

National Cancer Institute (NCI) Knowledge Acquisition Session Report

Session Date: May 8, 1998

Session Time: 12:00 P.M.

Session Topic: Overview of IDB Investigator Tasks

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Organization: Investigational Drug Branch (IDB), CTEP, NCI

Session Location: NCI

Type of Session:

Interview Task Analysis Scenario Analysis
 Concept Analysis Observation Structured Interview
 Other:

Documentation: Knowledge Acquisition Session Report

General Topic Area

Overview of Investigational Drug Branch Investigator tasks

Session Goals

Obtain a high level understanding of IDB Investigator roles, responsibilities and process/task flow.

Report Summary

The Investigational Drug Branch (IDB) implements and monitors a comprehensive cancer therapy clinical contract program designed to provide highly specific and immediate clinical trials of anti-cancer drugs that have demonstrated high activity in animals in the pre-clinical phase of the drug development aspect of the cancer therapy program. IDB also designs and monitors Phase II and III clinical trials of biological response modifiers. Meeting notes from the May 8, 1998 initial interview session are attached. Topics discussed included:

- ◆ Acquisition of Agents
- ◆ Formulation of Developmental Plans
- ◆ Review LOI's
- ◆ Review of Adverse Events
- ◆ Analysis Review & Reporting of Data
- ◆ Policy Issues in Drug Development

Overview

IDB is comprised of two sections: the Developmental Chemotherapy Section and the Biologics Evaluation Section.

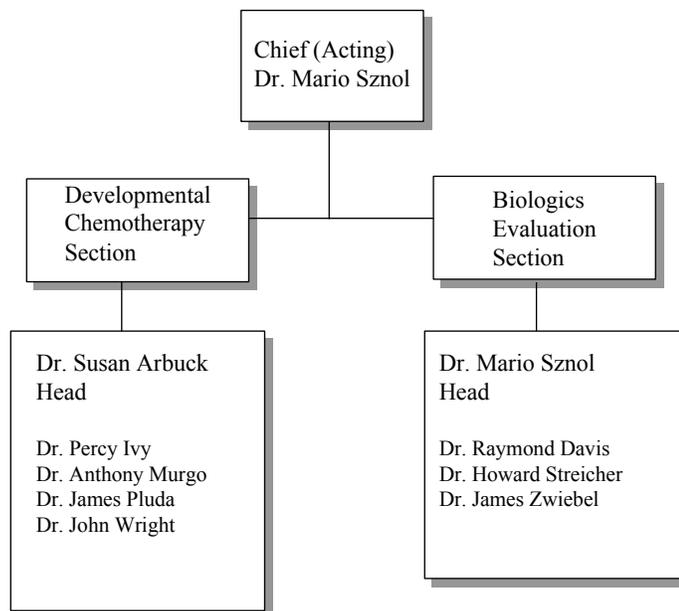
The Developmental Chemotherapy Section is responsible for:

- Developing drug development plans, including Phase I, Phase II and Phase III trials, for anti-cancer drugs
- Coordinating with both intramural and extramural investigators and pharmaceutical industry in the design and the conduct of anti-cancer drug trials
- Monitoring clinical trials of anti-cancer drugs for safety, efficacy, and clinical pharmacology
- Investigating and preparing reports concerning ADRs for all INDs
- Providing annual reports to FDA on Oncologic drugs

The Biologics Evaluation Section is responsible for:

- Developing drug development plans, including Phase I, Phase II and Phase III trials, for biological response modifiers
- Coordinating with both intramural and extramural investigators and pharmaceutical industry in the design and the conduct of biological response modifier trials
- Monitoring clinical trials of biological response modifiers for safety, efficacy, and clinical pharmacology
- Investigating and preparing reports concerning ADRs for all INDs
- Providing annual reports to FDA on Biological agents

IDB Organization Hierarchy



There is a great deal of cross-work load between these two sections.

The following is a list of drug categorizations and how they are assigned to people in IDB who are responsible for input to CTEP activities involving drugs in their assigned categories.

Immunotherapy

Cytotoxins
antibodies (AT)
Growth Factors
Vaccines
Differentiation
Anti-sense
Gene Therapy
Viral Therapy

Cytotoxins

Signal transduction
Apoptosis
Modulators
Angiogenesis

Note: Additional information in this area would be beneficial.

IDB Investigator Tasks

IDB Investigator responsibilities are categorized into the following six areas:

1. Acquisition of Agents
2. Formulation of Development Plans
3. Review of LOIs
4. Review of Adverse Events
5. Analysis Review and Reporting of Data
6. Policy Issues in Drug Development

Acquisition of agents

IDB Investigators are responsible for moving select agents from preclinical testing, through NCI clinical trial testing and on to licensing. IDB receives some new agent information through the Developmental Therapeutics Program (DTP). DTP works with drugs through the end of the preclinical stage. IDB frequently works together with DTP through the preclinical testing and then acquires the drug for use in clinical testing. Interaction between IDB and DTP includes an exchange of agent information regarding toxicology, efficacy, etc.

IDB has Agreements with drug companies which include CRADAs and CTAs. IDB makes decisions on whether or not to pursue clinical studies with specific agents based on the 'science' or pre-clinical information. IDB personnel attend presentations sponsored by drug companies where they learn about current agents and their preclinical results.

