



SPECIAL ARTICLE

Key points in the start and conduct of a clinical trial. From question to reality in an investigator-initiated clinical trial (I)

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Abstract Evidence-based clinical practice requires the integration of individual professional experience with the best objective data in order to make the best therapeutic decision. The best scientific evidence is derived from controlled, randomized clinical trials and post-marketing drug surveillance studies and meta-analyses. During our clinical activities, we often search unsuccessfully for a clinical trial which will provide answers to our scientific questions. It is at these times that we may, ourselves, sometimes consider conducting a clinical trial.

If you, as a clinical investigator, have a (relevant) scientific question that could potentially require the conduct of a clinical trial to achieve a response and have no support from a pharmaceutical company to perform it, you may find it useful to read this article, in which an attempt has been made to briefly and clearly explain the applicable regulations for planning a clinical trial. Our modest intention is that this paper may become a useful tool for any independent researcher.

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Puntos clave en la puesta en marcha y desarrollo de un Ensayo Clínico. De la pregunta a la realidad de un Ensayo Clínico investigador iniciado (I)

Resumen La práctica clínica basada en la evidencia requiere la integración de la experiencia profesional individual con los mejores datos objetivos para tomar la mejor decisión terapéutica. Los datos científicos de mejor grado de evidencia derivan de ensayos clínicos controlados y aleatorizados e investigaciones de vigilancia farmacológica poscomercialización y metaanálisis. En muchas ocasiones durante nuestras actividades clínicas buscamos sin éxito el ensayo clínico que conteste a nuestras preguntas científicas. Es en estos momentos cuando en ocasiones nos planteamos la puesta en marcha de un ensayo clínico.

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Si usted como investigador clínico tiene una pregunta científica (relevante), que potencialmente requeriría la realización de un Ensayo Clínico para alcanzar una respuesta y carece del respaldo de una Compañía Farmacéutica para llevarlo a cabo, quizá encuentre de utilidad la lectura de este artículo, en el que intentamos presentar de forma breve y clarificadora la normativa regulatoria para planificar un Ensayo Clínico, con la humilde intención de que se convierta en una herramienta útil para cualquier investigador independiente.

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Introduction

This article will attempt to provide a short and clear explanation of the regulations for planning a clinical trial (CT), with the modest hope that it may become a useful tool for any independent researcher.

It should first be noted that it is essential to have a relevant scientific question, and it is advisable that you are not the only one to consider the question relevant. Discussions with colleagues and a review of the literature will undoubtedly help you to assess the scientific quality of such a question.

The terms clinical study or clinical trial define any research conducted on humans aimed at determining or verifying the clinical and/or pharmacological and pharmacodynamic effects, adverse reactions and/or absorption, distribution, metabolism, and excretion of one or several investigational drugs in order to establish their safety and/or efficacy¹. All CTs with drugs conducted in Spain should be performed in compliance with good clinical practice (GCP) standards², a series of requirements ensuring the protection of the rights, safety, and well-being of trial subjects, as well as the reliability of CT results. Before continuing, it is important to know the different phases of a CT. Phase I trials assess the safety of a new treatment. The objective of a Phase I trial is to ascertain the dosage of a new drug that patients may receive without experiencing adverse side effects.

The main objective of a Phase II trial is to assess the efficacy of the new treatment in combating a given disease. Phase II is started if preliminary Phase I safety testing has been satisfactory. Phase II involves the administration of the drug to subjects who suffer the disease for which it is intended.

The objective of a Phase III trial is to compare the new treatment with a standard treatment. The aim is to assess whether the new treatment is more, equally, or less effective than the standard treatment. Apart from verifying drug efficacy, previously undetected toxicity signs are sought. Phase IV trials, also known as pharmacovigilance studies, consist of drug monitoring after marketing. They are mainly intended to detect previously unsuspected toxicity and to assess long-term efficacy. In any case, the following applicable regulations should be consulted whenever clinical trials are planned:

- Act 29/2006, of July 26³.
- RD 2183/2004, of November 12⁴.
- SCO Order/256/2007, of February 5⁵.

Table 1 Key points in the approval process of a clinical trial.

