of the legislative decree May 14, 2019, n. 52” [6] implemented the aforementioned delegation law.

Article 3 of Ministerial Decree of November 30, 2021 [6] confirms, in particular, that the transfer of data and/or results, obtained from non-profit trials, for registration purposes, is allowed, both when the trial is ongoing and at the end of the trial. The Decree [6] also disciplines the procedure for transferring trials’ data and results for registration purposes.

In detail, the sponsor or transferee is obligated to reimburse and pay for both the direct and indirect costs associated with the trial. Furthermore, should the trial be reclassified as commercial, the sponsor is required to pay the corresponding charges which include any revenues resulting from the exploitation of intellectual property.

If the usability of the data and results for registration purposes is recognized, the sponsor of the not-for-profit trial and the interested party - who becomes transferee of the data and results-appoint by mutual agreement an expert in patent consultancy, who has to meet the requirements established by the same Decree [6].

The aforementioned expert will provide an estimate of the value of the property in object with a view to its intended commercial use.

The charges relating to the enhancement of the asset remain the responsibility of the person interested in becoming the transferee.

If the subject is interested in becoming the transferee of the data and results and intends to proceed with the purchase according to the estimate reported by the expert, that amount has to be reported in the envisaged contract and has to be paid as indicated below:

- 50% in favour of the Sponsor;
- 25% in favour of the fund to conduct a not-for-profit clinical trial by clinical site;
- 25% in favour of the fund established at Agenzia Italiana del Farmaco (AIFA).

In case of a multicentric trial, the shares assigned to sponsor and clinical sites are defined proportionally based on the commitment in the trial through agreements between the parties.

Where the subject-interested in becoming the transferee of the data and results-does not intend to proceed with the purchase according to the estimate provided by expert assigned, the transfer of that data and results is not allowed to the same subject for a lower amount.

When a non-profit trial is changed into a profit-making by its Sponsor, the latter has to reimburse all direct and indirect costs associated with the trial and to correspond to the relative fees to AIFA and the involved Ethics Committees, as well as it has to pay back the funds received up to that relating to the same the trial.

Additionally, the Ministerial Decree of November 30, 2021 [6] confirms the previous criteria for identifying the types of and requirements for not-for-profit trials.

Indeed, the context is complex and unpredictable with a constantly evolving regulatory framework that needs to be tested. Other issues can arise from legal frameworks and operational practices. The law provides the possibility of transferring the data and results of the non-profit trials for registration purposes, however it poses some interpretative questions. In particular, it is necessary to determine whether the subject of the transfer is data *and* results ownership (as the wording of the law seems to indicate) or whether the assignment of a license of use for registration and commercial exploitation purposes is sufficient. The latter option seems more responsive to the interests of all the actors involved, especially if the trial concerns several investigational drugs and is conducted with the financial support of several pharmaceutical companies, all potentially interested in acquiring the registration and

economic exploitation rights of the results with reference to the drugs for which they hold the patent and/or marketing authorization.

Notably, Ministerial Decree of November 30, 2021 does not apply in the case of a trial co - sponsored (according art. 72 of CTR) by both commercial and non-commercial entities. Moreover, the possibility of the transferee exploiting the data does not conflict with the interests of the sponsor, who would instead be the “scientific” owner of the data, operating as a scientific research body; the latter would retain the rights of the publication data and results on an exclusive basis and in their name. Finally, in view of the importance that the protection of personal data has taken on, in the context of clinical trials, the focus is on the impact that the transfer of data and results may have on the reshaping of privacy roles. The relationship between the sponsor and the transferee may be such that each one is an autonomous data controller, each for different purposes.

Obviously, in order to cede the trial, a full transfer of property rights is needed.

In addition, another delicate aspect to be examined is regarding the informed consent originally collected from participants of the not-for-profit trial. From the point of view of personal data processing some obstacles could arise to the reuse of it, even for research purposes and even if the informed consent form includes a provision that the data may also be used for commercial purposes by a third party. The secondary use always requires the consent of the data subject according to the Privacy Code, as amended in 2018. Exceptions to this obligation are only possible under certain conditions, such as anonymization, and with the authorization of the Privacy Guarantor [7].

The collecting of new consent for each participant would paralyze operations under this rule. In the conversion process from not-for-profit to registration purpose trial, another important operating issue to consider is the need to submit several amendments.

Co-sponsorship, introduced by CTR, represents indeed another precious tool to academic clinical research.

As established in Article 72 [1] a clinical trial can have more than a Sponsor, as opposed to what has been allowed up until now [8,9]: a restriction that, to date, has prevented the possibility of public-private partnership.

This innovative aspect overcomes in fact a particular issue of academic research, which is performed, substantially, through two models, one foreseeing collaboration among academic researchers, either national or international, the other one foreseeing cooperation of one or more academic clinical research groups and one or more private companies (for example a pharmaceutical one).

