Oncology Studies from an IRB Perspective
Rebecca Carson Rogers, MA, CIP, CHRC
IRB Chair, Schulman IRB
About Schulman IRB

- Established in 1983
- Superior audit history with FDA—five consecutive audits with no findings
- 21 CFR Part 11 compliant electronic systems
- Compliant with FDA, OHRP and Health Canada requirements
- Full Board meetings **five days a week**
- Dedicated **daily expedited review** of qualifying minimal risk protocols
About Schulman IRB

- Review outcome provided within **one business day** of new study review
- **One business day** turnaround for complete new site submissions
- Dedicated streamlined processes tailored to **Phase I timelines**
- **Expert oncology IRB members** experienced in all phases of oncology research
  - National IRB for **Cancer MoonShot 2020** initiative
- Customized services for **institutions**
- **Experienced primary points of contact** for sponsors, CROs, institutions and sites
About Schulman IRB

- Clinical Quality Assurance (CQA) and Human Research Protection (HRP) consulting services provided by Provision Research Compliance Services

www.provisionrcs.com
The industry’s choice for central and local IRB services.

Get Started
Begin the initial review process.

Forms
Download the latest forms for your study.

Contact Us
Request more info & send feedback.
About Today’s Presenter

Rebecca Carson Rogers, MA, CIP, CHRC
IRB Chair, Schulman IRB

- IRB Chair at Schulman IRB since 2014
- Previously served as Assistant Director of Dartmouth College’s IRB and as IRB Member
- Former Research Regulatory and Compliance Officer at Dartmouth Cancer Center
- Served on Dartmouth College’s Cancer Center Scientific Review Committee and Gene Transfer Subcommittee of the Institutional Biosafety Committee
- Contributor to 1st and 2nd editions of Bankert and Amdur’s *IRB: Management and Function*
- Experienced educator and presenter on human subject protection topics
FDA described “Ages of Oncology Drug Approval”

- **Historical Era**
  - Response rates – approval

- **Current Era**
  - Statistical refinements, clinical benefits and surrogate endpoint

- **Moving into the Molecular Era**
  - Characterizing both disease and patient, individualized therapy, moving from phenotype to genotype

- **Hope**
  - We no longer have to tell someone, “There’s a chance this therapy may help you – but we can’t predict …”
Cancer MoonShot 2020

- Historic national coalition formed to accelerate next generation immunotherapy in cancer
- Includes leaders from large pharma, biotech, the health insurance industry, major academic cancer centers, community oncologists, and a pediatric consortium
- Will use a selected national IRB
New perspective:

Managing Cancer as a Chronic Condition

Focus on: The Role of the IRB

- Concern is that IRBs get in the way and slow down the conduct of clinical research
Objectives

- Review regulations that apply to IRB review of oncology studies
- Consider IRB concerns with Phase I oncology studies
- Describe IRB review of placebo use in oncology studies
- Discuss the impact of novel study design and treatment regimens on IRB review
- Explain IRB issues regarding the consent process and consent forms for oncology research

NOTE: This presentation is focused on adult oncology studies. At this time, most pediatric oncology studies are conducted through the National Cancer Institute Children's Oncology Group (COG) with IRB review required by the NCI Pediatric CIRB – this may change with Moonshot.
Which Regulations Apply to IRB Review?

Regulations: CFRs = Code of Federal Regulations

- FDA Regs: Full power of laws when adopted
- Title 21 Sec. 56.103 Circumstances in which IRB review is required
- (a) Except as provided in 56.104 and 56.105, any clinical investigation which must meet the requirements for prior submission (as required in parts 312, 812, and 813) to the Food and Drug Administration shall not be initiated unless that investigation has been reviewed and approved by, and remains subject to continuing review by, an IRB meeting the requirements of this part.

