DECEMBER 2020

CLINICAL TRIALS IN SPAIN

Transparency and COVID-19 research agenda

TranspariMED

SALUD por DERECHO
Right to health foundation

UAEM
UNIVERSITIES ALLIED FOR ESSENTIAL MEDICINES

CREDITS

CLINICAL TRIALS IN SPAIN: TRANSPARENCY AND COVID-19 RESEARCH AGENDA
DECEMBER 2020

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Endorsed by:

EXECUTIVE SUMMARY

Salud por Derecho, Universities Allied for Essential Medicines (UAEM- Europe) and TranspariMED have been closely advocating for transparency in biomedical research, R&D public funding investments, and pharmaceutical policies; and following up intellectual property, drug pricing, and many other issues around access to medicines. Clinical trials are in the core of biomedical research and posting the results becomes crucial for the best of science, patients, regulators, and the society.

With the objective of further exploring how Spanish sponsors are performing in reporting results and present a read out of COVID-19 research, we have joined forces to analyse the current status of due trials run by Spanish sponsors looking at the EU Trials Tracker, and all COVID-19 trials registered at the Spanish Registry of Clinical Studies (including both Spanish and international trials).

First, the present study focuses on the COVID-19 trials landscape in the Spanish Clinical Trials Registry (REec). From March 1st until October 1st 2020, there were 123 new clinical trials registered in the REec. From those, 64 clinical trials (52%) were publicly funded, whereas 54 trials (44%) have been sponsored by private funders. The analysis also shows the duplicity and the lack of coordination and overlapping in the COVID-19 research in Spain. In addition, further analysis from the European Clinical Trials Registry shows that current Spanish sponsors conducting COVID-19 research have a very weak reporting track record and highlights the imperative need to upload summary results to registries otherwise, important research risks to be wasted.

The second part of this report reflects EU Trials Tracker data on 32 Spanish trial sponsors with at least 15 drug trials registered as of 01 October 2020. Overall, the 32 largest trial sponsors in Spain are responsible for 1,036 clinical trials of investigative medicinal products that are listed on the EU Clinical Trials Register (EudraCT). Of these, only 142 trials are listed as having been completed more than a year ago and should thus have results available. Results are only available on the registry for 80 of those verifiably due trials (56%). Only three Spanish sponsors have made all their verifiably due results public on the registry as required by European transparency rules**.** Another five sponsors have made at some of their verifiably due trial results public. The remaining sponsors have not made any results for verifiably due trials public. Furthermore, the analysis suggests that an estimated total of 395 clinical trials would be missing results. Widespread data quality problems in many sponsors' registry records make it impossible to determine precise figures. It also remarks the steps in the right direction that institutions such as the Hospital Universitari Vall d'Hebrón is taking to improve their results reporting system.

According to data reviewed and the analysis made, reporting rates in Spain are far lower than in other European countries, including Austria, Denmark, Germany, Ireland, and the UK. Having said that, Spanish trial sponsors should establish central oversight over their clinical trial registry entries, adopt policies that reflect WHO best practices, audit existing registry records, and upload missing clinical trial results as rapidly as possible. The national medicines regulator AEMPS (Agencia Española de Medicamentos y Productos Sanitarios) should contact trial sponsors whose results are overdue, and ensure that data on the register is consistent and accurate. It should as well monitor compliance and strengthen mechanisms to assist sponsors as much as possible on the results reporting process. In addition, once the EU Clinical Trial Regulation fully comes into force in late 2021, sanctions are foreseen, and national legal frameworks should be adopted. Spain can always look to other countries which have undertaken similar process such as the UK with its national clinical trial transparency strategy. Likewise, funding institutions like the Instituto de Salud Carlos III should sign up to the WHO Joint Statement and monitor whether its grantees make trial results public in order to prevent non-compliance and research waste.

1. INTRODUCTION

In June 2020, Salud por Derecho published a policy paper with recommendations for regulators and decision makers to better address transparency and research agenda in clinical studies in Spain. The results were based on data analysed from the Spanish Registry of Clinical Studies (REec)[1] since 2014 until October 2019. TranspariMED has also conducted numerous studies to follow up across Europe how country sponsors are due with their transparency obligations and UAEM has tracked R&D public funding on biomedical research.

According to the European Union (EU) rules adopted in July 2014, it is required that sponsors[2] of each clinical trial registered on the EU Clinical Trials Register[3] post those trials' summary results to the registry within 12 months of trial completion (6 months for paediatric trials). These rules also apply to trials completed before 2014 and apply irrespective of whether a trial's outcomes have been published in the academic literature.

