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PHARMACOEPIDEMIOLOGY AND PRESCRIPTION

# Non-commercial trials on medicines submitted to the Ethics Committee of the University Hospital of Bologna (Italy) along 8 years of activity: time to update rules and recommendations

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## Abstract

**Purpose** In Italy, the non-commercial trials on medicines are regulated by the Ministry Decree 17 December, 2004. Its intent is of encouraging the independent research for the improvement of clinical practice. We aimed to analyze the main features of the proposals of non-commercial clinical trials on medicines submitted to the Independent Ethics Committee (IEC) of the University Hospital of Bologna in the period 2010–2017.

**Methods** Data were extracted from IEC registry and were organized with an ad hoc database. The relationships between the variables were examined using contingency tables. When appropriate, we applied the chi-square statistical test for the comparison of the categorical variables.

**Results** Over the 8-year period, the IEC evaluated 2931 studies, of which 1156 (39.4%) related to clinical trials on medicines; 245 (21.2%) out of the latter were non-commercial ones. A percentage of 49.8 of the trials were of phase II; 137 trials (55.9%) were promoted by hospitals, medical schools or institutes for research, hospitalization and health care. Non-profit organizations and scientific societies were promoters of 88 trials (35.9%). Most phase I and phase II trials received additional support from pharmaceutical companies.

**Conclusions** Our results show a not negligible industrial influence on non-commercial trials through additional support, mostly to those of phase II. An update of the present legislation on this matter is desirable, adopting clearer rules on the relations sponsor-industry.

**Keywords** Clinical trials regulation · Non-commercial trials · Non-profit organizations · Pharmaceutical industry · Ethics committee

## Introduction

In general, clinical trials on medicines may be subdivided in commercial and non-commercial with respect to their sponsorship. Commercial clinical trials are those promoted by the pharmaceutical industry and are generally product-oriented, i.e., addressed to test the clinical properties and the benefit/risk ratio of a treatment, usually a new medicine, whereas non-commercial ones usually aim at the improvement of effectiveness, safety, or cost-effectiveness of a given therapy among those available. Owing to the high costs of the development of new medicines and to other regulatory and organizational factors, it is rare to find academic or other independent trials addressing to the clinical development of a new compound [1]. On the other hand, it is not infrequent encountering independent trials on the efficacy and/or safety profile of existing medicines and sometimes even on neglected or not yet explored clinical properties of an old medicine [2].

The European Directive on Clinical Trials (EU 2001/20/EC), published in 2001, came into force in Europe in 2004 to harmonize and simplify multicenter clinical trials throughout the European Union and its preamble states that "Non-commercial clinical trials conducted by researchers without

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the participation of the pharmaceuticals industry may be of great benefit to the patients concerned" [3].

Literature on the regulatory and organizational aspects of non-commercial trials on medicines is rather limited, but a recent interesting report has given an example of the situation in Spain [4]. In Italy, independent clinical trials on medicines, i.e., those promoted by not-for-profit scientific or healthcare institutions, account for about 25% of all trials [5] and are regulated by the Ministry Decree 17 December 2004 [6], issued under the 2001 European Directive on Clinical Trials (EU 2001/20 / EC) [3].

This regulation gives the general conditions and prescriptions for carrying out independent clinical trials on medicines, and has the intent of encouraging and facilitating the independent research addressed to the improvement of clinical practice, as an integral part of health and medical care and not for industrial purposes. Therefore, such prescriptions entrust the Ethics Committees with a precise guidance for the evaluation of the protocols submitted as non-commercial trials. In general, these trials are funded by national or regional authorities, charities, foundations, scientific or clinical societies, medical organizations, or they employ the hospital funds intended for research.

According to article 1 of the above Decree, the property of the results belongs to the promoter and a future use of the results for commercial development of the drug under investigation is excluded. This last condition have been matter of debate in Italy, even recently, where the Federation of the Head Physicians of Internal Medicine (FADOI) claimed a revision of the present regulation, suggesting that the findings of non-commercial trials could be transferred (sold) to pharmaceutical companies and also used for registration purpose [7].