Documentation

Protocol writing

- Design of the case report form
- Writing of informed consent
- Sponsor file preparation
- Investigator file preparation

Application for a EudraCT number

Identification of the participating centers

Material acquisition

CREC approval procedure

- General dossier preparation and submission to the CREC*
- Response to clarifications requested by the CREC*

AEMPS APPROVAL PROCEDURE

- Preparation of a general dossier for the AEMPS*
- Telematic submission to the AEMPS*
- Response to clarifications requested by the AEMPS*

Insurance

Agreement negotiation and signature

Medication

Selection of the external monitoring team

Data management/biostatistics

Patient recruitment

Reporting of center closure to CREC

Reporting of study end to AEMPS

Final report preparation

Publication

- Volume X Eudralex - Clinical trials (developing Directive 2001/20/EC)⁶.
- Clarifications regarding the application of RD 223/2004⁷.

An important point to be considered is that the protocol should be written in collaboration with the different departments that will participate in its conduct.

It is advisable to design a timetable for the administrative steps required for obtaining all the necessary approval for you to be able to start the trial: approval by the Clinical Research Ethics Committees (CRECs) and the Spanish Agency for Medicinal Products and Medical Devices (AEMPS).

It is important that you do not work alone as a clinical investigator. Your hospital, through its research unit, the health department of your region, your foundation, your CREC, and undoubtedly AEMPS (which has an independent research support office) almost certainly have knowledgeable and experienced staff that may guide you during the difficult and laborious task of carrying out all the ethical/legal and administrative procedures necessary for initiating a clinical trial (Table 1) and preparing the essential documents before, during, and after the trial has started (Table 2, Table 3, and Table 4 respectively).

The creation and start-up of a web-based group for the support of biomedical research (*Consortio de Apoyo a la Investigación Biomédica en Red*, CAIBER [<http://www.caiber.net>]) also provides an essential support to independent clinical research by promoting the initiation of multicenter, prospective, randomized, quality CTs.

These are some of the key points we have worked on over the past two years, first in designing the study, subsequently to obtain approval from the European regulatory authorities, and finally to start the TRAMONTANA study: Multidisciplinary Treatment of Morbid Obesity.

Documentation

Protocol writing⁸

In our case, we have followed the standard structure of protocols for CTs with drugs available to all investigators at the AEMPS website, <http://www.aemps.es/invClinica/estruEstandarProto.htm>, as detailed in Figure 1.

Design of the case report form

The design of the case report form is a crucial step since, to a large extent, the quality of the final results achieved will depend on it. All efforts should be made to select all the data relevant for the study hypothesis. It is essential to clearly define not only the questions to be asked and the measurements to be recorded (and in what measurement units), but also how the questions will be asked, how the answers will be classified, and in what part of the CRF they will be recorded.

Writing of informed consent

When writing the informed consent form, the investigators should comply with the applicable regulations, GCP standards¹, and ethical principles originating in the Declaration of Helsinki⁹. Before the trial starts, the investigators must have received the written favorable opinion of the CREC, as stated in Art. 17 of RD 223/2004². CRECs include in their corresponding websites sample informed consent forms that may be used as a guide for writing one's own informed consent form.

Preparation and maintenance of sponsor and investigator files

A CT sponsor is the natural or legal person interested in the conduct of the trial, including its organization, start, and financing. The CT sponsor is also responsible for signing applications for approval submitted to the CREC or AEMPS.

Table 2 Documents required before trial start.

Type of document	Investigator file	Sponsor file
Investigator's manual	0	0
Signed protocol and its amendments (if any) and sample case report form	0	0
Information to be provided to trial subjects:	0	0
- Informed consent sheet		
- All written information		
- Advertisements for subject recruitment (when used)		
Financial aspects of the trial	0	0
Insurance certificate (when required)	0	0
Signed agreement between the parties involved	0	0
CREC membership	0	0 (when applicable)
Protocol approval by the regulatory authority	0	0
Curriculum vitae and other relevant documents showing the qualifications of the investigators	0	0
Normal values/ranges of medical/laboratory/technical procedures and/or tests included in the protocol	0	0
Medical/laboratory/technical procedures/tests	0 (when applicable)	0
Sample labels for investigational drug containers		0
Instructions for handling investigational drugs and trial-related materials	0	0
Certificates of analysis of investigational drugs sent		0
Unblinding procedures for blinded trials	0	0 (when applicable)
Randomization master list		0 (when applicable)
Pre-trial monitoring report		0
Monitoring report at trial start	0	0

Table 3 Documents to be filed during study conduct (1).

