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CLINICAL RESEARCH IN SPAIN:

A PROFILE OF CLINICAL TRIALS IN THE SPANISH REGISTRY.

CREDITS

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REPORT EDITED BY
SALUD POR DERECHO

This report was prepared by Irene Bernal and Eva Iráizoz from the Access to Medicines team of Salud por Derecho, revised by Vanessa López, Executive Director of Salud por Derecho, and edited by Lydia Molina, Communication Manager of Salud por Derecho.

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Salud por Derecho is a non-profit foundation that defends human rights so that all people, irrespective of where they live, can exercise their right to health. The organisation works to promote a global system for the social protection of health that guarantees access to quality public services for everyone and puts the focus on ensuring universal access to treatment, prevention and care in HIV/Aids to protect the rights of the most vulnerable populations. Salud por Derecho also works on initiatives that review the current model of innovation in medicines and seeks alternatives that guarantee the development of and access to accessible, efficient, and quality medications in Spain and abroad.

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CLINICAL RESEARCH IN SPAIN:

A PROFILE OF CLINICAL TRIALS IN THE SPANISH REGISTRY.

EXECUTIVE SUMMARY

Clinical trials are at the core of research and development (R&D) in therapeutics and medicines. The results and data derived from them confirm the efficacy, quality, safety, and value-added of a medicine or health technology, allow the implementation of pharmacovigilance, and provide the basis for decisions in terms of authorisation, reimbursement and drug pricing, and for other fundamental decisions for clinical practice and the future of patients.

Therefore, access to the data and results of clinical trials is of vital importance to conduct independent evaluations and to make informed decisions. In contrast, lack of transparency has direct negative consequences for decision-making, generates duplications and waste of resources, and ultimately affects patient well-being and safety.

In Spain the Spanish Clinical Studies Registry (REec) was implemented in 2013. It is a free public database that serves as the source of primary information on the clinical trials that are conducted in Spain. Nowadays, the REec is regulated under the Royal Decree 1090/2015 that is based on European regulations and international recommendations also in terms of transparency and public access to the information, requiring sponsors to make the results public within 12 months after trial completion.

Nevertheless, several analyses at the global level raise awareness about the lack of transparency, the poor quality of the data, and the non-compliance with the publication of results in national clinical trial registries. To date, there is no known analysis regarding the Spanish registry. The aim of this document is to present a general picture of clinical research in Spain and to identify the gaps on transparency and access to information in the REec. It includes a descriptive analysis of 5,251 trials corresponding to the records published from 2013 to September 2019 of clinical studies conducted in Spain.

The results of this analysis show that 41.8% of registered clinical trials have been completed and phase III trials are the most numerous (40% of the total). Moreover, around 35.4% of the trials are initiated and led in our country. The records are distributed throughout the Spanish territory. Catalonia and Madrid have the highest concentration with three quarters of the trials conducted in Spain passing through medical centres in these regions. In addition, a scarce distribution of research across therapeutic areas is observed. There is a high concentration in fields such as cancer (35%) and, yet, very little in infectious diseases (4% in viral and 1.9% in bacterial and fungal infections), which are more neglected and that, concretely in commercial funding, are especially in the minority.

Much important information from the registries is incomplete. 1,110 clinical trials (21%) do not indicate either the intervention or the active ingredient used. It also stands out that 70% of completed trials (1,499 trials) have no date for the finalisation of the trial at a global level, which makes impossible to know if more than 12 months had passed from their completion and, therefore, to monitor publication of results compliance. In terms of the completed trials that indicate
the date of global finalization and that are obliged to publish their results, we observe that approximately 20% (122 out of 528) have not reported their results and, therefore, were not complying with the publication required by regulations.

INTRODUCTION

Clinical trials are at the core of research and development (R&D) in therapeutics and medicines. They constitute the fundamental experimental stage in the evaluation that allows medicines to be authorised by the medicines regulating authorities and commercialised with the necessary guarantees of efficacy and safety that legislation requires to ultimately end up able to be used in clinical practice benefiting patients (1).

The results and data derived from clinical trials underpin the decisions to authorise new therapies, or the new use of existing medicines, and allow the implementation of pharmacovigilance when the medicine is commercialised. They also provide a basis for other fundamental decisions for clinical practice and the future of patients, such as the decision regarding which medicines are funded or reimbursed and, therefore, covered by the public health system, or the development of guidelines and protocols that determine clinical practice in our hospitals and healthcare centres. At the same time, clinical investigation concentrates a large amount of economic resources and involves numerous parties, above all patients that, altruistically, participate in support of scientific advancement.

For all these reasons, the development of research within a context of maximum transparency and ethical and scientific quality should be guaranteed (1). Nevertheless, during many years, many stakeholders have warned about the lack of transparency regarding the publication of clinical study results and how this opacity may bias knowledge and distort the available evidence on health technologies (2,3). All this has direct negative consequences for administrative and healthcare professionals' decision-making and ultimately affects patient well-being and safety. Similarly, it hinders independent evaluations and scientific advancement, generating duplications and a significant waste of resources (4–6).

In contrast, the ability to access information and results, both positive and negative, for all clinical studies contributes to informed decisions. This allows the sharing of evidence, thereby avoiding unnecessary repetition of research and a better distribution of investigation resources. Access also improves the efficiency of the management of pharmaceutical funding and ensures that adverse effects are also known to protect patient safety. In short, transparency is a fundamental tool to progress further in biomedical research, both in terms of accelerating discovery and development of new effective therapies and in terms of the efficacy and safety of approved medicines.

