

SDSU Bioethics Course

**Joe Tami, Pharm.D.
Therapeutics Inc.**

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Objectives

- **Discuss the design of ethical pharmaceutical studies**
 - **Randomized**
 - **Double-blind / Masked**
 - **Placebo controlled**
- **Informed Consent**
- **Pharmacogenetic Testing**

Topics for Discussion in the Design of Ethical Pharmaceutical Trials

- ◆ **Trials Performed in Third World Countries**
- ◆ **Trials with Sham Surgeries**
- ◆ **The Collaboration between Industry and Academia**
- ◆ **The Collaboration between Investigators and Wall Street**

Topics for Discussion in the Design of Ethical Pharmaceutical Trials

- ◆ **Trials Performed in Third World Countries**
- ◆ **Ethics of Placebo-Controlled Trials of Zidovudine to Prevent Perinatal Transmission of HIV in the Third World**
 - ◆ **Whether research conducted in developing countries should be held to different standards from those applied in developed countries**
 - ◆ **“Standard of Care in the Developing Country”**
 - **NEJM 2000;342:967-969.**
 - **NEJM 1998;338:836-841.**
 - **NEJM 1997;337:1003-1005.**
 - **NEJM 1997;337:853-856.**

Topics for Discussion in the Design of Ethical Pharmaceutical Trials

- ◆ **Performance of Sham Surgeries**
 - **J R Soc Med 2004;97:576-578.**
 - **NEJM 1999;341:992-996.**
- ◆ **Is Placebo Surgery Unethical ?**
 - ◆ **Introduction of surgical procedures into the mainstream without rigorous evaluation**
 - **NEJM 2002;347:137-139.**
 - ◆ **Placebo surgery for Parkinson's disease**
 - **NEJM 1999;341:988-92.**
 - ◆ **Arthroscopic surgery for osteoarthritis of the knee**
 - **NEJM 2002;347:81-8.**

Phase I Trial Risks and Informed Consent

- ◆ Normal volunteers typically used for the majority of Phase I studies, with the exception for oncology and HIV drugs
- ◆ Altruism in research
- ◆ Recent study with TGN1412 (TeGenero)
 - ◆ Cytokine storm in 6 subjects
 - Received anti-CD28 humanized MAb (agonist)
 - Developed severe headaches 1 hour post infusion, followed by hypotension, tachycardia, respiratory distress, renal failure and coagulopathy.
 - All six subjects survived.
 - Concern regarding sustained effects.
 - Participants paid approximately \$3,700 to complete the study.

Topics for Discussion in the Design of Ethical Pharmaceutical Trials

- ◆ **Collaboration between Industry and Academia**
 - **Confidentiality Disclosure Agreements**
 - **Contractual obligations**
 - **Obligation to publish**
 - **Ownership of data**
 - **Inventions**
- ◆ **The Academic Researcher with Start-Up Companies**
 - **NEJM 2001;345:825-7.**
 - **Nature 2001;409:119.**
 - **NEJM 2002;347:1335-41.**

Informed Consent

- ◆ **Part 50 of the Code of Federal Regulations**
- ◆ **Basic elements of informed consent**
 - ◆ **Statement that the study involves research**
 - ◆ **Explanation of the purposes of the research**
 - ◆ **Expected duration of the subject's participation**
 - ◆ **Description of the procedures to be followed**
 - ◆ **Identification of any procedures which are experimental**

Informed Consent

- ◆ **Basic elements of informed consent**
 - ◆ **Description of any reasonably foreseeable risks or discomforts to the subject**
 - ◆ **Description of any benefits to the subject or to others which may reasonably be expected from the research**
 - ◆ **Disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject**
 - ◆ **Statement regarding how confidentiality of records identifying the subject will be maintained**

Informed Consent

- ◆ **Basic elements of informed consent**
 - ◆ **For research involving more than minimal risk, an explanation as to whether any compensation occurs**
 - ◆ **An explanation as to whether any medical treatments are available if injury occurs, and if so what they consist of, or where further information can be obtained**
 - ◆ **Who to contact for answers to pertinent questions about the research or in the event of research-related injury**

Informed Consent

- ◆ **Basic elements of informed consent**
 - ◆ **A statement that participation is voluntary**
 - ◆ **Refusal to participate will involve no penalty or loss of benefits to which the subject is entitled**
 - ◆ **Subject may discontinue participation at any time without penalty or loss of benefits**

