Abstract: The number of clinical studies is in exponential increase. In our country there are registered numerous phase II, III and IV studies. Increasingly more medical doctors are involved as investigators and co-investigators. Also there is an increase in the number of clinical research organizations that are monitoring the studies. The inspections and audits are the practical instruments for the detection of imposture in the clinical studies. The Sponsor and the Regulatory Committees must be certain that the studies are running is accordance with the ethic criteria and respecting the human rights.

All the organizations associated with the clinical studies (pharmaceutical companies, academic institutions) have their own standard procedures for working in this domain.

This paper is an overview of the imposture spectrum in clinical trials.

Key-Words: - misconduct, clinical trials, fraud, investigator, clinical research organization.

1. Introduction

The word “deception” covers better the discussed problems. Synonyms as fraud, imposture, cheating does not cover all the considered aspects.

The deception can be before, during or after the completion of the study. It can be done by patients, investigators and the study team, sponsor, statistics or any person that has contact with the clinical study.

The misconduct can be minor, revised or significant and can be done by any person under contract for the clinical study. It defines an inadequate behavior, the most representative example being the unethical behavior. If the misconduct is illegal or significant it becomes infraction.

2. Deception in clinical trials

The deception can have many aspects from a date alteration to an entire study being fabricated. The specialty literature presented some cases of this type.

Usually the deceptions are connected with possible conflicts in medical research, as it could be saw in the fig.2.
Some frequent examples:
- To give the patient placebo without his knowledge. In 1984 was described the case of a clinical study in which the placebo group was led to believe that they receive oxprenol for stress relieving [1];
- To give the patient the active medication, but the patient is informed that is receiving placebo. There was the case of an American study [1] in which mentally impaired patients received active medication but the study staff and the institution informed the patient’s families that they received placebo;
- Giving false information to the patient. Ross and Phil [1] told to some patients that they will receive a negligible quantity of alcohol, but in fact the received quantity was over the limit for safe driving.
- There are some minor and frequent cases of deception, sometimes accepted:
  - The wash-out procedure of the previous medication without the patient’s knowledge. In many studies the protocol states a 2-3 weeks period for the previous medication wash-out. Some investigators do not inform the patient regarding this period for fear that the patient will no longer participate in the study;
  - Placebo run-in period. It is a current practice of current protocols to provide a run-in period. This is useful for the evaluation of patient’s compliance;
  - Gradual increase of the dosage. In many clinical studies (diabetes, hypertension et cetera) a dose taper of a medicine is necessary. At a standard time interval, after a reevaluation, the initial dosage can be augmented. Also, for some medications (like beta blockers) an up-titration or down-titration period is required. The patient must be informed about the nature of these changes.

The demarcation line between acceptable and unacceptable is hard to be traced. There is the risk that once accepted some serious reception error may occur.

3. The Measurement of Compliance and Deception

Not all the aspects of the clinical trial that are conducted without the knowledge of the patient are deceptions.

For example, the monitoring of the patient’s compliance associated with the treatment.
- The tablets are often counted without informing the patient. At each medication visit the patient returns the medication received at the previous medication visit. The Investigator evaluates the patient’s compliance by counting the tablets and makes comments only if there is noncompliance; [2]
- There are some electronic devices that record the opening of the medication box;
- The measurement of the serum values of the medication.

In all these situations and in other similar ones when the compliance is evaluated, the behavior of the patient is evaluated without his knowledge.

4. Deception by Patients

There are patients that pretend to participate in full and to respect all the study requirements but in reality there are many inadvertences:
- Concealment or omission of some medical history information. Some patients hesitate to mention dermatologic, gynecologic and other medical history;
- Unwillingness to participate in full to all procedures (forced expiratory volume in 1 second);
- Incompliance to the treatment regimen (lower dosage, inadequate time for medication intake);
- Unwillingness to follow some instructions (exercise);
- Inadequate completion of the patient’s diary

5. Deception by Investigators

The investigator has the mission to discover the actions of the patient and to modify the behavior in order to be compliant with the study protocol.

The investigator can willingly or without knowledge take part in “tricks” before the beginning of the study:
- Overestimation of number of patients that can be included in the study. There is, in general, an exaggerated optimism regarding the estimation of included patients in clinical studies. The feasibility data does not concur with the real data. Usually, the summary of the protocol does not offer sufficient
information on all the procedures; it gives the impression of an easy study;
• The reassurance of the monitoring team that he will conduct all the study procedures;
• Overstating the technical abilities of the equipments. In some situations the medical equipments used in trials are not standardized, are not periodically verified or are located far from the study site;
• Too optimistic data regarding the conduct of the study; [3]
• Assures the monitoring team that he has adequate staff for the study. Usually, the principal investigators are very busy persons with an academic life, active participation at congresses, symposiums; have a high number of patients. The duties are delegated to the study staff. There are situations when the delegation of duties is not correct or only the sub-investigators have the time for the clinical trials;

After the beginning of the study:
• Delay in the beginning of the study in the study site;
• Dispensing of the medication before the laboratory values from the screening visit are available;
• Commitment of the patient in two clinical trials at the same time;
• Commitment of a patient that does not have all the inclusion criteria (violation of protocol);
• Delayed CRF completion and antedate it;
• Changes the study team but does not train the new member according to the protocol;
• Changes the laboratory without informing the Sponsor;
• Unwilling or unable to communicate with the Sponsor or the CRO;
• The investigator takes an extended leave of absence and offers all the medication to the patient;
• Does not respect the date and duration of the study visit due to overburden.

6. Measuring Misconduct

Major methods to detect the inadvertences:
• In-house control with own procedures regardless of CRO, academic institutions or are included in the contract. All the organizations associated with clinical trials have their own in-place operations; [4]
• Independent audit. The “golden rule” of an audit is that of an auditor to be independent of the auditee. Else, there can be major conflict of interest. The audit can be done as global or be focused on some specific aspect (patient selection, enrollment, treatment reaction). The legality of the audit is given by ICH GCP guidelines and Directive 2005/28/EC. The plan of the audit is sent to the auditee. After the audit follows an initial feedback and one feedback after receiving the report;
• Authorized inspection. The inspection is performed by a competent authority (in Romania by the National Drug Agency). The authorities have a yearly inspection schedule and are legalized by the 2001/20/EC directive.

7. Conclusion

Compliance with informed consent is essential to reduce the risk of false results, respect for human rights and especially the development on a correct medicine

Inform consent, as is saw in the fig nr. 4 must response to few questions like: are the ethical and legal problem solved, but also is a important way fro development good practice rules, useful for all researcher, all over the world

References: