

REGULATORY PERSPECTIVE

Clinical trials of advanced therapy investigational medicinal products in Spain: preparing for the European clinical trials regulation

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Clinical trials (CT) of Advanced Therapy Medicinal Products are a reality worldwide. Although ATMPs are still very innovative therapies, it is interesting to investigate what relevant information can be obtained from the analyses of authorized CT and the investigated products. The aim of this study was to follow the evolution of CT with Advanced Therapy investigational Medicinal Products (ATiMP) authorized in Spain from May 2004 to June 2019 on the basis of information available at the Spanish Agency for Medicinal Products and Medical Devices and their real status (also taking into consideration their status in three different official Registries). We will also discuss how sponsors and Authorities can prepare for the coming new clinical trial regulation and take advantage of the opportunities it may present.

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INTRODUCTION

Clinical trials (CT) are essential to support the authorization of medicinal products and are the basis for their appropriate use in normal clinical practice. The knowledge of ongoing or finished CT is essential in order to favor better designs for future clinical investigations. There is a CT European legislation in force since 1st May 2004 (Directive 2001/20/CE) [1] that has been reviewed in CT Regulation 536/2014 [2]. Under both legislations, the conduct of a clinical trial with a medicinal product in any European Union (EU) Member State requires prior national authorization. In the case of Spain, such authorization is given by the Spanish Agency for Medicinal Products and Medical Devices (AEMPS) after internal CT review, provided that one Ethics Committee (Committee of Ethics of the Investigation with medicinal products – known in Spanish as CEIm) has also given a favorable opinion. The information that sponsors currently need to provide to the competent authorities (AEMPS in the case of Spain) to be published in either EU CT Register (EU CTR) [3] or Spanish Register on Clinical Studies (REec) [4] is shown in **Table 1**.

The above-mentioned reviewed Regulation came into force in June 2014 and introduced important changes; among them, a European coordinated assessment of CT and additional transparency requirements with respect to terms currently in force and shown in **Table 1**, related to CT information and documents that will be available to the public [5]. However, its whole applicability is still pending the availability of the new EU CT Portal and Database (CT Information

System), which is currently under development and will enormously simplify communications between sponsors and Member States (MS). In the meantime, a Voluntary Harmonisation Procedure (VHP), set up by the Clinical Trials Facilitation Group, serves as a pilot for the coordinated EU assessment of CT applications foreseen in Regulation 536/2014(2). The VHP was introduced in order to achieve harmonized assessments and decisions on clinical trials in the EU, and sponsors are encouraged to use it [6,7].

Advanced Therapy medicinal products (ATMP) are a particularly innovative medicinal class that includes gene therapy medicinal products (GTMP), somatic cell therapy medicinal products (sCTMP), tissue engineered products (TEP), and combined products (tissue or cell associated with a device). The legal and regulatory framework for ATMPs in the EU (ATMP Regulation 1394/2007) [8] came into force on 31st December 2008 and defined common rules for this very innovative group of medicinal products that have to comply with specific quality requirements [9].

Clinical investigation of ATMP has additional difficulties due to the nature of some of the products. For instance, many cell-based ATMPs are autologous (i.e. prepared from material taken from the patient) which makes standardization a real challenge for manufacturers. In addition, Advanced Therapy investigational Medicinal Products (ATiMP) have to comply not only with the general legislations for clinical trials and ATMP, but also with legislation from different frameworks, such as the tissues and cells Directive (Directive 2004/23)

▶ **TABLE 1**

Information to be provided by the sponsors to the AEMPS to be published in the EU CTR and REec according to EU and national legislation [2,14].

CT information to be provided by the sponsor to NCA to be public	Publication in EU CTR	Rules for publication of CT in REec
Summary of CT design (since initial CT application for authorization)	All CT authorized since 1st May 2004. However, Phase 1 CT not including pediatric population are not published	All CT authorized since 1st January 2013. Phase 1 CT not including pediatric population may only include abbreviated information, if this is the sponsor choice
Date of CT start (within following 15 days)	Yes	Yes
Date of end of recruitment in Spain (within following 15 days)	No	Yes
Dates of end of CT in Spain and of global CT end, clarifying if the end is premature or not (within following 15 days)	Yes	Yes and in case of premature end, reasons are also published after assessment
Temporary halts affecting Spain clarifying if global or not and reasons (within the following 15 days)	Yes, reasons are not published	Yes, and reasons are also published after assessment
Summary of CT results (within one year of the date of global CT end)	Results to be loaded in EudraCT and also submitted to the AEMPS	Results of Phase 1 CT not including pediatric population are currently not public

for the donation, procurement and testing of the starting materials to be converted into cell-based medicinal products [8], or that for genetically modified organisms (GMO) (Directives 2001/18 and/or 2009/41) [8] when the product belongs to this category. In this latter case, lack of harmonization between different GMO authorities across the EU has prompted the development of common voluntary procedures for some categories of products [10].

In spite of the above difficulties, Spain has been identified as the Member State with the highest number of CT on ATMPs [6,11]; taking advantage of this, we set out to analyze characteristics of these CT. This article is focused on the analysis of the characteristics of the clinical trials on ATiMP authorized by AEMPS from 1st May 2004 to 30th June 2019, also paying attention to the IMP being investigated. The purpose is to identify possible areas of improvement in order to

be able to comply with the new EU CT legislation.