Two articles of that Decree represent the major critical points for the Ethics Committee in the evaluation of the admissibility of a trial as an independent one.

Article 2 allows pharmaceutical companies or other third parties to furnish funds, equipment, drugs or services to the promoter, provided that the non-commercial profile of the study and the scientific, technical and procedural autonomy of the researchers remain unchanged. Therefore, the agreement act accompanying these provisions requires a careful scrutiny by the Ethics Committee.

An even more critical point is the Article 6, which states that the prescriptions of the Decree are also extended to the trials not addressed to the improvement of clinical practice, provided that they meet the general requirements mentioned in article 1, i.e. those assuring that the study has a non-commercial profile, the property of the results belongs to the promoter and a future use of the results for commercial development of the drug under investigation is excluded.

The facilitations offered by the two mentioned articles, 2 and 6, may act together, and this assigns a rather hard task to the Ethics Committee in evaluating a trial corresponding to both articles since the dividing line between a commercial initiative and a genuine non-commercial research is not always easy to detect.

The aim of the present study was to analyze the main features of the proposals of non-commercial clinical trials submitted to the Ethics Committee of the University Hospital of Bologna in the period 2010–2017 (where four of us were on activity). Our survey focused selectively to trials on medicines, i.e., those regulated by the above mentioned Ministry Decree 17 December 2004, with the purpose to examine the relationships between the clinical phases of the trials, the types of promoters, the sources of the research funds, and the presence of support from pharmaceutical companies, paying a particular attention to the connection between such industrial support and the above features of the trials.

## Methods

The present analysis concerns the proposals of non-commercial clinical trials on medicines submitted to the Independent Ethics Committee (IEC) of the University Hospital S. Orsola-Malpighi of Bologna in the period 2010–2017. The features of the University Hospital, having virtually all the medical and surgical specialties, as well as the mission and working procedures of its IEC have been already described in a previous work of ours [8].

The 2010–2017 IEC was established in accordance with the current legislation (first Ministry Decree 12 May 2006, then Ministry Decree 8 February 2013), and it has been replaced from January 2018 by a larger unified Ethics Committee dealing with all the health structures operating in the Provinces of Bologna and Ferrara. The IEC in the period covered by the present survey ranked in the top places in Italy in terms of volume of activity [9, 10].

Data concerning the present study were extracted from IEC registry and were organized with an ad hoc database having the following items:

1. IEC unique code with the date of submission (by year)
2. Study title
3. Promoter, according to the following categories:
   (a) Hospitals and medical schools, scientific institutes for research hospitalization and health care
   (b) Foreign universities or other foreign academic bodies
   (c) Non-profit organizations and scientific societies
4. Source of main funding, according to the following categories:
   (a) National or regional health authorities
   (b) Charities

(c) Non-profit organizations or scientific societies
(d) Research hospitals, foundations, research institutions
(e) Local funds (hospital/university)

5. Presence of additional support (e.g. funds, medicine(s), equipment(s), services) given by a private third party to the promoter with a specific agreement act
6. Clinical phase of the study

(a) Phase I
(b) Phase II
(c) Phase III
(d) Phase IV

7. Mono- or multicenter study
8. Medicinal compound(s) in the study
9. First IEC opinion and date

(a) Approval
(b) Request of changes or clarifications
(c) Rejected

10. Final IEC opinion and date

(a) Approval after requested changes
(b) Rejection after unsatisfactory changes
(c) Withdrawal/lapse

The relationships between the above variables were examined using contingency tables. Data were analyzed using Excel 2010. When appropriate, we applied the chi-square statistical test for the comparison of the categorical variables. Access to the information to be used for this survey has been approved by the present Ethics Committee, i.e., that in office from January 2018.

**Data availability** The dataset analyzed during the current study is available from the corresponding author on reasonable request.

## Results

In the period 2010–2017, the IEC evaluated a total of 2931 studies, of which 1156 (39.4%) related to clinical trials on medicines; 245 (21.2%) out of the latter were non-commercial ones.

Most of the trials (89.4%) were multicenter ones, with 24.5% having Bologna University Hospital as coordinating center.

Table 1 lists the trials by year of submission and clinical phase of the trial (I to IV); 49.8% of them were of phase II.

