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SPECIAL ARTICLE

New clinical trials regulation in Spain: analysis of royal decree 1090/2015

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Abstract The coming into force of Directive 2001/20/EC represented a step forward in harmonising clinical trial regulation in European countries, guaranteeing a uniform protection of subjects participating in clinical research across Europe. However, it led to a disproportionate increase in the bureaucratization, and thus, it became evident that procedures needed to be simplified without detriment to patient's safety. Thus, Regulation 536/2014, that repealed Directive 2001/20/EC, with the aim of decreasing the growing bureaucratization and stimulating clinical research in Europe, established simplified procedures, such as regulating a common procedure for authorising trials in Europe, the institution of strict assessment timelines, or the definition of new concepts, such as "low-intervention clinical trial". The legal form of a Regulation allowed the norm to be directly applied to Member States without the need for transposition. By means of the new Royal Decree, the national legislation is adapted to make the application of the regulation feasible and it allows the development of the aspects that the Regulation leaves to national legislation. Both documents seek to stimulate clinical research with medicinal products to foster knowledge, facilitate transparency, and reinforce subjects' safety. This will surely be the case, but with this revision, we will look at the novelties and key aspects that are most relevant to investigators and we will analyse the consequences for all parties involved in clinical research.

Keywords Clinical trials · Royal Decree 1090/2015 · Regulation 536/2014 · Transparency · Low-intervention clinical trials · Non-commercial trials

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Introduction

Directive 2001/20/EC of the European Parliament and of the Council, of 4 April 2001 on the approximation of the laws, regulations, and administrative provisions of the Member States, relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use [1], incorporated into the national legal code by means of Royal Decree 223/2204 dated, of February 6th, which regulates clinical drug trials [2], represented a step forward and an internationally renowned effort towards initiating regulatory harmonisation among the different Member States of the European Union. With the fundamental aim of increasing subjects' protection, it enabled that certain basic aspects were uniformly implemented in all Member States. The principles of Good Clinical Practice were incorporated into European legislation; standards that

improved both the reliability and the robustness of the data generated in clinical trials were established; the primacy of the subjects' interests over any other interest was recognised; and subject's protection was enhanced by virtue of the system of prior authorisation and by means of cooperation between the states by means of the EudraCT database.

Furthermore, this directive sought to harmonise the dispositions that governed conducting trials in different countries of the European Union and to simplify procedures. However, time proved that the latter had not been achieved; as the entry into force of Directive 2001/20/EC increased the administrative procedures associated with the authorisation of clinical trials and contributed to the 25 % decrease in the number of clinical trials being conducted in Europe in recent years [3]. It should be noticed that this decrease in the authorisation of clinical trials was not uniform throughout the entire Union, as in accordance to the Spanish Medicines Agency's data (Agencia Española del Medicamento y Productos Sanitarios; AEMPS), the number of clinical trials remained stable with an upward trend in the last 10 years (714 clinical trials authorised in 2014; 539 clinical trials authorised in 2002) [4–6] (Fig. 1).

On the other hand, the entry into force of the new directive increased the time needed to begin a clinical trial by 90 % [7], as well as the expense associated with administrative procedures. In a recent review, in European countries in which the directive had been adopted, the mean time needed to authorise a clinical trial was higher than that of countries that had not adopted it (75 versus 59 days); this difference was even more pronounced when comparing the data with the United States (15 days) [8].

For the pharmaceutical industry, the application of the directive increased the personnel needed to process the authorisation of a trial by 107 %, but the situation was even more serious for non-commercial academic research. The sponsors of these trials depend entirely or in part on public funding, social action programmes of private institutions, or charitable organisations, and a survey revealed that the costs of clinical trials conducted in the United Kingdom had doubled since the introduction of the directive [9] and that the personnel necessary to carry out the administrative procedures had increased by 98 % [7].