Type of document	Investigator file	Sponsor file
Investigator's manual updates	0	0
Any revision to:	0	0
- Protocol, amendments, and CRF		
- Informed consent document		
- Informed consent document		
- advertisement for subject recruitment (if used)		
Approval of protocol amendments and other documents by the regulatory authority	0 (when applicable)	0
Curriculum vitae of new investigators	0	0
Updates to the normal values/ranges of medical/laboratory/technical procedures and/or tests included in the protocol	0	0
Updates to the medical/laboratory/technical procedures/tests	0 (when applicable)	0
Documentation for the shipment of investigational drugs and trial-related materials	0	0
Certificates of analysis of new batches of investigational drugs		0
Reports of monitoring visits		0
Relevant reports other than center visits	0	0
Signed informed consents	0	
Completed, signed, and dated case report forms	0 (copy)	0 (original)
Documentation of CRF corrections	0 (copy)	0 (original)
Reporting of serious adverse events and related reports by investigator to sponsor	0	0
Reporting of serious, unexpected adverse reactions and other safety information to the regulatory authority and the CREC by the sponsor and/or the investigator	0 (when applicable)	0
Reporting of safety information to investigators by the sponsor	0	0
Interim or annual reports to the CREC and the regulatory authority	0	0 (when applicable)
Subject selection log	0	0 (when applicable)
List of subject identification codes	0	
Subject recruitment log	0	
Accountability of investigational drugs at the trial site	0	0
Signature page	0	0
Registries of body fluid/tissue samples (if any)	0	0

Table 4 Documents to be filed after the end of the trial.

Type of document	Investigator file	Sponsor file
Accountability of investigational drugs at the site	0	0
Documentation of investigational drug destruction	0 (if destructed at the site)	0
Full list of subject identification codes	0	
Audit certificate (if available)		0
Final trial monitoring report (closure)		0
Documentation of treatment assignment and decoding		0
Final report of investigator to CREC and regulatory authority		0
Clinical study report	0	0

Investigators should be qualified by degree, training, and experience for accepting responsibility for adequate CT conduct and should meet all the requirements set down in the relevant regulations.

Sponsor and investigator files must include a number of documents, as detailed in Tables 2, 3, and 4, which should be filed once the trial is completed.

Application for a EudraCT number

In order to provide a unique means of identification for CTs in which at least one site located in the autonomous region participates, each trial should be identified by a special number (the EudraCT number¹⁰) which should appear in all CT applications submitted in any Member State and will be

