TULANE UNIVERSITY IRB MEMBER TRAINING

- SCIENTIFIC REVIEW
- CRITERIA FOR IRB APPROVAL OF RESEARCH
- VULNERABLE SUBJECTS IN RESEARCH
- POSSIBLE IRB ACTIONS
- UNANTICIPATED PROBLEMS
- ICH-GCP (FOR BIOMEDICAL MEMBERS ONLY)

* PRESENTATION GIVEN AT BIOMEDICAL IRB MEETINGS 7/8/10 AND 7/22/10 AND SOCIAL/BEHAVIORAL IRB MEETING 7/27/10

TULANE UNIVERSITY IRB MEMBER TRAINING

SCIENTIFIC REVIEW:

- EACH INITIAL SUBMISSION THAT IS SUBMITTED TO THE IRB MUST BE EVALUATED FOR SCIENTIFIC OR SCHOLARLY VALIDITY.
- THE DEPARTMENT HEAD IS TYPICALLY RESPONSIBLE FOR ELECTRONICALLY (VIA IRBNET) SIGNING OFF ON THE SCIENTIFIC REVIEW AND VALIDITY OF THE PROPOSED RESEARCH.
- NOTE: IF THE PI OF THE STUDY IS THE DEPARTMENT HEAD, THEN THE DEAN OF THE SCHOOL IS TO PROVIDE THIS REVIEW AND SIGN OFF.
- NOTE: IF THE PI OF THE STUDY IS A STUDENT, A FACULTY ADVISOR MUST BE APPOINTED AND HE/SHE MUST PROVIDE THIS REVIEW AND ELECTRONIC SIGNATURE.
- THE DEPARTMENT HEAD/DEAN/FACULTY ADVISOR IS THE DESIGNEE WHO CAN BE RELIED UPON FOR SCIENTIFIC REVIEW.
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THE CRITERIA FOR APPROVAL CAN BE FOUND IN SECTION 45 CFR 46.111 OF THE FEDERAL REGULATIONS AND ALSO IN SECTION 3.7 (CRITERIA FOR IRB APPROVAL OF RESEARCH) IN OUR HUMAN RESEARCH PROTECTION PROGRAM STANDARD OPERATING PROCEDURES. WE HAVE ALSO PROVIDED A COPY OF THE CRITERIA.

IN ORDER TO APPROVE RESEARCH, THE IRB SHALL DETERMINE THAT ALL OF THE REQUIREMENTS ARE SATISFIED.

THESE CRITERIA OR REQUIREMENTS MUST BE PRESENTED AND DISCUSSED DURING MEETINGS OF THE CONVENED IRB.

TULANE UNIVERSITY IRB MEMBER TRAINING

THE FOLLOWING ISSUES MUST BE ADDRESSED AND DOCUMENTED FOR EACH INITIAL SUBMISSION PRESENTED DURING AN IRB MEETING:

RISK
THE IRB MUST DETERMINE WHETHER THE RESEARCH PRESENTS A MINIMAL OR GREATER THAN MINIMAL RISK TO THE SUBJECTS.

SUBJECT SELECTION
IS THE SELECTION OF SUBJECTS EQUITABLE, OR ARE THERE ANY ISSUES? DISCUSS THE INCLUSION/EXCLUSION CRITERIA.
TULANE UNIVERSITY IRB MEMBER TRAINING

THE FOLLOWING ISSUES MUST BE ADDRESSED AND DOCUMENTED FOR EACH INITIAL SUBMISSION PRESENTED DURING AN IRB MEETING:

-CONSENT PROCESS
IS THE PROCESS APPROPRIATE, OR ARE THERE ANY ISSUES?

-DOCUMENTATION OF CONSENT
IS THE DOCUMENTATION OF INFORMED CONSENT CONSIDERED APPROPRIATE?

*IT MUST BE NOTED IF A WAIVER OF DOCUMENTATION IS GRANTED UNDER 45 CFR 46.116(C) OR IF A WAIVER OF INFORMED CONSENT IS GRANTED UNDER 45 CFR 46.116(D).

