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SPECIAL ARTICLE

Participant-funded clinical trials on rare diseases☆

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Abstract The development of medicines for certain rare diseases can be cut short by lack of funding. In certain cases the patients themselves, or their relatives, occasionally fund the clinical trial in which they will be treated with the investigational medicine. There are three models of self-funded clinical research: two of them, 'pay to try' and 'pay to participate', have already been put into practice. The third, the 'plutocratic' proposal, which has been recently put forward is still a theoretical model. In this work the scientific, social and ethical benefits and risks of the two clinical research models, 'pay to participate and the 'plutocratic' proposal, are reviewed. Patient-funded clinical trials are frequently performed through crowdfunding. The most controversial aspects of this funding modality are also addressed in this article from several perspectives. Finally, a future scenario that would allow the launching of self-funded clinical trials in Spain by the 'plutocratic' proposal is proposed.

PALABRAS CLAVE
Microfinanciación;
Micromecenazgo;

Ensayos clínicos en enfermedades raras financiados por los participantes

Resumen El desarrollo de medicamentos para ciertas enfermedades raras puede verse truncado por la falta de financiación. En estos casos, en ocasiones, los propios pacientes —o sus

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familiares— financian el ensayo clínico en el que recibirán el medicamento experimental. Hay tres modelos de autofinanciación de ensayos clínicos: dos de ellos, 'pagar por probar' y 'pagar por participar', ya se han puesto en práctica; el tercero, el modelo 'plutocrático', que ha sido recientemente planteado es, hasta la fecha, un modelo teórico. En este trabajo se repasan los beneficios y riesgos científicos, sociales y éticos de los dos modelos de investigación clínica: 'pagar por participar' y el modelo 'plutocrático'. Una manera frecuente de poder autofinanciar estos ensayos clínicos es la obtención de fondos por micromecenazgo. Los aspectos más controvertidos de esta modalidad de financiación también son abordados en este trabajo desde diversas perspectivas. Por último, se plantea un escenario futuro que permitiera en nuestro país la puesta en marcha de estos ensayos clínicos autofinanciados mediante el modelo plutocrático.

A few months ago, the press worldwide[1,2] took notice of a clinical trial conducted in the United States in Mila, a 6-year-old girl with a genetic variant of Batten disease, a rare, fatal, inherited neurodegenerative disease.[3] What was exceptional about the case was not that a trial was conducted in a single patient, a study design known and used for decades,[4] but that the treatment (an antisense oligonucleotide delivered intrathecally 3) was developed and administered in a record time—a little over 1 year following diagnosis—and made possible by the funds raised by the parents by means of crowdfunding. But, is funding by participants an appropriate means to make possible clinical trials that do not receive financial support from any other sources? Would such trials be legal in Spain? Are they ethically acceptable? And, is crowdfunding a valid alternative that does not interfere with the system currently established for the development of new medicines?

The aforementioned trial adhered to United States regulation on expanded access to investigational drugs, and following the informed consent of the parents, the study protocol was approved by the competent regulatory agency (the Food and Drugs Administration [FDA]).[3] In Spain and in the European Union, current regulations require that researchers file an application to carry out a clinical trial, which would probably have considerably lengthened the process to the detriment of the clinical condition and prognosis of Mila. In principle, compassionate use of medicines cannot be applied to research, as in cases like that of Mila the drug would not meet either of the 2 criteria currently contemplated: there being a clinical trial of the drug underway, or an application for marketing authorisation having been filed for the drug.[5]

There is no question that patients funding the trial in which they participate is the exception. Usually it is public agencies, industry, charities and not-for-profit organizations that fund clinical trials. The possibility of patients with rare diseases funding their access to experimental treatments that they would otherwise not be able to have brings up a series of ethical dilemmas that must be addressed, even if it is believed, as it was the case of Mila, that everything was correct in what has been an outstanding advance in current medical research.

