

Conducting a Clinical Trial at Dartmouth Hitchcock Medical Center/Dartmouth College:

The Basics of Clinical Trial Management



**Office of Sponsored Projects
Clinical Trial Administration/Education Working Group**

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1. Introduction

This guide contains a fundamental overview of the administrative management involved in conducting a clinical trial at Dartmouth. The conduct of a clinical trial involves multiple layers of review and numerous entities throughout the institution. Dartmouth strives to ensure that all clinical trials are conducted according to federal and state regulations and ethical principles.

There are two offices with institutional authority to negotiate and sign Clinical Trial Agreements. The Office of Sponsored Projects at Dartmouth College and The Hitchcock Foundation at the Dartmouth Hitchcock Clinic. A PI does not have the institutional authority to sign a Clinical Trial Agreement on behalf of the Hitchcock Clinic or Dartmouth College.

Please note: Due to federal regulations, all federally funded clinical trials must be managed by OSP.

2. Roles and Responsibilities

Principal Investigator (PI):

- The PI has the ultimate responsibility of ensuring that all aspects of the trial are adhered to. This includes the scientific integrity of the trial, resource availability, and budget management. The PI is also responsible for informing study subjects of the nature of the trial and risk factors. Communication is either by direct contact with the study subjects or by an assigned designee with appropriate expertise.

Research Nurse/Coordinator or Practice Manager

- The PI may delegate billing plan, budgeting, IRB and regulatory responsibility to a Research Nurse/Coordinator or Practice Manager

Note: The Practice Manager and/or the Departmental Administrator are ultimately responsible for approving the budget. They also have the responsibility to understand the physician's time/effort and making sure they fulfill their clinical commitments.

Department Administrator/Department Grant Manager:

- Assists PI/Research Coordinator in assessing financial viability of trial
- Confirms available funding
- Reviews project for administrative and financial accuracy prior to Chair's signature
- Serves as a resource to PIs, Research Coordinators, and Administrators
- Invoices, monitors, and reconciles study account

Department Chair:

- Approves research and requested budget
- Certifies time commitment/effort of PI

Office of Sponsored Projects:

- A source for identifying funding opportunities
- Negotiates and signs agreements
- Creates award account number and enters budget when checks are received
- Coordinates all award-closing procedures with PI and department

Hitchcock Foundation:

- Assists department to complete the billing plan/schedule of events
- Assists with budget preparation
- Gives appropriate institutional contact information
- Negotiates and signs agreements
- Coordinates accounting procedures with Mary Hitchcock Memorial Hospital/Dartmouth Hitchcock Clinic

3. Clinical Trial Process**a. Budget Development**

As the Department Administrator, the first step in budget development is to arrange a meeting with the PI, study coordinator, clinical research associate (CRA), research pharmacist, nurse coordinator, the business/financial manager, and other specialists as appropriate. The attendees will discuss viability, and affordability of the study as well as standard of care costs vs. research costs.

If it is determined that the study will be pursued, the department administrator should contact the Institutional Review Board (IRB) and the Office of Sponsored Projects (OSP), or Hitchcock Foundation (HF) as soon as possible.

In the budget development phase, considerations must be given to determine study time and costs by developing a billing plan encompassing standard of care vs. non-standard of care costs using the above schedules.

A Billing Plan/Schedule of Events (Grid) that establishes standard of care costs and delineates responsibility for payment, is required for each clinical research proposal.
http://www.dhmc.org/dhmc-internet-upload/file_collection/ACFC09E.xls

The Schedule of Events is specific to **Drug** or **Device** trials (see appendix) and the protocol must match the budget used. This protocol can be used to set the schedule of events, such as flow charts (i.e. cycles, lab, etc.). Each event should be entered into the budget.

The **Budget Template** allows for recording all costs associated with the study. A list of resources is provided at the bottom of the template to assist in establishing study costs.
http://www.dhmc.org/dhmc-internet-upload/file_collection/THF%208-05%20Budget%20Template-0.xls

Considerations: Beware of hidden and/or unexpected costs and invoiced procedures such as CT scans. Also, the budget should allow for non-refundable fees such as IRB, Pharmacy Fees, etc.

It is also CRITICAL that Department Administrators work very closely with Lisa Bundy, in Billing Compliance at DHMC. Department Administrators should make sure to check with her that all clinical fees are correct.

Note: If it is determined that the reimbursement per patient will be significantly more than the cost per patient, the Department Administrator should notify the IRB office and their OSP Sponsored Research Manager. The information in the contract, budget, informed consent and the protocol should match. Informing your OSP Sponsored Research Manager of the variance in the reimbursement will also allow them to put a note in the file that will serve as a reminder that there will be a residual balance at the end of the study.

b. Contract Negotiation

Concurrently with the budget development, the contract is negotiated with the sponsor by the OSP Assistant Director or the Hitchcock Foundation. When negotiations are complete, a signed routing form, Billing Plan, and final budget are then sent to the appropriate negotiating office.

All studies must have a Proposal **Routing Form** signed by the department chair before a contract can be signed for sponsored research.

