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ORIGINAL RESEARCH ARTICLE

Non-profit research: an insight into the management and monitoring of clinical trials in Italy

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ABSTRACT

Introduction: In January 2022, Italy fully implemented EU Regulation No. 536/2014, revolutionizing the national framework for clinical research on medicinal products. This marked a critical shift for non-profit sponsors, who are now required to align with high-quality standards and ICH-GCP guidelines. Understanding their level of compliance is essential to identify systemic barriers and areas needing support.
Methods: In March 2024, a 50-item anonymous pilot survey was distributed via social media to assess the operational and regulatory compliance of non-profit sponsors managing clinical trials in Italy. The survey focused on three domains: data management, risk assessment, and monitoring practices. Responses were collected from 32 non-profit sponsors.
Results: The findings revealed substantial compliance gaps. Approximately 91% (n = 29) of respondents reported they rarely or never prepare core GCP-required documents, including Data Management Plans and Statistical Analysis Plans. Only 25% (n = 8) routinely conduct risk assessments before protocol drafting. Monitoring visits, either remote or on-site, were performed by 63% (n = 20) of sponsors. Among those not conducting on-site monitoring (n = 14), the primary constraints reported were staff shortages (29%, n = 4) and financial limitations (57%, n = 8). Alarmingly, within this same subgroup, 29% (n = 4) believed that on-site monitoring was unnecessary, despite regulatory mandates. This attitude extended to remote monitoring activities as well.
Conclusions: The survey highlights major challenges faced by non-profit sponsors in meeting regulatory expectations. Limited resources and a lack of trained personnel significantly impair compliance with GCP standards. To ensure research integrity and patient safety, targeted support strategies and policy interventions are urgently needed to empower non-profit research in adapting to the evolving regulatory landscape.

Keywords: Non-profit clinical research, Good clinical practice (GCP), Regulatory compliance, Risk assessment, European Regulation 536/2014

Introduction

In early 2022, the European regulatory framework for clinical trials underwent a significant transformation with the full implementation of European Regulation No. 536/2014(1).

This regulation aimed to harmonize clinical trial management and authorization processes across European Union member states, fostering collaboration. One of the most significant implications has been the alignment of responsibilities between for-profit and non-profit sponsors, requiring both to adhere to rigorous quality standards and the ICH-GCP guidelines on Good Clinical Practice (GCP). The distinction between for-profit and non-profit research has been historically pronounced, particularly in countries like Italy, where specific legislation has been enacted to support non-profit studies (2,3). The first version of the Italian decree specifically regulating non-profit research (2) legitimized non-profit sponsors to apply a quality system that was far less stringent than that required for sponsored research; for example, compliance was limited to the GCP principles rather than the full set of requirements. The recent revision of the decree (3) has instead eliminated this dualism, also because it opened up the possibility of transferring data from non-profit trials for registration purposes, marking a key development in Italy's approach to managing clinical research. This shift recognizes the innovative value of non-profit studies and their potential impact on clinical practice (1-4). However, the transition has posed challenges for non-profit sponsors, who have been

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forced to rapidly adapt to strict new criteria within an already constrained environment. Despite a temporary uptick in independent trials during the COVID-19 pandemic, especially in immunology, the overall trend has been one of decline, with a notable reduction. Data from the Italian Medicines Agency (AIFA) shows that between 2012 and 2023, the proportion of non-profit trials dropped by 56%, from 32.35% (n = 225) to 15% (n = 98) of all trials conducted in Italy, reaching its lowest level since 2000(5-7) (Fig. 1).

While there was a modest increase in 2023, it remains uncertain whether this marks the beginning of a sustained recovery. Moreover, the majority of academic clinical trials were proposed by a small number of non-profit sponsors. In fact, in 2022, just 16 non-profit sponsors started more than one trial, with none exceeding three (7). The causes of this decline are multifactorial, with financial constraints being a pivotal factor. Italy's investment in research and development stands at 1.4% of Gross Domestic Product (GDP), well below the European Union average of over 2%, and only a small portion of this is allocated to independent clinical research(8,9).

