CRITICAL RESEARCH ETHICS ISSUES IN THE ERA OF HIV IN TANZANIA

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REPORTING ADVERSE EFFECTS IN MULTICENTER CLINICAL TRIALS

NIH supported studies

BACKGROUND

- Streamline
- Reduce regulatory issues
- Reduce burden

A report was developed after extensive review and interviews. "NIH Initiative to Reduce Regulatory Burden"

(http://grants.nih.gov/grants/policy/regulatoryburden/index.htm).

FIVE MAJOR AREAS OF FOCUS

Federal regulations (45 CFR Part 46, Subpart A), shared by 17

Departments and Agencies as the Common Rule, ***require written***

procedures and policies for ensuring reporting of "unanticipated

problems" involving risks to participants to the IRB, appropriate

institutional officials, and the Department or Agency Head. Under

different set of regulations, 21 CFR 312, the FDA requires the

sponsor to notify the FDA and participating investigators of any

adverse event associated with the use of a test article that is ***"both***

serious and unexpected."

FIVE MAJOR AREAS OF FOCUS

- Definitions
- Issues
- Investigator responsibilities
- IRB responsibilities
- Implementation

DEFINITIONS

- **Differences:-**

- The notification requirements described in the Common Rule define adverse events as *"unanticipated problems" involving risks to study participants or others.*

- Generally, the funding Institutes and Centers establish operational definitions of adverse events that apply to the particular trial.
- E.g The National Cancer Institute (NCI), for example, defines adverse drug reactions in its clinical trials involving antineoplastic agents, as: (1) previously unknown toxicities; and (2) life-threatening or fatal toxicities regardless of whether or not previously unknown.
- Toxicity criteria are generally included in the protocols.

- The FDA, in Federal regulations 21 CFR Part 312, defines adverse events as *any untoward medical occurrence that may present itself during treatment or administration with a pharmaceutical product, and which may or may not have a causal relationship with the treatment.*

- Further clarified and includes serious adverse events stemming from a drug study as any untoward medical occurrence that at any dose results in death; is life-threatening; requires inpatient

ISSUES

For multicenter clinical trials, an IRB may receive individual adverse event reports from sites other than its own.

- Format
- Frequency
- No numerators or Denominators
- Disparate sources
- Specifics and Norms
- Action taken
- Infrastructure

INVESTIGATOR RESPONSIBILITIES

- Local Policy- Adherence, Maintaining, Accurate Documentation, Follow-up of AE, For NIH-supported multicenter clinical trials, investigators do not necessarily report these events to off-site IRBs as long as the local IRB has been notified.

- DSMB report summary in lieu of individual AE reports. Communication between local IRB and DSMB is important for integrity and protecting participants safety. The DSMB monitoring function is above and beyond the oversight traditionally provided by IRBs and as such is particularly important for multicenter

(NIH Guide For Grants and Contracts, June 12, 1998)

IRB RESPONSIBILITIES

- An IRB has the authority to suspend or terminate approval of research at its site that has been associated with unexpected serious harm to participants.

- When an IRB takes such action, it is required to provide a statement of reasons for the action and to promptly report this action to the investigator, appropriate institutional officials, the Department or Agency head, Office for Protection from Research Risks (OPRR), and the FDA if an investigational new drug or device is involved.

- For studies that have a DSMB, the investigator should forward summary reports to the IRB as soon as they are received; it is within the purview of the IRB to request this information.

- IRBs could make reporting contingent on IRB approval for specific studies that are deemed

IMPLEMENTATION

- The NIH program staff will review multicenter clinical trials with the following expectations:

A. Investigators submitting a protocol for IRB review must identify the DSMB involved, if any. They must describe plans for monitoring adverse events.

B. Investigators must submit a written summary of DSMB periodic review to their IRB.

C. When a study is conducted in multiple sites, the funding Institutes and

NIAID

- Clinical research
- PI's
- IRB's
- Definition
- Contacts/links
  - Human Subjects in Research SOP
  - Human subjects resources on the NIAID Funding Web site
  - July 8, 2002, *NIH Guide* notice, Monitoring of clinical trials and studies -- NIAID policy

DEFINITIONS

Adverse Events

Unfavorable and unintended diagnosis, symptom, sign (including an abnormal laboratory finding), syndrome or disease that occurs during a study, if absent at baseline, or if present at baseline, appears to worsen.

Definitions

Serious Adverse Events

Any untoward medical occurrences that:

1. Result in death.
2. Are life threatening.
3. Require or prolong hospitalization.
4. Cause persistent or significant disability or incapacity.
5. Result in congenital anomalies or birth defects.
6. Are other conditions which investigators judge to represent significant hazards.

(NB: Important medical events that may not result in death, be life-threatening or require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.)