From this point, we will discuss funding of clinical trials by participants (self-funding) as opposed to funding of trials by patient associations, in which the actual participants are not the patients that provide the funding. Examples of the latter situation in Spain include the trial of propranolol (EU-CTR 2014-003671-30), funded and sponsored by the Alianza Española de Familias de von Hippel-Lindau (Spanish Alliance of Families with von Hippel-Lindau), which raised funds through Christmas raffles, charity tournaments and grant applications (source, Ms. Susi Martínez, personal communication), which has been completed, or participation of Spain in the Fundación Stop Sanfilippo (a member of the international Alliance SANFILIPPO) to raise the nearly 14 million dollars required to conduct a phase 1/2 trial sponsored by Abeona Therapeutics that is currently underway in several countries.[6]

Participant-funded clinical trials

Self-funding of clinical trials by participants started in the 1980s in the United States (Table 1). Another quite relevant problem is that participant-funded trials are included in registers such as ClinicalTrials.gov (a public register of the National Institutes of Health of the United States), providing potential patients free access to information about studies that may not always be of good quality.[10]

Stem cell therapies are particularly ''appealing'' for performance of self-funded trials, as there are countries (such as the United States) where regulation of this type of trial is less stringent compared to trials of other forms of treatment that are more tightly regulated. This, however, is not the case in Spain (or the European Union), where clinical trials using advanced therapies (such as stem cell therapies) are subject to the same regulation as trials of any other drug with additional safeguards.[11,12]

Although self-funding of clinical trials has existed for a while, the use of crowdfunding for this purpose is a relatively recent phenomenon.[13] As we will discuss at a later point, funding of clinical trials through crowdfunding can take different forms, including fundraising based exclusively on altruistic donations by many different people or a mixed system in which altruistic donations are combined

Table 1 Examples of crowdfunding in patient-funded clinical trials.

In 1985, a private company in Tennessee, United States, carried out clinical trials of monoclonal antibodies in cancer patients that were charged $35 000 to participate[7]
Recently, there was a proposal in Florida, United States, for a trial in which seniors would pay a fee of up to $285 000 to receive young blood transfusions to forestall ageing[8]
In Panama, a clinic enrolled 20 children with autism spectrum disorder in a stem cell trial that were charged $7200 for participation[8]
In Mexico, patients with amyotrophic lateral paid up to $18 000 to participate in a clinical trial that tested a CD133+ cell therapy, although this contribution was waived for some patients[7]; also in Mexico, participants in a trial that tested a stem cell therapy for brain damage secondary to stroke were charged $30 000[9]

with significant contributions from patients interested in participating.

Models for access to experimental drugs through participant self-funding

There are 3 recognised types of patient-funded access to experimental drugs: pay to try, pay to play/participate, and the plutocratic proposal. An important aspect to consider is that these models are feasible in the early phases of drug development (phases 1 and 2a—the latter known as the proof of concept phase), when donors are guaranteed treatment with the experimental drug. It is very unlikely that patients would pay to participate in trials where they may be assigned to placebo. The 3 models are based on the individual freedom, based on the autonomy of the patient, to engage in free trade, assuming that this exchange is voluntary and the patient is well informed: the patient gains access to the experimental drug and the researcher to funding that makes research possible.[14] All of this is particularly relevant to patients with ultra-rare diseases (defined in Europe as those with a prevalence < 1 per 50 000 inhabitants[11]) in which the development of treatments is often hindered by lack of funding.