Failure to fully report trial results has substantial negative consequences: patients are harmed; public health agencies cannot make informed decisions; public health funds are wasted, and medical progress is slowed down. For these reasons, the Declaration of Helsinki has made reporting the results of every clinical trial a universal ethical obligation for all medical researchers worldwide. In the midst of the COVID-19 pandemic, clinical trials transparency is an extremely relevant issue to look at in order to better coordinate an effective response and advance towards quality clinical research on new therapeutics, vaccines and other COVID technologies.

Salud por Derecho, UAEM Europe and TranspariMED firmly advocate for stronger national policies with specific mechanisms to guarantee accurate and updated information of clinical studies, the need to improve the reporting of results and to establish monitoring and follow-up mechanisms. Our recommendations also aim at encouraging national authorities and policy makers to strengthen transparency throughout and to promote greater coordination. The purpose of this report is to identify how Spanish sponsors are performing reporting summary results as a key step for effective transparency and how COVID-19 research is behaving in Spain according to the Spanish Registry (REec).

[1] The Spanish register of clinical studies (REec) is a public database, for use outdoors and free to all users whose objective is to serve as a source of primary information for clinical studies with drugs in Spain. Its legal basis is article 62.1 of the revised text of the law of guarantees and rational use of medicines and sanitary products, approved by Royal Legislative Decree 1/2015, of 24 July. This precept has developed in articles 47 and 48 of the Royal Decree 1090 / 2015, 4 December, which regulates clinical trials with medicines, the research ethics committees with medications and the Spanish registry of clinical trials.

[2] A sponsor is defined as the institution, the company or the person conducting the trial and, therefore, responsible for it. Note that this term differs from "funder" (who economically supports or funds the trial). Sometimes the sponsor and the funder can be the same.

[3] EudraCT (European Union Drug Regulating Authorities Clinical Trials Database) is the European database for all interventional clinical trials on medicinal products authorized in the European Union (EEA) and outside the EU/EEA if they are part of a Paediatric Investigation Plan (PIP) from 1 May 2004 onwards. It has been established in accordance with Directive 2001/20/EC. Protocol and results information on interventional clinical trials are made publicly available through the European Union Clinical Trials Register (EUCTR) since September 2011.

2. COVID-RELATED CLINICAL TRIALS IN SPAIN

COVID-19 has been a unique booster for biomedical R&D. Some countries have specifically unblocked extraordinary grants and fostered partnerships with private companies (pharmaceutical and biotech companies, among others) to develop and test new therapeutics against SARS-COV2 or to treat its complications. Spain has not been an exception.

On March 17th 2020 the Spanish Government announced around 30 million euros in grants to fund relevant research to fight the pandemic. The most of this exceptional funding, more than 25 million euros, has been managed by the Instituto de Salud Carlos III, the most important public institution when it comes to managing public funds for biomedical research and setting the national R&D agenda.

Likewise, COVID19-related clinical trials have also been fuelled globally and nationally. Until October 1st 2020, there were 123 new clinical trials related to COVID19 registered in the Spanish Registry of Clinical Trials including national and international sponsors. The Spanish registry has been analysed before showing a worrying lack of transparency, missing information and data inaccuracy. It has also been criticised before for being disconnected from the WHO Primary Registry Network.

Launch of clinical trials in the middle of a pandemic

The first COVID-related trials in Spain were registered in March 2020, and they aimed at proving the efficacy and safety of the initial combinations of hydroxychloroquine, azithromycin, antiretrovirals, etc. Most of the trials (65%) were registered in the first 3 months of the pandemic.

Based on the REec's records, 64 clinical trials (52%) are publicly funded, whereas 54 trials (44%) have private sponsors. Funder information is lacking for 5 trials at the time of the analysis. The REec does not include the information on the amount of funding secured for the different trials. The origin of the funds to secure the launch and progress of the trials might have an impact in the evolution of the trial itself which depends on when the money arrives. Interestingly, 48.4% of the publicly funded trials are listed as "not started" and 45.3% are "ongoing". Private-funded trials seem to be thriving better: 72.2% of them were listed as "ongoing". The present status of COVID-19 trials registered in the Spanish website is displayed by month of authorization in *figure 1*.