In Italy, the shortage of funding directly impacts the availability of skilled staff dedicated to clinical research, which is 25% lower than the European average. As a result, the responsibility of managing clinical trials often falls to clinicians, who are already burdened with their healthcare duties (1). In 2023, only 42% of Italian sites had a dedicated clinical trial management unit, with staff typically employed on precarious or non-permanent contracts (10). This situation is further exacerbated by the lack of formal professional recognition and career paths for key clinical research roles, such as data managers, clinical research coordinators, and research nurses (11-13). The absence of recognized roles and structured training programs contributes to job insecurity, limits the ability of public institutions to recruit and retain qualified personnel, and leads to high turnover, with trained staff frequently moving to private sector, including contract research organizations and pharmaceutical companies (10,14). These structural challenges, combined with the requirements of the new regulation, underscore the need for a multidisciplinary team (10,11), comprised of highly specialized personnel, a critical resource for enhancing research quality, ensuring adherence to ethical standards, and providing essential bureaucratic support (10,15-17). Unfortunately, most public institutions in Italy lack such organization, and where it exists, staff are often inadequately trained due to the absence of formal training programs for roles such as clinical research coordinators or research nurses (10,18). Moreover, the increasingly inefficient Italian bureaucracy paradoxically complicates the authorization processes that Regulation (EU) No. 536/2014 intended to simplify (5,19-21). Given these challenges, it is reasonable to question how Italian non-profit research will be able to meet the stringent regulatory requirements. To address this, a pilot survey was conducted to provide an overview of the current state of practice and to assess researchers' general attitudes towards, and self-reported adherence to, Good Clinical Practice (GCP), and to evaluate whether, two years after the implementation of Regulation (EU) No. 536/2014, Italian non-profit sponsors are adequately positioned to manage interventional studies, both in terms of trained personnel and compliance with the current regulatory framework.

Material and methods

Between March and April 2024, a survey was conducted to assess the management practices of clinical trials within Italian public institutions. A preliminary version of the questionnaire was distributed to three clinical research

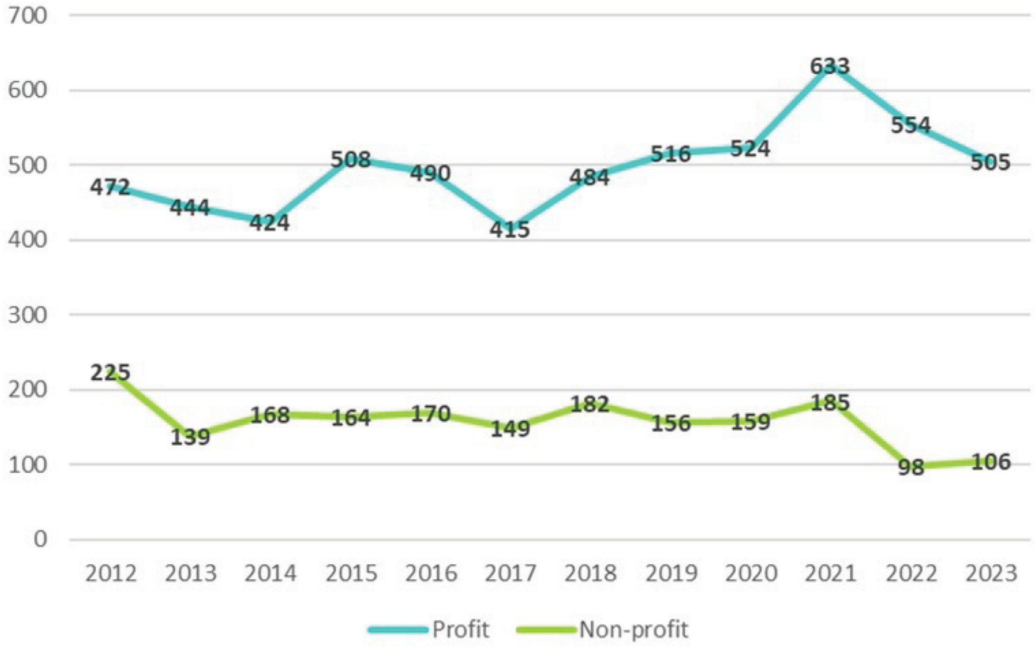

FIGURE 1 - Data trends from the AIFA national reports on clinical trials in Italy (2012–2023): number of trials per year by sponsor type (profit vs. non-profit)

coordinators for pilot testing, during which valuable feedback was collected to refine its structure. The final version contained 50 questions, both single and multiple-choice, designed to evaluate the management of clinical trials, ensure data quality, and assess adherence to regulatory requirements. Multiple responses were allowed, so sometimes the sum of percentages may exceed 100%.

