Appendix VI: ADVERSE EVENTS AND MANAGEMENT ISSUES

Non-serious Adverse Events

- A description of several events;
- And for each of them:
    - Severity (mild, moderate, serious);
    - Frequency in case of multiple episodes;
    - Dosage of the study drug (unchanged, decreased, terminated)
    - Possible re-challenge
    - Possible corrective therapy.

The investigator's opinion on the causal relationship is added in the form of a multiple choice question which may have a highly variable number of replies:

- Often in four grades (probably, possible, unlikely, excluded);
- And up to eight: excluded, unlikely, doubtful, conditional, possible, probable, definite, unknown.

Considering the uncertainty of these replies, it is preferable not to increase the shades of meaning.

This form is part of each visit in the CRFs.

Serious Adverse Events

A standard page for collection of a serious adverse event is inserted only once in each CRF because, most commonly the occurrence of such an event results in discontinuation of the study drug and specific follow-up.

Phone Numbers

Phone numbers of persons to be contacted in case of emergency may be listed in the protocol, for example, the study monitor's office phone number (and home phone if possible).

On-call rotation

Medical Decisions

- Withdrawal from the studied treatment;
- Code-breaking;
- A request for further appropriate laboratory tests;
- Administration of corrective therapy;
- Collection of additional information aimed at determining the causal relationship with therapy in the case involved;
- Reporting the event to the competent authorities, the ethics committee, and to other investigators, depending on modalities stipulated by local regulations.

Causal Relationship

- The Bégaud et al method
  This method is based on the combination:
    - of chronological criteria
    - clinical signs or investigations suggesting the role of the suspect medication
    - The conclusions are the causal relationship
        - I_0 appears excluded;

- I_1 doubtful;
- I_2 possible;
- I_3 probable;
- I_4 very probable.

- The Karch and Lasagne method
  This method, developed in the US, but not required by the US Food and Drug Administration (FDA), is based on a decision-tree consisting of five criteria (timing, previously known event, other possible cause, outcome following discontinuation of treatment and rechallenge). This method results in six ratings: definite, probable, possible, conditional, doubtful, or excluded relationship.

Reporting by the Sponsor

- International Regulations
  According to the recommendations of the International Conference on Harmonisation, an adverse event is one that has to be reported to the competent authorities (and the ethics committee if local legislation stipulates this) if it is:
  - **Serious**, i.e. significant enough to justify within a short time period a noteworthy change in dosage, monitoring or consent. In particular, this includes death; a real life-threatening risk (and not merely a potential risk) for the subject, hospitalization induced or prolonged by the event, a major or persistent or significant disability or incapacity, a congenital anomaly or birth defect, but also all other cases considered of concern based on medical judgment, in particular, if a treatment initiated to remedy it has had the effect of preventing its worsening to one of the cases mentioned in the above. It is necessary to differentiate a "serious" case from one that is "severe";
  - **Unexpected,** i.e. whose nature or severity do not correspond to the available information, in particular in the investigator's brochure;
  - **Possibly having a causal relationship** with the studied treatment, a suspected reasons sufficient for this.

In the European Union

- All **suspected unexpected serious adverse reaction**;
- Expected cases whose **outcome may be unexpected**;
- Any **increase in the frequency** of an expected serious adverse event, which may be clinically significant;
- Cases that have occurred **after the end of the trial**.

In the USA

The time frame within which cases must be reported can be negotiated ahead of time with the FDA, possibly for grouped reporting of case. The sponsor can at his convenience use either the US "Medwatch 3500A" form, or the international CIOMS-1 form. In every report, the sponsor should review previously reported, similar cases and analyze the new case in light of the previous ones.