Informed Consent

- ◆ **Additional elements of informed consent**
 - ◆ **Statement that the treatment may involve risks to the subject which are currently unforeseeable**
 - ◆ **Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent**
 - ◆ **Any additional costs to the subject**
 - ◆ **Consequences of the subject's decision to withdraw from the research**
 - ◆ **Statement that significant new findings developed during the course of the research may relate to the subject's willingness to continue participation**

Informed Consent

- ◆ **Additional elements of informed consent**
 - ◆ **The approximate number of subjects involved in the study**
 - ◆ **These Regulations are not intended to preempt other Federal, State, or local laws**
 - ◆ **These Regulations are not intended to limit the authority of the physician to provide emergency medical care**

Ethical Pharmaceutical Trials

◆ Series of Articles in Seattle Times

◆ Fred Hutchinson Cancer Center

- Seattle Times quote:

“In the two Hutch trials we're reporting on, it's clear patients didn't get full disclosure. In fact, they were misled. “

- Physicians involved in the studies had financial interests in start-up biotech companies that produced products under investigation.

- Protocol 126

- T-cell depletion of bone marrow thought to prevent graft versus host disease
- Some of the monoclonal antibodies were produced by Genetic Systems
- IRB questions regarding informed consent and financial interests
- High graft failure rate and higher relapse rates while other alternative options lowered GVHD rates

Ethical Pharmaceutical Trials

Protocol 681

- **High-dose chemotherapy for breast cancer with rescue therapy**
 - » **Financial interests of investigators in start up company (CTI)**
 - » **Intravenous formulation of product under investigation is no longer available, but informed consent is not changed**
 - » **Lisofylline patent**
 - » **Results of previous studies are known, but not published prior to financing in company**

Ethical Pharmaceutical Trials

◆ Hedge Fund Managers and Clinical Investigators

- “Drug Researchers leak secrets to Wall St.”
- UBS and Andrew Gitkin (Dec 6, 2002)
 - Isis and Affinitak
- Citigroup Smith Barney
 - Eyetech (Macugen) and Genentech (Lucentis)
- Encysive (Thelin) and the DSMB member
 - "the overall incidence of major bleeding events is rather low" statement made on conference call prior to release of study results
- Imclone (Erbix) – side effects linked to tumor regression in blinded study of colon cancer patients
- Gerson-Lehrman “Council of Advisors”
 - Hedge funds and other investors said they often are collecting information on how doctors will use drugs in the market.

Pharmacogenetics and Ethics

Drug Discovery in the Post-Genomic Age

- ◆ **Genomics research has made extraordinary progress in the sequencing and cataloging of all the genes in the human genome (and other species).**
 - ◆ **Completion of sequencing of human genome**
 - ◆ **Revolutionized the biological sciences in general; the Pharmaceutical sector in particular.**
- ◆ **Key next steps in creating therapeutic value from the “Genomics Revolution” are to determine:**
 - ◆ **Functions of the 30,000+ human genes**
 - ◆ **Role of these genes in human disease**
 - ◆ **Best gene targets for drug discovery**

Gene for Tumor Necrosis Factor Alpha (nt 601 to 2160) ACCESSION No.X02910

601 ttggttggcac accAGCCAG CAGACGCTCC CTCAGCAAGG ACAGCAGAGG ACCAGCTAAG
661 AGGGAGAGAA GCAACTACAG ACCCCCCTG AAAACAACCC TCAGACGCCA CATCCCCTGA
721 CAAGCTGCCA GGCAGGTTCT CTTCCTCTCA CATACTGACC CACGGCTTCA CCCTCTCTCC
781 CCTGGAAAGG ACACCATGAG CACTGAAAGC ATGATCCGGG ACGTGGAGCT GGCCGAGGAG
841 GCGCTCCCCA AGAAGACAGG GGGGCCCCAG GGCTCCAGGC GGTGCTTGTT CCTCAGCCTC
901 TTCTCCTTCC TGATCGTGGC AGGCGCCACC ACGCTCTTCT GCCTGCTGCA CTTTGGAGTG
961 ATCGGCCCCC AGAGGGAAGA ggtgagtgcc tggccagcct tcatccacte tcccacccaa
1021 ggggaaatga gagacgcaag agagggagag agatgggatg ggtgaaagat gtgcgctgat
1081 agggagggat gagagagaaa aaaacatgga gaaagacggg gatgcagaaa gagatgtggc

Testing of Genetic Material Obtained From Patients in Clinical Trials:

- ◆ **Single nucleotide polymorphisms**
- ◆ **Haplotype mapping**
- **Appropriate consent of subject to obtain genetic material**
- **Ownership**
- **Confidentiality**
- **Storage of samples**
- **Use of the information obtained**

Conclusions