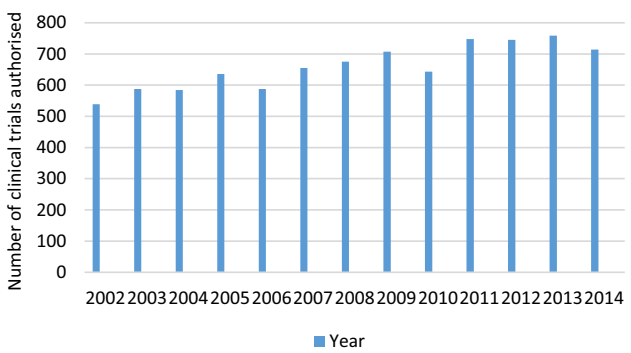

Fig. 1 Number of clinical trials authorised in Spain (years 2002–2014) Source: Yearly report of activities of the AEMPS, 2005-2006, 2010, and 2014

The European Commission, therefore, detected a loss of competitiveness in performing clinical trials, while, at the same time, the need to foster non-commercial research sponsors became evident. Thus, with the aim of promoting research in general, and non-commercial research in particular, Regulation (EU) No. 536/2014 of the European Parliament and of the Council, of 16 April 2014 on clinical trials on medicinal products for human use, repealing Directive 2001/20/EC [10], develops substantial modifications to simplify the procedures without undermining the guarantees for subjects in clinical trials. Common procedures set up for the authorisation of clinical trials in Europe by means of a single position; strict assessment timelines are established, and the concept of tacit authorisation is maintained without setting minimum authorisation timelines. By opting in favour of the legal form of a regulation, the norm could be applied directly to the member states without having to transpose it. However, this directive left out certain national aspects that needed to be developed. Furthermore, to apply the Regulation, relevant aspects of the national legislation had to be modified, by means of the publication and entry into force on 13 January 2016, of Royal Decree 1090/2015, of 4 December, regulating clinical trials with medicinal products, Ethics Committees for Investigation with medicinal products (Comité Ético de Investigación con Medicamentos; CEIm, for its acronym in Spanish) and the Spanish Clinical Studies Registry (Registro Español de Estudios Clínicos) [11]. All applications for authorisation of a clinical trial and applications for modifications of clinical trials must now be governed by this Royal Decree. The AEMPS has also published instructions about practical aspects that will be periodically reviewed [12], together with and a memorandum of collaboration between the AEMPS and the CEIm [13].

The new directive lays down new rules for the authorisation procedures, for notifications of recruitment of subjects, for safety notifications, and for notification of the trial outcomes. Clearly, the spirit and most relevant modifications in the current Royal Decree have their origin in the Regulation, and are directly affected by it. Moreover, many of the provisions are determined by the lack of full enforcement of the Regulation (such as the lack of implementation of the European database or the single portal of the European Medicines Agency—EMA). This article will focus on most relevant modifications and most important practical aspects, not only of the Royal Decree but also of the Regulation that affects it most directly, and will review the challenges associated with its entry into force.

Main changes and associated challenges

Scope of application

The scope of application of the current Royal Decree is identical to that of Royal Decree 223/2004, as it applies to all clinical trials with medicinal products for human use that are carried out in Spain, although some definitions have been clarified or defined for the first time.

Definitions of clinical trial, clinical study, and observational study. Low-intervention clinical trials and non-commercial trials

In Article 2 of Regulation 536/2014, the definitions of clinical trial, clinical study, and observational study have been clarified.

In addition, it is the first time in European legislation that the concept of the "low-intervention clinical trial" is introduced. This definition is maintained in Royal Decree 1090/2015. Therefore, it is acknowledged for the first time that the risks for the participants of clinical trials cannot be the same when the treatment applied is similar to that of routine clinical practice, i.e., when the medicinal product has had a marketing authorisation for several years and, hence, its quality, safety, and efficacy have been certified in prior clinical trials and by use. This is so even if this medicinal product is not used in accordance with the conditions of its marketing authorisation, but its use is supported by scientific data. Low-intervention clinical trials are, therefore, considered to be subject to less stringent rules as far as monitoring, and master file requirements and traceability of the medicinal products are concerned. A low-intervention clinical trial is deemed to be one that meets each and every one of the following conditions:

(a) "the investigational medicinal products, excluding placebos, are authorised;
(b) according to the protocol of the clinical trial,
    (i) the investigational medicinal products are used in accordance with the terms of the marketing authorisation; or
    (ii) the use of the investigational medicinal products is evidence-based and supported by published scientific evidence on the safety and efficacy of those investigational medicinal products in any of the Member States concerned; and
(c) the additional diagnostic or monitoring procedures do not pose more than minimal additional risk or burden to the safety of the subjects compared with normal clinical practice in any Member State concerned;"

On the other hand, the Regulation, although not defined as such in "Main changes and associated challenges", introduces the concept of non-commercial clinical trials establishing a clear distinction with low-intervention trial. The valuable contribution to society of this kind of research is acknowledged and the adoption of measures to foster it, such as lower authorisation fees or exemption of inspection fees, is recommended.

