PREP Course #14:
Advanced Good Clinical Practice (GCP)

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The Office of Research Compliance
CME Disclosure Statement

• The North Shore LIJ Health System adheres to the ACCME’s new Standards for Commercial Support. Any individuals in a position to control the content of a CME activity, including faculty, planners, and managers, are required to disclose all financial relationships with commercial interests. All identified potential conflicts of interest are thoroughly vetted by the North Shore-LIJ for fair balance and scientific objectivity and to ensure appropriateness of patient care recommendations.

• Course Director, Kevin Tracey, has disclosed a commercial interest in Setpoint, Inc. as the cofounder, for stock and consulting support. He has resolved his conflicts by identifying a faculty member to conduct content review of this program who has no conflicts.

• Emmelyn and Evelyn have nothing to disclose.
Today’s Objectives

Identify and discuss principles of conducting research in compliance with GCP standards including the following:

• Discuss Federal, State and local research requirements
• Discuss required documentation (ALCOA)
• Describe elements of a good quality assurance program
• Describe organizational and management techniques
• Discuss issues that occur during the conduct of the study and how to handle them
Regulatory Environment of Research

Investigator

Federal

State

GCP

NSLIJHS

IRB
Federal Requirements

FDA
- **Purpose**: Approval for marketing and research: Drugs, Devices, Biologics
- **Regulations**: 21 CFR 50, 56, 54, 312, 812
- **Focus**: Data Integrity and subject protection

OHRP
- **Purpose**: Provides leadership in the protection of the rights, welfare, and wellbeing of subjects involved in research conducted or supported by the HHS.
- **Regulations**: 45CFR46
- **Focus**: Protection of the rights, welfare and wellbeing of human subjects
Local Requirements

NY State Law Examples:
• Licensure (practice requirements/limitations)
• Minors/Legally Authorized Representative
• HIV Testing Requirements
• Controlled substances

Health System Policies
• Health System Research Policies on Health Port
• The Health System applies ICH GCP for clinical trials regardless of funding source or oversight agency
• Documentation associated with the conduct of clinical research should be ALCOA
• Institutional Review Board Policies

→ Ensure the protocol requirements don’t conflict with local requirements
Let’s Think

What rules and regulations do you need to follow for the following types of studies?

1) Interventional drug trial

2) Interventional drug trial where you hold an IND (or act as a sponsor-investigator as per FDA definition)
Let’s Review GCP E6

GCP = Good Clinical Practice

An international ethical and scientific quality standard for designing, conducting, recording, and reporting human subject research

Established by International Conference on Harmonization (ICH)

Created to establish a common standard for clinical research practice
What Are Principles of GCP?

2.1 Clinical trials should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with GCP and the applicable regulatory requirements.

2.2 A trial should be initiated and continued only if the anticipated benefits justify the risks.

2.3 The rights, safety and well-being of the trial subjects are the most important consideration and should prevail over interests of science and society.

2.4 Available nonclinical and clinical info on an investigational product should be adequate to support the proposed clinical trial.

2.5 Clinical trials should be scientifically sound, and described in a clear, detailed protocol.
What Are Principles of GCP?

2.6 A trial should be conducted in compliance with the IRB approved protocol.

2.7 Medical care and medical decisions made on behalf of subjects should always be the responsibility of a qualified physician (or dentist).

2.8 Each individual conducting a trial should be qualified by education, training and experience to perform his/her respective task(s).

2.9 Freely given informed consent should be obtained from every subject prior to participation.

2.10 All clinical trial information should be recorded, handled and stored in a way that allows its accurate reporting, interpretation and verification.
What Are Principles of GCP?

2.11 Confidentiality of records that could identify subjects should be protected, respecting the privacy & confidentiality rules.

2.12 Investigational products should be manufactured, handled, and stored in accordance with applicable good manufacturing practice (GMP). They should be used in accordance with the approved protocol.