TULANE UNIVERSITY IRB MEMBER TRAINING

THE FOLLOWING ISSUES MUST BE ADDRESSED AND DOCUMENTED FOR EACH INITIAL SUBMISSION PRESENTED DURING AN IRB MEETING:

-DATA SAFETY MONITORING (FOR BIOMEDICAL RESEARCH ONLY)
IS A PLAN NECESSARY? IS THE PLAN DESCRIBED IN THE PROTOCOL APPROPRIATE? ARE THERE ANY ISSUES WITH THE PLAN?

-PRIVACY AND CONFIDENTIALITY
ARE PROVISIONS FOR PRIVACY AND CONFIDENTIALITY NECESSARY WITHIN THIS RESEARCH? IS THE DESCRIPTION OF THE PROVISIONS PROVIDED APPROPRIATE FOR THE RESEARCH?
TULANE UNIVERSITY IRB MEMBER TRAINING

THE FOLLOWING ISSUES MUST BE ADDRESSED AND DOCUMENTED FOR EACH INITIAL SUBMISSION PRESENTED DURING AN IRB MEETING:

-VULNERABLE POPULATIONS
-IF PREGNANT WOMEN, HUMAN FETUSES, OR NEONATES ARE INVOLVED, 45 CFR 46 SUBPART B MUST BE TAKEN INTO CONSIDERATION AND MET.
-IF PRISONERS ARE INVOLVED, 45 CFR 46 SUBPART C MUST BE TAKEN INTO CONSIDERATION AND MET.
-IF CHILDREN ARE INVOLVED, 45 CFR 46 SUBPART D MUST BE TAKEN INTO CONSIDERATION AND MET.

-THIS CAN BE DETERMINED BY COMPLETING AND DISCUSSING THE ELEMENTS ON THE REVIEWER SHEET.

-PARENTAL CONSENT (ONE PARENT VS. TWO) NEEDS TO BE ADDRESSED
-CHILDREN GIVING ASSENT MUST BE ADDRESSED

TULANE UNIVERSITY IRB MEMBER TRAINING

THE FOLLOWING ISSUES MUST BE ADDRESSED AND DOCUMENTED FOR EACH INITIAL SUBMISSION PRESENTED DURING AN IRB MEETING:

-VULNERABLE POPULATIONS
-DISCUSS ANY OTHER VULNERABLE POPULATIONS AND THE PROTECTIONS NEEDED.

-INTERNATIONAL SUBJECTS, NON-ENGLISH SPEAKING SUBJECTS, STUDENTS, ILL SUBJECTS, ELDERLY SUBJECTS, SENSITIVE SUBJECTS, ECONOMICALLY DISADVANTAGED SUBJECTS, ETC. ARE ALL CONSIDERED VULNERABLE (NOT ONLY PREGNANT WOMEN, PRISONERS, AND CHILDREN). THE PROTECTIONS AND PROVISIONS CONSIDERED SHOULD BE DISCUSSED.
TULANE UNIVERSITY IRB MEMBER TRAINING

THE FOLLOWING ISSUES MUST BE ADDRESSED AND DOCUMENTED FOR EACH INITIAL SUBMISSION PRESENTED DURING AN IRB MEETING:

- VULNERABLE POPULATIONS

- IF NO VULNERABLE POPULATIONS ARE ANTICIPATED WITHIN THE RESEARCH, THIS SHOULD BE STATED, AS WELL.

- CONSULT SECTION 6 (VULNERABLE SUBJECTS IN RESEARCH) WITHIN THE HRPP SOPs FOR ADDITIONAL AND DETAILED INFORMATION.

