

# National Cancer Institute (NCI) Knowledge Acquisition Session Report

**Session Date:** October 1, 1997

**Session Time:** 11:30 AM

**Session Topic:** Clinical Trial Research Fellow Responsibilities

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**Organization:** Developmental Therapeutics Department, Lombardi Cancer Center

**Session Location:** Georgetown University Hospital, Washington, D.C.

**Type of Session:**

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

**Documentation:** Knowledge Acquisition Session Report

## General Topic Area

Protocol research, development, writing and submission.

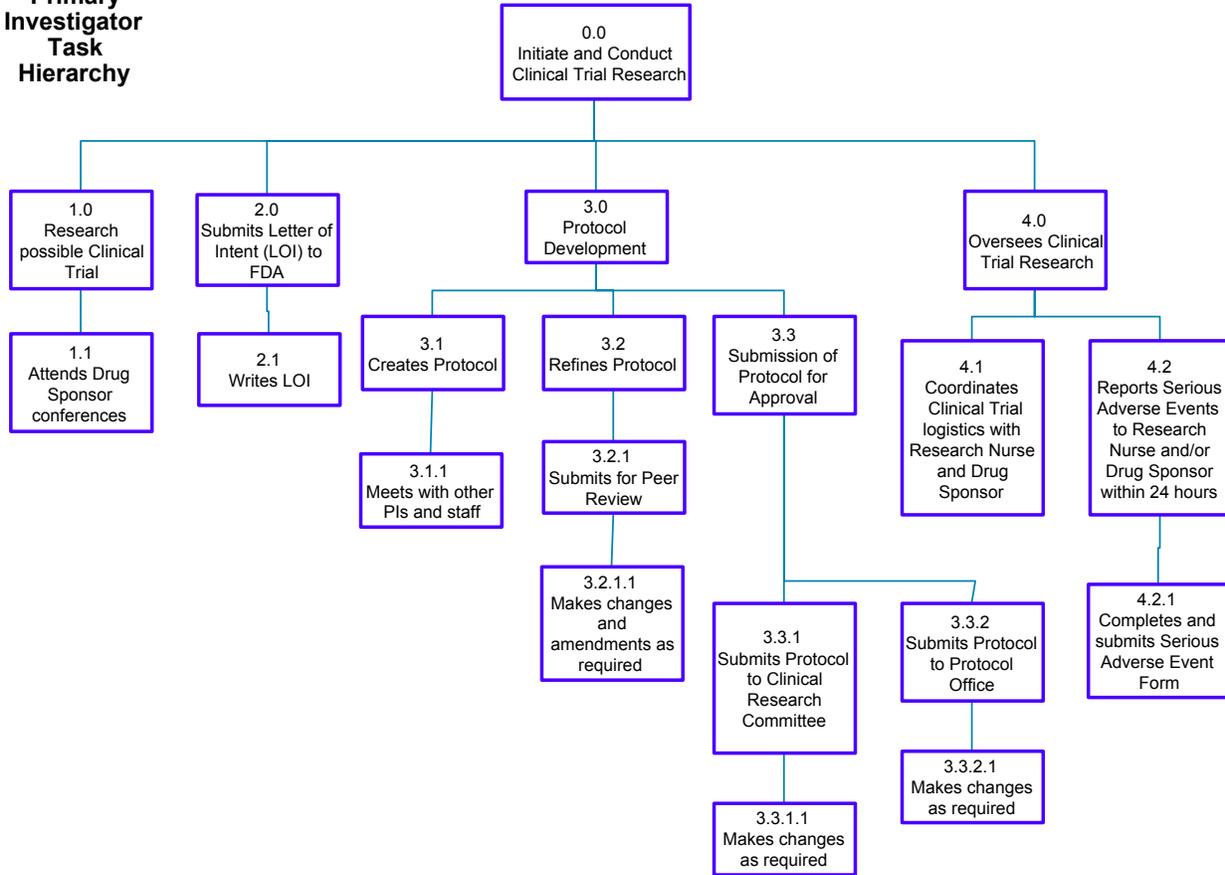
## Session Goals

Identify processes and procedures, information flows and problem areas for initiating protocol research, protocol development and authoring, and protocol submission for Phase I clinical trials.

## Report Summary

Dr. Bhagarva is a Research Fellow at the Lombardi Cancer Center, Georgetown University Hospital, Washington, D.C. He completed his residency at New York University and has come to the Lombardi Cancer Center (LCC) to complete a clinical fellowship in Developmental Therapeutics. His department is responsible for developing all Phase I clinical trials at the LCC. The Developmental Therapeutics Department also works with a limited number of Phase II and Phase III trials. This department's responsibilities include researching, developing, and authoring Phase I clinical trial protocols for new cancer drug therapies, and writing articles based on the results of this research. Dr. Bhagarva works with a team of doctors at LCC (including four other Phase I Primary Investigators). His primary research focus is on antiangiogenic drugs (drugs which halt the development of blood vessels in tumors). The report that follows was compiled from data collected during a task analysis session.

**Primary Investigator Task Hierarchy**



CMD/Primary Investigator Tasks/10-28-97

## Protocol Development Process

### Accessing Pre-Clinical Information

External agencies (i.e. NCI or pharmaceutical companies) conduct **multiple studies** (non-human experimentation) before a new drug or drug therapy is introduced to the medical community. The data from this research is presented to the medical community at NCI and / or drug company sponsored conferences. Here, physicians obtain new drug and drug therapy information. Physicians develop concepts for clinical trial research based on this pre-clinical data.

### MISSING INTERACTION HERE W/ CHAIRMAN HAWKINS

If a Primary Investigator is interested in developing a clinical trial using a new drug, he / she will call a meeting with the other Primary Investigators (there are four Phase I Primary Investigators at LCC) to discuss the viability of the new trial (could it be run at Lombardi and would it benefit LCC patients).

