



# Regulatory Operations and Other Trial Considerations

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Trini Ajazi, MM

Alliance Chief Administrative Officer

New Investigators Course, Alliance Group Meeting

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# Presentation Agenda

- Pharmaceutical Affairs, Regulatory, Protocol and Project Management Resources
- Conflict of Interest
- Investigational New Drug (IND)
- New Drug Application/Registration Trials
- International Collaborations

# Staff Resources

- Leslie Kelley, Regulatory Compliance Manager (COI)
- Ligi Matthews, Pharmaceutical Affairs Manager (IND/IDE)
- Aimee Farrell, Senior Project Manager (Registration Trials)
- Stacy Reeves, Senior Project Manager (International Collaborations)
- Michael Kelly, Director Protocol Operations
- Morgen Alexander-Young, Associate Director Protocol Operations

# Conflict of Interest/Financial Disclosure

Disclosure of financial interest required for those who directly or significantly affect design, conduct, analysis or reporting of the clinical research. This conflict could include any investigator with a significant interest in a drug or medical device, techniques or technology or proprietary arrangements which may impact research being done at the Alliance.

Alliance COI Committee reviews all COI disclosures and makes recommendations to Group Chair and Executive Committee

# Disclosure requirements and management

- $\geq$  \$5,000/year including travel, honoraria, private stock, public stock, ownership interest, intellectual property, unrestricted research grants
- $\geq$  \$5,000 < \$25,000 (\$50,000 public stock) requires management plan including study oversight by study co-chair and study statistician

# Financial Conflict Threshold

An investigator with financial relationships >\$25,000/year in a privately held business, equity interest in a publicly traded company sponsor that exceeds \$50,000/year, or >5% ownership interest (including common stock) in either a privately held or publicly traded business, will generally be prohibited from assuming chairmanship of a study.

# If Conflict...

- Investigator retains rights of authorship on publications derived from the study in accordance with the requirements for disclosure of conflicts of interest established by the relevant publishing authorities.
- Any individuals with a significant conflict of interest such that they are ineligible for a study chair or co-chair role cannot serve as either first, corresponding, or senior (last) author of an Alliance publication.
- Financial conflicts of interest must be disclosed in each public presentation of research results.

# Investigational New Drug (IND)

- An application to the FDA to test a new drug or a new use of a marketed drug in humans, in a *clinical investigation*.

## When do you need to request an IND?

- **When testing a new drug that currently is not used in the US.**
- **When you are using new indication of a drug that is currently marketed in the US.**

Generally a study with involving no significant change in the labelling use of the drug may be IND EXEMPT *however you still must submit an application to the FDA to confirm exemption.*

# Investigator-Initiated IND

Alliance submits **Sponsor/Investigator** IND applications

- Alliance is sponsor
- Monica Bertagnolli, MD is principal investigator
- Allows Alliance to manage and hold all INDs for Alliance trials
- CTEP may also hold IND

# IND Application

- FDA 1571- Investigational New Drug Application  
Investigator's CV including copy of your medical license  
FDA 1572-an agreement between an investigator and the FDA  
to comply with all FDA regulations while  
conducting a clinical trial.
- FDA 3674-Certificate of Compliance-an agreement to comply with  
ClinicalTrials.gov regulations
- A copy of the protocol, protocol and ICF  
Investigator Brochure/Package Insert  
Cross Reference Letter –provided by the drug manufacturer giving  
the FDA permission to reference another IND regarding this  
investigational drug.

# Now What?

**The FDA has 30 days from receipt of the application to request clarification or additional documents.**

After 30 days .....exhale! the IND application has been accepted. Shortly afterwards you will receive official notification.

Each year a progress report needs to be submitted as long as the IND is active. This report should include any protocol updates, changes in safety methods and accurate information.

# What is a Investigational Device Exemption (IDE)

An application to the FDA to test the effectiveness and/or safety of a device in a clinical study. This type of application covers both devices and **bio assays**.