METHODOLOGY

All valid clinical trial applications on ATiMP received at AEMPS since 1st May 2004 until 30th June 2019 have been considered for the analysis. Description of the characteristics of the clinical trials authorized by AEMPS takes into account the information available on the internal CT database of this Agency regardless of substantial amendments.

ATiMPs were classified according to the definitions set out in Regulation 1394/2007 and Directive 120/2009, and following the principles highlighted in the reflection paper on classification of ATMPs published by the Committee for Advanced Therapies (CAT) [12]. Products used in clinical trials before these definitions were published have been reclassified according to

these criteria in order to have a harmonized approach. Products containing or consisting on genetically modified cells (e.g., CAR-T cells) are generally considered GTMPs in the EU, except when the genetic modification is not directly linked to the therapeutic activity of the cells.

In Spain, all medicinal products without a marketing authorization in any country of the European Economic Area (EEA) that contain an active substance or combination of substances not included in any of the medicinal products marketed in Spain need to obtain a number of Product under clinical investigation (known in Spanish as PEI) and sponsors need to cross-reference this number for every new CT application. A PEI covers all pharmaceutical forms and strengths of an investigational product. ATiMPs and especially, cell-based ATiMPs, are very complex and sometimes it is difficult to determine whether a particular product should be considered the same or a different PEI. For instance, a different PEI number is required when the same cell product changes from an autologous to an allogeneic use. Normally, when changes were introduced – e.g., in final formulation – the new product was considered as being different. When substantial changes were introduced in manufacturing without a proper comparability study, the final products were also considered as being different. Different manufacturers require different PEI numbers unless equivalence of the products is shown through strong comparability studies. To clearly define and identify the different drug substances used in clinical trials in Spain, a guideline on nomenclature of cell-based medicinal products was followed [13]. This guideline,

developed by AEMPS, defines not only the cell type but a number of additional attributes (tissue of origin, expansion in culture, other manipulations, etc.) as a pre-requisite to the final identification. The analysis of the products' characteristics showed in this paper took into account our register of PEI ATiMP.

Number and characteristics of the ATiMP in the authorized CT, owners of such products (commercial, i.e., pharmaceutical companies, or non-commercial, i.e., facilities within the National Health System) and number of CT per ATiMP have been analyzed.

The following aspects have been analyzed and verified for all authorised ATiMP CT during this period on the basis of information available on CT Applications and electronic CT Dossier Documents:

- ▶ Type of sponsor (commercial or non-commercial [14]);
- ▶ Distribution of the CT according to type of ATiMP (sCTMP, GTMP, TEP) and GMO character;
- ▶ Phase of CT as indicated by the sponsor;
- ▶ Therapeutic area of investigation taking into account MeSH terms used by EudraCT [15] to define the Therapeutic Area;
- ▶ Population (i.e., adults (18–64 years), elderly (>65 years) and/or pediatrics (less than 18 years));
- ▶ National or International character taking into consideration geographical distribution of the participant sites;

- ▶ According to the number of sites in Spain, single-site or multi-site CT;
 - ▶ CT status and availability of results.
 - ▶ *End of Recruitment*: date of end of recruitment has been provided;
 - ▶ *Temporarily Halted*: temporary halt date has been received;
 - ▶ *Prematurely Ended* (According to the Regulation No 536/2014 [2], early termination of a clinical trial means the premature end of a clinical trial due to any reason before the conditions specified in the protocol are complied with)/ *Completed*: end of trial date has been received. CT having included a significantly lower than planned number of subjects or those not having completed all parts defined in the protocol have also been considered as prematurely ended for this analysis, even if the end was not notified as premature;
 - ▶ *Unknown*: in cases where there have not been notifications by the sponsor within the last 2 years.
- Results have been considered as:
- ▶ Yes: available results
 - ▶ No: no available results
 - ▶ NA (not applicable): when the CT has not finished yet or when

In addition, publication has been checked in REec [4], EU CTR [3] and ClinicalTrials.gov [16]. For CT found in these three registers, consistency in terms of the status displayed taking into consideration Table 2 and the availability of results with respect to the information received in AEMPS has been also reviewed. Taking into account that the status in REec reflects the situation of the CT in Spain, possible differences in the recruitment status among Registers for international CT have not been considered incoherent. Consistency of the end of trial status for international trials has also taken into account, if the global end of trial had been notified to the AEMPS. The latest available status from the following is shown, provided that at least one notification has been received for the trial in the last 2 years:

▶ **TABLE 2**

Equivalence of CT status among the different CT Registries checked on this research.

REec	EUCTR	Clinicaltrials.gov
-	-	Unknown
Not initiated		Not yet recruiting
Recruiting (or restarted)	Ongoing (or restarted)	Recruiting
End of recruitment		Enrolling by invitation
Temporarily halted	Temporarily halted	Active, not recruiting
Prematurely ended	Prematurely ended	Suspended
Completed	Completed	Terminated
		Withdrawn (no patients)
		Completed

the global end date of the CT has taken place within the last year and the deadline to submit official results has not been reached yet, according to National Law and European Regulation

Verification of all CT status and results has taken place during September 2019.

RESULTS

During the period from 1st May 2004 to 30th June 2019, AEMPS received 331 valid CT applications on ATiMP that represent 2.9% of the total number of valid CT applications in that period. Status for these CT applications on 20th July 2019 (data analysis starting date) was: 290 authorized, 14 rejected, 19 withdrawn and 8 under assessment. Spain takes part in approximately 23% of ATiMP CT authorized in Europe [3].

