Attributes to be considered for a site to participate in a pharmaceutical clinical trial in Mexico: A proposal of minimum criteria

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Abstract

Objective: The objective of the study was to offer a parameter to assess the different types of sites participating in a pharmaceutical clinical trial in Mexico. **Materials and methods:** A board of clinical investigators recognized by the industry in Mexico reviewed and discussed the most common requirements for a site to participate in a clinical trial within our country. The board defined a minimum standard by consensus. **Results:** A list of 68 criteria was set, divided into six sections: (1) general conditions, (2) research team, (3) infrastructure, (4) standard operating procedures, (5) committees, and (6) supervision. Special considerations were included where needed. **Conclusions:** This is the first tool published in Mexico designed to optimize the site selection process for clinical trials sponsored by the industry.

Key words: Clinical research. Attributes. Criteria. Standard. Center. Site.

Introduction

The development of a single clinical pharmaceutical study can cost up to 100 million dollars; between 30% and 50% of this investment is lost on inefficiencies in the process^{1,2}. A high percentage of these failures are due to the fact that selected sites do not have the minimum necessary infrastructure for the correct completion of clinical studies^{3,4}. It is worth noting that today, in the world, there are no accepted standards for the requirements; a clinical research center ought to meet to carry out a pharmaceutical clinical assay.

In everyday practice, the guidelines followed are those established by the International Conference of Harmonization in its Good Clinical Practices chapter⁵,

requirements which, directly or indirectly, are defined by some regulatory agencies, interpreted and respected⁶. Sometimes, guidelines proposed by different associations or academic organizations are taken into consideration⁷⁻¹⁰ and/or simply the sites follow the criterion imposed by the same pharmaceuticals or companies dedicated to Clinical Research Organizations (CROs). There are several areas of opportunity to improve the efficiency, productivity, and quality of the operations of the different components in the process of clinical research.

The objective of this paper is to highlight the minimum attributes that ought to be taken into consideration in a research site so that it can comply with its commitment to the implementation, carrying out, and operation of a pharmaceutical clinical essay. For the purposes of

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this report, the term “center” will be understood as a synonym of “site,” and both concepts are encompassed in the Mexican regulatory definition of “Establishment of Medical Care¹¹.”

Materials and methods

A board of nine clinical investigators with ample experience and good performance in trials within the pharmaceutical industry in Mexico (the list of participants can be found at the end of this text) was assembled. Each member of the board received the result of a search of medical literature on the quality of research sites⁶⁻¹⁰, and a list of criteria for the selection and evaluation of research centers used by the industry and CROs in Mexico. The board discussed each attribute and selected those that they considered by consensus as a minimum standard so that a center could conduct a pharmaceutical study.

Results

In **table 1**, there is a complete list of 68 attributes that conform to the proposed model, classified according to their principles: (1) criteria sustained in General Health Law, in a norm or a guideline, (2) recommendations made by the local authorities, without evident regulatory basis, (3) international guidelines, (4) additional recommendations made by the sponsor (industry or CROs), and (5) suggestions by the board by consensus. All criteria were divided into the following six sections for better management:

- I. General aspects of the site: Attributes which reflect in general the experience and function of the site
- II. Research team: Composition and qualifications of the personnel the center should have
- III. Infrastructure: Requirements of space and necessary equipment for the proper performance of the center
- IV. Standard operating procedures: Procedures that a research site must have as a minimum requested by the Commission of Sanitary Operation (COS by its Spanish acronym) of the Federal Commission for the Protection against Sanitary Risk (COFEPRIS by its Spanish acronym), to the establishments that have authorization to conduct a clinical trial¹²
- V. Committees: Due to local Mexican regulation, each site must have three properly registered committees: an Ethics in Research Committee (ERC) registered with the National Bioethics Commission (CONBIOETICA by its Spanish acronym), a Research Committee, registered with the COFEPRIS, and a Biosafety Committee, also registered with COFEPRIS

- VI. Supervision during the execution of the trial: Documentation of periodical personnel meeting through minutes.

Discussion and conclusions

Even though there are international proposals for the conformation of a research site^{13,14}, the environment in which we operate in Mexico, and our own regulations demand the creation of a local model that responds to our specific needs.

This is the 1st time that a standard in Mexico has been defined by agreement between independent experts, which allows the decision-makers of the different companies that sponsor research programs in our country to have a more objective and consensual approach in their center selection process for the assignment of a clinical study. This proposal may also help researchers who participate or who want to begin participating in these types of studies to search for a guideline with a national standard that can be accepted and acknowledged by all involved parties in our field.

To establish the list of criteria, the board had to discuss aspects of objective measurement or attributes related to the proper implementation and carrying out of a clinical pharmaceutical study. In each of these discussed criteria, there were different perspectives and the board set about searching for a consensus. Different aspects which may be considered controversial were approached, such as minimum necessary experience to be in charge of a study, preparation, and qualifications that the center's personnel must have, the minimum number of professionals which ought to make up the research group, and the amount of time each one should dedicate to their responsibilities in a trial. Concerning infrastructure, the board only recommended complying (as a minimum) with the space and equipment need related to the type of trial assigned, as well as the general and specific requirements established by the regulatory authority in our country.