2.13 Systems with procedures that assure the quality of every aspect of the trial should be implemented.
What Does GCP Cover?

Section 8: Essential Documents for the Conduct of a Clinical Trial – what you need to have on file before, during and after your trial.
What Does Compliance with GCP Ensure?

Provides public assurance that:

• The rights, safety and well-being of subjects are protected
• Clinical trial data are credible

→ What happens if you have practices that lead to “bad data”? 
If it's not documented (or documented inaccurately) it never happened.

Significance of Good Documentation Practices

Gives credibility to the data because it allows for the validation of study results.

Provides an audit trail.

Provides evidence of investigator involvement, compliance with local requirements and Federal regulations.
## Fundamental Elements of Data Quality

Is your documentation ALCOA compliant?

| A | Attributable – Does the documentation clearly demonstrate:  
|   | • Who created the record and when,  
|   | • What happened, and  
|   | • When it occurred? |
| L | Legible – Can the information be easily read and understood? |
| C | Contemporaneous - Was the information documented with timeliness?  
|   | • Complete – Does the documentation include all of the necessary info? |
| O | Original – Did you maintain the “source” of the information (see GCP Glossary, Sections 1.51 and 1.52)? |
| A | Accurate – Does the information represent what actually happened? |

→ What are some examples?
Universal Characteristics of Good Documentation Practices

Transparency
• Eliminate guess work
• Your documentation should clearly illustrate study-related events
• Make sure that the source of the data is maintained, organized and available

Consistency
• Develop standard documentation practices so that all members of your study team document information consistently for every subject
• Explain discrepancies
Universal Characteristics of Good Documentation Practices

Atypical Circumstances

• Clearly capture unusual circumstances so that there is no misunderstanding of study-related events.

Corrective and Preventive Actions

• When an error is made, address it with timeliness. When possible, take action to correct the error.
• If the error is related to a systemic problem, investigate the root cause, document the action as well as the steps taken to prevent future occurrences. Re-educate staff. Report the error when applicable.
• *Use notes to file wisely*
Recording Data on CRFs

Use ALCOA and complete as per protocol/SOP

- 4.9.2: Data reported on the CRF, that are derived from source documents, should be consistent with the source documents or the discrepancies should be explained

Make corrections appropriately

- 4.9.3: Any change or correction to a CRF should be dated, initialed, and explained (if necessary) and should not obscure the original entry (i.e. an audit trail should be maintained); this applies to both written and electronic changes or corrections
Short Exercise

You are doing an internal GCP audit on your consent form and CRFs within the research chart.
What Consent Documentation Issues Can You Find?

The Feinstein Institute for Medical Research
North Shore-Long Island Jewish Health System (NSLIJHS)

Research Questionnaire

Title: Sample Trial with Awesome Drug

Principal Investigator: Seymour Errors, MD

Please answer the following questions after reviewing the consent form for this study. The researchers doing this study want to be sure that you know what is involved in being in this research study. This questionnaire will help them make that decision. You may ask questions of the researcher and review the consent form again at any time.

I am being asked to be in a research study. True False

This study involves the use of investigational drugs. True False

I have to participate in this research study to receive treatment. True False

I can stop being in this study at any time. True False

There are risks to me from participation in this study. True False

I am guaranteed to feel better from being in this study. True False

Ivan Drough
Printed Name of Subject

Signature of Subject

Seymour Errors
Investigator’s Signature

Date 4/13/11
What Consent Documentation Issues Can You Find?

The Feinstein Institute for Medical Research
North Shore-Long Island Jewish Health System (NSLIJHS)

Who can answer my questions?
You should feel free to ask any questions. For questions about the Sample Trial, call 888-444-1234. For questions about your rights as a research volunteer, contact the NSLIJHS Institutional Review Board at 516-562-3101.

Summary:
I have read the above description of the Sample Trial. I have been informed of the risks and benefits involved and all my questions have been answered to my satisfaction. I have been informed that a member of the research team will answer any future questions that may arise. By signing this form I have not given up any of my legal rights.