Pay to try

In this modality, the patient pays for access to the experimental drug under compassionate use conditions. Thus, this does not fit the customary definition of clinical trial, although in the case of Mila, the girl with a variant of Batten disease, the researchers defined it from a methodological perspective as a trial with $n = 1$.[3] In this modality, the treatment is usually given to a single or very few patients, so that participants have to pay considerable sums.[14] Since these are not considered clinical trials in the United States, the treatment protocol does not need to be approved by a research ethics committee, as occurred in Mila's case, in which approval was given by the president of the ethics committee of the particular hospital.[3]

Pay to play

In this modality, each participant in the trial pays a certain amount of money, usually large. Table 2 summarises the positive and negative aspects of this model. There are some that consider that pay-to-play clinical trials are of little scientific quality, with some of the drawbacks including selection bias and the challenge of interpreting the results in the absence of a control group, and also ethically questionable, mainly as regards their value to society and fair selection of participants.[7,15] In fact, there are those that call for banning this model of patient-funded clinical trial.[15] One factor that promotes this attitude is that clinical trials are carried out in the United States that would not be allowed in the European Union. Thus, for example, stem cell trials in private clinics without public funding or the intent to obtain authorization to market the drug from the FDA do not require approval by a research ethics committee[9] (a scenario that would not be allowed in Europe). In the United States, there are corporate research ethics committees (which do not exist in Europe) that have approved trials of variable rigour.[10] That said, if all scientific and ethical standards are met, as would be the case if the study protocol adhered to European regulations on clinical trials, there is no reason to ban pay-to-play patient-funded trials.[14,16,17]

Plutocratic proposal

The plutocratic proposal model[21] can resolve most of the problems of the payment for participation model. However, it has had minimal reach, possibly because only a short time has passed since the model was first proposed in 2017 and because its implementation is very complex.

In the plutocratic proposal, the donor is offered the possibility—although not a guarantee—of participating in a clinical trial, a possibility that can be transferred to a third party (a relative, friend or total stranger); furthermore, eventual participation would take place 2 or 3 years after donation of funds, or possibly even later, for instance, if vectors for gene therapy need to be developed. These two characteristics differentiate the plutocratic proposal from the two previous models, which guaranteed access to the experimental drug within a short time frame to the donor. Correct implementation of this model requires the cooperation of an external ''matching agency'' serving as the intermediary between the patient/donor and the researchers and ensuring that the trial process that follows is ethical, scientifically useful and financially secure.[21] Table 3 presents the main characteristics of this model. In addition to repurposing or repositioning of known drugs, it can be used for development of gene replacement, molecu-

Table 2 Positive and negative ethical and scientific aspects of the pay to play model for performance of patient-funded clinical trials.

Positive aspects
a) Faster translation of basic and preclinical research to clinical research
b) Patient empowerment
c) Maximum commitment of patient to the trial (it is likely that the patient will adhere to all procedures and scheduled visits)
d) Social value of trial: the findings of the research will benefit other patients (if the trial is properly designed, rigorously performed and its results made public)
e) Certainty of informed consent: there is no question about participation being voluntary. The model allows the validity of informed consent in patients that may be desperate (a situation that is not considered an obstacle in, for example, cancer patients enrolled in phase 1 trials)
f) It justifies having the wealthy take on the risks of experimental treatment whose results might eventually benefit more disadvantaged patients (since the possibility of reaping therapeutic benefits is remote—only 10% of drugs investigated in phase 1 trials end up being authorised for distribution[19])
Negative aspects
a) Patients being both donors and participants pose potential conflicts of interest: it may force certain characteristics on the study design, such as not doing a comparative trial, affect the selection criteria or put pressure on researchers not to withdraw participants that are not responding well from the trial or to not report adverse effects of the experimental drug
b) A risk of participant exploitation either because the patient has unwarranted expectations of the experimental drug, with an increased risk of therapeutic misconception,[20] or because the potential benefits that the treatment offers the participant are insufficient (something that is nearly always the case)
c) Desperate patients may feel pressured to pay to participate, which would cast doubt on the voluntary nature of their participation, and they may be willing to accept substantial risks
d) Does not adhere to the justice principle, by which participant selection (and the distribution of benefits and risks) should be based on who may benefit from the trial and based on adequate selection criteria (to ensure the generalizability of the results), as opposed to the ability to pay
e) This model prioritises the research needs of the wealthy and their diseases, and not of society as a whole

Sources: Sipp,[7] Wenner et al,[9] King and Ballantine,[14] Emmanuel et al,[15] Shaw et al,[16] Fernandez Lynch and Joffe17 and MacPherson and Kimmelman.[18]

lar or gene editing therapies that presumably would require administration of a single or few doses.

