Independent Ethics Committee for Clinical Pharmacology Trials

Fundación de Estudios Farmacológicos y de Medicamentos « Prof. Luis M. Zieher »

Standard Operating Procedures Year 2022

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1. Background and General Considerations

The Research Ethics Committee named, 'Comité Independiente de Ética para Ensayos en Farmacología Clínica – Fundación de Estudios Farmacológicos y de Medicamentos (FEFyM) 'Prof. Luis M. Zieher'' [Independent Ethics Committee (IEC) for Clinical Pharmacology Trials – Fundación de Estudios Farmacológicos y de Medicamentos (FEFyM) 'Prof. Luis M. Zieher'] was established at the end of 1993 in the 1st Pharmacology Chair of the School of Medicine of the University of Buenos Aires, Argentina. Since the end of 2002, it has developed its functions physically and within academic field of Fundación de Estudios Farmacológicos y de Medicamentos 'Prof. Luis M. Zieher' (FEFyM).

The IEC's functions are legally embedded in FEFyM's framework (I.G.J. Resolution N° 001062 dated December 19th, 2001) and, operationally, since June 2012, in 'FEFyM Centro Medico' [FEFyM Medical Center] (Dossier: 1241832/2012 dated 14/Jun/2012- Provision DI-2012-81-DGTALAPRA), and has been accredited by the Central Ethics Committee of the Autonomous City of Buenos Aires (under Provision N° 174/DGDOIN/13 and subsequent re-accreditations) until August, 21st, 2022; as of the 2022 re-accreditation, it has developed its functions within the framework of the Poly-Consultation Center for Research 'Dr. Darío Scublinsky' (Rheumatology Comprehensive Center of Buenos Aires) (Dossier: 1-2002- 14711.16-5 dated October 13th, 2016, and Dossier: 2022-56076579-APN- DNHFYSF#MS).

The IEC provides independent evaluation services of clinical studies in which sites from the Argentine Republic take part.

Since its creation in 1993, the IEC unconditionally adheres to the universal Ethical principles (Beneficence, Non-Maleficence, Autonomy, and Justice), and, in its procedures and evaluations, to the criteria established in the international and national regulations protecting the rights, safety, and well-being of individuals participating in clinical trials, which include, among others:

International Ethical Guidelines for Health-related Research Involving Humans, published by CIOMS in 2016. ISBN: 978-92-9036088-9; International Ethical Guidelines for Health-related Research Involving Humans. ISBN: 978-929036090-2, and any update thereof;

Standards and Operational Guidance for Ethics Review of Health-related Research, and any update thereof;

Declaration of Helsinki of the World Medical Association (WMA), Helsinki, Finland, June 1964, and its amendments of Tokyo, Japan, October 1975; Venice, Italy, October 1983; Hong Kong, September 1989; Somerset West, South Africa, October 1986; Edinburgh, Scotland, October 2000 and the Notes of Clarification on Paragraphs 29 and 30, added by the WMA Assembly, Washington 2002; Tokyo 2004 and Seoul, Korea, 2008, and Fortaleza, Brazil 2013, and any update thereof;

The Belmont Report; 1978;

The Nuremberg Code; 1947;

The Document of the Americas; IV PAN AMERICAN CONFERENCE ON DRUG REGULATORY HARMONIZATION, 2005;

International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH: E6(R2) Current Step 4 version dated 9 November 2016-Endorsed Document, E6(R3) version dated 19 April 2021 (Draft Principles)- Endorsed Document, and all other relevant ICH Guidelines concerning the conduct of clinical trials, and any update thereof.

Universal Declaration of Bioethics and Human Rights (UNESCO, 2005);

Universal Declaration on the Human Genome and Human Rights (UNESCO, 1997);

International Declaration on Human Genetic Data (UNESCO, 2003);

Guidance for Health-related Research Involving Humans; Resolution 1480/2011, National Ministry of Health (Argentina);

Good Clinical Practice Regimen for Clinical Pharmacology Studies. Provision 6677/2010, Provision 12792/2016, Provision 4008/17, Provision 828/2017, Provision 10874-E/2017, Provision 9929/2019, Provision 9944/2019, Provision 5640/2022, and any other Provision or update thereof. Circular 0001/2011, Circular 0004/2018 and any other Circular as may be issued concerning clinical research;

Law 25326 and its Regulatory Decree 1558/2011 (Personal Data Protection Law);

Law 3301 on the Protection of Rights of Subjects Participating in Health-related Research, of the Government of the Autonomous City of Buenos Aires, and its Regulatory Decree 58/2011;

National Civil and Commercial Law, and all other Laws that may directly or indirectly be related to clinical research.

Recommendations for Research Ethics Committees (EC) on clinical research protocols involving the recruitment of a high number of participants (NO-2021-18834928- GCABA-DGDIYDP); 2021.

Accreditations:

Central Committee for Ethical Research (CCE) – Autonomous City of Buenos Aires; Provision No. 174/DGDOIN/13 and subsequent re-accreditations.

Registrations:

Office for Human Research Protection (OHRP) U.S. Department of Health and Human Services (HHS) Registration of an Institutional Review Board (IRB) IORG0005480
National Register of Health-related Investigations (ReNIS) CE000041
National Register of Databases of the National Directorate for Personal Data Protection, No. 19069.

2. Primary Objective

To safeguard the dignity, rights, safety and well-being of all the individuals participating in clinical research studies; in particular, of those considered vulnerable.

3. Responsibilities, Functions, and Scope

Since its creation, the IEC has adopted a robust attitude of support and commitment towards clinical research, always in keeping with its fundamental objective.

The IEC's main responsibilities are the following ones:

- Protecting the interests of subjects participating in clinical trials and ensuring that clinical research outcomes are foreseeably useful for the clinical trial subject groups, in terms of gender, age, disease, or any other feature.
- Issuing documentation that approves, rejects, requires changes, or suspends a clinical trial, and monitoring the trial conduct throughout its duration, with a predetermined frequency, through continued reviews.
- Evaluating and allowing the relevant changes of approved protocols, if deemed convenient.
- Establishing the substantial and formal requirements that clinical investigations must meet in order to be approved.
- Evaluating and approving (if applicable) any documentation to be given to the investigation subjects.
- If appropriate, determining the vulnerable populations included in the investigations, so as to ensure that the ethical principles of clinical research are met.
- Collaborating with investigators and institutions to allow them to meet the ethical, technical and procedural requirements laid down by the relevant regulations for conducting clinical research projects.
- Evaluating the commitments assumed with the subjects and their community.
- Assessing the investigators' competence and qualification, the investigation site's capacity to face demands, and monitoring the performance of principal investigators, sub-investigators, and all other members of the investigation team.
- Performing an investigation of the complaints received in connection with ethical irregularities and communicating them (if appropriate) to the CCE and the relevant health authorities, if the investigation outcomes make it necessary to do so.
- Maintaining a regular communication with the CCE and other Committees (if applicable), maintaining the IEC's independence and confidentiality.
- Preparing and updating standard operating procedures (SOPs) ruling its composition and functioning.
- Determining its composition and the authority under which it is established.
- Planning, notifying its members and conducting the meetings.
- Archiving any documentation pertaining to a clinical trial submitted for its consideration.
- Notifying Requesters and the competent health authority (as appropriate, pursuant to the current regulations) the disapproval of a protocol and its reasons, as well as the detection of minor deviations identified in an ethical monitoring.
- Safeguarding the confidentiality of all the documents and communications received from all the clinical study participants.
- Specifying that no deviation or change to a protocol should be made without a favorable prior authorization/opinion in writing (except in safety cases).
- Specifying that the investigator should immediately notify deviations or changes to the protocol, changes that may pose a higher risk to the investigation subjects or adversely affect the conduct of the clinical trial, unexpected serious adverse events, or information involving a risk to the safety of the investigation subjects or the clinical trial conduct.
- Notifying the investigator and/or the institution (if appropriate) in writing, the decisions/opinions relating to the clinical trial, their reasons, as well as the appeal procedures (if appropriate).
- Issuing documentation whereby a study is deemed terminated or suspended. If appropriate, notifying the relevant investigators, institutions, the CCE, and the competent health authority of the

suspension or early termination of the study and the reasons for the IEC's adopted decision.

- Permanently gathering information on the adverse events related to the protocols.
- Acting in full interest of the investigation's subjects and the communities involved, within the framework of the applicable regulations of Argentina and the international regulations.
- Receiving queries from clinical research subjects and/or their relatives and/or close relations, in order to give them advice in connection with their rights as participants or future participants, and also after their participation in a clinical study.
- Evaluate the methods for recruiting clinical research subjects to be followed-up in each site.
- Evaluating the contents of patient information sheets and informed consent form, respecting the good clinical practice guidelines and the current provisions and regulations.
- Evaluating the appropriateness of paying the research subjects for their participation in an investigation and establishing (if applicable) both the amount and the method of payment.
- Ensuring that both the amount as well as the method of payment do not affect the investigation subject's autonomy to make the decision to participate or continue participating in a clinical trial.
- Ensuring that any information relating to payments and reimbursements to the clinical research subjects (method, amount, pro ration, etc.) is correctly and clearly stipulated in the patient information sheets and written informed consent form for the investigation subjects to easily understand it.
- Verifying that the patient information sheet and informed consent form state the reimbursement of subjects for travel and meal expenses (as well as other expenses) incurred by them as a result of the investigation (if appropriate).
- Retaining all the IEC's documents (standard operating procedures, members' list, minutes book, CVs and confidentiality agreements).
- Archiving all the documents corresponding to the investigations (protocols, amendments, informed consent forms, Investigator's Brochure, etc.) for a period of ten years after the clinical study conclusion.
- Evaluating the agreements with the principal investigator, or bipartite or tripartite agreements (as appropriate)
- Evaluating the clinical study financial sources.
- Performing a continuous review of the study conduct in the investigation sites approved by the IEC, using procedures that enable to monitor the compliance with the applicable ethical requirements.
- Minutes Book: is in printed form, the members attending each meeting endorse it with their handwritten signature.
- Submitting the IEC's meeting minutes to the Director of the Rheumatology Comprehensive Center of Buenos Aires, who acknowledges them with his handwritten signature.

Scope:

The IEC evaluates clinical study protocols with medicines (in all of their investigational phases), nutritional supplements; protocols with therapeutic, preventive and/or diagnostic purposes; Pharmacovigilance studies; observational studies and clinical pharmacokinetics studies, bioequivalence studies, medical devices, biological products, advanced therapies; based on the methodology and procedures concerning the clinical trial itself or the epidemiological studies to be conducted in the Rheumatology Comprehensive Center of Buenos Aires as well as in other investigation sites which subrogate to this IEC.

The above responsibilities do not limit those which may in general be incorporated in the immediate future nor those which particularly apply to safeguarding the rights and safety of the subjects participating in investigations under the IEC's monitoring.

4. Functions

The IEC periodically meets according to a schedule published in https://fefym.org.ar/ Committee-Meetings Calendar (https://fefym.org.ar/sesiones/)

The IEC's membership composition must meet the diversity requirements stipulated by the current regulations in Argentina.

The IEC may receive spontaneous additional information from the investigator(s) participating in a clinical study submitted for its consideration, in connection with any aspect of the study, or at the IEC's request, forbidding the informants to participate in its deliberations or in the voting/opinion of the IEC's members in the meeting.

The IEC may seek the support of subject-matter experts, who should respect the confidentiality principle. Ad-hoc consultation may also be held with professionals of specific areas of application concerning certain topics, at the discretion of the Chairperson, Vice-Chairperson or the IEC's members, subject to the IEC's confidentiality and conflict of interest policies. Such experts may not vote or give their opinion during the IEC's meetings.

The IEC may make recommendations on the protocol with the aim of enhancing the study quality and avoiding difficulties that might compromise or hinder the normal study execution and/or the analysis of its results, since outcomes of lower validity/quality infringe participant's rights, as they would be exposed to an unnecessary risk.

Only the IEC's authorized members who participate in the review and discussion may vote/give their opinion and/or advice.