The survey focused on key procedures such as protocol development, the drafting of the Statistical Analysis Plan (SAP), the Data Management Plan, including risk assessment, and the preparation of the Trial Master File (TMF). Additionally, the survey examined the development of the Data Management and Data Monitoring Plan.

The survey remained open for 30 days, allowing respondents to complete it either anonymously or with identification of their institution, after reviewing the initial privacy notice. It was disseminated to members of the Italian Data Manager-Clinical Research Coordinators Group (GIDMcrc) and also to the wider Italian clinical research community via social media channels. As a descriptive survey and given the lack of an official list of clinical research professionals in Italy, no formal estimation of the required sample size was made, and the number of professionals invited to participate could not be determined. No specific reference period was defined, as the survey was designed to evaluate researchers' attitudes and self-reported practices regarding compliance with Good Clinical Practice (GCP) in order to characterize overall GCP adherence during a transitional regulatory phase.

Results

A total of 167 respondents from institutions operating within Italy participated in the study. However, a significant portion of the responses was excluded due to invalidity, resulting from incomplete (n = 82) or inconsistent (n = 4) responses, as well as submissions from individuals working in sites that do not conduct non-profit clinical trials (n = 33). Consequently, the final sample comprised 48 public sites. Half of these sites (50%, n = 24) were Research Hospitals and Scientific Institutes (IRCCS), with a similar proportion from Hospital Companies (46%, n = 22), including both university-based and non-university-based institutions, and 4% (n = 2) representing non-profit associations.

The majority of respondents primarily work as clinical research coordinators (83%, n = 40). The analyzed sites are engaged in clinical research either as sponsoring entities (n = 32) and/or as participant sites (n = 42) in non-profit interventional studies. Among the sponsoring sites, 72% (n = 23) conduct, on average, between one and four trials annually, while only 28% (n = 9) manage five or more. The participating sites (n = 42) are involved in a higher number of trials, with 62% (n = 26) reporting participation in five or more clinical trials per year (Fig. 2).

The survey analyzed the management practices of non-profit clinical trials sponsored by the responding sites (n = 32, 67%). Regarding trial design activities, only 25% (n = 8) of the sites reported conducting an adequate risk assessment to develop study procedures and protocols. Furthermore, the preparation of essential documents mandated by ICH-GCP standards was limited, with only a minority of sites preparing key documents such as the Statistical Analysis Plan (SAP) (50%, n = 16), the Data Monitoring Plan (DMP) (38%, n = 12), and the Data Management Plan (DMP) (22%, n = 7) (Fig. 3). In the majority of cases (72%, n = 23), the responsibility for the preparation and management of additional study documents and the Trial Master File (TMF) was fully entrusted to the clinical research coordinator at the sponsoring site. Only 3% (n = 1) of the sponsors report not preparing any TMF, while the remaining sites either assigned