For Hitchcock Foundation clinical trial agreements use:

http://www.dhmc.org/dhmc-internet-upload/file_collection/routing_form.xls

For all Dartmouth College agreements the routing form should be submitted electronically to the Office of Sponsored Projects via the following system:

http://oracle-www.dartmouth.edu/dart/groucho/gc_prf.main_menu

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b1. OSP

OSP (typically the Assistant Director) receives the protocol from the sponsor or department and reviews the contract while it is simultaneously being reviewed by the Cancer Center Review Committee (CCRC) or another scientific review group. Once the protocol has been reviewed and accepted, the budget committee meets.

When the budget is approved, the administrator from the department submits the routing form, budget, and billing grid to OSP and the study is entered into the proposal log.

Negotiations may continue but the agreement can not be signed until IRB has given final approval.

When the agreement has all required approvals and has been signed by OSP, it is sent to Information Systems at OSP for an account number assignment.

The complete file then goes to the Sponsored Research Manager at OSP for monitoring.

Documents required by OSP:

- Routing form
- Billing Grid
- Final budget
- Billing Plan
- Final protocol
- Any sponsor contact information that is not in the agreement
- Any attachments listed in the agreement

b2. Hitchcock Foundation

The Hitchcock Foundation will follow similar procedures as the Office of Sponsored Projects.

Documents required by Hitchcock Foundation:

- Billing Plan
- Contract
- Budget
- Checklist
- Routing Form (Practice Manager is the person who should sign off as the Financial Manager on the routing form certifying budget)

Note: MHMH/Clinic Accounts will initiated by the Hitchcock Foundation or OSP Sponsored Research Manager upon confirmation that all of the above required documents have been received.

c. Subcontract

If there is a subcontract, the Subaward Coordinator at OSP will be responsible for the administrative tasks such as agreement negotiations, obtaining signatures, and routing of the executed agreement to all parties.

4. Financial Management

OSP

a) Monthly account reconciliation:

For best practices, it is expected that the department manager will reconcile accounts with the billing plan at least every 30 to 45 days. Accurately charged expenses on clinical trials will depend on adequate budget preparation and understanding the charge-capture processes and systems. The department manager should develop procedures and tools to support correct expense charging and subsequent proper invoicing.

Communication is the key to account reconciliation. The PI should be kept informed of expenses and balances. OSP should also be informed of the status of the account, the milestones that have been met, and expected payments.

Here are some helpful financial management hints for reconciling:

- Are all charged expenses appropriate?
- Have professional fees been charged to the study account?
- Is all supporting documentation available?
- Have all charges been posted?
- Have all payments been received? If not, the department manager should follow-up with the sponsor for payments.
- Have all variable and/or additional costs been invoiced?

If the clinical trial account is over/under budget, the department manager will determine the cause. The department manager will review the contract for payment terms and compare to enrolled subject count to date. Unpaid invoices will then be discussed with the sponsor to determine if the sponsor's financial obligation can be met.

b) Invoicing & Payment:

Each department manager should create an invoicing system capable of tracking billing, including all up front non-negotiable fees, and payments received. For these particular invoices, the OSP Sponsored Research Manager should be notified of criteria completion and that payment is forthcoming. Generally, payment is submitted by the sponsor after receipt of an invoice, a case report form, or on regularly set intervals as outlined in the contract.

As per the agreement, checks for OSP clinical trials should be mailed to:

Trustees of Dartmouth College
Office of Sponsored Projects
11 Rope Ferry Road, HB 6210
Hanover, NH 03755-1404

Clinical trials are unique in that payments are based on established milestones such as patient enrollment or tasks completed. Payments are made by sponsor upon review of completed case report forms (CRFs).

Unlike other sponsored projects, the clinical trial budgets are not entered into the financial accounting system (FAS) at the beginning of the trial. This is done as checks are received. The department manager should work with the OSP Sponsored Research Manager on the budget breakdown for payments.

c.) Clinical Trial Close Out:

Before a clinical trial account can be closed out, the department manager will review the account to verify that all appropriate expenses have been charged per the Billing Plan.

The PI will submit a signed close out memo to the OSP Sponsored Research Manager certifying that all expenditures/obligations related to the project have been finalized.

If there is a residual balance, the PI will need to submit an explanation to the OSP Sponsored Research Manager. The existence of residual funds may indicate services not billed, unpaid invoices, or expenses billed inappropriately to another payer.

If diligent review indicates appropriate charges have been submitted, the OSP Sponsored Research Manager will be notified and in turn will review the terms and conditions of the agreement for handling of the residual balance. In some cases, the clinical trial agreement may reference that all unused funds will need to be returned to the Sponsor. The OSP Sponsored Research Manager will carefully review the clinical agreement for such clauses before approval is authorized for residual funds then may be moved to a research reserve account.

Hitchcock Foundation

The Hitchcock Foundation does not require a formal signed close out memo from the PI. The PI needs to submit an email request, verifying that the trial has closed, that all obligations under the agreement have been fulfilled and funds will be moved to an Advised Fund for future research or educational expenses.

