An Interactive Approach to Good Clinical Practices (GCPs)

Brandi N. Ring, M.A.
Boston University School of Medicine
Good Clinical Practices (GCPs)

- ICH E6 Definition

  “A standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects is protected.”
Good Clinical Practices (GCP)

- The term “GCP” was coined by industry
- FDA has specific regulations governing conduct of clinical trials
- The International Conference on Harmonization (ICH) has developed guidelines for conduct and reporting of clinical trials (ICH E6)
- Industry practices such as electronic data collection and monitoring practices ensure GCP and integrity of trials
Legal – Regulatory Framework

1. Statutes (Laws): e.g., FD&C Act of 1938
2. Regulations: e.g., 21 CFR Parts 50, 54, 56, 312 - implement the provisions of the FD&C Act
3. Guidelines: informal guidance provided to industry by FDA. Not binding on FDA or industry
4. Case law (court decisions): provide precedents on the ‘real world’ interpretation of the law
U.S. Regulations

- Cover obligations of Sponsors, Monitors, Investigators, and IRBs
  - 21 CFR Part 11: Electronic Records
  - 21 CFR Part 50: Informed Consent
  - 21 CFR Part 56: IRB/IEC
  - 21 CFR Part 312: Investigational New Drug Application (IND)
  - 21 CFR Part 314: Applications to market a new drug
Principles of GCP

- The benefits of the trial must justify the risks.

- **The rights, safety and well-being of the subject must be the priority throughout the study.**

- Non-clinical data support the clinical proposal.

- The trial is conducted under a scientifically sound protocol.
Principles of GCP

- The IRB/IEC must approve the clinical protocol prior to initiation.

- All study personnel and investigator must be adequately qualified.

- Data collection methods ensure factual data.

- All trials must be closely monitored.
The Sponsor and Investigator must assure patients’ rights and have evidence of appropriate informed consent.

Investigators must have all essential study documents at initiation, including the approved protocol, ICF, CRFs, SAE reporting forms, etc.

Study sites must follow the IRB approved protocol, without deviation.
Fundamentals of GCP

- All Sponsor responsibilities, such as monitoring, safety oversight and reporting, data collection, etc. must be met.

- Investigator and site personnel must understand responsibilities of conducting a trial that extend beyond routine clinical practice.
Interactive Workshop
Goals of The Workshop

- To familiarize everyone with study documents and provide good and bad examples of documentation

- SO . . . . ASK QUESTIONS

- Please feel free to interrupt!!
INFORMED CONSENT

HOW DO I BEGIN THE STUDY?
Informed Consent

- MUST BE PERFORMED BEFORE ANY STUDY PROCEDURES

- Informed consent is a **process**
  - Subject must read and understand the Informed consent form (ICF)
  - Must be given the opportunity to ask questions

- Both the subject and person conducting consent must sign and date the ICF **at the time of consent**
Informed Consent

- If a new informed consent is issued
  - **All** patients must be re-consented with the new Informed Consent Form at their **NEXT** visit
    - Explain the changes
  - **KEEP ALL ORIGINALS**
    - ICFs must be retained as a legal record of the patients consent to participate in the study
  - Provide the subject with a copy of the new ICF

- The most recent ICF must be used and all original copies must be retained
Informed Consent Form

- HOW DO I KNOW IF I’M USING THE RIGHT FORM?
  - IRB Approval Stamp
  - Date Issued / Approved

- You should record somewhere visible the date of the latest approved consent and double-check before every new subject
CONSENT STATEMENT

I voluntarily consent to participate in this study. I have thoroughly read and understand all the information in this consent form. I am free to not participate in this research study or to withdraw at any time.

I authorize the release of my study related medical records to the Sponsor, agents of the Sponsor, FDA, other governmental agencies, and the IRB.

I will receive a copy of this signed and dated consent form.

By signing and dating this consent form, I have not given up any of my legal rights.

______________________________
Printed name of Subject

______________________________   ______
Signature of Subject            Date

INVESTIGATOR STATEMENT

To the best of my knowledge, the subject signing this consent form had the study fully and carefully explained and has expressed understanding of the nature, risks, and benefits in his/her participation of this research study.

______________________________
Printed name of Person Conducting Consent Discussion

______________________________   ______
Signature of Person Conducting Consent Discussion            Date
Work Break
CONSENT STATEMENT

I voluntarily consent to participate in this study. I have thoroughly read and understand all the information in this consent form. I am free to not participate in this research study or to withdraw at any time.

I authorize the release of my study related medical records to the Sponsor, agents of the Sponsor, FDA, other governmental agencies, and the IRB.

I will receive a copy of this signed and dated consent form.