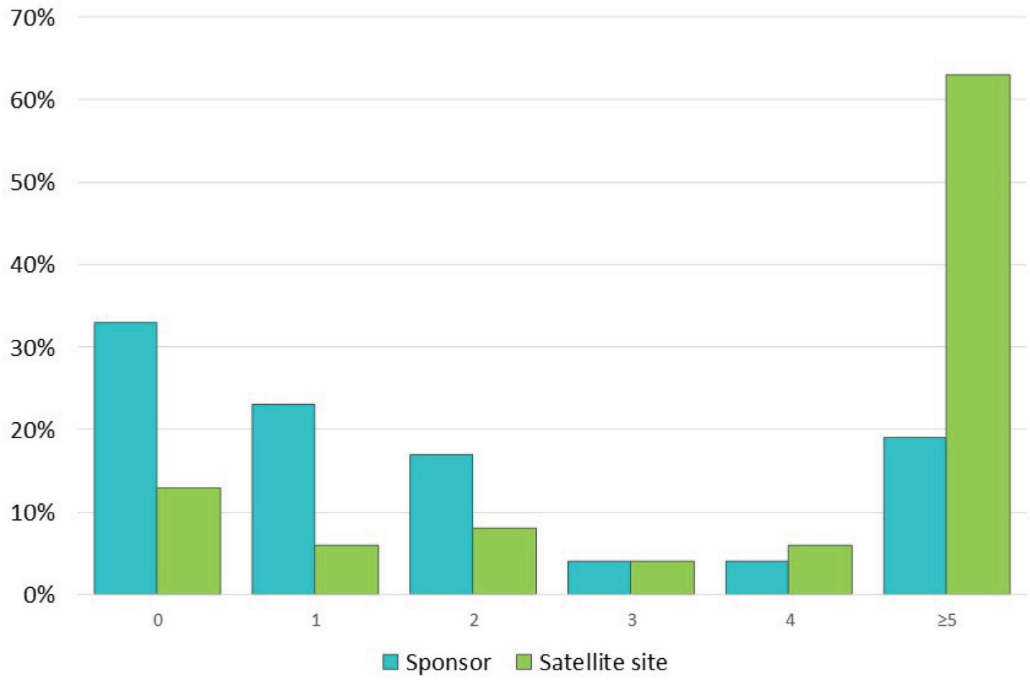

FIGURE 2 - Survey on clinical trials, responses to the question: "On average, how many non-profit clinical trials do you conduct per year?" Sample: 32 respondents conducting trials as sponsors and 42 respondents participating as satellite sites.

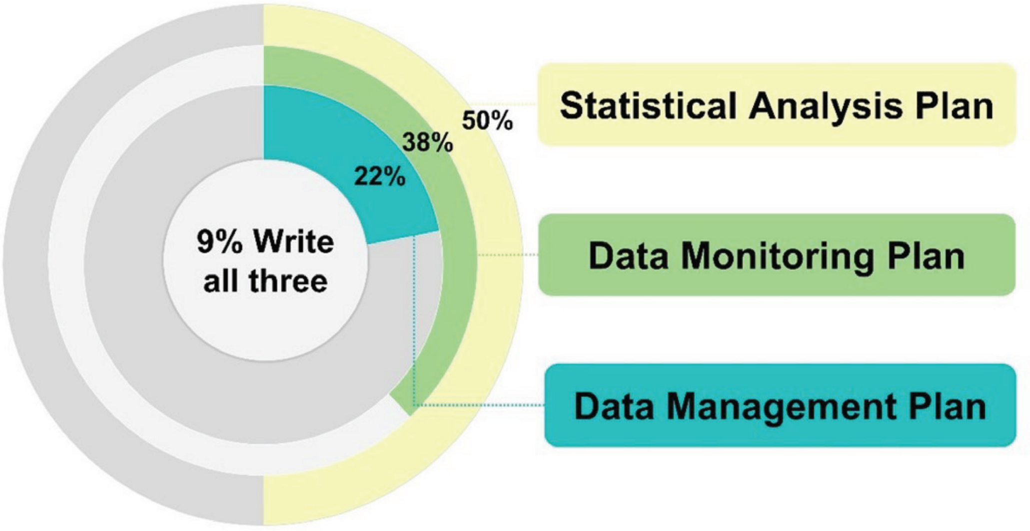

FIGURE 3 - Survey on clinical trials, responses to the question: “Does your organization prepare these documents for its sponsored clinical trials?” Sample: 32 respondents conducting trials as sponsors.

this task to the local Clinical Trial Quality Team (CTQT), where available, or delegated it to an external Contract Research Organization (CRO).

Regarding study management, staff training on trial procedures is ensured in the majority of cases, conducted both at the local level (84%, n = 27) and at satellite sites (72%,n = 23).

Monitoring of site activities is reported in 63% (n = 20) of cases, either on-site and/or remotely. On-site visits are conducted consistently in 31% (n = 10) of cases, while 13% (n = 4) of sponsors conduct them only occasionally, and an equal proportion report not knowing whether their sites organize monitoring activities (13%, n = 4). As for remote visits, despite being more cost-effective and easier to organize, they are conducted for each study in 38% (n = 12) of cases and occasionally in 16% (n = 5). Similarly, a proportion of respondents report not knowing whether any monitoring is performed (16%, n = 5) (Table 1). Although monitoring visits occur sporadically, when they do take place, compliance with protocol requirements is consistently verified (100%, n = 20), along with the proper completion, collection, and archiving of informed consents (95%, n = 19), and adherence to the ALCOA+ principles for data integrity (95%, n = 19) (19).