Table 4 presents the 3 basic ethical principles that must be fulfilled in research in humans[22] and the extent to which the pay to play and plutocratic proposal models adhere to these principles.

Crowdfunding for self-funding of clinical trials by participants

To this point, we have addressed the first 3 questions we formulated at the beginning of the article. We now have to answer the fourth: is crowdfunding a valid alternative that does not interfere with the system currently established for the development of new medicines?

Crowdfunding for medical research projects has mainly focused on cancer and rare diseases, including basic research and genomic, preclinical and clinical trials, using online platforms for fundraising.[23,24] These platforms are usually from the United States, but some now have an international scope, such as GoFundMe (the largest in the world), which operates in 20 countries, including Spain since 2017, in which health care-related campaigns are most common and bring in the most money in every country.[25] Most of these platforms are run by for-profit organizations, which usually charge a 5% commission and a little over 3% in additional transaction fees per donation. As these platforms have no control over who runs the campaigns or their objectives, they raise a variety of concerns. The biggest (and sometimes most striking) problem with medical campaigns is fraud: raising funds for inefficacious treatments that are potentially harmful.[26,27]

Crowdfunding in biomedicine

A recent study identified the 16 platforms in the United States, 5 in Europe (one of them in Spain: Funds4Research) and 1 in Australia exclusively dedicated to health care crowdfunding.[28] In addition, as concerns Spain, when it comes to general scientific crowdfunding, we ought to mention Precipita, the public platform of the Fundación Española para la Ciencia y la Tecnología (Spanish Foundation for Science and Technology, FECYT). For example, the researchers of the Lagenbio group of the Universidad de Zaragoza are using Precipita to raise funds to research the potential effect of 5-fluorouracil for treatment of amyotrophic lateral sclerosis.[29] There are also several initiatives of national scope (such as Stop-FA, for research of Friedreich ataxia[30]) or integrated in international frameworks (such as Apoyo-dravet, which operates within the International Research Network on Dravet Syndrome and Refractory Epilepsy[31]) that make possible a variety of scientific projects. The success of raising funds through donations received through crowdfunding campaigns depends to a great extent on the

Table 3 Main characteristics and advantages of the plutocratic proposal[a] as a model for patient-funded clinical trials in rare diseases.

Characteristics
1. This model can only be applied to early phases of drug development (phases 1 and 2a) and not to comparative efficacy trials, and it is particularly suitable for repurposing of a drug already marketed for other indications.
2. For clinical trials that would start 2 or 3 years after identification of the drug of interest and receipt of donations by potential participants. This time interval is necessary to complete the required research to obtain approval for the trial and produce the drug samples required for its completion. Thus, donors have to make a long-term commitment to the trial and should have a life expectancy of at least 3 years.
3. An external matching agency should be actively involved and serve as an intermediary between patients and the research time. The agency would also:
a) Maintain a database of potentially useful drugs that could be investigated in clinical trials. This would be an open- and free-access database.
b) Be responsible to ensure the proposed research project is of a good standard
c) Be responsible to ensure that the trial meets ethical and legal requirements
d) Ensure full funding of the trial
e) Ensure publication of the results of the trial
4. Once all of the above are met, donors can be invited to participate in the trial. Participation will only be offered if the donor meets the selection criteria of the clinical trial
Advantages
1. Patients do not have direct contact with the researchers until the clinical trial starts. This minimises the possibility of participant exploitation
2. The external agency acts as a guarantor for the donor and the researcher. To the donor, it guarantees that the trial, should it take place, will be ethically and scientifically sound, and to the scientist, adequate funding of the project
3. The matching agency is responsible for establishing the participant selection criteria in agreement with the researchers. Researchers will have no role in the selection of trial participants.
4. Donors must pay in full at the time they commit to participation, that is, several years before the potential beginning of the trial, a time during which other treatment alternatives may become available. Thus, donors cannot be in a desperate clinical situation. Thus, donated funds are held by the matching agency and remain available even if the donor cannot be included in the trial or dies before the trial starts.
5. Donated funds may be used to pay for any activities required for the trial, from obtaining ethical-administrative approval to production of drug samples to participation of patients that cannot afford to pay anything for the trial. It is considered ethically acceptable for donors to amount to up to half of the total participants.