Guidance: Issued by individual agencies (FDA or CDER) to reflect current thinking

- Not binding

References: http://www.fda.gov/RegulatoryInformation/Guidances/ucm122046.htm
Two types of FDA drug approval: Regular or Accelerated

- FDA Modernization Act 1997: For unmet medical needs
- FDAMA – 312 subpart E: Accelerated approval only applies in the setting of a new drug for a serious or life-threatening illness
- Fast track – Process for meeting with FDA
- Priority review – 6 month NDA review time frame for products addressing unmet medical need
- Endorsement possible with only one high quality study

1998 FDA Guidance: Characteristics of a single study to support effectiveness (with independent substantiation from related study data)

Vulnerable Populations: Cancer Is an Equal Opportunity Disease

- Terminally ill, life-threatening condition/seriously debilitating illness
- Adults with diminished or fluctuating decision making capacity
  - E.g., neuro-oncology patients, patients with brain mets
- Non-English speaking subjects
- Economically disadvantaged – uninsured, under insured
- Educationally disadvantaged
- Research site employees and family members as subjects

Title 21 Sec. 56.111 Criteria for IRB approval of research. (3) Selection of subjects is equitable. In making this assessment the IRB should take into account the purposes of the research and the setting in which the research will be conducted and should be particularly cognizant of the special problems of research involving vulnerable populations, such as children, prisoners, pregnant women, handicapped, or mentally disabled persons, or economically or educationally disadvantaged persons.
Phase I Oncology Studies

- Historically have enrolled cancer patients with no further treatment options as subjects, due to potential drug toxicities
- Recruitment concern: therapeutic misconception
- Consent essentials
  - Study is NOT designed to treat subject’s condition
  - Dose escalation design – the amount of the study drug received is determined by what point subject enters the study
  - Potential risks and side effects affected by study drug dose

- Trending now to enroll healthy subjects for first in human oncology drug trials due to molecularly targeted therapies with lower toxicities
**Placebo Use in Oncology Studies**

- **History**: In past, generally not necessary or possible to use placebos in cancer clinical trials because most chemotherapy treatments caused obvious tumor shrinkage and serious side effects that could not be produced by a placebo.
Placebo Use in Oncology Studies  (cont’d)

- TODAY: Targeted drug trials – Many of the newer, targeted drugs slow tumor growth but may not cause tumor shrinkage
  - Control group needed to tell whether stabilization of the tumor growth is an effect of treatment or reflects natural behavior of the tumor
  - Oral cancer meds may have side effects that are hard to distinguish from the symptoms of cancer itself, such as fatigue
- New drugs are often tested in patients who have already received all known, effective treatments
  - Comparing a new drug with a placebo may be appropriate and allows researchers to determine the good and bad effects of the new drug
Placebo Use in Oncology Studies (cont’d)

- Not always a straightforward determination
  - Placebo plus standard treatment is generally acceptable
  - Study drug only and Placebo only arms acceptable when no standard treatment exists or in the absence of effective therapy

- How effective is the current standard treatment? Placebo is acceptable when existing therapies are minimally effective or have serious side effects

Placebo Use in Oncology Studies (cont’d)

- **Crossover study design**: Crossover to the active drug permitted at the time of disease progression
  - All patients have the opportunity to receive the new treatment, although some receive it sooner than others do

- **IRB needs to carefully review the supportive care**
  - Placebo subjects must not be substantially more likely than those in active treatment groups to: die; suffer irreversible illness, disability, or other substantial harms; suffer reversible but serious harm; or suffer severe discomfort

A sample of 21st century terms being used in cancer research:

- Immunotherapy
- Dendritic cell vaccines
- Gene transfer
- Targeted therapies
- Proteomics
- Adaptive Phase I studies
- Basket study design

- Nanoparticle delivery systems
- Genetic sequencing
- Mitochondrial DNA analysis
- GWAS (genome-wide association studies)
- Precision medicine
What this means in terms of IRB review:

- IRB member continuing education is critical, including the oncology expert IRB members
- Research team member education is needed in order to be able to provide a fully informed consent process for oncology study recruitment
  - May be provided by a study sponsor
  - May need further training on the process of research informed consent
- Subject consent process becoming even more challenging
What this means in terms of IRB review:

