University of Nebraska Medical Center

BREAKTHROUGHS FOR LIFE.®

New Clinical Coordinators Workshop

July 2014 Seminar Recordings and Lecture Handouts

A Center for Clinical Translational Research sponsored event

University of Nebraska Medical Center

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Overview of Clinical Trials

R. Jennifer Cavalieri, BSN, RN, CCRC, CCRP

Watch this recorded session

Session Objectives

1. Attendees will describe the core elements of a research protocol
2. Attendees will identify the location of federal regulations and international guidelines
3. Attendees will provide examples of the four phases of clinical trials (human subject research)

Clinical Research

Laboratory (aka "bench")
Basic science experiments

Clinical Trials
A research study using humans to evaluate the effect of interventions or exposures on biomedical or health-related outcomes. Other clinical trials not directly involving humans can evaluate the health care environment, products, and processes.

Translational Research
Basic science ⟶ *Practical clinical uses*

Research searches for answers to scientific questions. These usually involve safety and efficacy.

Learning the Language

Glossary
- Usually included in the research protocol
- Trusted websites such as federal or professional societies
- Excellent glossary located at the National Institutes of Health website www.nih.gov

http://www.ors.od.nih.gov/ser/dpsac/policies/HSPD12/Pages/glossary.aspx

Research Protocols

Who: the sponsor or an investigator usually write the protocol

What: a written plan which describes the clinical trial activities

When: the protocol is typically created during the planning of a study. It may undergo revisions during the study. These are called amendments to the protocol

Where: every participating research site must get the protocol approved by their IRB before the study activities can start

Why: a protocol clarifies what is to be done, how it is to be done, and who will do it.

Protocol Contents

Key areas usually include:

- Scientific background including previous study results
- Study purpose
- Objectives
- A description of the study design
- Statistical plan

For more detail on protocols:

Chan, A., Tetzlaff, J., Altman D., Laupacis, A., Gøtzsche P., Krleža-Jerić, K., . . . Moher, D. (2013). SPIRIT 2013 statement: Defining standard protocol items for clinical trials. *Annals of Internal Medicine*,*158*(3), 200[ind]207. Retrieved from http://annals.org/article.aspx?articleid=1556168

Study Types

Case Reports: specific patient's illness or event

Ecologic Studies: compares trends in conditions, often uses databases ex: cigarette smoking and heart disease

Cross Sectional (aka point prevalence): surveys to determine if a risk factor is present ex: urinary catheters and bacteruria

Case Control: determine if there is an association between a risk factor and an outcome. Patients are enrolled and, based on the definition, are either cases or controls. Multiple risk factors can be evaluated. Retrospective. Carefully define cases and controls.
ex: presence or absence of symptoms of neuro-invasive disease

Quasi-experimental: nonrandomized, pre and post intervention often employed in outbreak situations or quality improvement interventions
ex: make a change and see what happens

Randomized, controlled trials: prospective, subjects usually assigned to intervention or control groups. High cost, many logistical and ethical considerations.
ex: drug and device trials

Key Regulatory Resources

United States Food and Drug Administration (FDA) regulations for human subject protections. www.fda.gov

21 CFR part 50, Protection of Human Subjects (U.S. Department of Health and Human Services, 2013a)[1].

21 CFR part 56, Institutional Review Boards (U.S. Department of Health and Human Services, 2013b)[2]

21 CFR part 54, Financial Disclosure (U.S. Department of Health and Human Services, 2013c)[3]

21 CFR part 312, Investigational New Drug Application (U.S. Department of Health and Human Services, 2013d)[4]

21 CFR part 812, Investigational Device Exemptions (U.S. Department of Health and Human Services, 2013e)[5]

The International Committee on Harmonisation (ICH) Good Clinical Practice Guidelines (GCP) http://www.ich.org/

Understanding the regulations can help research professionals can gain a deeper understanding of why policies and procedures at their institution exist and where the IRB gains its authority and approach to research issues.

Regulation vs Guidance

Regulations are required PERIOD

The FDA creates regulations and issues guidance documents.
Guidance documents represent their current thinking on a subject.
Is Guidance optional ? Its not a good idea to treat it as such.

If the protocol is stricter than the regulations require, which trumps?
The safest rule of thump is to follow whichever is stricter.

Stages of Research

Laboratory

Animal testing

Clinical testing in humans

Ongoing safety monitoring after FDA approval

Phases for Drug & Device Trials

Phase I: small number of subjects, usually healthy, to determine safety and effects of the drug on the body.

Phase II: approximately 100 subjects affected with the disease for the drug/device intervention, to determine safety & effects of the drug on the body, dosing levels

Phase III: up to thousands of subjects affected with the disease for the drug/device intervention, usually many research sites

Phase IV: aka "post marketing studies", may be FDA required to continue to gather safety data, may involve collecting pharmco-economic data

Study Design

Includes the hypothesis, study population, sample size, and statistical analysis of the study

- The hypothesis drives study design
- The inclusion and exclusion criteria describes the study population
- Sample size is the number of subjects or observations
- Statistical significance and dose-response needs to be carefully assessed. Can the results be extrapolated to individuals outside of the study? Use care to not overstate the study conclusion.

Funding Sources

Clinical Trials can be defined by how they are developed and funded

- Investigator-initiated and federally funded studies begin with investigator's idea and protocol design.
  Ex: private foundations, NIH, DOD
- Many industry trials are funded by pharmaceutical companies and device manufacturers. Most investigators are not involved with the protocol development and have no financial relationship with the investigational product or rights to intellectual property.
  Ex: Astellas, Bayer, 3M

Data Ownership

Institutional policies and sponsor contracts will specify data ownership

- Transfer of data may involve regulatory authorities
- Research personnel do not own the data they collect. They are compensated in the form of a salary or authorship
- Investigators may have limited or no claim on intellectual property when working on industry sponsored studies

Example of an Investigational Plan

- Screening and baseline assessments
- Treatment phase with scheduled assessments
- Safety and efficacy assessments (physical exams, laboratory and medical testing
- Monitoring for adverse effects

Schedule of Events

Protocol Title here						
	Screen	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5
		D1	D8	D15	D22	D29
Window plus/minus	minus 2	0	1	1	2	2
Study visit-clinical	X	X	X	X		
Study visit-telephone					X	X
Informed consent	X					
Medical History	X					
Concomitant Medication	X					
Physical Examination	X	X		X		
Body weight	X			X		
Vital signs	X	X		X		
12 lead ECG [a]	X					
Pregnancy test	X	X				
Echocardiogram	X	X				
Randomization		X				
Study drug administration		X	X			
Study diary		X	X	X	X	X
Safety laboratory tests [b]	X	X		X		
Stool sample [c]		X	X	X		
Adverse Events		X	X	X	X	X
Key:	a) local test		b) central laboratory			
	c) site to store and batch ship to central laboratory					

Data Collection

At protocol specific time points

- Data collection on paper Case Report Forms (CRF)
- Data collection into Electronic Data Capture (EDCs)

Source Documents

- The original source of information located in medical records
- Can also include x-rays, scans, or public records (death certificates)
- Data created at the time of the study visit such as vital signs

Summary

Learning about research fundamentals and operations is an ongoing process.

Being familiar with and following regulations is essential in all research trials.

Welcome to research!

MAKING THE IRB PROCESS SMOOTHER

FROM SUBMISSION TO ANALYSIS

Jenny Kucera, MS, CIP

IRB Administrator/Education Coordinator

Watch this recorded session

OUTLINE

- What is the IRB?
- Submission & Review Process
- Ongoing Review
- Informed Consent
- Demo electronic IRB application

WHAT IS THE IRB?

WHAT IS THIS "IRB"?

- Institutional Review Board (Research Ethics Committee)
- Oversee all research involving human subjects
- Governed by FDA (Food & Drug Administration) and/or HHS (Department of Health & Human Services)
- Local vs. Central

WHY DO YOU NEED IRB APPROVAL?

- Federally funded studies
- Publishing
- Clinical trials involving drugs or devices
- Institutional requirement

SUBMISSION & REVIEW PROCESS

WHAT IS THE PROCESS?

1. Is it human subject research?
2. Is it exempt? Expedited? Full board?
3. Choose the correct IRB application
4. Tips for filling out an application
5. Submit research materials to the IRB
6. Time for the IRB to do their part!
   a. *IRB approval criteria*
   b. *IRB actions*
7. Your responsibilities after approval

#1

HUMAN SUBJECT RESEARCH

- **RESEARCH**

  …***systematic*** investigation…designed to develop or contribute to ***generalizable*** knowledge

- **HUMAN SUBJECT**

  …**living** individual about whom an investigator conducting research obtains data through:

  1. **Intervention** or interaction with the individual
  2. Collection of **PHI**

45 CFR 46.102

#2

CATEGORIES OF REVIEW

- Exempt
- Expedited
- Full board

#2

REVIEW CONTINUUM

Level of risk and nature of the research primarily determines route of review

Exempt	Expedited	Full
Low Risk →	No More Than Minimal Risk →	More Than Minimal Risk

#2

REGULATORY DEFINITION OF MINIMAL RISK

Minimal Risk means that the ***probability*** and magnitude ***of harm or discomfort*** anticipated in the research ***are not greater*** in and of themselves ***than those*** ordinarily ***encountered in daily life or during*** the performance of ***routine*** physical or psychological examinations or ***tests.***

45 CFR 46.102(i); 21 CFR 56.102(i)

#2

EXEMPT RESEARCH (EX)

- Must meet one of the HHS requirements for exemption
- No deadlines
- Office of Regulatory Affairs (ORA) must make the final determination that the HHS requirements for exempt review are met
- Reviewed in ORA by IRB Administrator
- Reserves right to refer for Expedited or Full Board review
- If approved as exempt, permission to conduct research is valid for 5 years

45 CFR 46.101(b)

#2

EX Categories

1. Typical educational practices
2. Educational tests, surveys, interviews, or observation of public behavior (non-sensitive, or no identifiers)
3. Research with elected public officials, appointed public officials, candidates for public office)
4. Existing data, documents, pathological specimens, if publicly available or anonymized
5. Evaluation of public benefit service programs
6. Taste and food quality evaluation and consumer acceptance studies

Note: Exempt research in Category 2 cannot involve minors

45 CFR 46.101(b)

#2

EXPEDITED REVIEW (EP)

- No more than minimal risk to the subject
- Only involvement of subjects will be in at least 1 of 7 categories.
- No deadlines
- IRB member reviews & approves the research
- Reserve right to refer to the Full Board

45 CFR 46.110

EP Categories

- Clinical studies where an IND/IDE is not required
- Blood sample collection (routine methods –small amounts)
- Prospective collection of biological samples—noninvasive means
- Data collected though noninvasive means (routinely practiced in clinical settings)
- Materials (data, documents, specimens etc.) that have been collected or will be collected for non-research purposes
- Collection of voice, video or digital data for research purposes
- Individual or group behavior, surveys, interviews

45 CFR 46.110

#2

FULL BOARD (FB)

- Requires review & approval by a convened IRB meeting
- Schedule & deadlines available on the IRB website
  - *Pre-review deadlines*
  - *Submission deadlines are for receipt of paper packets, not electronic submission*
  - *There are differences between adult and pediatric IRB deadlines*
- Two reviewers assigned, but FB makes final decision

#2

FULL BOARD MEETINGS

4 IRBs registered with OHRP

- IRB-01 (Adult)
  - *Meets 1st Thursday of the month (except Jan & July)*
- IRB-02 (Adult)
  - *Meets 3rd Thursday of the month*
- IRB-03 (Rapid Response)
- IRB-04 (Joint Pediatric IRB)
  - *Meets 4th Tuesday each month*

#3

TYPES OF RESEARCH

BIOMEDICAL

- Human biological system & processes
- May be therapeutic or non-therapeutic research
- Much of research at UNMC & UNO HPER
- 2 versions: Adult and pediatric

BEHAVIORAL & SOCIAL SCIENCE

- Behaviors, attitudes, and interactions of, among & between individuals, groups, and cultures
- Much of research at UNO and some UNMC CON
- 3 versions: Adult and pediatric and exempt

#3

TYPES OF RESEARCH

HUMAN BIOLOGICAL MATERIALS (HBM)

- Research involving use of existing, left-over HBM obtained as part of a clinically indicated procedure
- Extra HBM will be obtained in the course of the clinical procedure solely for research purposes
- 1 version (adult, pediatric, EX, EP and FB=same application)

MEDICAL RECORDS

- Intent to summarize & analyze existing clinical information by examining clinical outcomes, relationships between variables & design of future studies
- Involves use of medical records to gather data
- 1 version (adult, pediatric, EX, EP and FB=same application)

#3

TYPES OF ACTIVITIES REQUIRING IRB APPROVAL

HBM BANKING

- Banking of HBM for future, unspecified research
- To conduct a study using HBM, a separate IRB application must be submitted
- 1 version (adult, pediatric, EX, EP and FB=same application)

DATA BANKING

- Banking of data for future, unspecified research
- 1 version (adult, pediatric, EX, EP and FB=same application)
- To conduct a study using HBM, a separate IRB application must be submitted

#4

IRB APPLICATIONS

- Online submission system link: https://net.unmc.edu/rss
- Found on the IRB website-www.unmc.edu/irb
- Applications & forms subject to change
- Read the instructions and educational notes within the application, forms and checklists
- Answer each question fully
- Review pdf versions of application and consent forms before submitting to IRB
- If the name is not listed, request that it be added

#5

IRB SUBMISSION REQUIREMENTS

- Checklist listed in Section III
- IRB application
- Informed consent forms & study information sheets
- Subject recruitment materials
- Letters from performance sites granting approval to conduct study at that site
- Surveys, assessment tools and materials given to subjects
- *Clinical Trial Master Matrix*
- *P&T Investigational Drug Study Registry Form or Drug Registry Form for Marketed Drugs*

#6

NEW PROTOCOL

IRB REVIEW PROCESS

- Submission sent to the ORA
- Application entered into the IRB database
- Database assigns the IRB number (e.g. IRB #123-09-FB)
  - *First three numbers = each yr starts at 001; consecutively # each protocol as arrives*
  - *Second number = year*
  - *Letters (suffix) = review requirements (FB, EP, EX)*
- Email sent to PI & coordinator with the assigned number and submission requirements

#6

NEW PROTOCOL

IRB REVIEW PROCESS

- If FB review is required, it will be scheduled for the next IRB meeting after packets are received in ORA
  - *If there are 15 already scheduled then the study will be reviewed at the next meeting*
  - *Dependent upon reviewer availability*

#6

IRB REVIEW CRITERIA

- Risks to subjects are minimized
- Risk/benefit relationship is acceptable
- Selection of subjects is equitable
- An appropriate study monitoring plan is in place
- Process of informed consent is valid
- Informed consent is documented appropriately
- Data Safety Monitoring plan is adequate
- Subject's privacy & confidentiality is protected
- Additional protections for vulnerable subjects

[45 CFR 46.111; 21 CFR 56.111]

#6

POSSIBLE IRB ACTIONS

- Approval and full release
- Conditional approval
  - *IRB Chair acceptance of minor mods*
  - *IRB Administrator acceptance of very minor mods*
- Tabled
  - *Full Board review of modifications or clarifications*
- Decline to complete the review
  - *Inadequate information and content*
- Disapproved
  - *Very serious design flaws or undue risk to subjects*

#6

COMPLETION OF IRB REVIEW PROCESS

- Following review, letter/email is sent to the PI within 10-14 days (sometimes takes longer)
  - *Given 45 days to respond.*
  - *If no response, IRB may decide to withdraw the study.*
  - *Call if you need more time.*
- PI response received & reviewed. Additional changes may be required.
- The IRB issues final approval for the study.*

Final approval may take 1-3 months or more

OTHER REQUIRED REVIEWS PRIOR TO FINAL IRB APPROVAL

#6

- Departmental Peer Review
  - *All non-exempt IRB Applications*
- Fred & Pamela Buffett Cancer Center Scientific Review Committee (SRC)
  - *All Oncology research*
- Sponsored Programs Administration (SPA)
  - *All commercially sponsored contracts*
- Conflict of Interest (COI) Committee
  - *All human subject research involving a significant financial interest*

OTHER REQUIRED REVIEWS PRIOR TO FINAL IRB APPROVAL

#6

- Pharmacy & Therapeutics Committee (P&T)
  - *All research involving investigational and/or marketed drugs*
- Institutional Biosafety Committee (IBC)
  - *All research subject to the Common Rule and the NIH Guidelines for Recombinant DNA Molecules*
- Embryonic Stem Cell Research Oversight Committee
- Coverage Analysis (CA)

ONGOING REVIEW & APPROVAL

#7

WHAT REQUIRES ONGOING IRB REVIEW & APPROVAL?

#7

- Changes to approved research
- Adverse event reports
- Continuing review
- Compliance incidents

REQUEST FOR CHANGE

#7

- All changes must be ***reviewed & approved*** by IRB ***prior*** to implementation
  - *Exceptions:*
    - *To eliminate immediate risk*
    - *Provide essential new information that may affect subjects' decision to participate*
- Rationale for each change must be provided
- Revise IRB application, consent forms, recruitment material, Clinical Trial Matrix, as applicable

REQUEST FOR CHANGE

#7

- Electronic: Make changes and hit "CHANGE REQUEST"
- Added personnel must have current CITI certification
- Provide adequate justification for making change
- Regardless of the review category, changes may be expedited or reviewed by the Full Board.

#7

CONTINUING REVIEW

All Full Board and Expedited studies

- Must occur no less than once a year – extensions *cannot* be granted
- Must remain active until all data analysis is complete
- As a courtesy, 2 reminder emails are sent
  - 60 days before expiration
  - 10 days later if no response
- Adult Full Board *only* considers continuing reviews at the 3rd Thursday meeting

#7

CONTINUING REVIEW

- Review the form when your study gets approved so you know what to keep track of
- Target accrual, accrual, and demographics
  - *Check previous CR & make sure numbers add up*
  - *Breakdown demographics by group (i.e., control vs. experimental; parents vs. children)*
- Provide new information but keep record of last report (e.g. previous protocol violations remain, new since last review marked with *)

#7

APPROVAL EXPIRATION

- ***DOES NOT*** mean the study is terminated
- Email sent by the database to the PI and coordinator who notify all study personnel to stop study activity
- Submit required CR or other missing materials to the IRB as soon as possible
- When IRB has info needed to approve continuation, IRB will return research to active status and research activities can resume

#7

ADVERSE EVENTS

1. Internal AEs
   - *Unexpected, related/possibly related and more than minor or alters risk/benefit*
   - *Report within 2 business days*
2. Internal Fatal AEs
   - *Report all fatal events within 24 hours*
3. External AEs
   - *IRB no longer reviews External AEs*
   - *If an External AE requires a change in the protocol and/or consent form, submit the AE with a request for change*

#7

PROTOCOL DEVIATION

- Prospective deviation from approved protocol
- Examples of possible deviations may be:
  - *Enroll a single ineligible subject*
  - *Enrollment of a single subject beyond the number approved by the IRB*
  - *Minor deviation from the protocol*

#7

NONCOMPLIANCE

Noncompliance is defined as the lack of compliance by the ***investigator or other study personnel*** with the requirements of:

- *Federal regulations*
- *HRPP policies*
- *The IRB-approved application*
- *Requirements or determinations of the IRB*

#7

PROTOCOL VIOLATION

- An event that is reported after it occurs
- Submit Non-Compliance Report within 5 business days.
- Corrective action plan
  - Provide a ***thoughtful*** response to avoid similar non-compliance incidents in the future
  - "I promise to never do it again" is insufficient

#7

COMPLETION OF STUDY
FINAL REPORT

- Once data analysis is complete, then a Study Completion Report must be submitted
- If no final report is submitted, the IRB may refuse to consider future submissions

INFORMED CONSENT

INFORMED CONSENT

- Informed consent is a ***process*** – not a piece of paper
- The Informed Consent Form (ICF) ***guides*** the process, so must be written for that purpose and contain the required elements of consent
- IRB Online Submission System has ICF templates that incorporate all the required elements using standard language

INFORMED CONSENT FORM

- ICF must:
  - *Be written in clear and simple language so subject can understand*
  - *Be written in non-coercive language*
  - *Match the application & full protocol*
- *Clinical Research:* TNMC Letterhead required
- *Non-clinical research:* Use department letterhead

INFORMED CONSENT

- Informed consent must be obtained and documented (as applicable) ***before*** any screening or study procedures
- Study personnel permitted to obtain (= sign the consent form) consent must:
  - *Be authorized by the PI*
  - *Listed by name in documentation of consent/assent section of the IRB application*
  - *Be approved by the IRB*
- The subject and person authorized to document the obtainment of consent must sign the form in the presence of each other, therefore dates of signatures must match

WHAT'S WRONG WITH HOW SUBJECTS ARE CONSENTED?