Source: Masters and Nutt.[21]

[a] The Dictionary of Spanish of the Real Academia Española defines plutocracy as a situation whereby the wealthy exert their preponderance in the government of the state (Diccionario de la Lengua Española).

Table 4 Belmont report: ethical principles and cuidelines for the protection of human subjects of research and their application in patient-funded clinical trials[a].

Belmont report		Patient-funded models	
Principle	How it is applied	Pay to play	Plutocratic proposal
Autonomy	Informed consent	Adheres[b]	Adheres
Beneficence	Evaluation of benefits and risks	(to the extent possible[c])	In adherence (to the extent possible[c])
Justice	Selection of participants	Does not adhere[d]	Adheres[e]

Source: The Belmont Report.[22]

[a] An appropriate interpretation of the contents of this table can be made by reading the text and the contents of Tables 2 and 3.

[b] Researchers must be particularly mindful of the information they give the patient to prevent therapeutic misconception.[20].

[c] Depends on the current knowledge on the experimental drug, but it is usually limited.

[d] Only patients that can afford the experimental treatment can participate in the trial and receive the drug under investigation.

[e] Only patients that can afford to pay are charged, but this does not guarantee that (years later) they will receive the experimental treatment in the future, when the trial will be open for enrolment.

researchers having extensive personal or professional contacts and participation in social media: each tweet or retweet increases the success of the campaign by 1 percentage point.[32]

An analysis of 13 crowdfunding campaigns for clinical trials found that 8 raised the target amounts, 5 of the 8 were for pilot studies or phase 1 trials; most successful campaigns had mixed funding, that is, funding from sources in

Table 5 Benefits and risks of crowdfunding in medical research, and in rare diseases in particular.

Benefits
1. Citizens take initiative and participate in the scientific agenda
2. Greater number of donors
3. Attracts attention and funding to medical research in areas with little or no financial support (such as some ultra-rare diseases)
4. Highlights the limitations of the current health care funding system by partially making up for gaps in public and private funding
5. Sponsors can hold researchers accountable and participate in the progress of research
Risks
1. The general population is unlikely to be able to efficiently select the projects that should be prioritised for the benefit of public health. The allocation of health care resources is altered so that medical need takes a backseat to the ability to pay in clinical trials
2. Projects may not be funded based on their scientific worth
3. Long-term goals may be replaced by short-term goals
4. Lack of transparency may preclude appropriate accountability to the public
5. Risk of fraud. There is nearly no scrutiny of the information provided to the public, which may be fraudulent
6. High fees charged by (commercial) platforms, usually amounting to 5% of the raised funds, may make crowdfunding inefficient
7. Crowdfunding of **clinical trials** by participants raises ethical dilemmas: privacy (a substantial amount of personal and medical information is usually given to maximise donations); inequity (crowdfunding is more successful for people with good social contacts and skills in online marketing and communications, which may perpetuate existing inequalities in health care systems); the voluntary nature of informed consent of the patient may be compromised by the external pressure exerted by crowdfunding; it may provide an incentive for researchers to include a greater number of patients than needed for the proposed objective; participants may have put excessive hope on the experimental treatment

Sources: Wenner et al,[9] Renwick and Mossialos,[23] Dragojlovic and Lynd,[24] Aleksina et al,[32] Dressler and Kelly,[34] Snyder et al,[35] Kenworthy et al[36] and del Salvio.[37]

Table 6 Data on the use of crowdfunding campaigns in biomedicine.