The cooperation between public and private entities does not always overlap with commercial and not-for-profit, as some academic entities are private. That limits this kind of cooperation, especially for the not-for-profit entities which are not able to reap the benefits stated in the Ministerial Decree of November 30, 2021 [6] and, as mentioned, they have less financial resources to invest. In the specific case of co-sponsorship between one or more not-for-profit entities and one or more pharmaceutical companies, an important aspect to be carefully considered is the risk assessment for assigned duties. The quality management system is still rather lacking in some academic entities and academic organizations are not ready to perform some specific duties. Management of a complex project, such as a clinical trial, by different Sponsors, increases the difficulty and consequently the risks.

However, the spirit of co-sponsorship is indeed to share your own know-how, and to exchange expertise and experience among sponsors. Each sponsor performs the activities in which they are the most experienced. This is the added value of co-sponsorship.

Another possible issue is that some small not-for-profit enterprises are not capable of managing large amounts of funds, and it is often not permitted by their charter.

The possibility of co-sponsorship prevents tensions caused by single-sponsor restrictions which created the establishment of unproductive relationships between the various actors who made their contributions

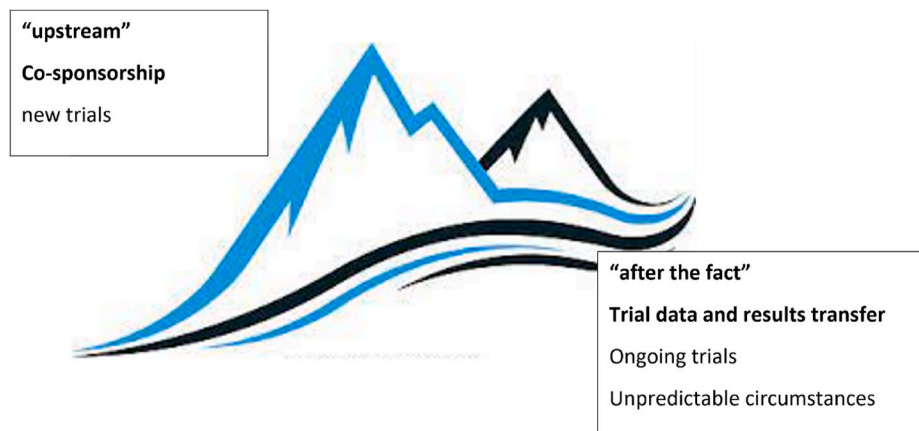


Fig. 3. Two precious tools for academic clinical research.

in the realization of a clinical trial.

A clinical trial, from its conception to its subsequent execution, is – indeed - a very complex activity that requires the sharing of different potentialities, expertise, and resources from scientific know-how to managerial expertise and financial means.

It is important, therefore, that the extension of each contribution is recognized, in such a way that the benefits can also be shared, for instance, the data ownership, which will be disciplined through appropriate agreements as foreseen by Regulation (EU) No 536/2014 [1]. In addition, the public-private cooperation represents a resource for health research and development in Italy which facilitates the collaboration among experts and allows knowledge sharing around the key health issues for instance, COVID, EU Beating Cancer plan, etc. which require large-scale trials in order to discover the answers.

#### 4. Conclusion

Between 90% and 95% of the clinical research spending is now borne by companies in Italy [10] and the pandemic has taught us how precious this cooperation is and that science cannot have prejudices.

Due to Regulation (EU) No 536/2014, there are two options: one, “upstream”, with an establishment of public-private partnership or the cooperation among groups of researchers, and the other one, “after the fact”, the rational data transfer for ongoing trials, trials which are soon to be finalized, and for unexpected situations (Fig. 3).

However, the Regulation (EU) No 536/2014 also issues some challenges to clinical research, like infrastructural efficiency, which is more complex for environments which are currently less structured.

The academic clinical environment is, unfortunately, affected by structural problems: limited resources (staff and finance), not homogeneous organizational structures, levels of experience, and, levels of professionalization. Sometimes, human resources [non-investigators] are insufficient in number and their expertise is not appropriate for conducting a clinical trial. The staff turnover is very high. Their roles are not in the organization chart of the membership organizations. These challenges can be overcome with common, but not trivial tools: the training of all involved human resources, operating fluxes and processes set-up, and cooperation among the different actors involved.

Before the reorganization is finalized, the less structured entities could benefit from “nonprofit research infrastructures” that exist in academic settings, which can provide the Sponsor with facilities, resources, or related services (firstly, a quality management system) to researchers to enable top-level scientific research to reach the same quality standard of the trials aimed at registration.

Building a robust network, alternatively joining an existing one, could be an appropriate solution [11].

From a funds perspective, it is paramount to take advantage of PNRR

(Piano Nazionale di Ripresa e Resilienza) [12] to strengthen the academic trial units, even if some complexities could arise from bureaucracy to use those funds, for example the restrictions posed by the Anti-Corruption Law, LAW November 6, 2012, n. 190 [13], e.g. about resource allocation.

The new regulatory framework inducted from Regulation (EU) No 536/2014 will raise a new dawn for academic clinical research.

#### Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

The figure was adapted from <https://mondoglobale.wordpress.com/2016/03/28/levoluzione-atravverso-la-cooperazione/and> <https://it.cleanpng.com/png-anh8sg/>.

#### Data availability

No data was used for the research described in the article.

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