Each document issued by the IEC shall be digitally signed by the Chairperson or Vice-Chairperson, as appropriate.

The IEC's members have access to the documentation they evaluate in the meetings, through the IEC's S.E.R.S. (Electronic Registry and Follow Up System) system, with sufficient time in advance.

The IEC conducts audits as described in section 15: 'Ethical Monitoring'.

In dated and numbered minutes, the following data are recorded: participating members, the evaluated documentation and its results, the daily minutes, the ethical audits performed (if appropriate), as well as any information discussed in the meeting. The information transcribed in the S.E.R.S. system forms part of the corresponding minutes.

5. Composition, Responsibilities, Selection and Renewal Mechanisms

5.1 Composition

The IEC is made up of the following sectors:

5.1.1 IEC's Members
5.1.2 Ethical Monitoring sector
5.1.3 Methodological Evaluation sector
5.1.4 Protocol Follow-Up sector
5.1.5 Legal Affairs sector
5.1.6 Pharmacovigilance sector
5.1.7 Administrative sector
5.1.8 IT

5.1.1 IEC's members

The IEC is comprised of 11 members (9 Permanent Members, including the Chairperson/Vice-Chairperson and 2 Substitute Members) all of whom have the ability and experience to review and evaluate the scientific, medical, legal and ethical aspects of the studies submitted for evaluation, without bias and influences that may affect their independence.

The IEC's composition is multidisciplinary and multifunctional. Its members are of different gender, creed and age, and at least one of them belongs to a non-scientific area, and at least three are external members who do not have any link with the institution, so that, together, they may represent the interests of the assisted community.

The IEC's composition is published in https://fefym.org.ar/ (Committee – Members' List https://fefym.org.ar/miembros/) and is systematically attached to the documentation issued in the meetings.

The IEC's composition is in accordance with the good clinical practice requirements and Law 3301 on the Protection of Rights of Subjects Participating in Health-related Research, of the Government of the Autonomous City of Buenos Aires, and its Regulatory Decree 58/2011. In this respect, it should be stressed that the IEC's composition is independent, multidisciplinary and made up of at least thirty percent of persons of the same gender. As a whole, the IEC's composition ensures its members' knowledge of, and experience with the methodological, ethical and legal aspects of the investigation, with pharmacology, and with clinical practice. Among its members, there is at least a specialist in research methodology, a lawyer, and a community member not linked to healthcare professions, and at least a Physician-scientist.

The IEC has substitute members with the same education and independent character as its permanent members, to fulfill the Committee's activities, as detailed in section 5.2.5.

Sections 5.1.2 to 5.1.8

The ethical monitoring, methodological evaluation, protocol follow up, legal affairs, Pharmacovigilance, IT, and administrative sectors, report to the IEC's members through the IEC's Chairperson / Vice-Chairperson, to discuss/take note (as appropriate) of the meeting's documentation.

5.2 Responsibilities

5.2.1 Of the Chairperson

The member selected as Chairperson should have experience in evaluating investigations, be competent, and qualified to treat and assess all of their aspects and fulfill the assigned and assumed responsibilities both appropriately and with dedication.

Responsibilities:

a) Comply with and enforce the IEC's standard operating procedures and the national and international ethical and regulatory standards which govern clinical research.
b) Establish the appointment of permanent and substitute members.
c) Arrange for the summoning of the IEC's members to the meetings, in accordance with a previously established schedule, published on https://fefym.org.ar/ (Committee – Meetings Calendar: https://fefym.org.ar/sesiones/).
d) Invite external advisers to participate in the meetings themselves, or in response to any of the IEC's members' proposal, as necessary.
e) Chair the meetings.
f) Lead the deliberations and endorse the resolutions, requests, or the adopted recommendations.
g) Represent the IEC before the different public and private institutions that the Committee should relate to.
h) Represent the IEC in acts related to its activity.
i) Declare the conflicts of interest that may arise.
j) Participate in ongoing educational activities pertaining to ethics in clinical research.
k) Respect the confidentiality of documents and IEC's discussions.
l) Declare the conflicts of interest that may arise.

5.2.2 Of the Vice-Chairperson

Substitute the Chairperson as necessary, in the Chairperson's absence, or by the Chairperson's delegation, fulfilling the same duties detailed in section 5.2.1.

5.2.3 Of the Permanent Members

a) Participate in the IEC's meetings.
b) Fulfill their assigned and assumed responsibilities both appropriately and with dedication.
c) Review, discuss, and consider the research proposals submitted for evaluation.
d) Respect the confidentiality of the documents and IEC's discussions.
e) Declare the conflicts of interest that may arise.
f) Participate in ongoing educational activities pertaining to ethics in clinical research.
g) Comply with the IEC's standard operating procedures as well as with the national and international ethical and regulatory standards ruling clinical research.

5.2.4 Of the Substitute Members

Same responsibilities as the Permanent Members, detailed in section 5.2.3. Such responsibilities become effective upon the replacement and last through the period the replacement lasts.

5.2.5 Of the different IEC's sectors:

a) Fulfill the assigned and assumed responsibilities both appropriately and with dedication.
b) Respect the confidentiality of documents and IEC's discussions.
c) Declare the conflicts of interest that may arise.
d) Comply with the IEC's standard operating procedures and the national and international ethical and regulatory standards ruling clinical research.

5.3 Members' Selection, Term of Office, and Renewal Mechanisms

5.3.1 The Chairperson's position and functions last for 3 (three) years and are assigned through direct vote and simple majority, with the subsequent approval of the Administrative Council of 'Fundación de Estudios Farmacológicos y de Medicamentos "Prof. Luis M. Zieher'" and the Director of the Rheumatology Comprehensive Center of Buenos Aires.

5.3.2 The Vice-Chairperson's position and functions last for 3 (three) years and are assigned through direct vote and simple majority, with the subsequent approval of the Administrative Council of "Fundación de Estudios Farmacológicos y de Medicamentos "Prof. Luis M. Zieher"" and the Director of the Rheumatology Comprehensive Center of Buenos Aires.

5.3.3 The positions and functions of the **permanent members** last for 3 (three) years, and the proportionality of those members is maintained throughout that period. The appointment of Members and their removal is performed at the Chairperson's / Vice-President discretion, in accordance with the simple majority vote of the Committee's members and the subsequent approval of the Administrative Council of "Fundación de Estudios Farmacológicos y de Medicamentos "Prof. Luis M. Zieher"" and the Director of the Rheumatology Comprehensive Center of Buenos Aires.

For the process of selection of the IEC's members, the IEC considers the candidates' experience in ethics in clinical research, in research methodology, particularly in the pharmacology field, in ethical research, as well as in the conduct of clinical studies. In the case of community's members, the relevant level of competence shall be required.

The prolonged permanence of the IEC's members is closely related to their experience in the field of ethics in clinical research, as well as in the evaluation of clinical research protocols during their permanence in the Committee. The IEC considers the permanence of its permanent/substitute members important and, therefore, promotes it, just as it promotes the permanence of the Chairperson and Vice-Chairperson as such.

5.3.4 The position and functions of the substitute members last for 3 (three) years, and follow the same procedures established for the permanent members.

5.3.5 The appointment conditions of the IEC's members follow the guidelines established by the Operational Guidelines for Ethics Committees that Review Biomedical Research, WHO, (TDR/PRD 2000 and updates) and Law 3301 on the Protection of Rights of Subjects Participating in Health-related Research, of the Government of the Autonomous City of Buenos Aires, and its Regulatory Decree 58/2011, for which members are renewed in thirds, maintaining their proportionality, as per article 16.1 of Law 3301, with the possibility of being re-elected.

5.4 Attendance Requirement

Permanent members have the obligation to attend (if possible) no less than 60% of the scheduled meetings of each calendar year.

5.5 Mechanism for Removing IEC's Members

Each IEC's member, who, for justified reasons, makes the decision to resign the Committee as member, should communicate it in writing to the Chairperson / Vice-Chairperson (as appropriate), and the latter should communicate it in writing to the Director of the Rheumatology Comprehensive Center of Buenos Aires and to FEFyM's Administrative Council, except in the event of force majeure, at least 30 days in advance of their resignation, so as to allow the implementation of the necessary means for their replacement.

In case the removal is for a justified reason, breach of confidentiality, failure to declare a conflict of interest, resignation, or death of any of the Members, the substitute member selected by simple majority voting of the Committee's members, shall be proposed by the Chairperson / Vice-Chairperson to FEFyM's Administrative Council as well as to the Director of Buenos Aires Rheumatology Comprehensive Center, who shall make the final decision.

5.5.1 Of the Chairperson: In the case that any member of the IEC considers that the IEC's Chairperson has committed a disciplinary offence or an ethical violation, he/she should send a duly justified written request for the assessment of the IEC's Chairperson's behavior, to all the IEC's members. The IEC's members shall, within no more than 5 (five) business days, communicate the Director of the Rheumatology Comprehensive Center of Buenos Aires and FEFyM's Director whether they deem the reasons valid or not, together with a consideration of the seriousness (mild or serious) of the offence or violation. The Director of the Rheumatology Comprehensive Center of Buenos Aires, in collaboration with FEFyM's Director, shall notify the IEC's Chairperson of the accusation brought against the latter, if the accusation is deemed to be viable by simple majority. Based on the IEC's members' responses, FEFyM's Director shall consider the following actions: a) Verbal warning; b) Written warning; c) Evaluating the Chairperson's removal in a plenary meeting of all the IEC's members. The alleged offender shall have the right to know about the existence of the accusation made against him/her and shall have the opportunity to deny the claim, whether verbally or in writing, to the Director of Rheumatology Integral Center of Buenos Aires and FEFyM's Director. The time elapsed between the accusation and its acknowledgement may not be less than five (5) business days.

The Director of the Rheumatology Comprehensive Center of Buenos Aires and FEFyM's Director shall propose and agree on a meeting date within 5 (five) business days of the communication to the IEC's members.

5.5.2 Of the Vice-Chairperson: In the event that the IEC's Vice-Chairperson commits a disciplinary offence or an ethical violation, the IEC's members / Chairperson, as appropriate, should send a duly justified written request for the assessment of the IEC's Vice-Chairperson behavior, to all the IEC members. The IEC's members shall, within no more than 5 (five) business days, communicate to the Director of the Rheumatology Comprehensive Center of Buenos Aires and FEFyM's Director whether they deem the reasons valid or not, together with a consideration of the seriousness (mild or serious) of the offence or violation. The Director of the Rheumatology Comprehensive Center of Buenos Aires, in collaboration with with FEFyM's Director, shall notify the IEC's Vice-Chairperson of the accusation brought against the latter, if deemed to be viable by simple majority. Based on the IEC's members' responses, the Director of the Rheumatology Comprehensive Center of Buenos Aires and FEFyM's Director shall consider the following actions: a) Verbal warning; b) Written warning; c) Evaluating the Vice-Chairperson's removal in a plenary meeting of all the IEC's members. The IEC's Vice-Chairperson shall have the right to know about the existence of the accusation made against him/her and shall have the opportunity to present a deny the claim, whether verbally or in writing, to FEFyM's Director. The time elapsed between the accusation and its acknowledgement may not be less than five (5) business days.

The Director of the Rheumatology Comprehensive Center of Buenos Aires and FEFyM's Director shall propose and agree on a meeting date within 5 (five) business days of the communication to the IEC's members.

FEFyM's Chairperson shall propose and communicate a meeting date within 5 (five) business days of the communication to the IEC's members.

5.5.3 Of the permanent and substitute members*:* Same procedure as the one that applies to the Vice-chairperson.

5.6 Ongoing Training

Notwithstanding the external training done by each of the members, all of them should participate in no less than 80% of the periodic training meetings held in the IEC. The meetings shall be organized following a preestablished schedule, at the proposal of the IEC's Chairperson/ Vice-Chairperson.

5.7 Conflicts of Interest

As per modification of May 9th, 1996 (Minutes N° 29) and August 28th, 1997 (Minutes N° 51), the IEC has established that all its members shall refrain from considering taking part and/or chair the meetings when a clinical study involves their participation or the participation of any individual who is a close relation of them, or when, due to their professional and/or work obligations, the independence and objectivity of IEC's decisions may become affected.