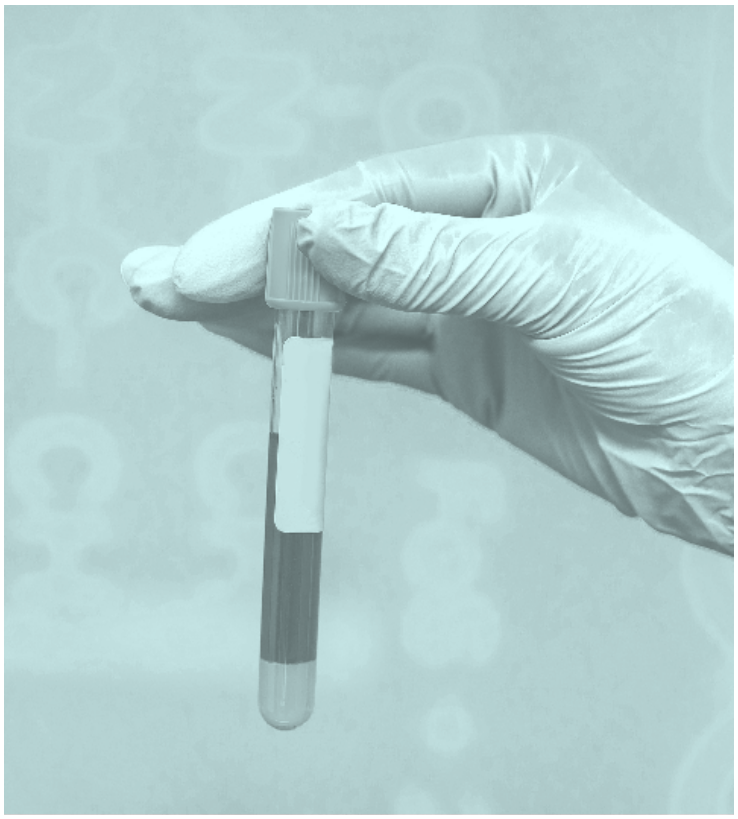
—— Despite the political focus, the poor quality of the data and the inaccessibility of the results have persisted.

Improvements in the transparency of clinical trials have been noticeable in recent years. Important regulations have been adopted since the first decade of the 2000s, both in the United States (US) and in Europe as well as on a global level, that recognises transparency and the right of citizens to have access to the protocols and results of clinical trials.

Based on these regulations, national and international registers have been implemented as necessary instruments for transparency and public access to all results at the end of clinical trials has been made obligatory. Nevertheless, and despite this political focus, the poor quality of the data and the inaccessibility of the results have persisted. A 2018 study reported that more than half of the registered clinical trials in the US had not published their results (7). In 2020, the same authors presented similar conclusions using data from the European registers: only 40.9% of the trials reported their results within the required deadline (3).

In Spain, as per European legislation and international recommendations, the Spanish Agency of Medicines and Medical Devices (AEMPS) implemented the Spanish Registry of Clinical Studies (REec) in 2013 (8). This registry comprises a public database that collects basic information on all clinical studies that are conducted in Spain and is an essential tool for transparency and accountability. However, to be useful and effective, it should contain complete and up-to-date data and guarantee continuous and adequate quality monitoring.

For this reason, some European and US initiatives (9–11) have been monitoring the registries to warn about any gaps that may compromise transparency or information access. To date, there is no known analysis regarding the Spanish registry. This document presents, for the first time, a descriptive analysis of the REec, an identification of gaps on data publication and transparency, and the development of recommendations for the improvements that should urgently be taken on by the AEMPS to guarantee that this tool responds to its original aim and is in line with Regulation (EU) No. 536/2014 of the European Parliament and of the Council of April 16, 2014, "with the aim of promoting and facilitating clinical research with medicines in Spain, the generation of knowledge, transparency, the safety of the participants and the usefulness of the results. In short, to consolidate society's confidence in research and promote its progress" (1). This analysis was conducted prior to the COVID-19 crisis, and therefore offers an insight into the clinical landscape in Spain before the pandemic.



TRANSPARENCY IN CLINICAL TRIALS

Transparency is the best tool to determine, demonstrate, improve, and maintain accountability in public policy. Within health innovation, clinical studies are the cornerstone of clinical investigation, and it is essential to understand their design, their development, and the results stemming from them.

Clinical studies confirm the efficacy, quality, safety, and value-added of a medicine or health technology compared to alternatives that already exist in the market. They also provide the basis for decisions in terms of authorisation, reimbursement, drug pricing, and of other processes that directly affect daily clinical decisions. Hence, access to the data and transparency in conducting independent evaluations is of vital importance as well as the ability of doctors, patients, and health administrations to use the results to make informed decisions regarding the benefits and safety of medicines and health technologies (7) for patient benefit.

Moreover, clinical studies are at the core of pharmaceutic research and development (R&D) (12) and where a large amount of human and economic resources are concentrated within the costs of the innovation chain. Public and private institutions, industry, patients, and researchers participate in this process, and all play a crucial role that should be fully recognised.

Spain is an important country in terms of conducting clinical studies. Within this context, public hospitals are involved with a large proportion of the clinical trials in which human resources and the public health systems own technologies are made available for the process. Nevertheless, the monetisation of these services and access to these costs remains unknown.

Assuming the principle of transparency and recognising the participation of all parties involved, the Declaration of Helsinki by the World Medical Association (WMA) considers that the fruits of this collective effort should be at the disposition of the public and the researchers should be responsible for the integrity and accuracy of their reports. In this process, the parties accept ethical norms bearing in mind that they should publish both negative or inconclusive results as well as positive results, or at the very least they should be at the disposition of the public (13) in the event they are requested. In short, this is a fundamental exercise for progress in medicine, promotion of public health, and meeting ethical obligations regarding those persons that participate in said trials (14).