TULANE UNIVERSITY IRB MEMBER TRAINING

POSSIBLE IRB ACTIONS
(SECTION 3.10 IN THE HRPP SOPs)

THERE ARE 4 MAJOR COURSES OF ACTION BY THE BOARD:

- APPROVAL
  (SECTION 3.10.1)
- DEFERRAL WITH MINOR MODIFICATIONS
  (SECTION 3.10.2)
- DEFERRAL WITH MAJOR MODIFICATIONS
  (SECTION 3.10.3)
- DISAPPROVAL
  (SECTION 3.10.4)
TULANE UNIVERSITY IRB MEMBER TRAINING

POSSIBLE IRB ACTIONS:
DEFERRAL WITH MINOR MODIFICATIONS:

- A SITUATION WHERE THE IRB CANNOT APPROVE THE RESEARCH AS SUBMITTED OR WHERE THE PROPOSAL, RECRUITMENT PROCEDURES, RESEARCH TOOLS, AND/OR CONSENT FORM REQUIRE MINOR REVISIONS.

- EXAMPLES OF MODIFICATIONS THAT ARE CONSIDERED MINOR:
  - WORDING CHANGES INVOLVING SIMPLE TYPOS, OR TEMPLATE LANGUAGE CHANGES
  - MINOR REVISIONS TO MATERIALS (EXAMPLE: ADDING PI'S CONTACT INFO)
  - REVISIING CONSENT TO IMPROVE READABILITY WITHOUT CHANGING CONTENT
  - SIMPLE REVISIONS TO ADVERTISEMENTS OR STUDY MATERIALS (SURVEYS, QUESTIONNAIRES, ETC)

TULANE UNIVERSITY IRB MEMBER TRAINING

POSSIBLE IRB ACTIONS:
DEFERRAL WITH MINOR MODIFICATIONS:

- NOTE: WITHIN OUR POLICY, UNDER DEFERRAL WITH MINOR MODIFICATIONS, IT IS STATED, "NONE OF THE REQUIRED MODIFICATIONS CAN BE RELATED TO THE REGULATORY CRITERIA FOR APPROVAL."

- AGAIN, YOU HAVE BEEN PROVIDED WITH THE CRITERIA.
TULANE UNIVERSITY IRB MEMBER TRAINING

POSSIBLE IRB ACTIONS:
DEFERRAL WITH MAJOR MODIFICATIONS:

- A SITUATION WHERE THE IRB CANNOT APPROVE THE RESEARCH AS SUBMITTED
  BECAUSE (1) THE PROPOSAL, RECRUITMENT PROCEDURES, RESEARCH TOOLS,
  AND/OR CONSENT FORM REQUIRE MAJOR MODIFICATION OR CLARIFICATION
  OR (2) INSUFFICIENT INFORMATION IS PROVIDED TO ADEQUATELY JUDGE THE
  PROTOCOL APPLICATION.

- EXAMPLES OF MODIFICATIONS THAT ARE CONSIDERED MAJOR:
  - THE RISK/BENEFIT RATIO CANNOT BE ASSESSED WITH THE INFORMATION PROVIDED
  - INCONSISTENCIES EXIST AMONG THE PROTOCOL, THE CONSENT FORM, AND THE IRB
    APPLICATION
  - MAJOR FORMATTING/LANGUAGE REVISION IS NEEDED TO INFORMED CONSENT DOCUMENT
    (EXAMPLE: CONSENT FORM IS TOO LENGTHY AND TECHNICAL; NOT AT AN 8TH GRADE
    READING LEVEL)

TULANE UNIVERSITY IRB MEMBER TRAINING

POSSIBLE IRB ACTIONS:
DEFERRAL WITH MAJOR MODIFICATIONS:

A VOTE TO DEFER A RESEARCH PROJECT FOR MAJOR REVISION IS
APPROPRIATE FOR PROTOCOLS:
- MISSING INFORMATION
- WITH MUCH INCONSISTENCY
- REQUIRING MAJOR REVISION TO THE CONSENT OR ANY OTHER
  DOCUMENTS
- INVOLVING VULNERABLE POPULATIONS THAT NEED PROTECTIONS

OR, SIMPLY IF A REVIEWER HAS CONCERNS AND WOULD LIKE THE
REVISIONS TO RETURN TO THE BOARD.
UNANTICIPATED PROBLEMS

Unanticipated Problems involving risk to subjects or others, and include any incident, experience, or outcome that meets all of the following criteria:

- Unexpected
- Related, or possibly related to the research
- Poses an increased risk to subjects, or others

Unanticipated Problems (cont’d)

- Not all Adverse Events are Unanticipated Problems

- Some adverse events are not unanticipated
  - *Depressed subject attempts suicide*

- Some adverse events are not related to the research
  - *Child subject falls down and is injured while playing at school*
Unanticipated Problems (cont’d)

- Not all Unanticipated Problems are Adverse Events

- Adverse Events are determined by the risk of harm to subjects or others, and not by the actual harm
  - Coordinator’s laptop computer used for the study is stolen;
  - New risk has been included in literature.