CT according to type of ATiMP, sponsor & international character

The **distribution of authorized CT according to the type of ATiMP and sponsor** along the analyzed period is shown in **Figure 1**. Total numbers of ATiMP CT and distribution according to type of product, sponsor, country of the sponsor, international character, number of sites in Spain and phase is shown in **Table 3**.

Clinical investigation of ATiMP shows an important increase since 2010. Until 2013, it was mostly focused on sCTMP and TEP and driven by Spanish non-commercial

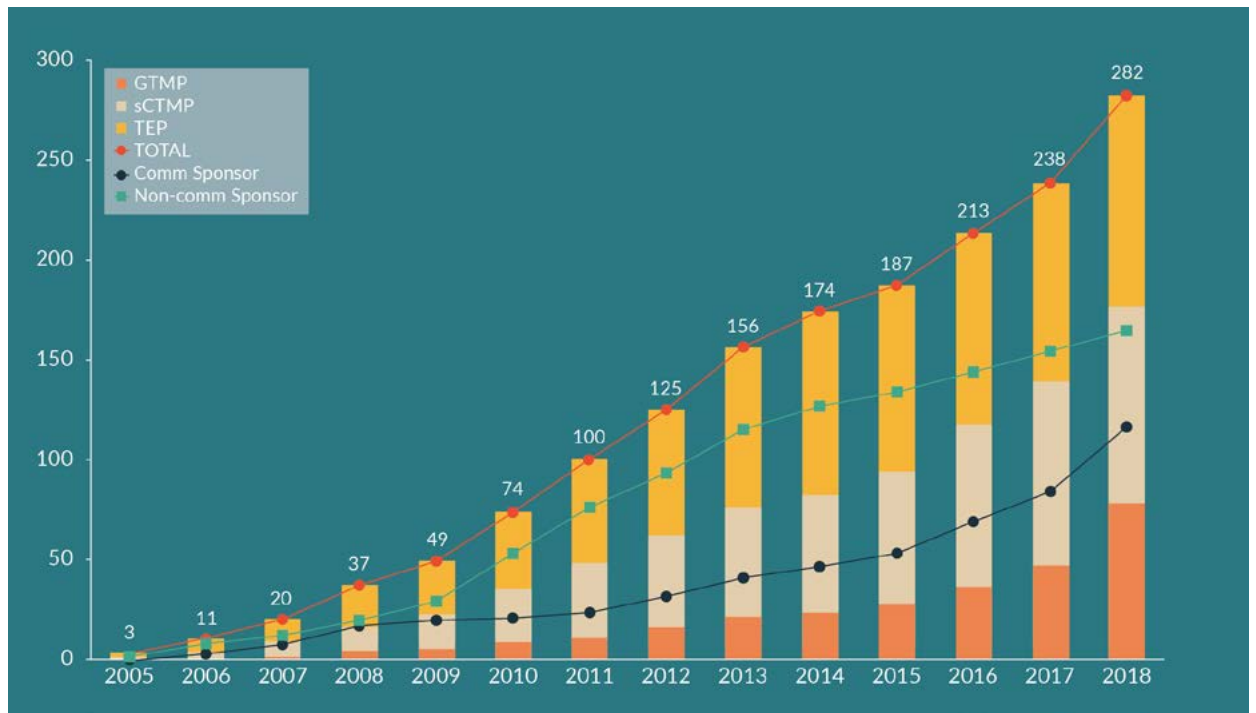
sponsors (in fact, from 2005 to 2010 ATiMP CT sponsors are only Spanish). From 2011 onwards, sponsors from other countries started to sponsor ATiMP CT in Spain. The proportion of international sponsors increased up until 2018, when approximately half of the sponsors were from other countries (see **Figure 2**). In this sense, the figures from 2018 are especially revealing, since 29 out of the CT run by a sponsor not based in Spain were authorized. CT on GTMP are mainly run by commercial sponsors and have a greater relevance since 2016, showing a great peak in 2018 coinciding with international CT increase, as shown in **Table 3**. This is consistent with the evolution in the type of ATMP being investigated (see **Figure 1**).

Most ATiMP CT are early phases: Phase 1, Phase 1/2 and Phase 2 represent 80.3% of all authorized CT during the study period. Non-commercial sponsors are more focused on early phases clinical trials, as opposed to commercial sponsors who conduct the majority of Phase 2/3, 3 and 4 trials. There is no significant relationship between the type of therapy and phases of CT. Most national clinical trials have non-commercial sponsors (88%). International trials are mostly Phase 2 or 3, while national trials are Phase 1 and 2. Non-commercial sponsors mostly conduct single-site trials while multi-site trials are conducted by commercial sponsor (see **Table 4**).

Regarding the **Voluntary Harmonisation Procedure (VHP)**, available for CT planned to be conducted in two or more EU Member States, Spain has participated in the evaluation of seven CT with ATiMP by this procedure, five of

▶ **FIGURE 1**

Cumulative data on authorized ATiMP CT in Spain (2005–2018).



which were with tissue engineered products. Most of these CT were Phase 2 or Phase 3, and both commercial and non-commercial sponsors used this procedure. Prevalence of these phases is also observed in all CT evaluated by VHP to date [6,7].