The 123 trials are designed to evaluate 76 different products. 91.1% (113 trials) evaluate a product as a treatment option, either for COVID-19 or to tackle its complications. Some drugs are being tested in more than one trial: hydroxychloroquine (20 trials), corticosteroids (8 trials), tocilizumab (8 trials), colchicine (6 trials) or remdesivir (5 trials), among others. Overall, REec data on COVID trials suggests that there has been considerable fragmentation and duplication in Spanish COVID research efforts. The proliferation of small and apparently uncoordinated clinical trials with overlapping research agendas in Spain is unlikely to contribute much to medical progress, and is likely to result in a high level of research waste.

This REec analysis on COVID-19 trials is part of a broader study "COVID-19 related clinical trials in Spain" available here.

TIMELINE AND STATUS OF COVID-19 TRIALS

Date of authorization and status of COVID-19 trials in the Spanish Registry (REec)

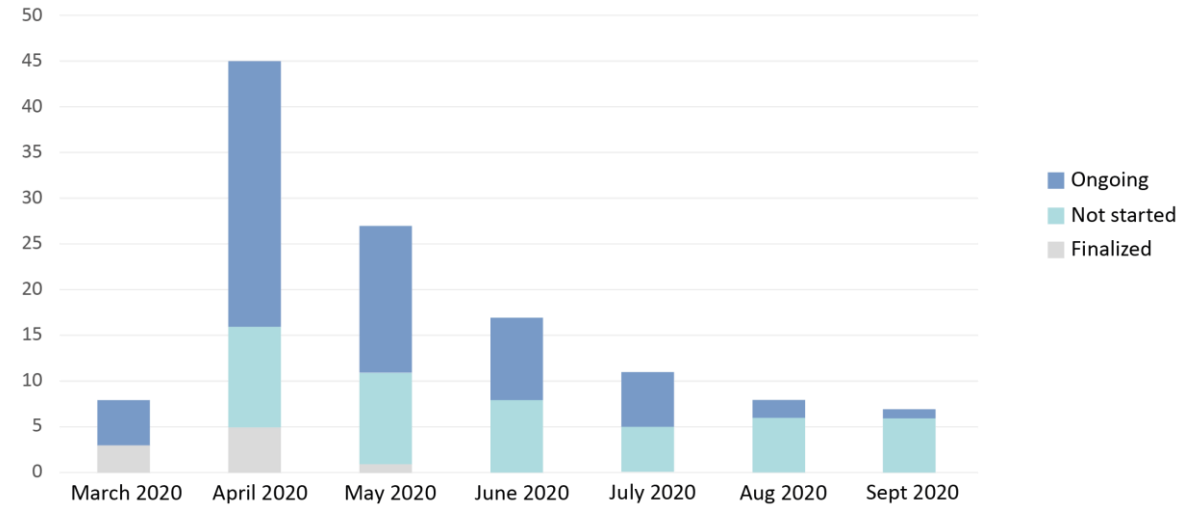

Figure 1. **Date of authorization and status (ongoing, not started or finalized) at the time of the analysis of COVID-19 trials registered in REec (123 trials).**

Monitor sponsors' reporting compliance. A crucial issue for COVID trials

A TranspariMED study published in June 2020 identified 48 Spanish COVID drug trials listed on the European trial registry. From those, 60% (29 trials) were being run by sponsors that according to current data had never completed a trial of an investigative medicinal product. 17 trials were being run by sponsors that had completed drug trials in the past but had not uploaded the results of a single verifiably due trial onto the registry. Only two trials were being run by a sponsor that had a good compliant record on results reporting. Given this weak reporting track record of Spanish sponsors, the study recalls on the imperative need of regulators to actively monitor compliance and encourage COVID-19 trial sponsors to voluntarily upload summary results onto the registry as soon as possible after trial completion.

This is especially relevant in COVID-19 clinical research. In general, many COVID trials will be terminated early, typically after treating only a small number of patients. However, we can't afford these trials becoming research waste, on the contrary, it is extremely important for the scientific community to be able to access and combine the results of every single trial, even those with negative or incomplete results. In many cases, scientists will only be able to gain an accurate and reliable picture of a COVID drug's benefits and harms by combining the results of many small trials, including trials that were terminated early.

Both the European and the Spanish trial registry provide a perfect platform for rapidly making public and available all COVID trial results, including the results of trials that were terminated early. The AEMPS, as the national drug regulator, is responsible for ensuring that data on Spanish trials in the European registry and the Spanish registry is accurate and up to date. For this reason, it is urgent that the AEMPS strengthens its policy to ensure consistency in reporting and training to sponsors, if needed, to guarantee compliance according to rules and ethical commitments. In addition, the Instituto de Salud Carlos III, as one of the main funding institutions in Spain, should ensure as well that their financed trials are registered following national and international rules.