Non-commercial clinical research is defined as the research conducted by the investigators without the participation of the pharmaceutical or medical devices industry that has all of the following characteristics:

1st The sponsor is a university, hospital, public scientific organisation, non-profit organisation, patient organisation, or individual investigator.
2nd The research data belong to the sponsor from the very beginning of the study.
3rd There are no agreements between the sponsor and third parties, so that the data can be exploited for regulatory uses or that can generate industrial property.
4th The research design, execution, recruitment, data collection, and communication of outcomes are kept under the sponsor's control.
5th These studies cannot be part of the development programme for a marketing authorisation of a medicinal product.

Obviously, many trials will belong to both categories, as they are not mutually exclusive; although not all of them will, as in the first year, post-authorisation clinical trials will sometimes be conducted with a commercial interest (whether performed by academic investigators with support of the marketing authorisation holder or directly performed by it).

Compensation for damages

The Directive establishes that compensatory mechanisms must exist for low-intervention trials, though this compensation will be "appropriate to the nature and the extent of the risk". It explicitly mentions that the Member States should not demand specific insurance if a guarantee which covers the damages that could arise is in place (i.e., that the insurance covers regular clinical practice). This will only be possible, when insurance policies stop excluding clinical trials coverage.

The Royal Decree also allows the submission of the authorisation dossier before the insurance contract is signed; although proof of insurance, guarantee, or similar

arrangement should be submitted within 30 calendar days in the event of a positive decision by the CEIm. The Royal Decree maintains this provision for low-intervention clinical trials, in which additional insurance is not compulsory should damages be covered by the individual or collective civil liability insurance of the centre where the trial is conducted.

Centralised submission of application for authorisation. EU portal and database

Both in the Regulation and in the Royal Decree, the multiple submissions of the different applications for authorisation dossiers to all Member States are involved and the CEIm is replaced by a single submission dossier through a single submission portal. This portal will also be used to present the application for authorisation of a clinical trial that is only carried out in one Member State. The Regulation states that, while the authorisation and supervision of clinical trials continue to be competence of Member States, the EMA should develop and maintain the clinical trials portal and database which will allow clinical trial authorisation and oversight. The timelines agreed upon in December 2015 foresee that the portal and database will be available for independent audit in August 2017 [14]. If the system successfully passes the audit, the Regulation will come into force no later than October 2018.

Until the EU portal is running, temporary provisions 2 and 3 of the Royal Decree establish that the submission of clinical trial dossier for authorisation and for substantial modification, and clinical trial communications and notifications will take place through the portal developed by AEMPS. In addition, the Agency will include the data from the clinical trials performed in Spain in EudraCT and will maintain the registry of clinical studies performed with medicinal products for human use. The Agency will be the only contact point described in the Regulation for clinical trial submission, assessment, and authorisation.

In accordance with Article 87 of the Regulation, multiple payments to different bodies involved in the assessment will not be required. Hence, for the time being, there will be a single fee per assessment that will be paid to the AEMPS. The AEMPS will then transfer the part corresponding to the assessment of the ethics committee to the CEIm.

Joint and coordinated assessment

The fact that a single joint position will be issued by the reporting Member State is probably one of the most important aspects of the Regulation and Royal Decree. This assessment enables that all Member States concerned shall jointly review the application based on a draft assessment report performed by a single rapporteur, and shall share any considerations relevant to the application. The reporting Member State will take due account of the considerations of the other Member States in the final assessment report.