CT according to targeted disease & CT population

Globally, the most predominant therapeutic area was cancer (31.7%) followed by cardiovascular (14.8%) and musculoskeletal (10.0%) diseases. 63% of cancer CT investigated GTMP, while 35.9% of them investigated sCTMP. However, 95.5% of CT on the cardiovascular area and 96.4% of those on musculoskeletal diseases investigated TEP. The indications of leukemia/lymphoma/myeloma with 32 CTs,

inflammatory bowel disease with 15 CTs, gastrointestinal system cancer with 13 CTs, and heart failure, ischemic and non-ischemic/cardiomyopathy with 13 CTs were the most frequent (Table 5).

17.9% of ATiMP CT include pediatric population (together with adults and/or elderly people [10.7%]; exclusively pediatric population [7.2%]). Most of these trials investigated GTMPs (48.1%) and have a commercial sponsor (61.5%). Regarding indication on exclusively pediatric CT, cancer remained the most prevalent (47.6%) followed by congenital, hereditary, and neonatal diseases and abnormalities (e.g., spinal muscular atrophy, Fanconi anemia, osteogenesis imperfecta, inborn errors of urea cycle, etc.; 38.1%).

CT were equally performed in both women and men.

▶ **TABLE 3**

Number of CT on ATiMP according to type of product, sponsor, country of the sponsor, international character, number of sites in Spain and phase.

	No. OF CT ON ATiMP (N = 290)	No. OF CT ON sCTMP (N = 99)	No. OF CT ON TEP (N = 107)	No. OF CT ON GTMP (N = 84)
Sponsor				
Commercial	124 (42.8%)	32(32.3%)	21 (19.6%)	71 (84.5%)
Non-commercial	166 (57.2%)	67(67.7%)	86 (80.4%)	13 (15.5%)
Sponsor country				
Spain	209 (72.1%)	80 (81.0%)	94 (87.8%)	35 (41.7%)
USA	49 (16.9%)	9 (9.0%)	2 (1.9%)	38 (45.2%)
Rest of EU	29 (10.0%)	7(7.0%)	11 (10.3%)	11 (13.1%)
Israel	3 (1.0%)	3(3.0%)	0 (0%)	0 (0%)
International				
Yes	109 (37.6%)	27 (27.3%)	22 (20.6%)	60 (71.4%)
No	181 (62.4%)	72 (72.7%)	85 (79.4%)	24 (18.6%)
Sites in Spain				
Multi-site	156 (54.1%)	52 (52.5%)	49 (45.8%)	55 (65.5%)
Single-site	133 (45.9%)	46 (46.5%)	58 (54.2%)	29 (34.5%)
Phase				
Phase 1	71 (24.5%)	19 (19.2%)	28 (26.2%)	24 (28.6%)
Phase 1/2	33 (11.4%)	14 (14.1%)	1 (0.9%)	18 (21.4%)
Phase 2	128 (44.2%)	46 (46.5%)	61 (57.0%)	21 (25.0%)
Phase 2/3	3 (1.0%)	1 (1.0%)	1 (0.9%)	1 (1.2%)
Phase 3	52 (17.9%)	19 (19.2%)	14 (13.1%)	19 (22.6%)
Phase 4	3 (1.0%)	0 (0%)	2 (1.9%)	1 (1.2%)

ATiMP

Regarding **investigated products**, 168 different ATiMP products are being investigated in the authorized CT, being 54 (32.1%) TEP, 51 (30.3%) sTCMP and 49 (29.2%) GTMP, while 14 (8.3%) products are being investigated as both sTCMP and TEP. They include ATiMP currently having a marketing authorization in the EU (Alofisel®, Holoclar®, Imlygic®, Kymriah®,

Yescarta® and Zalmoxis®), USA (Zolgensma®) or Spain (NC1). NC1 is a product prepared on a non-routine basis according to specific quality standards, and used within Spain in a hospital under the exclusive professional responsibility of a medical practitioner, in order to comply with an individual medical prescription for a custom-made product for an individual patient, authorized by the AEMPS, as defined in Regulation