<p>1. Justificación</p> <p>Justificación de la pertinencia de realizar el ensayo planteado (qué aportará el ensayo en relación con lo que ya se conoce), estimando los riesgos y beneficios para la población participante en el mismo. En su caso, se deberá justificar la inclusión de poblaciones vulnerables (Ej. menores, incapaces, embarazadas, etc.).</p> <ul style="list-style-type: none"> • Nombre y descripción del medicamento en investigación. • Resumen de los hallazgos de los estudios no clínicos y clínicos que puedan ser relevantes para el ensayo actual. • Resumen de los riesgos y beneficios conocidos y potenciales, si los hubiera, para los seres humanos. • Descripción y justificación de la vía de administración, dosis, pauta de dosificación y período de tratamiento. • Descripción de la población a estudiar. • Referencias de la literatura y datos que sean relevantes para el ensayo y que proporcionen una justificación del mismo. <p>2. Objetivo y Finalidad del Ensayo</p> <p>Descripción detallada de los objetivos y finalidades del ensayo.</p> <p>3. Diseño del Ensayo</p> <p>La integridad científica del ensayo y la credibilidad de los datos obtenidos en el mismo dependen de forma considerable del diseño del ensayo. La descripción del diseño deberá incluir:</p> <ul style="list-style-type: none"> • Descripción específica de las variables principales y secundarias, si las hubiera, que se evaluarán en el ensayo. • Una descripción del tipo/diseño del ensayo que se realizará (por ejemplo, doble ciego, controlado con placebo, diseño paralelo) y un diagrama esquemático del diseño del ensayo, procedimientos y periodos. • Una descripción de las medidas tomadas para minimizar o evitar sesgos, tales como: Aleatorización y Enmascaramiento. • Una descripción de los tratamientos del ensayo y de la dosis y pauta de tratamiento del medicamento(s) en investigación. Además, deberá incluir una descripción de la forma farmacéutica, envasado y etiquetado del medicamento(s) en investigación. • La duración esperada de la participación de los sujetos y una descripción de la secuencia y duración de todos los periodos del ensayo, incluyendo el seguimiento, cuando proceda. <p>4. Selección y Retirada de Sujetos</p> <ul style="list-style-type: none"> • Criterios de inclusión de los sujetos. • Criterios de exclusión de los sujetos. • Criterios de retirada de los sujetos (es decir, finalizar el tratamiento del ensayo) y los procedimientos que especifican: <ul style="list-style-type: none"> ◦ Cuándo y cómo retirar a los sujetos del ensayo o del tratamiento con el medicamento en investigación. ◦ El tipo de datos y el calendario en que se recogerán los datos de los sujetos retirados. ◦ Si van a ser reemplazados los sujetos y cómo se realizará. ◦ El seguimiento de los sujetos retirados del ensayo o del tratamiento con el medicamento en investigación. 	<p>5. Tratamiento de los Sujetos</p> <ul style="list-style-type: none"> • Los tratamientos que se administrarán, incluyendo el nombre de todos los medicamentos, la dosis, esquema de dosificación, la vía o modo de administración y los periodos de tratamiento incluyendo los tiempos de seguimiento para los sujetos de cada grupo o brazo de tratamiento del ensayo. • Los medicamentos o tratamientos permitidos (incluyendo la medicación de rescate) y no permitidos antes de y/o durante el ensayo. • Los procedimientos para monitorizar el cumplimiento del sujeto. <p>6. Valoración de la Eficacia</p> <ul style="list-style-type: none"> • La especificación de las variables de eficacia. • Los métodos y el calendario para la evaluación, registro y análisis de los parámetros de eficacia. <p>7. Valoración de Seguridad</p> <ul style="list-style-type: none"> • La especificación de las variables de seguridad. • Los métodos y el calendario para la evaluación, registro y análisis de los parámetros de seguridad. • Los procedimientos para obtener los informes de los acontecimientos adversos y enfermedades intercurrentes y para el registro y comunicación de los mismos y de las reacciones adversas a los medicamentos que se investigan. • El tipo y la duración del seguimiento de los sujetos después de los acontecimientos adversos. <p>8. Estadística</p> <p>Descripción de los métodos estadísticos que se usarán, incluyendo el calendario de todos los análisis intermedios planificados.</p> <p>El número previsto de sujetos que se incluirán. En los ensayos multicéntricos, se deberá especificar el número previsto de sujetos que se incluirán en cada centro donde se realizará el ensayo. Se incluirá la justificación del cálculo del tamaño de la muestra, incluyendo la explicación (o cálculo) del poder del ensayo y la argumentación clínica de dicho tamaño.</p> <p>9. Ética</p> <p>Descripción de las consideraciones éticas relacionadas con el ensayo.</p> <p>10. Financiación y Seguros</p> <p>La financiación y el seguro, si no se contemplan en un contrato independiente. Debe hacerse referencia a que se tendrán en cuenta los requisitos de la normativa vigente en España.</p> <p>11. Política de Publicación</p> <p>La política de publicación. Debe constar en el protocolo, o en el resumen del protocolo el compromiso expreso del promotor, de publicar los resultados del ensayo, tanto si fueran positivos como si fueran negativos.</p>
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Figure 1 Standard structure of protocols for clinical trials with drugs.

Source: Spanish Agency for Medicinal Products and Medical Devices. Clarifications on the application of clinical trial regulations from May 1, 2004 (version no. 6, May 2008).

used to identify the trial in the relevant documentation (e.g. in reports of serious, unexpected adverse reactions).

Identification of participating sites

Most investigators would like their ideas to be converted into relevant multicenter projects, but it should be borne in mind that one's closest colleague is not necessarily one's best partner.

It should be verified that the investigator is qualified by training and experience and has available adequate resources for the appropriate conduct of the trial. The suitability of the facilities of the site where it is planned to conduct the trial should also be verified.