Some of the most essential tools that facilitate transparency are the national and international clinical study registries that have been developed during the last two decades. These are not only tools that allow patients and researchers to understand the results of clinical studies better but are also the support developed by different administrations to supervise and thereby able to translate to the community effective innovation in a safe environment. The second element relates to the publication of the results, whether positive or negative, both in the registries as well as on platforms specifically developed for that.

In May 2005, the World Health Assembly approved a resolution to launch a platform that linked, voluntarily, the different clinical study registries to guarantee a single point of access and identification on a global level (15). The result was the implementation of

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the International Clinical Trials Registry Platform (ICTRP) of the World Health Organisation (WHO). Shortly thereafter, it defined the minimum amount of information that should appear in the registry for a clinical trial to be considered as fully registered (16). Recently, the WHO underscored the need to harmonise the collection and to perform data validation as a starting point in obtaining quality registries (17,18).

Of the most recent milestones in transparency for this institution, it is worth highlighting the approval by the 72nd WHO assembly of the Resolution for Improving the transparency of markets for medicines, vaccines, and other health products. In this, is specifically considered the "need to take the necessary steps, as appropriate, to support dissemination of and enhanced availability of and access to aggregated results data and, if already publicly-available or voluntarily-provided, costs from human subject clinical trials regardless of outcomes or whether the results will support an application for marketing approval, while ensuring patient confidentiality "(19).

The United States has had a registry since the year 2000 (20). Since 2007, institutions and companies are required by law to make the summary results of many of their clinical trials of medicines and medical devices public on the registry ClinicalTrials.gov within 12 months of trial completion. (21) The information collected in this registry goes through a systematised process of validation through which inconsistencies are addressed and is based on well-defined quality criteria (22) for the publication of clinical trials (23). Since then, independent initiatives have been emerging that monitor the reporting of results done by clinical trial sponsors and have contributed to an improvement in the level of this information. These initiatives include Trials Tracker (11,24), AllTrials (9), and Open Trials (10) as well as the actions launched by TranspariMED and UAEM (Universities Allied for Essential Medicines) (25,26).

In Europe, the registry began with the Directive 2001/20/EC. The publication of the summary of results in the register of clinical trials of the European Medicines Agency (EMA) —Clinicaltrialsregister.eu— has been compulsory since 21 July, 2014 (27,28). As in the US, institutions and companies running trials are required to upload results within 12 months of trial completion. The European rules cover all trials listed on the European register, including trials completed before 2014. With the exception of results of Phase I non-paediatric trials, all results are made publicly accessible. In contrast to US laws, EU disclosure rules focus narrowly on drug trials only; they do not cover medical devices. Trials of non-drug interventions such as surgery and physiotherapy also fall outside the scope of EU rules, as do observational studies.

Steps in transparency had already been commenced years ago with the EMA launching their own particular policies (29,30). The first of these, known as policy 0043, entailed the development of a specific framework for the access to extensive Clinical Study Reports that allowed an improved response to the requests by third parties and accompanied by the necessary standards regarding access to EMA documents. The institution continued the process with various consultations with industry, patients, and researchers, among others, (31) with the intention of promoting

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active transparency and not only for those petitions originating from third parties. During this process, the confidentiality of the results was redefined, assuming that it is only applicable to certain sensitive information.

Moreover, the EMA recognised the need for further progress in transparency owing to the importance of the large contribution patients provide to medical knowledge and the advancement of the scientific process in itself (31–33).

In 2014, the revision process of the clinical trial regulations in Europe concluded with the approval of Regulation (EU) No 536/2014. This regulation includes the obligation to present a results summary within12 months after the end of a clinical trial and to provide public access another more extensive one, known as the Clinical Study Report (CSR), within 30 days from the authorisation for the commercialisation of the medicine. Additionally, it considers the development of guidelines so that sponsors can, voluntarily, release the primary clinical data of the study (27).

Subsequently, the EMA approved policy 0070 in which it posits that clinical information and other non-clinical information in Clinical Study Reports are of public interest and, therefore, should not be considered commercially sensitive. At the same time, it sets clear limits to the information that can be considered confidential by the sponsors (12).

The second element was the development of another publicly accessible web platform for the publication of clinical data (34) that was launched in October 2016 with the publication of two clinical dossiers. Since then and until October 2018, more than 3000 reports have been made public (35). These advances have not been without certain disagreements resolved by the Court of Justice of the European Union that sided with the EMA in its policies for transparency and public access to CSR (36,37).

In Spain, the Royal Decree 1090/2015 regulates the Spanish Clinical Studies Registry (REec), in which all clinical trials with medicines for human use that are authorised by the AEMPS must be included, as well as the post-authorisation observational studies classified by this institution [1]. The REec aims to serve as an element of transparency for all parties involved in clinical research, including patients, sponsors, researchers, and managers (38). Additionally, it takes as reference the WHO recommendations for data collection and, explicitly, indicates that, in all cases, the sponsors should make public in the REec a summary of the results of the registered studies once concluded and follow the European standards in terms of deadline and form.