Two analyses of health care-related campaigns in found that in the United States the mean funds raised were $3000 to $3700, and on average campaigns raised only 41% of the target amount[36,38]
The interested individual, the parents or other close relatives organised 52% of the campaigns[36]
We ought to highlight the campaigns organised by relatives or friends of patients, usually through ad hoc foundations, which garnered considerable media attention. Some salient examples are the campaign for Mila, a girl with a variant of Batten disease[3] that raised 3 million dollars, and the campaign for Charlie Gard, a terminally ill English infant with progressive brain damage and muscle failure secondary to mitochondrial DNA depletion syndrome that raised 1.7 million dollars, both through the GoFundMe platform[1,34]
A salient case of mixed funding was the campaign that raised 2.2 million dollars for a phase 1 and 2 trial in patients with metastatic pancreatic neuroendocrine cancer through a combination of crowdfunding and a philanthropic donation by a wealthy donor that wanted participation in the trial[21]

addition to crowdfunding.[33] Table 5 summarises the benefits and risks of crowdfunding in health care research. Table 6 presents some interesting data on crowdfunding campaigns in biomedicine.

Crowdfunding for development of new orphan drugs

It must be taken into account that crowdfunding introduces new market norms in countries with well-established public health systems that may alter the traditional perception of healthcare of the population.[34] However, it is highly unlikely that crowdfunding for clinical trials will ever unsettle the existing system of drug development. The reason is that the number of trials for treatments of ultra-rare diseases that could be launched through this funding model is very small. Such trials would amount to a negligible percentage of the nearly 4000 clinical trials that are authorised each year in Europe, of which 61% (about 2450 a year) are sponsored by the pharmaceutical industry and the remaining 39% (about 1550 a year) by non-industry sponsors, mainly academia.[39] In Spain, the Agencia Española de Medicamentos y Productos Sanitarios (Spanish Agency of Medicines and Medical Devices, AEMPS) authorises approximately 800 clinical trials each year, of which 78% (about 625 a year) are sponsored by industry and the other 22% (about 165 a year) by researchers and not-for-profit organziations.[40] From a different perspective, in February 2020, based on the Spanish Register of Clinical Trials of the AEMPS, there were 379 clinical trials of treat-

Table 7 Crowdfunding campaigns in the press.

Murdoch et al[41] analysed 336 articles published between 2015—2017 about crowdfunding campaigns in newspapers with a high circulation in Canada and the United States.
The findings of this study regarding these articles were that: 1. Most articles portrayed campaigns neutrally (48%) or positively (44%) 2. Campaigns referred to cancer cases (49%) or rare diseases (36%) 3. Most articles (83%) noted how donations could be made 4. Few articles (9%) mentioned ethical issues with the phenomenon of crowdfunding 5. In relation to 21% of the campaigns discussed in the articles, it was noted that the treatment could be inefficacious, was unproven or lacked regulatory approval

ments for rare diseases in the patient recruitment period, while 110 had received approval and had yet to start. The addition in Spain of 1 or 2 trials per year funded by patients through crowdfunding would not create a disturbance in this system.