Ivan Drough
Subject’s printed name

Naive Lee
Witness’s printed name

Investigator’s Statement
In addition to advising the above subject of other forms of treatment and therapy which are appropriate, I have offered an opportunity for further explanation of the risks and discomforts which are, or may be associated with this study and to answer any further questions relating to it.

Seymour Errors
Investigator’s printed name

Date: 4-13-11
What CRF Documentation Issues Can You Find?

CASE REPORT FORMS (CRFs)
Sample Trial with Awesome Drug

Date of Visit: 1/3/04 (yy/mm/dd)
Subject ID: 0012

Visit:
- [ ] Screening
- [ ] Pre-randomization
- [ ] Randomization
- [ ] Month #1
- [X] Month #2
- [ ] Month #3
- [ ] Month #4
- [ ] Month #5
- [ ] Month #6

Physical Exam

<table>
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<tr>
<th>System</th>
<th>Normal</th>
<th>Abnormal Finding</th>
<th>Not Done</th>
<th>Description of Abnormal Findings</th>
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<tr>
<td>General Appearance</td>
<td>[X]</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Skin and mucous membranes</td>
<td>[X]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eyes</td>
<td>[X]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ears, nose, throat</td>
<td>[X]</td>
<td></td>
<td></td>
<td></td>
</tr>
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<td>Cardiovascular</td>
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<tr>
<td>Lymph nodes</td>
<td>[X]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other, specify:</td>
<td>[X]</td>
<td></td>
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</tr>
</tbody>
</table>

Blood Pressure (mmHg): 110/80
Pulse: 80
Temperature (°C): 38.1
Respirations: 15

BMI: 23.3

Arrhythmia

Check this at next visit

Completer Initials
Top Documentation Issues

Health System Audit and IRB Data

Consent Forms:
- Consent quiz completion errors without adequate documentation
- Completion issues (missing signature and/or date of witness or investigator; tiers incomplete)
- Inconsistent dates of signing parties

Regulatory:
- Incomplete staff signature/delegation log
- No subject study enrollment note or documentation of progress on trial
Top Documentation Issues

FDA Warning Letter Data

Adhering to the protocol – failure to:
• follow inclusion/exclusion criteria/document how exclusion criteria were met
• perform protocol-required testing within appropriate time frame or perform assessments/procedures
• report SAEs to sponsor/recording AEs on CRFs

Maintaining adequate subject records – failure to:
• maintain adequate case histories
• record overall observations
• maintain accurate records regarding receipt, use, and disposition of device

Top Documentation Issues

FDA Warning Letter Data

Adequately protecting human subjects – failure to:
• document informed consent through use of a written IRB approved consent form
• include all required elements in the consent form

Assuring proper IRB approval – failure to:
• promptly report to the IRB all changes in research activity
• obtain IRB approval for changes prior to implementing changes
Case Study

FDA Warning Letter$^2$ - Documentation

What’s in the protocol:

Sec. 7.3.3 “Nonserious AEs, requires that all identified nonserious AEs must be recorded and described on the appropriate nonserious AE page of the CRF”

Sec. 7.3.1 “Serious Adverse Events, requires that all SAEs must be reported within 24 hours.”

What the FDA found:

“AEs/SAEs identified in either clinic visits or hospital reports were neither documented in the CRFs nor appropriately reported to the sponsor.”

2. FDA warning letter for clinical investigator issued 8/12/11
Case Study

FDA Warning Letter - Documentation

What’s the site said: AEs identified were ER visits and that at study visits, the PI and study coordinator asked subjects whether they had had any AEs or hospitalization, and the subjects said “No”

Their corrective and preventive action:
1) During the AE interview, information regarding ER visits, hospitalization and other complaints would be requested
2) Prior to the subject’s visit, chart preparation would also involve reviewing hospital records for ER visits
3) An inservice will be provided to all physician’s office staff to discuss communication of ER visits of research subjects

→ What was the FDA’s response to this?
FDA Warning Letter - Documentation

FDA’s response: The site’s response was inadequate.