Member States will be able to express disagreement when they consider that the subjects involved in the investigation will receive the standard treatment that is inferior to the one corresponding to routine clinical practice, if it infringes national law as referred to in Article 90 of the Regulation (special groups of medicinal products), or if they present objections to subjects' safety or to outcome reliability and robustness (paragraph 5 or 8 of Article 6). The assessment is differentiated into two parts, Parts I and II, the content of which is listed in Articles 6 and 7 of the Regulation.

Part I covers the assessment of the classification of the trial as a low-intervention clinical trial (if it has been requested by the sponsor), the anticipated therapeutic and public health benefits (considering the relevance of the study and the reliability and robustness of the data generated by the trial, with special attention to methodological aspects), and the risks and disadvantages of the study (characteristics of the investigational medicinal products and auxiliary medicinal products, characteristics of the intervention, safety measures, and risk for the subject). This part also includes the evaluation of compliance with the requirements concerning manufacturing, import, and labelling of investigational and auxiliary medicinal products, as well as the completeness of the investigator's brochure. In summary, this part will cover quality and preclinical data, and the pharmacology, toxicology, and clinical and safety evaluation, including methodological aspects. The assessment of Part I will be performed by a single State by means of an assessment report that will be reviewed and commented by the remaining Member States.

Part II encompasses the intrinsically national aspects that must be evaluated by each Member State for its own territory and covers aspects related to informed consent, compensations for the subjects and investigators of the study, how subjects are to be selected, personal data protection, suitability of the investigators, and facilities and compliance with collection, and storage and use of data for future research.

To respect the different traditions of the ethical review boards of the different EU countries, the distribution of Part I and Part II assessment is defined by each Member State; though each State will issue a single, common position notifying the sponsor through the EU portal as to whether the clinical trial is authorised.

In Spain, the Royal Decree establishes that the sharing of responsibilities and collaboration between the AEMPS, as the competent authority, and the CEIm, shall be registered in a collaboration agreement. The first version of this

document was published in February 2016 [13]. By means of this agreement, the Clinical Trial Coordination Group is likewise constituted and is formed by the Head of the Department of Medicinal Products for Human Use of the AEMPS, the Head of the Clinical Trials Unit of the AEMPS, and a representative of each of the CEIm qualified for the assessment of trials. The documentation to be submitted is established in the same document.

In accordance with the Royal Decree and with the memorandum, the Agency will authorise the trial, deny it, or authorise it with conditions. Part I will be evaluated by the AEMPS and the CEIm, whereas the CEIm is in charge of the assessment of Part II. The AEMPS will then issue a final position within a period of 5 days from the last date on which the sponsor was notified of the conclusions.

In the collaboration agreement, it is further established that the AEMPS will write the draft assessment report of phase I clinical trials and that of clinical trials that include advanced therapy medicinal products or allergens. The CEIm shall prepare the draft report of all other trials. Phase IV trials and low-intervention trials will only be assessed by the CEIm.

In general, the quality, preclinical, pharmacology, and toxicology data will be evaluated by the AEMPS. As regard clinical data, the AEMPS will assess aspects pertaining to statistics, GCP compliance, the presence of a Data Safety Monitoring Committee, and the definition of end of trial; in addition to contributing to the consistency of the classification as a low-intervention trial, evaluating if the study is a requirement of regulatory authorities or part of a paediatric plan and contributing in some of the issues evaluated by the CEIm. The CEIm will assess the classification as a low-intervention trial, the relevance of the trial, its design, treatments, target population, birth and pregnancy control measures, procedures to minimize risk, criteria for treatment suspension and the early termination of the trial, blinding, overall assessment of burdens for the subjects, accessibility to treatment once the trial has concluded, and the overall assessment of benefit and risk.

The requesting Member State will, therefore, submit the definitive version of Part I of the assessment report with its conclusion to the sponsor and other Member States involved within 45 days from the validation date. If the trial affects more than one Member State, the process will consist of three phases: the initial assessment by the Member State (26 days), the coordinated review phase (12 days), and the consolidation phase (7 days from the coordinated phase). These timelines can be extended by an additional 50 days in certain cases (for example, when clinical trials include advanced therapy medicinal products). To obtain and examine the supplementary information requested to the sponsor, the period may be extended to a maximum of 31 days. The sponsor shall submit the requested information within a period of no more than 12 days. As per the specifications of the Directive, the clock will stop between 23rd December and 7th January , except when the AEMPS and the CEIm agree that such will not be the case.

