

# New perspective and new challenges in clinical trial regulation in Italy

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**Summary.** Since 2004 the European Directive 2001/20/EC concerning the implementation of good clinical practice in the conduct of clinical trials on medicinal products has become operative in Italy (Decreto legislativo 24 giugno 2003, n. 211). It is therefore the intention of the Ministry of Health to obtain through an intelligent application of the recent national decree clear indications on how to conduct and to monitor transparent and useful clinical trials and to best exploit the results emerging from clinical studies in our country, both and equally from “commercial” and “non commercial” clinical studies. Using data coming from the National Register on Clinical Trials, we have observed that the absolute number of clinical research has significantly increased raising 845 interventional trials in 2008. Even if the total number of researches seems to have a positive trend and the well designed clinical trials remain the most reliable way to get unbiased information, probably we need to integrate clinical trial data with other type of clinical research, in order to better manage the post-marketing uses. Furthermore, a new pathway for “from clinical trials to the market” has to be explored through a scientific debate among the scientific community.

*Key words:* clinical trials, regulatory authority, pre- and post-marketing registries.

**Riassunto** (*Nuove prospettive e nuove sfide nella regolamentazione italiana delle sperimentazioni cliniche*). Dal 2004 è entrato in vigore in Italia il Decreto legislativo 24 giugno 2003, n. 211 che ha recepito la Direttiva Europea 2001/20/EC sull'applicazione della buona pratica clinica nell'esecuzione delle sperimentazioni cliniche di medicinali per uso clinico. Questo evento è stato colto dal Ministero della Salute come un'opportunità per rivedere e migliorare la ricerca clinica in Italia e per raggiungere l'obiettivo importante di idealmente congiungere lo sviluppo della ricerca clinica con le esigenze di sanità pubblica. Guardando i dati della ricerca clinica nazionale, si può osservare come il numero assoluto di studi clinici ha raggiunto nel 2008 il ragguardevole numero di 845. Anche se il numero assoluto di studi ha un trend sicuramente positivo e le sperimentazioni cliniche rimangono lo strumento più affidabile per testare i nuovi prodotti farmaceutici, con molta probabilità avremo in futuro la necessità di integrare questi dati con quelli provenienti da altre ricerche, per poter gestire al meglio l'uso post-marketing di questi prodotti. Inoltre, sarà necessario probabilmente rivedere l'intero percorso che va dalla sperimentazione clinica al mercato; questo sarà possibile solo tramite un profondo dibattito e confronto tra tutta la comunità scientifica.

*Parole chiave:* sperimentazione clinica, autorità regolatoria, registri pre- e post-marketing.

## CLINICAL TRIALS IN ITALY

Since January 1<sup>st</sup>, 2004 the European Directive 2001/20/EC concerning the implementation of good clinical practice in the conduct of clinical trials on medicinal products has become operative in Italy (Decreto legislativo 24 giugno 2003, n. 211). The new decree has integrally implemented the European Directive, anticipating a few additional provisions that have been issued in order to better regulate the responsibility and role of Ethics Committees, to establish the minimal insurance requirements that cover the risks of clinical research, to specify the reporting system of adverse events, to give instructions about the type of information to be submitted to the National Monitoring Centre of Clinical Trials.

The completion of these further regulations has been obtained by the participation and active contribution of all involved parties: Ethics Committees, scientific societies, pharmaceutical industries, health administrators, hospitals, clinical researchers.

The Ministerial decrees on clinical research that have been published on the *Italian Official Journal* since 2003 are:

- no-profit clinical trials (2004);
- establishment and functioning of EC (2006);
- good clinical practice (implementation of EU Directive 2005/28/CE) (2007);
- clinical trial application – procedures and forms (2007);
- guidance on observational studies (2008);

