Where are we in clinical research, and how have we gotten here?

A brief history of clinical research and clinical research ethics.

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Pulmonary and Critical Care Medicine
Research Subject Advocate, UC Davis CTSC
DISCLOSURE

I have no disclosures to make pertaining to this talk.

Research Funding: State of CA, NIH, America Asthma Foundation
Outline

- Case histories in clinical research ethics
- The Nuremberg code
- Case study: Clinical research at its finest?
- World Medical Association declarations
- CTSC/ Research Subject Advocate role
NEBUCHADNEZZER II
605-562 BC

- **FIRST RECORDED CLINICAL TRIAL:**
  - STRICT DIET
  - MEAT+WINE x 3 YEARS

  (ALMOST IMMEDIATE PROTOCOL BREAK BY 4 CHILDREN WHO PREFERRED BREAD AND WATER)
JAMES LIND, ROYAL NAVY, 1747
What are the barriers in clinical research?

Efficacy trials for "serious and life-threatening" conditions and interventions regulated by FDA.

FDA Modernization Act of 1997

Registration required for publication

International Committee of Medical Journal Editors

Legal requirement for registration of trials

FDA Amendments Act of 2007
1947

The Doctors Trial
The Medical Case of the Subsequent Nuremberg Proceedings
2011 National Predoctoral Clinical Research Training Program Meeting
A combined meeting of the NIH/NCRR CTSA Predoctoral Programs
and the Doris Duke Clinical Research Fellowship for Medical Students

May 11th - 13th, 2011
UNIT 731 - MANCHURIA

Physician-scientist commanders at Ping Fan BW complex.

Dr. Shiro Ishi in uniform.
THE NUREMBERG CODE-1948

1. The **voluntary consent** of the human subject is absolutely essential
   - legal capacity to give consent
   - free power of choice, without constraint or coercion
   - knowledge and comprehension of hazards, effects, duration, method, purpose of experiment.

   ....investigator (no other) must obtain consent
THE NUREMBERG CODE

2. The experiment should be such as to yield fruitful results for the good of society, unprocurable by other methods or means of study, and not random and unnecessary in nature.
THE NUREMBERG CODE

3. The experiment should be so designed and based on the results of animal experimentation and a knowledge of the natural history of the disease or other problem under study that the anticipated results will justify the performance of the experiment.
THE NUREMBERG CODE

4. The experiment should be so conducted as to avoid all unnecessary physical and mental suffering and injury.

5. No experiment should be conducted where there is an a priori reason to believe that death or disabling injury will occur; .....except, perhaps, in those experiments where the experimental physicians also serve as subjects.
THE NUREMBERG CODE

6. The **degree of risk** to be taken should never exceed that determined by the humanitarian **importance of the problem** to be solved by the experiment.

7. Proper preparations should be made and adequate facilities provided to **protect the experimental subject** against even remote possibilities of injury, disability, or death.
8. The experiment should be conducted only by **scientifically qualified persons**. The highest degree of skill and care should be required through all stages of the experiment of those who conduct or engage in the experiment.

9. During the course of the experiment the human **subject** should be at liberty to **bring the experiment to an end** if he has reached the physical or mental state where continuation of the experiment seems to him to be impossible.
THE NUREMBERG CODE

10. During the course of the experiment the scientist in charge must be prepared to terminate the experiment at any stage, if he has probably cause to believe, in the exercise of the good faith, superior skill and careful judgment required of him that a continuation of the experiment is likely to result in injury, disability, or death to the experimental subject.
Clinical Research at its finest?
Jonas Salk and the race to eradicate polio
F.D.R. calls for National Foundation of Infantile Paralysis in 1938

“March of Dimes” raises $500 million over 20 years
Polio Vaccine Timeline

- **1947** - Jonas Salk accepts a position in Pittsburgh at the new medical laboratory funded by the Sarah Mellon Scientific Foundation.

- **1948** - Salk's laboratory is one of four awarded research grants for the polio virus typing project. Salk decides to use the newly developed tissue culture method of cultivating and working with the polio virus that has recently been developed by John Enders at Harvard University.