Despite the drive and modernisation of the clinical trial registries, the poor quality of the data from the registered trials persists, and the registries are incomplete and inconsistent in many cases (39), creating a barrier to better understanding of the trial. Additionally, the failure to comply with the regulations for the publication of results should be an issue that worries the regulator with the evaluation of the possibility of sanctions or fines for the sponsors that do not comply. The regulation provides this in the US (21), with a fine that can reach more than 10,000 dollars for each day publication is delayed. Nevertheless, to date, this policy has not been implemented (40). It is worth noting the response of countries such as Denmark that, recently, implemented a reminder system for those sponsors that do not comply with the reporting of results and has warned that it will use their legal framework to impose sanctions on all those that continue to fail to comply (41).

Ultimately, it is very important that the regulatory steps and recommendations that have been produced over the last decade are implemented, and monitoring is conducted establishing, when appropriate, a system of pertinent sanctions by the competent authorities, as set in article 94 of Regulation (EU) No 534/2014.

[1] For clinical trials in paediatrics, the reporting period is reduced to 6 months, although there are exceptions.

— Three quarters of the trials conducted in Spain pass through medical centres in Catalonia and Madrid.

ANALYSIS OF THE SPANISH CLINICAL STUDIES REGISTRY (REEC)

The Spanish Clinical Studies Registry (REec) is a public database, with free and unrestricted use and accessible from the AEMPS web page. It constitutes a source of primary information on the clinical trials that are conducted in Spain. For the present study, in September 2019, all the records contained in the REec's public web were downloaded, comprising two databases in XML format that were subsequently combined for its use and analysis.[2]

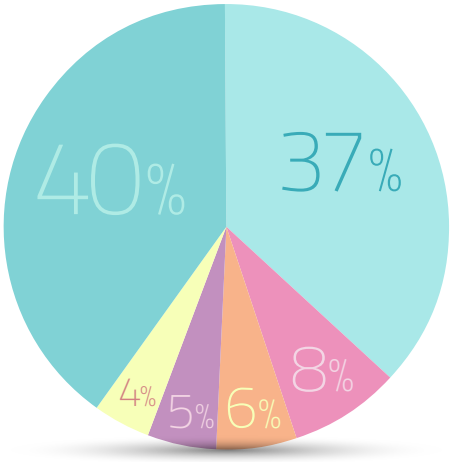
This combined database contains a total of 5,251 clinical studies, corresponding to the records published from 2013 up to the date of our search of clinical studies conducted in Spain. Of these, 41.8% have been completed, 32.7% are ongoing and recruiting, 12.9% recruitment completed, and 12.8% have not yet started. Phase III trials are the most numerous (40% of the total), followed by those in phase II (27%), and phase I (15%)[3]. The rest corresponds to phase IV trials and trials categorised as being in intermediate stages.

Spain is the main sponsor country[4] of the registered trials; around 35.4% of the trials are initiated and led in our country. In second place, we find the US, with 26.1% of the total trials conducted in Spain. Followed by other European countries: Germany (6.9%), Belgium (6.5%), and Switzerland (6.5%).

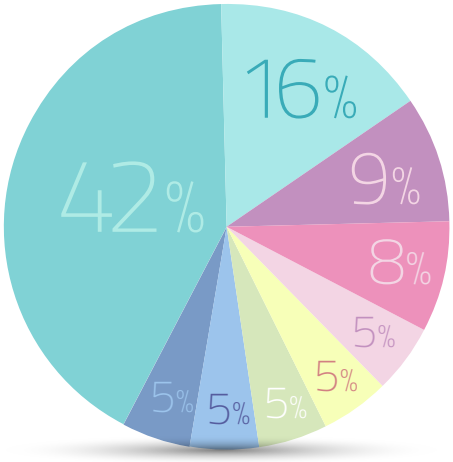
Territorial differences

The records are distributed throughout the Spanish territory and various centres located in different autonomous communities may participate in one trial. This territorial organisation results in practically all autonomous communities, with the exception of the autonomous city of Melilla, having clinical trials in progress in their hospital centres. Nevertheless, large differences can be observed in territorial distribution. Catalonia (with 3,885 registered trials) and Madrid (with 3,713 trials) are those that have the highest concentration. In other words, approximately, three quarters of the trials conducted in Spain pass through medical centres in Catalonia and Madrid. Followed by Andalusia (2,308 trials) and Community of Valencia (2,172 trials). Other territories, such as Extremadura or La Rioja, have 296 and 25 trials registered, respectively.

[2] More information on methodology: https://saludporderecho.org/wp-content/uploads/2020/06/Metodologia-EECC.pdf
[3] Clinical studies can be classified into four phases: Phase I: evaluates the safety and behaviour of the drug in healthy individuals (less than 100); Phase II: tests efficacy and complements safety data with that in patients that have the disease of interest (between 100 and 200); phase III: evaluates the safety and efficacy in real-world conditions of use and in comparison with available therapeutic alternatives and provide the basis for future approval of the drug (includes between a few hundred to thousands of patients); phase IV: studies that are conducted after commercialization to check the appearance of long term secondary effects and those not previously described (pharmacovigilance).
[4] The sponsor country is the country that hosts the sponsor of the clinical trial, that is, who leads, authorizes, and hold final responsibility for the trial, whether it is a pharmaceutical laboratory, research centre, hospital, or other.



PRINCIPAL THERAPEUTIC AREAS OF **COMMERCIAL TRIALS**



PRINCIPAL THERAPEUTIC AREAS OF **NON-COMMERCIAL TRIALS**

CANCER
CARDIOVASCULAR DISEASES
NERVOUS SYSTEM
THERAPEUTIC TECHNIQUES AND DEVICES
VIRA DISEASES
MUSCULOSKELETAL DISEASES
BACTERIAL AND FUNGAL INFECTIONS
PATHOLOGIES OF THE DIGESTIVE SYSTEM
IMMUNE SYSTEM
REST

Funding

The funding sources of clinical trials are diverse and include numerous public and private stakeholders. However, in the case of Spain, the participation of public hospital centres is particularly significant and should be taken into account in the total funding contribution of a clinical study. Nevertheless, the information currently available in the registry does not allow quantification of public direct funding nor the monetisation of the public human resources or supporting services.