INFORMED CONSENT PROCESS

- *Too short*
- *The ICF is not used as a dialogue guide*
- *Not continuous or reinforced*
- *PI's involvement is cursory*
- *Inappropriate consent environment*

WHAT'S WRONG WITH HOW SUBJECTS ARE CONSENTED?

INFORMED CONSENT PROCESS

- *Insufficient use of subject advocates*
- *Not enough involvement of family members*
- *Insufficient cultural sensitivity*
- *Presumption of consent before the fact*
- *No assessment of subject comprehension*
- *Subjects are not encouraged to ask questions*

WHAT'S WRONG WITH HOW SUBJECTS ARE CONSENTED?

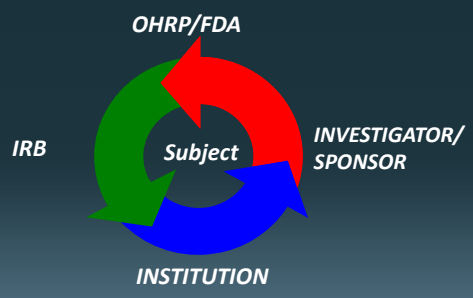
INFORMED CONSENT PROCESS

- *The dominant "white coat" authority figure*
- *Physician vs. investigator not distinguished*
- *Patient vs. subject not distinguished*
- *Therapeutic misconception prevails*

DEMONSTRATION OF ELECTRONIC IRB APPLICATION

https://net.unmc.edu/rss

HUMAN SUBJECTS PROTECTION IS A SHARED RESPONSIBILITY



FOR MORE INFORMATION

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The Recruitment Process for Clinical Trials

Jen Cavalieri, BSN, RN, CCRC, CCRP

Watch this recorded session

Objectives:
At the end of this session

- attendees will describe the core steps in the clinical trial recruitment process
- attendees will identify several examples of tools used in recruitment
- attendees will provide examples of how recruitment efforts are monitored and evaluated

What is research recruitment?

Public Relations?
The practice of managing the flow of information between an organization to its public

Advertising?
A form of communication that typically attempts to persuade customers to purchase or consume a particular brand of product or service

Recruitment?
The process of screening and selecting qualified people for a job or vacancy in a group

Special Regulations for Research

Ethical Access

Good Clinical Practice, the CFR (protection of human subjects), and the rights of human subjects

HIPAA

IRB guidelines and policies
- Rights of Research Subjects
- New forms on the website

Research Subjects

- Subjects may be hospital patients or outpatients receiving medical care
- Subjects may be healthy members of the community
- Subjects may be objects in the health care environment

The recruitment process needs to be customized for the type of research subjects needed

The Recruitment Process

Plan

Potential subjects are Pre-screened

Communicate

Approach

The Recruitment Process: Plan

Gather information and tools:
•Information from the Principal Investigator and study sponsor (investigator meeting or discussions)
•The research protocol
•Identify team members & roles
•Resources
•Reference information about previous studies with that type of trial, disease under study & subjects
•Describe the plan in IRB Application

The Recruitment Process: Plan…continued

•Identify the WWWWH in your recruitment process:
  Presenting the opportunity
  Intake & screening of interested potential subjects
  Separation of Qualifiers and Non-qualifiers
  enrollment
•Identify how you will mitigate the risks & barriers
•Identify your documentation methods
•How will you assess progress (set concrete goals against the timeline)
•What are your intervention triggers

Be preparing "Plan B" <u>now</u>

The Recruitment Process: Pre-Screen

•Trackers: sponsor screen log, pre-screen, quick AZ

•Assess progress, volumes, success and failures

•Reports to PI and sponsor: weekly, monthly, study to date

Study Example

- ID source of potential patients (ethical access)
- Create lists
- Recruitment Reference (contains Inclusion/Exclusion list, sponsor screen log, sponsor visit log)
- Create and maintain pre-screen log

Example Study: Pre-screen Log

Pre-Screen Log Uses:

- Communication w/PI
- Track total potential subjects reviewed
- Track failure reasons
- This is for site use only as these are unconsented patients

Potential Subject

- Use Inclusion/Exclusion worksheet for notes
- Review chart for appropriate information as a preliminary check. You want to have a reasonable expectation that the patient would qualify for the study. In-depth information can be gathered if subject consents
- Other important questions: for your study, will it matter if they are living independently or in SNF. Distance issues?
- Confer w/Investigator

Inclusion Exclusion Checklists as Documentation Tools

Detailed Eligibility Evaluation

Potential In-Patient Subject

- Communication with PCP
- Go to bedside and connect w/clinical caregiver: issues, family, provide CTS sheet
- Communicate w/Investigator

The Recruitment Process: Communicate

- Clinical Trial Summary sheet
- Ads and Flyers: internal and external

Clinical Trial Summary

Ads and Flyers

Be sure to:

- Consider your audience
- Accurately and concisely convey the study opportunity message
- Use non-coercive language
- Get IRB approval!
- Place contact information on the forms

Potential Subject Outcomes

- Subject needs to think about it
- Subject says yes
- Subject declines

…or Subject does not qualify

The Recruitment Process: Approach

•Ready-to-Roll folders

•Education

•Logistics

•Body Language

•Include significant others

Our Professional Responsibilities

•Retention is the best measure of effective recruitment
•**You** are the subjects' advocate
•Non-verbal messages and timing
•Therapeutic Misconception
•Research may be the patients' last hope
•"if we knew the outcome, we wouldn't have to do the study"

The Process and Documentation of Informed Consent for Subjects Involved in Research

Watch this recorded session

General Requirements of Informed Consent

No investigator may involve a human being as a subject in research unless the investigator has obtained legally effective informed consent of the subject or the subject's legally authorized representative (LAR) unless a waiver is granted by the IRB.

45 CFR 46.116; 21 CFR 50.20

General Requirements of Informed Consent cont'd

- Provide prospective subject/LAR sufficient opportunity to consider whether or not to participate
- Presented in a language understandable to the prospective subject/LAR
- Minimize the possibility of coercion or undue influence
- Can not include exculpatory language through which:
  - The subject/LAR is made to waive or appear to waive any of their legal rights
  - Releases or appears to release the investigator, sponsor, institution or its agents from liability for negligence.

UNMC HRPP Policy #5.1

Process of Informed Consent

Informed consent is a ***process*** in which:

- The prospective subject/LAR is given all of the information needed to make an informed decision about whether to participate in the study
- Investigator/designee fully explains all required elements of consent and rights of research subjects
- The prospective subject/LAR has the opportunity to have all of their questions answered and to exchange information freely with the investigator/designee

Process of Informed Consent cont'd

Informed consent is a ***process*** in which:

- The prospective subject/LAR has an opportunity to consider participation in the study
- The prospective subject/LAR demonstrates sufficient comprehension of the elements of consent by either:
  - Responding to appropriate questions
  - Describing the research in their own words

Process of Informed Consent cont'd

Informed consent must be provided:

- Voluntarily
- Without coercion or undue influence
- On an ongoing basis
- As new information becomes available

Process of Informed Consent cont'd

- Depends on the nature of the study and/or the degree of risk
- Considerations:
  - Environment and location where consent will be discussed
  - Amount of time allotted to the process
  - Use of a delayed consent procedure
    - Delayed consent allows the subject/LAR to take hours or days to read the consent form and speak with others (e.g. family, personal physician) about the research
  - A fully translated consent form must be used for non-English speaking subjects/LARs
  - The use of a witness or subject advocate

UNMC HRPP Policy #5.1

Process of Informed Consent cont'd

Personnel involved in the process must be:

- Knowledgeable about the protocol and UNMC HRPP policies
- Approved by the IRB
- In a position to fully answer all questions from the prospective subject/LAR
- Individuals typically involved in the process may be:
  - A physician or dentist
  - Research nurse/coordinator
  - Other healthcare personnel

UNMC HRPP Policy #5.1

Documentation of Informed Consent cont'd

- Written consent is **required** except when specifically waived in accordance with 45 CFR 46.117(c) or 21 CFR 56.109(c)
- The subject/LAR must sign and date the consent form in the presence of the investigator/designee authorized by the IRB to document consent
  1. *Backdating and forward-dating are never permitted*
- Consent can only be documented on the most current IRB-approved consent form
- A witness may be required in certain circumstances

UNMC HRPP Policy #5.1

Documentation of Informed Consent cont'd

- The process must be documented in the medical and research record
  1. Exception is genetic research due to concerns over insurance company accessibility and confidentiality. Keep in the research record only.
- Original consent document must be kept in the research record
- Subject/LAR must be given a copy of:
  1. The signed consent form(s) and study information sheet(s)
  2. "What Do I Need to Know before being in a Research Study?"
  3. "Rights of Research Subjects" (you must review it with them)

Documentation of Informed Consent cont'd

Documentation of the process of consent must consist of the following in the medical or research record:

1. Name of the individual(s) involved in the explanation of the study to the subject.
2. The period of time over which the study was discussed.
3. Any relevant information that is important (e.g. questions or concerns expressed by the subject /LAR).
4. A notation that the subject received a copy of the consent document with all required signatures is a great idea.

Documentation of Informed Consent cont'd

Study personnel authorized to document consent/assent must be:

- Authorized by the Principal Investigator
- Listed by name in the "Documentation of Consent/Assent" section of the IRB Application
- Approved by the IRB

Study personnel authorized to document consent/assent must have:

- Necessary expertise
- Sufficient knowledge of the protocol and UNMC HRPP Policies
- Any required medical/dental licensure
- Authorization per The Nebraska Medical Center and/or Children's Hospital & Medical Center hospital policies to perform the procedures in a non-research clinical care/diagnostic context

Documentation of Informed Consent cont'd

The PI is ultimately responsible for assuring that:

- Ethically and legally effective informed consent has been obtained from all research subjects no matter who obtained or documented consent.
- All persons involved in the process of informed consent are familiar with the research and with the elements of informed consent.

UNMC HRPP Policy #5.1

Telephone Consent

- Telephone consent process may be used in both clinical and non-clinical research when it is justified for:
  1. Convenience of the subject
  2. Provision of new information
  3. Safety or therapeutic benefit of the subject
- Must be documented in the research record
- Use of telephone consent must be approved by the IRB or IRB Chair/designee prior to its use

UNMC HRPP Policy #5.4

Telephone Consent

- Applies to:
  - Therapeutic Research
  1. Initial consent for screening to determine eligibility
  2. Re-consent for protocol changes or disclosure of additional risks
  3. Consent to enroll a subject whose LAR is unavailable in person
     - The IRB may grant approval during initial review of the protocol
     - The IRB Chair/designee is authorized to approve a telephone consent procedure on a case-by-case basis as the situation arises
  4. Non-Therapeutic Research
     1. The IRB may approve use of a telephone consent procedure for a study if both:
        - The study is classified as minimal risk **and**
        - Research personnel are not expected to see potential subjects

UNMC HRPP Policy #5.4

Telephone Consent cont'd

- Consent form, "Rights of Research Subjects" and "What Do I Need to Know?" must be provided to the potential subject/LAR prior to the telephone consent process.
- Investigator/designee must obtain consent with an independent institutional witness on the phone line
- Investigator/designee:
  1. Explains each element of consent and Rights of Research Subjects
  2. Answers all of the subject/LAR's questions
  3. Subject/LAR's comprehension assessed
  4. Instructs subject/LAR to sign, date and return the consent form if he/she agrees to participation/permission for subject participation

Telephone Consent cont'd

- The ***signed*** consent form must be received by the research personnel (mail, email or fax) before ***any*** research procedures are performed
- Upon receipt, investigator/designee signs and dates the consent form, as well as adds a note on the consent form which explains the lapse in time between signatures ("received in the mail 10/30/10; telephone consent obtained on 10/28/10")
- Where telephone consent was used to determine subject eligibility, the subject/LAR must be re-consented in person by the investigator/designee ***prior*** to performance of any additional research interventions

Telephone Consent cont'd

- In addition to the requirements for documentation of informed consent (HRPP Policy #5.1), documentation of telephone consent includes:
  - Rationale for the use of telephone consent
  - Date and time of telephone consent
  - Identification of all personnel involved in obtaining, witnessing and documenting the consent process.

Child Assent

- The IRB must determine whether adequate provisions are made to obtain assent of children based on their age, maturity and psychological state
- The age of majority is 19 years old in Nebraska
- Children who do not provide assent or who actively dissent may **not** be enrolled in the research unless assent has been waived

Child Assent cont'd

- If the subject is < 7 years old
  1. Need Parental Consent only
- If the subject is 7-12 years old
  1. Parental Consent is required
  2. Child Study Information Sheet is provided and discussed
  3. Verbal assent is documented in the research record
- If the subject is 13-18 years old
  1. Parental Consent is required
  2. Youth Study Information Sheet is provided and discussed
  3. Assent is documented by the minor on the Parental Consent form

Children Who Reach the Age of Majority

- Children who reach the age of majority while actively participating in an IRB-approved study must:
  - Give their consent to continue participation in the research
  - Sign the IRB-approved adult informed consent document
- If the study only involves data analysis, children who reach the age of majority do not need to provide consent
- If unable to provide consent, the parental consent remains in effect. This must be documented and the IRB must be notified
- The now adult subject has right to refuse continued participation in the study
  - New data may not be collected
  - Existing data collected under the parental consent process can be used

Adult Decisionally-Impaired Subjects

- LAR consent may be obtained only
  1. After IRB approval of the process and LAR consent document
  2. Subject is not competent to consent to participation in research on his/her own behalf
- Provision of an Adult Study Information Sheet to the subject is based upon the subject's level of cognition
- If subject regains competency, he/she must be consented for continued participation in research and provided the opportunity to withdraw from research

UNMC HRPP Policy #4.6

Single Subject Protocol Deviation

- Approval may be granted for an IRB-approved protocol to:
  1. Enroll a single ineligible subject
  2. Make a subject-specific deviation
- A patient enrolled in a study thru a Single Subject Protocol Deviation **is** a research subject
- Informed consent of the subject/LAR must be obtained prior to participation in the study

UNMC HRPP Policy #8.1

Common Violations Related to Informed Consent

- Not documented on the most current version
- "Person Obtaining Consent" was not authorized to document consent (i.e. not listed in Section II of the IRB Application)
- No signature for "Person Obtaining Consent"
- Dates that subject/LAR and "Person Obtaining Consent" sign the consent form don't match

UNMC HRPP Policy #8.5

QUESTION

When consenting a subject, it is important to consider which of the following?

A. Environment and location of the consent process
B. Time allotted to the consent process
C. Prospective subject has sufficient time and opportunity to ask questions
D. Prospective subject has the opportunity to discuss the study with other individuals, such as family, their primary physician, etc.
E. All of the above are necessary considerations

QUESTION

True or False

You are the research coordinator for a study evaluating the safety and efficacy of Drug X in the treatment of unstable angina. You encounter a patient on the PI's clinic schedule that is eligible for the study, but does not speak English fluently.

You are allowed to enroll this patient in the study using the English consent document and an interpreter since you do not have the consent form translated in his language.

QUESTION

Which violation is not reportable to the IRB?

A. The PI failed to date the consent form on the day that it was signed
B. An outdated consent form was used, but there were no changes between the current version and the outdated one
C. A subject read each page of a ten page consent document, but failed to initial all of the pages
D. The person that documented consent is not authorized to do so in Section II of the IRB Application

QUESTION

True or False

The IRB anticipated that the population of patients in the ICU that will be eligible to participate in a study will have an impaired decision-making capacity. Therefore, the IRB approved only an LAR consent form and an adult study information sheet (i.e. no adult consent form was approved).

You encounter a potential subject that is eligible for the study and has demonstrated the cognitive ability to provide consent and there is no LAR available. You are allowed to enroll the subject by having her sign the LAR consent form.

QUESTION

Which of the following research personnel should assess and document comprehension of the subject's understanding of a significant risk clinical trial?

A. Physician
B. Nurse Coordinator
C. Either A & B

Research Subject Advocate Office

UNMC Center for Clinical and Translational Research

Bruce Buehler, MD, Research Subject Advocate
Deborah Meyer, RN,CCRP, Associate Research Subject Advocate

Watch a recording of this session

Research Subject Safety

- UNMC's top priority-minimize risk for research participants
- Currents safeguards to assess and assure research safety
  - National standards and regulations
  - IRB reviews all protocols
  - Required investigator training (CITI)
  - New GCP training for coordinators has been recently added to the CITI training
  - **Research Subject Advocate (RSA) Office**

RSA Office

- Required for many NIH funded grants
- Resource for investigators, trainees, research participants and community members
- Includes a faculty member
  - Bruce Buehler, MD, Research Subject Advocate
- Also includes a research nurse
  - Deb Meyer, RN, CCRP Associate Research Subject Advocate

Guidelines

- The RSA and Associate RSA are required to be free of any conflict
- Compliments the IRB and existing institutional resources that promote safe and ethical research
- Provides a resource to communities on topics of research ethics, patients rights, and research safety

UNMC Research Subject Advocate Office

Research Subject Advocate:
Dr. Bruce Buehler
bbuehler@unmc.edu

Associate Research Subject Advocate:
Deb Meyer, RN, BGS,CCRP
(402) 559-6941
dmeyerk@unmc.edu

Key Functions

Key Functions

Education and Training

1. Investigators and research personnel
2. Research participants
3. Community

Advocacy

1. Evaluate research protocols for safety concerns
2. Review and develop policies to promote safety

Outreach

1. Discuss research safety with the community
2. Explain the research process
3. Listen to community concerns

Education & Training

Provide information on clinical research processes

- ***Research Participants***— answer questions or concerns about specific protocols
- ***Researchers***—provide assistance on ways to minimize risk to subjects and conduct recruitment and consent processes that are sensitive to the needs of the subjects
- ***Communities***—explain the research process and safeguards that protect research participants

Advocacy & Support

- Source for general safety information or concerns
- Partner with the IRB to promote research subject safety
- Review all CCTR protocols for research safety
- Monitor and report research safety concerns
- Support UNMC's work with other IRBs that monitor safety in the region

Outreach

- Provide pathways to learn about clinical trials and research opportunities
- Explain clinical research processes
- Create a forum to discuss research safety and safety concerns with the broader community

Research Resources: Access to Electronic Health Records

Purnima Guda, PhD, **Director**

- The Electronic Health Records Research Core facility has been established to more rapidly access electronic health data from our health care information system [EPIC and Carecast].
- This new resource will allow more rapid assessment of feasibility and data acquisition when considering a clinical study.
- The RSA Office reviews and assists with ethical or IRB issues when requesting access to the Electronic Health Records

Nebraska Biobank

- The Nebraska Biobank is a joint effort of UNMC & The Clinical Enterprise
- The aim of the Nebraska Biobank is to speed research in health care
- The Nebraska Biobank is made up of left-over blood samples from patients who want to take part.
- For further information, please refer to this link http://www.unmc.edu/nebraska_biobank.htm
- Any questions about the Nebraska Biobank can call the confidential line of the RSA Office

Further questions?

The Research Subject Advocate Office fields all hospital and UNMC phone calls regarding clinical trials and research questions or concerns

You can call the confidential line of the Research Subject Advocate Office at 402-559-6941

E-Mail: dmeyerk@unmc.edu

ASSESSING THE FEASIBILITY OF CLINICAL TRIALS

Sue Erickson, BSN, MSN, MBA
LuAnn Larson, RN, BSN, CCRP
Deb Vetter, MS

Watch a recording of this session

Objectives

- Identify the different components of a feasibility assessment.
- Recognize common contract components that impact the budget.
- Evaluate when it is not feasible to do the study.

Feasibility Criteria

- Population
- Resources
- Risk Management
- Time Line
- Costs

Population

- Do you have the patient population
  - Is there a minimum or maximum number of subjects
  - Is the enrollment criteria too strict
  - Not all will agree to do your study
  - What percentage of your patient population meet the criteria?
- Strategy
  - Purnima Guda can do a search
    - Phone
    - Email
- What strategies have you used?

Resources

- Personnel
  - Who is doing what? Name staff & define their roles.
  - Does PI have the time to commit to the study?
  - Does the agreement define which personnel?
- Space
  - Using Clinic/CRC/Off Site
- Equipment
  - Sharing patient care equipment
  - Purchasing of equipment necessary

Risk Management

- Medicare Coverage Analysis
- Level of Liability
  - PI Initiated Studies – we are the sponsor and are not indemnified by a third party.
- Private Healthcare Information (PHI) – SPA Admin
  - Need for data use agreement
- Sub-Contracting – SPA Admin
  - Requires a legal contract
  - Additional monitoring/oversight
- Biobanking -
  - Defining ownership of tissues
  - Special consents
  - Know the regulations

Time Lines

- Are other sites already up and running? How long ago?
- What is the recruitment period?
- How long is the study?