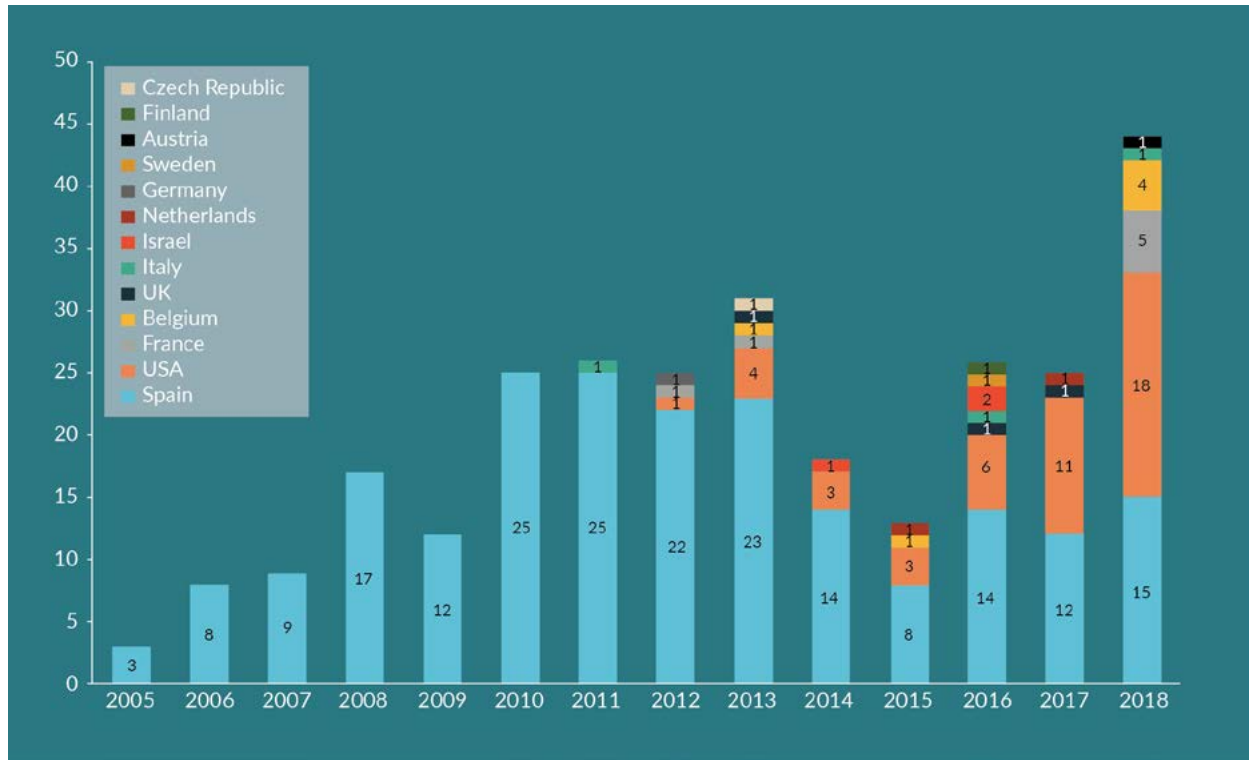
▶ **TABLE 4**

National or International character and number of sites in Spain for CT on ATiMP according to type of sponsor.

	Non-commercial	Commercial
National (N = 181)	159 (87.8%)	22 (12.2%)
Single-site	103	5
Multi-site	56	17
International (N = 109)	7 (6.4%)	102 (93.6%)
Single-site	2	23
Multi-site	5	79

▶ **FIGURE 2**

Authorized ATiMP CT per Sponsor country.



[EC] No 1394/2007 [8] and Royal Decree 477/2014 [17]).

40 of the GTMP and two of the sCTMP are GMO and they are being investigated in 75 CT. Their Product Owners are mainly commercial (85.7%). Sponsors for GMO CT are from Spain and USA (43% each), while sponsors for the other 14% are from other European countries.

The number of CT per PEI has ranged from 1 (for 112 ATiMP) to 9 (for 2 ATiMP). 21 products have been investigated on at least four CT, including Alofisel®, Imlygic® and Kymriah®, which have a marketing authorization in the EU, and NC1 (authorized in Spain according to the national legislation for ‘hospital exemption’). Twelve out of these 21 products are manufactured in a facility pertaining to the national health

system, while the other nine pertain to a pharmaceutical company.

It is remarkable that 91 out of 168 ATiMP belong to non-commercial owners; most of them are sTCMP and TEP, in consistency with the type of CT run by non-commercial sponsors. On the other hand, most of the products that belong to commercial owners are GTMP.

CT status

According to EU legislation, sponsors have the obligation to report National Competent Authorities relevant dates and information for the CT in order to make its status transparent. Certain information, such as the annual safety report, should be provided yearly along the CT duration. In addition, the

▶ **TABLE 5**

Number of trials in the four most investigated disease areas: cancer, cardiovascular diseases, musculo-skeletal diseases and digestive system diseases.

Disease area	Diseases	Number of trials
Cancer	Leukemia/lymphoma/myeloma	32 (34.8%)
	Gastrointestinal system cancer	13 (14.1%)
	Brain cancer	9 (9.8%)
	Skin cancer	8 (8.7%)
	Bladder or renal cancer	5 (5.4%)
	Respiratory system cancer	4 (4.3%)
	Prostate cancer	3 (3.3%)
	Breast cancer	3 (3.3%)
	Others	15 (16.3%)
	TOTAL	92
Cardiovascular diseases	Heart failure, ischemic and non-ischemic/ cardiomyopathy	13 (30.2%)
	Myocardial infarction/coronary	12 (27.9%)
	Limb ischemia and peripheral arterial disease	12 (27.9%)
	Stroke	6 (14.0%)
	TOTAL	43
Musculoskeletal diseases	Joint or bone arthrosis	11 (37.9%)
	Bone defects	9 (31.1%)
	Spinal defects or pathology	6 (20.7%)
	Tendinopathy/ligament defects	3 (10.3%)
	TOTAL	29
Digestive system diseases	Inflammatory bowel diseases (perianal fistules)	15 (65.3%)
	Hepatic failure/cirrhosis	7 (30.4%)
	Fecal incontinence	1 (4.3%)
	TOTAL	23

CT should be published in the EU CTR [3] and in the REec [4] as is indicated in Table 1. However, considering the international character of part of the CT and the relevance of ClinicalTrials.gov [16] also for EU investigators and sponsors, the registration status of all ATiMP CT authorized in Spain has also been checked in that register.