Such refrainment is based on the grounds of recusal or disqualification set forth in the National

Code of Civil and Commercial Procedure, as well as on any reasonable grounds that the IEC's members participation under such circumstance might eventually affect the IEC's impartiality. It is to be clarified that this refrainment clause applies to IEC's members but does not prevent the IEC from treating the protocols to which the conflict of interest relates.

5.8 Confidentiality Agreement

All the IEC's members, whether permanent or substitute members, members from other areas and external consultants must meet the requirement of confidentiality by signing a confidentiality agreement.

5.9 Decision-making Process

To evaluate and eventually approve an investigation or any other documentation, as well as to agree upon it, the IEC's members shall meet up to assess and discuss, among other topics, the following ones:

- Methodological and ethical aspects of the investigation.
- Characteristics of the study population.
- Compliance with the ethical principles of clinical research.
- Protection of the rights and safety of potential subjects of investigation.
- Eligibility of principal investigators, their investigation teams, and the investigation sites.

5.9.1 Committee's meetings/ sessions

The meetings/sessions are held on a weekly basis, with the Chairperson / Vice-Chairperson having the authority to request extraordinary meetings/sessions or suspend a meeting/session owing to reasons of force majeure. Every six-months, a meetings schedule is generated, which is published on https://fefym.org.ar/ (Committee – Meetings Calendar https://fefym.org.ar/sesiones/).

5.9.2 Quorum and Coordination of Meetings /sessions

The quorum to start each meeting is of at least 5 members, with the highest possible gender diversity to reach a consensus, if possible, or to vote.

In the event of absence of the Chairperson/Vice-Chairperson, the IEC members present, shall appoint a Deputy Chairperson. All the members shall have access to the complete documentation of the studies through the S.E.R.S. system – Electronic Registry and Follow-Up System.

5.9.2 Functioning of Meetings / Sessions

The IEC's members take note of the meeting/session by checking the S.E.R.S., where the members of the following meeting are listed.

The meeting agenda is communicated to the members at the beginning of the meeting, by whom leads the meeting, and, afterwards, the documents submitted for evaluation are put into consideration.

The introduction of projects consists in the description of their characteristics through the analysis of a pre-designed technical report (which may be reviewed by the members prior to the meeting for its detailed analysis). Following that, the ethical evaluation of the project is performed, during which members provide their input, laying emphasis on those viewpoints that may differ in terms of in criterion.

The project is then put forward to all the members, and any clarification or concern is dealt with at this point.

Despite decision by consensus is encouraged, given the need, on certain occasions, to adopt the decision reached by simple minority after voting, the number of members must be odd. In the event that the number is even, the Chairperson or Vice-Chairperson, as appropriate, shall refrain from voting.

In the case that an expeditious evaluation and eventual approval is required, it shall be performed by the Chairperson / Vice-Chairperson *ad referendum* of the next scheduled meeting.

The documentation issued by the IEC may be: approved, notified, disapproved, or be assigned a stop-the-clock status.

A stop-the-clock status entails the IEC's need to ask for new documentation, request modifications and/or additions to the dossier for an additional evaluation.

Once the meeting is over, the corresponding meeting minutes and daily minutes are prepared. Afterwards, the attending members have access to them for their review. Then, the minutes are printed and made available to the members for them to sign and date in writing and are archived inside a fire-proof archive.

5.10 Archival

The documentation pertaining to the protocols can be found in the S.E.R.S. system.
The Minutes Books are kept in a fire-proof archive of the Rheumatology Comprehensive Center of Buenos Aires.

6. Documentation

The IEC receives protocols, amendments, expanded-access programs, post-studies, protocol approval renewal requests, administrative changes, informed consent forms and their updates, procedures for the recruitment of investigation subjects, information for the volunteers, Investigator's Brochure and its updates, available safety information, adverse event reports, information on payments or compensations available for the research subjects, requests for approval of principal investigators and investigation sites, agreements, insurance policies, regulatory authority approvals, other information documents accrediting the principal investigators' and/or the investigation sites' qualifications; affidavits, requests for discharge and/or changes of principal investigators and/or investigation sites, different administrative changes, progress and final reports, clinical study suspensions or terminations, deviation reports/notifications and other documents requiring specific treatment, as appropriate.

For each submission made on the S.E.R.S. system, the IEC shall not initiate the evaluation process until all the required documentation is submitted in full. Furthermore, it is important that upon uploading any document the system, the option "SUBMIT DOCUMENTATION' is clicked on. Only then shall the IEC consider the documentation to be SUBMITTED, and the corresponding acknowledgement of receipt shall be issued.

6.1 Electronic Registry and Follow Up System (S.E.R.S.)

The IEC has designed an electronic Registry and Follow Up System (S.E.R.S.) for protocols, to which principal investigators and Requesters (Sponsor / CRO / Investigator) may access by selecting the corresponding section of the system after accessing the following webpage: https://fefym.org.ar/ (Committee – SERS).

S.E.R.S. Requesters:

Requesters shall register in the S.E.R.S. system only once, entering the required data in the section: "Requestors' Registration'. If appropriate, a confidentiality agreement shall be signed to use the system. In the event of a Requester's change of name, this should be notified to the IEC both in time and in due form. The IEC shall then evaluate the need to sign a new confidentiality agreement. Requesters may access the S.E.R.S. to carry out all the follow-up activities pertaining to the protocols submitted for the IEC's evaluation.

S.E.R.S. Investigators:

Principal investigators should register in the S.E.R.S. system only once, entering the required data in the section: "Investigators' Registration". Failure to complete this step shall result in the principal investigator's not being granted approval for any protocol. Upon registration, the investigator should upload their CV and edit and fill out their profile. Once the registration step is completed, the investigator may enter the system with his/her DNI and password and select the protocols for which he/she has been approved as principal investigator, with the possibility of fulfilling the obligation of sending:

6.1.1 Through the S.E.R.S. Requesters system:

- ✓ Protocol, amendments, renewal requests, informed consent/assent forms, patient's documentation, safety information and any other information listed in section 6 but not in section 6.12;
- ✓ A.N.M.A.T.'s approval, if applicable.

6.1.2 S.E.R.S. Investigators system:

- ✓ Requirements for requesting the IEC's approval of principal investigators and their sites (as detailed in section 7).
- ✓ Progress reports.
- ✓ Notification of date of site initiation.
- ✓ Notification of date of first patient incorporation in the site.
- ✓ Major deviation reports which occurred at the site.
- ✓ Listings of serious adverse event reports which occurred at the site.
- ✓ Listings of non-serious adverse event which did not occur at the site.
- ✓ Pregnancy reports.
- ✓ Final Reports.

All the mentioned notifications should be forwarded in accordance with the timeframes stipulated in the current IEC's Standard Operating Procedures.

Data referring to the first and last name of investigators shall be taken from this registry in order to issue the approval documents: it is therefore essential that the investigator's full names are provided in the registration step.

6.2 General Requirements for Evaluation Requests

The documentation submitted to the IEC by means of the S.E.R.S. system should be accompanied by:

- ✓ Cover letter (if appropriate) clearly specifying the request being made (evaluation, notification, as appropriate) along with the details of the accompanying documentation. Any new version of documentation already evaluated by the IEC, which includes modifications, should be accompanied by a track of changes made with respect to the latest version evaluated by the IEC, and state the reasons for the changes, as well as who required those changes.

6.3 Documentation Processing

6.3.1 Acknowledgement of Receipt

The submission of documents to be evaluated or notified by the IEC should only be made through the S.E.R.S. system. Upon the submission, the system sends an acknowledgement of receipt to the email addresses recorded by the recipient in the registration step.

NOTE: The IEC may require additional information as a result of its analysis of the submitted documentation.

6.3.2 Documentation Control

The IEC shall proceed to evaluate and/or notify all the documentation in the 'submitted' status in the system, as long as it is properly uploaded in the corresponding section of the system.
If the documentation to be effectively submitted is in the process of submission (i.e.: the button "Submit Documentation" has not yet been clicked on), for which the acknowledgement of receipt has not been issued by the IEC, the documentation shall be removed from the system, after 15 (fifteen) business days with prior notice.
If the received documentation is incomplete or incorrect, notice shall be given to the recipient via the S.E.R.S messaging service. If after 7 (seven) business days there is no reply, the submission shall remain pending a response (it shall be assigned a stop-the-clock status), and the IEC shall not proceed to its evaluation or eventual approval until after receiving the recipient's reply.

6.3.3 Delivery of Documentation to the IEC's Members

All the documents received are made available to the IEC's members for their consultation and evaluation before and during the meeting or anytime they deem it convenient. The documentation is always available for them in the S.E.R.S. system.

6.3.4 Document Issuing

Once the documentation has been processed, the recipient shall be given notice of the evaluation process conclusion through the S.E.R.S. system and shall have available the generated digitally signed documents.
The response documents to be issued by the IEC in relation to protocols, amendments, and annual renewals, shall be issued on the meeting following their submission (i.e.: after 5 business days).

The 5-business day period may be extended at the IEC's discretion depending on the complexity of the documentation to evaluate. If so, this shall be communicated through the SERS's messaging service with sufficient time in advance. Any other response documentation shall be issued by the IEC through the S.E.R.S. system within 7 business days (as long as the documentation is complete). The 7-business day period may be extended depending on the complexity of the documentation to evaluate, in which case, the recipient shall be notified through the S.E.R.S. messaging service system.

6.4 Specific Requirements

6.4.1 Protocol

6.4.1.1 Documentation Receipt

Upon submitting a clinical trial protocol to the IEC, at least 5 business days in advance of the scheduled meeting, the following documentation should be uploaded via the S.E.R.S. Requesters system, within the section called 'New Protocol':

- ✓ Cover letter clearly specifying the request being made, along with the details of the accompanying documentation: informed consent/assent form(s), patient's documentation, Investigator's Brochure and any other documentation, as appropriate.
- ✓ Protocol in Spanish.
- ✓ Protocol in English (its submission is not compulsory although recommended); *if the

English version of the protocol is not submitted, it is recommended to enter its title in English (within the corresponding field of the system) so as to ensure the completeness of the documents issued in such language.

The following data should be entered in S.E.R.S.:

- ✓ Protocol title in Spanish and English (in accordance with the recommendation made above*).
- ✓ Protocol number
- ✓ Protocol version and date
- ✓ Requester / Sponsor
- ✓ Protocol type (observational / therapeutic / Bioequivalence)
- ✓ Investigational Phase (if appropriate)

With each new protocol submission, the following documents should be uploaded: Investigator's Brochure (in the case of a therapeutic protocol), informed consent/assent form(s) (if appropriate) and the Clinical Trial Agreement (both the last ones, preferably in generic form).

6.4.1.2 Document Processing and Issuing by the IEC

All the IEC's members attending the scheduled meeting discuss and evaluate the pre-evaluative technical and methodological report resulting from the protocol evaluation, along with the documentation put forward to the IEC. Afterwards, they proceed to discuss the ethical aspects related to the study and the informed consent/assent form and the patient documentation, as appropriate, as well as any other submitted documentation.

As a result of the above-mentioned process, the IEC issues the following documents within 24 hours of the meeting:

- ✓ Letter listing the documents reviewed and the IEC's conclusions together with the relevant methodological and ethical considerations. If other documents have been evaluated in addition to the already mentioned ones (e.g. patient's documentation, principal investigator approvals, safety information, etc.), they shall be mentioned in the letter.
- ✓ Protocol approval form (stating the attending members, as well as whether the study has been approved or not.
- ✓ Methodological Technical Report including the Annex Technical Report.
- ✓ Current List of Members: if the study is approved.

6.4.2 Amendment, Sub-Study / Post-Study Access Program

6.4.2.1 Documentation Receipt

Upon submitting a(n) Amendment / Sub-Study / Post-Study Access Program to a study already approved by the IEC, at least 5 business days in advance of the scheduled meeting, the following documents should be uploaded in the S.E.R.S. Requestors system by selecting the relevant protocol first, and then clicking on the section: 'Amendments / Sub-Study', as appropriate:

- ✓ Cover letter clearly specifying the request being made together with the details of the accompanying documentation (in order to submit the accompanying documentation, i.e., Amendment / Sub-Study, its corresponding version and date, as well as its character and whether it involves or not a new informed consent version, should be specified in the system.