There are 2 types of classifications for these devices:

Significant Risk (SR)-poses a potential risk to health or safety of the subject. An example would be implantable devices

Non-significant Risk (NSR)

# Registration Trials

- New Drug Application (NDA) for marketing of an investigational new drug
- Retrospective
  - Pharmaceutical company decides to file NDA after Alliance study results are released; e.g., supplemental NDA for label extension of drug approved for another indication
- Prospective
  - Pharmaceutical company requests development of trial with registration intent
- NDA filed by pharmaceutical company for approval by US Food and Drug Administration (FDA)

# NDA (New Drug Application)

- *It is the process by which the sponsor formally request the regulatory body (FDA) to grant approval to market and sell a new drug.*

*(The data gathered during the animal studies and human clinical trials of an Investigational New Drug (IND) become part of the NDA)*

*The goals of the NDA are to provide enough information to permit FDA reviewer to reach the following key decisions:*

- *Whether the drug is safe and effective in its proposed use(s), and whether the benefits of the drug outweigh the risks.*
- *Whether the drug's proposed labeling (package insert) is appropriate, and what it should contain.*
- *Whether the methods used in manufacturing the drug and the controls used to maintain the drug's quality are adequate to preserve the drug's identity, strength, quality, and purity.*

# Key Issues for IND/NDA Studies

- Sponsor Oversight
- Investigator Oversight
- Study Monitoring
- Data Integrity
- Pharmacovigilance
- Inspection Readiness
- Regulatory Documentation
- Overall Compliance with FDA regulations and ICH Good Clinical Practice

# Investigator Responsibilities

- Scientific contribution to study design
- Participation in meetings with FDA
- Assist with pharmaceutical collaboration
- Study monitoring in close conjunction with statistical, data center and operations staff
  - *Case evaluations of eligibility and disease outcomes/primary endpoints—real time, ongoing is best*
  - *Protocol deviations*
  - *Safety reviews*
  - *Site inquiries*

# Related Initiatives: Central Monitoring

- Central Data Monitoring
  - Source documents uploaded in Rave
  - Source data review and verification
  - Key eligibility, disease outcomes/primary endpoints, treatment, AE, patient termination
  - Conducted by central monitor at data center
  - Applies to investigational new drug (IND) studies, even if not planned for NDA/registration

# Related Initiatives for IND/NDA

- Audits with documented targeted source data verification (TSDV) in Rave
- Delegation of Task Log (DTL)
- Registration and Credential Repository (RCR)
  - Training documentation (GCP, protocol-specific)
  - Financial disclosure
  - Investigator registration
- CTEP-AERS/Rave integration

# Alliance International Collaborations

- International collaborations provide unique opportunities to enhance research in areas such as study design, analysis, and accrual.
- The Alliance International Collaborations oversees the operational activities of international sites that participate in Alliance trials; this includes full member and non-member collaborators.
- Non North American sites participate on Alliance trials as Members or Non Member Collaborators (NMCs).
  - NMCs are institutions or networks that participate on Clinical Therapy Evaluation Program (CTEP) and Division of Cancer Prevention (DCP) sponsored protocols but are not full member institutions of the lead protocol organization or a participating organization.

# Criteria and Issues Considered for International Collaborations

- **Accrual and Accrual Duration**
- **Rare Tumors**

## **NCI reviews proposal with following in mind**

- necessity of contribution of the collaborating organization/sites
- past experience with the collaborating organization/sites
- potential contributory accrual of the collaborating organization/sites
- country of the collaborating organization/sites

# Considerations per NCI

- plan for auditing/monitoring of collaborating organization/sites can be implemented
- ability to execute necessary MOU/agreement
- ability for collaborating organization/sites to comply with applicable regulatory requirements and NIH grant requirements (e.g., FWA and State Dept. clearance)
- whether the trial is conducted under an IND or not, and if so, who is the IND sponsor
- IND agent supplier, distributor and company collaborator approval, if applicable
- cost implications

# Regulatory Filings in other countries

- European Union
  - Clinical Trials Application- The CTA is submitted to the Competent Authority (CA) of each EU member state participating in the clinical trial in the member state's official language. The preparation, submission and verification of CA approval should be handled by the EU member state collaborating institution.
  - European Clinical Trials Database (EudraCT)
- Australia
  - Australian New Zealand Clinical Trial Registry (ANZCTR)

# Alliance International Collaborators

- **Full Members**

- Swiss Group for Clinical Cancer Research (SAKK)
  - N1048 - Phase II/III Trial of Neoadjuvant FOLFOX, with Selective Use of Combined Modality Chemoradiation Versus Preoperative Combined Modality Chemoradiation for Locally Advanced Rectal Cancer Patients Undergoing Low Anterior Resection with Total Mesorectal Excision

- **Non-Member Collaborators**

- European Organization for Research and Treatment of Cancer (EORTC)
  - A031102 - A Randomized Phase III Trial Comparing Conventional-Dose Chemotherapy Using Paclitaxel, Ifosfamide, and Cisplatin (TIP) with High-Dose Chemotherapy Using Mobilizing Paclitaxel Plus Ifosfamide Followed by High-Dose Carboplatin and Etoposide (TI-CE) as First Salvage Treatment in Relapsed or Refractory Germ Cell Tumors
  - N0577 - N0577 (CODEL): Phase III Intergroup Study of Radiotherapy with Concomitant and Adjuvant Temozolomide versus Radiotherapy with Adjuvant PCV Chemotherapy in Patients with 1p/19q Co-deleted Anaplastic Glioma or Low Grade Glioma
- Australian and New Zealand Urogenital and Prostrate Cancer Trials Group (ANZUP)
  - Recently approved to participate on A031102