Regarding relevant trial modifications; i.e., when they affect the performance, design, methodology, investigational medicinal product or auxiliary product, or the investigator or clinical trial site involved, and can, therefore, have significant repercussions on the safety and the rights of the subjects, or on the outcome, reliability, and robustness of the trial; the modification authorisation procedure shall be similar to the initial procedure. The timelines for the assessment of the relevant modification will vary between 38 days (if no clarifications or rectifications are requested) and 85 days (in the event that both of them are necessary).

The first assessment report within the provided timeline will result from the collaboration of the Agency and the CEIm. In our country, the agreement between these two entities has been defined in the "Memorando de Colaboración e Intercambio de Información entre la Agencia Española de Medicamentos y Productos Sanitarios y los Comités de Ética de la Investigación con medicamentos" [Memorandum of Collaboration and Exchange of Information between the Spanish Agency of Medicines and Medical Devices and the Ethics Committees for Investigation with Medicinal Products] [13]. This document sets forth the acquired responsibilities by the CEIm and the AEMPS and further develops the assessment criteria. It also lists the parts of the dossier that should be submitted in Spanish and those that can be presented in English, as in accordance with the Regulation, it is up to each country to establish the language requirements of the submission dossier, though it is recommend that the documentation not intended for patients is provided by a commonly understood language by the medical community. Therefore, the Royal Decree establishes that all documents corresponding to Part I can be submitted in English; except for the authorisation form that shall be presented both in Spanish and English, as this document will feed the Spanish Clinical Studies Registry. The protocol's summary and the labelling and documentation intended for the patient will also be presented in Spanish.

Transparency

Directive 2001/20/EC established that clinical trials should be registered in a central database (EudraCT). However, the access to this database is restricted except for paediatric clinical trials (some protocol-related data are available through EudraPharm). The current Regulation institutes the creation of a new European database that will contain all

the information and data related to clinical trials, including those that come from the EU portal. The database will include the final trial report, which should be available within 30 days of marketing authorisation or withdrawal of the application for authorisation; together with a summary in lay terms intended for the general public. As previously mentioned, the EU database is not expected to be available until October 2018.

Until then, clinical trials conducted in Spain will be registered in the Spanish Clinical Studies Registry. In the current Royal Decree, this Spanish registry is developed from an even broader perspective, since it calls for the complete registration not only of clinical trials with medicinal products, but also of studies with medicinal products, in addition to allowing for the voluntary registration of prospective clinical studies without medicinal products, in line with the purposes set forth in the international clinical trials registry platform of the World Health Organization (WHO) [15]. As per WHO, the registry, publication, and public access to the relevant contents of clinical studies are a scientific, ethical, and moral responsibility, and the minimum set of clinical trial data that should be made public has been published. This is the standard adopted by the European Parliament and by the Council for the creation of the EudraCT database, and by the AEMPS for the Spanish Registry.

Clinical Investigator with a contractual relationship with an institution

For the first time, the Spanish legislation envisages clinical investigators with a contractual relationship with an Institution, or Hired Clinical Investigator, who were common at certain sites, but had not legal recognition until now. It is defined as that investigator, hired by the site or related research body to conduct clinical trials, as long as their functions can be carried out within the centre's care framework. However, it goes on to state that the actions of these investigators should be covered by a guarantee similar to that of the rest of the site's staff for those aspects not covered by the trial's insurance.

Reporting of suspected unexpected serious adverse reactions to the AEMPS

Notifications of suspected unexpected serious adverse reactions (SUSAR) shall be made via the European EudraVigilance database, although until the date of application of the Regulation, SUSAR can be reported to the AEMPS. Thus, notification to the CEIm is eliminated.

The period of notification is as per the Regulation (as soon as possible and in any case, within 7 days of the sponsor having knowledge of the unexpected life-threatening or fatal reaction or within 15 days in the event of a non-fatal or life-threatening SUSAR). In addition, the AEMPS shall provide a system that will make them available to the competent bodies of the regional authorities in real time (Comunidades Autónomas).

