Objectives

- Discuss how new treatments are studied in humans.
- Explain how the rights of human volunteers are safeguarded.
- Discuss features of the design of clinical studies that minimize the potential for bias influencing the results.
- Identify potential outcomes for diabetes-related clinical trials.

History of Clinical Trials

- 1747 – Experiment with untreated control group
- 1799 – Use of a sham procedure
- 1863 – Use of placebo treatment
- 1923 – Application of randomisation to trials
- 1931 – Random allocation of treatment to groups of patients
- 1946 – Publication of the Nuremberg Code for Human Experimentation
- 1966 – Publication of U.S. Public Health Service regulations leading to creation of institutional review boards
- 1967 – Structure for separating treatment administration from treatment monitoring

Scope of Clinical Trials

- New drugs
  - First in class
  - Comparison of drugs within a class
- Existing drugs for a new indication
- Surgical Procedures
- Medical Devices
- Proof of Principal
  - Diabetes Control and Complications Trial (DCCT)
- Lifestyle intervention

FDA Classification of Clinical Studies/Trials

- Phase I
- Phase II
- Phase III
- Phase IV

Phase I

- Initial introduction of an investigational drug into humans
- Usually conducted in healthy volunteers
- Determine metabolic and pharmacologic actions of the drug
- Identify side effects associated with increasing doses
- Gain early evidence on effectiveness
- Typically 20-80 subjects
Phase II

- Early controlled studies to obtain preliminary data on effectiveness in patients with a disease or condition for which the treatment is targeted
- Determines common short-term side effects and risks
- Well controlled, closely monitored
- Typically involve several hundred people

Phase III

- Expanded controlled and uncontrolled studies
- Performed after preliminary data on effectiveness has been obtained
- Obtain additional information of effectiveness and safety to evaluate the risk/benefit of the drug
- Form an adequate basis for extrapolating the results to the general population
- Involve several hundred to several thousand people

Phase IV

- A clinical trial or other investigation usually conducted under a single protocol to gather specific information about an approved drug or biological product

Protection of Human Subjects

- Protocol approved by Institutional Review Board
  - Physicians, lay, ethics
- Informed consent/assent obtained prior to performance of any study procedure
- External data and safety monitoring committee
- Independent medical monitor

Stages of a Clinical Trial

- Initial design
- Protocol development
- Patient recruitment/intention
- Treatment and follow-up
- Patient close-out
- Termination
- Post-Trial follow-up

Desirable Features of Clinical Trials

- Address an important question!
- Multiple treatment centers
- Common protocol
- Controlled
- Randomization
- Masking of treatments and outcomes
- Independent data analysis based on an analysis plan
Study Documents
- Protocol
  - Background Information
  - Inclusion/Exclusion criteria
  - Study Plan
  - Outcome measures
    - Primary endpoints
    - Secondary endpoints
    - Analytical/Statistical Methods
    - Assessment of risk/benefit
    - Alternative treatments
    - Withdrawal from study
- Informed Consent/Assent
- Study Forms
- Manual of Operations

Background Information
- Historical Information
  - Impact of the disease on individuals, society
  - Compelling arguments for conducting the research and exposing study volunteers to potential inconvenience, hazards, and risks
  - A clear statement of the study hypothesis

Inclusion/Exclusion Criteria
- Age
- Gender
- Race
- Underlying disease(s)
  - limit participation in study
  - increase risk to patient
- Substance abuse
- Behavioral problems
- Reproductive status
- Pregnancy/nursing

Study Plan
- How will subjects be recruited?
- Method of randomization to treatment groups
- Study intervention/control intervention
- Frequency of follow-up
- Study measures/procedures/surveys that will be performed and frequency
  - examinations
  - blood work
  - procedures
  - instruments/surveys

Outcomes
- Hard endpoints
  - death, stroke, amputation, blindness, kidney failure
- Softer endpoints
  - measures of disease progression
- Surrogate endpoints
  - HbA1c, cholesterol, blood pressure
- Psychosocial Outcomes
  - Quality of life
  - Depression/anxiety