By signing and dating this consent form, I have not given up any of my legal rights.

KEVIN HENNEGAN
Printed Name of Subject

Signature of Subject  8/17/04

INVESTIGATOR STATEMENT

To the best of my knowledge, the subject signing this consent form had the study fully and carefully explained and has expressed understanding of the nature, risks, and benefits in his/her participation in this research study.

KATHRYN R. KANE
Printed name of Person Conducting Consent Discussion

Signature of Person Conducting Consent Discussion  8/17/04
CONSENT STATEMENT

I voluntarily consent to participate in this study. I have thoroughly read and understand all the information in this consent form. I am free to not participate in this research study or to withdraw at any time.

I authorize the release of my study related medical records to the Sponsor, agents of the Sponsor, FDA, other governmental agencies, and the IRB.

I will receive a copy of this signed and dated consent form.

By signing and dating this consent form, I have not given up any of my legal rights.

__________________________
KEVIN HENNEGAN

Printed Name of Subject

__________________________  AUGUST 17, 2004
Signature of Subject        Date

INVESTIGATOR STATEMENT

To the best of my knowledge, the subject signing this consent form had the study fully and carefully explained and has expressed understanding of the nature, risks, and benefits in his/her participation in this research study.

__________________________
KATHRYN R. KANE

Printed name of Person Conducting Consent Discussion

__________________________  8/17/04
Signature of Person Conducting Consent Discussion        Date
FDA Inspection

- Common Deficiencies
  - Inadequate consent 51%
  - Protocol Non-adherence 31%
  - Records Inadequate/Inaccurate 26%
  - Drug Accountability Inadequate 20%
  - IRB deficiencies 11%

- Investigator Failure to report Adverse Events

ICF Helpful Hints

- The subject must sign and date their own signature – study staff may NOT fill in the date for the subject!

- Double check the ICF before you and the patient leave the room – correct any mistakes immediately

- If the time the ICF was signed needs to be recorded in the source documents – make sure your clocks are synchronized and write the exact time down (NO ROUNDED)

- The ICF process should be documented for each patient – better to document at the beginning than to wait
  - May be in a note to file
  - Needs to be subject specific

- May want to create a sample sheet/binder to remind you of pages needing signature, initials etc.
WHAT DO I DO NEXT?
FDA Inspection

- **Common Deficiencies**
  - Inadequate consent 51%
  - **Protocol Non-adherence** 31%
  - Records Inadequate/Inaccurate 26%
  - Drug Accountability Inadequate 20%
  - IRB deficiencies 11%

- Investigator Failure to report Adverse Events

Protocol Non-adherence

- Enrolling subjects that do not meet eligibility requirements
- Not completing visits according to the protocol
- Not performing procedures
Work Break
FDA Perspective

Patricia Holobaugh  Chief of BIMO Branch of DIS of OCBQ

- MOST SIGNIFICANT DEVIATIONS
  - Enrollment of ineligible subjects
  - Violations of protocol affecting safety
  - Extensive data corrections and questionable changes
  - Inadequate oversight of study personnel
    - Inappropriate delegation of authority
    - Poor oversight of satellite sites
  - No informed consent
  - Failure to communicate with IRB

http://videocast.nih.gov/ppt/NIAID_gcp_041505.ppt
Helpful Hints - Enrollment

- Double check all Inclusion/Exclusion Criteria
  - Make sure you have documentation
  - Make sure you have asked the subject about all points
- If a subject avoids a question or gives you an ambiguous response – re-address
- Follow the protocols numerical limits with lab results – even if they can be explained or are not clinically significant
  - A Hematocrit of 44 does not fit the qualification if the inclusion criteria states:
    - Must have hematocrit greater then 45%
Helpful Hints

- Write a note to file on your screening procedures, follow the same procedure for each patient.
- Use Notes to File to explain anything that needs to be explained.
FDA Inspection

- Common Deficiencies
  - Inadequate consent 51%
  - Protocol Non-adherence 31%
  - Records Inadequate/Inaccurate 26%
  - Drug Accountability Inadequate 20%
  - IRB deficiencies 11%
  - Investigator Failure to report Adverse Events

Source Documents

What is a source document?
- The first place things are written down
  - Traditionally Chart notes

Examples
- Chart Notes
- Clinic Charts
- Lab Reports
- Phone Logs
- Physician Letter
- X-rays, CTs, MRI etc.
Source Documents

- For some studies (traditionally industry)
  - Pre-templated Source documents could be provided for you
  - This will make your life easier!!!!!
  - The source documents walk you through all the questions you need to ask and the procedures you need to perform!
Case Report Forms (CRF’s)

- What is a case report form?
  - Collects the trial required data
Case Report Forms (CRF’s)