TABLE 1 - Survey on clinical trials, responses to the question: "Do you conduct monitoring visits during your multicenter trial?” Total respondents n = 32.

Do you conduct monitoring visits during your multicenter trial?	***On-site monitoring 44% (n = 14)***	***Remote monitoring 53% (n = 17)***
Yes	31% (n = 10)	38% (n = 12)
Sometimes	13% (n = 4)	16% (n = 5)
I do not know	13% (n = 4)	16% (n = 5)
No	44% (n = 14)	31% (n = 10)

Among sponsors who do not conduct on-site monitoring visits (44%, n = 14), responses were heterogeneous as multiple reasons could be selected; the most frequently cited challenges were limited financial resources (57%, n = 8) and a shortage of dedicated staff (29%, n = 4), with these factors often being interrelated. Additionally, some sponsors who do not perform on-site monitoring (29%, n = 4) consider it unnecessary, despite legislative requirements, and the majority of these sponsors (75%, n = 3) do not perform a risk assessment during protocol development. A similar trend was observed for remote visits, with 30% (n = 3) of those not conducting them (31%, n = 10) stating that they do not find them necessary (Table 2).

TABLE 2 - Survey on clinical trials, responses to the questions: “What are the reasons for not conducting monitoring visits?”. The sample sizes (n=14 for on-site monitoring; n=10 for remote monitoring) represent the subgroups of respondents who reported not conducting monitoring visits (the "No" group from Table 1).

What are the reasons for not conducting monitoring visits?	***On-site monitoring***	***Remote monitoring***
Budget Problems	57% (n = 8)	20% (n = 2)
Lack of trained staff	29% (n = 4)	10% (n = 1)
Not felt necessary	29% (n = 4)	30% (n = 3)

To further support the findings reported by non-profit sponsors, we surveyed participants regarding the management of non-profit clinical trials in which they are involved as satellite sites and 42 answers were collected (88%). According to the findings, non-profit sponsors organize training on study procedures prior to the initiation of most trials (69%, n = 29). Additionally, the majority of respondents (88%, n = 37) reported receiving monitoring visits, whether on-site and/or remotely. Focusing specifically on this subgroup, we analyzed the verification of study documentation during these visits. The majority of these 37 respondents indicated that the sponsor frequently checks the accuracy of informed consents (78%, n = 29), adherence to ALCOA+ principles in data collection (76%, n = 28), proper management of the Investigator Site File (ISF) (65%, n = 24), and compliance with the study protocol (92%, n = 34).

Discussion

The survey results indicated that a substantial portion of clinical trials promoted by Italian public sites, in their role as non-profit sponsors, did not fully comply with regulatory requirements and ICH-GCP standards (22). These guidelines required that clinical trial designs adopt a risk-proportional approach, based on a thorough analysis of the study procedures, followed by the development of appropriate risk management plans to safeguard participant safety and ensure the scientific integrity of the collected data (22). Of particular concern, 91% (n = 29) of the surveyed sponsors reported that they either never or only partially prepared the documents necessary for optimal trial quality management.

These findings provided a valuable overview of clinical research practice in Italy, offering insights into researchers' attitudes and self-reported adherence to Good Clinical Practice, and highlighting the challenges faced during the study period. They were intended to provide an overview of the situation immediately following the introduction of the new regulation. It should be acknowledged, however, that the survey had limitations. In particular, it did not include items specifically designed to capture potential differences in management quality between studies initiated before and after the implementation of Regulation (EU) No. 536/2014, and practices may have evolved since data collection. Accordingly, the findings should be interpreted within their temporal and national context, providing insight into the quality and organizational characteristics of ongoing research during the transitional phase. While they may not fully reflect current practices or broader international experiences, the results remain informative regarding studies that could be ongoing or whose data were being collected during that period, potentially supporting assessments of study quality.

The increasingly complex regulatory landscape, with its high standards, presents significant challenges in the academic research context. This situation is particularly difficult for non-profit sponsors, who must meet stringent requirements without sufficient resources, ultimately leading to partial compliance. Nonetheless, a noteworthy and encouraging finding from the survey is the consistent effort to provide training to site staff prior to trial initiation. This practice reflects a clear commitment by sponsors to maintain the integrity and reliability of clinical trial conduct, despite existing resource constraints. This approach is further corroborated by satellite sites, which also report pre-study training as a standard and routine component of trial preparation.