3. REPORTING PERFORMANCE OF SPANISH TRIAL SPONSORS

There are good reasons why global best practices require posting the results of all trials to registries. Posting results to registries accelerates medical progress because the 12-month timeline permits far more rapid results sharing than the slow academic publication process allows. Secondly, posting results to registries minimises the risk of a trial never having its results reported and becoming research waste, which can happen when a principal investigator leaves their post during the prolonged process of submitting an academic paper to a succession of medical journals. In addition, research shows that trial results posted on registries typically give a more comprehensive and accurate picture of patient-relevant trial outcomes than corresponding journal articles do. Finally, results posted on registries are easier to locate and are open access. Also, registry reporting facilitates the comparison of trial outcomes with a trial's originally stated aims.

Uploading results to trial registries typically precedes publication in academic journals. There is no recorded case, ever, in which a manuscript was rejected by a journal because the trial results had already been uploaded to a trial registry. The International Committee of Medical Journal Editors has explicitly stated that the posting of summary results to trial registries is not considered prior publication by academic journals. Thus, because results reporting on registries is typically faster than academic publication, making trial results public on registries before they are published in an academic journal is becoming the new norm in scientific communications.

The results presented in this report reflect EU Trials Tracker data on 32 Spanish trial sponsors with at least 15 drug trials registered as of 01 October 2020. Overall, the 32 largest trial sponsors in Spain are responsible for 1,036 clinical trials of investigative medicinal products that are listed on the EU Clinical Trial Register. Of these, only 142 trials are listed as having been completed more than a year ago and should thus have results available. Results are only available on the registry for 80 of those verifiably due trials (56%). Results are missing for the other 62 verifiably due trials (44%). Although the true number of missing results could be far higher since many of these trials are not up to date. Only three sponsors, pharma company Almirall and the non-profits Grupo de Tratamiento de los Tumores Digestivos and Grupo Español de Cáncer de Pulmón have a perfect compliance record. All other sponsors with due trials in their portfolios do not fully comply with transparency rules[4]. On average, pharma companies perform far better than universities, hospitals, and other non-commercial sponsors (*figure 2*).

[4] *Figure 2* includes four of the major sponsors that (implausibly) have no trials in their portfolios that are marked as due: Corporació Sanitària Parc Taulí, Fundación Pública Andaluza FIMABIS, Hospital Sant Joan de Déu, and Hospital Universitario La Paz.