Costs

- You have to be willing to negotiate and not accept the first offer.
- Have a clear and accurate understanding of study costs.
- Be willing to walk away from the study is the stars do not align!

Tools for Creating the Budget

- Sponsor's budget
- Sponsor's contract agreement
- Protocol
- Flow chart/schema
- Informed consent
- Case Report Forms
- Investigational Pharmacy fee calculator
- Fee Schedules:
  - Centricity Charge Master
  - Department managers
  - Actual charges on a patient bill
  - Professional fees
- What other tools do you use?

Creating the Budget

- Calculate one-time "start-up" fees and "per patient" fees
- Know the "research rate" associated with each item billed to the grant if there is a "research rate"
- Identify hidden costs at start-up (e.g., record storage, faxing, calibration of machines)
- Remember to include inflation at 4-10%
- Indirect F&A costs for industry-sponsored trials (26%)

One Time Start-up Fees

A strategy to ensure incidentals are covered

- Negotiate these fees to be non-refundable
- IRB fee for industry sponsored trials ($2500)
- Administrative costs, such as personnel time (including benefits) to set up the study, attend investigator meetings, etc.
- Equipment
- Investigational Pharmacy set up
- Also consider charging a cancellation fee e.g. cost of one subject, 10%, etc.
- Hidden costs, such as long distance phone calls, etc

Start-Up Costs

STANDARD FEES FOR EACH STUDY

Item	Fee	26% F&A	Fee + Overhead
Local IRB Fee	$2,500.00	$0.00	$2,500.00
Regulatory Submission	$2,000.00	$520.00	$2,520.00
IRB Amendment Submission	$500.00	$130.00	$630.00
IRB Annual Review Submission	$250.00	$65.00	$315.00
Study Start-up	$4,400.00	$1,144.00	$5,544.00
Study Storage	$1,000.00	$260.00	$1,260.00
Pharmacy Start-up	$1,500.00	$390.00	$1,890.00
Pharmacy Annual Fee - applied at the end of Year 2	$750.00	$195.00	$945.00
Patient Stipends	$250.00	$65.00	$315.00
TOTAL FOR STANDARD FEES	$13,150.00	$2,769.00	$15,919.00

Study Start-up Includes:
Presite Evaluation Visit
Investigators meeting
Site Initiation Visit
Developing Source Docs
Budget
Education of Site Personnel
Coverage Analysis
Feasibility Analysis

"Per Patient" Fees

- Personnel costs – PI, study coordinator, data coordinator, office associates, administrator (including benefits)
- Screen failures
- "Non-Standard" clinical evaluations, tests, and procedures along with professional fees, outside consults
- Supplies (clinical and office supplies)
- Treatment room charges
- Investigational Pharmacy

Is Your Budget Realistic?

- Determine the charge/cost for each item.
- Compare your budget to the sponsor's proposed budget
- Review your budget with the PI.
- Send your budget to the sponsor. Use discretion with the information you release. Use summary information when appropriate, e.g. cost of screening, cost of week 2 eval.
- Negotiate the "per patient" fees and "start-up" costs.
- The budget and payment schedule are part of the Clinical Trial Agreement (CTA).
- You need to AT LEAST break even on your budget

As the Study Proceeds

- Schedule renegotiation for unexpected expenses or changes that occur during the study
- Know if you are expected to invoice for payment
- Send invoice if payment has not been received
- Track your income and your expenses
- Produce accurate and timely financial reports
- Consider a fine for late payments from the sponsor
- If payment is tied to monitor visits, ensure that the monitor comes as scheduled
- What experiences have you had?

Monitor-Monitor-Monitor

- Are you getting the enrollment ?
- What is the PI's effort?
- What is the coordinators' effort?
- Do you need to negotiate some more?
- Ask the hard questions

THIS TAKES A LOT OF EFFORT

Scenario

- You have been invited to participate in a 3 month trial of a new weight reduction therapy. The product is a once-daily, orally administered medication. The schedule of events will be given to you. We want to enroll 100 participants. Investigators' meeting is in 2 months.
- List the expected resources necessary to conduct this study
  - Estimate the cost of each resource, the total cost per participant and the total cost of the study
  - Make note of any assumptions

Weight Reduction Study	Screening	Month 1 Visit	Phone Call	Month 2 Visit	Month 3 Visit
H&P	X				
Physical					X
Chemistry Panel-send out	X				
Chest X-Ray	X				
Dispense Drug X	X	X		X	
Collect Drug X		X		X	X
Quality of Life Questionnaire	X	X		X	X
Height	X				
Weight/BMI	X	X		X	X
Monitor for AE's		X	X	X	X
Cost per subject	0	0		0	0
Number of subjects	100	100		100	100
Total subject costs	0	0		0	0
Additional Costs					
Total cost for the study	0	0		0	0
List of Additional Costs					

Things to Include

Things We Included

- Advertising
- $3000 Start-Up Fee
- Screen Failures
- CXR - Pro-fee
- Process/ship labs
- Pharmacy start-up/dispensing fee
- Long distance phone calls
- IRB $2500
- Purchase a bariatric scale
- Record Storage 7 years
- Room Charge
- Stipend for subject
- Travel
- Cancellation/Close-out Fee
- F & A 26%

Weight Reduction Study	Screening	Month 1 Visit	Phone Call	Month 2 Visit	Month 3 Visit	
H&P	200					
Physical					150	
Chem Panel- send out -Processing	30					
Chest X-Ray + profee	400					
Dispense Drug X	9	9		9		
Collect Drug X		10		10	10	
QOL Questionnaire	20	20		20	20	
Ht/Wt/BMI	15	15		15	15	
Monitor for AE's		20	20	20	20	
Room Charge	25	25		25	25	
Stipend	20	20	10	20	20	
Cost per subject	$694	$94	$30	$119	$240	
#of subjects	100	100	100	100	100	Total
Total subject costs	$69,400	$9,400	$3,000	$11,900	$24,000	$117,700
Additional Costs						
Start-Up	$3,000	Scale	$300	Close out	$1,000	
Pharmacy start-up	$500	Record Storage		$2,000		$ 6,700
		Subject Cost + Additional Costs				$124,400
					Overhead	$ 32,344
Advertising	$2,000	IRB Fee		$2,500		$4,500
					Grand Total	$ 161,244

Long Term Study Budgets

Revenue Center	Procedure Code	Procedure Description	Hospital Charge per single unit	4 pts x2 scans = 8	Cost increase 10%/yr 2*	Hosptial charge /unit	4 pts x 2 scans = 8	Cost increase 10%/yr 2*	Hosptial charge /unit	4 pts x 2 scans = 8	Cost increase 10%/yr 2*	Hosptial charge /unit	4 pts x 2 scans = 8
426	70555	Functional MRI	$3,807.45	$30,459.60	0.10	$4,188.20	$33,505.56	0.10	$4,607.01	$36,856.12	0.10	$5,067.72	$40,541.73
426	70556	DTI volumetric imaging	$3,535.49	$28,283.92	0.10	$3,889.04	$31,112.31	0.10	$4,277.94	$34,223.54	0.10	$4,705.74	$37,645.90
418	74188	Syringe	$41.06	$328.48	0.10	$45.17	$361.33	0.10	$49.68	$397.46	0.10	$54.65	$437.21
426	A9579	Contrast agent (Multihance) ($12.62/ml; 85 kg avg at 0.3cc/kg; average total 53cc per study	$656.24	$5,249.92	0.10	$721.86	$5,774.91	0.10	$794.05	$6,352.40	0.10	$873.46	$6,987.64
					Cost increase 5%/yr			Cost increase 5%/yr			Cost increase 5%/yr		
414	95966	MEG testing, 1 modality	$3,663.25	$29,306.00	0.05	$3,846.41	$30,771.30	0.05	$4,038.73	$32,309.87	0.05	$4,240.67	$33,925.36
414	95967	Meg testing, additional modality	$3,663.25	$29,306.00	0.05	$3,846.41	$30,771.30	0.05	$4,038.73	$32,309.87	0.05	$4,240.67	$33,925.36
profee	76377	MEG, 3D rendering	$398.00	$3,184.00	0.05	$417.90	$3,343.20	0.05	$438.80	$3,510.36	0.05	$460.73	$3,685.88
profee	95966	MEG testing, 1 modality	$460.00	$3,680.00	0.05	$483.00	$3,864.00	0.05	$507.15	$4,057.20	0.05	$532.51	$4,260.06
profee	95967	Meg testing, additional modality	$402.00	$3,216.00	0.05	$422.10	$3,376.80	0.05	$443.21	$3,545.64	0.05	$465.37	$3,722.92
TOTAL				$133,013.92			$142,880.71			$153,562.45			$165,132.05
Grand Total													$594,589.14
This budget is based on the followning assumptions:													
You need 20 pts and they each get two sets of tests													
You already have 4 complete so that leaves 16													
You estimated that you can get 4 per year so we have 4 more years to go													

Getting Paid for What You Do

- See that internal budget sheet is set up and a WBS grant account is established
- Ensure that the correct charges are applied to the budget
- Know what the Clinical Trial Agreement says about payment amounts and payment schedules
- Know if you have to invoice to get payments
- Coordinator should know where everything is billed.
  - Complete the Master Matrix
- Track patient events that are tied to payments. Could use the subject list
- Track monitoring visits.
  - Payments are often tied to those visits
- Match payments to the charges/invoice
  - Sponsor needs to provide details as to what they are paying

IRB # 475-06-FB
Title of Protocol: Sitagliptin Treatment in Patients with Type 2 Diabetes Mellitus after Kidney Transplant

Grant #: MXH-99-925-1326 37-5360-9910-019
Medicare Qualifying Study?

Coordinator: Claire Haire, RN
Phone: 559-8555
Pager: 888-3395

PI: James Lane, MD
Phone: 559-8176
Pager: 888-3762

Department: DEM
Zip: 1230

Billed Sponsor | PAID

Patient #	Gender	Ethnicity	Subject Name	MR #	Consent to MR	Baseline Study visit 1	Except	Visit Monitored	Study Visit 1	Except	Visit Monitored	Study Visit 2	Except	Visit Monitored	Study Visit 3
1	male	cau	RS	xxxxx	yes	5/21/07	no	yes	5/29/07	no	yes	6/4/07	no	yes	6/12/07
2	male	cau	SR	xxxxx	yes	7/23/07	no	yes	8/6/06	no	yes	8/12/07	no	yes	8/23/07
3	female	S. asian	NH	xxxxx	yes	7/16/07	no	yes		yes	yes	9/12/07	no	yes	9/19/07
4	male	cau	TL	xxxxx	yes	1/21/08	no	yes	1/28/08	no	yes	2/4/08	no	yes	2/11/08
5	male	cau	MM	xxxxx	yes	2/25/08	no	yes	3/3/08	yes	yes	3/12/08	no		3/21/08
6	male	Hispanic	RJ	xxxxx	yes	5/12/08	no	yes	7/1/08	yes	yes	7/8/08	yes		7/14/08
7	female	cau	DB	xxxxx	yes	6/19/08	no	yes	6/30/08	no	yes	7/7/08	no		7/15/08
8	female	cau	PS	xxxxx	yes	6/30/08	yes								
9	male	african-American	CP	xxxxx	yes	8/18/08	no	yes	8/22/08	no		8/29/08	no		9/10/08
10	female	cau	AW	xxxxx	yes	10/20/08	no	yes	11/3/08	no		11/12/08	no		11/18/08
11	female	cau	WW	xxxxx	yes	10/27/08	yes		11/11/08	no		11/18/08	no		11/24/08
12	male	cau	TM	xxxxx	yes	1/12/09	no		2/5/09	no		2/11/09	no		2/19/09

SPA Contract Negotiations: Clinical Trial Budgets

- Fundamental Principle
  - SPA does not negotiate budgets with the sponsor
  - PI and PI's staff are responsible for budget negotiations
- Essential Practices
  - SPA verifies salaries and standard costs, including 26% indirect cost rate
  - SPA discusses with PI's staff contract terms that relate to costs, such as reimbursement/payment language

Contract: Budgetary Appendices

- Budget **Spreadsheet**
  - Line item costs
  - Numerical format
    - Per patient
    - Per event
- Budget **Narrative**
  - Commonly called "Payment Schedule"
  - Text format
    - Defines process
    - Defines payment terms

Contract Budget Negotiation

- Budget **Spreadsheet**
  - Department negotiates
  - Sponsor appends to contract
  - SPA does not review or approve
    - SPA cannot access clinical care cost systems
- Budget **Narrative**
  - SPA redlines sponsor's budget narrative
  - Department reviews and modifies SPA redlined version
  - SPA appends negotiated Narrative to contract

Contract: Budgetary Components

SPREADSHEET

- Advertising
- IRB Fees (price)
- Indirect Costs
- Patient Stipends
- Pharmacy Set-Up/ Dispensing Fees
- Travel

PAYMENT SCHEDULE

- Advanced Payment
- Adverse Events/ Unscheduled Visits
- Final Payment/Hold Back
- Invoicing
- IRB Fees (practice)
- Screen Failures

Contract: Spreadsheet

- Advanced Payment
  - Site may need to cover costs prior to patient enrollment
- Advertising
  - Excluded from IDC calculation
- Indirect Costs (IDC)
  - 26% of direct costs
  - Exception: IRB and Advertising not charged IDC
  - Costs reimbursed outside of sponsored agreement

Contact Information

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- Deb Vetter
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Patient Charges

- Budgets ultimately direct patient charges
- Correct billing is of utmost importance
- Use the budget to build the matrix
- Make certain the consent form reflects accurately who pays
- Make certain you are on top of the billing so insurance companies are not getting research charges

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Contact Information

Contract Specialists

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Study Feasibility, Using the EHR form

Purnima Guda, PhD

Electronic Health Records Access Core

Introduction

- EHR (Electronic Health Record) includes a whole range of data in comprehensive and summary form.
- Our EHR system Centricity is replaced by EPIC in 2012.
- A new core facility is developed to retrieve data from EPIC and Centricity (retrospective research).
- Data is migrated from Centricity to EPIC from April 2009 to current. Retrospective data can still be obtained from Centricity (1989).

Limitations with Centricity

- Some data elements are not routinely captured
  - Not a relational database
  - Ethnicity is merged with race
  - Many clinics don't enter weights or blood pressures
  - Not all medications are entered or removed when not taking
  - Many reports are text files that have to be scanned using a word search and can never be queried
  - Smoking and aspirin unreliably recorded
  - Date of diagnosis (onset date)

Watch a recording of this session

EPIC: How will it be different?

- EPIC will improve some of these things as everyone will be using the same EHR in all clinics and units (customized to clinics)
- Examples
  - Current EPIC database (Clarity) is a relational database
  - Smoking and aspirin will be more reliably recorded
  - Medications and problem lists will be reliably maintained
  - Primary care physician will be more reliable to track by unit
  - Some search functions of your own patients will be available (like social history, medical history, family history)
  - Immunizations are recorded separately
  - Diagnosis is linked to medication and procedures
  - More discrete data available compared to centricity

Current Data Elements Available in EPIC

- Demographics
- Problem List
- Medications
- Allergies
- Immunizations
- Laboratory tests
- Admit/Discharge dates and diagnosis
- Outpatient visit dates
- Date of death
- Pathology, Radiology and Vascular reports
- Surgery reports
- Diagnosis (ICD-9, CPT and procedural codes)
- Provider information
- Departments or Clinics
- Best Practice Alerts (BPA) – Customized functionality to alert physicians or healthcare professionals when a patient meets certain criteria that may make them eligible for certain studies , diagnostic procedures or allergies and reportable

EPIC DataMarts (Chronic Disease Registries)

(pre-build but not populated)

- Asthma
- Coronary artery disease
- Congestive heart failure
- Chronic kidney disease
- Chronic obstructive, pulmonary disease (COPD)
- Diabetes (Populated)
- HIV
- Hypertension
- Osteoporosis
- Obesity

DataMarts (Registries) can be created and populated upon request.

NEW DataMarts (Registries)

- Cystic Fibrosis
- Chronic Liver Disease

Wellness Registries

- These wellness registries are broken down by age, and after age 13, they are also broken down by gender.

SmartData Elements

- SmartData Elements are values entered by users through SmartTool (SmartLinks,SmartLists,SmartText), NoteWriter or other documentation tools that file discrete data and can be reportable.
- Used to create charts, progress notes, documentation flow sheets to include vital signs, procedures etc.

Reports

- Meaningful Use
  Program initiated by federal organization to promote reporting of quality information by eligible professionals electronically.
- Billing
- Routine lab results
- Medications
- Diagnosis
- Oncology Data
  - Cancer staging
  - Treatment plans
  - Chemo cycles

New Reports

- Cather associated UTIs
- Hospital transfer and discharge
- Readmission
- Ventilator-Associated Pnemonia
- Central line associated bloodstream infections
- Umbilical catheter associated bloodstream infections

What is new ?

- OB/GYN (Storke)
- Beacon (cancer)
- Best Practice Alerts
- New Views, reports and tables 2014 (for eg: readmission data)

What we do at our EHR core facility ?

Types of projects that may need this service

- Retrospective data analysis
- Cross sectional studies
- Health outcomes
- Feasibility analysis (to compete for NIH multicenter trials or decide if it is worth contract negotiation for a pharma trial)
- Case finding for subject recruitment
- Quality improvement
- Transfer of datasets to a locally maintained registry
- Specific data fields to correlate with or add to other data collected elsewhere
- Public health research

Questions we can ask EPIC database

- Patients with type 2 diabetes and are on metformin and not insulin
- Patients who had kidney transplant and their out comes
- Patients seen at pulmonary care dept, diagnosed with pneumonia and admitted in the hospital
- Patients in a certain age group and immunized with 3 doses of DTaP
- New born babies in our hospital with low birth weight
- Transplant patients diagnosed with cancer in last 20 years

Getting started

- To get the right data, you need to think about how the data will be categorized
- Examples:
  - To find "Diabetes", you have to decide which ICD-9 code to use or some specific lab values (HbA1C)
  - To find cases of "polycystic ovarian syndrome", you may want to also look at "amenorrhea", "hirsutism", "hyperandrogenism"
- If you want to access any "Protected Health Information", you will need to obtain an IRB

Protected Health Information (PHI)

There are 18 variables considered as PHI

- Name
- Date of Birth
- SSN
- Address
- Phone numbers
- Medical record numbers
- Full face photographs
- Fax numbers
- Email address
- Health plan numbers
- IP address
- Unique identifiers
- Biometric identifiers (finger prints/voice prints etc)
- Account numbers
- URLs
- Certificate/license numbers
- Vehicle identifiers/serial numbers
- Device identifiers

We evaluate your ethical access to the requested datasets

- Requesting PHI? Requires one of the following…
  - IRB approved…..or
  - Evidence that you have ethical access to the data
    - Your own patient data (can include your "team", "unit", "clinic" although evidence of support of the unit director may be requested)
    - Questions regarding ethical access data can be forwarded to Deb Meyer, RN (Associate research subject advocate)

Projects without identifiers or for specific purposes, can request directly

- Feasibility for a potential study (How many patients do we have with…)
- Health outcome project: aggregate data only for health operations does not require IRB approval
- Health professional board certification projects or quality improvement
- Public health research
- If it is a trainee-directed project, needs signature of the faculty mentor

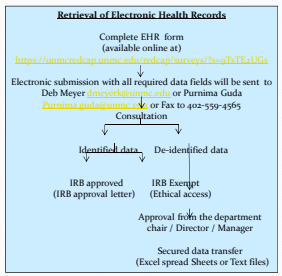
How to get started

- Need to complete the Electronic Health Records Data Access Core Form
- Online form to request data

https://unmcredcap.unmc.edu/redcap/surveys/?s=9TsTE2UGsM

- Requests information on type of data requested, type of project
- Consultation or further questions likely required

Request Form for Electronic Health Data



Many requests require the following:

- Inclusion criteria: need to be specific and need to consider what data is likely to be available and reliable
  - ICD-9 codes for a specific disease, age criteria based on today's date or at the time of the encounter?, gender
- Exclusion criteria: be specific
  - Exclusion by medication may not be accurate while age will
- Specific data elements ---time consuming and expensive to go back and do it again so try to be complete and specific
  - What is the name of the laboratory test in the database, particularly when there may be more than one (calculate and measured LDL?, which PSA or all)
  - Be inclusive of medication names that could be included/excluded (generic and brand and combinations)
- Can generate datasets monthly or other intervals, for recruitment or follow-up of patients

Who can request data?