**Table 1** Non-commercial trials on medicines submitted to Bologna University Hospital Ethics Committee from 2010 to 2017 subdivided by clinical phases

| | Phase I | Phase II | Phase III | Phase IV | Total |
|---|---|---|---|---|---|
| 2010 | 2 (0.8%) | 12 (4.9%) | 10 (4.1%) | 3 (1.2%) | 27 (11.0%) |
| 2011 | 1 (0.4%) | 15 (6.1%) | 11 (4.5%) | 5 (2.0%) | 32 (13.1%) |
| 2012 | 0 (0.0%) | 18 (7.3%) | 11 (4.5%) | 5 (2.0%) | 34 (13.9%) |
| 2013 | 0 (0.0%) | 17 (6.9%) | 13 (5.3%) | 7 (2.9%) | 37 (15.1%) |
| 2014 | 1 (0.4%) | 14 (5.7%) | 7 (2.9%) | 2 (0.8%) | 24 (9.8%) |
| 2015 | 0 (0.0%) | 17 (6.9%) | 11 (4.5%) | 6 (2.4%) | 34 (13.9%) |
| 2016 | 0 (0.0%) | 15 (6.1%) | 11 (4.5%) | 6 (2.4%) | 32 (13.1%) |
| 2017 | 0 (0.0%) | 14 (5.7%) | 8 (3.3%) | 3 (1.2%) | 25 (10.2%) |
| Total | 4 (1.6%) | 122 (49.8%) | 82 (33.5%) | 37 (15.1%) | 245 (100.0%) |

As Table 2 shows, 137 trials (55.9%) were promoted by hospitals, medical schools or institutes for research, hospitalization and health care. Non-profit organizations and scientific societies were promoters of 88 studies (35.9%), in particular 82 for non-profit organizations and 6 for scientific societies. Foreign universities or other foreign academic institutions promoted 20 studies (8.2%).

Table 3 shows the trials receiving financial support from third parties, comparing the trials of I and II vs those of III and IV phases. Such additional support always came from pharmaceutical companies and was addressed to trials of phases I and II in the majority of cases (62%), whereas less than 30% of trials of phases III and IV received such economic support. This difference was statistically significant (chi-square = 26.0; df = 1; $p < 0.001$). The funds received for these trials vary widely, and, in some instances, it was very high (from about fifty thousand euros up to one million euros) and regulated by agreements having often some critical clauses, such as the industry request of receiving for approval the final report of the study or examining in advance the text of a manuscript prepared for publication or the possibility to use the trial results. The monetary supply was accompanied by the supplying of the investigational drug when it was not yet available on the market, and, in some cases, the support of the pharmaceutical company consisted only in the latter supply.

Table 4 shows that 113 trials out of 245 (46.1%) received additional economic supports from third parties (pharmaceutical companies), and 63 out of them (71.6%) were promoted by non-profit organizations or scientific societies, whereas the majority of hospitals, medical schools and institutes for research, hospitalization and health care (94 out of 132; 68.6%) did not receive such type of support. The overall comparison resulted highly significant (chi-square = 35.94; df = 2; $p < 0.0001$) and almost all this significance was taken by the contrast between non-profit organizations and scientific societies vs the remaining promoters (chi-square = 35.84; df = 1; $p < 0.0001$).

**Table 2** Non-commercial trials on medicines submitted in the 2010–2017 period to Bologna University Hospital Ethics Committee subdivided by clinical phases and type of promoter

| Promoter | Phase I | Phase II | Phase III | Phase IV | Total |
|---|---|---|---|---|---|
| Scientific institutes for research. hospitalization and health care, hospitals and medical schools | 2 (0.8%) | 61 (24.9%) | 43 (17.6%) | 31 (12.7%) | 137 (55.9%) |
| Foreign universities or other foreign academic bodies | 0 (0.0%) | 6 (2.4%) | 12 (4.9%) | 2 (0.8%) | 20 (8.2%) |
| Scientific societies and non-profit organizations | 2 (0.8%) | 55 (22.4%) | 27 (11.0%) | 4 (1.6%) | 88 (35.9%) |
| Total | 4 (1.6%) | 122 (49.8%) | 82 (33.5%) | 37 (15.1%) | 245 (100.0%) |