CLINICAL TRIAL RESULTS REPORTED BY SPANISH SPONSORS

Number of total trials and due trials by reporting status on EudraCT

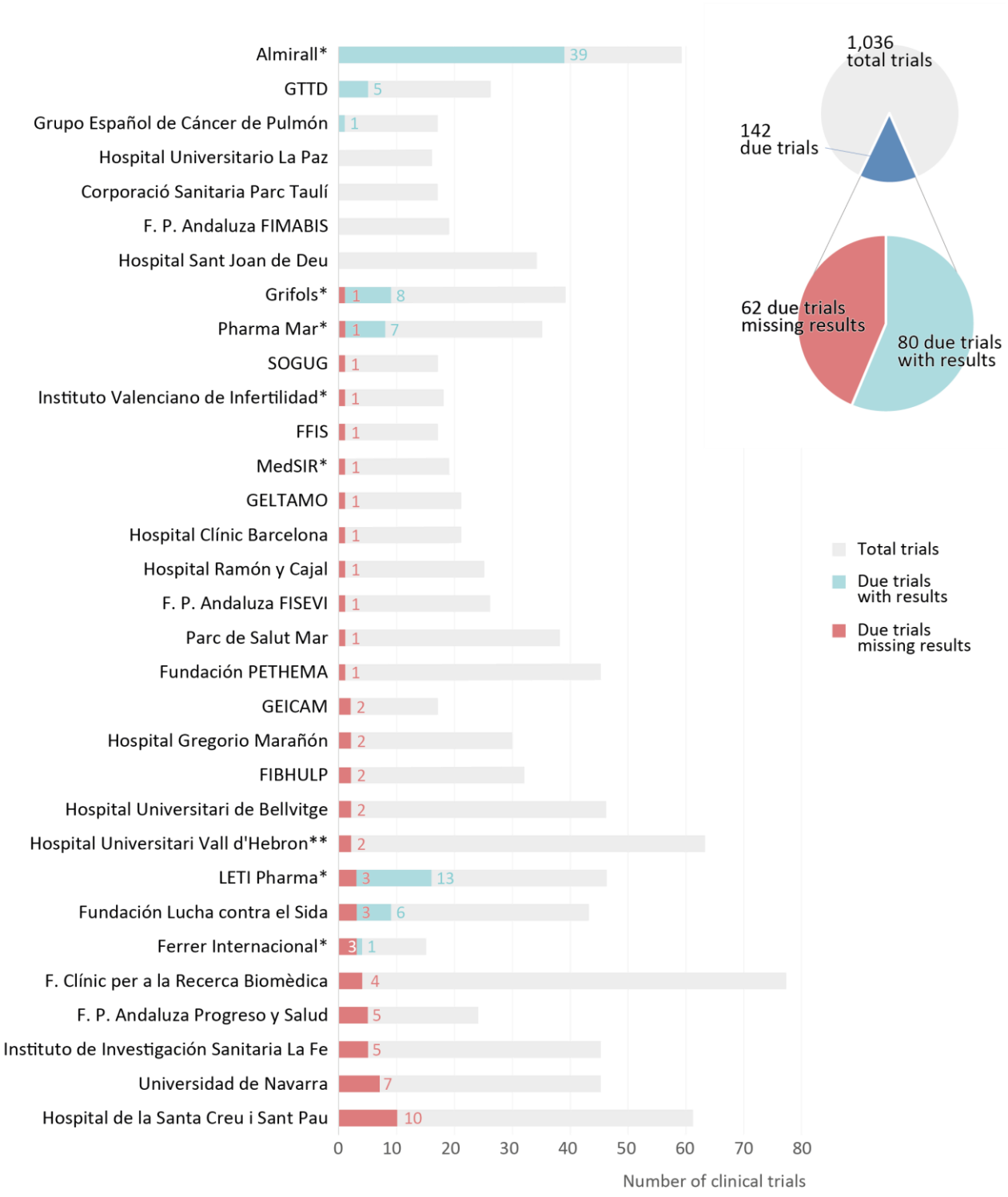

Figure 2. **Number of total trials and due trials with results or missing results by sponsor in the European Clinical Trials Registry based on EU Trials Tracker data (1,036 trials).**

Note: * Private companies; ** VHIR is currently working to improve its disclosure. F.P.: Fundación Pública; GTTD: Grupo de Trabajo de los Tumores Digestivos; SOGUG: Grupo Español de Oncología Genitourinaria; FFIS: Fundación para la Formación e Investigación Sanitarias de la Región de Murcia; GELTAMO: Grupo Español de Linfomas y Trasplantes de Médula Ósea; GEICAM: Grupo Español de Investigación en Cáncer de Mama; FIBHULP: Fundación para la Investigación Biomédica del Hospital Universitario La Paz.

Missing results and data quality problems

Data inconsistency and inaccuracy have been found to be main issues for many trials run by selected Spanish sponsors. One the most common inconsistencies is that many completed trials are falsely marked as 'ongoing' on the registry. Since there is no information to update the status of the trial, this situation could lead to a higher number of thus verifiably due trials missing results (see the methodology section for more details).

Based on our estimates, 395 clinical trials run by Spain's 32 largest trial sponsors would be missing results. Fundació Clínic per a la Recerca Biomèdica accounts for the largest number (38) of estimated missing results, followed by Vall d'Hebron University Hospital (31) and Hospital de la Santa Creu i Sant Pau (30).

An ongoing positive example in Spain

Hospital Universitari de Vall d'Hebron (VHIR) has already started addressing the problem and is working on improving its disclosure policy. VHIR's efforts will probably take a few months to translate into improved performance on the EU registry but we welcome VHIR's strong commitment to transparency, and hope that other clinical trial sponsors in Spain will soon follow this positive example.

Quality problems with Spanish sponsors' entries on the European Clinical Trial Register include incomplete, incorrect, inconsistent, and out-of-date data. Inconsistent data means the registry is either not fully completed or key information is missing. For example, Fundació Clínic per a la Recerca Biomèdica's portfolio has 77 drug trials and 28 are marked as 'completed' but lack a completion date. Another trial has a completion date but remains marked as 'ongoing'. For all these trials, it is impossible to definitively determine whether results are due or not. Other inconsistencies are related to ongoing trials which should have finalized decades ago. Looking at this same sponsor, its records show 7 trials that started before 2010 are still listed as 'ongoing' over a decade later, an implausibly high number.
These findings about data inconsistency in the European Registry are coherent with data revealed from the Spanish Registry of Clinical Studies in a recent report. Lack of some relevant information, such as data on completion date, and inconsistencies between both registries were frequently found.