# Requirements for International Collaboration Approval

- Alliance International Feasibility Assessment
- Alliance Executive Committee Review
- NCI review and approval
  - Request for International Site Participation in CTEP Studies (form submitted at the time of LOI/concept submission)
  - Request to Amend Ongoing Study for International Site Participation
  - The CTEP International Site Coordinating Group (ISCG) will review the request. **A final decision will be sent approximately 4-6 weeks from submission**

# Logistical Considerations

- Regulatory
  - Registration and Credentialing (Investigators, Research site staff in the future)
  - CTEP-ID/CTEP-IAM Account (Investigator and Research site staff)
  - Human Research Subjects training – GCP training documentation for investigators and site staff. Submission of this information to the NCI will change with implementation of the NCI Registration and Credential Repository (RCR).
  - Ethics Approval
  - Federal Wide Assurance (FWA)
  - State Department Clearance
- Execution of Memorandum of Understanding (MOU)
- Drug Access and Distribution
- Audit & Monitoring Plan
- AE and Expedited AE Reporting
- Translational Research and specimen submissions
- System Access and Training (OPEN, Rave, BioMS, CTSU, CTEP-AERs)

# Regulatory

- Registration and Credentialing
  - Investigator
    - Prior to participation in NCI sponsored clinical trials investigators must register with the Pharmaceutical Management Branch (PMB) of the Cancer Trial Evaluation Program (CTEP).
      - FDA Form 1572, Supplemental Investigator Data Form (IDF), Financial Disclosure Form (FDF), Current Curriculum Vitae (CV)
    - After PMB registration investigators must register with CTEP IAM; an active user account and password will be provided.
  - Research staff or associates (*non-investigator clinical site staff*)
    - Must obtain CTEP IAM user account. **Registration with the NCI will also be required for all research staff once the RCR is implemented.**
- FWA - All NMCs must have an active FWA (<https://www.hhs.gov/ohrp/register-irbs-and-obtain-fwas/index.html> )

# Regulatory

- State Department Clearance (SDC)
  - Advance clearance from the US Department of State is needed for each non-US component
  - Alliance will submit the information to NCI, and the NCI will submit to the State Department. **Approval is received in approximately 3-6 months.**
  - Information needed for the International partner:
    - CTEP Site code for institution
    - Address of institution
    - Name, phone, and email of Principal Investigator
    - **CTEP ID of PI (Required for SDC submission)**
    - **FWA# (Required for SDC submission)**

# Group Specific Appendix

- The GSA must be included as an appendix to the protocol, per NCI policy. The document serves as a reference for International participants and identifies processes that may be country specific, including:
  - Trial organization
  - Investigator and site registration procedures
  - Patient registration and randomization procedures
  - Study procedures
  - Safety reporting
  - Drug Access and Distribution
  - Audit & Monitoring Plan
  - Administrative contacts

# Challenges

- Timeline for activating international sites (approximately 6-8 months)
- Navigating local and international regulations
  - NCI Guidance for International Collaborations-2007 *revised NCI guidance to be released*
  - Non North American regulations
- QA/QC and equivalency of quality between countries
- Funding (drug shipment, correlatives)
- Lapse in NCI Registration
  - Investigator
  - Site Staff (with new RCR)
- Each protocol is unique with varying requirements

# Alliance International Team

- Trini Ajazi, Chief Administrative Officer [tajazi@uchicago.edu](mailto:tajazi@uchicago.edu)
- Michael Kelly, Director Protocol Operations  
[mkelly1@uchicago.edu](mailto:mkelly1@uchicago.edu)
- Morgen Alexander-Young, Associate Director Protocol Operations  
[malexanderyoung@uchicago.edu](mailto:malexanderyoung@uchicago.edu)
- Yujia Wen, Director Translational Research  
[ywen@bsd.uchicago.edu](mailto:ywen@bsd.uchicago.edu)
- Marcia Kelly Administrative/Membership Manager  
[marciak@uchicago.edu](mailto:marciak@uchicago.edu)
- Stacy Reeves, Sr. Project Manager  
[stacyreeves@uchicago.edu](mailto:stacyreeves@uchicago.edu)

# Questions