All authorized ATiMP CT since 1st January 2013 (n=165) are registered and published in REec [4]. In 230 out of 290 CT, Spain is a participating country in a record in the EU CTR [3]. The 60 not published CT are phase I and do not include pediatric population. 235 CT are registered in ClinicalTrials.gov [16]. Only 8 CT, authorized before

August 2011, are not published in any of these registers, and only 117 out of 290 CT are published in all of them.

Considering the information available at AEMPS, the status of ATiMP CT is reflected in Table 6.

The public status displayed for the CT published in REec, EU CTR [3] and ClinicalTrials.gov [16] was consistent in most cases (98 out of 117 cases). For 12 CT the status in ClinicalTrials.gov [16] was not updated according to the information available in the AEMPS and in 6 cases the information seemed to be more updated in ClinicalTrials.gov [16] than in the AEMPS. Coherence of the CT status in REec [4] and the status for Spain in EU CTR [3] is seen but this is expected since

AEMPS is responsible for keeping it updated.

During the analyzed period, 142 CT were ended by the sponsor, 47 of which were terminated earlier than expected. **Table 7** shows the number of prematurely ended clinical trials in relation to the reasons for it. The main reasons for early termination included lack of recruitment (53.2%) and business reasons (21.3%). It is remarkable that lack of efficacy and safety were the reason for the early termination in just five and two CT, respectively.

Regarding the time elapsed from the authorization until the early termination, less than 1 year passed in 31.9%, between 1 and 3 years in 27.6% and more than 3 years in 40.4%. Finally, the predominant therapeutic areas on these CT were cancer (40%), and cardiovascular diseases, coinciding with the two most investigated therapeutic areas for ATiMP CT.

ATiMP CT results

According to the EU legislation, sponsors should upload a summary of CT results in EudraCT [15].

These results are published in the EU CTR except if the CT is only Phase 1 and does not include pediatric population. Results should also be submitted to EU Member States National Competent Authorities. In both cases, the deadline for this submission is within a year of the end of trial (usually the last visit of the last patient). For CT authorized in Spain since 1st January 2013, the summary of the results is published at REec, except for Phase 1 CT not including pediatric population, for which there is limited information published.

According to these criteria, AEMPS should have received the summary of results for 73 completed CT for which the due date has expired. Twenty-three of these trials have a commercial sponsor while 50 of them have a non-commercial one. Results for only 45 CT (61.6%) have been received and only 14 CT have results publicly available either in REec (n= 4) [4], in EU CTR (n=7 plus intermediate results for 1 CT, authorized since 2007) [3] and/or in ClinicalTrials.gov (n=5 CT authorized since April 2012) [16].

With respect to prematurely ended CT, results are expected to

► **TABLE 6**

Status of ATiMP CT according to information available in AEMPS.

CT status	Number of CT per status according to information available in AEMPS
Not initiated	16
Recruiting	74
End of recruitment	30
Temporary halted	3
Prematurely ended	46
Completed	79
Unknown	42

Unknown status for 17 CT authorized before 2013 might be due to the fact that for these trials part of the information could be in a paper File on CT, not checked for this review, which was previous to the current AEMPS database that contains all documents in the CT dossier presented in an electronic format.

▶ **TABLE 7**

Number of prematurely ended clinical trials distributed by reasons for early termination (CT authorized before and after 2013).

Reasons	No. of CT (auth. < 2013)	No. of CT (auth. ≥ 2013)
Lack of recruitment	20	5
Business reasons	4	6
Enough data	1	1
Lack of efficacy	2	3
Safety	0	2
Other reasons	3	0
TOTAL	30	17

be made public as soon as possible within the year following the end of the CT, especially information related to safety or lack of efficacy, unless the CT ends with no relevant subject participation. Following these criteria, results have been accessible for the AEMPS in most of the cases (72.8%). Results are published in a CT register in seven cases, including all CT stopped due to lack of efficacy.

DISCUSSION

This article analyses all CT on ATiMP authorized by AEMPS from 2004 to 2019. This group of 290 studies represents around 22% of the entire CT with ATiMP conducted in the EU. As already stated, Spain is one of the countries in the world with more significant activity in this area [6,11].

The interest in identifying specific numbers for IMP investigated is highlighted, since these numbers are difficult to find due to the natural evolution of the names in products under clinical development. However, in the field of cell and tissue research, where the nature and origin of the cells as well as the autologous or allogeneic character could greatly influence the efficacy and safety of the products, having

a more systematic way of describing the ATiMP under development could be of great interest as AEMPS has previously highlighted [13].

Regulation 1394/2007 [8] set a clear and common framework for ATMPs in the EU. This regulation, amongst other things, added tissue engineered products as a new class of ATMPs to the previously defined gene therapy and somatic cell therapy medicinal products. This meant that many cells and/or tissue-based treatments that were already in clinical use outside the pharmaceutical legislation, became regulated as medicinal products when the ATMP regulation came into force (December 2008).

Publication of the ATMP regulation clearly had a positive effect on the number of clinical trials in Spain, as observed by the increase from 2010 in Figure 1. At that time, most of the trials had an academic sponsor and research was mainly focused on TEP and sCTMP (Figure 1). The number of trials stayed relatively high up to 2014, when a clear drop is observed, presumably due to the restrictions in public investments in clinical research associated with the worst years of the economic crisis. Recovery in number of clinical trials started from 2016, but this time driven mainly by commercial research (Figure 1).