Given the vast variability of perspectives and requirements within the industry and the methodological limitations of the work, we must be careful in the application of conclusions in this report. The minimum criteria model proposed is a guide, which can be of great help in the selection of a research center. However, by no means does this replace the attention that should be given to the following up of the site once the trial begins. Its final value should be evaluated in practice, searching to widen its reach and applicability.

Table 1. Attributes for the participation of a research site or center in a clinical pharmaceutical study in Mexico

I. General aspects	Considerations	Basis
Site: Number of studies conducted completed	Three studies completed. If the center has < 3 studies completed, they must have a PI with ≥ 2 studies completed in the past 3 years	Suggested by the council
Site: Number of active studies	At least one. If the center does not have active studies, it must have an IP with ≥ 2 studies completed in the past 3 years	Suggested by the council
Site: Number of principal investigators	At least one	Suggested by the council
Site: Number of subresearchers	At least one. The same person can be a subinvestigator and coordinator	Suggested by the council
Site: Number of coordinators	At least one. The same person can be a subinvestigator and coordinator	Suggested by the council
Site: Number of Personnel for handling and sending samples (certificate in IATA)	At least one. It can be any team member	Sponsor/CRO recommendation
II. Research team	Considerations	Basis
Principal investigator (PI) PI: Minimum academic degree	Specialty related to the therapeutic class of the clinical study	Local regulation
PI: Number of completed studies related to the industry (such as PI) in the past 3 years	At least one. If the researcher has < 2 years of experience, he must have been a subinvestigator in at least two studies completed in the past 3 years	Suggested by the council
PI: Hours/week for research PI: English level	6 h per week per study Intermediate level, at least. Technical English, reading level, and basic conversation	Suggested by the council Suggested by the council
PI: Training good clinical practices	Yes	International guidelines
Subinvestigator (SI) SI: Minimum academic degree SI: Hours/week for research SI: English level	General practitioner 12 h per week per study Intermediate level, at least. Technical English, reading level, and basic conversation	Local regulation Suggested by the council Suggested by the council
SI: Training good clinical practices	Yes	International guidelines
Study coordinator (SC) SC: Minimum academic degree or equivalent experience SC: Hours/week for research SC: English level SC: Training good clinical practices	Technician 12 h per week per study Basic Yes	Local regulation Suggested by the council Suggested by the council International guidelines
III. Infrastructure	Considerations	Basis
Physical area Designated office for research subjects Office has a questioning area Office has an exploration board Office has a washbasin Exclusive, independent, and restricted area for material and supplies protection Exclusive, independent, and restricted area to protect research products Exclusive, independent, and restricted area for documentation safekeeping, including clinical records Exclusive, independent, and restricted area of handling and sample preparation Sample collection area Monitoring/auditing area	Yes Yes Yes Yes Yes As part of the center or by agreement The dead file can be external As part of the center or by agreement Yes Puede ser un espacio compartido	Local regulation Local regulation Local regulation Local regulation Sponsor/CRO recommendation Sponsor/CRO recommendation Sponsor/CRO recommendation Local regulation Sponsor/CRO recommendation

(Continues)

Table 1. Attributes for the participation of a research site or center in a clinical pharmaceutical study in Mexico
(Continued)

III. Infrastructure	Considerations	Basis
Medical emergency area 24 h medical emergency area Has an ambulance Emergency cart	As part of the center or by agreement As part of the center or by agreement Yes	Local regulation National regulatory authority recommendation National regulatory authority recommendation
Equipment Minimum equipment (sphygmomanometer, stethoscope, thermometer) Basic laboratory equipment for the processing of biological samples (centrifuge and micropipettes) Refrigerator 2-8°C (temperature graph or calibrated thermometer) Freezer -20°C (temperature graph or calibrated thermometer) Emergency power plant (for refrigerators/freezers) Computer equipment Internet Copier Scanner Equipment maintenance and calibration program	Yes Internal or by agreement When the study requires it, as part of the center or by agreement When the study requires it, as part of the center or by agreement Yes Yes Yes Yes Yes Yes	Local regulation Suggested by the council International guidelines International guidelines Sponsor/CRO recommendation International guidelines International guidelines International guidelines International guidelines Local regulation
Research product management Investigation product management log Products identified (by protocol) Logbook of refrigerator and/or freezer temperature Temperature log of protected areas	Yes Yes Yes Yes	International guidelines International guidelines International guidelines International guidelines
Security IBHW containers and proper handling Fire extinguishers Smoke detectors and alarms Safety signs Emergency contingency plan Pest control	Yes Yes Yes Yes Yes Yes	Local regulation Local regulation Local regulation Local regulation Local regulation Local regulation
IV. Standard operating procedures (SOPs)	Considerations	Basis
SOP: Issuance, review, approval, dissemination, and update of SOPs	Yes	National regulatory authority recommendation
SOP: Follow-up to the authorized protocols	Yes	National regulatory authority recommendation
SOP: Roles and responsibilities of the staff participating in the protocols	Yes	National regulatory authority recommendation
SOP: Selection of staff that is part of the group participating in the study	Yes	National regulatory authority recommendation
SOP: Recruitment of subjects that include the inclusion and exclusion criteria	Yes	National regulatory authority recommendation
SOP: Management, identification, temporary storage, collection, external transportation, and final disposal of infectious biological hazardous waste (IBHW)	Yes	National regulatory authority recommendation
SOP: Reports of adverse events according to the NOM-220-SSA1-2002	Yes	National regulatory authority recommendation
SOP: Management of conflicts of interest between the sponsor, research center, participating staff, and principal investigator	Yes	National regulatory authority recommendation
SOP: Transportation of biological samples that consider the type of container and records of transport conditions	Yes	National regulatory authority recommendation