- Any UNMC faculty
- Any TNMC physician
- Any student or trainee with a UNMC faculty mentor
- UNMC/TNMC staff if they have ethical access
- Investigators outside UNMC must have collaborator within UNMC
- Corporations outside UNMC cannot request data other than that established through MOUs such as UHC (United Health Care), AHA (American Heart Association), or other collaborative groups

What does it cost?

- Current rates can be found on the web-site at
  - http://www.unmc.edu/cctr/ehr_fees.htm
- Happy to provide a cost estimate for grant proposal budgets
- Contact EHR core for details

EHR contact

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Coverage Analysis (CA) and Its Role in Research

Katie Penas, MHA, CNMT, RT (N)
Finance Analyst
The Nebraska Medical Center
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Watch a recording of this session

Objectives

- By the end of today's presentation, participants will be able to:
  - Define Coverage Analysis (CA)
  - List the documents that are necessary in performing a Coverage Analysis (CA)
  - Understand the future direction of coverage analysis

Background Information

- On September 9, 2000, Centers for Medicare & Medicaid Services (CMS) introduced National Coverage Determination (NCD) 310.1 (also known as the Clinical Trial Policy).
  - Covers:
    - Routine costs of qualifying clinical trials
    - Reasonable and necessary items and services used to diagnose and treat complications arising from participation in all clinical trials regardless of qualifying status

Routine Costs

- Medicare defines routine costs as:
  - 1) Items or services that are typically provided when the patient is not on a clinical trial (ex. Conventional care or standard of care services)
  - 2) Items or services required for the provision of the investigational item or service (ex. Administration of a non-covered chemotherapeutic agent)
  - 3) The clinically appropriate monitoring of the effects of the item or service or the prevention of complications
  - 4) Items or services needed for reasonable and necessary care arising from the provision of an investigational item or service—in particular, for the diagnosis or treatment of complications.

Non-Routine Costs

- The investigational item or service itself, unless the item or service is already covered outside a clinical trial
- Items or services provided solely for research purposes (ex. data collection, tests performed more frequently than dictated by conventional standards, etc.)
- Items or services solely to determine eligibility
- Items or services provided or paid by the sponsor
- Items or services promised free in the Informed Consent Document
- Items or services not generally available
  - Fall outside of a Medicare benefit category
  - Statutorily excluded by NCDs or LCDs

Overview of How Medicare is Structured

MEDICARE

NATIONAL LEVEL

National Coverage Determinations (NCDs)

Determine what is and isn't covered by Medicare on a national level

REGIONAL LEVEL

Medicare Administrative Contractors (MACs)
•CMS has divided the country into 15 regions

Nebraska, Iowa, Kansas, & Missouri belong to the J5 MAC
• Contracted by Wisconsin Physicians Services

Local Coverage Determinations (LCDs)

Determine what is and isn't covered by Medicare on a local/regional level

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MEDICARE QUALIFYING CLINICAL TRIALS FLOWCHART FOR DRUG STUDIES

(*Source:* Medicare National Coverage Decision-NCD)

Does the trial evaluate an item or service that falls within a Medicare benefit category (e.g., physician's service, durable medical equipment, diagnostic test) and is not statutorily excluded from coverage (e.g., cosmetic surgery, hearing aids)? ***AND***
Does the trial have therapeutic intent and is not designed exclusively to test toxicity or disease pathophysiology? ***AND***
If the trial evaluates a therapeutic intervention, does it enroll patients with diagnosed disease rather than healthy volunteers? (Trials of diagnostic intervention may enroll healthy patients as a control group.)

NO / YES

Project ***DOES NOT*** qualify for Medicare coverage under NCD; **DO NOT BILL MEDICARE**

NO

Is the trial:
- Funded by NIH, CDC, AHRQ, CMS, DOD, VA; ***OR***
- ✓Supported by centers or cooperative groups funded by NIH, CDC, AHRQ, CMS, DOD, or VA; ***OR***
- ✓Conducted under an IND reviewed by the FDA; ***OR***
- ✓Exempt from having an IND under 21 CFR 312.2(b)(1) (until qualifying criteria are developed and certification process is in place?) (See below for exemptions from IND under the regulations)

YES
Trial qualifies under NCD 310.1

NO

May bill Medicare for routine costs of trial when the involved items and services are otherwise available to Medicare beneficiaries (i.e., there exists a benefit category, it is not statutorily excluded, and there is not a national non-coverage decision.)
Routine costs include items or services:
- ✓Typically provided outside of a clinical trial (e.g., medically necessary conventional care)
- ✓Required solely for the provision of the investigational item or service (e.g., administration of a non-covered chemotherapy agent); clinically appropriate monitoring of the effects of the item or service, or the prevention of complications; and
- •Needed for reasonable and necessary care arising from the provision of an investigational item or service, in particular for the diagnosis or treatment of complications.

May *not* bill Medicare for:
- ✓The investigational device, drug, or procedure itself (except for Category B devices identified as such and not previously deemed non-covered).
- ✓Items and services provided solely to determine trial eligibility.
- •Items and services provided solely to satisfy data collection and analysis needs and not used in direct clinical patient management (e.g., monthly CT scans for a condition usually requiring a single CT scan).
- •Items and services customarily provided by sponsor without charge.
- ✓Items and services for which sponsor has specifically paid provider.
- •Items and services for which there is no Medicare benefit category.
- ✓Non-covered items and services because they are statutorily excluded or fall under a national non-coverage policy.

Exemptions allowed under 21 CFR 312(b)(1): The purpose of the research is not intended to change the drug indications or labeling, advertising, route of drug administration or dosage, or patient population and the trial will undergo IRB review and approval as well as meet all other federal regulations. ***Note:*** A process for self-certifying under the NCD has not yet been established by CMS.

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MEDICARE QUALIFYING CLINICAL TRIALS FOR DEVICE STUDIES

Device Type:	Device Number:
☐ IDE	
☐ HDE	
☐ 510(k)	
☐ PMA (premarket approval)	
Post Approval Study	
☐ Combination product	
Compassionate Use	

Device Class:	
☐ Class I	General controls
☐ Class II	Special controls
☐ Class III	Pre-Market Approval

Device Category:	
☐ Category A	Experimental / Investigational
☐ Category B	Non-experimental and / or Investigational

What is Coverage Analysis (CA)?

- A systematic process that verifies conventional "standard" care vs. research only costs to identify what can or cannot be billed to a third party payer (either private insurance or Medicare).

Coverage Analysis: 3-Part Process

1. Verify that the trial "qualifies" for coverage
2. Identify what items or services are "routine costs"
3. Verify that Medicare rules allow coverage of specific "routine costs" and their frequency

Why use Medicare Rules in Determining Coverage of Costs?

- Medicare is considered the "gold standard" for comparison.
- NCD 310.1 provides guidelines, referencing Medicare, for determining the qualifying status and what may be covered.

Why use Medicare Rules in Determining Coverage of Costs? (continued)

Blue = States that have laws or legislation addressing the payment of routine costs in clinical trials

- Many states have passed legislation that requires private payers to follow the Medicare rules.
  - Health benefit providers who are members of the Nebraska Insurance Federation have voluntarily agreed to provide this coverage as part of health insurance contracts that they underwrite.
- As of January 1, 2014, the Affordable Care Act ensures that **new** health insurance plans cover the routine care costs of people taking part in clinical trials.
  - A loop hole still exists for "grandfathered" health insurance plans

What are the Benefits of Coverage Analysis?

- Enables institutions to make informed, fact-based decisions relative to the financial costs and benefits associated with each clinical trial
- Provides a guideline for appropriate billing
- Assists in budget development
- Assures that the study budgets reflect the true cost of research
- Prevents the IRB from tabling studies for questions with the coverage of specific items or procedures

Coverage Analysis: Drugs vs. Devices

- DRUGS
  - Governed by FDA
    - Division of Drug Information (CDER)
  - Coverage Analysis performed by Katie Penas

- DEVICES
  - Governed by FDA
    - Center for Devices and Radiological Health (CDRH)
  - Coverage Analysis performed by Grace Videtich

What are the Steps in the Coverage Analysis Process?

- Pre-IRB Submission/Feasibility

Coordinator emails the required documents to either Katie Penas (drug studies) or Grace Videtich (device studies).

Katie Penas and/or Grace Videtich review the required documents along with the appropriate national coverage determinations, local coverage determinations, and clinical practice guidelines to complete the preliminary coverage analysis.

Katie Penas or Grace Videtich email the coordinator with any questions and/or comments they have during the preliminary analysis.

Coordinator answers the applicable questions and the preliminary coverage analysis is completed.

What are the Steps in the Coverage Analysis Process? (continued)

- Post-IRB Submission/Final Review

Coordinator emails the documents submitted for the IRB review process to either Katie Penas (drug studies) or Grace Videtich (device studies).

Katie Penas and/or Grace Videtich review the documents submitted for the IRB review process and compare them to the results of the preliminary coverage analysis.

Katie Penas or Grace Videtich draft a letter to the IRB summarizing the research-related financial risk to patients participating in the clinical trial.

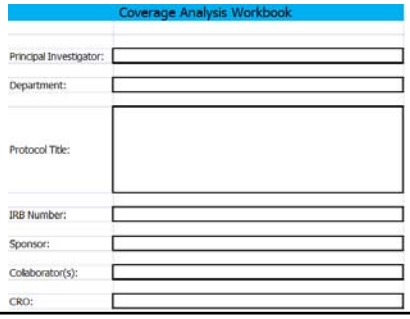
Katie or Grace email the draft IRB Coverage Analysis Summary letter to the Coordinator and PI for formal acknowledgement.

PI formally acknowledges the content of the IRB Coverage Analysis Summary letter.

Katie Penas or Grace Videtich email the IRB Coverage Analysis Summary letter to the IRB.

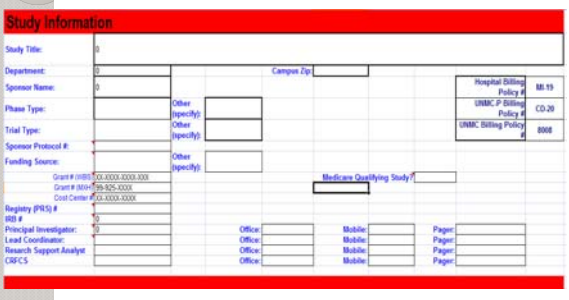
Coverage Analysis Workbook

- Cover Page



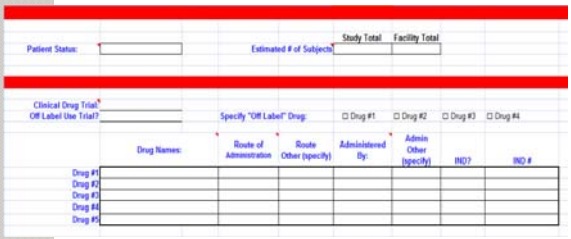
Coverage Analysis Workbook

- Drug Info



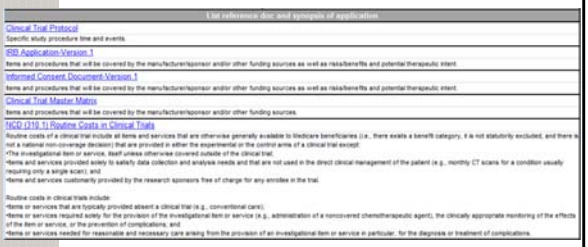
Coverage Analysis Workbook

- Drug Info (continued)



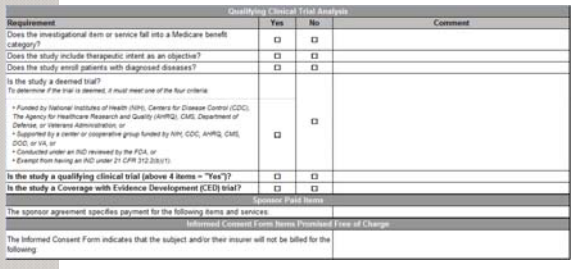
Coverage Analysis Workbook

- Medicare Info Drug



Coverage Analysis Workbook

- Medicare Info Drug (continued)



Coverage Analysis Workbook

- Device Info

DEVICE INFORMATION

http://www.fda.gov/MedicalDevices/default.htm
http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/default.htm

Device Name: Manufacturer:

1	Is this device currently used at the Nebraska Medical Center?	☐ YES	☐ NO
2	Will this device be supplied by sponsor at no charge?	☐ YES	☐ NO
3	Do you plan to use hospital stock devices for this trial?	☐ YES	☐ NO
4	Where will the device be used / procedure performed? (list all that apply)	☐ TMMC surgery suite ☐TMMC Cath/EP Lab ☐TMMC Clinic ☐UNMC-P Clinic ☐CRC ☐MMI Clinic ☐Epley ☐CU ☐CCU ☐PCU ☐ Other, specify_____	
5	Where will the device be stored? (list all that apply)	☐Pyxis unit ☐Coordinators office ☐Pis office ☐Clinic Storage unit ☐Other, specify _____ ☐Other, Specify _____	
6	Is special training required to install device?	☐ YES	☐ NO
7	Is special training required to use or monitor device?	☐ YES	☐ NO
8	Has draft contract been forwarded to Sponsored Programs	☐ YES	☐ NO
9	Has draft contract for TMMC been forwarded to the Hospital?	☐ YES	☐ NO

Principal Investigator

Name	
NPI Number	
Address	Department of MDXXXX Nebraska Medical Center Omaha, NE 68198-XXXX
Phone Number	402-55X-XXXX
Fax Number	402-55X-XXXX
e-mail	

Coverage Analysis Workbook

- Medicare Info Device

COVERAGE ANALYSIS - DEVICE TRIAL

STUDY TITLE:

This coverage analysis is intended as a general guideline for use in determining which items and services are billable to Medicare based upon current benefit policies, coverage determinations, coverage decisions, and federal guidelines. All items and services that are billable to Medicare must be supported by medical necessity.

Documents Received

DOCUMENTS		VERSION
Protocol		
Informed Consent		
Clinical Trial Agreement /Contract		
Budget		
FDA correspondence (un-redacted)		
2-3 Peer Reviewed Articles		
CMS correspondence if applicable		
Principal Investigator basis/reference for conventional care determination:		

GUIDANCE

Coverage Analysis Workbook

- Medicare Info Device (continued)

Qualifying Clinical Trial Analysis

Questions		Rationale / Information
Is the device intended for the diagnosis, monitoring, or treatment of an immediately life-threatening disease or condition?	☐ Yes ☐ NO ☐ N/A	
Does a CMS policy, NCD, or LCD prohibit Medicare coverage for this device?	☐ Yes ☐ NO ☐ N/A	
The sponsor agreement specifies payment for the following items and services:	☐ Yes ☐ NO ☐ N/A	
The Informed Consent Form indicates that the subject and/or their insurer will not be billed for the following:	☐ Yes ☐ NO ☐ N/A	
Items/services promised in the Protocol	☐ Yes ☐ NO ☐ N/A	
SOC items/services paid in the budget	☐ Yes ☐ NO ☐ N/A	

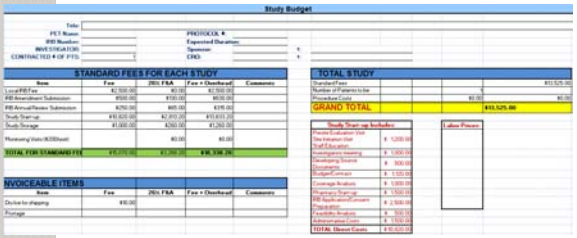
CONCERNS

Coverage Analysis Workbook

- CA Matrix

Coverage Analysis Workbook

- Budget



FAQs

Is Coverage Analysis Required for My Study?

- Drug Studies
  - Currently coverage analysis is required for clinical trials in the following departments:
    - Oncology
    - Radiation Oncology
    - Fred & Pamela Buffet Cancer Center
    - Clinical Research Center (CRC)
    - Psychiatry
    - Diabetes, Endocrinology, Metabolism (DEM)
    - Ophthalmology
- Device Studies
  - Coverage analysis is required for ALL clinical trials regardless of department.

The long-term goal is to have coverage analysis performed for all clinical trials on campus

What Documents are Required for a Coverage Analysis?

- DRUG STUDIES
  - Protocol
  - Informed Consent
  - IRB Application
  - Matrix
  - Preliminary Budget
  - Investigator's Brochure (if applicable)
- DEVICE STUDIES
  - Protocol
  - Informed Consent (stamped)
  - Matrix
  - Preliminary Budget
  - Investigator's Brochure (if applicable)
  - Copies of FDA Correspondence (un-redacted)
  - Copies of 2-3 peer-reviewed articles
  - Copy of IRB approval letter

Is There a Fee for Coverage Analysis?

- Yes
  - Full Review = $750
    - Studies that generate charges in One Chart
  - Modified Review = $250
    - Studies that do not generate charges in One Chart
- Fees are invoiced to the department

Can the Coverage Analysis Fee be Waived?

- Yes
  - A waiver is available for PI-initiated and cooperative group studies
  - If you would like to request a waiver for the coverage analysis fee, contact Katie Penas or Grace Videtich and they can provide the waiver request form.
    - Waivers are approved by Dr. Kratochvil, Associate Vice Chancellor for Clinical Research.
    - A copy of the approved waiver is emailed to the coordinator and saved in the Clinical Trials folder along with the matrix.

Can I request a coverage analysis of my study even if my department is not included on the required list?

YES!

Future Direction of Coverage Analysis

- The number of coverage analyses for drug studies is increasing.
  - 2012: 23 reviews
  - 2013: 63 reviews
- Coverage analysis is currently covering about 50% of the full board studies that are performed on campus.
- The CRC is in the process of hiring another Finance Analyst.
- The plan is to continue the coverage analysis expansion efforts.

Questions?

Contact Information

Katie Penas, MHA, CNMT, RT (N)
Finance Analyst
Phone #: 402-552-6601
Email: kpenas@nebraskamed.com

Everything you need to know

Watch a recording of this session

An Introduction

- Grace Videtich, B.S.
  Clinical Research Financial Compliance Specialist
  - Work History includes a broad base knowledge of Clinical Research start to finish acquired at:
    - Lab of large teaching hospital
    - Pathology firm (subcontractor to NIEHS – a branch of NTP)
    - Information Technology firm
    - Contract Research Organization (CRO)
    - Pharmaceutical Firm
    - Medical Practice w/ASC (coded encounters and surgeries)
    - UNMC (Clinical Research Financial Compliance)

What will we cover?

- What is a Matrix?
- Why is it required?
- Who completes the Matrix?
- When is it created?
- Where is it stored?
- What documentation is needed for Matrix completion?
- How is the Matrix completed?
- What else do I need to know?

What is a matrix?

- The Clinical Trial Matrix Workbook
  - An Excel Spreadsheet workbook
  - Contains 8 types of pages (each collects specific info regarding the trial)
  - Designed to act as a "stand alone" document for personnel who do not have access to the protocol or IRB application
  - Provides a visual roadmap to your study by identifying:
    - All tests/procedures conducted during study,
    - Study Visit Schedule,
    - How each test/procedure will be billed at each study visit

Why do I have to create and maintain a matrix?

- Serves as the foundation for other required functions
- Required for review cycle
- The Federal regulations for billing have become more stringent
  - demonstrates due diligence
- Required by Policy and Procedure
- Provides a road map to your study for personnel who do not have access to your protocol or IRB application

What are these more stringent requirements?

- Requirements include:
  - Registry of studies on ClinicalTrials.gov
  - Listing the registry number assigned (NCTXXXXXXXX) on insurance claims
  - Including the V70.7 diagnosis code on all encounters that are research related
  - Adding appropriate modifiers to identify the charges (i.e.)
    - Q1 modifier = Routine clinical service provided in an approved clinical research study (Standard of Care)
    - Q0 Modifier = Investigational clinical service provided in an approved clinical research study

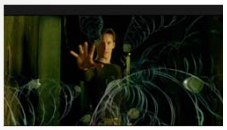
Who completes the matrix?

- Can depend upon the department
- The PI is ultimately responsible for all facets of the clinical trial regardless of the duties delegated
  - Even if Coordinator/Administrator creates the matrix the PI should review and approve

When should the matrix be created?

- We recommend creating the matrix during the feasibility or consideration phase (the earlier the better)
  - The matrix will help visualize the study
  - Can assist in budget preparation
  - Serves as the basis for the Coverage Analysis and the OneChart study build
  - Utilized by other departments (Billing, Compliance, IRB, Patient Financial Services, Radiology, etc.)