- The data that is collected by the sponsor
- OR
- The data used for analysis

- Usually separate from your source documents (but not always)
  - Some Mixing
  - Some studies do not have ‘official’ source docs to capture study information
Documentation in Source Docs / CRFs

- Complete in black ink only
- Cross out error with a single black line
- Write correct information in as close as possible
- Date and initial the change
- Both original and new information must be legible
Demographic Data

Sex:  
- [ ] Male  
- [X] Female

Date of Birth: 15-Mar-1956

Race / Ethnicity:

- [X] Caucasian  
- [ ] Native American  
- [ ] Hispanic  
- [ ] African-American  
- [ ] Asian  
- [ ] Other, specify:

Vital Signs

Sitting Blood Pressure: 120/70 mmHg  
Pulse Rate: 80 beats/min

Respiratory Rate: 20 resp/min

Urine Pregnancy Test, females of childbearing potential only

Is the patient a female of childbearing potential?  
- [ ] Yes*  
- [X] No

*If "Yes", was a urine pregnancy test performed?  
- [ ] Yes  
- [ ] No

If "Yes", result:  
- [ ] Positive  
- [ ] Negative

If "Positive", was a serum HCG blood test taken?  
- [ ] Yes  
- [ ] No

If "Yes", result:  
- [ ] Positive  
- [ ] Negative

If "Positive", patient must be excluded from study.
Demographic Data

Sex: 1 Male 2 Female

Date of Birth: 15 MAR 1956

Race / Ethnicity: 1 Caucasian 2 Native American 3 Hispanic
4 African-American 5 Asian
6 Other, specify: 

Vital Signs

Sitting Blood Pressure: 120/107 mmHg  Pulse Rate: 80 beats/min
Respiratory Rate: 20 resp/min

Urine Pregnancy Test * females of childbearing potential only

Is the patient a female of childbearing potential? 1 Yes* 2 No

*If "Yes", was a urine pregnancy test performed? 1 Yes 2 No

If "Yes", result:
1 Positive 2 Negative

If "Positive", was a serum HCG blood test taken? 1 Yes 2 No

If "Yes", result:
1 Positive 2 Negative

If "Positive", patient must be excluded from study.
Source Document Helpful Hints

- Obtain as much information on medical history and concomitant medications as is available – if the patient does not know (ex: dosage) ask them to find out and to call you

- If patient has been diagnosed with depression the Investigator should indicate that subject is stable or the depression will not interfere with the study

- Document Birth Control as well as the discussion about proper birth control
Source Document Helpful Hints

- Make sure all clocks are synchronized and if possible, use 24:00 digital clocks
- Include explanations of mistakes
  - (Ex: Patient accidentally wrote the incorrect year)
- Initial and Date Mistakes
- Document reason for late entries
- Document all attempts to contact subject and schedule visits
CRF Helpful Hints

- Remember on NCR pages – use the cardboard divider so you have clean records
  - It may help to put some plain white paper between the source docs and CRFs as well
- USE BLACK BALLPOINT INK
- Remember to fill out your headers
- Take your time when transcribing
  - Make sure you are using the right patient binders
  - Copy neatly and correctly
  - Correct mistakes immediately
Helpful Hints

- Double check everything **before** the patient leaves
- Document everything!!
  - Use Notes to File
- Re-check documents BEFORE the next patient visit – FLAG missing items
  - If you fix / correct / add anything make sure you initial – date – explain the addition
FDA Inspection

- Common Deficiencies
  - Inadequate consent 51%
  - Protocol Non-adherence 31%
  - Records Inadequate/Inaccurate 26%
  - Drug Accountability Inadequate 20%
  - **IRB deficiencies** 11%

- Investigator Failure to report Adverse Events

FDA Inspection

- Common Deficiencies
  - Inadequate consent 51%
  - Protocol Non-adherence 31%
  - Records Inadequate/Inaccurate 26%
  - Drug Accountability Inadequate 20%
  - IRB deficiencies 11%

- Investigator Failure to report Adverse Events

Adverse Events

An adverse event (AE) is any untoward medical event that occurs in a subject receiving a pharmaceutical product: it does not necessarily have a causal relationship to the treatment.

- Quick Reference Guide
AE OR NOT AE?
(That is the question)

- Patient goes to dentist for a scheduled cleaning
  - NO
- Patient goes to dentist for toothache, has root canal procedure
  - YES (Toothache is the AE, Root Canal is the treatment – recorded on the con meds page)
- Patient goes to gynecologist for scheduled annual exam, is prescribed HRT as a prophylactic
  - NO (but it is a change in con meds)
- Patient has a cosmetic procedure scheduled before start of study
  - NO (but record treatment as a con med)
- Patient has a cosmetic procedure scheduled after start of study that is performed during the study
  - NO (but record treatment as a con med)
Adverse Event Recording

- If a procedure is planned and scheduled before a patient enters a clinical trial then that procedure and associated underlying condition are not considered as (S)AEs. The underlying condition should be recorded as medical history.