6.4.2.1.1 For Amendments / Sub-Studies, the following data/documentation should be entered/uploaded in the S.E.R.S. system:

- ✓ Amendment / Sub-Study version and date
- ✓ Amendment character (Substantial / Non-substantial)
- ✓ Protocol including the Amendment(s) / Sub-Study in Spanish (if appropriate)

- ✓ Amendment(s) / Sub-Study in Spanish (if appropriate)
- ✓ Amendment(s) / Sub-Study Summary in Spanish (if appropriate)
- ✓ Amendment(s) / Sub-Study in English (optional)
- ✓ Amendment(s) / Sub-Study Summary in English (optional)

6.4.2.1.2 For Post-Study Access Programs, the following data/documentation should be entered/uploaded in the S.E.R.S. system:

- ✓ Post-Study date: if the document lacks a version / date, '00' should be entered in the version field and in the date field, the date in which the Principal Investigator has made the request.
- ✓ Letter from the Principal Investigator (signed and dated), containing the risk-benefit assessment for the relevant indication, especially in the event that the study investigational drug is intended to be administered outside the protocol. In this respect, the Principal Investigator who proposes a Post-trial access program for an investigational medicine for which no results are yet available should either justify the risk-to-benefit relationship (e.g., by providing clinical examples/ scales, etc. that demonstrate it) or provide justification for the fact that its suspension might either cause harm to the individual's health, for which its administration is the only available alternative, or deprive the participants of their basic capacities, or considerably reduce the quality of life they achieved during the study), and, if applicable, the rationale for those conclusions should further be provided, particularly in the case of double-blind studies.
- ✓ Letter stating that the Sponsor shall take on the responsibility for supplying the investigational drug (as indicated by the Principal Investigator and agreed by the Sponsor) and meet the costs resulting from adverse events and the relevant procedures / medical assistance. If the Sponsor does not assume the potential consequences associated with participant's adverse events/effects and procedures/ medical assistance, it should clarify in writing who shall bear such responsibility instead, and its acceptance shall be at the IEC's discretion (this consideration should be expressed in the informed consent form). If appropriate, the healthcare service provider's agreement to take on this responsibility should be submitted, or the Principal Investigator's Letter of Commitment (signed) specifying that as responsible for the indication he/she undertakes to furnish the necessary means for the Post-Study participant to receive, as appropriate, cover against a potential adverse effect/event.
- ✓ In the case of an investigational drug whose results have not yet been determined by any Regulatory Authority, the letter should state how the Sponsor will manage the return of unused drugs.
- ✓ Authorization by the Site's Highest Authority (responsible Medical Director) stating the acceptance of the Post-Study access program, and, as appropriate, authorizing the investigational drug administration outside the protocol in their site.
- ✓ Informed Consent Form (which should be uploaded in the corresponding area of the S.E.R.S. system, within the corresponding principal investigator's linkage to the protocol).

6.4.2.2 Documentation Processing and Issuing by the IEC

All the IEC's members attending the scheduled meeting discuss and evaluate the pre-evaluative technical and methodological report resulting from the protocol evaluation, along with the documentation put forward to the IEC for consideration.

Afterwards, the members proceed to discuss the ethical aspects related to the Amendment(s) / Sub-Study / Post-Study Access Program, and informed consent/assent form (if appropriate).

6.4.2.2.1 Substantial Amendment

As a result of the above-mentioned process, the IEC issues the following documents within 24 hours of the meeting:

- ✓ Letter listing the documents reviewed and the IEC's conclusions, together with the methodological and ethical considerations. If other documents have been evaluated in addition to the already mentioned ones (e.g., informed consent forms), such documents shall be mentioned in the letter.

- ✓ Amendment / Sub-Study Approval Form (including the attending members): if the amendment has been approved.
- ✓ Methodological Technical Report.
- ✓ Current Members' List: if the amendment has been approved.

6.4.2.2.2 Non-Substantial Amendment

As a result of the evaluation of a Non-Substantial Amendment, the IEC shall issue the corresponding acknowledgement of receipt. In the event that Requester still requires its approval with the resulting issuing of approval certificates, the Amendment shall be treated as a Substantial Amendment.

6.4.2.2.3 Post-Study Access Program

As a result of the above-mentioned process, the IEC issues the following documents within 24 hours of the meeting:

- ✓ Letter listing the documents reviewed and the IEC's conclusions, to together with the methodological and ethical considerations. If other documents have been evaluated in addition to the already mentioned ones (e.g., informed consent forms), such documents shall be mentioned in the letter.
- ✓ Methodological Technical Report (if appropriate).

6.4.3 Protocol Approval Renewal

The IEC's approval period of any protocol, whether therapeutic or observational, is extended for 12 (twelve) months from the IEC's protocol approval date.

The protocol renewal automatically extends for 1 (one) year the approval of its related Sub-Stud(ies).

The approval renewal of the approved Site is automatically extended for 1 (one) year.

6.4.3.1 Documentation Receipt

The request for renewal of a protocol approval period for clinical studies should be presented at least 5 business days in advance of the date of the scheduled meeting. The following documents should be submitted through the S.E.R.S. Requestors system:

- ✓ Cover letter clearly specifying the request being made. The approval renewal of any protocol should be requested for each active site participating in the study; in the case there is more than one active site, all of them should be listed. This request should be uploaded to the relevant protocol, within the section, "Annual Renewals".
- ✓ Updated Insurance Policy (if appropriate): it should be sent through the system by selecting the corresponding protocol first, and afterwards, uploading the Policy within the section: 'Policies'.

6.4.3.2 Documentation Processing and Issuing by the IEC

All the IEC's members who attend the scheduled meeting discuss and evaluate the background details of the protocol to be renewed.

As a result of the above-mentioned process, the IEC issues the following documents within 24 hours of the meeting:

- ✓ Letter stating the renewal of the relevant protocol approval.
- ✓ Annual Approval Renewal Form (including the attending members)
- ✓ Annual Renewal Note to Principal Investigator(s)

- ✓ Current members' list.
- ✓ Distance monitoring to each of the active Sites and Investigators approved.

The resulting monitoring report can be found inside the investigator's linkage to the system.

7. Investigator and Site Approval

7.1 Documentation Receipt

For the process of approval of a principal investigator and site, the IEC should perform the preliminary linking of the Principal Investigator to the protocol to be evaluated or already evaluated. To do so:

7.1.1 The following information should be sent through the S.E.R.S. Requestors system, within the section, "Investigators and Sites Approval':

- ✓ Cover letter requesting the approval of a new investigator and/or site, and specifying the principal investigator's first and last name, the site's registered name, and any other data relating to it (Province-City-Address-ZC-Telephone/Fax-Email address).

7.1.2 In the event that the protocol Agreement (preferably in generic form) has not yet been submitted, it should be submitted at this time, in accordance with the requirements detailed in section 14, as no approval shall be granted to any site or investigator if the Agreement has not been previously approved (with the exception of the approval of independent investigators, whose studies lack the existence of an Agreement).
The agreement customized for the principal investigator and signed by all the intervening parties does not need to be submitted for the investigator and site approval, but its submission is an essential condition for IEC to grant the Enrollment Permission.
In order to link the principal investigator to the relevant protocol, the proposed Investigator should be registered in the S.E.R.S. Investigators system, fill out their profile there, and upload the following documents to the SERS:

- Physician's Degree.
- Specialist's Degree/ Internship Certificate/ Postgraduate Degree in the corresponding disease area concerning the study.
- Proof of training in ICH-GCP.
- Proof of training in the current Provisions and Regulations.
- (Current) Medical License.
- Curriculum Vitae (CV).

Once the preliminary link step has been completed, the proposed principal investigator(s) should proceed to do the following in the S.E.R.S Investigators system:

- Fill out the affidavit in its current form (available in the Investigator's linkage to the protocol, by selecting the option 'Delivery of Forms– Principal Investigator's Affidavit'). Affidavits should be filled out per protocol. Once the investigator has been granted approval, if their original affidavit has suffered any change, the investigator should fill out a new one.
- Upload the following documents and any other information deemed appropriate (i.e., all the documents required by the IEC and mentioned in the protocol approval letter):

Through the Site linkage to the protocol: The principal investigator shall ensure that the following documents have been previously uploaded, or upload / modify them:

- Current site's operating license, which should be available at the site upon an ethical monitoring by the IEC, without exception.
- Copy of the valid agreement/contract between the site and an emergency system for the transfer of patients in emergency situations (if applicable), stating the parties' acceptance to it, or, lacking the mentioned agreement, proof which certifies the parties' acceptance. The agreement or proof should, without exception, be available at the site upon an ethical monitoring by the IEC.
- Copy of the valid agreement/contract between the site and a healthcare institution (if applicable), stating the parties' acceptance to it, or, lacking the mentioned agreement, proof that certifies the parties' acceptance). This agreement or proof should, without exception, be available at the site upon an ethical monitoring by the IEC, without exception.

Within the section: Investigators and Sites Approval:

- Letter from the investigation site's Director to the IEC's Chairperson, accepting the study conduct in their site.
- Letter of subrogation to the IEC.
- If the site has an IRB, its approval (if applicable); if this approval is not submitted upon requesting the IEC's approval, it may be submitted once it is obtained, uploading it to the S.E.R.S. Requestors system within the section, 'Other Documents', or to the S.E.R.S. Investigators system, within the section, 'Document Submissions-Other Documents'.
- Annex III of the government of the Autonomous City of Buenos Aires (CABA), (if applicable)
- Proof of study registration (if applicable), which should be uploaded to the S.E.R.S. Investigators system within the section 'Document Submissions-Proof of Study Registration'.

In the case that the Principal Investigator does not have the expertise in the pathology in study, and, owing to his/her experience he/she has been proposed as principal investigator/, he/she shall be granted approval (if appropriate) as long as his/her investigation team has a physician as sub-investigator who is a specialist in the pathology (this consideration should be stated in the Principal Investigator's Affidavit, and the CV should be uploaded to the section 'Documentation for Approval Request – Response to IEC Requests-.

For each approval request, each principal investigator is responsible for verifying the validity of his/her medical license (if applicable), the site's operating license (if applicable) and the agreements with emergency and hospitalization services (as appropriate).

7.2 Document Processing and Issuing by the IEC

If appropriate, the IEC shall conduct a feasibility monitoring of the Principal Investigator and his/her investigation site.

As a result of the analysis of the Investigator's and their Site's submitted information and the feasibility monitoring (if appropriate), the IEC shall issue, within 7 business days of receiving all the necessary documents for the investigator and site approval, the following documents:

- ✓ Letter stating the Principal Investigator and Site approval. In the event that informed consent form(s) and patient's documentation are submitted in customized form for the principal Investigator, its approval, if appropriate, shall be mentioned in the same letter.
- ✓ Investigator's Protocol Approval Form.
- ✓ Monitoring Plan.
- ✓ Current Members' List.

<u>NOTE:</u> To issue the relevant 'Investigator's Form', the IEC shall transcribe the Investigator's data from such Investigator's registration in the S.E.R.S. system, and the site name, from their registration too. Once performed the temporary linkage of the principal investigator to the relevant protocol, both the principal investigator and the Requester, should verify that the data pertaining to the investigation site match those of the corresponding site's operating license.

The IEC requires that the Site meets all the requirements established by the good clinical practice guidelines to comply with the Protocol specifications concerning infrastructure and material resources. The principal investigator should, therefore, ensure:

- ➢ The skill of the auxiliary staff designated by him/her.
- ➢ The staff continuous training.
- ➢ The ongoing technical and scientific training.
- ➢ The quality control of procedures.
- ➢ The availability of material and infrastructure resources necessary to conduct the protocol.
- ➢ Cover against damages and losses caused by such procedures, with special emphasis on those ones which are invasive in nature.