Why?

- In a previous inspection in 2008 the FDA had identified findings related to delay in reporting SAEs and inaccuracies in documentation of AE/SAEs
- The site had developed SOPs related to AE reporting, but the site did not follow their SOPs
- The study coordinator had informed the FDA that she was unaware of any written clinical research procedures at the site

FDA Final Determination: Failure to ensure the investigation was conducted according to the investigational plan [21CFR312.60]
Case Study

FDA Warning Letter - Documentation

What’s in the protocol:
After reviewing a subject’s international normalized ratio (INR) value, the investigator was to make a final dosing decision.

What the FDA found:
“The only documentation of dosing decisions for subjects was the unsigned “face sheets” filled out by the study coordinator. Review of face sheets found no documentation that the PI ordered the study drug dose to be maintained, withheld or adjusted or that he confirmed that the drug dosing decisions recorded by the study coordinator were in line with his orders.”
Case Study

FDA Warning Letter - Documentation

What’s the site said: ”their process for relaying dosing information included the study coordinator relaying blinded INR results to the PI verbally or via text message, and the PI would tell the coordinator to maintain, withhold, or adjust the current dose. The coordinator would issue dosing instructions according to verbal orders.”

Their corrective and preventative action:
1) Will prevent recurrence by documenting this process via a late entry
2) Not use a sponsor provided source sheet that the coordinator could use to sign off on changes

→ What was the FDA’s response to this?
FDA Warning Letter - Documentation

FDA’s response: The site’s response was inadequate.

Why?

• Does not address the root cause of the violation or ensure appropriate corrective and preventive actions
• PI indicated that he would review and sign off on all medical decision making in writing, but did not actually do this
• Failure to maintain adequate and accurate case histories compromises the interpretation and validity of the investigational endpoint

FDA Final Determination: Failure to prepare and maintain adequate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation[21CFR312.62(b)]
Good Quality Assurance Program (GQAP)
Quality Assurance

The systematic and independent examination of all trial-related activities and documents.

It determines whether the evaluated activities were appropriately conducted and that the data were generated, recorded, analyzed, and accurately reported according to protocol, standard operating procedures and good clinical practices.
Why Do We Need the GQAP (1)

Trends in the Regulatory Process

- Increasing surveillance and regulatory oversight emerged over the past 25 years
- FDA employs comprehensive program for on-site inspections and data audits
- Inspections of US sites & sponsors by non-US regulatory agencies
- Premarket requirements become more stringent
- Greater emphasis on training methods and programs
Why Do We Need the GQAP (2)

The FDA highlighted the PI’s responsibilities in conducting clinical trials:

• Ensuring that a clinical investigation is conducted according to the signed investigator statement for clinical investigations of drugs, including biological products, or agreement for clinical investigations of medical devices, the investigational plan, and applicable regulations

• Protecting the rights, safety, and welfare of subjects under the investigator’s care

• Controlling drugs, biological products, and devices under investigation
Why Do We Need the GQAP (3)

The ICH (International Conference on Harmonization) is also very clear on the responsibilities of research sponsor, and we have many investigator-initiated studies in the health system

- Assurance and quality control systems with written SOPs to ensure that trials are conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP and the applicable regulatory requirement(s)
- Quality control should be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly
- The PI will protect the safety and well-being of all participants in the clinical study at all times
What Does the GQAP Include? (1)

• Ensuring that the study personnel are appropriately and adequately trained
• Conducting regular internal self-audits by dedicated personnel
• Actively implementing and revising SOPs
• Recording protocol deviations, violations and unanticipated problems
What Does the GQAP Include? (2)