Where is the matrix stored?



- The Matrix is stored in two formats in two different places
  - Clinical Trial Matrix workbook in Excel format is stored on the NHSsecure drive in the clinical trials folder
    - The workbook is active and can be edited
    - This is where you maintain the current study subject listing
  - PDF copy is stored in RSS with the IRB application
    - Only the CTMM page of the workbook is stored with IRB application
    - CTMM PDF can not be edited (it is a snapshot of the CTMM)

What information is needed to complete the matrix?

- Study protocol
- Informed Consent Document
- Sponsor's proposed budget (if available)
- Investigator's Brochure (if available)

How do I complete the matrix?

- Access the current Matrix template on the NHSsecure drive
  - Do not store a copy on your PC
  - Do not use a previous completed matrix
- Name the matrix using the standard naming convention which is:

  IRB# Funding Source # Study Pet Name
  (List all grants, WBS#, MXH#, CC#)
- Click on page tabs and enter study information
- Save in PI's subfolder in Clinical Trials folder of NHSsecure drive

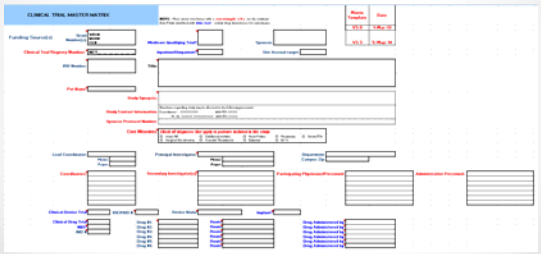
What are the 8 types of pages?

- Internal metrics - Required for compliance personnel
- Clinical Trial Master Matrix (CTMM) – Required page
- Subject listing – Required page
- Medicare Qualification – Drugs (required for Drug and combination studies)
- Medicare Qualification – Devices (required for Device and combination studies)
- Research Treatment Exceptions – Optional page
- Individual Subject Matrix – Optional Page
- Matrix Check List – Task Sequence Instructions

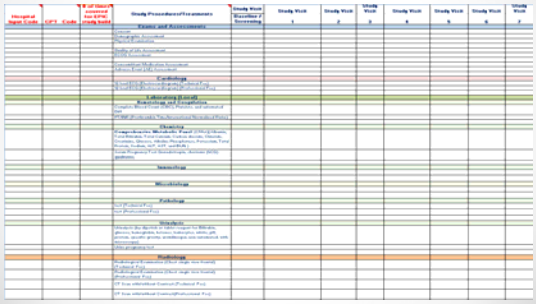
Internal Metrics

Matrix Version	Initials	Receipt Date	Task	Task Completion Date	TaskType	Matrix on Secure drive	Grant Budget Rec'd?	Contract Required	Contract Signed	Consent Doc Reviewed?	IRB Approval?	Approval Date	Revision sent to IRB?	Comments
Initial Draft - V1														

CTMM info - header



CTMM - body



CTMM Body - continued

Protocol information

- Chemistry
  - Alkaline phosphatase, alanine aminotranserase, aspartate aminotransferase, total, direct, and indirect bilirubin, blood urea nitrogen, creatinine, creatine phosphokinase, lactate dehydrogenase, sodium, potassium, glucose, albumin, total protein, calcium, chloride, and bicarbonate

Matrix entry

- Chemistry
  - **Comprehensive Metabolic Panel** (Albumin, Total Bilirubin, Total Calcium, Carbon dioxide, Chloride, Creatinine, Glucose, Alkaline Phosphatase, Potassium, Total Protein, Sodium, ALT, AST, and BUN)
  - **Direct and Indirect bilirubin**
  - **Creatine Phosphokinase** (CPK)
  - **Lactate dehydrogenase** (LDH)

CTMM body - continued

			Study Medication							
			Study Drug							
			Administration Study Drug							
			Reconciliation of Study Drug							
			Research Pharmacy Fee (one time fee)							
			Pharmacy Dispense Fee							
			Specimen Collection							
			Specimen collection (Blood)							
			Specimen collection (Urine)							
			Specimen Processing (Slides)							
			Specimen Processing (Blood)							
			Specimen Processing (Tissue)							
			Specimen Processing (Urine)							
			Specimen Shipping							
			Central Labs							
			Pharmacokinetic Testing							
			ECG (Flood)							
			CT Scans (Flood)							
			MRI Scans (Flood)							
			Labs (Blood, Serum, etc)							
			Labs (Urine)							
			Labs (Tissues, blocks, slides)							

CTMM – Additional Comments

Additional Comments:	Routine standard of care procedures will be billed to insurance. The study subjects are responsible for all copays and deductibles of routine tests/procedures.
	Data results obtained from testing performed as routine standard of care procedures, before informed consent is signed, will be used for screening and eligibility purposes.
	Bundled Charge =
	Do Not Bill =
	Other =
	Patient compensation =
	Provided by Sponsor =
	Waivers requested : ☐ Coverage Analysis Fee ☐ IRB Fee ☐ Pharmacy Fees ☐ Professional Fees
	Waivers granted : ☐ Coverage Analysis Fee ☐ IRB Fee ☐ Pharmacy Fees ☐ Professional Fees
	Principal Investigator's Signature:

Subject List

Gender	Age	Ethnic Origin	Trial Arm	Pt ID #	Subject Name	MR #	Subject Status	Consent Date	Consent to MR	Completion Status	Study End Date	Study Visit 2	Except

Medicare Qualification - Drugs

Drug trials are covered under National Coverage Determination (NCD) for Routine Costs in Clinical Trials (310.1)

Three Mandatory criteria:

		Yes	NO
1	Is the subject or purpose of the trial to evaluate an item or service that falls within a Medicare benefit category (e.g., Physician's service, durable medical equipment, diagnostic test) and is not statutorily excluded from coverage (e.g., cosmetic surgery, hearing aids)?	☐	☐
2	Does this trial have therapeutic intent ? (must not be designed exclusively to test toxicity or disease pathophysiology)? *To have therapeutic intent, the trial must, to some extent, assess the effect of the intervention on the patient outcome. The trial must not be designed to exclusively test toxicity or disease pathophysiology.*	☐	☐
3	If the trial evaluates a therapeutic intervention, does it enroll patients with diagnosed disease rather than healthy volunteers? (Trials of diagnostic intervention may enroll healthy patients in order to have a proper control group.)	☐	☐

If the answer is NO to _any_ of the 3 mandatory questions, STOP HERE, this is not a Medicare Qualifying t

If the answer is YES to all 3 of the mandatory questions, proceed to the "qualifying criteria" questions b

Deeming Criteria

		Yes	NO
a	Is the trial funded by NIH, CDC, AHRQ, CMS, DOD, VA or one of the other government agencies? OR	☐	☐
b	Is the trial supported by centers or cooperative groups funded by NIH, CDC, AHRQ, CMS, DOD, VA or one of the other government agencies? OR	☐	☐
c	Is the trial conducted under an IND reviewed by the FDA? OR	☐	☐
d	Is the trial exempt from having an IND under 21CFR 312.2(b)(1) and qualifying criteria are developed and certification process is in place? Exemptions allowed under 21 CFR 312.2(b)(1) (The purpose of the research is not intended to change the drug indications or labeling, advertising, route of administration or dosage, or patient population, and the trial will undergo IRB review as well as meet all other federal regulations)	☐	☐

If the answer to **YES** to all 3 of the mandatory questions and any one of the Qualifying Criteria questions, **this is a Medicare Qualifying Trial**

If the answer to **NO** to one of the mandatory questions or all of the qualifying criteria questions, **this is not a Medicare Qualifying Trial**

Medicare Qualification – Drugs (continued)

For trials qualified under NCD 310.1

Medicare may be billed for routine costs of trial when the involved items and services are otherwise available to Medicare beneficiaries (i.e., there exists a benefit category, it is not statutorily excluded, and there is not a national non-coverage decision.)

Routine costs include items or services:

- ✓ Items or services that are typically provided absent a clinical trial (e.g., medically necessary conventional care)
- ✓ Items or services required solely for the provision of the investigational item or service (e.g., administration of a non-covered chemotherapy agent), the clinically appropriate monitoring of the effects of the item or service, or the prevention of complications; and
- ✓ Items or services needed for reasonable and necessary care arising from the provision of an investigational item or service, in particular for the diagnosis

Medicare may not be billed for:

- ✓ The investigational device, drug, or procedure itself
- ✓ Items and services provided solely to determine trial eligibility
- ✓ Items and services provided solely to satisfy data collection and analysis needs and not used in direct clinical patient management (e.g., monthly CT scans for a condition usually requiring a single CT scan).
- ✓ Items and services customarily provided by sponsor without charge
- ✓ Items and services for which sponsor has specifically paid provider.
- ✓ Items and services for which there is no Medicare benefit category.
- ✓ Non-covered items and services because they are statutorily excluded or fall under a national non-coverage policy.

Medicare Qualification - Device

Device Information for consideration

http://www.fda.gov/MedicalDevices/default.htm
http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/default.htm

Device Name _____ Manufacturer _____

Device Type:	Device Number
☐ IDE	
☐ HDE	
☐ 510(k)	
☐ PMA (premarket approval)	
☐ Post Approval Study	
☐ Combination product	
☐ Compassionate Use	

Device Class:
☐ Class I General controls
☐ Class II Special controls
☐ Class III Pre-Market Approval

Device Category:
☐ Category A Experimental/Investigational
☐ Category B Non-experimental and/or Investigational

1 Is this device currently used at the Nebraska Medical Center?	☐ YES	☐ NO
2 Will this device be supplied by sponsor at no charge?	☐ YES	☐ NO
3 Do you plan to use hospital stock devices for this trial?	☐ YES	☐ NO
4 Where will the device be used / procedure performed? (list all that apply)	☐ TNMC surgery suite ☐TNMC Cath/EP Lab ☐TNMC Clinic ☐UNMC-P Clinic ☐CRC ☐ Other, specify	
5 Where will the device be stored? (list all that apply)	☐Pyxis unit ☐Coordinators office ☐PIs office ☐Clinic Storage unit ☐Other, specify	
6 Is special training required to install device?	☐ YES	☐ NO
7 Is special training required to use or monitor device?	☐ YES	☐ NO
8 Has draft contract been forwarded to Sponsored Programs Administration?	☐ YES	☐ NO
9 Has draft contract for TNMC been forwarded to the Hospital?	☐ YES	☐ NO
10		
11		

Medicare Qualification – Device (continued)

Principal Investigator			
Name			
NPI Number			
Address	Department of XXXXXXXXXX 98XXXX Nebraska Medical Center Omaha, NE 68198-XXXX		
Phone Number	402-55X-XXXX		
Fax Number	402-95X-XXXX		
e-mail	XXXXX@unmc.edu		

Lead Coordinator			
	Department of XXXXXXXXXX 98XXXX Nebraska Medical Center Omaha, NE 68198-XXXX		
	402-55X-XXXX		
	402-95X-XXXX		
	XXXXX@unmc.edu		

Sub Investigator			
Name			
NPI Number			
Address	Department of XXXXXXXXXX 98XXXX Nebraska Medical Center Omaha, NE 68198-XXXX		
Phone Number	402-55X-XXXX		
Fax Number	402-95X-XXXX		
e-mail	XXXXX@unmc.edu		

Sub Investigator			
	Department of XXXXXXXXXX 98XXXX Nebraska Medical Center Omaha, NE 68198-XXXX		
	402-55X-XXXX		
	402-95X-XXXX		
	XXXXX@unmc.edu		

Medicare Qualification – Device (continued)

Checklist for CMS for Medicare Coverage Determination for IDE studies

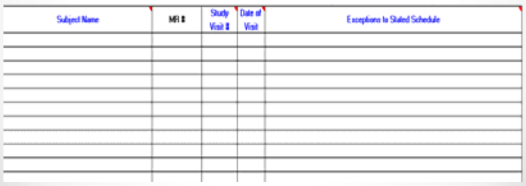
- ☐ The Final FDA letter (unredacted)
- ☐ If only conditional approval, provide the entire series of unredacted FDA letters to the manufacturer.
- ☐ A copy of the IRB approval letter
- ☐ A copy of the IRB stamped Consent form(s)
- ☐ A copy of the complete protocol
- ☐ 2 or 3 supporting peer reviewed articles

Who provides	Date rec'd	Doc Version
PI / Coordinator		
PI / Coordinator		
IRB		
IRB		
PI / Coordinator		
PI / Coordinator		

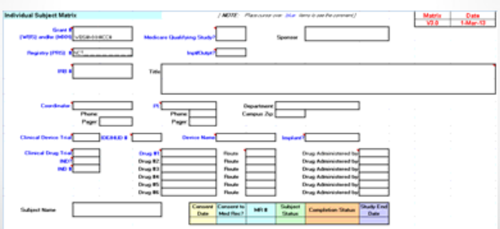
Send a copy of each document to the Clinical research financial Compliance Specialist (Grace Videtich)
The CRFCS will compile the documents, generate the coverletter, and transmit to CMS Medical Director
The CRFCS will track the packet and upon receipt of the Part A and Part B letters from CMS, notify TNMC/UNMC-P billing
The original documents will be given to the Study Coordinator for inclusion in the study source documents.

http://www.wpsmedicare.com/jfmacpartb/policy/ide_submissions.shtml

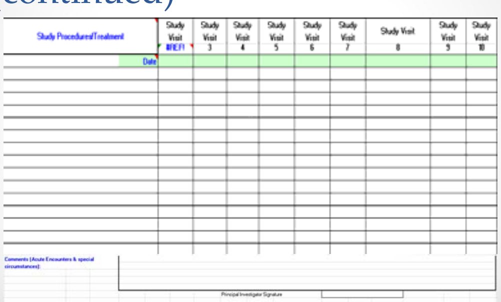
Research Treatment Exceptions



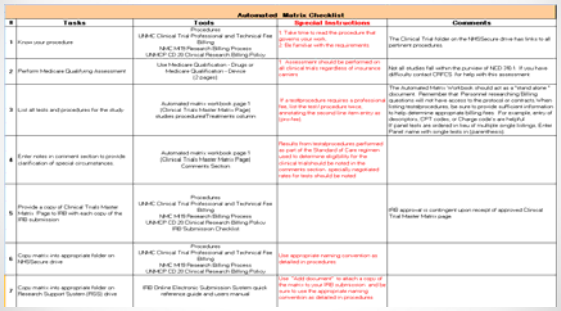
Individual Subject Matrix



Individual Subject Matrix (continued)



Automated Matrix Checklist



#	Tasks	Tools	Special Instructions	Comments
1	Know your procedure	Procedures UNMC Clinical Trial Professional and Technical Fee Billing NHC MSI Research Billing Process UNMCP CD 20 Clinical Research Billing Policy	1. Take time to read the procedure that governs your work. 2. Be Familiar with the requirements	The Clinical Trial folder on the NHSSecure drive has links to all pertinent procedures.
2	Perform Medicare Qualifying Assessment	Use Medicare Qualification - Drugs or Medicare Qualification - Device (2 pages)	1. Assessment should be performed on all clinical trials regardless of insurance carriers	Not all studies fall within the purview of NCD 310.1. If you have difficulty contact CPFCS for help with this assessment.
3	List all tests and procedures for the study	Automated matrix workbook page 1 (Clinical Trials Master Matrix Page) studies procedures/Treatments column	If a test/procedure requires a professional fee, list the most procedure twice, annotating the second time item entry as (pro fee).	The Automated Matrix Workbook should act as a "stand alone" document. Remember that Personnel researching Billing questions will not have access to the protocol or contracts. When listing tests/procedures, be sure to provide sufficient information to help determine appropriate billing fees. For example, entry of descriptors, CPT codes, or Charge code's are helpful. If panel tests are ordered in lieu of multiple single listings, Enter Panel name with single tests in (parentheses).
4	Enter notes in comment section to provide clarification of special circumstances.	Automated matrix workbook page 1 (Clinical Trials Master Matrix Page) Comments Section	Results from tests/procedures performed as part of the Standard of Care regimen used to determine eligibility for the clinical trial/should be noted in the comments section. specially negotiated rates for tests should be noted.	
5	Provide a copy of Clinical Trials Master Matrix. Page to IRB with each copy of the IRB submission	Procedures UNMC Clinical Trial Professional and Technical Fee Billing NHC MSI Research Billing Process UNMCP CD 20 Clinical Research Billing Policy IRB Submission Checklist		IRB approval is contingent upon receipt of approved Clinical Trial Master Matrix page.
6	Copy matrix into appropriate folder on NHSSecure drive	Procedures UNMC Clinical Trial Professional and Technical Fee Billing NHC MSI Research Billing Process UNMCP CD 20 Clinical Research Billing Policy	Use appropriate naming convention as detailed in procedures	
7	Copy matrix into appropriate folder on Research Support System (RSS) drive	IRB Online Electronic Submission System quick reference guide and users manual	Use "Add document" to attach a copy of the matrix to your IRB submission and be sure to use the appropriate naming convention as detailed in procedures	

What else do I need to know?

- Create matrix early in process
- All items on schedule of events should appear on matrix
- Request matrix review early
  - It is the foundation for other functions to follow
- Matrix must be stored and updated on the NHSsecure drive (Clinical Trials folders)
- Keep matrix current
  - Revisions to protocol may mean revisions to the matrix
  - Policy / Procedure requires subject list update within 1 week (5 business days) of patient enrollment on study
- A copy of the signed informed Consent ***must*** be placed in the Medical Record

Questions?

Reach out, We're only a phone call away!

Grace Videtich

Clinical Research Financial Compliance Specialist

Sponsored Programs Administration
Academic Research Services Bldg.
(ARS building – 3rd floor)
Room 3011
Campus Zip – 7835

Phone (Direct line) – 402-559-7421

Email – gvidetich@unmc.edu

Policy for Investigational Devices

MI29 – Investigational Devices

Grace Videtich
402-559-7421
gvidetich@unmc.edu

MI29 Investigational Devices

- Effective **06/11/2014**
- Applies to any device, used in a clinical trial, that:
  - Has not been approved by the Food and Drug Administration (FDA)
  - Has been approved by FDA, but is being used for purposes other than those stipulated by FDA [off label use]
  - Is being used for Humanitarian purposes [as a Humanitarian Use Device (HUD)]
  - Has received a Humanitarian Device Exemption (HDE)
  - Has received an Investigational Device Exemption (IDE), or
  - Has been approved by the FDA; but, additional data must be collected for submission to the FDA

When do we initiate the process?

- The earlier the better!
  - Contact the Clinical Research Financial Compliance Specialist (CRFCS) when a study using a device is being considered
  - There is a committee review process similar to SRC that must take place prior to IRB review
    - Investigational Device Review Committee (IDRC)
      - Committee composed of personnel from:
        - Department initiating study
        - Research Enterprise
        - SPAdmin
        - IRB
        - source matter experts as needed

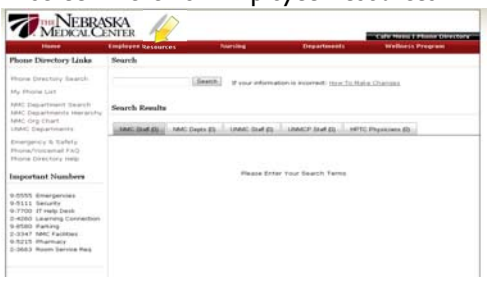
How do I find this policy?

- Start with PHONE DIRECTORY
- Choose "OTHER DIRECTORIES tab"

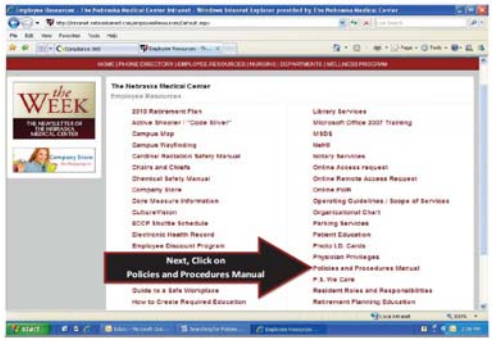
- Select "TNMC Directories – Hospital Phone Directory" link

How do I find the policy? continued

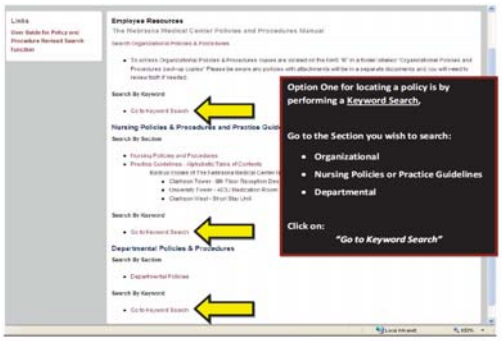
- The link will take you to the directory screen – click on Employee Resources



How do I find the policy? continued



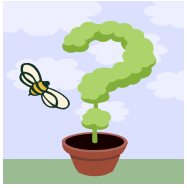
How do I find the policy? continued



How do I find the policy? continued

- Type in 'Investigational Devices' and press Search button
- The following screen should appear

Questions?