Definitions cont

Expected Adverse Events

- For approved and marketed drugs or devices, adverse events described in the approved package insert. For investigational new drugs or devices, adverse events described in the FDA investigator's brochure. In clinical research studies, information on expected adverse events is also in the protocol and the consent form.

Unexpected Adverse Events

- Adverse events not described in the package insert, investigator's brochure, published medical literature, protocol, or informed consent document.

Definitions cont

Intensity or Severity of Adverse Events

Assignment of a grade of adverse events or side-effects based on intensity of symptoms, degree of limitation of daily activities, or level of abnormality of objective clinical signs or laboratory parameters. Schemes for assessing and monitoring adverse events drawn from existing models or customized for a protocol must be justified by the PI and approved by the IRB.

Definitions cont

Relatedness of Adverse Event to an Intervention

- The best estimate of the PI at the time of reporting of the causal relationship between an experimental intervention and an adverse event; the degree of certainty about causality is graded as follows:

Unrelated

- Adverse event is clearly due to extraneous causes (e.g., underlying disease, environment)

Definitions cont

Unlikely (must have 2)

Does not have temporal relationship to intervention.

- 1. Could readily have been produced by the subject's clinical state.
- 2. Could have been due to environmental or other interventions.
- 3. Does not follow known pattern of response to intervention.
- 4. Does not reappear or worsen with reintroduction of intervention.

Definitions cont

Possible (must have 2)

- 1. Has a reasonable temporal relationship to intervention.
- 2. Could not readily have been produced by the subject's clinical state.
- 3. Could not readily have been due to environmental or other interventions.
- 4. Follows a known pattern of response to intervention.

- **Probable (must have 3)**
- 1. Has a reasonable temporal relationship to intervention.
- 2. Could not readily have been produced by the subject's clinical state or have been due to environmental or other interventions.
- 3. Follows a known pattern of response to intervention.
- 4. Disappears or decreases with reduction in dose or cessation of intervention.

Definitions cont

Definite (must have all 4)

- 1. Has a reasonable temporal relationship to intervention.
- 2. Could not readily have been produced by the subject's clinical state or have been due to environmental or other interventions.
- 3. Follows a known pattern of response to intervention.
- 4. Disappears or decreases with reduction in dose or cessation of intervention and recurs with re-exposure.

WHO GUIDELINES

Definitions

Adverse Event (or Adverse Experience)

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment to drugs,

An adverse event (AE) could as well be any unfavorable an unintended sign including:

- An abnormal laboratory finding,
- Symptom, or disease temporarily associated with the use of a medicinal product, whether or not considered related to the medicinal product.
- All suspected adverse medication reaction
- Injuries or accidents
- Abnormalities in physiological testing or physical examination

WHO definitions..

Adverse Drug Reaction (ADR)

All noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reaction.

- Response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease or for modification of physiological function (WHO Technical Report 498 9 1972)

- **Unexpected Adverse Events**

- **Drugs (Unexpected Adverse Drug Reaction)**
- An adverse reaction, the nature or severity of which is not consistent with applicable product information for example investigator's Brochure for an unapproved investigational medicinal product
- For example under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the investigator brochure only referred to elevated hepatic enzymes or hepatitis.

WHO definitions..

- **Serious Adverse Event (SAE) or Adverse Drug Reaction (ADR)**

During clinical investigations, adverse events may occur which, if suspected to be medicinal product- related (adverse drug reaction) might be significant enough to lead to important changes in the way the medicinal product is developed, (for example change in dose, population, needed monitoring, consent forms).

A serious adverse event (experience) or reaction is any untoward medical occurrence that at any dose:

- 1.Result in death
- 2. Is life threatening
- ✓ (The term "life threatening" in the definition of "serious" refer to an event in which the patient was at risk of death at the time of event it does not refer to an event which hypothetically might have caused death if it were more severe)
- 3. Requires inpatient hospitalization or prolongation of existing hospitalization.
- 4. Results in persistent or significant disability/ incapacity, or
- 5. Is a congenital anomaly/birth defect

EXPERIENCE FROM TANZANIA

- Trial of Multivitamins (MUCHS-Harvard Research collaboration)
- HPTN trial
- Jaundice e.g reporting in PNS
- Hepatotoxocity and NVP
- Deaths
- Verbal Autopsies
- IRB responses
- DSMB reports

Trial of multivitamins (MUCHS-Harvard Research collaboration)

During 1995 MUCHS Harvard research collaboration started implementing Trial of multivitamin supplements, o HIV progression and transmission.

All serious adverse events were reported to the IRB and the sponsor upon learning of the event.

Total number of adverse events reported to IRB.

Type of event:

Abortions 29 (29 mothers had abortions)

Stillbirths 51(51 mothers had stillbirths)

Child deaths 412

Adult deaths 349


THANK YOU