Clinical research ethics committee

The ethical review boards will continue to be linked to the assessment of authorisation applications and its responsibilities, and composition will continue to be determined by each country.

In the first additional disposition of the Royal Decree, there is a brief description of the procedure by which the previous Ethics Committees of Clinical Research (CEIC) will be accredited as CEIm by the competent authority of the regional authority (Comunidades Autónomas), considering the criteria set in chapter IV. During the first 2 years following the entry into force of the Royal Decree, the CEIC will assume the functions of the CEIm. After this period, the CEICs that have not been accredited as CEIm will be able to continue their activity in clinical research, but not in clinical trials with medicinal or healthcare products. In accordance with the data of the Ministry for Health, Social Services and Equality, there are currently 126 CEIC in Spain [16]; though it is expected that the number of CEIm will be much smaller. To be qualified, the CEIm will meet the requirements set forth in Law 14/2007 [17] and in the current Royal Decree, in addition to those that will be set by the AEMPS, in coordination with regional authorities by means of the Inspection Committee.

Article 9 of the Regulation establishes that the assessment shall be done by a reasonable number of persons with the necessary qualification and expertise; and that at least one layperson shall participate in the evaluation. Royal Decree 1090/2015 establishes that the CEICm will be composed of a minimum of 10 members, one of whom will be a layperson. Royal Decree 223/2004 previously established that one member to the CEIC should be independent of the centres at which research projects were conducted and that at least two members were to be unrelated to healthcare professions (one of which should hold a Law degree). Although it was not directly addressed, these members represent the interests of the participants.

In addition, the committee should be composed of physicians (one of whom will be a clinical pharmacologist), and should include a hospital pharmacist or primary care pharmacist and a nurse. One of the members of the committee will be qualified in bioethics. The CEIm will also be advised by the appropriate experts whenever the evaluated protocols include surgical or diagnostic procedures, healthcare products, or advanced therapies.

Discussion

In Regulation 536/2014 and in Royal Decree 1090/2015, the scope of application is not modified; as it applies to all clinical trials with medicinal products for human use. However, some definitions in Article 2 are clarified; specifically those regarding clinical trial, clinical study, and observational study. This aspect is of the utmost importance as prior definitions led to differences of opinion among investigators and regulatory authorities and among the regulatory authorities of the different States, occasionally causing paradoxical situations, since the very same study could be considered to be a clinical trial in some countries, but not in others [18].

Furthermore, for the first time in European legislation, Regulation 536/2014 includes the concept of "low-intervention clinical trial". This definition is maintained in Royal Decree 1090/2015 and represents a fundamental step forward for academic research, which comprises around 40 % of clinical trials carried out in Europe [7]. For the first time, it is considered that the risk for subjects in clinical trials is not the same when the treatment applied is similar to that of routine clinical practice; as its quality, safety, and efficacy have been established in previously conducted clinical trials and by use. Hence, it is considered that low-intervention clinical trials should be subject to less stringent standards as regards monitoring, master file requirements, and traceability of the medicinal products. In this regard, a significant decrease is anticipated in the administrative and financial burdens derived from the less strict monitoring requirements of medications with a well-characterised toxicity profile [19].

The inclusion of low-intervention clinical trials has been acknowledged by most scientific associations [18, 20–22]. Obviously, the safety requirements for well-known medications need not be as demanding as for medicinal products that might be first-in-class drugs that have specific regulations to reduce risks [23]. The patent of many of these well-known medications may have expired; however, they may still have a high treatment index, although the lack of trials dedicated to their study may bias the perception of efficacy in comparison to newer drugs. The future development of these medicinal products may lack commercial interest for the companies that market them; nevertheless, studying how to optimize the use of these medications in terms of duration of treatment, treatment regimes, new indications for less frequent diseases or minority populations; comparative cost-benefit or drug utilization studies in real-life conditions, or those studies aimed at examining the rational use of the medicinal product may portray an enormous benefit for patients and the society in general.