**Table 1** | *Clinical trials in Italy per year*

Year	CT	Phase III (%)	Phase II (%)	Phase IV (%)	Phase I (%)	Bioeq I Bioav (%)
2000	562	61.6	27.8	7.7	0.9	2.1
2001	610	53.8	33.3	9.0	0.8	3.1
2002	570	51.2	37.5	7.0	1.9	2.3
2003	579	53.9	34.9	8.1	1.9	1.2
2004	624	52.6	35.6	9.1	0.8	1.9
2005	661	49.2	34.8	11.6	3.3	1.1
2006	773	45.9	38.9	10.2	2.6	2.3
2007	777	44.9	38.7	12.9	2.6	0.9
2008	845	45.4	36.6	11.8	5.4	0.7
<b>Total</b>	<b>6001</b>	<b>50.3</b>	<b>35.6</b>	<b>10.0</b>	<b>2.4</b>	<b>1.7</b>

- minimum requirements for Contract Research Organisation, CROs (2008);
- minimum requirements for insurance policies (2009).

It is also possible to say that the relevant expertise of Italian researchers during this period has considerably increased. In fact, Italy is in the 6-8 ranking position of scientific publications worldwide in the health sector.

If we consider the cost-efficiency of research in Italy, we can state that the scientific excellence has been confirmed by over 150 specialized research centres, a highly-competitive cost among EU countries and over 2/3 of 3500 clinical trials carried out over last 4 years were in cooperation with foreign centres. Moreover, in Italy there is a noticeable incidence of research in Phase II (37% of all clinical trials) and Phase III (46%) and there are many active networks involved in diseases' treatment (IRCCS and universities: oncology, neurology, cardiovascular diseases, paediatric diseases). In this context, we are seeing the opening of new dedicated centers for "early phase" clinical trials, also on healthy volunteers.

### THE LEVEL OF EVIDENCE BEFORE REGISTRATION AND POST-MARKETING USES

Well-designed clinical trials remain the most reli-

able way to get unbiased information but the process is slow, risky and costly. In the near future, probably, we need to integrate CT data with other types of clinical research (e.g. registries, compassionate use etc.) providing additional data to national competent authorities (NCAs) because they will surely have an increased number of accelerated and conditional approvals.

For these purposes, it is crucial to better manage the post-marketing uses.

NCAs will perhaps ask the pharmaceutical companies to perform new clinical trials (mandatory), collecting more data in the "real" clinical practices, using the new drugs in appropriateness way (not off-label).

In the past years, Italy has modified its approach in this field introducing the "risk sharing" approach for reimbursement.

Up to now, there are many types of contracts with pharmaceutical companies (*Figure 1*):

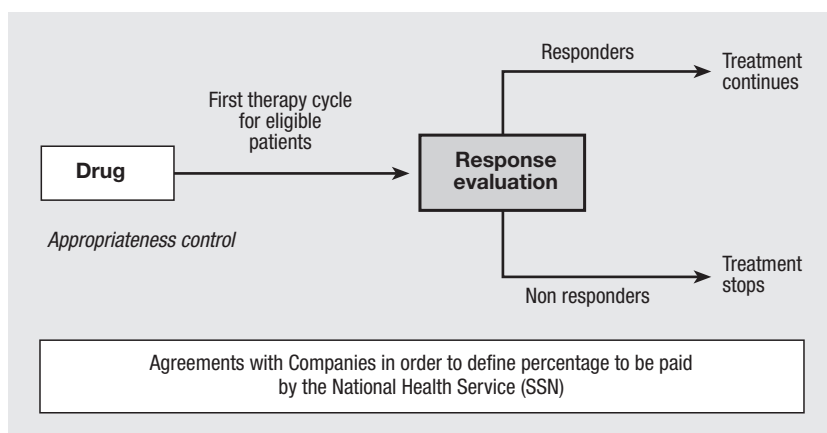
- cost sharing, special discount applied to the initial cycles of therapy for all eligible patients;
- risk sharing, special discount applied to the initial cycles for non responder patients after the first re-evaluation;
- payment by results, total refund applied to the initial cycles for non responder patients after the first re-evaluation.

These new concepts have been made possible only through a telematic tool that, since 2005, AIFA has implemented specifically for the post-marketing use in some therapeutic areas. At present, eight main registries are active and operating and over 50 drugs are under monitoring per over 60 therapeutic indications.