- If a procedure is scheduled after the patient enters a clinical trial and the procedure occurs during the trial without aggravation of the underlying condition then the procedure is recorded as an (S)AE and the underlying condition is medical history.
Adverse Event Recording

- If a procedure is scheduled after the patient enters the clinical trial due to aggravation of the underlying condition then the underlying condition is recorded under medical history the aggravation is recorded as an (S)AE, the procedures is treatment of the (S)AE.
Adverse Events

ALL untoward medical events need to be recorded as AEs, including exacerbations/recurrences of pre-existing conditions

e.g. Subject with a history of migraine headache reports a headache while on study – headache is an AE

Treatment (drug and procedure) of AEs must be recorded on concomitant medications page

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Onset Date</th>
<th>Resolution Date</th>
<th>Severity</th>
<th>Relation to Study</th>
<th>Drug</th>
<th>Action Taken</th>
<th>Outcome</th>
<th>Investigator's Initials and Date</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Severity
1 = Mild
2 = Moderate
3 = Severe

Relation to Study
1 = Probable
2 = Possible
3 = Unlikely

Drug

Action Taken
1 = None
2 = Monitoring
3 = Optimization
4 = Study Drug

Outcome
1 = Recovered without Sequence
2 = Recovered with Sequence
3 = Not yet recovered
4 = Deaths
5 = Unknown
Adverse Event Narrative

- Subject 99-045 (Initials ABC) comes in at the day 14 visit (6-Jun-2005), and reports a migraine on 31-May-2005 lasting an entire day (24 hours). Subject mentioned they could not get out of bed and had to take migraine medicine every time they woke up to relieve the pain. When asked the patient indicates treatment as Excedrin Migraine approximately every 8 hours.

- Now fill out the AE document
Let’s fill out the AE Page

- Subject: 99-045
- Event: Migraine
- Onset Date: 31-MAY-2005
- Resolution Date: 1-JUN-2005
- Severity:
- Relation to Study Drug:
- Action Taken: Medication (Excedrin Migraine)
- Outcome: Recovered
- Serious: NO
Date: **6/ JUN/ 2005**  
Subject Number: **0 4 5**  
(Site #)  
(ID #)  

### ADVERSE EVENTS

List all new and/or continuing Adverse Events below:

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Onset Date</th>
<th>Resolution Date</th>
<th>Severity</th>
<th>Relation to Study Medication</th>
<th>Action Taken</th>
<th>Outcome</th>
<th>Serious? (yes or no)</th>
<th>Investigator’s Initials and Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Migraine</td>
<td>31 May 2005</td>
<td>1 June 2005</td>
<td>2</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>NO</td>
<td>Dr. Smith 11-Jun-05</td>
</tr>
</tbody>
</table>
All medications need to be recorded (including, supplements, vitamins and topical medications)

Get as much information (dose, route, frequency etc) as you can the first time

Make sure that AE form is completed if the conmed indication was an AE
Medication: Excedrin Migraine
Dosage: 2 Tablets
Administration
- Route: Oral
- Frequency: Every 8 hours
Indication: Migraine
Date Started: May 31st, 2005
Date Stopped: June 1st, 2005
<table>
<thead>
<tr>
<th>Medication or Treatment Name</th>
<th>Dosage</th>
<th>Administration</th>
<th>Indication</th>
<th>Date Started</th>
<th>Date Stopped</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excedrin Migraine</td>
<td>2 tab</td>
<td>PO PRN</td>
<td>Migraine</td>
<td>31 May 2005</td>
<td>1 June 2005</td>
</tr>
</tbody>
</table>
Helpful Hints

- If a medication changes, ask why, the underlying cause may need to be recorded as an adverse event.
- Document Reasons for all missed visits or out of window visits:
  - These may be due to an AE that may need to be recorded.
Overall Some Helpful Hints

- KEEP ALL STUDY RELATED DOCUMENTS
  - Even if they seem outdated – file in the regulatory binder or in patient binders
- Write EVERYTHING down, before you forget
- Put subject numbers on every piece of paper
  - So you know which subject it belongs to
- Address all issues in your monitor follow up letters ASAP
- Initial and date everything
  - When in doubt initial and date anyway
Helpful Hints

- WHEN IN DOUBT
- ASK QUESTIONS
  - Call / Email Monitor
  - Contact IRB
  - Talk to PI
Questions