Material acquisition

Adequate planning will allow for an easier material acquisition process. When an application for the financing of a research project is submitted, an adequately itemized budget will ensure the financial feasibility of the project.

CREC approval procedure

The role of the CREC is of paramount importance. According to RD 223/2004², CRECs have the following functions:

1. To assess the methodological, ethical, and legal aspects of CTs submitted to them in agreement with the provisions in section 2 of chapter IV.
2. To assess relevant amendments to approved CTs.
3. To monitor the trial from its start to the receipt of the final report.

General dossier preparation and submission to the CREC

Each CREC requires a number of documents (full protocol, case report form, informed consent, patient information sheet, commitment to publish results, statement of conflicts of interest, etc.) to be provided before the CT can be accepted for review by CREC members.

Response to clarifications requested by the CREC

Once the documentation has been reviewed, the CREC sends a report to the investigator including the items to be included or modified before the CT may be approved.

This process usually takes 1 to 2 months depending on the questions asked, the changes to be made, and the documents requested by the CREC. In some extreme cases where final protocol approval may be difficult to obtain, it may be useful to ask the CREC for the opportunity to defend the study at its meeting in order to be able to directly answer any queries that may have arisen.

Insurance

Before clinical research can be started, an insurance policy covering any potential damage experienced by subjects as a result of the clinical trial must be taken out.

The clinical research sponsor is responsible for taking out such civil liability insurance, which must cover the responsibilities of the sponsor, investigator and his/her collaborators, and the manager of the hospital or site where the clinical research is to be conducted.

When the insurance does not fully cover damages for any reason, the clinical research sponsor, principal investigator, and manager of the hospital or site where the clinical research is to be conducted will jointly be responsible, without the need to prove individual fault, for any health damage experienced by a subject in a CT, and also for any financial damage directly derived from such health damage, provided this is the consequence of treatment with the product subject to clinical research or the therapeutic or diagnostic actions taken during the conduct of the trial.

The cost of insurance will depend on population type, number of patients recruited, trial duration, and medicinal product/therapeutic process used. This is a significant amount in most cases (6,000-12,000 €). Any exemption from this requirement should be duly justified and must be assessed and approved by the CREC.

Approval procedure by the Spanish Agency for Medicinal Products and Medical Devices

The role of the AEMPS is to guarantee, from the public health perspective, the quality, safety, and efficacy of medicinal products and medical devices as well as to provide adequate information about them. Such information must cover all stages from research to use in the interest of protecting and promoting of health of people and animals.

Telematic submission of the clinical trial application to the AEMPS

The website for clinical trials with medicinal products for use on humans of the Spanish Ministry of Health allows for the preparation and submission of new CT applications and any other application related to a CT pending approval by the AEMPS.

Application forms may be filled in, printed, filed, and submitted online, and any necessary documentation may also be sent to them.

We advise you to start this process from http://aemps.es/aplicaciones/usoHum/ensaClin/portal_ensaClinicos.htm#entrada, where you will find plenty of detailed, very helpful information.

The virtual office of AEMPS (<http://aemps.es/aplicaciones/home.htm>) provides access to the website for clinical trials with medicinal products, <https://sinaem4.agemed.es/ecm/paginaPresentacion.do>, which allows for official submission of the initial application, pending CT documentation, and relevant amendments to a CT in electronic format. It also provides manuals for help in making an online application.

Before the submission process is completed, a screen will appear listing the documents that must be enclosed: Protocol, Investigator's Manual, clinical trial application fees, CREC opinion, information sheet for trial subjects, electronic mail assigning the EudraCT number, prescribing information, etc. It is recommended that the .pdf file is given the descriptive name of the type of document to

which it refers, because this will be the name which subsequently appears in the acknowledgment of receipt.

Response to clarifications requested by the AEMPS

Responses to clarifications may be of two types, with or without changes, depending on whether or not any document submitted in the initial application has been changed.

Agreement negotiation and signature

The financial aspects of the trial must be documented in an formal agreement between the sponsor and the investigator/site¹.

The negotiation and signature of clinical research agreements is a subject of great interest because many such agreements for the conduct of trials are signed between sponsors and public hospitals and are legally more complex because of the public character of the latter.