5. Institutional Reviews Required

All clinical trials must have sufficient resources and scientific merit to be conducted at DHMC. Depending on the nature of the project there may be other Institutional Reviews Required prior to initiation.

The Committee for the Protection of Human Subjects

The Committee for the Protection of Human Subjects (CPHS) is a federally mandated committee in charge of overseeing all institutional research projects involving human participants. All research involving humans (regardless of funding) must be reviewed and approved by the CPHS prior to initiation. <http://www.dartmouth.edu/~cphs/>

Nationally this committee may be referred to as the Institutional Review Board (IRB). The names are synonymous.

The Trustees of Dartmouth College in alliance with: Dartmouth College (including the College of Arts & Sciences, Tuck Business School, Thayer School of Engineering, and Dartmouth Medical School), Dartmouth - Hitchcock Clinics, Dartmouth Hitchcock Alliance Hospitals, and the Department of Veteran Affairs (White River Junction, VT) have signed a contract with the federal government, called a Federal Wide Assurance of Compliance (FWA00003095), and abide by 45 CFR 46, 21 CFR 50 and 56 where applicable, and 38 CFR 16 and any additional VA specific regulations for protocols to be conducted under the auspices of the Veterans Hospital, White River Junction.

The primary mission of the CPHS is to ensure that the rights and welfare of human research participants are protected.

The CPHS has the authority to approve, require modifications in, or disapprove all research activities that fall within its jurisdiction as specified by both the federal regulations and local institutional policy. Research that has been reviewed and approved by the CPHS may be subject to review and disapproval by officials of the institution. However those officials may not approve research if it has been disapproved by the CPHS.

6. Environmental Health & Safety (EHS)

EHS needs to be contacted if the research involves the following:

1. Work with hazardous chemicals, including toxins and chemotherapeutic drugs in a non clinical setting
2. Work with radioactive materials, lasers, x-rays, etc. in a non clinical setting
3. Work with biological materials, including recombinant DNA, bacteria, yeast, cell culture, viruses, tissue (animal or human), etc.

In addition, the removal and disposal of hazardous waste generated in research activities is handled through EHS. <http://www.dartmouth.edu/~ehs.html>

7. Technology Transfer

For issues related to intellectual property, its ownership and disposition, please contact Dartmouth's Technology Transfer Office:

Alla Kan, Director
Phone: (603) 646-3027
Fax: (603) 646-3670
Email: technology.transfer@dartmouth.edu
Website: <http://www.dartmouth.edu/~tto/>

8. Resources

Office of Sponsored Projects: <http://www.dartmouth.edu/~osp/resources/clinical.html>

Hitchcock Foundation: <http://www.dhmc.org/goto/hitchcockfoundation>

IRB: <http://www.dartmouth.edu/~cphs/>

EHS: <http://www.dartmouth.edu/~ehs.html>

A Phase One Study:

Phase I studies are primarily concerned with assessing a drug's safety. This initial phase of testing in humans is done in a small number of volunteers (20 to 100), who are usually paid for participating in the study. The study is designed to determine what happens to the drug in the human body--how it is absorbed, metabolized, and excreted. A Phase I study will investigate side effects that occur as dosage levels are increased. This initial phase of testing typically takes several months. About 70 percent of experimental drugs pass this initial phase of testing. Please note phase one studies may also be conducted in disease specific populations (e.g. cancer).

A Phase Two Study:

Once a drug has been shown to be relatively safe, it must be tested for efficacy. This second phase of testing may last from several months to two years, and involve up to several hundred patients. Most Phase II studies are randomized trials. One group of patients will receive the experimental drug, while a second "control" group will receive a standard treatment or placebo. Often these studies are "blinded"--neither the patients nor the researchers know who is getting the experimental drug. In this manner, the study can provide the pharmaceutical company and the FDA comparative information about the relative safety of the new drug, and its effectiveness. Only about one-third of experimental drugs successfully complete both Phase I and Phase II studies.

A Phase Three Study:

In a Phase III study, a drug is tested in several hundred to several thousand patients. This large-scale testing provides the pharmaceutical company and the FDA with a more thorough understanding of the drug's effectiveness, benefits, and the range of possible adverse reactions. Most Phase III studies are randomized and blinded trials.

Phase III studies typically last several years. Seventy to 90 percent of drugs that enter Phase III studies successfully complete this phase of testing. Once a Phase III study is successfully completed, a pharmaceutical company can request FDA approval for marketing the drug.

APPENDIX

List of Acronyms/definitions

CCRC-Clinical Cancer Research Committee

CPHS-Committee for the Protection of Human Subjects

CRA-Clinical Research Associate

CT- Computed Axial Tomography

DHMC - Dartmouth Hitchcock Medical Center

DMS-Dartmouth Medical School

EHS-Environment Health and Safety

FAS-Financial Accounting System

HF-Hitchcock Foundation

IBC- Institutional Biosafety Committee

IRB-Institutional Review Board

MHMH – Mary Hitchcock Memorial Hospital

OSP-Office of Sponsored Projects

PI-Principal Investigator

VA-Veteran Affairs