(Continues)

Table 1. Attributes for the participation of a research site or center in a clinical pharmaceutical study in Mexico (Continued)

IV. Standard operating procedures (SOPs)	Considerations	Basis
SOP: Final destination of expired medicines	Yes	National regulatory authority recommendation
SOP: Informed consent process, whether personalized/group and who is responsible for applying it	Yes	National regulatory authority recommendation
SOP: Confidentiality management	Yes	National regulatory authority recommendation
V. Committees	Considerations	Basis
Research ethics committee registered with CONBIOÉTICA	Internal or external	Local regulation
Research committee registered with COFEPRIS	Internal or external	Local regulation
Biosafety committee registered with COFEPRIS	Internal or external, according to protocol	Local regulation
VI. Supervision during study execution	Considerations	Basis
Minutes of research team meetings	As applicable	International guidelines

COFEPRIS: Federal Commission of Health Risk Protection; CONBIOÉTICA: National Bioethics Commission; IATA: International Air Transport Association; IBHW: infectious biological hazardous waste; PI: principal investigator; SI: subinvestigator; SOP: standard operating procedure.

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Conflicts of interest

The authors declare that there are no conflicts of interest.

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Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

References

1. Clinical Trials Analysis. Mexico Health Review. Mexico: Clinical Trials Analysis; 2018. p. 284-5.
2. Goldfarb NM. Clinical research: a time to change. J Clin Res Best Pract. 2014;10:1-2. Available from: <http://www.firstclinical.com>.
3. Minisman G, Bhanushali M, Conwit R, Wolfe GI, Aban I, Kaminski HJ, et al. Implementing clinical trials on an international platform: challenges and perspectives. J Neurol Sci. 2012;313:1-6.
4. An Industry in Crisis. The Escalating Cost to Society of Our Inability to Sustain the Performance of Clinical Research Sites Today and Into the Future. SCRS Society for Clinical Research Sites; 2014. Available from: <http://www.myscrs.org>.
5. International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH). Integrated Addendum to ICH E6(R1): Guideline for Good Clinical Practice E6(R2). Available from: https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R2_Step_4_2016_1109.pdf.
6. Lopez-Pacheco MC, Pimentel-Hernández C, Rivas-Mirrelles E, Arredondo-García JL. Normatividad que rige la investigación clínica en seres humanos y requisitos que debe cumplir un centro de investigación para participar en un estudio clínico en México. Acta Pediatr Mex. 2016;37:175-82.
7. Johnston SC, Austin CP, Lewis-Hall F. Voluntary site accreditation improving the execution of multicenter clinical trials. N Engl J Med. 2017; 377:1414-5.
8. Koski G, Kennedy L, Tobin MF, Whalen M. Accreditation of clinical research sites moving forward. N Engl J Med. 2018;379:405-7.
9. Johnston SC, Lewis-Hall F, Bajpai A, Blumenfeld TH, Goldschmidt P, Koski G, et al. It's Time to Harmonize Clinical Trial Site Standards. Perspectives. Discussion Paper Expert Voices in Health and Health Care; 2017.
10. Bajpai A, Koski G, Tobin M. Aiming High. ACRES. ICT; 2015. p. 32-36. Available from: <http://www.samedanltd.com>.
11. DOF: 17/07/2018, DECRETO por el que se Reforman, Adicionan y Derogan Diversas Disposiciones del Reglamento de la Ley General de Salud en Materia de Prestación de Servicios de Atención Médica. Available from: https://www.dof.gob.mx/nota_detalle.php?codigo=5531691&fecha=17/07/2018.
12. COFEPRIS, Acta de Verificación Sanitaria para Establecimientos que Realizan Ensayos Clínicos. Available from: <https://www.gob.mx/cms/uploads/attachment/file/172739/COS-AC-17.pdf>.
13. ACRES-QC S001 ACRES Quality Continuum Standard for the Quality Management of Clinical Research Sites; ACRES (Alliance for Clinical Research Excellence and Safety), SASI (Site Accreditation and Standards Initiative), Available from: <http://www.acresglobal.net>.
14. SCRS, Society for Clinical Research Sites. Available from: <http://www.myscrs.org>.