United Nations
Interregional Crime and Justice
Research Institute

INSPECTION OF INDEPENDENT ETHICS COMMITTEES (IEC)

The Italian Experience

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DIRECTIVE 2001/20/EC of 4 April 2001

Article 15

Verification of compliance of investigational medicinal products with good clinical and manufacturing practice

1. To verify compliance with the provisions on good clinical and manufacturing practice, Member States shall appoint inspectors to inspect the sites concerned by any clinical trial conducted, particularly the trial site or sites, the manufacturing site of the investigational medicinal product, any laboratory used for analysis in the clinical trial and/or the sponsor's premises.

Why IEC inspection?

- Because the role of the IEC is crucial for CTs

According to GCP and other relevant guidelines

Commencement of a clinical trial

The sponsor may not start a clinical trial until the Ethics Committee has issued a favourable opinion ecc.

Ethics Committee's Opinion

2. The Ethics Committee shall give its opinion, before a clinical trial commences, on any issue request.

3. In preparing its opinion, the Ethics Committee shall consider, in particular:

a) the relevance of the clinical trial and the trial design;

b) whether the evaluation of the anticipated benefits and risks is satisfactory and whether the conclusion are justified;

c) the protocol;

d) the suitability of the investigator and supporting staff;

e) the investigator's brochure;

f) the quality of the facilities;

g) the adequacy and completeness of the written information to be given and the procedure to be followed for the purpose of obtaining informed consent and the justification for the research on persons incapable of giving informed consent as regards the specific restrictions laid down in the specific guidelines

h) provision for indemnity or compensation in the event of injury or death attributable to a clinical trial;

i) any insurance or indemnity to cover the liability of the investigator and sponsor;

j) the amounts and, where appropriate, the arrangements for rewarding or compensating investigators and trial subjects and the relevant aspects of any agreement between the sponsor and the site;

k) the arrangements for the recruitment of subjects.

AIMS OF IEC INSPECTION

The approach of IEC inspections has the following aims:

I.

Verify that IEC has evaluated that CT are in compliance with GCP Principles

FROM ICH-CGP PRINCIPLES
A) ETHIC GUARANTEE

2.1 Clinical trials should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with GCP and the applicable regulatory requirement(S).

2.3 The rights, safety, and well-being of trial subjects are the most important considerations and should prevail over interests of science and society.

2.9 Freely given informed consent should be obtained from every subject prior to clinical trial participation.

B) TECNICAL-SCIENTIFIC GUARANTEE

2.4 The available nonclinical and clinical information on an investigational product should be adequate to support the proposed clinical trial.

2.7 The decisions made on behalf of, subjects should always be the responsibility of a qualified physician or, when appropriate, of a qualified dentist.

2.8 Each individual involved in conducting a trial should be qualified by education, training, and experience to perform his or her respective task(s).

2.12 Investigational products should be manufactured, handled, and stored in accordance with applicable good manufacturing practice (GMP). They should be used in accordance with the approved protocol.

C) PROCEDURAL GUARANTEE

2.10 All clinical trial information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation and verification.

2.11 The confidentiality of records that could identify subjects should be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement.

2.13 Systems with procedures that assure the quality of every aspect of the trial should be implemented.

AIMS OF IEC INSPECTION

II.

a) To strengthen links, between Regulatory Authorities and IEC, they have to be created by training courses and meetings with IEC.

b) Clarify ambiguous regulatory aspects on Legislation.

c) Know how IEC are dealing with their tasks.

d) Obtain information about IEC difficulties.

e) Evaluate IEC activities and their compliance with GCP and national requirements.

f) Support IEC in their work.

DETAILS ABOUT ETHICS COMMITTEE INSPECTION

- Usually, IEC inspection is performed during the investigator site inspection, the day before the end of site inspection.
- The inspection starts with a meeting among inspectors, IEC chairman and secretary
- Lead inspector describes the aims of inspection in the framework of GCP, EU Directive and national requirement, stressing the collaboration aims between AIFA and IEC.