Some scientific associations, however, have expressed their concern, because, in accordance with the fundamental principles of pharmacovigilance, the safety and efficacy profile of drugs during the first years after marketing authorisation may not be fully characterised [21]. Moreover, medicinal products authorised under "exceptional circumstances" or by "conditional approval" by definition display an incomplete characterisation of their safety profile and as such, when proceeding to classify a study as a low-intervention trial, regulatory authorities and the CEIm should consider the fact that the monitoring and notification of adverse events in the case of clinical trials performed with medicinal products during the first years of marketing, or for products authorised under special conditions, or even in the case of clinical trials requested by the regulatory agencies to characterise certain safety aspects (trials conducted in special populations, etc.), should be similar to those of the conventional clinical trials.

The concept of proportionality of risk establishes that there should be compensatory mechanisms in place for low-intervention trials that are "appropriate to the nature and the extent of the risk". That is, that from a theoretical perspective, if the risks are similar to those of routine clinical practice, a compensatory system other than that of routine clinical practice should not be necessary.

This aspect has received strong support from scientific societies [18, 20], although in general, it has been deemed insufficient. It must be acknowledged that the need of an insurance policy is one of the basic obstacles to academic research in Spain and probably elsewhere; and causes that a large part of the funding of public or charitable origin must be spent on this expense. Since the previous Directive came into force, insurance expenditures have risen by 800 % [24]. Of course, this does not unbind investigators from their responsibility under the law. However, it is certainly an unresolved issue from the investigator's perspective. It is acknowledged that the proportionality of risk prevails over the type of funding for trials, and it is possibly the first step toward financial guarantees being covered by the professional or trial site's civil liability insurance.

From a practical standpoint, in neighbouring countries where, prior to the effective date of the new Directive, there was no formal obligation to take out insurance, it was up to the regulatory bodies and to the ethical review boards to examine whether or not the sponsor would be capable of assuming claims for compensation; which predetermined that, de facto, a specific insurance policy had to be taken out to cover the trial. Bearing in mind the experience in countries, such as Great Britain, it is not foreseeable that in the short term, financial guarantees can be considered

covered by the standing guarantees outside the trial. Nonetheless, in countries, such as Denmark, the usual mechanism of compensation already covers most academic clinical trials [24]. Undoubtedly, getting the States or private bodies to accept these proposals in current times is tremendously challenging. However, when one considers the large sums of public money used for private individual insurance policies for each trial and the benefits of academic research for public health and the society in general, the idea begins to make sense. Moreover, non-commercial sponsors might be the ones most interested in carrying out research to optimize already established treatments in terms of treatment duration or new schemes or to examine which medicinal product provides better outcomes, and this is the research that can optimize healthcare costs, allowing healthcare systems to save great sums of money in the long run.

This would most certainly require a great pact with the State, other pertinent bodies, and with those healthcare centres that are truly committed to research; together with the formal recognition that the real risks of some interventions cannot truly impact the subject's health differently from what would occur in routine clinical practice.

The Royal Decree also establishes that, in the case of non-commercial research, the clinical trial authorisation application can be submitted without having taken out the insurance, although the contract must be submitted after a positive judgment from the CEIm. This provision can be an advantage for the small percentage of trials, generally promoted by non-commercial investigators, that will ultimately not be authorised (in Spain, 714 trials were authorised; 9 were rejected, and 33 trials were withdrawn in 2014) [6].

Another critical point of the current regulation is the submission of a single dossier for clinical trials conducted in different countries (including the submission made to the Ethics Committee), which was one of the most important demands made by the pharmaceutical industry and cooperative groups in recent years to avoid having to submit basically identical information to all Member States and multiple committees, in most cases in specific formats [7, 18, 20, 24–26].

Undoubtedly, the single portal for the European Union will simplify the administrative procedures for industry and cooperative groups once it is operating. The current submission though the AEMPS portal by means of a single contact point also simplifies the process for multicentre trials. The establishment of a single template for the contract for the entire National Healthcare System has also received strong support, even though this template has not yet been provided.