- **1952** - There are 58,000 cases of polio in the United States, the most ever.

- **1953** - Early versions of the Salk vaccine, using killed polio virus, are successful with small samples of patients at the Watson Home for Crippled Children and the Polk State School.

- **1954** - Massive field trials of the Salk vaccine are sponsored by the National Foundation for Infantile Paralysis.
1954 Polio Vaccine Trials

- 1.7 million children enrolled in 1954
  - 11 states: > 600,000 injected with vaccine or placebo
  - 33 states: 1 million injected vaccine (2nd grade) vs observed control
- Results “80+ % effective” announced in 1955
- Salk killed vaccine licensed by federal government in 2 hrs
Polio Vaccine Timeline

- **1955** - News of the successful vaccine trials is announced by Dr. Thomas Francis Jr. of the University of Michigan at a formal press conference held April 12 in Ann Arbor (the site where the research data from the field trials had been gathered and analyzed). A nationwide vaccination program is quickly started.

- **1957** - After a mass immunization campaign promoted by the March of Dimes, there are only about 5600 cases of polio in the United States.

- **1958 and 1959** - Field trials prove the Sabin oral vaccine, which uses live, attenuated (weakened) virus, to be effective.

- **1962** - The Salk vaccine is replaced by the Sabin oral vaccine, which is not only superior in terms of ease of administration, but also provides longer-lasting immunization.

- **1964** - Only 121 cases of polio are reported nationally.
RADIOACTIVE STUDIES-1940s AND 50’s.

- MANY, AMONG WHICH WAS FEEDING RADIOACTIVE CEREAL TO MENTALLY RETARDED CHILDREN IN FERNALD SCHOOL IN MASSACHUSETTS.
WILLOWBROOK-1960’s

MENTALLY IMPAIRED CHILDREN DELIBERATELY INFECTED WITH HEPATITIS A
INJECTION OF CANCER CELLS INTO ELDERLY PATIENTS WITHOUT THEIR KNOWLEDGE

Subjects not told because the investigators "did not wish to stir up any unnecessary anxieties in the patients" who had "phobia and ignorance" about cancer.

2 years later, the American Cancer Society elected the PI to be their Vice-President.
Modern clinical research at its worst?
TUSKEEGE: 1932-1973

AFRICAN-AMERICANS FOLLOWED FOR NATURAL COURSE OF SYPHILIS; WHEN PENICILLIN INTRODUCED, THEY WERE DELIBERATELY NOT TREATED.*
<table>
<thead>
<tr>
<th>Guideline</th>
<th>Source</th>
<th>Year and Revisions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fundamental</strong></td>
<td></td>
<td></td>
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<tr>
<td><strong>Other</strong></td>
<td></td>
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</tr>
<tr>
<td>Good Clinical Practice: Consolidated Guidance[44]</td>
<td>International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use</td>
<td>1996</td>
</tr>
<tr>
<td>Medical Research Council Guidelines for Good Clinical Practice in Clinical Trials[46]</td>
<td>Medical Research Council, United Kingdom</td>
<td>1998</td>
</tr>
<tr>
<td>National Statement on Ethical Conduct in Research Involving Humans[49]</td>
<td>National Health and Medical Research Council, Australia</td>
<td>1999</td>
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*CFR indicates Code of Federal Regulations. More extensive lists of international guidelines on human subjects research can be found in Brody[20] and Rusz[41]. An extensive summary of US guidelines can be found in Sugarman et al.[41]*
HELSINKI DECLARATION(S)

- WORLD MEDICAL ASSOCIATION —
  establish principles for human experimentation

  1964-HELSINKI
  1975-VENICE
  1983-HONG KONG
  1989-S.AFRICA
  2000-EDINBOROUGH
  2002-WASHINGTON D.C.
  2004-TOKYO
  2008-SEOUL