In addition, information about many trials is provided in Spanish. While this is technically permissible, it becomes very difficult for medical researchers – including Spanish researchers – to locate trials on the registry, as search strategies usually use English keywords only.

Unfortunately, this generalised inconsistency and inaccuracy have great impact on patients and medical progress at multiple levels. As the national regulator, AEMPS is ultimately responsible for safeguarding the quality of Spanish trial data on the European register. AEMPS should engage in a dialogue with Spanish trial sponsors and work together with them to improve data quality and ensure that data on the register are consistent and accurate. Lastly, Spanish pharmaceutical companies, universities and hospitals should review their clinical trial portfolios across the EU registry, the US registry ClinicalTrials.gov, and other WHO primary trial registries, identify those trials that have remained completely unreported, and ensure that their results are made public as soon as possible.

4. RECOMMENDATIONS

All the clinical trials identified in this report as missing summary results do not comply with EU transparency rules that were designed to protect the interests of patients and taxpayers. In addition, once the EU Clinical Trial Regulation comes into force in 2021, national regulators will have the power to fine institutions for not uploading trial results to the European trial registry. For these reasons, the purpose of this report is to present certain recommendations which will certainly contribute to improve compliance and transparency of clinical trials and to enhance clinical research to ensure access to medicines and to all health technology products which are funded with public funding.

- Transparency and accountability are essential conditions for the access of researchers, clinicians, patients, and 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. Having said that, clinical trial sponsors and national regulator (AEMPS) should establish the necessary mechanisms to ensure timely reporting of summary results. In addition, the AEMPS should dedicate resources and efforts to help sponsors to better accomplish their weaknesses on reporting and with the purpose to overcome registry problems such as: inconsistency of the registry, incomplete and missing data and lack of up to date data. In addition, the AEMPS should develop a mechanism that will enable it to impose fines on sponsors as soon as the new regulation fully comes into force

- Sponsors should upload all currently missing clinical trials results onto the European trial registry and REec. It is also important, in the coming future, to upload the results of all interventional clinical trials onto a WHO Primary Registry within 12 months of trial completion, as recommended by the WHO

- Research and funding institutions such as Instituto de Salud Carlos III, should sign the WHO Joint Statement on clinical trials committing through international consensus to promote transparency, accountability and compliance of its funding results.

- Quality 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.

- 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.

- 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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ANNEX 1: DATA TABLE

The table below presents the data underlying the section of this report that discusses Spanish drug trials registered on the European trial registry. Institutions that wish to improve their reporting performance can find useful tools and guidance on the TranspariMED website.

The true number of due trials missing results is an estimate; please see the methodology section for details. All other data are based on EUCTR data aggregated by the EU Trials Tracker. To see a detailed breakdown of the portfolio of any individual trial sponsor, please visit the EU Trials Tracker website and enter the sponsor's name into the search field.

SPONSOR NAME	TYPE	TOTAL TRIALS	VERIFIABLY DUE TRIALS	VERIFIABLY DUE		ESTIMATED RESULTS MISSING
				With results	Missing results	
Almirall	C	59	39	39	0	0
Corporació Sanitaria Parc Taulí	NC	17	0	0	0	8
F. Formación e Investigación Sanitaria (FFIS)	NC	17	1	0	1	8
F. P. Andaluza FIMABIS	NC	19	0	0	0	9
F. P. Andaluza FISEVI	NC	26	1	0	1	13
F.P. Andaluza Progreso y Salud	NC	24	5	0	5	12
Ferrer Internacional	C	15	4	1	3	6
FIBHULP	NC	32	2	0	2	16
Fundació Clínic per a la Recerca Biomèdica	NC	77	4	0	4	38
Fundación Lucha contra el Sida	NC	43	9	6	3	3
G.E.I. Cáncer de Mama (GEICAM)	NC	17	2	0	2	8
GELTAMO	NC	21	1	0	1	10
Grifols	C	39	9	8	1	11
Grupo de Tr. de los Tumores Digestivos	NC	26	5	5	0	0
Grupo Español de Cáncer de Pulmón	NC	17	1	1	0	0
Hospital Clinic Barcelona	NC	21	1	0	1	10
Hospital de la Santa Creu i Sant Pau	NC	61	10	0	10	30
Hospital Gregorio Maranon	NC	30	2	0	2	15
Hospital Ramon y Cajal	NC	25	1	0	1	12
Hospital Sant Joan de Deu	NC	34	0	0	0	17
Hospital Universitari de Bellvitge	NC	46	2	0	2	23
Hospital Universitario La Paz	NC	16	0	0	0	8
Instituto de Investigacion Sanitaria La Fe	NC	28	5	0	5	14
Instituto Valenciano de Infertilidad	C	18	1	0	1	9
LETI Pharma	C	46	16	13	3	3
MedSIR	C	19	1	0	1	9
Parc de Salut Mar	NC	38	1	0	1	19
PETHEMA Foundation	NC	45	1	0	1	22
Pharma Mar	C	35	8	7	1	1
S.O. Genito-Urinary Group (SOGUG)	NC	17	1	0	1	8
University of Navarra	NC	45	7	0	7	22
Vall d'Hebron University Hospital	NC	63	2	0	2	31
	TOTAL	**928**	**133**	**80**	**53**	**342**