Table 5 illustrates the opinions issued by the IEC on the submitted non-commercial trials. Overall, the committee approved 82% of the trials, of which 42% at the first opinion and the other 40% after the requested changes. Two trials were immediately rejected, and 10 were rejected after unsatisfactory changes. Six trials (50%) were rejected for unacceptable conditions accompanying the additional funding given by pharmaceutical companies (e.g., industrial request of check and approval of a final investigators' manuscript for publication); Four trials (33%) for serious flaws of the protocol (e.g., inappropriate use of placebo); one (8%) for denial of approval by AIFA, and one (8%) for administrative reasons.

As for medicines investigated by the non-commercial trials, 150 trials (61.2%) were on antineoplastic and immunomodulating agents (ATC = L), 27 (11.0%) were on antiinfectives for systemic use (ATC=J), 16 (6.5%) were on medicines for blood and blood-forming organs (ATC=B), 11 (4.5%) on systemic hormonal preparations (ATC=H). Most of trials on the onco-hematological field were of phase II.

## Discussion

The results of the present survey on 8 years of activity of the Independent Ethics Committee of Bologna University Hospital show that the non-commercial trials represented about 21% of the trials on medicines, being within to the national range of 20–25% as from the National Monitoring Centre for Clinical Trials (OsSC) [11]. Apart from a preliminary note of one of us [5], to our knowledge, this is the first manuscript addressing the regulatory and organizational aspects of non-commercial trials in Italy. The most notable finding of our investigation was that phases I and II trials were about 50% of all the non-commercial trials proposed according to the Italian Ministry Decree Law [6], which however concerns "the conduct of clinical trials of medicines with special reference to those designed to improve clinical practice as an integral part of health and medical care". It is true that the Decree also allows studies not having such target (article 6), but this does not justify a so high rate of trials on the initial clinical steps of a new compound. Our survey has also shown that scientific societies and non-profit organizations acted more frequently as promoters of phases I and II trials, and, again, they were the subjects more active in obtaining financial support from third parties (generally pharmaceutical companies) for their trials. This finding is not surprising, since the relatively scarce independence of scientific societies and similar organizations from the pharmaceutical industry have been largely discussed in the literature [1, 12, 13]. Altogether, the picture that emerges from our findings is a prominent role of scientific societies and non-profit organizations in exploring the initial profile of new medicines with the help of the pharmaceutical industry.

The above scenario opens two main questions: (a) why the pharmaceutical industry follows such practice of large supports instead of going directly to promote commercial trials, and (b) what may be the destiny of the results of those non-commercial phase I and II trials, given that they cannot be used for registration or other commercial purposes, according to the present Italian legislation. Our survey did not face the above questions, and perhaps, an answer may be given by ad hoc study based on questionnaire administered to the various actors of this field. As provisional answer, it can be assumed that the pharmaceutical industry may be interested in exploratory findings that, if positive, can encourage undertaking appropriate commercial trials on the compound investigated and, if negative, can be ignored. Interestingly, Ridker and Torres [14] noted that cardiovascular trials funded by for-profit organizations are more likely to report positive findings than trials funded by not-for-profit organizations, and trials jointly funded by not-for-profit and for-profit organizations

**Table 3** Non-commercial trials on medicines submitted in the 2010–2017 period to Bologna University Hospital Ethics Committee subdivided by clinical phases (I + II vs III + IV) and by presence of additional funding given by a third party (according to the Ministry Decree 17 December 2004)

| Additional funding | Phases I + II | Phases III + IV | Total |
|---|---|---|---|
| No | 48 (38.0%) | 84 (71.0%) | 132 (53.9%) |
| Yes | 78 (62.0%) | 35 (29.0%) | 113 (46.1%) |
| Total | 126 (100.0%) | 119 (100.0%) | 245 (100.0%) |

Chi-square = 26.0022; $p$ value < 0.01

The chi-square statistic with Yates correction is 24.7111. The $p$ value is .000001. Significant at $p < 0.01$