The type of funding was analysed as per the categories used in the European Clinical Trials Registry (EudraCT): commercial trials, non-commercial, and mixed funding [5]. The analysis in Spain shows that 79% of clinical trials are commercial, and 15% are non-commercial, and 6% have mixed funding.

In commercial trials, Novartis is the company with most trials registered; 5.6% of the total. Followed by Merck, Roche, Bristol-Myers Squibb (BMS), Astrazeneca, GSK, Pfizer, Bayer, Janssen, and AbbVie.

The non-commercial stakeholders that fund the largest number of trials in Spain are the Carlos III Health Institute (ISCIII) and the European Commission. Followed by the Ministry of Health and various private foundations, such as the Research Institute of the Hospital de la Santa Creu i Sant Pau, World Anti-Doping Agency, Parc Taulí Foundation, the Clinic Foundation for Biomedical Research, and the Foundation for Biomedical Research of the Hospital Clínico San Carlos.

Therapeutic areas and medicines

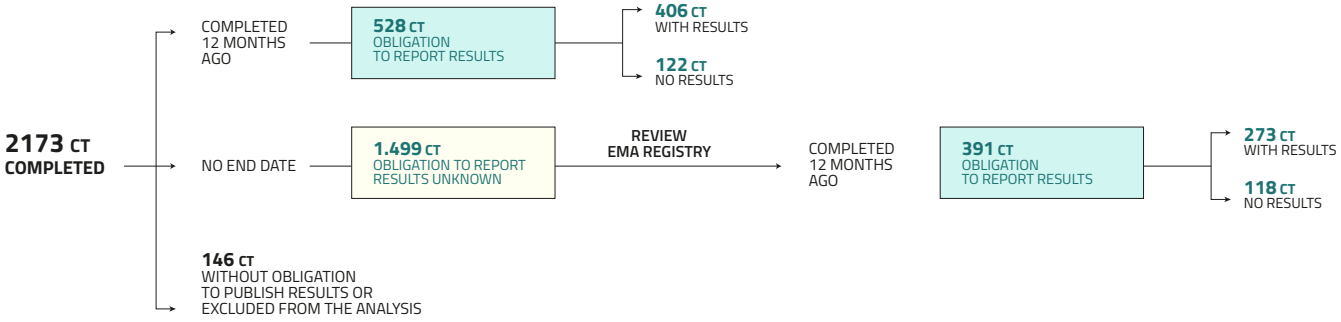
Cancer occupies a central position in clinical research in Spain: Of all the clinical trials registered in the REec, 35% are focused on investigating oncological therapies. Followed well below, by clinical trials for diseases of the nervous system (8%), immune system pathologies (6%), cardiovascular pathologies (5%), and trials aimed at viral diseases (4%). In commercial clinical trials, these five investigative areas comprise 60% of trials (more than half are for cancer, 37%). In contrast, the other areas are relatively minor, such as as bacterial and fungal infections, which only makes up 1.9% of the total trials registered.

In non-commercial trials a better distribution is observed of the different therapeutic areas, compared with commercial trials. Nevertheless, cancer continues standing out at 15.9% of non-commercial trials. Followed by cardiovascular pathologies (9.3%), the nervous system (7.6%), viral diseases (5.3%), musculoskeletal diseases (5.3%), and pathologies of the digestive system (5%). The field of devices and therapeutic techniques, analytics, and diagnostics that includes anaesthesia and analgesia makes up 5.5% of the total. The field of bacterial and fungal infections comes in at eighth place with 4.5%.

The medicines with the larger number of studies accumulated are nivolumab (118 trials), pembrolizumab (115 trials), and paclitaxel (101 trials). Followed by gemcitabine (83) and carboplatin (81). All these are antitumor agents. Likewise, it is noteworthy to find that 1,110 clinical trials (21% of the total) do not indicate either the intervention or the active ingredient used.

[5] The variable "type of funding" was created and the trials are organized in three categories: "Commercial", trials whose funding and sponsors are businesses or for-profit companies; "non-commercial", if the funder or sponsor were public centres or non-profit organizations (universities, hospitals, foundations, etc.); and "mixed", when both commercial and non-commercial entities co-existed as funders and sponsors (see methodology).

GRAPHIC 1.
SUMMARY OF THE RESULTS OF THE ANALYSIS OF COMPLIANCE WITH THE PUBLICATION OF RESULTS IN THE REec (COMPLETED CLINICAL TRIALS). CT, CLINICAL TRIAL.



On the other hand, 18% of the total trials registered in the REec investigate rare diseases, predominantly cancer and haematological diseases.

Publication of results

As stated in the previous point and in compliance with the 2014 European regulation (27) and the 2015 Royal Decree (1), the sponsors of clinical trials must upload a summary of the results to the registry within a maximum period of 12 months from the end of the global trial. The analysis of the data from the Spanish registry also focused on ascertaining if the sponsors were adequately complying with the reporting of the results and in the specified form (graphic 1).

