


National Cancer Institute

What is an IND and How Does it Affect ACRIN Clinical Trials

Paula M. Jacobs, Ph.D.
 Deputy Associate Director,
 Division of Cancer Treatment and Diagnosis
 Cancer Imaging Program
 ACRIN Fall Meeting October 2009
jacobsp@mail.nih.gov

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
 National Institutes of Health



Overview

- Medical imaging agents and devices are regulated by the Food and Drug Administration (FDA)
- Different regulatory requirements for:
 - Agents approved for use
 - Investigational agents
 - Radioactive drugs – approved or not
- Brief review of regulatory issues
- How to obtain investigational agents
- How are IND trials different from other trials

Regulators: The Alphabet Soup

- FDA: US Food and Drug Administration
 - CDER: Center for Drug Evaluation & Research
 - CBER: Center for Biologics Evaluation & Research
 - CDRH: Center for Devices & Radiological Health
- IND: Investigational New Drug (exemption)
- IDE: Investigational Device Exemption
- RDRC: Radioactive Drug Research Committee
- IRB: Institutional Review Board
- DSMB: Data Safety Monitoring Board
- NDA: New Drug Application

Imaging Probes

- Why do we use probes?
 - Screening
 - Staging
 - Stratification of patients for specific therapy
 - Evaluation of patient response to therapy
- Approved or investigational probes
- Regulatory Guidelines
- Availability

Issues for ACRIN

- Is an IND or IDE required?
- Who will be the sponsor?
- How can the probe or device be obtained?
- How does an IND drug change the trial?
 - SAE reporting
 - Consenting

Investigational New Drug

- A drug that does not have FDA approval to market *for the indication being studied*
- More oversight than for approved drugs
- Safety and efficacy much less known
- The sponsor must apply for permission to study drugs in humans
 - From FDA for IND
 - From IRB as usual
 - Perhaps others (CTEP, RSC)

Implications of IND/IDE Trials

- FDA adds another layer to protocol review
 - Safety oriented review
 - Can stop the trial at any point
- Sponsor has legal obligation to report to FDA
 - Basics: PI & site Info including CMC if relevant
 - SAEs
 - Site reports to ACRIN and CIP
 - IND/IDE holder reports to FDA
 - Annual or semi-annual report required
 - Protocol amendments and new sites/Pis

Implications of IND/IDE trials - 2

- Drug or device supply
 - Must be in accord with the filed IND/IDE
 - Must meet quality standards
 - May impose geographical limits
 - May have special control requirements
 - May come with confidentiality requirements
- FDA can audit trial sites or the group
- If any data to be used in submission for marketing, financial disclosure required
- Informed consent highlights the experimental nature of the agent

Cancer Imaging Program INDs

- [F18]-fluoro-D-thymidine – FLT – proliferation
 - three commercial suppliers
- [F18]-fluoromisonidazole – FMISO – hypoxia
 - one commercial supplier
- [F18]-fluoroestradiol – FES – estrogen receptor
- [F18]-sodium fluoride – NaF – bone metastases
 - three commercial suppliers
- ferumoxtran-10 – lymph nodes
- ferumoxytol – blood pool, delayed detection of tumor associated macrophages

ACRIN IND/IDE Trials

- Multicenter trials with investigational agents
 - 6671: Ferumoxtran-10
 - 6682: [Cu64]- ATSM
 - 6684: [F18] Fluoromisonidazole (FMISO)
 - 6687: [F18] sodium fluoride
 - 6688: [F18] Fluoro-D-thymidine (FLT)
- IND holders
 - Cancer Imaging Program
 - Investigator
- Device: 6673: RFA for HCC

How can this affect RAs?

- May have unusual supply issues & documentation
- Need to be prepared to discuss “investigational drug” with patient
- Multiple IND agents are possible
- SAE reporting may be
 - More rigorous
 - Shared with another Cooperative Group (6671)

Probe Availability

- | | |
|----------------------------|--|
| • Approved drugs | <u>Examples at ACRIN</u> |
| - On label | [F18]-FDG |
| - Off label - IND required | None |
| • Investigational drugs | |
| - Contract synthesis | [F18]-FMISO (6684)
[F18]-NaF (6687)
[F18]-FLT (6688) |
| - Site-made from kit | [Cu64]-ATSM |
| • Devices | |
| - Commercially provided | RFA ablation |

Supply methods currently used

- [F18]-FDG: buy from a commercial vendor/make on site
- Ferumoxtran -10 (Combidex®) – CIP IND
 - Provided by AMAG Pharma
- [F18]-FMISO – CIP IND
 - Prepared on site at U. Washington under CIP IND
 - Sourced from commercial vendor with DMF/LOA
 - [Cu-64]-ATSM – Investigator IND
 - Kit to prepare on site from supplied Cu-64
- [F18]-FLT– CIP IND
 - Prepared on site at U. Washington under CIP IND
 - Sourced from commercial vendors with DMF/LOA
- [F18]-NaF– CIP IND
 - Sourced from commercial vendors with DMF/LOA

Special considerations

- For an IND trial, the drug must be supplied from the IND holder or made under the IND
 - Cannot just “make it the same way”
 - Cannot just “follow USP”
- A formal filing of manufacturing under either an IND or a DMF is required
- DMF holder can provide LOA

Questions?

Thank you for your attention!

jacobsp@mail.nih.gov

301-496-9531

Informative Links

- Data & Safety Monitoring
 - <http://cancer.gov/clinicaltrials/conducting/dsm-example-plans>
 - <http://cancer.gov/clinicaltrials/conducting/dsm-example-plans>
 - <http://cancer.gov/clinicaltrials/conducting/dsm-guidelines/page3>
 - <http://ctep.cancer.gov/handbook/index.html>
 - <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/ucm115894.htm>
- Agencies
 - FDA <http://www.fda.gov/>
 - CMS <http://www.cms.hhs.gov/>
 - OHRP <http://www.hhs.gov/ohrp/>
 - OCR <http://www.hhs.gov/ocr/hipaa/>
- FDA Guidance on the IND process with multiple links to other documentation:
 - <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/default.htm>
- Comprehensive Guidance Page
 - <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>
- An “how-to” guide from the Biological Development Program at NCI-Frederick with multiple links
 - <http://www.bdp.ncifcrf.gov/pdf/GuidetoResSubs.pdf>