Clinical Trials
at
the Yale Cancer Center

Office of Protocol Review & Monitoring
OPRM
Director, Susan Anderson
February, 2007
Milestones in Regulating Research on Human Subjects

- 1947: Nuremberg Code: ethical code, informed consent
- 1962: Kefauver-Harris: Thalidomide, FDA reporting
- 1964: Declaration of Helsinki: informed consent
- 1970: Revelations about Tuskegee experiments
- 1972: National Research Act: IRBs
- 1978: Belmont Report: Good Clinical Practices
- 1981: FDA guidelines
- 2000: Gene therapy: Federal penalties
Good Clinical Practice

GCP

is an international ethical and scientific quality standard for designing, conducting, recording, and reporting trials that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety, and well being of trial subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical trial data are credible.
Code of Federal Regulations

**Title 21 Food & Drugs**
- Part 50 Protection of Human Subjects
- Part 56 Institutional Review Boards
- Part 312 Investigational New Drug Application
- Part 600 Biological Products: General
- Part 812 Investigational Device Exemptions

**Title 45 Public Welfare**
- Part 46 Protection of Human Subjects
- Parts 160 & 164 Standards for Privacy of Individually Identifiable Health Information
National Cancer Institute
NCI

- Government funded (NIH)
- Basic and Clinical Research
- Prevention and Epidemiology
- Centralized – more efficient, can prioritize
- Collaborative – multi-disciplinary
- Oversight – quality control
NCI Designation

- Highest standards/Advancement in treatment
- Translational Research
- Encourage collaboration
- Share resources among investigators
- Competitive Renewals every 5 years
How does NCI Evaluate Us?

- Annual report
- Five Year Renewals
- Basic and Clinical Collaborations
- Multi-faceted (Prevention, Cure, Pilot, Novel, Basic)

- ENROLLMENTS – “Summary -4”
“Summary 4”

Enrollment & Update Forms
Patient Registration – Trial Tracker

Safety
NCI Status update
Priorities

- Therapeutic
- Innovative, based on good science
- Yale Investigator Initiated Studies
- Coop & Industry with Yale Involvement
- Contribute to the development of further investigations
What is it all about?
Pluses & Minuses

Finding better ways to treat cancer by identifying cause and effect: Pluses and Minuses

- **Efficacy**
  
  Does it work? Is it effective? How effective? Better than other treatments?

- **Toxicity**

  What are the side effects? How does the new drug or treatment interact with other drugs?
# Types of Clinical Trials

<table>
<thead>
<tr>
<th>Phases</th>
<th>Sponsor</th>
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<tbody>
<tr>
<td>Phase I</td>
<td>Investigator Initiated</td>
</tr>
<tr>
<td>Phase II</td>
<td>Investigator Initiated IND</td>
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<tr>
<td>Phase III</td>
<td>Cooperative Group</td>
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<tr>
<td>Phase IV</td>
<td>Industrial</td>
</tr>
<tr>
<td></td>
<td>Combination</td>
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<td></td>
<td>Industrial – Y</td>
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<tr>
<td></td>
<td>Cooperative Group - Y</td>
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# Phases of Drug Development

<table>
<thead>
<tr>
<th>Phase I</th>
<th>Phase II</th>
<th>Phase III</th>
<th>Phase IV</th>
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<tbody>
<tr>
<td>1&lt;sup&gt;st&lt;/sup&gt; time in humans</td>
<td>Efficacy in specific disease</td>
<td>Compare to standard txment</td>
<td>Expanded access</td>
</tr>
<tr>
<td>Safety &amp; toxicity</td>
<td>Efficacy &amp; safety</td>
<td>Compare to standard</td>
<td>New indications</td>
</tr>
<tr>
<td>Determine dose (MTD)</td>
<td>Determine efficacy at MTD</td>
<td>Identify better txment</td>
<td>Determine new applications, long term effects</td>
</tr>
<tr>
<td>Escalating dose Cohorts</td>
<td>One txment; one dose; one disease</td>
<td>Randomized, multiple arms</td>
<td>Open label</td>
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<tr>
<td>PKs, PDs Tissue studies</td>
<td>QOL, symptom management</td>
<td>QOL, symptom management</td>
<td>Compassionate</td>
</tr>
<tr>
<td>&lt;100 patients</td>
<td>Can be &lt; 100, no more than 300</td>
<td>1000’s patients</td>
<td>QOL</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Cost/benefit</td>
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</table>
THE SUBCOMMITTEE TO OVERSEE THE OVERSIGHT COMMITTEE NEEDS INVESTIGATION.