The doctors at IDB also try to counsel people to work with NCI on drug development. IDB doctors have a great deal of interaction with companies

Formulation of Drug Development Plans

A Drug Development Plan is a living document about a specific drug. In it IDB documents issues regarding the drug and predicts (defines?) how an agent should be studied clinically. As part of developing a plan, IDB solicits for trials. Mass solicitations are sent to a subset of investigators that have expertise with the type of drug that IDB wants to study. IDB doctors

know and keep manual files on investigators who have special expertise. This investigator information may include:

- disease specialty
- areas of special expertise (such as bone marrow transplantation, vaccines, etc.)
- cooperative group affiliations

It would be very helpful to IDB to have this information available electronically. PMB currently has a database that classifies investigators.

Review LOIs

IDB Investigators participate in two types of reviews: protocol reviews and consensus reviews. Protocol reviews are high priority for IDB. Protocol Reviews take place before a Protocol Review Committee (PRC) meeting and involves reviewers from many CTEP branches. Dr. Mario Sznol provided an example of his Document Review Checklist, which refers to this activity.

Consensus Reviews are put together by the lead investigator. This activity takes place after the PRC meeting. A Consensus Review is the document which conveys CTEP comments to the submitting investigator for LOIs, protocols, or concept reviews. A Consensus Review – or “LOI response” – is sent to the investigator for all LOIs, not just those that are approved. Many of these Consensus Reviews are analogous to the “Pending” letter for protocols. Investigators are told to do or consider some issue and are then asked to reply to CTEP, where their document will be re-reviewed.

Currently, the LOI responses are drafted by the drug monitor’s CRS, then the drug monitor edits/updates the response before it is sent to the investigator.

IDB also approves Letters of Intent (LOIs) submitted by investigators. If the LOI is approved, IDB writes a Consensus Review, which details issues, problems, questions, and suggestions to the PI for his/her consideration and/or response. The Consensus Review could be standardized to provide a minimum of abstracted information. This requires further discussion. Dr. Mario Sznol created a Document Review Checklist: a list of all the topics looked at when reviewing a document. Note: FDA does not review Informed Consent unless asked to.

It would be beneficial for Oracle/ScenPro to attend a PRC (Protocol Review Committee) meeting. There was also discussion to re-reviews of protocols. CTEP performs an initial review of a protocol and send back a Consensus Review in which required changes are outlined. These documents are generally not reviewed in a PRC meeting a second time. They are usually reviewed privately by the relevant reviewers. Dr. Sznol is interested in finding a way to automatically figure out who the “relevant” reviewers are for a given protocol, who signs off on it, etc. The primary reviewer signs off on all re-reviews. Areas for further discussion include: Who reviews it and whose responsibility is it to send it out to all the reviewers? How is it tracked, if it needs to be tracked?

Review Adverse Events

Rules for reviewing adverse events (ADRs) can be found in the Investigator Handbook, which is available electronically on the web. ADRs are classified based on importance, age (old, new), frequency (rare). IDB Investigators assess the relationship of the adverse event to the IND drug, other drugs, the disease, or to other causes and determine whether an ADR needs to be submitted to the FDA.

All ADRs are submitted to the FDA (some within 24 hours to 10 days – depending upon the nature of the ADR) but the majority of ADRs are held for submission as a part of the Annual Report. IDB docs make this determination. IDB makes a determination based on the characteristics of the ADR and whether the ADR constitutes the need for an amendment to the clinical trial protocol. Warning Letters are a part of this process. IDB Investigators may or may not request an amendment to the clinical trial protocol. IDB communicates closely with the PIs to determine solutions to ADRs.

Analysis Review and Reporting of Data

The bulk of the trial data comes to IDB via CDUS, CTMS, ADUs, Study Summary reports, or cooperative group agendas. IDB is responsible for analyzing the data that is submitted to CTEP from investigators, FDA, and management. This information is essential in creating a Drug Development Plan.

IDB needs to be prepared to respond to Congressional Inquiries at a fairly detailed level. It is also important for them to have records of meetings with companies.

The following is a check list of important data to be retained for each agent:

- Log:
- Phone
- correspondence
- meeting
- action items that resulted from conversation
- CRADA, CTA, docs...link to DTP data
- genetics Institute
- Drugs
- Protocols/LOIs
- correspondence
- meeting
- development plan
- CRADA/CTA
- IND
- Adverse Events

Policy Issues in Drug Development

In addition to the tasks outlined above, IDB Investigators also:

- Serve on committees
- Attend Patient care
- Review Journal articles
- Provide scientific input for drug development
- Obtain access to and review literature to support them in staying current
- Act as Program Directors for grants
- Develop Policy Issues (E.g., pediatric accrual)
- Develop scientific approaches
- Write scholarly papers (2-3/year/doc)
- DCS also includes novel cytotoxic agents
- IDB also acts as CTEP coordinator for phase I and II studies of NCI- IND agents (prepares consensus review, re-reviews responses and oversees approval reviews and oversees responses to amendments, etc.)

Wish List

- ◆ IDB would like documentation and electronic management for telephone, email, and verbal interactions, which may provide additional data
- ◆ IDB would like some very user-friendly software to allow them to capture interactions with drug companies and other outside **agencies**