With this aim, the trials in progress were excluded from the analysis and, of those reported as completed, it was determined if more than 12 months had passed from finalisation on a global level and, therefore, obliged to have published their results . In this sense, the percentages found in the Spanish registry were worrying[6]. In 70% of completed trials (1,499 trials), no date for the finalisation of the clinical trial at a global level exists, which makes monitoring this impossible.

In terms of the completed trials that indicate the date of global finalisation, 528 trials were calculated to be obliged to publish their results. However, of these, approximately 20% had not reported their results and, therefore, were not complying with the publication requisites as required by Spanish and European regulations.

To further this analysis, the European Clinical Trials Registry (EudraCT) was consulted and the data for the 1,499 completed trials that did not include the global finalisation date was completed. In this way, it was possible to verify that, of these, almost half (45.2%) were also completed at a global level and, therefore, should have their finalisation date included in the Spanish registry. Additionally, it was observed that almost a third of those completed more than 12 months before had not published their results in the REec and, therefore, were not complying with the regulations.

At the same time, this process has permitted the observation of inconsistencies between the status indicated in the Spanish registry and the European registry for the same trial in Spain: Some trials completed in Spain, according to the REec data, appear as still open in the European registry. This lack of updating makes it difficult to obtain reliable data for precise monitoring

TABLE 1.
SUMMARY OF THE PRINCIPAL RESULTS OF THE ANALYSIS OBTAINED FOR THE SPANISH CLINICAL STUDIES REGISTRY (REec).

	VALUE	PERCENT
STATUS		
Completed	2.173	41,8%
In process of recruitment	1.731	32,7%
Recruitment finalised	675	12,9%
Not started	672	12,8%
FUNDING		
Commercial	4.134	79%
Non-commercial	776	15%
Mixed	337	6%
PRINCIPALES MEDICAMENTOS EN ESTUDIO		
Nivolumab	118	0,02%
Pembrolizumab	115	0,02%
Paclitaxel	101	0,02%
No information on active ingredient or intervention	1.110	18,2%
Other characteristics		
THERAPEUTIC AREAS AND MEDICINES		
Cancer	1.815	35%
Nervous system	410	7,8%
RARE DISEASES	953	18,2%
TOTAL REGISTERED TRIALS	**5.251**	**100%**

[6] For this calculation, a new variable was created, subtracting the date of global finalization from the date of our analysis (01/10/19), which determines if the trial had complied with the 12 month period from its finalization.

CONCLUSIONS OF THE DATA ANALYSIS

The REec constitutes a useful tool for exercising transparency and accountability in clinical trials for patients and the scientific community in Spain. Additionally, the present data analysis has allowed us to obtain a general picture of clinical research in Spain. What is the profile of the funder, how the trials are distributed geographically, or which medicines are more researched, are some of the issues explored. In the current context of global epidemics, the scarce distribution of research across therapeutic areas stands out. A high concentration is observed in fields such as cancer and, yet, very little in infectious diseases (viral, bacterial, or fungal), which are more neglected and that, concretely in commercial funding, are especially in the minority.

At the same time, the information contained in the REec is not entirely satisfactory, and some aspects can be improved. First, we can conclude that the REec is an incomplete registry in terms of the reporting of fundamental information for the monitoring of clinical trials. This applies to many of the fields, but the case of the date of global finalisation stands out. Knowing this data is essential to be able to verify compliance with the reporting and publication of results. Nevertheless, many trials did not record this. The impossibility of knowing if trials have been completed at a global level and when hampers monitoring and the exercise of accountability by the competent authority (42).

The second conclusion made is the lack of consistency in data within the registry itself. The indicated status of the trial did not always coincide with that which was recorded in each of the participating centres. Hence, we found discrepancies such as a trial being categorised as completed in Spain, but a participating hospital continues to record it as ongoing. The same inconsistencies were found with the review of some trials in the European registry where the status in Spain, as recorded in the REec, did not always correspond with that in the European registry for the same trial.

Besides, data are not precise and generate confusion for, at least, two important elements. The first refers to the number of patients. In the REec the total expected patients on a global level are recorded, without information on the expected or participating patients in Spain which can be found in the European registry. The second relates to the categorisation of status and, specifically, for completed trials, which is too ambiguous and open. In contrast to other registries (43), the Spanish registry does not collect other details such as, for example, if the trial has been authorised, if it has been suspended, if temporarily interrupted, or if it has been prematurely ended.

Although not compulsory, some registries open the possibility of collecting publications related to the results of the clinical trials. If the REec had this possibility, it would enable knowing the relevant information published in scientific journals related to the trial. On the other hand, it would also be interesting to link the European entry of the trial. In the case of a multicentre trial outside of Europe, it is also not possible to determine the corresponding identifiers of the other countries. This makes it difficult to determine the status of the trial in other centres and significantly limits the information.

In terms of the publication of results, the current field allows for the direct insertion of one or various documents. In general, we observe pdf or Word documents that report the results in a free format. The European regulations require the presentation of these results in various formats: a summary at two levels—scientific and layman—and a Clinical Study Report. As a minimum, the indicated summaries should be accessible to the public (active publication) and is the responsibility of the competent national agencies to ensure that this occurs. Nonetheless, the analysis of our representative sample indicates that very frequently only one document written in English with scientific language is present, far from meeting the expected regulations that will be completely implemented in the following months.

The liberties taken in format also affect the content in the results section. The analysis of the sample allows the conclusion to be made that, in the vast majority of cases, the trial sponsors attach a synopsis extracted from the CSR report that was presented to the EMA. This synopsis—corresponding to a form—should highlight and detail the relevant and most valuable information of the trial. In our sample analysed, however, significant heterogeneity was found in the content and, in a few cases, long detailed and extensive reports were found.