If a physician is interested in authoring a new protocol, but requires more pre-clinical information, he / she contacts the sponsoring organization (via phone or fax). The company who has developed the drug or drug therapy is usually cooperative when a request for additional information is made. Based on the information requested, the sponsoring organization may perform additional pre-clinical tests in order to provide more complete information to the medical community.

### **Submitting a Letter of Intent (LOI)**

Physicians (**in this instance, any practicing oncologist**), who are interested in developing a clinical trial, must first submit a Letter of Intent (LOI) to the Food & Drug Administration (FDA) Investigational Drug branch. The FDA is the initial point of contact for all clinical trial proposals. The FDA forwards all LOIs to the sponsoring company.

The LOI (a brief proposal, approx. 2-3 pages) outlines the physician's plans for conducting the clinical trial, including: proposed schedule of administration, proposed dosages, and type of patients targeted. The drug company selects which institutions will participate in the clinical trial. This decision is based on a number of criteria, including: where the drug will be developed, the track record of the institution in the development of Phase I drugs, and whether or not that institution has the resources available to conduct Phase I trials.

At Lombardi Cancer Center, the Primary Investigator writes the LOI, and then provides it to the head of the department and a Phase I RN for review. Once approved, the department head co-signs the Letter of Intent and forwards it to the FDA (via fax, US mail or e-mail). The drug company usually calls within the a, verifying receipt of the LOI. The drug company may also call if they have any questions about the submitted LOI.

Generally, a Primary Investigator will have an idea of whether or not the submitted proposal will be accepted. This is based on informal conversations with sponsoring companies at conferences, and the research history of the institute.

### **Writing the Protocol**

The Primary Investigator is responsible for authoring the protocol for a clinical trial. The protocol outlines, in detail: dosage levels, schedule of administration, patient eligibility criteria, adverse event procedures, expected toxicity levels, etc.

The sponsoring organization is also involved in the protocol authoring process. A PI will typically send a draft of the protocol to the sponsoring organization for suggestions and revisions prior to formal submittal. A PI might also ask another doctor, who has experience with the drug, to review the protocol and offer suggestions. Authoring a protocol takes anywhere from one to three months and requires input from both internal and external sources.

### **Submitting the Protocol for Approval**

After submitting a Letter of Intent (LOI), obtaining sponsor approval to conduct a trial, and authoring the protocol, the Primary Investigator submits the protocol to the Clinical Research Committee (CRC). At the LCC, a one page electronic Summary Form which briefly outlines the basic concept behind the trial (drug type, rationale, expected results) is attached to the protocol.

The CRC is an internal committee comprised of doctors, nurses and pharmacists who review all protocols before they are submitted to the Institutional Review Board (IRB). The CRC reviews the protocol for clinical soundness and technical merit. The PI incorporates CRC changes into the protocol prior to IRB submission. Once the CRC approves the submission, the PI provides a copy

to the Protocol Office, along with any pre-clinical support documentation.

The Protocol Office is responsible for submitting the protocol documentation to the Institutional Review Board (IRB).

## Phase I Clinical Trials

### Overview

The purpose of a Phase I clinical trial is to determine the toxicity (measurable reaction) of a new drug or drug therapy. The most important data collected during a Phase I clinical trial is toxicity levels. The Primary Investigator usually has an idea of patient symptoms to expect based on toxicity symptoms, based on levels recorded in the pre-clinical studies. Dr. Bhargava pointed out that pre-clinical studies cannot always predict patient reactions. It is critical that all toxicity data is accurately recorded throughout the clinical trial.

### Data Collection

Attached to each protocol is the detailed toxicity criteria for each drug. This criteria is usually presented as a scale. There are two / three types of scales that have been devised to represent data. LCC uses the scale developed by the National Cancer Institute (NCI). What differs from protocol to protocol is not the scale, but what toxicity on that scale is considered significant.

For example: Nausea has a scale of Level 1 to Level 4. For one drug, the dose limiting toxicity (the point at which you stop increasing the dose of the drug) might be Level 1. Another drug might have a dose limiting toxicity at Level 3, because the nausea can be controlled with other medication.

### Side Effects and Dose Limiting Toxicity

Typically, in a Phase I trial, physicians do not try to control side effects with other medication. This is because part of the trial is understanding how severe side effects can become. Of course, if side effects reach an intolerable level (determined by the physician or the patient), the dosage is adjusted (either reduced or stopped completely). **The first consideration is always the safety of the patient.**

The protocol specifies procedures once a dose limiting toxicity is reached. For example: A protocol outlines the dose limiting toxicity of a drug as Level 3 for nausea. The protocol would state that if the side effect, nausea, reaches a dose limiting toxicity of Level 3 then the drug should be stopped immediately. Then the protocol details how much time passes before the toxicity (i.e. nausea) resolves itself, if it resolves at all. Then, once the toxicity has resolved, the protocol may state that administration of the drug can be resumed, but only at a 50% dosage level.

### Publishing Clinical Trial Results

Part of the Dr. Bhagarva's responsibility as a research fellow is to produce articles or abstracts for publication summarizing clinical trial findings. Interpreting the clinical trial data is one of the most time important and consuming aspects of his job. Physicians do not have a standard method for

reporting patient toxicities (side effects).

Each protocol outlines the criteria for grading symptom severity for that clinical trial. For example: there is a Grade 1 nausea (0-2 episodes a day); grade 2 is 2-4 episodes a day. However, the physicians rarely have a copy of the protocol toxicity scale for the trial to review during patient exams. Doctors and RN's who see patients, often must report the symptoms in a subjective manner. This is a problem when what one doctor classifies as "severe nausea" is classified by another physician as "moderate nausea".