The huge increase in the last 2 years is a clear reflection of the success in gene therapy clinical research directly related to industry (including big pharma) becoming increasingly interested in the development of advanced therapies (Figure 1) and expressed in the availability of several GTMP marketed both in the EU and USA since 2015 [18-20]. This increase has occurred despite the additional difficulties imposed on most gene therapy medicinal products because of their consideration as Genetically Modified Organisms (GMO). Application of the GMO regulation [21] in the EU to clinical trials with most gene therapy products means the involvement of a different competent authority to assess the potential environmental effects of such products, complicating the authorization procedure. This has a greater impact on multinational trials, because each MS has its own GMO competent authority and the procedures are far from harmonized across the EU. In an effort to unify criteria and streamline the process several activities have been initiated, which have already yielded a number of consensus documents [10]. Although these documents are not obligatory, a good number of MS (including Spain) have adopted them on a voluntary basis. This is expected to ease the administrative burden for clinical trials authorizations of medicinal products containing or consisting of GMOs.

The main characteristics of academic studies (n=166), as can be seen in Tables 3 & 4, are: early Phase 1, 1/2 and 2 CT (94%), national (95.8%), unicentric (62%) and focused on the investigation of sCTMP or TEP (92.2%). This is consistent with the logistical difficulties

in organizing late-phase CT that normally involve hundred or even thousands of patients, and require the involvement of many investigators and sites in different countries. An example of these difficulties is highlighted in the article by investigators of the study MESEMS [22] which due to financial constraints has been designed to merge partially independent clinical trials. In fact, 91 out of 168 ATiMP investigated are produced within the National Health System in non-commercial GMP-compliant facilities. It is remarkable that sometimes the results of early academic studies are the basis for the further development of a marketed product as was the case for Alofisel [23]. The fact that only 6 of the non-commercial products were GTMP could be due to the more complex manufacturing process of these products.

On the other hand, 82.8% of the CT on Phase 2/3, 3 and 4 and 84.5% of the CT on GTMP are run by commercial sponsors. Additionally, commercial CT stand out in their international (82.3%) and multicenter characteristics, as can be seen in Tables 3 & 4. This is in line with the characteristics necessary for confirmatory CT required to support the application for the marketing authorization of any medicinal product.

Our results show that 290 ATiMPs CT were conducted in different therapeutic areas. Cancer, with almost a third of the trials (31.7%), cardiovascular (14.8%) and musculoskeletal (10.0%) diseases were the most prevalent ones. Cancer diseases were also prevalent for pediatric patients (47.6%) due to their severity and scarce therapeutic alternatives, as well as congenital diseases (38.1%).

Our results regarding indications are in line with the search in the main international CT databases performed by Hanna *et al.* [24] or the review of ATiMP CT between 2004 and 2010 by Maciulatis *et al.* [11] in the EU, or even in European-country publications such as by the Czech Republic [25]. Although there were multiple indications, it is important to highlight refractory and recurrent characteristics, and the scarce and poor therapeutic alternatives for them (e.g., refractory and metastatic tumours, critical limb ischemia, non-revascularisable myocardium, complex perianal fistulas, osteogenesis imperfecta, spinal muscular atrophy, etc.). It is remarkable that 30.8% (n=16) of pediatric ATiMP CT were authorized in 2018. Indeed, 36.4% of authorized ATiMP CT in 2018 included pediatric population, while only 14.9% of total authorized CT (on any kind of medicinal product) in 2018 included pediatric population. This seems consistent with the increase in the GTMP CT.

Regarding the reasons that motivated a premature end for a CT, shown in Table 7, the main reason was lack of recruitment. The importance of a correct design that takes into account all actual population characteristics should be pointed out, in order to avoid lack of recruitment after all the efforts deployed to set up the trial. It is important to indicate that 30 of the prematurely ended CT were authorized before 2013, and for 20 of them, reasons for stopping the CT were related to a lack of feasibility in recruiting the necessary patients. This seems to indicate that nowadays, protocols are better adapted to true patient characteristics, which marks an improvement in their quality.

Only two CT on a GTMP have been stopped due to safety reasons, one of them with no patient participation because the safety problem was detected prior to enrolment. The time elapsed between the date of authorization of the CT and the premature end seems to be related to the reason for stopping the trial: the CT ended because of a lack of recruitment tended to last longer while those CT ended due to business or safety reasons usually stopped within the first year.

Currently, all CT should be uploaded to the European CT database EudraCT and be published in the EU CTR, except for those Phase 1 studies not including pediatric population. It is remarkable that the commercial confidentiality principle that supported hiding these Phase 1 CT not in the EU CTR for many years is not applicable in CT.gov, where 48 out of 60 non-pediatric Phase 1 CT are published.

Under-reporting of CT results is a serious problem which has been frequently highlighted [26–28]. Publication of results is not only an ethical issue but a legal requirement [1,2,14]. Our analysis shows that AEMPS has received an on-time report on the results for 65 out of 105 expected. 36 of these were with a commercial sponsor and 69 from a non-commercial sponsor. This means a rate of proper reporting of 72.2% for commercial and 53.6% for non-commercial sponsors, confirming the lower rate of reporting results for academic sponsors previously shown [29].