RECOMMENDATIONS FOR IMPROVEMENT OF THE REGISTRY

The current registry is a good starting point for further improvement. Therefore, it is important not to lose sight of the objectives set out in Royal Decree 1090/2015 (1) and ensure that the registry is found at the service of good governance, transparency, and accountability in the field of clinical research, responding to public interest, to the responsible advancement of science and, at the same time, make it possible for researchers, patients and the general public to access correct, complete and quality information.

The public information shown in the REec is valuable and presented on a simple website, which is easy to use and accessible to the user. The fields that collect information comply, in general, with international standards (17) and are similar to those found in other registries (44,45). Nevertheless, some areas of deficiencies and questions that need revising were observed.

Update and accuracy of the information.

If the REec's intention is to "serve as a source of relevant information to anyone interested in clinical trials with medications," it must ensure that this information is useful. First, the registry should collect a sufficient set of data to meet this objective, and second, data must be complete and up-to-date, a task that corresponds to the sponsors (8). To comply with this objective, the AEMPS:

— Should ensure that all the fields included in the registry are correctly filled and kept updated by the sponsors with all the required information. The AEMPS should urgently contact the sponsors of the clinical trials and request the update of the records.

— The mandatory reporting of all data should be widened, paying special attention to the dates of global finalisation [7], the correct notification of results, as well as completing other information, such as the area of intervention and the active ingredients administered in the clinical trial.

— New data that improves the precision and utility of the information should be incorporated. For example, the inclusion of the number of patients in Spain, improve the categorisation of the status of the trials, link each trial with their entry in the European registry or other registries—such as the ICTRP and ClinicalTrials.gov—or add a specific section for the publications that stem from the trial.

— Ensure the consistency, constant updating of the information, and inclusion of a section with the update history of the clinical trial.

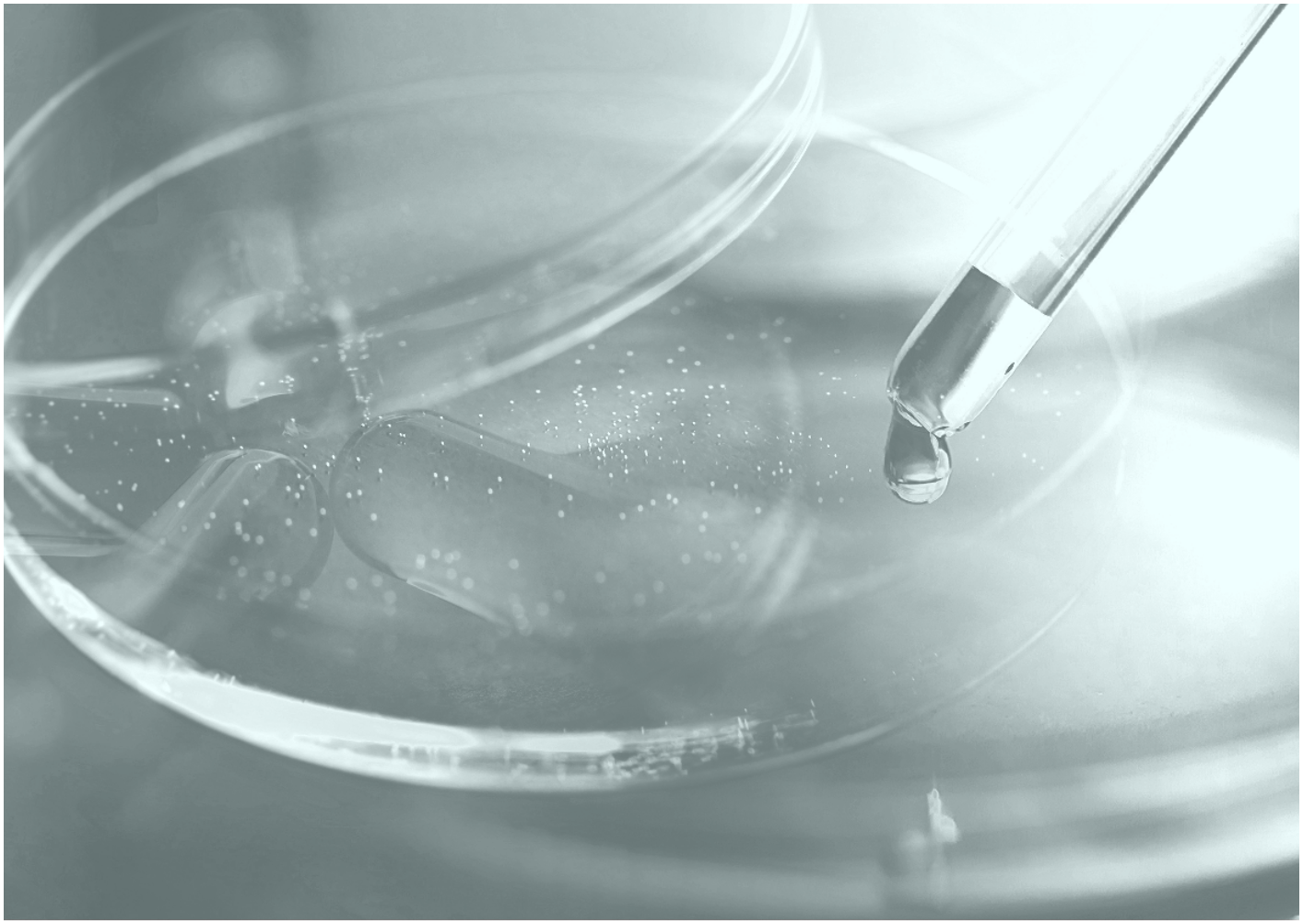
Improve the system of reporting the results.