WHY SO MANY REVISIONS?
Helsinki Declarations I-VI

- Separate research and clinical care
- Establish IRBs
- Journals must refuse unethical studies
Helsinki Declarations I-VI

- LEGAL GUARDIANS (PROXY) CONSENT
- CONTROLS MUST GET BEST CLINICAL CARE
- PATIENTS AT END OF STUDY MUST HAVE CONTINUED ACCESS IF BENEFIT
Helsinki Declarations I-VI

- UNPROVEN RX O.K. IN CONTROLS IF OFFERS HOPE TO THEM
- PRIVACY MAINTAINED FOR SUBJECTS
- PLACEBO O.K. IN CONTROLS ONLY IF NO PROVEN RX OR DISEASE SO MILD THERE WILL BE NO HARM
WHY DO INVESTIGATORS GO ASTRAY?

The Academic Enterprise
- Publications
- Grants
- Promotions
- Approval/ Fame
- Awards
“Non-Academic” Clinical Trials

- $$ PER PARTICIPANT
- DATA MAY BE SENT DIRECTLY TO COMPANY
- DATA MAY BE ANALYZED BY THE COMPANY
- PAPER MAY BE GHOST WRITTEN BY THE COMPANY
Rofecoxib does not delay the onset of Alzheimer’s disease: results from a randomized, double-blind, placebo-controlled study

External author?, W.H. Visscher¹, E. Yuen¹, C. Assaid¹, M.L. Nessly¹, B.A. Norman¹, C.C. Baranak¹, C.R. Lines¹, S.A. Reines¹, G.A. Block¹ on behalf of the Rofecoxib Protocol 078 study group

A Randomized, Double-Blind, Study of Rofecoxib in Patients with Mild Cognitive Impairment

Leon J Thal¹, Steven H Ferris², Louis Kirby³, Gilbert A Block⁴, Christopher R Lines⁵, Eric Yuen⁴, Christopher Assaid⁴, Michael L Nessly⁴, Barbara A Norman⁴, Christine C Baranak⁴ and Scott A Reines⁴, on behalf of the Rofecoxib Protocol 078 study group⁵

¹University of California, San Diego, CA, USA; ²New York University School of Medicine, New York, NY, USA; ³Pivotal Research Centers, Peoria, AZ, USA; ⁴Merck Research Laboratories, West Point, PA, USA; ⁵?
# The Drug Development and Approval Process

<table>
<thead>
<tr>
<th>Preclinical Testing</th>
<th>Clinical Trials</th>
<th>Post-Clinical Trials</th>
<th>Total Years for Drug Approval</th>
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</thead>
<tbody>
<tr>
<td><strong>Step 1</strong></td>
<td><strong>Step 3</strong></td>
<td><strong>Step 6</strong></td>
<td><strong>Step 7</strong></td>
</tr>
<tr>
<td>Laboratory/Preclinical Testing</td>
<td>Phase 1</td>
<td>File NDA² or BLA³ with FDA</td>
<td>FDA Approval</td>
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<tr>
<td><strong>Step 2</strong></td>
<td><strong>Step 4</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>File IND¹ application with FDA</td>
<td>Phase 2</td>
<td>Evaluate effectiveness, looks for side effects</td>
<td></td>
</tr>
<tr>
<td><strong>Step 5</strong></td>
<td><strong>Step 7</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phase 3</td>
<td>FDA Approval</td>
<td>Inform the FDA or Phase 3 data which supports drug safety and better performance over standard treatment</td>
<td>Review process/approval</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>Purpose</th>
<th>Preclinical Testing</th>
<th>Clinical Trials</th>
<th>Post-Clinical Trials</th>
<th>Total Years for Drug Approval</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Assess safety and biological activity in the laboratory and in animal models</td>
<td>Obtain FDA approval to begin clinical testing in humans after promising results in laboratory</td>
<td>Determine what dosage is safe, how treatment should be given</td>
<td>Evaluate effectiveness, looks for side effects</td>
</tr>
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### Average Time for Drug Approval