Any change of Investigator or Site (including a change to another site or a change of address of the same site, which requires a new operating license), shall be processed in accordance with the documentation detailed in the section: 'Investigator and Site Approval', as the change entails granting a new approval. Furthermore, the Investigator and/or Site (as appropriate) discharge should be submitted, by uploading the relevant discharge request through the Investigator's linkage to the protocol. If for a same site, the admission of participants is through a site other than the one indicated in the approval, and there is a change of the site's fantasy name (i.e., a name does not involve a change of operating license), a change of site request shall not be required, but such change should be stated in the new informed consent form.

7.3 Enrollment Permission

7.3.1 Documentation Receipt

Each investigator granted approval shall be given the enrollment permission after the following is received through the S.E.R.S. Requestors system:

- ✓ Current insurance policy (if applicable), which should be uploaded to the S.E.R.S. Requestors within the protocol section called 'Policies'.
- ✓ Clinical study agreement signed by the parties (if applicable), which should be uploaded to the S.E.R.S. Requestors system, though the investigator's linkage to the protocol. In the event that the agreement has been observed and the corresponding responses have not yet been presented, they should be submitted upon presenting the agreement signed by the parties.
- ✓ ANMAT's protocol approval (if applicable).

7.3.2 Documentation Processing and Issuing by the IEC

The principal investigator shall receive via email the enrolment permission as soon as the IEC has the current insurance policy in its possession (if applicable) and the agreement (bi- or tripartite, as appropriate), together with the corresponding budget, duly signed and approved by the IEC, ANMAT's approval (if applicable) and any other document pending for submission at the IEC's discretion.

The investigator may not obtain any informed consent (i.e., recruit research subjects) unless he/she has previously been granted the enrollment permission by the IEC.

It is to be noted that the date in which the IEC grants the enrolment permission can be found in each Investigator's linkage to the protocol, which may both be visualized on the S.E.R.S. Requestors system as well as on the S.E.R.S. Investigators system.

7.4 Recruitment Suspension

7.4.1 Documentation Receipt

If a temporary or definite suspension of subject recruitment is established for a given clinical trial or investigation site, the following documents should be submitted through the S.E.R.S. Requestor system, within the section, 'Other Documentation or Requests':

- ✓ Cover letter clearly specifying the request, the reason for the request, as well as any additional information accounting for the suspension. Where appropriate, the protocol status in each of the active sites approved by the IEC should be communicated.

7.4.2 Documentation Processing and Issuing by the IEC

The IEC automatically gets notified through the S.E.R.S. Requestors system.

The IEC proceeds to perform an overall review of the documentation sent and, if applicable, requests the sender additional information, clarifications, or any other type of information it deems necessary to continue with the follow-up of the issue in question.

7.5 Investigator and/or Site Discharge

It should be notified using the specific form available in the S.E.R.S. Requestors system, within the section: Investigator and/or Site Discharge (through the corresponding Investigator's linkage to the protocol).

7.5.1 Sites with recruited active Volunteers

7.5.1.1 Documentation Receipt:

The discharge request should be made within 5 days of its occurrence, filling out the pre-established form and uploading the corresponding letter (through the Investigator's linkage to the protocol first, and then within the section: 'Investigator and/or Site Discharge').

The procedures to be followed to ensure the continuity of treatment/follow up of active research subject inside or outside the protocol (as appropriate) should be informed. If applicable, an annex (addendum) to the informed consent form should be submitted for evaluation and eventual approval, notifying the mentioned change to the participants for them to accept or decline their continuation in the clinical study (if appropriate).

In the case of change of principal investigator, all of the documentation for the approval of the new investigator should also be submitted (Refer to the section, 'Investigator and Site Approval'). It is hereby clarified that that the new investigator and/or site may not fulfill any function unless the IEC issues a resolution for the mentioned request.

The discharge request should be accompanied by the corresponding final report of the investigator and uploaded to the S.E.R.S. Investigators system.

7.5.1.2 Documentation Processing and Issuing by the IEC

The IEC automatically gets notified through the S.E.R.S. Requestor system.

The IEC proceeds to perform an overall review of the documentation sent and, if applicable, requests the sender additional information, clarifications, or any other type of information it deems necessary to continue with the follow-up of the issue in question. Refer to the sections, 'Investigator and Site Approval' and to the section, 'Informed Consent', if necessary.

7.5.2 Sites with No Active or Recruited Volunteers

7.5.2.1 Documentation Receipt:

The discharge request should be made within 5 days of its occurrence, by filling out the pre-established form and uploading the corresponding letter (through the Investigator's linkage to the protocol, first, and then, within the section: 'Investigator and/or Site Discharge').

The discharge request should preferably be accompanied by the corresponding final report of the investigator, which should be uploaded to the S.E.R.S. Investigators system, filling all the fields with '000').

7.5.2.2 Documentation Processing and Issuing by the IEC

The IEC gets automatically notified through the S.E.R.S. Requestors system.

The IEC proceeds to perform an overall review of the documentation sent and, if applicable, request the sender additional information, clarifications, or any other type of information it deems necessary to continue with the follow-up of the issue in question.

7.5.3 Change of Subrogation to Another Institutional Review Board

7.5.3.1 Documentation Receipt:

The discharge request should be made within 5 days of its occurrence, by filling out the pre-established form and uploading the corresponding letter (through the Investigator's linkage to the protocol first, and then within the section: 'Investigator and/or Site Discharge').

The formal discharge request submitted via the S.E.R.S. system should specify that an annex to the informed consent form shall be drawn up to communicate the participant subjects about the IEC's discharge and inform the data of the new Ethics Committee which will take on the study monitoring in which the subjects are participating. No new informed consent version/annex including the data of the new Committee will have to be submitted to the IEC as such document shall be subject to the evaluation and eventual approval of the new intervening Research Ethics Committee.

By issuing the corresponding acknowledgement of receipt, the IEC certifies the validation expiry of all the documents approved by it, which are intended for the patient (e.g., informed consent forms, their addendums, and any other document containing the IEC's data), as well as the protocol follow up in the investigation site.

Each principal investigator to be discharged shall follow one of the following procedures, as appropriate:

- If the site has initiated or not, but no subject has been recruited, or if it does not have any patient participating in the study, only the final report should be sent, clarifying in the Observations field that the ethical follow up shall be taken on by another Ethics Committee, filling in the fields with '000'.
- If the site has participating subjects: the corresponding final report should be sent through the S.E.R.S. system, clarifying in the Observations field that the study ethical monitoring shall be subrogated to another ethics committee.

Given the immediacy required by this communication, in this second case, the IEC suggests that the patient should be informed by telephone in order to avoid a non-scheduled visit to the site by them with the sole purpose of receiving this information, and that the signing of the previously mentioned informed consent form/annex is carried out in the patient's first scheduled visit. Both procedures should be duly documented on the patient's Medical Record.

7.5.3.2 Documentation Processing and Issuing by the IEC:

As acknowledgement of receipt, the Requester shall receive the IEC's automatic confirmation it

usually sends upon each receipt of documentation.

The IEC shall proceed to perform an overall review of the submitted documentation, and, if appropriate, it shall require the sender to provide additional information, clarifications and any other type of information it deems necessary.

7.6 Administrative Change in a Site

7.6.1 Documentation Receipt:

The administrative change request should be made within the following 5 days of its occurrence, uploading the corresponding letter in the Informed Consent section together with the informed consent/assent form including the change.

Administrative changes may include, among other changes, the following ones:

Change in the site's telephone number or in the contact number of the principal investigator, change of admission site other than the one indicated in the approval request (as referred to in section 7.2), change of the site's fantasy name (as referred to in section 7.2). In any case, the communication to the IEC should be made within 5 days of the administrative change occurrence, attaching the corresponding letter in the informed consent section of the S.E.R.S. system, together with the informed consent/assent/addendum form (as appropriate) including the changes (the track of changes should always be attached). The administrative change must be informed to the participating subjects. Given the immediacy required by this communication, the IEC suggests that the patient should be informed by telephone to avoid a non-scheduled visit to the site by them for the sole purpose of receiving this information, and that the informed consent process involving the modified data is carried out on the patient's first scheduled meeting. This procedure must be duly recorded in the patient's Medical Record.

Change involving a modification to the hospitalization agreement or the agreement between the site and an emergency service. In any case, the communication to the IEC should be made within 5 days of the administrative change occurrence, uploading the corresponding letter to the informed consent section of the S.E.R.S. system, together with the informed consent/assent/addendum form (as appropriate) including the changes (the track of changes should always be attached). The administrative change must be informed to the participating subjects. Given the immediacy entailed by this communication, the IEC suggests that the patient should be informed by telephone to avoid a non-scheduled visit to the site by them for the sole purpose of receiving this information, and that the informed consent process involving the modified data is carried out on the patient's first scheduled meeting. This procedure must be duly recorded in the patient's Medical Record. In addition, the new agreements should be uploaded to the corresponding section of the S.E.R.S. Investigators system (i.e.: Site-Site's Documentation).

Change in the investigation team, which should be communicated within 5 days of its occurrence, through the S.E.R.S. Investigators system. A new Affidavit should be filled out and attached to the necessary documents through the section, 'Other Documentation' (if applicable). If the change involves a member (e.g., sub-investigator), whose contact data appear in the informed consent form, the informed consent form should be modified accordingly.

7.6.2 Documentation Processing and Issuing by the IEC:

As acknowledgement of receipt, the Requester shall receive the IEC's automatic confirmation it usually sends upon each receipt of documentation.

For requesting the evaluation and eventual approval of a new informed consent / annex (addendum) to informed consent form, refer to section 8.1, 'Informed Consent Forms'.

7.7 Temporary/Definite Investigator and/or Site Suspension or Recruitment Suspension

The IEC may determine the temporary or definite suspension of a(n) investigator/site in the following circumstances:

✓ Proceedings taken by the Central Ethics Committee of the Government of the Autonomous City of Buenos Aires, by the A.N.M.A.T or by other provincial or national entities or other International Regulatory authorities.

✓ Proceedings taken by the IEC or other Committees.

✓ Proceedings taken by the Requester (Sponsor/ CRO).

In every case, the IEC shall communicate its decision to the interested party through the S.E.R.S. system, and, eventually, to the corresponding regulatory authorities, providing:

✓ The elements considered for reaching the final decision.

✓ The possibility of presenting the defense if so desired by the interested party.

8. Documentation for the Volunteer

Documentation for the Volunteer includes:

- Informed Consent form.
- Informed consent addendum.
- Patient cards, diaries, questionnaires, scales, forms, and any other type of instruction on the management of devices, intended for the administration of the drug or for diagnostic purposes.
- Patient recruitment advertisements.
- Volunteer Retention Program.

All of the above documents should be submitted in Spanish through the S.E.R.S. Requesters system, within the corresponding section, and none of them may be implemented before obtaining the IEC's positive approval, except in the event that, in order to protect the safety of the research subjects, its immediate implementation is necessary, as stipulated by the good clinical practice guidelines. If this were the case, the relevant document should be submitted for the IEC's evaluation and eventual approval as soon as possible.

8.1 Informed Consent / Assent / Addendum

Informed consent/assent forms to be evaluated may be:

✓ Generic and/or customized, submitted with a new protocol.

✓ Generic and/or customized, submitted after the protocol has been evaluated.

✓ Customized, with the generic version having been validated by the IEC.

Changes to informed consent/assent forms may include:

✓ Modification at the IEC's request.

✓ Modification at the request of A.N.M.A.T. or other regulatory authority (as appropriate), other committees or other clinical research institution (in this case, the document that certifies the required modification should be submitted).

✓ Modification at the Requester's own request or due to protocol changes.

✓ Modification due to new safety information.