The REec is responsible for reviewing not only that the published trials contain complete and updated information, but also that it is correct, useful, and consistent. This question especially affects the reporting of results, whose quality needs improvement.

On the one hand, and in anticipation of pending regulatory application, the results section can be expanded to include fields filled in a table format, including at least the content defined in regulation 536/2014[8] (27). In this way, the sponsors can homogenise the report format with respect to the European registry and present their results under the concrete requirement of publication, guided and common throughout, and no in a free format like up to now. Evidence suggests that the results that are published in a table format are more precise and complete than those that can be published without any requirements or particular guidance (46,47).

On the other hand, the AEMPS should prepare and conform to the requirements of the implementation of the European regulation and the forthcoming European portal for clinical trials (CTIS), adopting specific plans that promote the adequate reporting of results and reinforce transparency.

[7] Currently, the RD in Art. 48 only requires updating the start date of the study in Spain, the participating centres, the date of recruitment in Spain, substantial modifications, and the end date of the study in Spain.
[8] The content to be included in the public summaries of results is detailed in annexes IV and V of Regulation (EU) No 536/2014 of clinical trials for medicines for human use.



— The AEMPS should prepare and conform to the requirements of the implementation of the European regulation.

Establish monitoring and follow-up mechanisms

Although the study sponsor is responsible for the quality, accuracy, and periodic updating of the information, it is the AEMPS that must verify before its inclusion in the registry that the data provided is complete and adequate[9] (1).

The AEMPS should establish the necessary internal mechanisms of monitoring, surveillance, and auditing to ensure that the information collected in the REec is correct, updated, and good quality. For this, they require sufficient and specific resources to initiate support of the sponsors in this task and to put into effect an adequate system of monitoring and quality control. It is necessary:

— To ensure the validity and quality of the results reported in the registry. Initiate routine procedures of the monitoring of information to ensure that the data of the results published are complete, precise, and consistent. Annual review is recommended.

— Monitor the adequate reporting of results on time and correct format. If the sponsors have not reported the results of their trials when required, they should be notified of the failure to comply and call for its rectification. Evidence exists that support the success of this practice (48).

— Develop a document of standards in coordination with initiatives at a European level, as well as elaborate on the instructions and guidelines for the correct recording of the trials. These documents could easily be annexed to the Instruction document of the AEMPS, for the Elaboration of Clinical Trials in Spain (49).

— Require the compliance of the regulations by sponsors and establish a system of fines and sanctions for individual or recurrent cases of non-compliance.

— Facilitate the support of the AEMPS and provide the sponsors with the materials and training supports required to resolve the possible difficulties that may arise when reporting the information (28).

[9] Art. 48.2 of RD 1090/2015.

RECOMMENDATIONS FOR GREATER TRANSPARENCY IN CLINICAL RESEARCH

The lack of transparency with regards to clinical trials is another piece of the opaque machinery that surrounds the whole system of innovation and development of medicines and therapies. A firm and real commitment to transparency should go further than technological advances, cut-across the whole innovation model, and permeate national, European and international pharmaceutical policy. Accordingly, below is detailed the general recommendations that should be met if we want quality science that serves the public interest and places people at its centre.

01 Transparency and accountability

Transparency and accountability are essential conditions for the access of researchers, clinicians, patients, and political decision-makers to quality and ethical scientific evidence that provides the basis for clinical, economic and social decisions and that, ultimately, protects and ensures patient benefit and good governance of science.

02 Foster the WHO Transparency Resolution

The Transparency Resolution agreed at the 72nd WHO General Assembly recognises the need to improve transparency in clinical trials to facilitate knowledge regarding costs, to promote the advancement of science, and provide the best therapies for patients. It is necessary to foster this resolution in Spain taking the required steps for its effective implementation.

03 Monetise the public contribution

Clinical research is at the core of R&D and many stakeholders participate in this, including, among others, public institutions. The role of each should be recognised and value placed on the essential participation of public hospitals in conducting clinical trials. This involves monetising the public contribution in the form of direct funding, human resources, services, and infrastructure; to determine the real costs of clinical research; and act in favour of transparency, accountability, and good governance of R&D.

04 Protect public health needs

Clinical research should also take into account the priorities for population health. It is necessary to rebalance the research agenda and protect public health needs. A worrying lack of diversity in the investigated therapy areas exists and some areas are particularly lacking, such as infectious diseases. Revising priorities and investing in crucial research fields such as the development of new antibiotics are urgently required, along with fostering better utilisation of science from a basis of transparency, data sharing, avoiding duplications, and a research effort that responds to the real needs of health.

05 Promotion of independent clinical trials

Quality clinical research should commit to the promotion of independent clinical trials lead by public institutions. The expansion of resources and funding of public initiatives that contribute to strengthen the public state network in R&D and the public health system is needed.

06 Improve the Spanish Clinical Studies Registry

The Spanish Clinical Studies Registry is a valuable tool that should be improved if we want it to be useful and that meets the function for which it was designed. The REec has the potential to become a baseline registry for access to information on the clinical trials that occur in Spain. Otherwise, we can hope that the European registry meets this need, and the national registry will be relegated. This should be accompanied by adequate investment and provision of the required resources for its correct functioning.

07 Adapt to the European context

Spain should adapt, without delay, to the new European context and demand better monitoring and supervision of clinical trials in terms of transparency and publication by the competent national authorities.

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