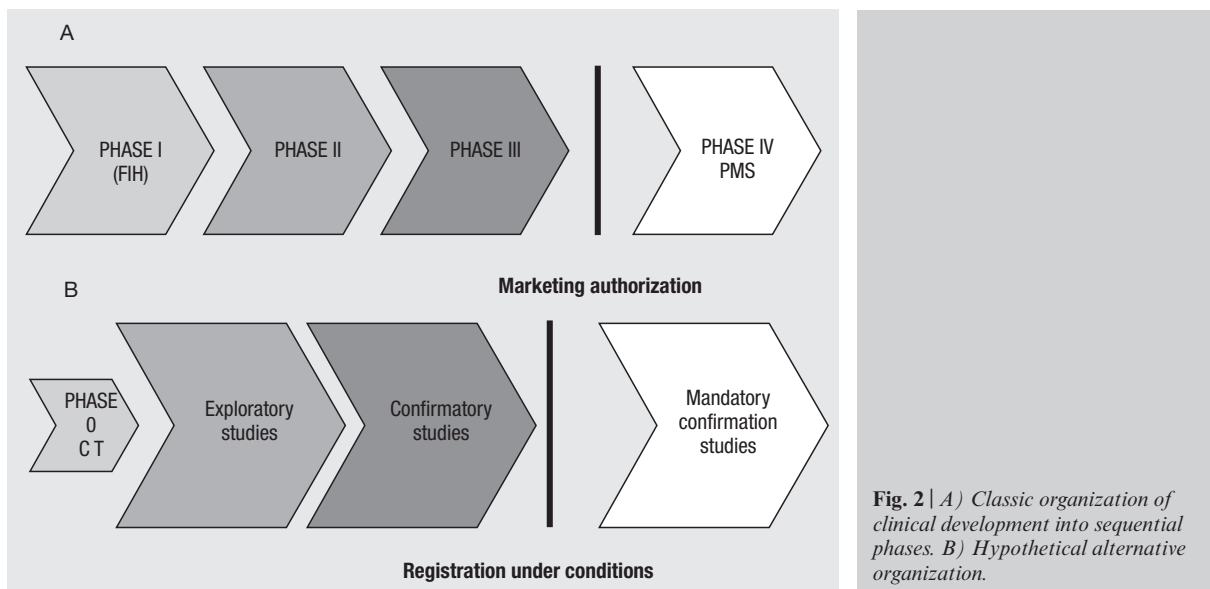
A huge number of operators are in the network and more than 200 000 patients have been inserted in an anonymously way in the different registries: these represent a wide reservoir of information that we will analyze in the coming months.

### HOW CAN THE FUTURE CLINICAL RESEARCH BE OPTIMIZED

In the near future, to better understand and manage the complexity of research and post-marketing



**Fig. 1** | *Cost sharing, risk sharing and payment by results: pathway.*



uses, Italy needs to optimize both. We will discuss about the effectiveness of Ethics Committees in clinical research and the role of the competent authority, foreseeing a centralisation in order to be compliant with the European request.

In the future trials, more information will be needed on special patients categories (very elderly, paediatric, co-morbidity, etc.) that will take the new drugs, especially in consideration of new life expectancy. The traditional clinical trial approach (Phase I, II, III and IV) will have to be redesigned to investigate tolerability, safety and efficacy, also in public-private partnership.

At the moment, the classic pathway for clinical trials is described in *Figure 2A*.

A public debate should be stimulated on how we can modify this process, in order to give a concrete answer to the right of research and obtain a shorter time to market access without any walking-back on patient' safety. A possible new pathway for clinical

trials classification is shown in *Figure 2B*.

In this hypothetical scenario, we could use adaptive design tools and we need to pay more attention either on responder and non-responder pts (intensive use of pharmacogenetic test). In some cases we can also use, as additional data, new methodological and technological approach (e.g. registries, neural network, etc.). Obviously it will not be easy, but only if all the scientific community will discuss in collaborative way we will have a chance to change the route giving decisive answers to the patients.

#### Conflict of interest statement

There are no potential conflicts of interest or any financial or personal relationships with other people or organizations that could inappropriately bias conduct and findings of this article.

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