In this perspective, the upfront investment required to strengthen quality frameworks in non-profit research may be balanced over time by the added value of rigorously generated datasets. High levels of data quality and governance can enhance the potential transfer of research data for commercial use, thereby supporting sustainable funding mechanisms and contributing to the long-term viability of academic and non-profit clinical research, ultimately fostering a self-reinforcing cycle that can propel academic research forward in the long term.

Conclusion

The survey was designed to assess the state of public non-profit research in Italy, two years after the full implementation of Regulation (EU) No. 536/2014. While the regulation's objective was to harmonize clinical trial regulations across European Union member states, improving the management of trials, its most significant impact has been the creation of increasingly high barriers for independent research. Considering the presence of at least 134 institutions engaged in oncology-related clinical research (23), along with a significant number of sites not yet included in other therapeutic areas, it is evident that the survey described here represents only a small portion of the potential sample size (n = 48). To strengthen the findings, it would be valuable to replicate the survey focusing on already registered sites. Despite the limited sample size, however, the results already indicate that sponsor sites face considerable challenges in fully complying with the stringent legislative requirements, primarily due to insufficient financial and human resources. Consequently, a significant proportion of non-profit sponsors, including Research Hospitals and Scientific Institutes (IRCCS) as well as hospital companies, lack the necessary resources to manage clinical trials in compliance with ICH-GCP guidelines (22). This highlights the pressing need for targeted interventions to support public non-profit sponsors. Streamlining processes could represent a crucial step toward improving trial management and enhancing compliance across these sites. Furthermore, increasing funding for the non-profit sector would enable institutions to recruit sufficient and adequately trained personnel to manage clinical trials, in line with the complexities of both the European regulatory environment and Italy's bureaucratic framework. In addition, the development of national templates to assist in drafting essential yet often overlooked documents, such as the data management plan, could significantly improve compliance among non-profit sponsors, thereby enhancing the overall quality of clinical trials conducted in Italy. Finally, it is critical to recognize the need to incorporate specialized roles within research teams, such as clinical research coordinators and data managers, key figures in clinical research that remain insufficiently recognized and unevenly distributed across clinical sites.

Disclosures

Conflicts of Interest: The authors declare no conflicts of interest.

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Author contributions: Conceptualization, FT, BB and CC; methodology, ST; formal analysis, FT and VA; investigation, FT and ST; resources, FT; writing—review and editing, FT, VA and CC; visualization, SL. All authors have read and agreed to the published version of the manuscript.

References

1. Regolamento (UE) n. 536/2014. Regolamento (UE) n. 536/2014 del Parlamento europeo e del Consiglio del 16 aprile 2014 sulla sperimentazione clinica di medicinali per uso umano e che abroga la direttiva 2001/20/CE. Gazzetta ufficiale dell'Unione europea; 2014. Online (Accessed October 2025)

