An Interactive Approach to Good Clinical Practices (GCPs)

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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 54: Financial Disclosure
  - 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
  - 45 CFR Part 46: Protection of Human Subjects

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.

Fundamentals of GCP

- 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

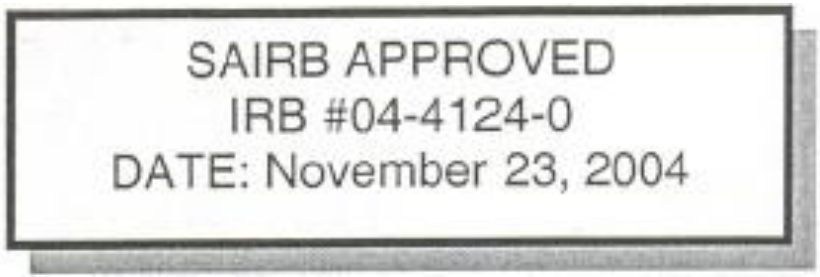
- Both the subject and person conducting consent must sign and date the ICF **at the time of consent**

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

Informed Consent Form

Must be signed and dated at the time of consent by BOTH the subject and the person conducting consent

Work Break

PAGE 1

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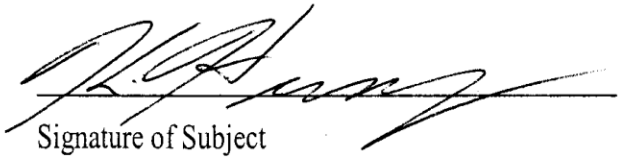
KEVIN HENNEGAN

Printed Name of Subject



Signature of Subject

8/17/04

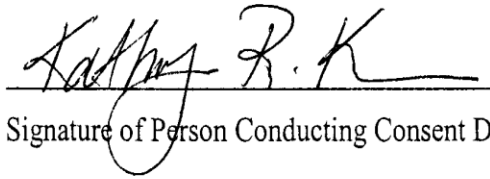
Date

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



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8/17/04

Date

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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

AUGUST 17, 2004

Date

INVESTIGATOR STATEMENT

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KATHRYN R. KANE

Printed name of Person Conducting Consent Discussion

Signature of Person Conducting Consent Discussion

8/17/04

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

http://www.irbforum.org/documents/documents/Module4.pdf

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 ROUNDING!)
- 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.

Procedures

WHAT DO I DO NEXT?

FDA Inspection

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Protocol Non-adherence

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

Work Break

PAGE 2

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 a 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

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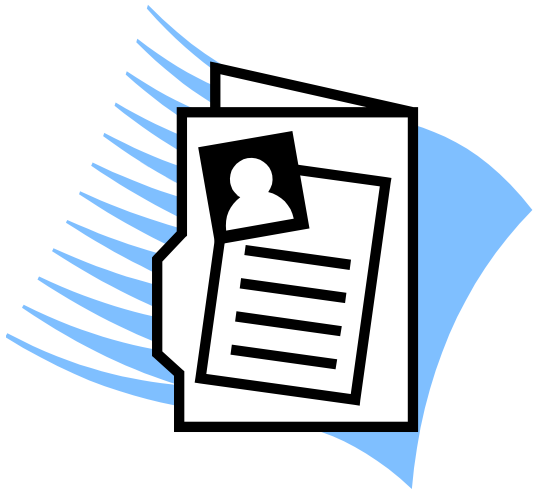
Source Documents

- 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

STUDY NUMBER [redacted] For use only

STUDY PERIOD	SCREENING NUMBER	PATIENT NUMBER	PATIENT INITIALS	Page
SCREENING	SC [redacted]	[redacted] Randomization	A B C (first, middle, last)	4

Demographic Data

Sex: 1 ☐ Male 2 ☑ Female Date of Birth: 15 (dd) - MAR (mmm) - 1956 (yyyy)

Race / Ethnicity: *(Please check only one)*
1 ☑ Caucasian 2 ☐ Native American 3 ☐ Hispanic
4 ☐ African-American 5 ☐ Asian
6 ☐ Other, specify: _____

Vital Signs

Sitting Blood Pressure: 120 / 070 mmHg Pulse Rate: 080 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.

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1 ☑ Caucasian 2 ☐ Native American 3 ☐ Hispanic
4 ☐ African-American 5 ☐ Asian
6 ☐ Other, specify: _____

Vital Signs

Sitting Blood Pressure: ~~110~~ 120 KK 8/16/04 / 070 mmHg Pulse Rate: 080 beats/min

Respiratory Rate: 20 resp/min

Urine Pregnancy Test *females of childbearing potential only*

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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

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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

Date: ___/___/___ Subject Initials ___ ___ ___

Subject Number: ____ ____ . ____ ____ ____
(Site #) (ID #)

ADVERSE EVENTS

List all new and/or continuing Adverse Events below:

Adverse Event	Onset Date	Resolution Date	Severity	Relation to Study Medication	Action Taken	Outcome	Serious? (yes or no)	Investigator's Initials and Date

Severity
1 = Mild
2 = Moderate
3 = Severe

Relation to Study Drug
1 = Probable
2 = Possible
3 = Unlikely
4 = Not Related

Action Taken
1 = None
2 = Medication
3 = Hospitalization
4 = Study Drug Interrupted

Outcome
1 = Recovered without Sequelae
2 = Recovered with Sequelae
3 = Not yet recovered
4 = Death
5 = Unknown

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

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

AE Page

Date: 6/JUN/2005 Subject Initials A B C

Subject Number: 9 9 . 0 4 5
(Site #) (ID #)

ADVERSE EVENTS

List all new and/or continuing Adverse Events below:

Adverse Event	Onset Date	Resolution Date	Severity	Relation to Study Medication	Action Taken	Outcome	Serious? (yes or no)	Investigator's Initials and Date
Migraine	31 May 2005	1 June 2005	2	3	2	1	NO	Dr. Smith 11-Jun-05

Concomitant Medications

Date: ___/___/___ Subject Initials ___ ___ ___

Subject Number: _____ _____ - _____ _____
(Site #) (ID #)

CONCOMITANT MEDICATIONS

Medication or Treatment Name	Dosage	Administration		Indication	Date Started	Date Stopped
		Route	Freq			

*(taken within 4 weeks of enrollment)

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

Let's fill out the Con Meds Source Page

- 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

Con Med Source Document Page

Date: 6 / JUN / 2005 Subject Initials A B C

Subject Number: 9 9 . 0 4 5
(Site #) (ID #)

CONCOMITANT MEDICATIONS

Medication or Treatment Name	Dosage	Administration		Indication	Date Started	Date Stopped
		Route	Freq			
Excedrin Migraine	2 tab	PO	PRN	Migraine	31 May 2005	1 June 2005

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