<table>
<thead>
<tr>
<th>Category</th>
<th>Average Time (years)</th>
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<tbody>
<tr>
<td>All anticancer drugs</td>
<td>4.4</td>
</tr>
<tr>
<td>All drugs</td>
<td>3.8</td>
</tr>
<tr>
<td></td>
<td>8.6</td>
</tr>
<tr>
<td></td>
<td>10.4</td>
</tr>
<tr>
<td></td>
<td>1.4</td>
</tr>
<tr>
<td></td>
<td>15.7</td>
</tr>
</tbody>
</table>

¹ IND: Investigational New Drug Application
² NDA: New Drug Application
³ BLA: Biologics License Application
Factors Most Often Causing Study Delays
United States

- Contract/budget negotiation & approval: 38%
- Patient recruitment & enrollment: 31%
- Protocol amendment & refinement: 26%
- Legal review & approval: 24%
- Review & approval of consent form: 24%

Source: Thomson CenterWatch 2007 Survey of 522 Investigative Sites in the U.S.
Future of Clinical Research
Shifting Share of Clinical Projects
Share of Industry-Sponsored Projects

Source: Thomson CenterWatch Analysis 2007
EXPORTING CLINICAL RESEARCH?

PROBLEMS OF CLINICAL RESEARCH IN DEVELOPING NATIONS:
THE NEED IS THERE
THE CULTURE IS DIFFERENT:
LITERACY
ECONOMICS
ACCESS TO ALTERNATIVES
AUTHORITY STRUCTURE
Bronchial Thermoplasty for Asthma

Castro et al. Am J Respir Crit Care Med. 2010; 181:116

- Technology is changing how we do clinical trials.
- FDA approved for severe persistent asthma 4/27/10
Study Design

- Randomized, double-blind, sham-controlled
- 30 investigational sites in six countries
- 2:1 randomization to bronchial thermoplasty (BT) or sham
- Three bronchoscopies performed 3 weeks apart
- One year follow-up
How do we design these studies? Stem cell grafts: Drugs or Devices?
(Courtesy: M. Birchall)
Unfortunate outcomes still dominate the trials process.
1999-2001, Jesse Gelsinger and Ellen Roche

UNIVERSITY OF PENNSYLVANIA.
GENE INSERTION USING ADENOVIRAL VECTOR

JOHNS HOPKINS
NORMAL VOLUNTEER
HEXAMETHONIUM
Research Subject Advocates

- CCRC RSA position created in May, 2001 based on recommendations by the National Advisory Research Resources Council

  . . . to ensure that studies on the CCRC are designed and conducted safely and ethically with protection of human subjects accorded the highest priority.
Institutional Clinical and Translational Science Award (U54)

- Regulatory Support should include an individual independent of the IRB or compliance office who acts as a sounding board for potential research participants, serves as an advocate for research participants, and works with investigators, trainees, and research teams to ensure that research involving human subjects accords the highest priority to human subject protections.

RSAs Serve a Unique role in Subject Protection

- IRBs are removed from issue of protection
- Compliance office is regulatory
- RSAs bridge the disciplines of ethics, safety, & compliance
- RSAs serve investigators, research staff and participants as advisors, facilitators and problem-solvers
CTSC RSAs: Who are they?

- MD and Ph.D: 6 (03), 5 (07)
- MD and Masters: 31 (03), 36 (07)
- MD only: 14 (03), 23 (07)
- MS: 18 (03), 18 (07)
- BS: 9 (03), 14 (07)
- RN: 7 (03), 5 (07)
- Other: 5 (03), 3 (07)
What is the Primary way the RSA Increases Subject Safety?

- 39% Education of investigators & subjects
- 22% Clinical monitoring of PI
- 12% Audits
- 5% Increased involvement in IRB review process
- 3% Evaluating of consent process
Summary

- Code of Ethics in clinical research defined in statements by almost every medical body.
- New and old ethical problems in clinical research continue to surface.
- Each of us has primary professional responsibility to the research subject.
- Clinical research must remain within the academic medicine realm.