- Contact
  - Grace Videtich
  - 559-7421
  - gvidetich@unmc.edu

Industry Contracts University Philosophy & Systems

Deborah Vetter, Director
Sponsored Programs Administration

July 15, 2014

Watch a recording of this session

Presentation Overview

- About Sponsored Programs Administration
- Clinical Trial Roles and Responsibilities
- Clinical Trial Workflow
- Budget Negotiation
- Contract Negotiation
- Contract Types
- Strategies to Avoid Delays
- Contact Information and Resources

About SPAdministration

- SPA Team
  SPA Services
  SPA vs. SPA
  Role and Authority

SPAdministration Team

Deborah Vetter, Director
Bethany DeCarolis, Assistant Director

Industry Team

- Contract Specialists
  - Barbara Mattson
  - Tara Scrogin
  - Kara Schmidt
  - Amy Carson
- SPA Coordinator
  - Karla Klaus
- Clinical Research Financial Compliance Specialist
  - Grace Videtich

Grant Team

- Grant & Contract Specialists
  - William Woodman
  - Robert Hansen
  - Matthew McCoy
  - Sean Giles
  - Holly Dunning
  - Amy Carson
  - Kara Schmidt

SPAdmin Services

- Support pre-award activity
  - Grants and contracts
  - Federal and non-federal
- Authorize awards
  - Signature authority
- Track submissions and awards
  - Extensions
  - Amendments

SPA vs. SPA

SPA – one acronym; two separate entities

Sponsored Programs **ADMINISTRATION**

- Pre-award functions
  - Contract negotiation
  - Grant and contract administration

Sponsored Programs **ACCOUNTING**

- Post-award functions
  - Accounting
  - Receives funds from sponsors

Today's presentation focuses on:
SPAdmin
Clinical Trials

Clinical Trial Roles and Responsibilities

- Department
- SPAdministration
- Collaborators / Affiliates
- Different Perspectives & Authority

Department Responsibilities

- Clinical Trial Matrix
- Regulatory documents
- Budget negotiations / feasibility
- Contract submission to SPAdmin
  - Protocol
  - Editable contract template
  - Contract questionnaire signed by PI
  - Sponsor/CRO contact information
- IRB submission
- Conflict of interest
- Internal routing forms

SPAdmin Responsibilities

- Contract negotiation

Focus: legal/policy issues
- Federal regulations
- State law and constitution
- BOR/UNMC policy
- Sponsor terms and conditions
- Insurance
- Compliance with collaborator requirements

References:
- Protocol
- Budget
- IRB application
- Consent form
- Contract questionnaire signed by PI

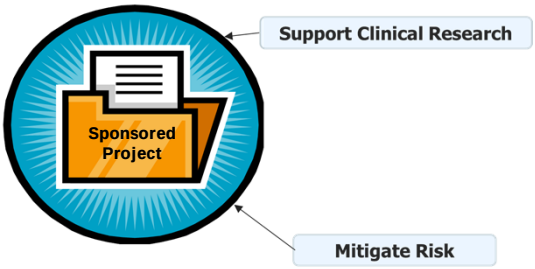
SPAdmin Responsibilities (continued)

- Contract execution

  Parties to agreement:
  - UNMC (signature authority)
  - Sponsor

- Contract administration
  - Internal routing form review and approval
  - Accounting set-up
    - WBS vs. cost center
    - Grant account or research account
    - Award

SPAdmin Role and Authority



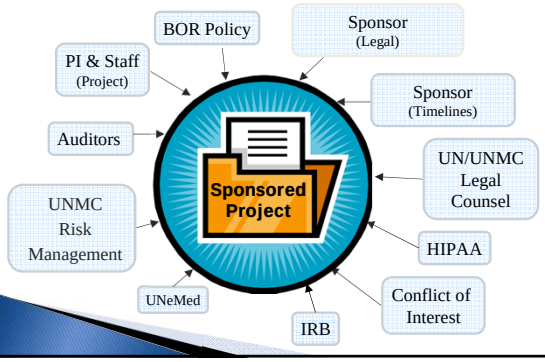
Mitigating Risk

- Animal subject protections (IACUC)
- Award monitoring
- Clinical trial billing
- ClinicalTrial.Gov
- Conflict of interest
- Cost accounting standards
- Cost sharing
- Cost transfers
- Direct charging practices
- Effort reporting
- Environmental health & safety
- Faculty owned start-ups
- Genomics
- Grants.gov
- Human subject protections (IRB)
- Interdisciplinary Research
- International collaborations
- Invention disclosure & reporting
- NIH salary cap
- OMB Circular A-21
- Other support
- Pre-authorized spending authority
- Program income
- Recharge centers
- Scientific misconduct
- Scientific overlap
- Subcontracts
- Stem cell research
- Technology transfer
- Unallowable costs
- University equity interests

Collaborators / Affiliates

- Multiple **entities** impacted by UNMC clinical research
  - UNMC
  - UNMC-P (Physicians)
  - TNMC
  - Children's Hospital and Medical Center
  - Veterans Administration
  - Other affiliations
- Multiple **perspectives**

Different Perspectives & Authority



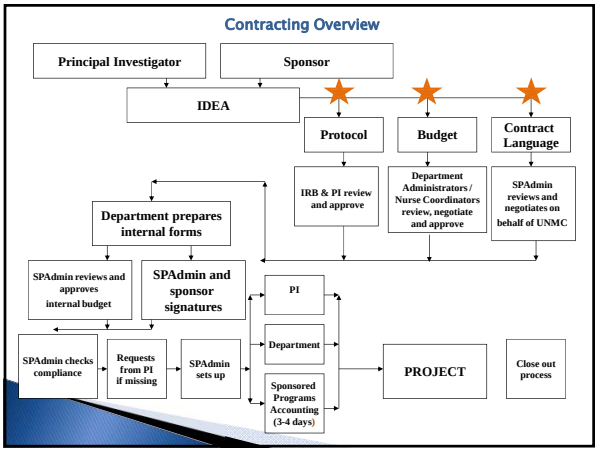
Clinical Trial Workflow

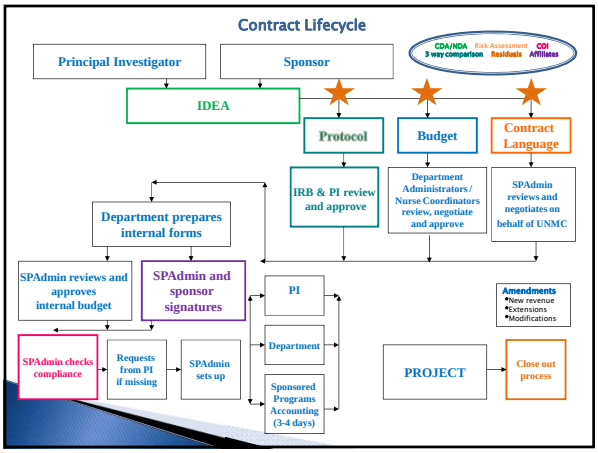
- Parallel Processes
- Contracting Overview
- Contract Lifecycle

A Parallel Processes

Simultaneously

- SPAdmin negotiates the contract
- Department negotiates the budget
- IRB reviews the protocol/consent
- Investigators disclose (or review) conflicts of interest





Budget Negotiation

- Budget Preparation Checklist
- Direct Costs vs. Indirect Costs
- Negotiation Tools
- Translating Sponsor Budget

Budget Preparation: A Checklist

- "Understanding Clinical Trial Budgets"
  - Carol McAlister and Virginia M. Bruce
  - *Clinical Researcher, 2003*
    - Offers insights for building an accurate and adequate study budget
    - Describes realistic payment structures
    - Includes techniques for budget negotiations

(See Resource slide at end of presentation for link)

Direct Costs vs. Indirect Costs

- Direct costs – easily attributed to project
  - Project staff
  - Consultants
  - Project supplies
  - Publications
  - Travel
- Indirect costs – **not** easily attributed to project
  - Calculated as percentage of direct costs
  - Also known as Facilities & Administrative Costs (F&A)
- Total direct costs (TDC)
  - Indirect costs applied to **full direct cost base** for industry studies

Negotiation Tools

- Clinical Trial Matrix
  - Grace Videtich
- Medicare Coverage Analysis
  - Katie Penas
- Common Guidance
  - Avoid backloaded payment structure
  - Consider seeking start-up costs
  - Negotiate for milestone/quarterly payments
  - Expect to negotiate
  - Examine first offer carefully
  - Know your costs

(See contact information at end of presentation)

Translating Sponsor Budget

- Sponsor Budgets
  - Requires review
    - Compare to the protocol
    - Review for accuracy and adequacy
  - Becomes part of legal contract
  - May or may not match UNMC internal budget
- UNMC Internal Budget
  - Reflects salaries as percentage of effort
  - Reviewed and approved by SPAdmin
  - Salaries defined by UNMC

Contract Negotiation: SPA Requirements

- Submitting to SPA
- Conflicts of Interest

Submitting to SPA

- Two options
  - Automation
  - Paper/Email
- Contract submission to SPAdmin
  - Protocol
  - Editable contract template
  - Contract questionnaire signed by PI
  - Sponsor/CRO contact information
- Internal routing forms
  - Internal budget

Conflicts of Interest

- Automated process
- New regulations August 2012
- Completed disclosure required prior to obtain institutional signature

Contract Negotiation: Legal Review

- Confidential Information
- HIPAA
- Record Retention
- Future Unspecified Research
- Publication
- Negotiation is a Balance

Confidential Information / Intellectual Property

Sample Contract Language:

"**Confidential Information**" means any data and information related to the terms of this Agreement, the Study, including without limitation, the Sponsor Test Drug and Study Documentation, all Background Intellectual Property (as defined in Section 8), Sponsor Intellectual Property and Institution Intellectual Property (as defined in Section 8), that is provided by either party or otherwise developed or generated in connection with the discussions and negotiations pertaining to, or in the course of performing, this Agreement.

Section 8:

"Background Intellectual Property" means any Intellectual Property that was owned or controlled, directly or indirectly, by a party prior to the effective date.

HIPAA

Sample Contract Language:

Sponsor agrees to use and disclose Protected Health Information gathered in this Study at Study Center in accordance with the informed consent/HIPAA authorization form, to the extent such document has been approved by Sponsor and the IRB, and to the extent any use and disclosure limits in such document apply to Sponsor under HIPAA

Record Retention

- May exceed the period of confidentiality
- Consider costs of storage or conversion to electronic format (e.g. CD-ROM service)

Future Unspecified Research

Sample Contract Language:

Study Center shall provide Subject's Protected Health Information to Sponsor, other member's of Sponsor's Group and their representatives, collaborators and licensees for the purposes of:

- Conducting the Study;
- Conducting research directly related to Disease under Study and related Diseases and/or the use of Study Drug in any disease therapy or diagnosis

Publication

- UNMC maintains right to publish
- UNMC will…
  - Allow sponsor to review in advance of publication
  - **Not** allow company to approve
  - Agree to protect sponsor confidential information
  - Allow publication delay to protect intellectual property (patentable information)
  - Agree to special considerations for multi-center studies

Negotiation is a Balance

- Balance time and expense of agreement negotiation with risk to UNMC
- Great negotiation time may mean less time for study; may miss out on subject recruitment in multi-site trials

Contract Types

- Master Agreements
- SPA Agreement Types

Masters: CTAs and CDAs

MASTER CLINICAL TRIAL AGREEMENTS (CTAs)

- Existing: Finalized
  - Bayer Healthcare Pharmaceuticals
  - Biogen Idec, Inc.
  - Celgene Corp.
  - Discovery Life Sciences
  - General Electric Company
  - Genzyme Corp.
  - InterMune
  - Lilly USA, L.L.C.
  - Millenium
  - Myrexis, Inc.
  - Novartis Pharmaceuticals
- Existing: Finalized (continued)
  - Novo Nordisk Pharmaceuticals
  - Pfizer
  - Pharmacyclics, Inc.
  - Philips Medical Systems MR, Inc.
  - Sanofi Aventis
- Pending:
  - GlaxoSmithKlein
  - Seattle Genetics, Inc
- MASTER CONFIDENTIALITY AGREEMENTS (CDA)
  - Abbott
  - Amgen
  - Quintiles
  - Siemens [to be negotiated]

SPA Agreement Types

- CDA/NDA
- Clinical Trial
- Material Transfer
- Master
- Work Order
- Registry
- Subcontract
- Testing/Research Services
- Research
- International
- Emergency Use
- C-GMP (Good Manufacturing)
- State of Nebraska
- Federal flow-through
- Non-federal
- Data Use
- Core Facility
- Cooperative
- Other

Strategies to Avoid Delays

- Strategies
  Three Players. Three Perspectives

Strategies to Avoid Delays

- Determine if study is a "right fit" before moving forward
  - Consider availability of subjects, staff, space, time, funds
- If study is complex, consider meeting with SPA early in the process
  - Complex = multiple sites, device study, CRO function
- Communicate concerns to SPA
  - Some studies are creating first-time experiences for the PI, coordinators and SPA
  - Learning together has advantages
  - "None of us is as smart as all of us"

Strategies to Avoid Delays

- Become familiar with SPA process
  - SPA uses first-come, first-serve and prioritization
  - SPA consults with multiple UNMC offices
    - Compliance office
    - Legal counsel
    - IRB
    - Risk management
    - More…
- Look for study events that involve TNMC
  - TNMC wants to understand true cost of research
  - TNMC wants to participate in management risk

Strategies to Avoid Delays

- If you have several contracts under negotiation, prioritize the order in which they should be negotiated – and advise SPA
- If you change your mind about a study and no longer want to participate remember SPA needs to know, too
  - Maximize limited resources!
- Understand differing perspectives held by sponsor vs. SPA

Three Players. Three Perspectives.

Sponsored Programs Administration

Sponsor

Principal Investigator

Clock Starts
SPA DEFINITION = Day contract package received in SPA

Clock Stops
SPA DEFINITION = Day contract is fully-executed

Clock Starts
SPONSOR DEFINITION = Day materials sent to department

Clock Stops
SPONSOR DEFINITION = Day of first subject enrollment

Contact Information

- Industry Team
  Budget Negotiation Resources

SPA Contact Information

- Location: Academic Research Services
  ARS 2000 (SW corner, 42nd & Emile)
- Zip: 7835
- Phone: 402-559-7456
- Web: www.unmc.edu/spa

Industry Team

- Sponsored Programs Coordinator
  - Karla Klaus, B.S.
  - P: 9-7456
  - E: kklaus@unmc.edu
- Karla is your first point of contact for new agreements

Industry Team

- Contract Specialists
  - Barbara Mattson, M.P.A.
    - P: 9-7156
    - E: bmattson@unmc.edu
  - Tara Scrogin, J.D.
    - P: 9-7479
    - E: tscrogin@unmc.edu
  - Kara Schmidt, M.P.A.
    - P: 9-5659
    - E: kaschmidt@unmc.edu
  - Amy Carson, B.A.
    - P: 9-2174
    - E: acarson@unmc.edu

Budget Negotiation Resources

- Clinical Trial Matrix
  - Grace L. Videtich, Clinical Research Financial Compliance Specialist
    - P: 402-559-7421
    - E: gvidetich@unmc.edu
    - Campus Zip: 7835
- Medicare Coverage Analysis
  - Katie Penas, Clinical Trials Business Analyst
    - P: 402-552-6601
    - E: kpenas@nebraskamed.com
    - Campus Zip: 7435

Other SPA Resources

Using UNMC Quick Link, go to Sponsored Programs Administration:

- Contract Questionnaire
  - SPA/ Industry Contracts
- Matrix and Coverage Analysis
  - SPA/ Clinical Research Billing
- "Understanding Clinical Trial Budgets"
  - SPA/Industry Contracts

Questions

Organizing Study and Regulatory Start Up

Peggy Heires, BA, RD
Clinical Research Center

Watch a recording of this session

Objectives of this Talk

- Identify regulatory and IRB documents to be completed for study start up
- Identify study data collection tools to keep organized

Key Players

- Principal Investigator
- Sub-Investigators
- Approval departments – IRB, SRC, P&T, SPA
- Ancillary Departments
- External contacts – sponsor, CRO, Core Facilities

University of Nebraska Medical Center

Study Start-Up

- Part 1: IRB submission
- Part 2: Regulatory Work
- Part 3: Study Binders

University of Nebraska Medical Center

IRB Submission - Setting Time Lines

1. Know the approving department submission deadlines
   - IRB - http://unmc.edu/irb/schedule_dates.htm
   - SRC http://www.unmc.edu/cancercenter/prms.htm
2. Budget negotiations
3. Sponsor timelines

University of Nebraska Medical Center

IRB Submission

1. Review your protocol
2. Identify ancillary departments
3. Draft the Informed consent form
4. Draft Clinical Trial Matrix
5. Complete other forms

Organizing Regulatory Documents

Protocol Signature Page—PI to sign
Investigator Brochure Receipt-sign
Financial Disclosures
FDA Form 1572
Obtain CVs *(signed & dated)* and medical/nursing licenses
CITI/GCP Certifications
Lab Certifications (CAP & CLIA) and normal reference ranges
Certification of study equipment calibrations
IRB Membership/FWA Letter

TNMC Laboratory Values

http://www.preceptor.com/ → Laboratory Services → Reference range

Consent Folder

Items in this folder that are needed when a potential subject appears

- Consent forms + ("What do I need to know" as cover & "Rights of Subjects" as last page)
- Consent Documentation form
- Inclusion/Exclusion checklist

University of Nebraska Medical Center

Contact Information

- Site Contact Information Sheet
- External contact information

University of Nebraska Medical Center

Items for Subject

- Copy of Informed Consent
- Study Visit Schedule/Timeline of Events
- Coordinator/ PI / Emergency Contact Information
- Patient Teaching / Study information (handouts must be IRB approved)
- Maps and/or printed directions of appointment locations

University of Nebraska Medical Center

Visit Guidelines

Chronological description and/or checklist of study-related visit requirements

- Data collection procedures
- Medical supplies/equipment/personnel needed for each study visit
- Overview and brief description of visit events
- Defined role responsibilities

Example of Visit Guidelines

What are Source Documents?

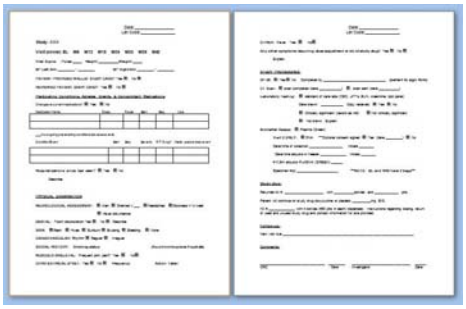
- Any signed notes by care providers
- Laboratory tests or image reports
- ER Records
- Telephone Notes
- E-mail conversations
- Data worksheets

Source Docs - Data Collection

The coordinator's primary role in data collection is to maintain data integrity.

- Determine in advance how you are going to gather the data
- Develop source document data collection forms that directly reflect the data collected on the CRFs
- Assure source documents are a complete, authentic, and accurate accumulation of patient-specific information

Visit Source Docs Example



Required Source Documents

- Exclusion/Inclusion Criteria Checklist
- Health History Log
- Adverse Event Log
- Concomitant Medication Log
- Vital signs/collection of blood or tissue samples log

Other Source Documentation Considerations

- Patient symptoms diaries
- Obtain at least one signed Release of Information Form for each enrolled patient
- Create a standardized study “Progress Notes” form with signature and date line

Summary

Source Documents Address:

- ICF Process
- Pre-existing Conditions and Relevant Medical History
- Laboratory Reports and Results
- Efficacy Evaluations
- Adverse Events and Concomitant Medications
- Drug Accountability
- Ongoing Patient Status

When Creating Source Documents for Study Start-Up Remember:

The source document worksheets are a critical element in the study start-up process. They should be created to facilitate the telling and understanding of the complete timeline of study events and aid in reconstruction of what happened at any point of time.

Questions ?

University of Nebraska Medical Center

Working with Sponsors & Contract Research Organizations (CROs)

Melanie Schrack
Program Coordinator
Pediatric Research Office

Watch a recording of this session

Overview - Sponsors and Contract Research Organizations

- Definition of a Sponsor
- Responsibilities of Sponsor
- Definition of CRO
- Responsibilities of CRO
- Monitoring
- Study Closure and Record Storage

Definition of a Sponsor

- The Sponsor can be a pharmaceutical company, an individual investigator or device company. The Sponsor has sole responsibility for the clinical trial to the FDA.

