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

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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
  - On label
  - Off label - IND required
- Investigational drugs
  - Contract synthesis
    - [F18]-FMISO (6684)
    - [F18]-NaF (6687)
    - [F18]-FLT (6688)
  - Site-made from kit
    - [Cu64]-ATSM
- Devices
  - Commercially provided
    - RFA ablation

Examples at ACRIN

- [F18]-FDG
  - None
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!

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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-example-plans
  - http://cancer.gov/ClinicalTrials/conducting/dsm-example-plans
  - http://cancer.gov/ClinicalTrials/conducting/dsm-example-plans
- Agencies
  - FDA http://www.fda.gov/
  - CMR http://www.merit.fda.gov/
  - ONC http://www.hhs.gov/ocr/hipaa/
- FDA Guidance on the IND process with multiple links to other documentation:
  - Comprehensive Guidance Page
  - An "how-to" guide from the Biological Development Program at NCI-Frederick with multiple links