- Not all Unanticipated Problems involve the subjects (risk to subjects, or others)
  - Researcher is injured by the research subject during a study visit;
  - Subject discloses a personal family matter during the research.

Unanticipated Problems (cont’d)

Investigator makes an initial determination as to whether an event is an unanticipated problem; however, Tulane IRB makes a final determination.

Possible actions that may be required when an event is determined to be an unanticipated problem:
- Revise informed consent process/form
- Revise protocol
- Inform current and previous research subjects
- Suspension or termination of the research
Conclusion Unanticipated Problems

It is the policy of Tulane University that Investigators follow HRPP Policy, Section 8.0 related to reporting to IRB unanticipated Problems (http://tulane.edu/asvpr/irb/index.cfm)

OHRP provides guidance on reviewing and reporting Unanticipated Problems Involving Risks to Subject or Others and Adverse Events (http://www.hhs.gov/ohrp/policy/AdvEvntGuid.htm)
WHAT IS ICH?

- The International Conference on Harmonization of Technical Requirements for the Registration of Pharmaceuticals for Human Use, commonly referred to as the International Conference on Harmonization (ICH) is an attempt to streamline the process for developing and marketing new drugs internationally.

- The ICH is comprised of representatives from the pharmaceutical industry and the regulatory bodies of the United States, Japan and the European Union. In addition, observers include Canada, the European Free Trade Area, and the World Health Organization.
ICH Purpose

- To produce a single set of technical requirements for the registration of new drug products to streamline development.

- To reduce or obviate duplicate testing during the research and development of new medicines.

- To provide more economical use of human, animal, and material resources.

- To eliminate unnecessary delay in the global development and availability of new medicines, whilst maintaining safeguards on quality, safety, efficacy, and regulatory obligations to protect public health.

Importance of ICH to Pharmaceutical Industry

- Reduces drug development time and cost.

- Simultaneous new drug submissions in participating countries.

- Facilitates intra-company globalization among multiple sites.
ICH History

- European Union began to successfully harmonize member country regulatory requirements in the 1980's.

- WHO Conference of Drug Regulatory Authorities (Paris, 1989) was start of the harmonization process between Europe, United States, and Japan.

- First meeting held in April, 1990 (Brussels) and bi-annual meetings continue between the three regions.

- ICH “Process” first drawn up at Steering Committee in March, 1992 (Washington), and amended September, 1992 (Tokyo).

ICH Categories

- **Quality** (38 guidelines) - related to chemical and pharmaceutical quality assurance (*Stability Testing, Impurity Testing*).

- **Safety** (15 guidelines) - related to pre-clinical studies (*Carcinogenicity Testing, Genotoxicity Testing*).

- **Efficacy** (20 guidelines) - related to clinical studies in human subjects (*Dose Response Studies, Good Clinical Practices*).

- **Multidisciplinary** (5 guidelines) – i.e., Medical Terminology (MedDRA) (*cross-cutting Topics not fitting into one of the other categories*).
**Efficacy Guidelines**

- E1 - Assess Drug Safety for Long-Term Treatment of Non-Life-Threatening Conditions
- E2 - Clinical Safety Data Management
- E3 - Structure and Content of Clinical Study Reports
- E4 - Dose-Response Information to Support Drug Registration
- E5 - Ethnic Factors in the Acceptability of Foreign Clinical Data
- E6 - Good Clinical Practice
- E7 - Studies in Support of Special Populations/Geriatrics
- E8 - General Consideration of Clinical Trials
- E9 - Statistical Principles for Clinical Trials
- E10 - Choice of Control Group and Related Issues in Clinical Trials
- E11 - Clinical Investigation in the Pediatric Population
- E12 - Clinical Evaluation of New Antihypertensive Drugs

**ICH GCP Guideline (E6)**

- International ethical and scientific quality standard for designing, conducting, recording, and reporting trials that involve human subjects.