The formal agreement is a necessary tool in clinical research with drugs which is subject to debate, mainly because of the CT contracting system with public hospitals, but also because of the difficulties (practical and legal) which arise for pharmaceutical companies due to the lack of homogeneity in the contents of such agreements (which show marked variations depending on the hospital concerned).

Many of the parties to an agreement demand a single standard model. What are the reasons for this? The main reason is to try and ensure the inclusion of certain minimum contents in such agreements, which would result in a greater legal guarantee. An additional objective is to shorten the negotiation period, an aspect which has clear financial consequences, particularly if trials are connected to the marketing of a drug protected by a patent. Why is this?

It is because CTs are usually conducted during the validity period of the patent, in which priority is obviously given to the earlier phases of development. Any delay in the development of products covered by a patent uses part of the exclusive marketing period granted by patent rights, and therefore decreases the chance of writing off the costs incurred in product development. This urgency contrasts with administrative constrictions on public health centers, their bureaucratized structures, and the work overload of the bodies involved. RD 223/2004, of February 6, on CTs² imposes two time periods (which may partly overlap) for the issue of the CREC's opinion and for trial approval by the AEMPS. According to the "Survey on RD 223/2004 implementation, Results at 12 months and comparison with the situation at 6 months", carried out and published by AMIFE y MDS Pharma Services, the mean time needed for meeting these requirements by the industry is 204 days in the best of cases, through the participation of CROs (Contract Research Organizations). This is quite a long time.

From 24 to 64 additional days are required for agreement negotiation and signature. Since the sponsor has no possibility of shortening the time delay before the issue of the CREC's opinion and the approval of the AEMPS, efforts to shorten times should be concentrated on the agreement negotiation period.

Medication

Drugs must only be kept, stored, and dispensed by the pharmacy departments of hospitals or primary care structures of the National Health System in accordance with article 2.6 of Act 29/2006³.

Since the pharmacy department will collaborate with the study either in discussions with AEMPS and/or manufacture, import, blinding, dispensing, and control of the drug or substance, the participation of this department in protocol writing is considered advisable. If the department does not participate at this time in the study design, its participation will probably be required at a later time, and the lack of prior communication with the department may delay final project approval.

Data management/biostatistics

Act 41/2002, of November 14, regulating patient autonomy and rights and obligations regarding clinical information and documentation¹¹, Organic Act 15/1999, of December 13, on personal data protection¹², and RD 223/2004, of February 6, governing CTs with drugs form the legal framework applicable for the management and control of data collected in a CT. It is of paramount importance that the sponsor guarantees the statement in the protocol or in another written agreement that the investigator or institution will allow direct access to source data or documents for monitoring, auditing, and CREC review purposes, as well as trial inspection by the regulatory authorities.

A statistical plan should be prepared describing the statistical methods to be used, including the times for all planned interim analyses.

Patient recruitment

Before the start of the trial, the investigator must have available a written favorable report from the CREC on the informed consent form and any other written information to be provided to subjects, in accordance to Art. 17 of RD 223/2004².

To recruit patients into a CT, the following applicable regulations must also be complied with: Title I, Art. 4 of Act 14/2007, of July 3, on biomedical research¹³, Title II, Chapter II, Art. 13 of the same act, GCP standards¹, and ethical principles originating in the Declaration of Helsinki⁹.

Patients must meet all inclusion criteria stated in the protocol and no exclusion criteria at the time of trial entry.

Preparation of reports to sponsor and updates to regulatory authorities

Different types of reports should be prepared and submitted to the CREC, the regulatory authorities and/or the sponsor during the conduct of a trial. These include notifications by the investigator to the sponsor of any serious adverse events and related reports, updates to the normal values/ranges of medical/laboratory/technical procedures and/or tests

included in the protocol, annual reports to the CREC (most CRECs have a standardized operating procedure [SOP] for this purpose), relevant reports other than site visits, and other reports which must be filed in all cases, as stated in Table 3.

Once the trial is completed, the end of study report to the AEMPS and the preparation of the final report will terminate the process. With their scientific, ethical, and legal quality fully guaranteed, the results of the research will now be ready for publication.

Acknowledgement

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Conflict of interest

The authors state that they have no conflict of interest.

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