- Equitable selection of subjects
  - Careful scrutiny of eligibility criteria: previous & current treatments, potential drug interactions that may be associated with standard treatment
The Consent Process

- Vulnerable subject population for reasons presented earlier AND a population vulnerable to undue influence from their oncology treatment team and family members

- Timing concerns
  - Does the potential subject have time to process their diagnosis and prognosis prior to considering a research treatment option?
  - Is adequate time allowed for research team members with appropriate knowledge of the specific trial to conduct initial and ongoing consent presentations and discussions with the subject and their family?
Oncology Consent Forms

- Lengthy and complicated consent forms
- Cutting edge, 21st century scientific and medical concepts unfamiliar to even well educated lay people
- Often includes unexplained technical terms and lacks definition of terms
Risk Information in Oncology Consent Forms

- Contain lengthy lists of risks associated with standard treatments and procedures
  - Rather than explaining that the addition of an investigational product may produce unknown or poorly understood risks

- NPRM suggests use of a consent form addenda
  - This maybe a good solution to the presentation of risks associated with standard treatment and procedures
More Consent Concerns

- Inconvenience of study participation and its foreseeable effects on quality of life
  - Need to be stated clearly in consent form and discussed as they will relate to the specific potential subject

- Study participants need to be protected from financial risks resulting from study participation, such as:
  - Being charged for non-standard imaging procedures
  - Copayments may be in the tens of thousands of dollars
  - Insurance denial of payments
Consent for Collections of Biospecimens

- Standard in oncology research: collection of biospecimens with associated genomic, epigenetic, and phenotypic data

- As a result of the NPRM, consent requirements for these specimens and data is under intense scrutiny

- Collection of these materials and the possibility of future research needs to be carefully detailed in the consent form and reviewed during the consent process
Oncology studies are well served by eConsent processes
- Multimedia reference materials instantly available to support subjects and their families educational efforts

Learn your IRB review requirements for eConsent

IRBs gaining familiarity with vendors and vendors with IRB review requirements – confidentiality and security concerns

Often begins with initial IRB review and approval of a “standard written” study consent form
- This is then put in eConsent format – IRB reviews final version on appropriate device
Putting It Together
IRB review of Phase I oncology studies include which of the following:

A. Review of data to support initial starting dose
B. Consent form wording describing the purpose of a Phase I study
C. Eligibility criteria to ensure population is limited to cancer patients with no further treatment options
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A. Documentation of current standard of care for the study population

B. Justification for lack of a crossover design

C. Consent form wording defining placebo and its use in the study
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Putting It Together

- IRB reviews of oncology immunotherapy site qualifications include which of the following:
  
  A. Institutional Biosafety Committee review and approval of the study
  
  B. Sponsor or CRO contract with the site
  
  C. PI experience in use of oncology investigational vaccines
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- Oncology research consent forms would all benefit by being limited to 8 pages in length.

True or False?
Putting It Together

- Oncology research consent forms would all benefit by being limited to 8 pages in length.

  *False*

- Oncology disease standard and research treatment options are complicated.
  - Fully informed research consent decisions, including the collection and storage of biospecimens for future use, may benefit from use of novel technology enhanced strategies to educate potential subjects and their families and friends.
Summary

- Current developments in oncology research study designs and novel treatment approaches are pushing IRBs and research teams to stay up to date and well educated.
- Oncology disease diagnosis, prognosis, and both standard and research treatment options are complicated.
- Honoring the need for voluntary, fully informed consent decision making is challenging and takes time.
- 21st century technology is being used inventively to design novel diagnosis and treatment approaches, as well as aid in the research consent process.
Examples of other required reviews:

- Contract and MCA
- Protocol Scientific Review Committee
- Radiation Safety Committee
- Institutional Biosafety/Gene Transfer Committee
- Investigational Pharmacy

Learn which reviews may be conducted concurrently and which require sequential review – this is not consistent between sites and their IRBs.

Remember: More than IRB review is needed to open an oncology study at most research sites.
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