- Compliance with this standard provides assurance that the rights, safety, and well-being of trial subjects are protected, and consistent with the principles of the Declaration of Helsinki, and that the clinical trial data are credible.

- E6 guidelines that primarily affect investigators in the daily practice of clinical research.

- The initial basis for drafting the E6 guidelines was the U.S. FDA regulations for the protection of human subjects (21 CFR 50 and 56).
ICH GCP E6 (Eight Sections)

Chapter 1 - Glossary
Chapter 2 - Principles of ICH GCP
Chapter 3 - Institutional Review Board
Chapter 4 - Investigator
Chapter 5 - Sponsor
Chapter 6 - Protocol and Amendments
Chapter 7 - Investigator's Brochure
Chapter 8 - Essential Documents

IRB Responsibilities (ICH 3.1)

- FDA and ICH both require the IRB to review informed consent, protocol, advertisements, and the Investigator's Brochure.

- ICH also requires IRB submission of:
  - Subject recruitment procedures
  - Written information provided to subjects
  - Information about subject compensation
  - Investigator's current CV and/or other documents evidencing qualifications
IRB Composition (ICH 3.2)

- Both FDA and ICH require IRBs to be composed of the following members:
  - At least five members
  - One non-scientific member
  - One member not affiliated with the institution
  - Members involved in the protocol do not have a voting role

- FDA also requires the following (56.107a-f):
  - One scientific member
  - Diversity in race, gender, cultural backgrounds
  - Varying backgrounds - not composed of only one profession
  - Members qualified to assess the acceptability of the protocol with institutional SOPs & professional practice standards
  - Members with a conflicting interest cannot vote for protocol approval

Investigator Agreements (ICH 4.1)

ICH requires Investigators to maintain a list of appropriately qualified persons to whom significant trial-related duties have been delegated.

Investigator Resources (ICH 4.2)

ICH requires Investigators to demonstrate potential for recruiting the required number of patients within the agreed recruitment period.

- Retrospective data
- Patient database analysis
Subject Medical Care (ICH 4.3)

- ICH requires Investigators to inform subjects when medical care is needed for an intercurrent illness.

- ICH recommends that Investigators inform the subject's primary physician of trial participation (with the subject's permission).

- ICH requires Investigators to make every reasonable effort to ascertain the reason(s) for subject early withdrawal (although the subject is not obliged to give a reason).

Protocol Compliance (ICH 4.5)
ICH requires Investigators (or his/her designees) to document and explain any deviation from the approved protocol.

Note: Tulane University HRPP Policy Section 9.0 requires investigator to report protocol deviations to the HRPO/IRB.

Investigational Product (ICH 4.6)
- ICH allows the delegation of study drug dispensing, patient counselling, and drug accountability to a designee.

- FDA has no regulations concerning delegation of these duties but published a Guidance for Industry (October 2009) on the supervisory responsibilities of investigators.
Informed Consent (ICH 4.8)

- ICH allows the delegation of the informed consent process to a designee.

- FDA has no regulations concerning delegation of this duty although it is discussed in the FDA Information Sheets. (NOTE: Provided in the May 2007 FDA draft guidance on the supervisory responsibilities of investigators)

- ICH requires the person conducting the informed consent process to sign and date the consent form.

- ICH requires that the subject receive a signed and dated copy of the consent form. FDA only requires that a copy be provided.
Informed Consent (cont’d)

- ICH requires the following informed consent elements not required by the FDA:
  - Discussion of trial treatments and probability of random assignment
  - Subject responsibilities
  - Anticipated payment, if any, to the subject
  - Important potential risks and benefits of alternative treatment
  - Authorization to access medical records by regulatory authorities (FDA and foreign)

Impartial Witness for Illiterate Subjects
ICH 4.8.9 if a subject is unable to read or if a legally acceptable representative is unable to read, an impartial witness should be present during the entire informed consent discussion.

