Clinical Cancer Research:  
*Alternative IRB Models and Enhancing Progress*

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Dynamics of Clinical Cancer Research: History

• Empirical in approach: cytotoxicity (cell killing) the goal
  – Non-specific cellular targets (chemicals or radiation)
  – Primary targets
    • DNA
    • nucleic acid synthesis
    • mitosis
Classical Oncology Research

• Startling developments
  – 70% pediatric cancer curable
  – Curative therapy for several adult cancers
    • Hodgkins and non-Hodgkins Lymphoma
    • Testicular cancers
    • Some leukemias
    • Breast Cancer
Classical Oncology Research

• Some Progress
  – Colo-rectal cancers: 20% improvement in survival (curability)
    • Prolonged survival with metastasis
  – Breast Cancer-increased long-term survival
  – Lung cancer--very limited success

• *but haltingly slow progress in most prevalent cancers*

So, what’s new?
Cell Biology of Cancer

Hormone or Growth Factor → Receptor

Nucleus
- DNA
- RNA

→ Angiogenesis
→ Proliferation
→ Metastasis

Protein
The Cancer Process: Targets

Angiogenesis
• Drugs that inhibit Growth factors that Stimulate new blood Vessels, e.g., Bevacizumab (anti-body directed against VEGF)

Hormone or Growth Factor ➔ Receptor

Inhibitor

Nucleus

DNA
RNA

Protein

Anti-sense

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The Cancer Process: Novel Target CML

Hormone or Growth Factor → Receptor

bcr/abl TK

Gleevec-CML

Nucleus

DNA

RNA

Protein

Growth Factor Inhibitors
Epidermal Growth Factor Receptor Inhibition-Lung Cancer

- EGFR mutation can be activating: increased sensitivity to EGF=tumor is EGF hypersensitive
- Inhibiting EGFR inhibits the dominant growth promoting influence in the tumor
- This is clinically important-NEJM July 04;2004
Truisms About Clinical Cancer Research

• Molecular targets: many are “druggable”
• Any one of these targets may be expressed in a small number of cancers
• Different cancers will/do have different targets, as a function of the pathways that drive them

What to do?
Truisms About Clinical Cancer Research

Since most cancers are heterogeneous:

• Must evolve smart studies - those that evaluate the test agent against cancers that have the "druggable" target

• These may require collecting patients from many sites across the nation or world-wide

• There are a large number of targets against which compounds have been developed

• **Speed and high quality data become the essence of performing clinical research in this context**
ASCO Oversight of Clinical Research

Goals of Policy Statement

- Ensure Safety Precautions for Clinical Trial Participants
- Ensure the Validity and Integrity of Scientific Research
- Enhance the Educational Training of Clinical Scientists and Research Staff
- Promote Accountability and Responsibility Among all Those Involved in Clinical Research and Ensure Support for an Effective Oversight Process
- Enhance the Professional and Public Understanding of Clinical Research Oversight
- Enhance the Efficiency and Cost-Effectiveness of the Clinical Research Oversight System
ASCO Task Force Findings

Observations from IRBs:

– Overwhelmed with volume
– Difficult and time consuming to analyze adverse events from multi-site trials
– Variability in oncology expertise
– Limited funding
– Challenge to identify members
– Challenge to monitor implementation of trials
Task Force Findings Addressed in Policy Statement

- Expert review critical but not always available
- Reviews are variable in quality
- Investigators need education
- Informed consent process
  - Do we miss the forest for the trees?
  - Differing regulations/guidelines from FDA and HHS create confusion
- Conflict of interest review process not uniform and often not tied to IRB review
Centralization of Review (ASCO)

- Concentrate expertise
- Promote efficiency
- Anticipated to be cost effective
- Need not be a single IRB--consider a regional approach
- NCI pilot has crystallized much debate and garnered justified praise for initiating this effort
- ASCO’s task force seeks additional ideas about understanding barriers to participation and enhancing the process for phase III, and ultimately, other types of trials
ASCO Task Force
Can the System be Modified to:

• Assure broad scientific expertise?
• Promote efficiency?
• Be cost effective?
• Support the “smart” trials that the next phase of cancer research is demanding?

• Centralizing review became a focal point for discussion
Attributes of of Centralized Review

– Potential to reduce costs
– Eliminate duplicative reviews of multi-site trials - *enhance speed while retaining quality of oversight, i.e., human subject protection*
– Allow the local IRB to focus resources on monitoring onsite trial
Attributes of Centralized Review

- Help ensure consistency across trial sites
- Standardize submission forms, protocol changes, and consent forms (relates to enhanced efficiency)
- Board members with expertise (especially lay members)
- Dedicated IRB staff
- Equally appropriate for investigator-initiated, NIH sponsored, or industry trials
- Incorporate plan for thorough evaluation
- Suitable for the "smart trials" that will be the mainstay of future clinical research in cancer
Conclusion

• Dynamism in research creates huge opportunities

• Infrastructure to support protection of human subjects in research must adapt in order to support the potential for progress