I’LL FORM A COMMITTEE TO LOOK INTO IT.
Committees

- Clinical Research Steering Committee (CRSC)
- Protocol Review Committee (PRC)
- Human Investigation Committee (HIC)
- Institutional Review Board (IRB)
- Quality Assurance Compliance and Safety Committee (QUACS)
- Oversight Committee
Clinical Research Steering Committee

Only for studies using YCC CRS resources

- Protocol Concept Review
- Held twice a month
- Concept approved or disapproved
- Once concept approved moves into protocol development

- OPRM Coordinator: Diane Miranda
- Chair: Edward Chu, M.D.
Protocol Review Committee
PRC

- Scientific review for new protocols
- Set YCC priority
- Assign a Data and Safety Monitoring Plan
- Review amendments to protocols

- OPRM Coordinator: Diane Miranda
- Chair: Mario Sznol, M.D.
Human Investigation Committee
(Yale’s IRB – Institutional Review Board)

- Protect Human Subjects/Federal Regulations
- Meets weekly (HIC #1 and HIC#2)
- Ensure integrity and ethics of protocol
- Primary focus includes informed consent document, conflict of interest of investigators and protection of all subjects with particular attention to vulnerable populations
- Chairs: Drs. Mahoney & Alfano
Yale Cancer Center
Steering Committee

Protocol Development
PI

Idea!
Disease Unit

Human Investigation Committee (HIC or IRB)

Protocol Review Committee

Grants & Contracts

STUDY ACTIVATION

Protocol Review Committee (amendments)
Quality Assurance Compliance & Safety (DSMP & audits)
HIC (SAE & renewals)
Quality Assurance, Compliance & Safety Committee
QUACS

- NCI mandate for Data and Safety Monitoring
- Meets quarterly and ad hoc
- Audit Reviews
- Data and Safety Monitoring Reviews
- Reviews for Scientific Progress & Accrual

- OPRM Coordinator: Claire Veilleux
- Chair: Mario Sznol, M.D.
Yale Cancer Center
Steering Committee
Protocol Development
Protocol Review Committee
Human Investigation Committee (HIC or IRB)
Grants & Contracts

Idea! Disease Unit

PI

STUDY ACTIVATION

Protocol Review Committee (amendments)
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HIC (SAE & renewals)

OVERSIGHT COMMITTEE

Yale Cancer Center
Oversight Committee

- Chair YCC Leadership

Convenes on ad hoc basis to address issues not resolvable in the PRC or QUACS Committees

OPRM Coordinator: Claire Veilleux
Chair: Richard Edelson, M.D.
Informed Consent

- Why do we do it?
- What is it?
- When do we do it?
- Can it be withdrawn?
- What must it include?
Toxicity Assessments

- Event
- Grade – NCI Criteria
- Duration
- Attribution

- Reporting Guidelines – Protocol Specific
Serious Adverse Event

Serious Adverse Event
Refers to any event

- in which the outcome is fatal or life threatening
- causes permanent disability or incapacity or is a congenital anomaly, cancer or overdose
- that causes or prolongs a hospitalization

“Unexpected” - Refers to those not identified in specificity or severity in the current risk documents – such as the investigators brochure or package insert – or in the literature to date.
Response (Efficacy)

- Tumor Measurements
  - Imaging CT, PET, MRI
- Bio Markers
  - PSA, CA125
- Clinical Assessment
  - PE, Photography
- Laboratory Assessments
  - Bone Marrow, Flow Cytometry
Protocol Violations/Deviations

Any variance from protocol specific requirements

- **Major**
  - No consent or IRB approval
  - Inadequate drug accountability
  - Ineligible patient
  - Wrong drug Wrong dose Wrong schedule Wrong route
  - Failure to evaluate response
  - Recurring or multiple minors

- **Minor**
  - Sporadic missing information that will not impact on the outcome or interpretation of the study
Oversight, Audit, Monitoring

- Internal & External Audits
- Monitoring visits
- Cooperative Group – Audit every 3 Years
- QA or GCP Audit - Sponsor
- FDA Audit – Random or Target
- NCI Audit (CTEP or Theradex)
- Financial Compliance Audit
Oversight, Audit, Monitoring

- Inform OPRM of any upcoming external audit
- Send reports to OPRM
- Send routine monitoring reports to OPRM

- Coordinator: Claire Veilleux
YCC Director
Richard Edelson, M.D.

Oversight Committee
Appeals
Reviews appeals and issues of major concern as referred from PRC, QUACS, or PIs. Has authority to close studies.

Clinical Research Steering Committee
Edward Chu, M.D., Chair
- Reviews protocol concepts
- Prioritizes for resources

Protocol Review Committee
Mario Sznol, M.D., Chair
- Scientific review of all new protocols & amendments
- Assigns scientific priority score
- Assigns data submission and review schedule
- Assigns internal auditing schedule
  Yale Cancer Center

Office of Protocol Review and Monitoring (OPRM)
Administration
Provides full administrative support for three committees. Maintains files for Oversight Committee. Conducts audits and reviews all external audits & monitoring reports.

Quality Assurance, Compliance and Safety Committee
Mario Sznol, M.D., Chair
- Responsible for all protocol monitoring following approval
  - Review of patient data for safety
  - Accrual issues
  - Annual reviews
  - Reviews internal & external audit reports
  - Enforces compliance/protocol closures

Yale Cancer Center Protocol Review and Monitoring System
- Scientific review of all new protocols & amendments
- Assigns scientific priority score
- Assigns data submission and review schedule
- Assigns internal auditing schedule
- Yale Cancer Center
WEBSITES OF INTEREST:

YCC: Yale Cancer Center:  http://info.med.yale.edu/ycc/
HIC: Yale Human Investigation Committee:  http://info.med.yale.edu/hic/index.html
FDA: U.S. Food & Drug Administration:  http://www.fda.gov/
GCRC: Yale General Clinical Research Center:  http://www.gcrc.yale.edu/

OPRM: Office of Protocol Review & Monitoring:
http://yalecancercenter.org/clinical_trials/protocol.html