The IEC requires that:

- ✓ In the Confidentiality section of the informed consent form, its name appears in generic form.
- ✓ In the Contact section of the informed consent form, its contact data are mentioned in full: telephones, address, email; in the following way:

'If you have any questions regarding your rights as clinical research study participant, you may contact the Independent Ethics Committee for Clinical Pharmacology Trials on (the telephone): (011) 5765-4624, or via email: info@fefym.org.ar'

Below the IEC's contact data, the following text should appear:

As part of the Ethics Committees' responsibility to safeguard the rights of the volunteers participating in a clinical trial, this Committee has designed voluntary opinion surveys with the purpose of gathering information on the aspects that shape your decision to participate. If you wish to fill them out, please visit: https://fefym.org.ar/ (Community section). You will be asked to provide the Protocol number and the Principal Investigator's last name).

- ✓ Each informed consent form submitted for the IEC's evaluation should contain a version, date, and number.

8.1.1 Documentation Receipt

For requesting the evaluation and eventual approval of patient information sheets and informed consent form, the following documentation should be submitted through the S.E.R.S. Requesters system, within the section, 'Informed Consent / Assent Forms':

- ✓ Cover letter clearly specifying the request, as well as the version and date of the submitted document. If an amended version of informed consent/assent/addendum is submitted, the source of the changes should also be specified.
- ✓ Fill in the following data in the corresponding section of the S.E.R.S., as appropriate:
  - Informed Consent textual naming
  - Type of Informed Consent (e.g. Adult, Minors.)
  - Version
  - Version date
- ✓ New Generic Version (if applicable)
- ✓ New Customized Version (if applicable)
- ✓ New Generic Addendum (if applicable)
- ✓ New Customized Addendum (if applicable)
- ✓ New (Generic) Version (if applicable)
- ✓ New version with tracked changes (in Generic form); (compulsory)
- ✓ New version (in Customized form) (if applicable)
- ✓ New version with tracked changes (in Customized version); (compulsory)
- ✓ Supporting documentation of the incorporated changes (if appropriate). Those new versions generated at the request of ANMAT, other Ethics Committees or authorities, invariably require the endorsement of the incorporated change.

Generic informed consent forms should be uploaded through the corresponding Protocol, first, and then within the section, 'Informed Consent / Assent Forms'; customized informed consent forms should also be uploaded through such section, but within the investigator's linkage to the protocol first.

- ✓ All the documents should be in A4 form ((297x210 mm) in portrait orientation, in

PDF format compatible with ISO 19005-1 (PDF/A), leaving a 4cm-margin on the left of the document first page, so that the Committee's validation stamp may be inserted.

- ✓ Any change to the informed consent/assent form involves the generation of a new document version, irrespective of whom has requested such change (A.N.M.A.T., the IEC, the Sponsor, or any other clinical research institution). This requirement does not apply in the event that the only changes introduced are the customization (information on the site/investigator) of the relevant document which was in generic form.
- ✓ When requesting the approval of a new version of patient information sheets and informed consent/Assent/Addendum, a copy of the tracked changes must be uploaded to the S.E.R.S. system, which specifies the relevant addition, deletion, and any other changes made to any part of the document to be evaluated.

8.1.2 Documentation Processing and Issuing by the IEC

Once the evaluation process is completed, and as long as the informed consent has been granted approval, the IEC will issue the following documents:

- ✓ Letter specifying the Committee's resolution
- ✓ Patient information sheets and informed consent form, validated and dated

Validated Informed Consent/Assent/Addendum means its endorsement by the Independent Ethics Committee for Clinical Pharmacology Trials.

It is hereby clarified that a generic Informed Consent/Assent/Addendum approved (validated) by the Independent Ethics Committee for Clinical Pharmacology Trials, may only be used in the sites approved by such Committee.

A document is considered validated when it bears the following stamp on the left margin of the document first page:

DOCUMENTO VALIDADO POR EL COMITÉ INDEPENDIENTE DE ÉTICA PARA ENSAYOS EN FARMACOLOGÍA CLÍNICA "PROF. L. M. ZIEHER" -FEFYM- EL [redacted].

'DOCUMENT VALIDATED BY THE INDEPENDENT ETHICS COMMITTEE FOR CLINICAL PHARMACOLOGY TRIALS 'PROF. L. M. ZIEHER' –FEFYM- ON _ _/ _ _/ _ _ _ _'.

The Informed Consent/Assent/Addendum for the patient, approved by the IEC, may only be implemented after having been approved by all the applicable regulatory instances.

Any modification to a validated document entails a change of version and date, as well as its evaluation and eventual approval and new validation. Any change introduced to a new version of a validated document which has not been submitted for the IEC's evaluation and eventual approval shall not be considered valid, generating liabilities for whom has implemented and used it.

NOTE: **Informed Consents/Assents/Addendums require the IEC's approval and ANMAT's authorization (as appropriate) before their implementation, unless the need exists to immediately implement them to protect the participants' safety.**

8.2 Patient Documentation

Some examples of patient documentation are: cards, diaries, questionnaires, scales, instructions, images and/or pictures of handbags, pens, volunteer retention program, and other documents and/or elements to be handed or addressed to the volunteers.

The Requestor shall:

- ✓ Allocate, if appropriate, a version number and date to any material and/or documentation for the volunteer submitted to the IEC.

8.2.1 Documentation Receipt

For requesting the evaluation and eventual approval of the relevant documentation, the following documents should be uploaded through the S.E.R.S. Requestors system, within the section: 'Patient Documentation' (in the event such documentation is customized for the principal investigator and their site, they should be uploaded through that same section, but within the investigator's linkage to the protocol first):

✓ Letter clearly specifying the documents to evaluate with a brief justification of the request. If a recruitment advertisement for the volunteer is submitted, the media used for its diffusion should be specified: where, how, when and who is going to implement it.

✓ As appropriate, fill in the following data in the following sections of the S.E.R.S.:

Patient Documentation Title

Type of Patient Documentation (e.g. Patient Card)

Version

Version Date

✓ Material and/or documentation for the volunteer including the protocol identification (if appropriate), version, date (if applicable) and any other data, as the case may be.

Any change to a Material and/or documentation handed to the volunteers involves the generation of a new version, irrespective of whom has requested such change (A.N.M.A.T., the IEC, the Sponsor, or any other clinical research institution). This requirement does not apply in the event that the only changes introduced are the customization (information on the site/investigator) of the relevant document which was in generic form. A copy of the tracked changes must always be attached to the S.E.R.S. system, which specifies the relevant addition, deletion, and any other changes made to any part of the document to be evaluated, if changes have actually been made to it.

8.2.2 Documentation Processing and Issuing by the CIE

The IEC issues the following document:

- ✓ Letter communicating its resolution, stating (if applicable) the approved document, its version and date (if appropriate). Any change introduced to a new version of an approved document which has not been submitted for the IEC's evaluation and eventual approval shall not be considered valid, generating liabilities for whom has implemented and used it.

9. Stop-the-clock Resolution for Protocols/Amendments, Requests for Responses by the IEC or ANMAT (among others)

9.1 Documentation Receipt

The letter containing the stop-the-clock resolution should be uploaded to the S.E.R.S. Requestors system, within the section: 'Stop-the-clock to protocols / amendments, by the IEC / ANMAT'.

In the case that the stop-the-clock resolution is established by ANMAT, the document that certifies it should be uploaded to the corresponding sector of the system.

It is hereby clarified that any stop-the-clock resolution established by ANMAT for informed consents / assent forms should be uploaded to the section: "Informed Consent / Assent / Addendum'.

9.2 Documentation Processing and Issuing by the IEC

All the members attending the IEC's scheduled meeting, discuss and evaluate the stop-the-clock resolution, as well as the documents put forward for consideration (if applicable), and proceed to discuss the relevant ethical aspects, if appropriate.

As a result of the above-mentioned procedure, the IEC issues the following document within 24 hours of the meeting.

- ✓ Letter specifying the IEC's resolution (if appropriate).

10. Adverse event –Pregnancy Reports

10.1 Adverse Event Classification

Adverse events may be serious or non-serious, expected or unexpected, and related or not to the study drug. Moreover, they may have occurred in sites approved by the IEC or in other sites.

10.2 Notification of Adverse Events and Pregnancies in Sites Approved by the IEC

The principal investigator is responsible for reporting Adverse Events and pregnancies which occur in their site, using the S.E.R.S. Investigators system as the ONLY means of reporting.

10.2.1 Serious Adverse Events

10.2.1.1 Documentation Receipt

The principal investigator is responsible for reporting Adverse Events and pregnancies which occur in their site, using the S.E.R.S. Investigators system as the ONLY means of reporting. The reporting should be through the system's specific section which contains the pre-established document.

- Principal investigators should communicate deaths or any life-threatening event, whether related or not to the study drug, within *7 (seven)* business days of becoming aware of them.

- Principal investigators should communicate any serious adverse event, whether related to the study drug or not (other than the events mentioned above) within *14 (fourteen)* business days of becoming aware of them.

- Initial reports should be followed by detailed reports and made within 7 (seven) or 14 (fourteen) business days after the initial report, respectively, or after the event has ended.

10.2.1.2 Documentation Processing and Issuing

The system shall automatically issue an acknowledgement of receipt of the submitted documentation.

Furthermore, the IEC may pass opinion, either on its own account or at the request of the regulatory authority or the parties involved in the investigation, after conducting a detailed assessment of the serious adverse event, as required by the event seriousness and/or incidence.

Any serious adverse event communication requiring an ad-hoc assessment by the IEC shall be notified in the upcoming meeting and shall be documented in the corresponding meeting's minutes.

The IEC shall prioritize the principal investigator's adopted criterion in terms of the level of relationship that the notified adverse event may have with the study drug.

10.2.2 Non-Serious Adverse Events

10.2.2.1 Documentation Receipt

The principal investigator should communicate non-serious adverse events to the IEC via the S.E.R.S. system in Excel form (for example) together with the minor protocol deviations upon submitting progress reports and the final report.

10.2.2.2 Documentation Processing and Issuing by the IEC

The system shall automatically issue an acknowledgement of receipt of the submitted documentation.

Furthermore, the IEC may pass opinion, either on its own account or at the request of the regulatory authority or the parties involved in the investigation, after a detailed assessment of the serious adverse event, as required by the event seriousness and/or incidence.

Any non-serious adverse event communication requiring an ad-hoc assessment by the IEC shall be notified in the upcoming meeting and documented in the corresponding meeting's minutes.

10.2.3 Pregnancy Reports

10.2.3.1 Documentation Receipt

Despite pregnancies are not technically an adverse event, all the pregnancies occurring in a clinical pharmacology trial should be followed up until their conclusion so as to establish their outcome.

The principal investigator is responsible for reporting those pregnancies which occur in their site, using the S.E.R.S. Investigators system as the ONLY means of reporting. Their reporting should be through the system's specific section which contains the pre-established document (**In-utero exposure reporting form**), within *14 (fourteen)* business days of the principal investigator's awareness of the event, and, afterwards, indicating its progression and conclusion (if applicable).

The IEC suggests that the site should contact the pregnant participant on a monthly basis at a minimum (and after obtaining the participant's consent) and to document the participant's condition until the pregnancy has concluded or is put to an end in the corresponding medical record.

If the pregnancy outcome meets the criteria to be classed as a serious adverse event (such as miscarriage, fetal death, neonatal death, or birth defect), the principal investigator should take the steps to report the SAE (section 10.2.1).

10.2.3.2 Documentation Processing and Issuing

The system shall automatically issue an acknowledgment of receipt of the submitted documentation.

Furthermore, the IEC may pass opinion, either on its own account or at the request of the regulatory authority or the parties involved in the investigation, after a detailed assessment of the serious adverse event, as required by the pregnancy incidence.

Any pregnancy communication requiring an ad-hoc assessment by the IEC shall be notified in the upcoming meeting and shall be documented in the corresponding meeting's minutes.

10.3 Reporting of SUSARs (Suspected Unexpected Serious Adverse Reactions) and Any Other Safety Information from Sites Approved by the IEC

10.3.1 Documentation Receipt

SUSARs/safety information (e.g., periodic safety update reports) relating to an investigational product should be communicated via the S.E.R.S. Requestors/Investigator (within the section: 'SUSARs and Other Safety Information', which is accessed through the 'DRUG' link).