Protocol
Analytical/Statistical Methods
- Specification of type 1 and type 2 statistical errors (alpha and beta)
  - Type I, alpha – the probability of rejecting the null hypothesis when it is true
  - Type 2, beta – the probability of accepting the null hypothesis when it is false
- Study power (1-beta)
- Sample size calculations based on primary endpoint
- Study outcomes/Analytical methods
Assessment of Risk/Benefit

• Risks and inconveniences to study subjects
  – pain (blood drawing)
  – complications of procedures (hematoma, infection, death)
  – drug toxicity
  – discovery of genetic information (paternity, risk of diseases)
  – radiation exposure
  – time away from work, travel etc

Informed Consent/Assent

• Document approved by IRB that describes in plain language what the study is, and what the risks and potential benefits are
  • Usually in 6th grade language
  • Must be signed by study subject before any study procedure
  • A new consent must be signed if there is any change to the protocol
  • Assent is obtained from minors, and consent from parents or legal guardian

Study Forms and Manual of Operations

• Ensure that all the data is collected in a consistent way
• Careful design to avoid ambiguity is critical
• Manual of Operations (MOO) specifies precisely how study procedures are to be performed, including sample handling, mailing etc.
• Study personnel are trained on all procedures and must demonstrate proficiency before patients are enrolled

Activities During the Study

• Recruitment of patients
• Implementation of the protocol
• Investigators meet regularly to discuss study progress with staff
• Changes in protocol are undesirable, but may be necessary as new information emerges (such as emerging drug toxicity, unanticipated side effects)
• Amendments require IRB approval
• Patients must be reconsented if there is a protocol change

Activities During the Study

• Independent medical monitor reviews unmasked clinical data, alerts investigators if problems occur
• Independent Data Safety and Monitoring Committee
  – monitors recruitment, study progress
  – reviews unmasked outcome data
  – develops statistical plan in greater detail, stopping rules
  – ultimately decides when the study should end

Events at Study Termination

• Investigators/study personnel are unmasked to outcome data
• Study subjects are informed of their results
• The subjects in the control group may be offered training or use of the study intervention
• Study is closed out, data archived, funding ceases
• Plans for long-term follow-up of the study subjects (those no longer on randomized treatment assignment) have often been in development during the later stages of the trial and are implemented
• Presentation of results at scientific meetings, publication
• New treatment integrated into the health care system
THE GLUCOSE HYPOTHESIS

TREATMENT THAT NORMALIZES GLUCOSE LEVELS WILL PREVENT OR DELAY THE LONG-TERM COMPLICATIONS OF DIABETES MELLITUS

IMPACT OF LONG-TERM COMPLICATIONS OF IDDM

VISUAL IMPAIRMENT: 14%
BLINDNESS: 16%
RENAL FAILURE: 35%
STROKE: 10%
AMPUTATION: 12%
MYOCARDIAL INFARCTION: 29%

Diabetes Control and Complications Trial

1982 - 83: PLANNING PHASE
1983 - 85: FEASIBILITY STUDY
1985 - 93: FULL-SCALE TRIAL
JUNE 1993: FINAL DATA ANALYSIS
1993-1996: EDIC

KEY STUDY FEATURES

- MULTICENTERED
- PRIMARY PREVENTION
- SECONDARY INTERVENTION
- ADEQUATE POWER
- RANDOMIZED
- OBJECTIVE OUTCOME MEASURES
- CENTRAL LABORATORIES
- INVESTIGATORS & SUBJECTS MASKED TO OUTCOMES

STRUCTURE

- POLICY ADVISORY GROUP
- NIDDK
- DATA, SAFETY AND QUALITY REVIEW
- STEERING COMMITTEE
- CENTRAL LABS & READING UNITS
- 22 CLINICS
- COORDINATING CENTER