- Statistical Analysis Process- DSMB, DSMP, data analysis tools
- Corrective and Preventive Action Process - Initiating procedures to correct any shortcomings and prevent their recurrence
- Continual Improvement Process- continually monitor and evaluate study activities and to improve processes
Ensuring That Study Personnel Are Appropriately and Adequately Trained

FDA focuses on four major areas:

• Whether individuals who were delegated tasks were qualified to perform such tasks,
• Whether study staff received adequate training on how to conduct the delegated tasks and were provided with an adequate understanding of the study,
• Whether there was adequate supervision and involvement in the ongoing conduct of the study,
• Whether there was adequate supervision or oversight of any third parties involved in the conduct of a study to the extent such supervision or oversight was reasonably possible.
Conducting Regular Self-audits by Dedicated Personnel

- Identify and train study personnel to conduct self-audits for the department
- Develop self-audit plans for the department
- Develop different templates for the self-audits
- Create a database for the self-audit analysis
- Update and implement the SOP based on the audit findings
Actively Implementing and Revising SOPs

• Setting up and implementing the SOP
• Regularly reviewing the SOP with research personnel
• Updating the SOP based on audits findings, regulation and policy changes
Recording Protocol Violations, Deviations and Unanticipated Problems

During the study conduct, if any protocol violations, deviations, and unanticipated problems appear:

- The PI must submit to the IRB with reports that meet the submission criteria within the proper timeframe.
- The IRB must review and make appropriate determinations regarding risks, potential benefits, the adequacy of the consent documents, ensure the provision of updated information to subjects, reevaluate whether adequate safeguards are in place to protect human subjects, including subject privacy and the confidentiality of data.
- The PI must make any changes to the protocol, recruitment materials, and/or consent documents as required by the IRB.
- The IRB will report the events determined to represent an unanticipated problem to regulatory agencies and the appropriate organizational officials.
Statistical Analysis Process- DSMB, DSMP, Data Analysis Tools

- Identify unacceptably slow rates of accrual
- Identify high rates of ineligibility determined after randomization
- Identify protocol violations that suggest clarification of changes to protocol are needed
- Identify unexpectedly high dropout rates that threaten the study’s ability to produce credible results
- Ensure the credibility of the study
- Ensure the validity of study results
- Protect the safety of study participants
Corrective and Preventive Action Process

Initiate procedures to correct any shortcomings and prevent their recurrence

- To identify study personnel responsible for defining and implementing the corrective actions
- To ensure that complaints, discrepancies, and noncompliance are visible, prioritized, and tracked
- To ensure that the root cause is determined and resolved
- To provide a system to track issues of noncompliant that have not been resolved
Continual Improvement Process

- Continually monitor and evaluate the research activity and to improve all study development process

- Update and implement the SOP reflecting the improvement process
The Shewhart Model of Quality Assurance
Organizational Management Techniques

• Managing clinical studies, of whatever size and complexity, requires efficient study management techniques

• Study management is essential among the key competencies that are needed to deliver high-quality trials

• Actively managing every aspect of the study is the key to success
What Kind of Techniques Would You Need?

- Dedicated and experienced investigators and research staff
- Education, training and experience
- Research Study planning
- Collaboration
- Efficient work for investigators and participants
- Communication
- Efficient systems
- Efficient recruitment of study participants
Dedicated and Experienced Investigators and Research Staff

- Investigators and Research Staff are qualified by training and experience for their research roles, including knowledge of applicable laws, regulations, codes, and guidance.
- Investigators maintain appropriate oversight of each research study, as well as Research Staff and trainees, and appropriately delegate research responsibilities and functions. The ability to organize and motivate other team members.
- Investigators and Research Staff follow the requirements of the research protocol or plan and adhere to the policies and procedures of the Organization and to the requirements or determinations of the IRB.
- Investigators and Research Staff recruit participants in a fair and equitable manner.
Education, Training and Experience

- Qualified academic educational credentials for study personnel
- Appropriate and adequate training must remain current in human research protections. This consists of completing the initial training and educational requirements prior to submitting any research projects to the IRB and renewing the educational requirements prior to the training expiration date. Additional training and education will be required periodically
- Continuing education depends on the roles in the team
- Sharing successful experiences with other research team within or outside the health system
A clinical study shares many features with any other type of business project as defined in the field of project management.