Crowdfunding in the media

It is well known that the mass media (press, radio, television) play a key role in the success of some crowdfunding campaigns, especially if a famous figure or celebrity is involved. Furthermore, the use of social media (such as Twitter or Facebook) is very important for the purpose of attracting an audience with an interest in the project and to sustain this interest.[32]

Murdoch et al. analysed how these crowdfunding campaigns are represented in the press (Table 7).[41] A striking aspect that is consistent with the coverage of other subjects related to science is that the press, unlike academic publications, rarely brings up the potential drawbacks of crowdfunding. This may generate a favourable perception of crowdfunding in society and legitimise it as a source of funding for health care,[41] as reflected by the nearly 7.5 million dollars raised by campaigns to fund therapies against cancer of highly questionable nature through 2 platforms in 16 countries and 4 continents.[26]

Future perspectives

Self-funding of clinical trials by participants suffering from specific ultra-rare diseases is an avenue that opened years ago and that is likely to grow in the near future. Nothing is ethically questionable in patients themselves—or their parents, relatives or friends—funding their participation in trials, and therefore there is no reason to ban trials funded by this method as long as they meet the requisite standards that apply to any clinical trial.[14,16,17] Most of the problems that have been identified, especially those concerning a lack of scientific and social value, can be avoided by applying current Spanish regulation on clinical trials: all patient-funded trials must be approved by the competent research ethics committee and the AEMPS.[12] Patient funding of clinical trials may be particularly useful for repositioning of already known treatments or even repurposing of drugs already marketed for other indications.[42]

Of the 3 models of patient funding (pay to try, pay to play and the plutocratic proposal), the plutocratic proposal seems to be most appropriate for early investigation of new orphan drugs. Although this new option is perceived positively,[43] to our knowledge it has not been introduced in any country. The need for a ''matching agency'' (which has the most significant role in this model and is the main innovation in it) may be the most complicated aspect that is hindering its implementation. This matching agency should be a not-for-profit organization run by a committee including, at minimum, basic scientists, clinicians, patients, lawyers and financial experts. In Spain, the Federación Española de Enfermedades Raras (Spanish Federation of Rare Diseases, FEDER) could become the matching agency or integrate within its structure an organization that could fit this role, although this would require amending the statutes of said organization. The CIBERER, or networking centres for research of rare diseases of the Instituto de Salud Carlos III, could offer scientific consultation, and the AEMPS should be involved in the evaluation of projects from an early stage in a regulatory role. Thus, FEDER is ideally positioned to be the key intermediary in projects concerning orphan drugs requiring self-funding by participants and to collaborate with associations of patients with rare diseases or their families that seek to start clinical trials with funding to be raised by them through different means.

Self-funding of clinical trials by participants—stemming from a lack of public or private funding—may in most cases require resorting to crowdfunding. The use of crowdfunding in biomedical research is controversial,[33,44] although in and of itself this approach does not entail ethical conflicts and provides a way for society to support those affected by a rare disease. There are those that consider that this is not the best way to address the deficiencies of health care systems.[32] However, this does not mean that crowdfunding could not play a role in the early phases of development of certain orphan drugs, as crowdfunding campaigns are frequently successful[33] and, in principle, would have a negligible impact on the currently established system for drug development.

As our knowledge of the genetic basis of many ultra-rare diseases is advancing at an unstoppable pace, Spain (and the European Union) should have an administrative procedure in place to allow the AEMPS to streamline authorization of trials of new experimental drugs under the condition of compassionate use. For this to be possible, the two provisions that we mentioned at the beginning of the article (for the drug to be currently in clinical trials or an application for marketing authorization to have been filed) in current regulation[5] should be expanded with a third provi-

sion allowing the initial administration of an experimental drug to a first patient, and possibly a few others, exempting researchers from having to file all the documentation normally required for performance of a clinical trial. The clinical situation of patients affected by ultra-rare diseases, which, by definition, are chronic or severely disabling and possibly even life-threatening, requires that regulations adapt to scientific advances so that delivery of potentially beneficial treatments is not delayed. This is even more so in the case of the adaptation proposed here, which would apply to the development of orphan drugs indicated for treatment of the very few patients affected by diseases with extremely low prevalence that, due to lack of public or private funding, would have to be financed through crowdfunding, a factor adding to the delay in their development and subsequent administration.

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Conflicts of interest

The authors have no conflicts of interest to declare.

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