2. Decreto Ministeriale del 17 dicembre 2004 - Prescrizioni e condizioni di carattere generale, relative all'esecuzione delle sperimentazioni cliniche dei medicinali, con particolare riferimento a quelle ai fini del miglioramento della pratica clinica, quale parte integrante dell'assistenza sanitaria. Online (Accessed October 2025)
3. Decreto Ministeriale n. 341 del 30 Novembre 2021 Misure volte a facilitare e sostenere la realizzazione degli studi clinici di medicinali senza scopo di lucro e degli studi osservazionali e a disciplinare la cessione di dati e risultati di sperimentazioni senza scopo di lucro a fini registrativi, ai sensi dell'art. 1, comma 1, lettera c), del decreto legislativo 14 maggio 2019, n. 52. (22A01189) (GU Serie Generale n.42 del 19-02-2022). Nov 30, 2021. Online (Accessed October 2025)
4. Legge 11 gennaio 2018, n. 3 Delega al Governo in materia di sperimentazione clinica di medicinali nonche' disposizioni per il riordino delle professioni sanitarie e per la dirigenza sanitaria del Ministero della salute. (18G00019) (GU Serie Generale n.25 del 31-01-2018). Online (Accessed October 2025)
5. FADOI. *Manifesto per la Ricerca Clinica - Proposte per Sviluppo.* Innovazione, Semplificazione e Qualità; 2023.
6. AIFA, Agenzia Italiana del Farmaco. 12° Rapporto nazionale sulla Sperimentazione Clinica dei medicinali in Italia 2013- Rapporto OsSC 12/2013. Online (Accessed October 2025)
7. AIFA, Agenzia Italiana del Farmaco. 20° Rapporto nazionale sulla Sperimentazione Clinica dei medicinali in Italia 2023 - Rapporto OsSC 20/2023. 2023. Online (Accessed October 2025)
8. Angerame L, Cicchetti A, Farmaindustria. Il valore delle Sperimentazioni Cliniche in Italia - Laboratorio sul Management delle Sperimentazioni Cliniche. 2021. Online (Accessed October 2025)
9. Gussoni G, Scaccabarozzi S, Associazione FADOI. Fondazione Roche. Libro bianco per la ricerca biomedica e il rapporto pubblico privato. 2021. Online (Accessed October 2025)
10. Cagnazzo C, Guarrera A, Cenna R. Ricerca clinica: abbastanza giocatori per vincere la partita? Recenti Prog Med 2019;110(6):285-291. CrossRef
11. Amicucci M, Resente F, Mampieri M, et al. Clinical trial nurses in centers of the Italian Association of Pediatric Hematology and Oncology (AIEOP): a multicenter observational study. *Pediatr Blood Cancer*. 2025;72(10):e31900. CrossRef PubMed
12. Martucci M, Guarrera A, Valente D, et al. Clinical research nurse in Italian centers: a mandatory figure?. *Recenti Prog Med*. 2020;111(9):535-538. PubMed
13. Cagnazzo C, Testoni S, Guarrera AS, et al. Coordinatori di ricerca clinica: una risorsa indispensabile. *Recenti Prog Med*. 2019;110(2):65-67. CrossRef PubMed
14. Cagnazzo C, Filippi R, Zucchetti G, et al. Clinical research and burnout syndrome in Italy - only a physicians' affair? *Trials*. 2021;22(1):205. CrossRef PubMed
15. Davis AM, Hull SC, Grady C, et al. The invisible hand in clinical research: the study coordinator's critical role in human subjects protection. *J Law Med Ethics*. 2002;30(3):411-419. CrossRef PubMed
16. Rico-Villademoros F, Hernando T, Sanz JL, et al. The role of the clinical research coordinator – data manager – in oncology clinical trials. *BMC Med Res Methodol*. 2004;4(1):6. CrossRef PubMed
17. Cagnazzo C, Testoni S, Suellen Guarrera A, et al. Coordinatori di ricerca clinica: una risorsa indispensabile. *Recenti Prog Med* 2019;110(2):65-67. CrossRef
18. Mozersky JT, Antes AL, Baldwin K, et al. How do clinical research coordinators learn good clinical practice? A mixed-methods study of factors that predict uptake of knowledge. *Clin Trials*. 2020;17(2):166-175. CrossRef PubMed
19. Vose JM, Levit LA, Hurley P, et al. Addressing administrative and regulatory burden in cancer clinical trials: summary of a stakeholder survey and workshop hosted by the American Society of Clinical Oncology and the Association of American Cancer Institutes. *J Clin Oncol*. 2016;34(31):3796-3802. CrossRef PubMed
20. Gehring M, Jommi C, Tarricone R, et al. Towards a more competitive Italy in clinical research: the survey of attitudes towards trial sites in Europe (The SAT-EU Study TM). *Epidemiol Biostat Public Health*. 2015;12(1). CrossRef
21. Appolloni V, Ignazzi G, Salvatore D, et al. The impact of the new European CTR on academic clinical research: a survey by the Italian Sarcoma Group Federated Trial Centre. *Tumori*. 2025;111(3):246-252. CrossRef PubMed
22. GCP (R2). Guideline for good clinical practice E6(R2) - EMA - European Medicines Agency. EMA - European Medicines Agency; 2017. Online (Accessed October 2025)
23. FICOG F of IOG, AIOM AI di OM. Centri di Ricerca Oncologica in Italia - Annuario. 2024. Online (Accessed October 2025)