ELIGIBILITY CRITERIA

<table>
<thead>
<tr>
<th>PRIMARY PREVENTION</th>
<th>SECONDARY INTERVENTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>AGE</td>
<td>13-39 Y</td>
</tr>
<tr>
<td>DURATION</td>
<td>1-5 Y</td>
</tr>
<tr>
<td>RETINOPATHY</td>
<td>NONE</td>
</tr>
<tr>
<td>ALBUMINURIA</td>
<td>&lt; 40 MG/24 H</td>
</tr>
</tbody>
</table>
CONVENTIONAL THERAPY
INTENDED TO MIMIC CONVENTIONAL CARE

- CLINICAL GOALS: NO SYMPTOMS OF HYPERGLYCEMIA OR HYPOGLYCEMIA
- 1 OR 2 INSULIN INJECTIONS PER DAY
- DAILY SELF MONITORING
- QUARTERLY HbA1c
- PREGNANT WOMEN TREATED INTENSIVELY
- DIET AND EXERCISE EDUCATION
- QUARTERLY VISITS

DCCT

INTENSIVE THERAPY GOALS

- SAME CLINICAL GOALS AS CONVENTIONAL TREATMENT PLUS
- MAINTAIN BLOOD GLUCOSE AS CLOSE TO NON-DIABETIC RANGE AS POSSIBLE
- FASTING POST-PRANDIAL
  - Fasting: 70 - 120 mg/dl
  - Post-prandial: < 180
  - > 65
- HEMOGLOBIN A1c < 6.0%

DCCT

INTENSIVE THERAPY METHODS

- > 3 DAILY INJECTIONS OR INSULIN PUMP
- 4 OR MORE BLOOD GLUCOSE TESTS DAILY
- HOSPITALIZATION FOR INITIATION OF THERAPY
- FREQENT DIETARY INSTRUCTION TO HELP ACHIEVE GOALS
- MONTHLY CLINIC VISITS

DCCT

DCCT Outcome Measures

- MICROVASCULAR DISEASE
  - Eye disease (retinopathy)
  - Kidney disease (nephropathy)
  - Nerve damage (neuropathy)
- MACROVASCULAR DISEASE
  - Heart attack
  - Stroke
  - Lower extremity amputation

DCCT

DCCT Outcome Measures

- CARDIOVASCULAR RISK FACTORS
  - Cholesterol and other lipids
  - Blood pressure
  - Smoking
  - Neurobehavioral measures
  - Psychological
  - Quality of Life

MEASURES OF OPHTHALMIC OUTCOME

<table>
<thead>
<tr>
<th>TEST</th>
<th>FREQUENCY</th>
</tr>
</thead>
<tbody>
<tr>
<td>STERE FUNDUS PHOTOS</td>
<td>6 MONTHS</td>
</tr>
<tr>
<td>EYE EXAMINATION</td>
<td>YEARLY</td>
</tr>
<tr>
<td>VISUAL ACUITY</td>
<td>YEARLY</td>
</tr>
</tbody>
</table>

DCCT

Retinopathy Outcomes

OUTCOME
≥ 1 MICROANEURYSM
≥ 3 STEP PROGRESSION SUSTAINED ≥ 3 STEP

Retinopathy Scale

<table>
<thead>
<tr>
<th>STEPS</th>
<th>LEVEL OF RETINOPATHY</th>
<th>ELIGIBILITY</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NO RETINOPATHY</td>
<td>1 PREV</td>
</tr>
<tr>
<td>2</td>
<td>MICROANEURYSMS ONE EYE</td>
<td>2 INTER</td>
</tr>
<tr>
<td>3</td>
<td>MICROANEURYSMS BOTH EYES</td>
<td>2 INTER</td>
</tr>
<tr>
<td>4 - 5</td>
<td>MILD NPDR</td>
<td></td>
</tr>
<tr>
<td>6 - 9</td>
<td>MODERATE NPDR</td>
<td></td>
</tr>
<tr>
<td>10 - 13</td>
<td>SEVERE NPDR</td>
<td></td>
</tr>
<tr>
<td>14 - 15</td>
<td>MILD PDR</td>
<td></td>
</tr>
<tr>
<td>16 - 17</td>
<td>MODERATE PDR</td>
<td></td>
</tr>
<tr>
<td>18 - 25</td>
<td>HIGH RISK PDR AND WORSE</td>
<td></td>
</tr>
</tbody>
</table>