The communication should be in the form of a single summary per investigational product and contain all the SUSARs/safety information which arouse at the site throughout the corresponding period. Its submission should be on the same dates as the dates of submission to the ANMAT, i.e., on a six-monthly basis from the ANMAT's date of authorization of the first study with the investigational drug. An exception to these timeframes is when, throughout the course of a clinical trial, the risks outweigh the benefits observed. In these cases, the IEC should be notified within a period of 10 days.

The information may be either submitted in Spanish or in English, at the Requester's/Investigator's discretion.

Each adverse event communication should be based on complete and comprehensible information.

Only in exceptional cases in which Requesters (due to their internal procedures) need to send the IEC information requiring the protocol unblinding should those reports be sent encrypted, together with the corresponding decryption key, which should be sent simultaneously (using the private messaging service of the S.E.R.S.), or uploading a letter with the information through the section 'Other Documentation'), so as not to reveal the unblinding to the investigator. In the case that the persons responsible for the data analysis and interpretation do not have a password to access the SERS, the decryption key should be sent to info@fefym.org.ar with copy to the IEC's Chairperson/ Vice-Chairperson.

10.3.2 Documentation Processing and Issuing

The system shall automatically issue an acknowledgment of receipt of the submitted documentation.

Furthermore, the IEC may pass opinion, either on its own account or at the request of the regulatory authority or the parties involved in the investigation, after a detailed assessment of document received, as required by its seriousness and/or incidence.

10.4 Data and Safety Monitoring Board Reports

10.4.1 Documentation Receipt

The clinical study Data and Safety Monitoring Board reports should be submitted via the S.E.R.S Requesters/Investigators system (within the section: 'SUSARs and Other Safety Information', which is accessed through the 'DRUG' section of the system), together with any other relevant safety information (if applicable).

10.4.2 Documentation Processing and Issuing

The system shall automatically issue an acknowledgment of receipt of the submitted documentation.

The IEC may pass opinion, either on its own account or at the request of the regulatory authority or the parties involved in the investigation, after a detailed assessment of document received, as required by its seriousness and/or incidence.

11. Investigator´s Brochure

11.1 Documentation Receipt

To upload an Investigator's Brochure, its corresponding drug should be loaded in the S.E.R.S. system (within the section: 'DRUGS'). If the DRUG has been previously uploaded, the system shall automatically notify the sender.

Once the DRUG has been entered, the IEC links it to the corresponding protocol(s).

Investigator's Brochures should always be uploaded for each submission of clinical research study involving investigational drugs. If the drug is already loaded, and after the IEC has linked it to the protocol, the sender should make sure that the latest version of the Investigator's Brochure is already on the S.E.R.S.

Each time an Investigator's Brochure needs to be submitted, it may be uploaded through the relevant drug (it is not necessary do it through the protocol), so that, in the event that the Investigator's Brochure is linked to more than one protocol, it only needs to be uploaded once.

The subsequent versions and updates of the Investigator's Brochure should be uploaded to the

S.E.R.S. system together with a summary of the changes introduced (if applicable).

11.2 Documentation Processing and Issuing

The IEC shall acknowledge receipt of the received documentation. In addition, it may state its opinion, if appropriate, after a detailed assessment of the documentation.

12. Investigator and Study Reports:

Investigators/Requesters are responsible for notifying the IEC, via the S.E.R.S. system, information on the study progress in their sites and any contingency that occurs irrespective of the protocol, through the following documents:

- ✓ 12.1 ANMAT's Protocol Approval Report (if applicable)
- ✓ 12.2 Site Initiation Report
- ✓ 12.3 First Patient Enrollment Report
- ✓ 12.4 Progress Report
- ✓ 12.5 Protocol Deviation Report
- ✓ 12.6 Final Report
- ✓ 12.7 Other Documents

12.1 ANMAT's Protocol Approval Provision

12.1.1 Documentation Receipt

The protocol date of approval by ANMAT must be communicated without exception, and the relevant Authorizing Provision (if applicable) should be uploaded through the S.E.R.S. Requestor system within the section: 'ANMAT's Approvals'.

The submission of ANMAT's protocol approval through the S.E.R.S. system is an essential condition for the IEC to grant the Enrollment Permission.

12.1.2 Documentation Processing and Issuing

The IEC shall acknowledge receipt of the submitted documentation.

12.2 Site Initiation Report

It is the investigator's obligation to communicate the IEC the effective site initiation date (i.e., the site initiation visit performed by the Requester), uploading it through the S.E.R.S. Investigators system, within the corresponding section. The site shall not be deemed to be active until such date has been communicated to the IEC.

The IEC shall acknowledge receipt of the submitted reports through a confirmation email automatically sent through the system to the first email address provided by the principal investigator in his/her profile of the S.E.R.S. Investigators system. The reports shall automatically remain loaded in the system, so that both the investigator and the Requester may have access to them (in this case, by selecting the relevant protocol, first, and then, through the corresponding investigator's linkage to the protocol).

12.3 First Patient Enrollment Report

It should be notified by the Principal Investigator through the S.E.R.S. Investigators system, in the corresponding section, **within the first five business days** of the event occurrence. This data shall be automatically recorded in the System.

Is the date in which the first subject of the investigation signs the informed consent.

NO INFORMED CONSENT MAY BE OBTAINED UNTIL AFTER THE IEC HAS GRANTED THE 'ENROLMENT PERMISSION'.

In the case of a change of Investigator, if the recruitment is still open, the new investigator should enter the date of the first enrolled patient; if the recruitment is closed, the next investigator shall enter the date of the first patient enrolled after the succession.

In the event of a change of site with no patients recruited in the previous site, the date of the first patient enrollment should be entered for the new site; otherwise, the date entered for the first site should be entered.

The IEC shall acknowledge receipt of the submitted reports through a confirmation email automatically sent through the system to the first email address provided by the principal investigator in his/her profile of the S.E.R.S. Investigators system. The reports shall automatically remain loaded in the system, so that both the investigator and the Requester may have access to them (in this case, by selecting the relevant protocol, first, and then, through the corresponding investigator's linkage to the protocol).

12.4 Progress Reports

12.4.1 Experimental Studies

The principal investigator should inform the study progress throughout the study investigation, on a six-monthly basis (or within the timeframes stipulated by the IEC for a particular protocol or population), from the date of the enrollment permission granted by the IEC, providing an accurate description of the information required in the specific document of the S.E.R.S. Investigators system.

The IEC shall acknowledge receipt of the submitted reports through a confirmation email automatically sent through the system to the first email address provided by the principal investigator in his/her profile of the S.E.R.S. Investigators system. The reports shall automatically remain loaded in the system, so that both the investigator and the Requester may have access to them (in this case, by selecting the relevant protocol, first, and then, through the corresponding investigator's linkage to the protocol).

12.4.2 Observational Studies

The principal investigator shall report the study progress on a yearly basis (or within the timeframes stipulated by the IEC for a particular protocol or population) as from the date in which the enrollment permission has been granted by the IEC, providing an accurate description of the information required in the specifically designed document of the S.E.R.S. Investigators.

The IEC shall acknowledge receipt of the submitted reports through a confirmation email automatically sent through the system to the first email address provided by the principal investigator in his/her profile of the S.E.R.S. Investigators system. The reports shall automatically remain loaded in the system, so that both the investigator and the Requester may have access to them (in this case, by selecting the relevant protocol, first, and then, through the corresponding investigator's linkage to the protocol).

12.4.3 Unscheduled Progress Reports

The principal investigator should communicate the IEC, through the S.E.R.S. Investigators messaging system, any negative and serious change in the risk-to-benefit relationship of the study medication, before the timeframe established for the mentioned six-monthly reporting (if appropriate). The principal investigator shall additionally fill out an unscheduled progress report.

The IEC shall acknowledge receipt of the submitted reports through a confirmation email automatically sent through the system to the first email address provided by the principal investigator in his/her profile of the S.E.R.S. Investigators system. The reports shall automatically remain loaded in the system, so that both the investigator and the Requester may have access to them (in this case, by selecting the relevant protocol, first, and then, through the corresponding investigator's linkage to the protocol).

Any progress report communication requiring an ad-hoc evaluation by the IEC shall be notified in the upcoming meeting and documented in the corresponding meeting minutes.

12.5 Deviation Reports

Deviation is any alteration or modification to a protocol previously approved by the IEC.

12.5.1 Major Deviation/Violation

Is the one that impacts on the subject's safety and/or alters the risk-to-benefit relationship or compromises the integrity of the study data and/or affects the voluntariness of the subject participating in the study.

The list of examples below serves as a guide but does not include all the possible cases:

- ✓ Relating to the Informed Consent (IC): The IC is not obtained by an authorized person to do so; A clinical research subject who signs an IC version not approved by the IEC; the fulfillment of a study procedure prior to the IC signing.
- ✓ Relating to inclusion/exclusion criteria: The enrollment of clinical research subjects who do not meet all the inclusion criteria and/or who meet any exclusion criteria; enrollment of clinical research subjects considered to be part of the so-called vulnerable population.
- ✓ Relating to the study medication: An error in the study medication delivery or dosing.
- ✓ Relating to concomitant medicine: use of a forbidden medication.
- ✓ Relating to the study procedures: those studies which, in the principal investigator's opinion, peril the clinical research subject's safety and are therefore not conducted.
- ✓ Relating to serious adverse event reporting: those which are reported outside the timeframe stipulated by the IEC.

MAJOR DEVIATIONS/VIOLATIONS should be reported by the Principal Investigator within fourteen business days through the S.E.R.S. Investigator system, within the specific section of the system containing the pre-designed document.

The IEC shall acknowledge receipt through a confirmation email automatically sent to the first email address provided by the principal investigator in their S.E.R.S. Investigators profile. The deviation report shall automatically remain uploaded in the system, so that both the investigator and the Requester may have access to it (in this case, by selecting the relevant protocol first and then, clicking on the corresponding investigator's linkage to the investigator).

12.5.2 Minor Deviation

Is that which does not have an impact on the subject's safety, does not alter the risk-to-benefit relationship, does not compromise the integrity of the study data and/or does not affect the subject's voluntariness to participate in the study.

The list of examples below serves as a guide but does not include all the possible cases:

- ✓ The patient's omission to take the study medicine.
- ✓ The patient's failure to return the study medicine.

MINOR DEVIATIONS should be reported every six months in the form of a chart, through the S.E.R.S. Investigators system, within the corresponding section of the system.

The IEC shall acknowledge receipt through a confirmation email to the first email address that the principal investigator has provided in their profile. The deviation report shall automatically be uploaded to the system, so that both the principal investigator and the requester may have access to it (in this case, by selecting the relevant protocol first and then, clicking on the corresponding investigator's linkage to the system).

At its discretion, the IEC may (both in the case of minor and major deviations):

- ✓ Require additional information
- ✓ Summon the investigator and/or the members of his/her team.
- ✓ Temporarily suspend the investigator from present and/or future investigations until the situation is resolved and/or the explanations given by the deviation responsible(s) are deemed satisfactory.
- ✓ Require monitoring reports from all the sponsors of those clinical studies in which the presumed responsible(s) for the deviation have been participating.
- ✓ Require the communication of eventual proceedings taken or planned to be taken by ANMAT in connection with the deviation.
- ✓ Perform a 'for-cause' monitoring/audit.

Any major or minor deviation communication requiring an ad-hoc evaluation by the IEC shall be notified in the upcoming meeting and documented in the corresponding meetings minutes.

12.6 Final Report

- ✓ Upon the end of **the last subject's participation in a site,** the principal investigator shall inform the IEC what occurred in the site, from the study initiation until the end of the last recruited patient participating in the study, with an accurate description of the information required by the IEC, in a document specifically designed of the S.E.R.S. Investigators system.

- ✓ If the site has not recruited patients after the recruitment has concluded, the Requester shall fill out the discharge form (through the Investigator's linkage to the system, within the section 'Investigator and/or Site Discharges', and, if possible, the Investigator should complete the final report (filling in the fields with '000')

- ✓ When all of the investigators who participate in a study have sent their final reports, the IEC shall proceed to close the protocol and archive its documentation

***NOTE:* Investigators shall receive in their mailbox, the IEC's receipt confirmation of the corresponding reports.**

The reports shall automatically remain loaded in the system, so that the Investigator and the Requester, as well as each of the IEC's members, may have access to them (in this case, by selecting the relevant protocol first and then, clicking on the investigator's linkage to the system).