Interview with Ethics Committee's representatives and related documentation control

- *Inspectors ask IEC to describe following aspects and control the related documentation*:

1. GENERAL ASPECTS

a) Rules, composition and independence of IEC; conflicts of interests;

b) Issues submitted to IEC (only clinical trial or other bioethics problems) and evaluation modalities of Clinical Trial submissions

c) Frequency of IEC meetings

d) Minutes of IEC meeting (at random)

e) Evaluation modalities of supervision on ongoing clinical trials and relationship with investigators and other IECs

f) Payment of IEC members

g) Insurance of IEC members

h) Modalities of payment of investigators

i) Measures to increase awarness of investigators on the importance of Informed Consent and on appropriate ways to obtain it

j) How IEC deals with investigators who perform too many clinical trials simultaneously

k) Evaluation modalities of reporting serious and unexpected reactions

l) Academic clinical trial evaluation

m) IEC SOPs

n) Documentation archiving

o) Compliance with national database and related problems

p) Clinical trials authorisation log

q) General problems of IEC dealing with its duties

r) IEC suggestions for improvement of national normative

2. SPECIFIC CLINICAL TRIAL ASPECTS

It is considered the clinical trial inspected in the same hospital where IEC is established.

General overview on the trial:

a) how it was approved;
b) specific issues of ethic/scientific nature;
c) compliance of the protocol with the Efficacy Guidelines EMEA concerning inspected trial;
d) reliability of the site carrying out the trial and other trial ongoing in the same site.

Verification of following documentation:

a) Protocol and amendments

b) Informed consent and information for the patient

c) Investigator's Brochure and its update

d) safety documentation

e) Payments of investigators

f) Patients' insurance

g) Investigator's CV

h) Minute of IEC meeting of approval of the study and its amendments

i) Periodic investigator's report for IEC evaluation

j) Adverse reactions serious and unexpected reports

k) assessment of suitability's of the facilities and staff

CLOSING MEETING

Inspectors have to:

- summarise findings
- suggest operative strategies (if necessary)
- give right interpretation of rules misunderstood
- invite ethics committee to contact AIFA in case of future problems

Ethical Specific aspects to be evaluated where applicable

CT in Vulnerable Population such as:

- Racial minorities, economically disadvantantaged, the very sick,etc.

Has the IEC

- Protected these groups against the danger of being involved in research solely for administrative convenience,or because they are easy to manipulate ?

(Belmont Report: ethical principles and guidelines for the protection of human subjects of research)

- Has the IEC evaluated the compliance of CT to the following statements?

a) Medical research involving a disadvantaged or vulnerable population or community is only justified if the research is responsive to the health needs and priorities of this population or community and if there is a reasonable likelihood that this population or community stands to benefit from the results of the research

(Art.17 of Declaration of Helsinki (2008))

b) Vulnerable subjects should not be recruited into a trial where this was not explicity foreseen in the trial protocol or the other information provided to and approved by the ethics commitee.

c) Any special consent procedures or the other precautions required should have explicity described to the ethics commitee approved by them.

Access to post trial treatment, Placebo and Active Comparator

Has the IEC evaluated the compliance to the following statements?:

a) Research shall neither delay nor deprive trial partecipants of medically necessary preventive,diagnostic or therapeutic procedures

(Article 23 of additional protocol on biomedical research (COE)

b) In some circumstances it may be acceptable to use an alternative comparator,such as placebo or “no tratment”,whilist taking into account that “the rights,safety and wellbeing of the trials subjects are the most important considerations and shall prevail over the interests of science and society.

(EMA Refl.Paper Ema 2012)

c) Regardless of the location of the trial,all patient partecipating in these trials should be receive the same or a similar standard of care and comparable tratment options as trial partecipants within the EEA.

(EMA Refl.Paper Ema 2012)

Access to post trial treatment

Has the IEC evaluated the compliance of CT to the following statements?

- Paragraph 14 of Declaration of Helsinki requires that the research protocol describes arrangements for post-study subjects to interventions identified as beneficial in the study or access to other appropriate care or benefits.

- If a product developed is unlikely to be reasonably avaible to, or applied to benefits of, the population of a proposed host country or community after the conclusion of the research,the etichs of conducting the research in the country need to be carefully considered

Has the IEC taken every effort to ensure that:

a) The research is responsive to the health needs of the population?

a) There is resonable likelihood that any intervention or product developed,will be made reasonably avaible?

(WHO (CIOMS) and 17 of Declaration of Helsinki (2008))

IEC and Regulatory Authorities (RA) collaboration

- **Has the IEC implemented the following principles?**

a. “The IEC must have the right to monitor ongoing studies (DofH) and to report to RA any serious non compliance with ethical standards (WHO (CIOMS) Guideline 2)

b. Any IEC reviewing the trial should be able to withhold approval of the research proposal and, when there are doubts about the scientific or safety or ethical validity of the CT, should be able to suspend or prohibit the trial.