**Table 4** Non-commercial trials on medicines submitted in the 2010–2017 period to Bologna University Hospital Ethics Committee: Type of promoter and presence of additional funding from a third party (according to Ministry Decree 17 December 2004)

| Promoter | Presence of a third party economic support | No third party economic support | Total |
|---|---|---|---|
| Hospitals, medical schools and scientific institutes for research, hospitalization and health care, | 43 (31.4%) | 94 (68.6%) | 137 (55.9%) |
| Foreign universities or other foreign academic bodies | 7 (35.0%) | 13 (65.0%) | 20 (8.2%) |
| Non-profit organizations and scientific societies | 63 (71.6%) | 25 (28.4%) | 88 (35.9%) |
| Total | 113 (46.1%) | 132 (53.9%) | 245 (100.0%) |

Chi-square = 35.9372; $p$ value < 0.00001

appear to report positive findings at a rate approximately midway between rates observed in trials supported solely by one or the other of these entities.

This objective of the Italian law on non-commercial trials of medicines to encourage the independent trials aimed at improving the clinical practice has been achieved only half, since its article 6 offered the way to have the 50% of the trials be out of the main essence of that law.

The present survey has strengths and limitations. The main strength of our study is given by the level of excellence of our University Hospital, which represents a point of attraction and irradiation of clinical research, and this allowed us having a large number of non-commercial trials to examine. Another noticeable strength is the high activity of our Ethics Committee, which in 8 years processed about 3000 studies, about 1000 of them concerning trials on medicines, with one-fifth of them of the non-commercial type, a figure reflecting the national one.

A possible limitation of this study may consist in a scarce representativeness of a survey coming from a single IEC, although that of the University Hospital of Bologna is one of the most active Ethics Committee in the national panorama according to AIFA registry [9]. Moreover, the high percentage of multicenter trials examined suggests that many other Ethics Committees shared those evaluations. A second limitation is the lack of a detailed information on various aspects of the trials considered, such as design of the trials, masking, sample size, number of centers involved, national/international, etc. These aspects may be evaluated in a further survey.

Our results show a not negligible commercial influence on non-commercial trials. To consider this occurrence, the Ethics Committee adopted an internal evaluation grid weighing the possible commercial potential of a study submitted as non-commercial one [5].

Our results, as well as other positions (e.g., that by FADOI [7]), suggest that the national legislation needs to be reviewed and also harmonized with other European countries to encourage a broader use of non-commercial trials for the improvement of daily clinical practice. In particular, an update of the legislation should introduce the possibility of using the results of non-commercial trial in the drug authorization process. Moreover, it should overcome the present ambiguity between the primary purpose of improving clinical practice and the possibility of trials exploring early stages of drugs. A recent law [15] delegates the government to update the national regulations on clinical trials. A more recent act of the present government (15 February 2019) [16] set 1 October 2019 as deadline to implement such updating, envisaging a public-private coordination in clinical trials on medicines as well as a regulation of the transfer of the findings of a trial and their use for registration purposes. The near future will show whether and to what extent these perspectives have been kept.

**Table 5** Mandatory opinions of the Bologna University Hospital Ethics Committee on the non-commercial trials on medicines submitted in the 2010–2017 period

| Opinion | *N* (%) |
|---|---|
| Approval | 102 (42%) |
| Approval after requested of changes | 98 (40%) |
| Immediate rejection | 2 (1%) |
| Rejection after unsatisfactory changes | 10 (4%) |
| Withdrawal/lapse | 33 (13%) |
| Total | 245 (100%) |

**Author's contributions** Contributions to conception or design of the study (NM, DM, GB), analyzed data (NM, GB, SP, GC) or interpretation of data for the work (NM, DM, GC, SP); wrote the paper (NM, GB, DM) or revising it critically for important intellectual content (GC, SP); all the authors approved the submitted final version to be published and all the authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

## Compliance with ethical standards

The manuscript does not contain clinical trials or patient data. For this type of study, formal consent is not required but only notification to the Ethics Committee.