Summary of Risk Reduction with Intensive Therapy

OUTCOME           | RISK REDUCTION |
------------------|----------------|
PRIMARY PREVENTION|                |
≥ 1 MICROANEURYSM | 27%            |
≥ 3 STEP PROGRESSION| 66%           |
SUSTAINED ≥ 3 STEP PROG. | 76%       |
SECONDARY INTERVENTION|          |
≥ 3 STEP PROGRESSION | 34%          |
SUSTAINED ≥ 3 STEP PROG. | 56%        |
PROLIF. OR SEVERE NPDR | 46%       |
LASER TREATMENT    | 56%            |

Risk Reduction with Intensive Therapy

<table>
<thead>
<tr>
<th>OUTCOME</th>
<th>RISK REDUCTION (C.I.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AER ≥ 42 MG/ 24 H</td>
<td>35% (16 - 49)</td>
</tr>
<tr>
<td>AER ≥ 300 MG/ 24 H</td>
<td>56% (21 - 75)</td>
</tr>
</tbody>
</table>

Prevalence of Clinical Neuropathy

<table>
<thead>
<tr>
<th>PRIMARY PREVENTION</th>
<th>5 YEARS</th>
<th>REDUCTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>CONVENTIONAL</td>
<td>16%</td>
<td>70%</td>
</tr>
<tr>
<td>INTENSIVE</td>
<td>7%</td>
<td>56%</td>
</tr>
</tbody>
</table>

Separation of HbA1c

CON        INT

STUDY YEARS
0  0  1  1  2  2  3  3  4  4  5  5  6  6  7  7  8  8  9  9

DCCT
### Major Macrovascular Events

<table>
<thead>
<tr>
<th>Event</th>
<th>Episodes per 100 PT-YRs</th>
<th>Risk Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac</td>
<td>0.06</td>
<td>80%</td>
</tr>
<tr>
<td>Peripheral</td>
<td>0.39</td>
<td>24%</td>
</tr>
<tr>
<td>Combined</td>
<td>0.86</td>
<td>44%</td>
</tr>
</tbody>
</table>

### Incidence of Cardiac Risk Factors

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Cases per 100 PT-YRs</th>
<th>Risk Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>1.8</td>
<td>NS</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>.04</td>
<td>NS</td>
</tr>
<tr>
<td>LDL - Chol</td>
<td>1.1</td>
<td>35%</td>
</tr>
</tbody>
</table>

### Neurobehavioral Events

<table>
<thead>
<tr>
<th>Event</th>
<th>Cases (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac</td>
<td>7 (0.9%)</td>
</tr>
<tr>
<td>Peripheral</td>
<td>10 (1.4%)</td>
</tr>
</tbody>
</table>

### Adverse Events

<table>
<thead>
<tr>
<th>Event</th>
<th>Cases per 100 PT-Yrs</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight Gain (&gt; 120% IBW)</td>
<td>11</td>
<td>1.6</td>
</tr>
<tr>
<td>Catheter</td>
<td>12</td>
<td>----</td>
</tr>
<tr>
<td>Infections</td>
<td>2</td>
<td>NS</td>
</tr>
</tbody>
</table>

### Severe Hypoglycemia

<table>
<thead>
<tr>
<th>Event</th>
<th>Episodes / 100 Patient-YR</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe</td>
<td>62</td>
<td>3.3</td>
</tr>
<tr>
<td>Coma / Seizure</td>
<td>16</td>
<td>2.0</td>
</tr>
<tr>
<td>ER / Hospital</td>
<td>9</td>
<td>2.3</td>
</tr>
<tr>
<td>Deaths</td>
<td>0</td>
<td>----</td>
</tr>
</tbody>
</table>