Note: C: commercial; NC: non-commercial.

ANNEX 2: METHODOLOGY AND LIMITATIONS

Authorship

Report authors: Dr Till Bruckner (TranspariMED), Irene Romero (UAEM- Europe), Irene Bernal and Eva Iráizoz (Salud por Derecho)

REec data analysis: Irene Romero (UAEM- Europe)

EUCTR cohort selection: Nicholas DeVito (EBM Data Lab, University of Oxford)

EUCTR data analysis: Till Bruckner (TranspariMED)

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- The full methodology for extracting and analysing data on Spanish COVID-related trials listed on **REec** can be found here.
- The methodology for extracting and analysing data on Spanish COVID-related trials listed on the European trial registry **EUCTR** can be found here.

EUCTR data extraction, selection and analysis

Data extraction

The EU Clinical Trial Register (EUCTR) was scraped and processed using EU TrialsTracker code and the standard methodology to determine the reporting status of each trial. As part of the process, free-text sponsor names are normalised for display on the website. Alongside the standard EUCTR scraper, a second scraper was run to obtain detailed sponsor info from section B of each EUCTR country level protocol (specifically the sponsor name, country, and sponsor status). This detailed sponsor information was then combined with the processed EU TrialsTracker data, and normalisation data, to extract all trials with an Spanish sponsor.

The data in this report reflects data publicly available on EUCTR as of 01 October 2020.

The codes used are available on Github:

- EU Trials Tracker code and data
- EUCTR Sponsor section scraper
- The code for generating the dataset

Cohort selection

The main cohort for this study consists of the 32 clinical trial sponsors located in Spain that had sponsored 15 or more clinical trials on EUCTR as of 01 October 2020.

Measuring verifiable sponsor performance

Data on the clinical trial performance of each sponsor was manually extracted from the EU Trials Tracker on 20 October 2020.

The tracker data reflected trials results that were publicly available on EUCTR as of 01 October 2020. Due to delays by the European Medicines Agency in making public trial results submitted by sponsors, the tracker data might not include all trial results that were uploaded by sponsors during September 2020. Thus, the data in this report reflect sponsors' trial reporting performance as of early September 2020.

The EU Trials Tracker was built by the EBM Data Lab, University of Oxford, and its methodology published in a peer reviewed paper. The tracker is based exclusively on data that are publicly available on the EU Clinical Trial Register; the tracker is updated on a monthly basis. To the best of the author's knowledge, to date no instances of a trial incorrectly flagged as being due and missing results by the EU Trials Tracker based on registry records have been detected. The EU Trials Tracker individually lists every trial flagged as overdue, and includes a link back to the original registry entry for every trial. Thus, all data in this report is externally replicable.

Estimating the true number of trials missing results

Because the national regulator and trial sponsors in Spain have collectively failed to ensure that data on the European trial register is accurate and up to date, many completed trials are falsely marked as 'ongoing' or lack a completion date. This makes it impossible to precisely determine the real number of trials missing results.

Estimates on the number of trials missing results were calculated based on the assumption that 50% of each institution's trials were completed more than a year ago and are therefore currently due to upload their results. TranspariMED divided the total number of trials per institution in half to arrive at an estimate of due trials, and then subtracted the number of trials listed as both 'due' and 'reported' by the EU Trials Tracker. The resulting numbers were rounded down to the next integer if applicable.