The single joint position by all Member States is even more relevant. The assessment is divided into Part I (quality, preclinical, pharmacology, toxicology, clinical efficacy and safety data, and methodological aspects), that will be carried out by a single State by means of an assessment report that will be reviewed by the rest; and Part II (consent, compensations, how subjects will be selected, personal data protection, suitability, compensations, and compliance with the rules for the use of samples for future research) that is deemed to cover aspects that are intrinsically national in nature and that, in our country, will be performed by a single CEIm. In the establishment of the assessment consensus reached by the AEMPS and the CEIm, it is important to acknowledge that consideration has been given to avoid a complete dissociation between the evaluation of the scientific and ethical aspects, i.e., Part I and II, as both will be assessed by the AEMPS and CEIm, since the scientific robustness of a study is a pre-requisite for it to be ethically acceptable. Thus, certain intrinsically national aspects, such as informed consent, determined to a large extent by educational, social, and cultural issues, will remain outside the scope of the cooperation between Member States. In this regard, it must be pointed out that from now on, a single CEIm shall be responsible for assessing the suitability of the investigators and that of the facilities of all centres in Spain, which will demand that both sponsor and researchers pay special attention to those aspects that objectively justify the conditions of suitability.

Therefore, the CEIm continues to play an essential role in the assessment of the ethical components of the study, which, as previously mentioned, cannot be dissociated from the methodological aspects. Nevertheless, there can be situations in which a methodologically impeccable trial can be deemed adequate in one European country, but not in another, including the different standard treatments, general vulnerability of the patients, as well as the different educational, cultural, or historical determinants. Even today, the wording of the informed consent form, advertising and the methods for subject recruitment, and all closely linked to the aforementioned conditions determine the largest discrepancies between different countries and between the different ethical review boards of a single country.

This simplified assessment procedure will not only decrease the administrative procedures that investigators must carry out, but will probably also enrich the assessment from a scientific standpoint, as the experience from the centralised authorisation procedure shows us. One clear risk of this new form of coordinated assessment is that the applicants give priority to the assessment by one Member State over the rest, with the consequent economic and scientific repercussions for the others, since, in the event of disagreement between the Member States, the country proposed by the applicant will be the reporting party [27].

Another central aspect of this Directive is the increase in transparency. The Declaration of Helsinki and its

subsequent revisions determine that all research involving human subjects must be registered prior to recruitment of the first patient and that there is an ethical obligation to publish the results of these studies, including negative or inconclusive outcomes [28].

The current Directive regulates the creation of a new European database containing all the information and data related to clinical trials. This database will not only include the final report of the trial, but also summarise the results in lay terms intended for the general public. This increase in transparency has been acknowledged by patients and professional associations [18, 20], since it has been estimated that up to 50 % of all trials are never published, which can lead to the repetition of trials and a biased view of the efficacy and safety of the medicinal products involved [29]. Of course, personal data protection, commercially sensitive information, and communications between the Member States during the assessment will be guaranteed. As previously mentioned, the EU database is not expected to be available until October 2018.

By means of the current Directive, general safety notifications are also simplified, since serious and unexpected adverse event shall be reported through EudraVigilance, although until the effective date of the Regulation, notifications can be made to the AEMPS. Notification to the CEIm of information that, in general, the committee was not capable of processing, and is thereby ended.

Conclusions

The coming into force of EU Regulation 536/2014, which will be directly applicable in our country, and Royal Decree 1090/2015 that adapts the Spanish legislation to the new situation is a step toward harmonisation in clinical trial legislation in the European Union. It will simplify the authorisation and the notification of unexpected serious adverse events procedures; it will decrease the administrative burden and response times by the AEMPS and CEIm, possibly bolstering our country's competitiveness and European research as a whole, with the aim of speeding up the availability of new drugs on the market and the optimal use of medicinal products for new indications. In addition, the coordinated assessment of clinical trials will probably enhance the scientific quality of the assessments, as it will foster the debate between the different European agencies and between the agencies and CEIm. Another crucial aspect is the increase in transparency, since clinical trial data accessibility for the general public in general and the stimulation of cooperation among the Member States in assessing safety will strengthen the system of guarantees.

Last but not least, non-commercial research will probably be stimulated by means of the inclusion of a monitoring strategy and compensations system which is proportionate to the risks for subjects. It might be deemed insufficient, but there is no doubt that it is the first step toward the recognition of the fact that the risk for subjects participating in certain studies does not differ substantially from that of routine clinical practice. Of course, progress in this sense cannot make without the collaboration of all the social stakeholders involved.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest and received no funding.

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