Records and Reports (ICH 4.9)

ICH requires Investigators (or designees) to:

- Document explanations for discrepancies between data in the CRFs and the source documents
- Initial, date and explain (if necessary) all CRF changes/corrections
- CRF designees must be documented
- Endorse & retain records of all CRF changes made by the Sponsor
- ICH requires the retention of “essential documents” for at least two years after the approval of a marketing application in an ICH region, or until there are no pending or contemplated applications in an ICH region or development is formally discontinued
- ICH compliance generally requires a longer retention time than FDA regulations
**Sponsor QA & QC (ICH 5.1)**
ICH requires Sponsors to secure agreement from all involved parties to ensure direct access of study records to foreign regulatory authorities.

**Record Keeping (ICH 5.5)**
ICH requires Sponsors to inform Investigators in writing of:
- Study record retention requirements
- Notification of when records are no longer needed

**Compensation (ICH 5.8)**
ICH requires Sponsors to provide insurance or indemnify the investigator against claims arising from the trial.

**Financing (ICH 5.9)**
- FDA requires extensive disclosure of the Investigator's financial relationship with the Sponsor (21 CFR 54).
- ICH has no comparable guideline and only requires that financial aspects of the trial be documented in an agreement between the Sponsor and Investigator.
IRB Review (ICH 5.11)

ICH requires Sponsors to obtain a statement from Investigators that their local IRB is organized and operates according to GCP and the applicable laws and regulations.

The Biomedical Institutional Review Board (IRB) for Tulane University assures the following:

- The responsibilities of the Tulane University Biomedical IRB are in agreement with the ICH-GCP section 3.1 requirements.
- The composition, function, and operations of the Tulane University Biomedical IRB are in agreement with the ICH-GCP section 3.2 requirements.
- The Tulane University Biomedical IRB operates under a written standard operating procedure, documenting all committee actions in agreement with ICH-GCP section 3.3 requirements.
- The records of the Tulane University Biomedical IRB are maintained in accordance with the ICH-GCP section 3.4 requirements.

Supplying Investigational Product (ICH 5.14)

ICH requires Sponsors to obtain documentation of IRB approval prior to shipping investigational product to an Investigator.
Research Monitoring (ICH 5.18)

- FDA specifies that Sponsors shall monitor the progress of all clinical investigations (21 CFR 312.56) and that monitors be qualified by training and experience (21 CFR 312.53).

- FDA has a guidance document on the topic, "Guideline for the Monitoring Clinical Investigations" (January 1988).

- ICH includes the following items not addressed in the FDA guidance:
  - Monitor qualifications must be documented
  - Monitors must verify that trial functions have not been delegated to unauthorized individuals
  - Sponsors must document review and follow-up of the monitoring report

Protocol and IB (ICH 6 & 7)

- ICH has more detailed outline of contents of the protocol and Investigator Brochure than the FDA regulations [21 CFR 312.23(a)(5-6)]

- ICH requires that the protocol identify any data to be recorded directly on the CRFs and to be considered source data (ICH 6.4.9)
Essential Documents (ICH 8)

ICH requires the following documents not specified by the FDA:
- Subject Screening Log (documenting subjects included in the research study screening)
- Subject Identification Code List (confidential list of subject names in the event subject's identity must be revealed for follow-up)
- Signature Sheet (to document signatures and initials of persons authorized to make CRF entries and CRF corrections)

ICH requires the following documents be filed at the site:
- Trial Initiation Monitoring Report (to document that trial procedures were reviewed with the Investigator and staff)
- Relevant Trial Communications (letters, e-mails, meeting notes, telephone call notes)

Conclusion ICH

In the U.S., compliance with the ICH E6 guideline is voluntary in that it is not federal regulation.

It is the policy of Tulane University HRPP Policy, that only Investigators conducting clinical trials of drugs, and **required by their sponsor** must follow the ICH E6 guidelines.