The 50% assumption is based on the fact that the European register captures trials that began as early as 2004, and trials usually only run for a few years. Therefore, the register contains many trials that have been completed. In the trial portfolios of major sponsors in other European countries for which more reliable data are available, around half of all trials are marked as being due to report results.[5]

Exception: TranspariMED performed a manual review of the trial portfolios of the 7 Spanish sponsors with an EU Trials Tracker reporting rate of more than 50% (Almirall, Fundación Lucha contra el Sida, Grifols, Grupo de Tratamiento de los Tumores Digestivos, Grupo Español de Cáncer de Pulmón, LETI Pharma, and Pharma Mar). All of those sponsors appear to be actively managing their portfolios, and in many cases have made public the results of trials that are falsely listed as 'ongoing' or that have inconsistent completion data on EUCRT. Therefore, for those 7 sponsors, the true number of trials missing results is (conservatively) assumed to be the same as the number of verifiably due trials missing results identified by the EU Trials Tracker.

Limitations

- Reliance on estimates of trials missing results

Many Spanish trials are almost certainly falsely marked as 'ongoing' in the registry even though they were in fact completed long ago (see above). However, the exact number of such trials is impossible to determine based on registry data. Accurate figures will become publicly available only if and when sponsors and the national regulator work together to bring all registry data up to date.

- Undercounting of results posted

Due to delays by the European Medicines Agency in making public trial results submitted by sponsors, trial results that were uploaded during late September 2020 may not have been captured by the EU Trials Tracker. In consequence, some trials whose results were only recently made public on EUCTR may have been counted as unreported. In TranspariMED's experience, the number of such trials is

[5] For example, data on Imperial College London's trial portfolio can be considered reasonably reliable because the university has reported over 97% of its verifiably due trials, has nearly no trials with inconsistent completion data, and has few very old trials that are still marked as 'ongoing'. Out of Imperial's 139 trials total, 76 trials (55%) are marked as being due to report results.

likely to be very low in a cohort this size. In addition, the Tracker lists trials with results that are not marked as completed and/or have no completion date in the protocol as being still "ongoing" or having "inconsistent data"; such trials are not counted as 'reported' by the Tracker or in this report. The number of such trials is low in the context of the overall trial cohort.

- Trials not listed on the EU Clinical Trial Register

The data in this report exclusively cover clinical trials that were registered on the EU Clinical Trial Register. Under EU rules, all clinical trials of investigative medicinal products (CTIMPs) conducted in the European Union must be registered on the EU Clinical Trial Register, and must post their results there within 12 months of trial completion.

Non-drug trials, including trials of medical devices (e.g. pacemakers) and non-drug treatments (e.g. surgery or physiotherapy), cannot be registered on the EU Clinical Trial Register and are thus registered on other trial registries. Such trials can be of even greater medical importance than drug trials, and sponsors are required to make their results public under global ethics rules. However, assessing sponsors' reporting performance for these non-drug trials is beyond the scope of this report.

Spanish Registry of Clinical Studies (REec)

Search strategy

We searched used the in-built search engine of the REec (Registro Español de Ensayos Clínicos) to identify relevant clinical trials.

The search terms were COVID (125 results), COVID-19 (120 results), COVID19 (25 results), SARS-COV2 (12 results), SARS COV2 (15 results), coronavirus (49 results).

Inclusion criteria

COVID-19 clinical trials registered on REec from 1st March 2020 to 30th September 2020.

Exclusion criteria

Clinical trials not focused on COVID19 or SARS-COV2 associated conditions; trials that were registered before the pandemic. Two of the trials were duplicates and were eliminated from the analysis. One of the trials was eliminated because its registration date was in December 2019, prior to the pandemic announcement and the start of clinical studies.

Data extraction and analysis

The included trials were added to an Excel database with the following variables: funding institution, recipient institution, sum of funding, type of grant, title of the trial, type of trial (phase I, II, III, IV), research focus, tested product or technology, research stage (ongoing, not started or finalized), authorization date (as per the REec) and the registry identification number. Details of the contact person of the trial were also registered (email address).

Data validation was performed twice. The statistical analysis was done using the same Excel database. Irene Romero (UAEM- Europe) designed the study, collected the data, performed the analysis, and wrote the report. Till Bruckner (TranspariMED) provided input on the study design and contributed editorial suggestions to the report.

Limitations of this study

- The quality of the data collected and analysed in this study depends on the quality and accuracy of the information entered into the REec.

A previous study by Salud por Derecho has shown that REec data is often incomplete, inaccurate, and/or outdated. Email exchanges with several researchers confirmed that this limitation also applies to REec data on COVID-19 studies.
In addition, structured data in REec only capture three different trial statuses: "not started", "ongoing", and "completed". Free text notes are added to a trial's 'timeline' in REec sometimes, but not always, and provide further information on the circumstances in which a trial was "completed". Thus, it is often unclear whether trials that are marked as "completed" in REec were fully completed, prematurely ended, or terminated early.