When looking into the structured format required to provide the results for the EU CTR [3] and ClinicalTrials.gov [16] registers, it is remarkable the fact that only 15 CT from

commercial sponsors have results uploaded to EU CTR (out of 103 registered CT for which such results could be expected). In addition, only nine CT (five from non-commercial sponsors and four from commercial sponsor) out of 104 registered and for which results could be expected have results uploaded to ClinicalTrials.gov [16] with a similar structured format. However, for 27 CT (12 from academic sponsors and 13 from commercial ones) not having loaded the structured results as required, there is at least one paper in a medical journal focused on the results referenced within the record of the CT in ClinicalTrials.gov [16] as ‘Publications automatically indexed to this study by ClinicalTrials.gov [16] Identifier (NCT Number)’. The lapsed time between the end of CT date and the publication has been 1 year for only one CT, longer than 1 and less than 2 years for nine CT, longer than 2 and up to 3 years for five CT, and longer than 3 years for the other ten CT.

These data could point to difficulties in completing the current structured summary of results, especially for academic sponsors. In addition, this shows the need to increase awareness around the legal need for sponsors to organize CT activity in such a way that a summary of results could be available within 1 year of the end of CT date (usually the date of last visit of the last patient). It would be important that editors of Medical Journals do not reject the publication of CT results due to the public availability of the aforementioned legally required summary in official CT registers.

As this sample includes a big portion of non-commercial trials, this concern may not only be specific to ATiMP research but can also reflect the general difficulties related to

academic research of medicinal products. It is remarkable that the vast majority of CT for which the status is unknown are old and non-commercial CT, showing that there has been an increasing interest in complying with regulations thanks to efforts from several networks such as STARS Project (Strengthening Training of Academia in Regulatory Science) [30] – an initiative funded by the EU with the aim of analyzing and improving training of non-commercial sponsors on regulatory science in order to have better and faster access to innovative therapies. In the case of Spain, AEMPS has created the Office for the Support of Innovation and Knowledge with Medicinal Products [31], responsible for giving technical and administrative advice to every innovative project that is going to take place in Spain or EU. Within this Office we can find a specific Office for non-commercial research, where special support from the beginning of projects is usually needed.

Regulation 536/2014 [2] is still not fully applicable in Europe. In the meantime, all stakeholders should get prepared to work according to the new CT Regulation rules. This implies (among other things) having a single national contact in the EU to organize access for the sponsor’s users to the future EU CT database and portal on the basis of the *who does what* principle (viewer, preparer or submitter roles) and taking into account the future transparency rules [5] and the principle of having single consolidated documents for all MS [32] when preparing the CT dossier.

Transparency should be seen as an opportunity to identify serious health problems not yet investigated, to identify known risks to be avoided/minimized in future CT, to

facilitate recruitment and to cooperate with other sponsors (as well as many other positive things). However, to see this benefit, all stakeholders should commit to comply with this principle that is very much emphasized in the new EU legislation.

In the EU, the EudraCT number is a unique identifier necessary for all CT on medicinal products. It would be very helpful if medical Journals always required the inclusion of the EudraCT number, together with any other relevant identifier, in any publications related to this type of CT with participation of EU sites. Currently, this number is only present in about 56% of the CT records identified in ClinicalTrials.gov [16], but it would be very helpful if sponsors could reference this number every time the CT is identified for a CT Register.

VHP [7] has been the basis for the coordinated evaluation procedure established in EU Regulation 536/2014 [2]. For this reason, it is the perfect place for active adaptation to the changes that will be implemented by the new European Clinical Trials Regulation. By using VHP, sponsors will not only get experience on the European coordinated assessment but could also influence possible improvements on the application of the future legislation itself with real cases that are presented to us on a day-to-day basis. However, the VHP was only used by a minority of the international CT with ATiMP conducted in Spain. This may reflect a perception of a higher complexity for this procedure, especially by academic researches. In the case of GTMP, application of the GMO regulation may have also interfered with a harmonized assessment process

between different MS, as described above. These issues will be taken into account for the implementation of the new Regulation.

Problems highlighted here especially for non-commercial trials may not be specific to ATiMP research, but can also reflect the general difficulties related to academic research on medicinal products due to the large number of this type of sponsor represented in this sample.

In Europe, there are several initiatives ongoing trying to facilitate CT under the scope of the new regulation. Discussions on possible improvement of VHP, simplification in the Environmental assessment of GMOs, the 'Strengthening training of academia in regulatory sciences and supporting regulatory scientific advice' (STARS) project, and an update of the guidance related to the CT Regulation in volume 10 Eudralex [33] are among them.

CONCLUSION

Clinical research on ATMP has seen a clear increase, especially on GTMP, during the last few years. This increase has been in parallel with an improvement in the quality of CT, highlighted with the rising number of multi-site and international CT (also a consequence of the increasingly commercial sponsoring of CT).

Our analysis also shows some difficulties in complying with regulatory requirements, especially for non-commercial sponsors. In this regard, it is notable that there are several initiatives at a European and Spanish level, such as the STARS Project [30] and European Commission initiatives to unify GMO requirements [10] in the EU, or the Office for the

Support of Innovation and Knowledge with Medicinal Products [31] in Spain, that are trying to facilitate clinical research.

Last but not least, it should be noted that Regulation 536/2014 [2] is intended to be an instrument for cooperation between EU MS and

sponsors in order to ease the regulatory framework burden and promote clinical research in the EU. Since this regulation is not yet fully applicable, all stakeholders still have time to adapt their workflows and national legislations to the new way that lies ahead.

AUTHORSHIP & CONFLICT OF INTEREST

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