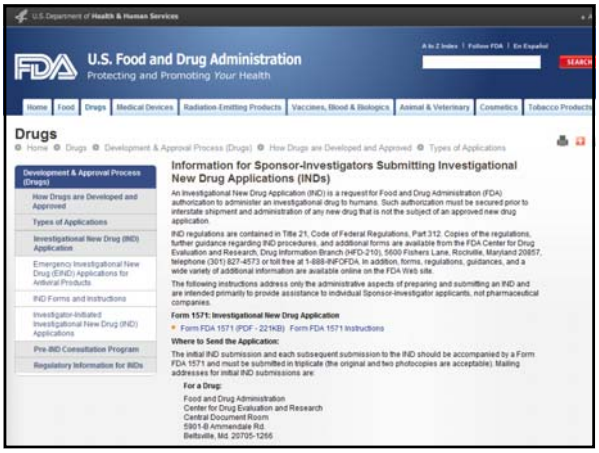
General Responsibilities of a Sponsor

- Present a Drug or Device to the FDA via a clinical protocol to gain approval for clinical testing of a drug or device
- Provide investigator with essentials to conduct trial including appropriate training, funds and ongoing assistance throughout the trial
- Ensure proper monitoring of trial
- Ensure the FDA & Investigators are all informed of significant new risks
- Maintain quality of study

New Drug Development

"Some health economists peg the current cost of drug development at US$1.3 billion, others at US$1.7 billion."

Drug development cost estimates hard to swallow
Roger Collier,CMAJ. 2009 February 3; 180(3): 279–280. PMCID: PMC2630351



New Device Development

http://www.fda.gov/MedicalDevices/default.htm

Definition of a Contract Research Organization (CRO)

- A **contract research organization** (CRO) is an organization that provides support to the pharmaceutical, biotechnology, and medical device industries in the form of research services outsourced on a contract basis. A CRO may provide such services as biopharmaceutical development, biologic assay development, commercialization, preclinical research, clinical research, clinical trials management, and pharmacovigilance (drug safety). CROs also support foundations, research institutions, and universities, in addition to governmental organizations (such as the NIH, EMEA, etc.).[1]
- Many CROs specifically provide clinical-study and clinical-trial support for drugs and/or medical devices.[2] CROs range from large, international full-service organizations to small, niche specialty groups.
- CROs that specialize in clinical-trials services can offer their clients the expertise of moving a new drug or device from its conception to FDA/EMA marketing approval, without the drug sponsor having to maintain a staff for these services

Selecting Investigators

Principal Investigators have sole responsibility of operation of the clinical trial at their site.

- Selected investigators must be qualified by training and experience
- Must have the resources and subject population
- Must sign an FDA1572, which is a contract with the FDA and delineates the responsibilities of the Investigator.

On-Going Review of Investigators

- The Sponsor is required by CFR guidelines (US Code of Federal Regulations) to monitor the progress of all trials
- Sponsors must promptly identify investigators who do not comply with the CFR guidelines and/or the study protocol
- If insufficiencies are identified the Sponsor will

--Secure compliance or

--Discontinue shipments of the investigational drug/device and

--End the investigator's participation

Keeping Investigators Informed

- The Sponsor must provide the investigator with an Investigator Brochure (IB)
- As the trial proceeds, the Sponsor must keep all investigators informed of new observations discovered or reported

--Adverse Events

--Investigator Alerts

--Safety Letters

On-Going Study Review

* The Sponsor must review safety and efficacy data regularly to update the FDA

Purpose of Monitoring

* Proper monitoring is essential

--To assure protection of the rights of human subjects

--To assure the conduct of the trial is in compliance with the protocol

--To the safety of all subjects involved in clinical research

--To assure the quality and integrity of the resulting data submitted to the FDA

Selecting Monitors

* A Sponsor/CRO will select a monitor qualified by training and experience to oversee the progress of the trial
* The monitor must be familiar with the investigational product, the protocol, the consent, SOPs and other regulatory documents

Monitoring Guidelines

* The "Guidelines for the Monitoring of Clinical Investigators" are not legal requirements, but rather a standard of practice that is acceptable to the FDA
* It reflects principles recognized by the scientific community as desired approaches to monitoring clinical research involving human subjects

Type of Monitoring Visits

* Pre-investigational Visits – Site Qualification Visit
* Site Initiation Visits – prior to enrollment at your site
* Periodic Visits – usually after first enrollment and at designated intervals thereafter
* Close-out Visits

Review of Subject Records

* The Sponsor is responsible for assuring data submitted to the FDA is accurate and complete.
* This is achieved through a review of the actual subject record against data transcribed into the CRF.

Record of On-Site Visits

The Sponsor/CRO representative (the monitor) must maintain a record of findings, conclusions and actions taken to correct deficiencies for each on-site visit.

Review of Subject Records

They will verify:

* --recruitment process is ethical and ongoing
* --eligibility is verified
* -- informed consent obtained
* --protocol is being followed
* --investigational product is maintained appropriately
* --all documents are present and completed appropriately by the investigator and study staff

Inspection of Sponsor's Records and Reports

* The Sponsor is subject to inspection from the FDA (all records and reports)
* If the Investigational drug is a controlled substance, the DEA may also inspect

Recordkeeping and Retention

* The Sponsor must maintain records showing receipt, shipment, and disposition of study drug
* The Sponsor must maintain complete and accurate financial disclosure records
* The Sponsor must retain records and reports for 2 years after a marketing application is approved by the FDA
  --If an application is NOT approved, records must be retained for 2 years after the shipment and delivery of drug being discontinued and the FDA has been notified

Close-Out Visits

* Purpose
  --Ensure that all known data has been collected and verified
  --Complete final accounting and disposition of investigational drug
  --Verify the investigators regulatory files are complete and accurate
  --Ensure that all study specimens have been shipped or stored appropriately

Close-out Reminders

* Prepare a master subject list complete with unique identifiers (this is not submitted to the sponsor)
* Notify the IRB of study closure
* IRB Policies and Procedures manual is available online
* Follow the Sponsor requirement for document retention as negotiated in the contract
* Adhere to the publication policy within the contract

Record Storage Suggestions

- Collect all study records and pertinent files
- Determine the location for study storage
- Prepare/maintain inventory checklists for all source documents to ensure the presence of all study documents and prepare a method for retrieval
- Systematically box and label all documents for storage
- Notify Sponsor and IRB of the storage location

"Human clinical trials start in six months. Sooner if we run out of mice."

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Document-Document-Document

Regulatory Documents,
Source Documents,
Case Report Forms, and
Adverse Event Reports

Sheree Gilmore, BA, CCRC
Manager, Pediatric Hematology/Oncology Clinical Trials Office
and
Matched Unrelated Stem Cell Donor Transplant Services

Watch a recording of this session

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Who Says What Documents are Essential?

- International Conference on Harmonization (ICH) aka: Guideline on Good Clinical Practice (GCP)
- Code of Federal Regulations (CFR)

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Characteristics of Essential Documents

- Demonstrate compliance and validate the study data
- Accurate, complete and appropriate to allow evaluation of the trial conduct

Why Have Essential Documents?

For the Protection of Human Subjects
For the Validity of the Study Data

ICH, CFR and GCP require

- Written, informed subject consent prior to the start of study related procedures AND
- Accurate, complete, and appropriate documentation to validate the study

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What are Essential Documents?

Regulatory Documents
Source Documents
Case Report Forms
Adverse Event Reports

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Regulatory Documents

- Form 1572
- Financial Disclosure
- Protocol (all versions)
- Informed consent (all versions)
- IRB documents and communication
- Study correspondence
- Tracking logs (screen, enrollment, visit)
- Signature log
- Delegation of authority form
- Conflict of Interest Statement

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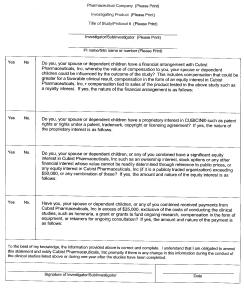
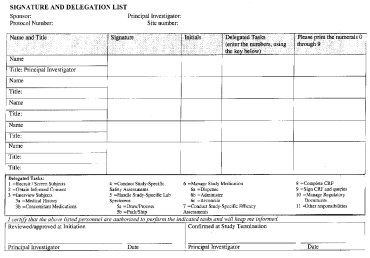
Form 1572

Financial Disclosure Form



Signature/Delegation of Authority Log



Form 1572

Required by the FDA
- Names the Investigator + Subinvestigators
- Names participating laboratories
- Identifies current addresses
- Indicates where to ship drug
- Signed by the PI, copies at site, original to sponsor
- Most important document because Investigator commits to study and acknowledges their ability to fulfill the requirements of the study

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Coordinators Workshop

Source Documents

- Are the first record of an observation or data
- Are the foundation for all clinical studies
- Confirm the completeness and accuracy of the CRF
- Show that the study followed the protocol and was ethically conducted

Examples include, but are not limited to:

consent forms	correspondence
medical records	subject diaries
notes to file	laboratory & procedure reports

the paper towel you jotted the BP down on!

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Screening Enrollment Log

Screening/Enrollment Log

Site #: 011

After each patient completes the Screening Evaluations (as described in Section 11.2 of the protocol), complete Section 1 information below and fax to Kristine Barras at ***281-820-3366***.

Section 1: Required Screening Information				
Prescreen #	Screening Date	Unique Screening #	Date ICF Signed	ICF Version Date

Upon confirmation of enrollment eligibility, complete Section 2 information below and fax to Kristine Barras at ***281-820-3366.***

Section 2: Required Enrollment Information					
Was patient randomized (Y/N)	If the patient was not randomized, please provide reason for screen failure.				
If the patient was randomized, complete the information below.					
Subject Randomization Number	Subject's Initials	Gender (M/F)	DOB	Type of PJI (hip or knee)	Baseline CLcr category (<50 mL/min or ≥50 mL/min)

D T-06-02 Screening/Enrollment Log 2008Jan30

Enrollment and Visit Log

Enrollment and Visit Log Treatment Phase
A Randomized Study of the Safety and Efficacy of in Subjects with Renal Anemia Not Requiring Dialysis and Not Receiving Recombinant Human Erythropoietin

Principal Investigator:
Site #: 024

Subject Initials	Subject No.	Screen Visit Date	Randomization Date	Week 1 Day 1	Week 1 Day 2	Week 2 Day 8	Week 3 Day 15	Week 4 Day 22	Week 5 Day 27	Week 6 Day 36	Week 7 Day 43	Week 8 Day 50	Week 9 Day 57	Week 10 Day 64	Week 11 Day 71	Week 12 Day 78	Week 13 Day 85	Week 14 Day 92	Week 15 Day 99	Week 16 Day 106
	001	04/10/06	05/12/06	05/15/06	05/16/06	05/22/06	05/30/06	06/05/06	06/12/06	06/20/06	N/A	07/05/06	07/10/06	07/17/06	N/A	07/31/06	08/07/06	08/14/06	08/21/06	08/25/06
	002	04/18/06	05/08/06	05/09/06	05/10/06	05/16/06	05/23/06	05/30/06	06/06/06	06/13/06	N/A	06/27/06	07/05/06	07/11/06	N/A	07/25/06	08/01/06	08/08/06	N/A	08/22/06
	003	04/24/06	05/17/06	05/31/06	06/01/06	06/07/06	06/14/06	06/21/06	06/28/06	07/05/06	N/A	07/19/06	07/26/06	08/02/06	N/A	08/16/06	08/23/06	08/30/06	N/A	09/13/06
	004	08/30/06																		
	005	08/31/06	09/15/06	09/19/06	09/20/06	09/26/06	10/03/06	10/10/06	10/16/06	10/24/06	10/31/06	11/07/06	11/14/06	11/21/06	11/28/06	12/5/06	12/12/06	N/A	N/A	12/19/06
	006	11/1/06	11/9/06	12/13/06	12/14/16	12/20/06	12/26/06	01/03/07	01/10/07	01/17/07	01/24/07	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	01/31/07
	007	11/14/06	12/18/06	12/19/06	12/20/06	12/26/06	01/02/07	01/09/07	01/16/07	01/23/07	01/30/07	02/06/07	02/13/07	02/20/07	N/A	03/06/07	03/13/07	03/20/07	N/A	04/03/07

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Enrollment and Visit Log

Enrollment and Visit Log [1] **Follow-up Phase**
A Randomized Study of the Safety and Efficacy of FG-2216 in Subjects with Renal Anemia Not Requiring Dialysis and Not Receiving Recombinant Human Erythropoietin

Principal Investigator:
Site #: 024

Subject Initials	Subject Number	Week 20 Day 134	Week 24 Day 162
	001	09/25/06	10/23/06
	002	09/19/06	10/16/06
	003	10/11/06	11/08/06
	004		
	005	01/16/07	02/14/07
	006	02/26/07	02/28/07
	007	05/01/07	05/30/07

[1] Enter 'ET' for early termination and indicate the date, if subject terminated study prior to completion of Week 24 visit

Page _1_ of ___

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History and Physical Form

Site #:
Investigator:

Date: ____________
Subject's Name: ____________
Subject Initials: ____________
Study #: ____________

Visit: ☐ **Screening** ☐ **Baseline** ☐ **EOT** ☐ **Surgery 2** ☐ **Other:** ________

Physical Examination

Date of Assessment: ____________ or check box if Not Done ☐

Check Abnormal for any ***significant*** *physical examination findings and describe.*

Clinical Assessment	Check (☑) One: Not Done	Normal	Abnormal	Specify Abnormal Conditions
1. Skin				
2. Eyes				
3. Ears/Nose/Throat				
4. Head/Neck				
5. Lungs				
6. Chest				
7. Heart/Vascular				
8. Musculoskeletal				
9. Abdomen				
10. Anorectal/Genital				
11a. Neurological – sensory				
11b. Neurological – motor				
12. Lymphatic				
13. Extremities				
14. Other				

Comments: ____________

Signature of **physician** performing PE ____________ Date ____________

Signature of Primary Investigator ____________ Date ____________

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CRFs
aka Case Report Forms

Sponsor prepared forms which allow the investigator and coordinator to document study procedures

- May be carbonless paper pages or electronic
- Accuracy is of the utmost importance
- Complete with black pen
- No blanks to be left
- Corrections are a single strike through, with date, initials and explanation if needed

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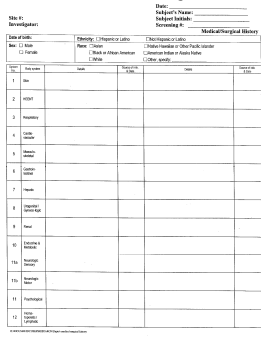
Medical History Form



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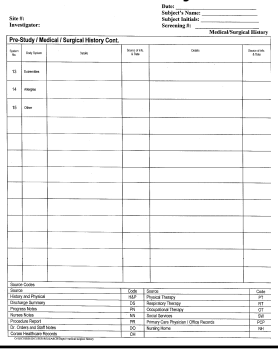
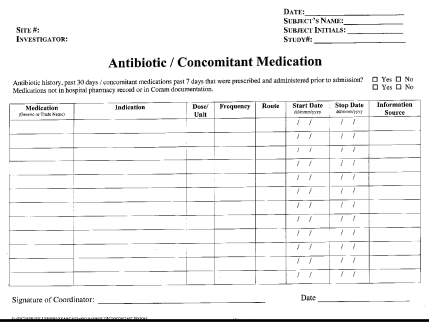
Medical History Form



Concommitant Medication Log



DATE: _____
SUBJECT'S NAME: _____
SUBJECT INITIALS: _____
STUDY#: _____

SITE #:
INVESTIGATOR:

Antibiotic / Concomitant Medication

Antibiotic history, past 30 days / concomitant medications past 7 days that were prescribed and administered prior to admission? ☐ Yes ☐ No
Medications not in hospital pharmacy record or in Comm documentation. ☐ Yes ☐ No

Medication (Generic or Trade Name)	Indication	Dose/ Unit	Frequency	Route	Start Date (dd/mm/yyyy)	Stop Date (dd/mm/yyyy)	Information Source
					/ /	/ /	
					/ /	/ /	
					/ /	/ /	
					/ /	/ /	
					/ /	/ /	
					/ /	/ /	
					/ /	/ /	
					/ /	/ /	
					/ /	/ /	
					/ /	/ /	
					/ /	/ /	

Signature of Coordinator: _____ Date _____

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Additional Comments

Study: Patient Initials: _____
Investigator: Patient Number: _____

Additional Comments:

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The Data Collection Process Summary

- Source Documents
  - The location of the original information
  - Created by sponsor and or site staff
- CRFs
  - Provided by the sponsor, belong to the sponsor
  - Compiled in book or electronic
  - Contain protocol required data regarding each subject

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Adverse Events

Any adverse experience: medical complaint, change or possible side effect that may or may not be related to the test article or investigational product

- Vital to document! May not appear to be significant at the site level but may represent a study related pattern or medical danger.
- **At each study visit, check with the subject about new and ongoing events**
- Investigator evaluates and the CRA may have questions

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Adverse Event log

Date: ____________
Subject's Name: ____________
Subject Initials: ____________
Study #: ____________

Site #:
Investigator

Adverse Events

Did the patient have any treatment-emergent adverse events? ☐ Yes ☐ No

List all treatment-emergent adverse events. All treatment-emergent adverse events must be followed until resolution or until a stable clinical end-point is reached.

All serious adverse events, regardless of relationship to study drug, must be reported via telephone or fax within 24 hours of discovery.

Adverse Event	CS/NCS	Mark if SAE	Date of onset dd/mmm/yyyy	Intensity 1=Mild 2=Moderate 3=Marked	Relationship to Study Drug 0=Not related 1=Possible 2=Probable	PI Signature	Action(s) taken 0=None 1=Study med discontinued 2=Dose reduced 3=Conmed required 4=Other *(record on AE comments page)*	Outcome 1=Resolved 2=Ongoing 3=Death 4=Unknown	Date Resolved dd/mmm/yyyy
	☐CS ☐NCS	☐	/ /						/ /
	☐CS ☐NCS	☐	/ /						/ /
	☐CS ☐NCS	☐	/ /						/ /
	☐CS ☐NCS	☐	/ /						/ /
	☐CS ☐NCS	☐	/ /						/ /
	☐CS ☐NCS	☐	/ /						/ /

Needs to be reported in CRF if CS, i.e., requires diagnostic or therapeutic intervention beyond confirmation alone.

Physician's Signature ______________________ Date ______________
dd/mmm/yyyy

Adverse Event log

Date: ____________
Subject's Name: ____________
Subject Initials: ____________
Study #: ____________

Site #:
Investigator

Adverse Event	CS/NCS	Mark if SAE	Date of onset dd/mmm/yyyy	Intensity 1=Mild 2=Moderate 3=Marked	Relationship to Study Drug 0=Not related 1=Possible 2=Probable	PI Signature	Action(s) taken 0=None 1=Study med discontinued 2=Dose reduced 3=Conmed required 4=Other *(record on AE comments page)*	Outcome 1=Resolved 2=Ongoing 3=Death 4=Unknown	Date Resolved dd/mmm/yyyy
	☐CS ☐NCS	☐	/ /						/ /
	☐CS ☐NCS	☐	/ /						/ /
	☐CS ☐NCS	☐	/ /						/ /
	☐CS ☐NCS	☐	/ /						/ /
	☐CS ☐NCS	☐	/ /						/ /
	☐CS ☐NCS	☐	/ /						/ /
	☐CS ☐NCS	☐	/ /						/ /
	☐CS ☐NCS	☐	/ /						/ /
	☐CS ☐NCS	☐	/ /						/ /
	☐CS ☐NCS	☐	/ /						/ /

Needs to be reported in CRF if CS, i.e., requires diagnostic or therapeutic intervention beyond confirmation alone.

Physician's Signature ______________________ Date ______________
dd/mmm/yyyy

Serious Adverse Events

- Are
  - Death
  - Life threatening experience
  - In-patient hospitalization or prolongation
  - Persistent/significant disability
  - Medically Significant
  - Congenital anomaly
- **Sponsor** guidelines for reporting will be identified in the **protocol**
- Report to sponsor within 24 hours of learning of the event
- Sponsor has 7-15 days to report to the FDA
- **IRB** guidelines for reporting found at http://www.unmc.edu/irb/
- Death - within 24 hours, other internal - within 48 hours, external - only if requires change in consent and/or protocol

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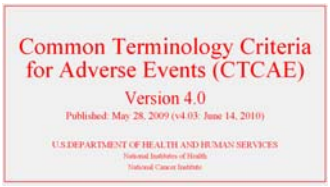
How do you know this adverse event is serious?