These features include the following:

- A clear objective aimed to bring about change
- Research team
- A set time scale
- Defined resources to achieve the objective
- Tasks analysis for which need to be completed
Research Study Planning (2)

All studies consist of a series of processes, a set of actions to bring about results.

The five basic process stages are:

- Planning
- Initiating
- Conducting
- Self-auditing and self-monitoring
- Analysis and final report
Collaboration (1)

• All studies need to be actively promoted and marketed. It is well established that interdisciplinary collaboration offers greater potential for success.

• To be successful, most studies depend on developing some sort of collaborative group. The aim of a collaborative group or network is to be inclusive rather than exclusive. Proactively raising the profile of any developing project and creating a group of interested people takes time and commitment.
Collaboration (2)

• For large, multi-center studies, this will be a diverse multidisciplinary group including research staff from each participating site.

• For smaller and single-center studies, the group will be less formal and may be just a handful of like-minded people.

• Collaboration could be done in many ways, through personal contact, presentations at relevant conferences, mail, newsletters, from the professional colleges, journal articles, and general word of mouth.
Efficient Work for Investigators and Participants

Efficient work for investigators and participants means ensuring recruitment procedures run alongside routine practices.

- Site visits will evaluate the trial conduct and will become part of the daily routine
- The recruitment procedure needs to be realistic and practical
- Development of the data collection forms should begin early in the process of trial development (only for investigator initiated studies)
Communication among research staff:

1. Regular and frequent staff meetings provide forums for discussion of logistical issues such as problems with clinic flow and recruitment and compliance
2. Comments and suggestions from co-workers
3. Staff members know to whom they should report and with whom they could consult about particular issues

Communication with investigators and subjects’ physicians:

1. Establish early contact with subjects’ physicians to inform their patients’ involvement in the trial
2. Share and update information about the trial with all the study’s investigators;

Communication with the Coordinating Center and/or the study Sponsor: Could be classified into three categories: routine, safety related, and clarification.
Efficient Systems

• A study, particularly a large study, needs robust computerized systems and procedures that monitor every aspect of the day-to-day running of the trial

• A reliable system that will monitor recruitment, randomization procedures, stock control, data management, data cleaning, and central data monitoring and that will produce useful report should be developed

• There needs to be a logical and transparent structure, concise documentation (standard operating procedures) and accountability of every process employed in the study
Efficient Recruitment of Study Participants

The investigative site is responsible for recruiting and enrolling study subjects who meet the protocol’s criteria for inclusion and exclusion.

When approached about conducting a study, carefully assess whether your site can meet the enrollment goals in the timeframe stipulated for the study. Sponsors would prefer that the investigator turn down a study rather than inflate their ability to meet enrollment goals.

The following are some reasons sites do not meet enrollment goals:
• Ineffective recruiting from available resources
• Ineffective forecasting of number of subjects during the planning stages of the study
• Diversion of potential subjects to competing studies
• Improper understanding of the enrollment criteria
• Overly restrictive enrollment criteria
• Higher percentage of dropouts or more concurrent illness than anticipated
Case Study: What Can We Learn From Them?

ORC conducted an audit for a multi-center, randomized study which involves emergency medical intervention, complicated consenting process, and multi-task study personnel.

- The study’s PI is the head of the department and has experiences in conducting the clinical research.
- It has more than 20 sub-PIs and dedicated study personnel.
- The research manager oversees the program with many active studies and provide education to new members.
- The manager maintains good communication with the team about all studies activities.
- Team members are very responsible for their roles on the study.
- The department has developed the internal SOP to promote good documentation practices: source documents templates, enrollment note, etc.
Questions about GCP? Contact us

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