12.7 Other Reports

In the S.E.R.S. Investigators system there is a section called, 'Other Documents', through which any documents considered necessary by the Investigator may be sent, with no need to upload them in an incorrect section of the S.E.R.S. Investigators system.

13. Protocol Termination

The Requester should notify the IEC of the protocol termination. The clinical trial final report containing the study results and overall analyses should be sent to the IEC via its S.E.R.S. Requesters system and uploaded to the section: 'Other Documents'. The IEC shall simultaneously send an acknowledgement of receipt to the Requester's email address.

In the event of an early protocol termination, the principal investigator should notify the IEC by stating, in the Observations field of the Final Report, the reasons for its termination, and if there are still patients in study, the procedures to be followed to ensure the subjects' treatment/follow-up continuity, as well as how they have been communicated such situation.

14. Clinical Trial Agreement and Insurance Policy

The principal investigator may not enroll any subject until the IEC has granted him/her the enrollment permission, which is closely related to the valid insurance policy (if applicable), to ANMAT's protocol approval (if applicable) and to the Agreement signed by the parties (together with its corresponding budget, who should also be duly signed and approved by the IEC); (if appropriate).

14.1 Clinical Trial Agreement

14.1.1. Documentation Receipt

Requestors should send, via the S.E.R.S. Requestors system, within the section: 'Agreements':

- Cover letter

As well as any of the following documents:

- New General Agreement, in Spanish
- New version of General Agreement, in Spanish
- New customized Agreement, in Spanish
- New version of customized Agreement, in Spanish
- Addendums to the frame Agreement and to those related to the Site
- Agreement signed by the Parties, in Spanish
- Addendums to the frame Agreement and to those related to the Site, signed by the Parties

14.1.2. Documentation Processing and Issuing the IEC

The Agreements between the Investigator-Site-Requestor/Investigator-Requestor are evaluated by the IEC's Legal Advisory Commission. All the IEC's members attending the scheduled meeting acknowledge the Professional Pre-qualifying Report generated by the Legal Advisory Commission and express their adherence or not to it.

Progress to the approval instances of a Clinical Trial Agreement which has been observed in the corresponding Professional Pre-qualifying Report depends exclusively on the Requestor.

As a result of the previously described process, the IEC issues a document containing the following information:

✓ Letter stating the evaluated documents and the evaluation results. If the Agreement has been submitted in conjunction with the protocol, the results shall be specified in the protocol response letter.

✓ Professional Pre-Qualifying Report digitally signed.

To allow the Agreement identification, the IEC recommends allocating it its corresponding version, using the same criteria as with Informed Consent Forms, taking into account that each version is equivalent in content and form (with the exception of each investigator-site specific data).

If the Budget does not form part of the main text of an Agreement, but is in the form of annex, the Budget may be submitted at any time, but its submission shall invariably be necessary for the IEC to grant the enrollment permission, without whom the investigator may not obtain any informed consent (i.e.: enroll subjects).

In the case of a change of Site, if the previous Agreement approved by the IEC was tripartite, a new Agreement or Addendum to the prior Agreement should be submitted, which clearly states the change of Site.

In the case of a change of Investigator, the Agreement previously approved by the parties should be submitted (which includes the new Investigator).

14.2 Insurance Policy

The insurance policy may be sent at any time, but its submission, or the submission the valid insurance certificate **shall be invariably necessary for the IEC to grant the Enrollment Permission,** without which the Principal Investigator may not obtain any informed consent (i.e.: enroll subjects in the investigation).

When the policies encompass several protocols, they should be obligatorily uploaded to the S.E.R.S. system through each of the corresponding protocols.

For each approval renewal request, the valid insurance policy or insurance certificate should be uploaded (if appropriate).

14.2.1 Documentation Receipt

The following documents should be sent through the S.E.R.S. system:

- ✓ Cover letter

And any of the following documents:

- ✓ Generic Policy
- ✓ Customized Policy
- ✓ Generic or customized Policy update.

14.2.2 Documentation Processing or Issuing by the IEC

The IEC shall acknowledge receipt of the relevant documentation.

15. Ethical Monitoring by the IEC

The IEC shall conduct an ethical monitoring, with the following objectives:

Main Objective: To safeguard the rights and well-being of humans participating in a clinical trial. The main objective is to contribute to the quality and consistency of the ethical review of the investigation, to ensure that research subjects receive an optimal level of care, by safeguarding their rights, safety and well-being, in particular, those considered vulnerable. All of this is based on the ethical basic principles: Non-maleficence, Beneficence, Autonomy and Justice.

Scope: the ethical monitoring applies to all the sites and investigations approved by the IEC, who participate in studies which have been granted the favorable approval by the IEC.

Monitoring Plan: With each investigator/site approval, the IEC issues a monitoring plan.

The ethical monitoring to be conducted involves the following modes:

On-site Mode:

Not-for-cause Audit: The selection of sites to monitor follows the IEC's internal operating procedures to be performed after Investigator reports the date of the first patient enrolled to the IEC. The audit date is communicated to the Principal Investigator with sufficient time in advance to enable the investigation team the necessary preparation and collaboration with the activity. The Requester shall be notified by the Investigators. Requesters may not participate in the audits.

***For-cause Audit*:** The IEC shall conduct for-cause audits of certain sites, in those cases which call for it, and at its discretion. Each for-cause audit is communicated to the Principal Investigator and the Requester, as well as to the CCE, and to other Central Committees and the A.N.M.A.T. (as appropriate), together with the reasons for the audit. The Principal Investigator should necessarily be present, and representatives of the mentioned institutions and the of the Requestors may also be present.

At the Requester's Request: Audits are requested by Requesters for the sites approved by the IEC. The audit is communicated to the Principal Investigator with sufficient time in advance to enable the Principal Investigator's proper preparation and active participation with their investigation. The Requester is informed the proposed date.

As per Resolution 1480/2011, the IEC has the authority to monitor the conduct of any investigation, including the informed consent obtaining procedure, if it deems so appropriate and necessary, and shall give notice to the investigator. It is the IEC's essential condition that the participating subject provides their consent to participate in the study.

Distance Mode:

Feasibility Audit: Upon a new Investigator and Site approval (i.e.: any Site and/or Investigator that have never been monitored by the IEC), or even when the Investigator/Site have been previously monitored, the IEC, at its discretion, may consider a feasibility audit prior to the new eventual approval.

Distance Follow-up Monitoring: Is conducted through the IEC's continuous monitoring throughout the study follow-up and the site analysis. Its report is issued with each protocol approval period renewal.

15.1 IEC's Communication of Ethical Monitoring

Notifications for the arrangement of the different types of monitoring with on-site modality are sent to the Principal Investigator through the S.E.R.S. messaging system. If no answer is obtained from the Investigator, the IEC shall contact the Requester (if appropriate).

15.2 On-site Monitoring Process

During the onsite monitoring, both the Principal Investigator and members of his/her team may be present and participate. The ethical monitoring ends with a closing meeting in which monitors provide a preliminary analysis of the findings.

15.3 Ethical Monitoring Report

15.3.1 Without Findings

In the event of an onsite monitoring, after the monitoring visit conclusion, the IEC uploads the Monitoring Report to the S.E.R.S. system, within no more than 10 business days. The Principal Investigator and Requester receive an e-mail informing them that the report is available in the S.E.R.S. system, within the principal investigator's link to the system, through the corresponding protocol.

15.3.2 With Findings

During the closing meeting, the monitoring team agree with the Principal Investigator and/or their delegate, on the corrective/preventive actions to take in relation to the findings. This consensus is included in the IEC's Audit Report.

15.3.3 Actions to be taken in the event of findings

The IEC's members acknowledge the outcomes of the monitoring visit (for which they may read out the Report, in detail, available in the S.E.R.S. system). The members have the authority to request additional actions and/or recruitment suspension/termination, as well as the discharge of the investigation site, duly justifying the decision made.

In those cases, in which, owing to the tenor of the findings, the IEC considers to suspend/to close the recruitment or an investigation site, or take any other action it deems appropriate, it shall give due notice to the Principal Investigator within 24 hours of the decision made. In addition, the IEC's decision shall be communicated to the to the Requester, to the CCE, or to other Central Committee and the ANMAT (as appropriate), together with the reasons of such decision, within 5 (five) business days.

15.3.4 Document Archival

All the documents issued by the IEC in relation to its audits remain uploaded, inside the principal investigator's linkage to the corresponding protocol in the SERS system.

16. IEC's Communication of its Decisions

16.1 To the Investigator

The IEC issues a communication via the S.E.R.S. system, informing the tenor of the audits, and that the supporting documents are uploaded in the principal investigator's linkage to each of the protocols in which the Investigator's participates.

16.2 To the Institution's Director

Decisions arising from the IEC's meetings: They are communicated through the meeting minutes / daily minutes, which is prepared at the end of each meeting.

16.3 To the Central Ethics Committee of the Government of Buenos Aires

Communication shall be sent as per Law 3301 (Law on the Protection of Rights of Subjects participating in Health-related Research) and the applicable current Resolutions, and, as appropriate, through a due communication of the decisions adopted by the IEC which are considered necessary to be communicated to the CCE. For example, the results of the assessment of complaints or ethical-related irregularities of which the IEC becomes aware.

16.4 To the ANMAT

The regular communications shall be done pursuant to the current regulations, and each time the IEC considers that an event not provided for in the current regulations needs to be informed to the national regulatory authority, this communication shall be done using the administrative channels made available by it for such purpose.

16.5 To other Committees

The IEC remains at the disposal of the Research Ethics Committee which require information on the IEC's primary objective.

16.6 To other Institutions

The IEC remains at the disposal of other institutions such as ministries, academies (as appropriate) which require information on the IEC's primary objective.

17. Special Considerations for Investigation Sites from the City of Buenos Aires

For Sites located in the Autonomous City of Buenos Aires, Investigators who subrogate the evaluation and eventual approval to this Committee and register in the Clinical Trials Registry Platform of the city of Buenos Aires (PRIISA.BA).

The following link contains instructions for Principal Investigators: https://www.buenosaires.gob.ar/sites/gcaba/files/instructivo_para_investigadores_v_1.8_agosto_19.pdf

In order to meet the current regulatory requirements to keep all the relevant documents of investigations for a period of ten years after the study conclusion and make them available to the regulatory health authorities if required by them, as well as to proceed with the digital signature implementation, this Committee shall continue issuing the documentation as described in the current standard operating procedures, apart from meeting the requirements of the Central Ethics Committee of the city of Buenos Aires relating to its PRIISA BA platform. To do so, upon the Investigator's registration in the PRIISABA platform, he/she should verify that he is registered in the SERS Investigators system, and fill out only once the following data in the SERS Investigators profile, and update them the case of expiration: - CV – Medical Degree – Specialist's Degree/Internship/Specialty Certificate – Training Certificate in ICH-GCP – Training Certificate in the current Provisions and Regulations – Valid Medical License. In addition, the Investigator should upload the following through the Investigation Site he was linked to in the S.E.R.S. system: - The Site's current Operating License – Copy of the Agreement between the investigation site and the emergency system for emergency transfers (if applicable, which should contain the parties' agreement or certification of their agreement). – Copy of the valid Agreement with a healthcare institution (if applicable) (which should state the parties' agreement or its certification) – Affidavit.

Once the principal investigator has enrolled in the PRIISA BA platform, he/she may perform all the submissions for the research protocols to the IEC, through PRIISA BA platform.

The IEC shall use the platform to communicate any observation and issue all its corresponding decisions.

It is the responsibility of the Investigators and the Sponsors to download the valid signed certificate, which is issued from the PRIISA platform, bearing the watermark with the date and time.

Once the above processes are over, the Central Ethics Committee of the Ministry of Health of the City of Buenos Aires, shall, after verifying the documentation, send the data concerning each research to the Public Registry, so that they are accessible to all the population.

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