**Conflict of interest** The authors declare that they have no conflict of interest.

**Disclaimer** The views and opinions expressed in this article are those of the authors and do not necessarily reflect the position of the Ethics Committee, where four of us were (NM, DM, GC, SP) or are (GC, SP) in activity.

## References


1. Bergmann L, Berns B, Dalgleish AG, Von Euler M, Hecht TT et al (2010 Aug) Investigator-initiated trials of targeted oncology agents: why independent research is at risk? Ann Oncol 21(8):1573–1578. https://doi.org/10.1093/annonc/mdq018
2. Pushpakom S, Iorio F, Eyers PA, Escott KJ, Hopper S, Wells A, Doig A, Guilliams T, Latimer J, McNamee C, Norris A, Sanseau P, Cavalla D, Pirmohamed M (2018) Drug repurposing: progress, challenges and recommendations. Nat Rev Drug Discov 18:41–58. https://doi.org/10.1038/nrd.2018.168
3. Directive 2001/20/EC of The European Parliament and of the Council, available at: https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-1/dir_2001_20/dir_2001_20_en.pdf. Accessed 21 Feb 2019
4. Fuentes Camps I, Rodríguez A, Agustí A Non-commercial vs(2018) Commercial clinical trials: a retrospective study of the applications submitted to a research ethics committee. Br J Clin Pharmacol 84:1384–1388. https://doi.org/10.1111/bcp.13555
5. Montanaro N. Studi no-profit sui farmaci: è tempo di una normativa 2.0. Evidence, December 2014, volume 6, issue 12, e1000099, available at: https://www.evidence.it/articoli/pdf/e1000099.pdf. Accessed 21 Feb 2019
6. Ministerial Decree 17.12.2004. Available at http://www.gidm.org/doc/DM_17_dicembre_2004.pdf. Accessed 21 Feb 2019
7. Document on clinical research by non-profit promoter (2018) available at: https://www.fadoi.org/wp-content/uploads/2018/11/FADOI.CRNP_.2018.Documento.propositivo.FINAL_.pdf. Accessed 21 Feb 2019
8. Montanaro N, Melis M, Proni S, Chiabrando G, Motola D (2017) Six-year activity on approval of compassionate use of medicines by the Ethics Committee of the University Hospital of Bologna (Italy): time to update rules and recommendations. Eur J Clin Pharmacol 73(4):479–485. https://doi.org/10.1007/s00228-016-2186-y
9. 11th National Report on Clinical Trials of Drugs in Italy, 2012. Available at: http://www.agenziafarmaco.gov.it/sites/default/files/11_rapporto_lug_12_ita_0.pdf. Accessed 26 Oct 2016
10. 12th National Report on Clinical Trials of Drugs in Italy, 2013. http://www.agenziafarmaco.gov.it/sites/default/files/12_Rapporto_dic%2013_ITA.pdf. Accessed 26 Oct 2016
11. National Monitoring Centre for Clinical Trials (OsSC) available at: http://www.agenziafarmaco.gov.it/content/osservatorio-nazionale-sulla-sperimentazione-clinica-dei-medicinali. Accessed 21 Feb 2019
12. Remuzzi G, Schieppati A, Boissel JP, Garattini S, Horton R (2004) Independent clinical research in Europe. Lancet 364:1723–1726. https://doi.org/10.1016/S0140-6736(04)17360-1
13. Rothman DJ, McDonald WJ, Berkowitz CD, Chimonas SC, DeAngelis CD et al (2009) Professional medical associations and their relationships with industry: a proposal for controlling conflict of interest. JAMA 301(13):1367–1372. https://doi.org/10.1001/jama.2009.407
14. Ridker PM, Torres J (2006) Reported outcomes in major cardiovascular clinical trials funded by for-profit and not-for-profit organizations: 2000-2005. JAMA 295(19):2270–2274. https://doi.org/10.1001/jama.295.19.2270
15. Italian Law 11.01.2018 n. 3, available at: http://www.gazzettaufficiale.it/eli/id/2018/1/31/18G00019/sg. Accessed 21 Feb 2019
16. Http://www.senato.it/leg/18/BGT/Schede/docnonleg/37870.htm. Accessed 22 Feb 2019