- Check the guidelines outlined in the protocol
- ICF will offer insight to toxicities/side effects that are expected vs. unexpected and common vs. uncommon
- The NIH developed a grading system, the Common Terminology Criteria for Adverse Events, to assist clinicians in defining the seriousness of an adverse event. Available online: http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf
- CTCAE along with protocol guidelines helps determine the next steps in reporting adverse events.



MedWatch Reports

- aka: “Safety Reports”
- The sponsor files a MedWatch report with the FDA for SAEs which are related or may be related to study drug. This gives the FDA pertinent details of the event
- Medical records, procedures, meds, interventions
- Each site gets a copy of the report

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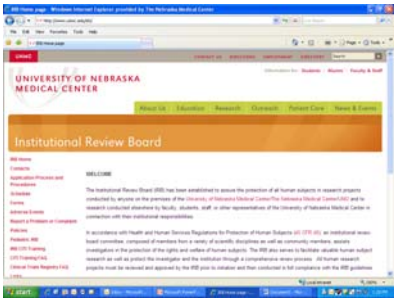
IRB Website



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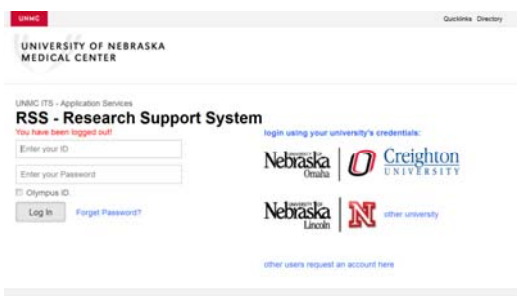
RSS Website



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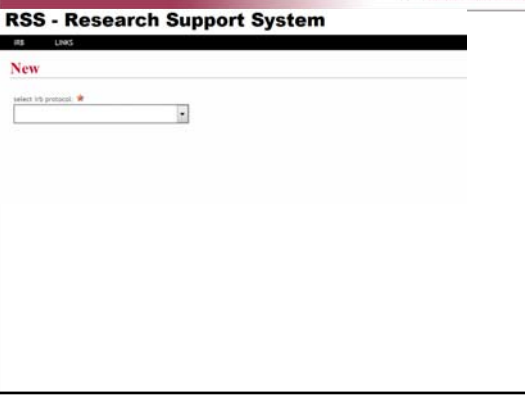
Follow Links



RSS Reporting Choices

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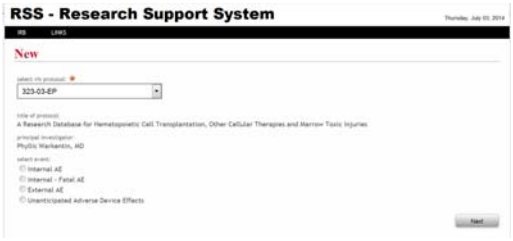

Internal AE

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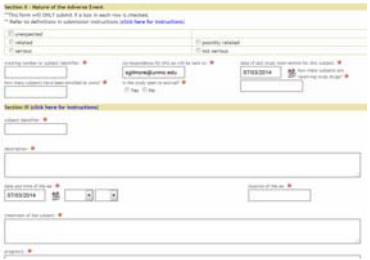
Experienced by a subject at any site under the jurisdiction of the UNMC IRB

Internal AEs/UADEs must be reported to the IRB ***if*** the PI determines that all of the following conditions are met:

- The AE/UADE is *unexpected*.
- The AE/UADE is *related to, or possibly related to*, the research intervention or procedures.



External AE Policy

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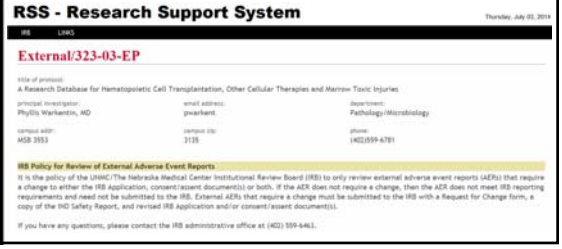
Maintain a Copy in the Regulatory Binder

External AEs which occur at other institutions must be promptly reported to the IRB (in no case later than five (5) business days following PI notification that the event occurred) ONLY ***if*** the PI determines that ***all*** of the following conditions are met:

- The external AE is *unexpected*
- The external AE is *related or possibly related* to the research intervention or procedure.
- The external AE is *serious*.
- The external AE requires a change to the protocol and informed consent form and reconsent of subjects is required.



The Data Review Process

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- **Monitoring**
  - Sponsors send representatives to come periodically to review the study data in the CRF with source documents
  - Pulls copies of the CRF for data processing
  - Query is generated when discrepancy is found
- **Close Out**
  - Final visit by monitor to collect documents, all subjects have completed follow-up visits and data submission is complete
  - Documents are stored by site for 2 years per federal law or as specified in protocol, whichever is longer
  - IRB Closeout, final Continuing Review, IRB application is considered COMPLETED

Documentation Tips
Diligence Pays Off!

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- Record every visit and conversation with the subject. If information is missing or unavailable, document this also.
- Notes to file, but whenever possible make a notation in the medical record
- Maintain logs for tracking regulatory submissions, equipment calibration, temperatures.
- Be complete on the source document. Fill out the CRFs in a timely manner. Information should be clear to a third party reviewer.

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Documentation Tips

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- Prepare for your monitor by
  - Keeping documents up to date
  - Provide a work area for her
  - Allow time in your schedule to address her questions/queries
  - Request access to the medical record
    - SOP 39 Release of Information
    - Confidentiality Agreement for Monitors
    - Monitor Request form

Suggested Reading

Journals

- Applied Clinical Trials
- Clinical Researcher
- The Monitor (ACRP)

Government Publications

- GCP Reference Guide
- Structure & Content of Clinical Study Reports & Statistical Principles
- Common Terminology Criteria for AE's

In conclusion…

IF IT WAS NOT DOCUMENTED,
IT WAS NOT DONE

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INVESTIGATIONAL PHARMACY

Jon Beck BS, PharmD
Research Pharmacist
Investigational Drug Service
The Nebraska Medical Center

Watch a recording of this session

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Contact Information

- Office phone: 559-5255 fax: 559-8762
- Pager: 888-3418
- Mailing address:
  Pharmaceutical & Nutrition Care
  Investigational Drug Service
  981090 Nebraska Medical Center
  Omaha, NE 68198-1090

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Shipping Address

The Nebraska Medical Center
Investigational Drug Shipment
Attn: Jon Beck
Durham Outpatient Care Center Dock
4401 Dewey, OCC 0631
Omaha, Nebraska 68105

Services

- Protocol Assistance and Design
- Regulatory
- Inventory Control
- Documentation
- Dispensing
- Drug Information

Protocol Assistance and Design

- Participate in site initiation visits, start-up meetings, routine monitor visits, audits, closeouts, etc.
- Provide pharmaceutical expertise to Investigators, Coordinators and other participating personnel in regards to trial procedures
- Orient pharmacy staff to ongoing studies in their work area

Protocol Assistance and Design

- Blinded studies
  - Unblinded pharmacist can help with randomization
  - Masking syringes and IV bags
  - Order entry issues
- Compounding
- IV Admixture
- Patient Packaging
- Mail Service
  - Regular ground
  - Overnight requires your Fed-Ex account number

Regulatory Issues

- State and FDA regulations
- Nebraska Medical Center Policy and Procedures
- IRB
- Pharmacy and Therapeutics (P&T)
  - Marketed drug form & Investigational drug form
  - Soon will have one form on the IRB application

Inventory Control

- Ordering and receiving medication
- Storage/Security
- Temperature Control
  - All refrigerators and freezers are on generator back-up
  - Room temperature, 4C (refrigerator), -20C and -80C freezer available
  - Daily logs are kept and maintained by IDS
- Return/Destruction
- Documentation

Documentation

- Computerized order entry in FSI and EPIC
- Sponsor logbooks
  - Shipping/Receiving records
  - Drug accountability records
  - Patient specific records
  - Return/Drug destruction records
- IVRS systems

Dispensing Medication

- Inpatient
  - Hospital Units
  - ER
  - OR
- Outpatient Infusion clinics
  - Lied
  - Village Pointe

Dispensing Medication

- Outpatient
  - Internal Medicine outpatient – infusions
  - Clinical Research Center infusion clinic
  - Off site
  - Outpatient clinic pharmacy – mainly oral medications
    - Green Rx (call Jean Mateljen @ 9-5220 to order)
    - White informational sheet indicating pickup time and mailing information if applicable

Drug Information

- Provide Medication Administration Guidelines (IV cards or MAGs) on our intranet drug information site
- Provide written guidelines to pharmacy personal
- Assist P&T committee
- Provide staff protocol/drug information for patients that may enter hospital already on a study drug

Budgeting for Pharmacy Services

- Each study varies in need and complexity
- IDS receives compensation for these services
- IDS budget calculator available on IRB site
- IDS compensation needs to be added to every budget contract

- Pharmacy start-up fees: $1500.
- Outpatient dispensing fees (oral): $20/Rx
- Standard infusions: $75 (Fees may vary based on complexity.)
- Annual fee at end of year 2 and each year thereafter $750
- Copy of letter/fees on website
  http://www.unmc.edu/cctr/docs/Investigational_pharmacy_fee_letter_2_4.pdf

Orders – outpatient pharmacy

- If patient requires investigational medication for home use, or use in a clinic other than Lied, Village Pointe, or Bellevue infusion clinics, then you will need to provide a prescription to the outpatient pharmacy

- **Handwritten prescriptions**: Green, carbon copy investigational prescriptions are available for handwritten prescriptions. Contact Jon Beck for blank prescriptions.
- **OneChart printed prescriptions:** Patient's information, including medical record, needs to be accurate in OneChart. For this reason, all investigational medications should be listed in your patient's electronic medical record. A printed prescription can be generated during this process and presented to the outpatient pharmacy.
- **OneChart investigational orders** are never sent electronically to the outpatient pharmacy. A hardcopy must be provided.

In Conclusion…

- The investigational drug service (IDS) is involved with the protocol from IRB application/ P&T review to the final audit
- Together we can provide exceptional services for the patient and sponsor

Communication is vital. Please do not hesitate to contact me as soon as a potential study patient is identified, or if you have any questions or concerns.

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Thank you!!

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Questions?

Site Monitoring

Brigette Vaughan MSN, APRN-BC, NP
Research Coordinator
UNMC Department of Psychiatry

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Background

Sponsors of clinical investigations are required to provide oversight to ensure adequate protection of the rights, welfare, and safety of human subjects AND the quality and integrity of the resulting data submitted to the FDA.

MONITOR

*n: Any large Old World lizard - The Egyptian species (**Varanus Niloticus**); useful because it devours the eggs and young of the crocodile. It is sometimes five or six feet long.*

More like this?

DEFINITIONS

- SPONSOR
- CONTRACT RESEARCH ORGANIZATION (CRO)
- CLINICAL RESEARCH ASSOCIATE (CRA)
- MONITOR

Monitoring Visit?

- Who is the monitor and what is his/her role?
- What is a monitoring visit, and when and why do they occur?
- What is monitored?
- What relevance does a visit have to coordination of a study and your role as a study coordinator?

Monitoring vs Audit

- A monitoring visit is not a sponsor audit.
- Monitoring is an on-going process throughout the life of the study.
- Audit is a point-in-time snapshot of status of compliance with specific audit points.
- Types of audit:
  - FDA
  - Sponsor

KEY POINTS:

- **PATIENT SAFETY**
- **DATA QUALITY**

Monitoring: An FDA Requirement

- A part of a quality risk management program
- Regulations are not specific
  - On-site versus remote
  - Frequency
  - Focus
  - Extent
- Sponsor to demonstrate adequate monitoring
- Follow-up to monitoring results/observations

Risk Based Monitoring

"Monitoring should be commensurate with risks—the method and degree of monitoring needed is related to the degree of risk involved."

(NIH Policy for Data and Safety Monitoring: release Date June 10, 1998)

TYPES OF SITE VISITS

- **PRE-TRIAL**—before first participant enrolled
  - QUALIFICATION SITE VISIT
  - SITE INITIATION VISIT (SIV)
- **DURING AND POST-TRIAL**—during active enrollment and at trial end
  - MONITOR-PERIODIC VISITS
  - STUDY CLOSURE VISIT

SITE QUALIFICATION VISIT

- CONDUCTED PRIOR TO PATIENT ENROLLMENT
- SPONSOR ASSESSMENT

SITE INITIATION VISIT (SIV)

- CONDUCTED BEFORE PATIENTS ENROLLED
- TRIAL INITIATION

MONITOR PERIODIC VISIT

- BEGINS AFTER FIRST PATIENT ENROLLED

STUDY CLOSURE VISIT

- CONDUCTED AT THE END OF STUDY

SITE QUALIFICATIONS & INITIATION VISIT RESPONSIBLITIES

- SITE RESPONSIBILITIES:
  - Locate/reserve room
  - Key personnel
  - Agenda
  - Lab/pharmacy visits

SITE QUALIFICATION & INITIATION VISIT PREPARATION

- PREPARE STUDY DOCUMENTS
  - 1572
  - CV's
  - LAB CERTIFICATIONS
  - CONFIDENTIALITY AGREEMENT

SITE QUALIFICATION & INITIATION VISIT PREPARATION

PREPARE STUDY DOCUMENTS

- Signed Protocol
- Budget
- Contract
- IRB Membership
- Financial Disclosure
- SOP's

MONITOR GUIDELINES

PRESERVE CONFIDENTIALITY

Establish Guidelines

PREPARATION FOR MONITOR VISITS

- Room Reservation
- Availability of PI/Staff
- Patient Medical Records
  - Access to EMR
- Source Documents
- Shadow Files
- Patient Binders

PREPARATION FOR MONITOR VISITS

- Regulatory Binders
- Communication Binders
- Logs, logs and more logs
- CVs current/signed
- Licenses/Training Documentation
- SAE/AE Binders
- Investigator Brochure Binders

WHAT HAPPENS DURING A MONITOR VISIT?

- PATIENT ACCRUAL
- INFORMED CONSENT
- PATIENT STATUS

WHAT HAPPENS DURING A MONITOR VISIT?

- Protocol and GCP Compliance
- CRFs and Source-Data Verification

WHAT HAPPENS DURING A MONITOR VISIT?

- DATA QUERIES
- DRUG ACCOUNTABILITY
- REGULATORY BINDERS
- ADVERSE EVENT REPORTING

Post Monitoring Visit

- Site letter
- Follow-Up

STUDY CLOSURE RESPONSIBILITIES

- Address Monitoring-Visit Items
- Organize CRFs/Study Files
- Return of Study Drug and Equipment
- Final Regulatory Documentation/IRB
- Long-term Storage of Study Documents/CRF's
- Follow-up for Patients

Monitoring Visits Should NOT Be a Passive Event!!!!!

- Know your contacts home and away
- Ask questions and clarify
- Take advantage of the learning opportunity
- Make sure you have the tools needed to conduct your site study safely, fully, and efficiently
- Anticipate or follow-up on problems

Summary

- Anticipation and preparation are key
  - *CONFIDENTIALITY*
  - *COMMUNICATION*
  - *ORGANIZATION*

- Use the monitor's presence to your advantage
- Collaborate to make the study safe and data-quality-driven

Monitoring Guidance Resources

- NIH Policy for Data and Safety Monitoring: Release Date June 10, 1998)
- FDA Draft Guidance on Risk Based Monitoring: August 2011

Date:_____
Let Code:_____

Study: XXX

Visit (circle): BL M6 M12 M18 M24 M30 M36 M42

Vital Signs: Pulse _____ Height _____Weight _____

BP Left Arm _____ / _____ BP Right Arm _____ / _____

PATIENT PROVIDED WALLET STUDY CARD? Yes ☐ No ☐

REVIEWED PATIENT DIARY CARD? Yes ☐ No ☐

Pre-Existing Conditions, Adverse Events, & Concomitant Medications:

Changes to current medications? ☐ Yes ☐ No

Medication Name	Dose	Route	Start	Stop	Use

___No ongoing pre-existing conditions/adverse events

Condition/Event	Start	Stop	Severity	R/T Drug?	Meds used to treat event

Hospitalizations since last seen? ☐ Yes ☐ No

Describe:

PHYSICAL EXAMINATION:

NEUROLOGICAL ASSESSMENT: ☐ Alert ☐ Oriented x ___ ☐Headaches ☐Dizziness >1x/week

☐ Visual disturbance

DENTAL: Tooth discoloration Yes ☐ No ☐ Describe: _____

SKIN: ☐Rash ☐ Hives ☐ Sunburn ☐ Bruising ☐ Bleeding ☐ None

CARDIOVASCULAR: Rhythm ☐ Regular ☐ Irregular

SOCIAL HISTORY: Smoking status _____ **(Record start/stop dates if applicable)**

MUSCULO-SKELETAL: Frequent joint pain? Yes ☐ No☐

GI/INTESTINGAL UPSET: Yes ☐ No ☐ **Frequency**_____ **Action Taken** _____

Date:_____
Let Code:_____

OTHER: Fever Yes ☐ No☐

Any other symptoms requiring dose adjustment or d/c of study drug? Yes ☐ No ☐

Explain:

STUDY PROCEDURES:

SF-36: ☐ Yes ☐ No Completed by _____ ***(patient to sign form)***

CT Scan: ☐ scan completed (date _____) ☐ scan sent (date _____)

Laboratory Testing: ☐ standard of care labs (CBC, LFT's, BUN, creatinine, lipid panel)

Date drawn: _____ Copy received: ☐ Yes ☐ No

☐ Clinically significant (record as AE) ☐ Not clinically significant

☐ Not drawn. Explain:

Biomarker Assays: ☐ Plasma (Green)

Visit 2 ONLY: ☐ DNA ***Optional consent signed ☐ Yes (date _____) ☐ No

Date/time of collection _____ Initials _____

Date/time aliquots in freezer _____ Initials _____

0.5ml aliquots PLASMA (GREEN) _____

Specimen #(s) _____ ******NOTE: BL and M42 have 2 bags******

Study Drug:

Returned kit # _____ with _____bottles and _____ pills.

Patient will continue on study drug doxycycline or placebo _____mg BID.

Kit # _____ with 4 bottles (#50 pills in each) dispensed. Instructions regarding dosing, return of used and unused study drug and contact information for site provided.

Follow-up:

Next visit due _____.

Comments:

_____ _____ _____ _____
CRC Date Investigator Date

Protocol #XXXX Site #XX IRB # XXX Primary Investigator: Dr.	**Study Name or Logo**	Subject Initials: _____ Subject #: _____ Visit Date: _____

STUDY VISIT: WEEK 12 & WEEK 36

The following table includes a checklist of the materials needed to perform study-related procedures at this visit. **Important:** ***Please note that all equipment must be calibrated as per local requirements and that equipment records must be available for review upon request.***

Week 12 & Week 36 Visit Guidelines	Equipment	Other
____ Completed *Reported Outcomes Assessments* (Located in ***Questionnaire Binder)*****:** ____ MSWS-12 ____ ABILIHAND ____ Vital Signs ***(Subject must remain quiet in same Body position for 5 minutes prior to obtaining vital signs).*** ____T25FW ____9HPT ____**500 Meter Walk for EDSS (PA or APRN)** ____**EDSS Assessments (PA, or APRN)** ____**Neurostatus Exam (Neurologist to complete)** ____ 6MWT (≥ 1 hour delay between 500MWT) ____ SDMT ____ Labs (Research assistant) ____ Infusion Visit Checklist completed (See Infusion Guidelines tab in Master Subject Binder). ____Study Drug Infusion (See Infusion Guidelines tab in Master Subject Binder) ____ Check In & Check Out in EPIC ____ Visit Documented in Matrix ____ Completed eCRFs	• Blood Pressure Monitor • Thermometer • Access to Facilities and Equipment for Timed 25-Foot Walk, 9-Hole Peg Test, and 6MWT • Accelerometer, cones, stopwatch, and Stanley Walking Wheel for 6MWT • Opthalmoscope • Questionnaire Binder • IV pump(Aleris) • Infusion set/Extension Set/IV start supplies • Stand-by Emergency medications including: ✓ Diphenhydramine 50mg solution, ✓ Solu-Cortef 100 mg solution ✓ Epinephrine 1:1000 solution. **(Check expiration dates of emergency drugs prior to initiating infusion.)** • Oxygen tank with tubing and AMBU bag (stand-by). Check tank pressure for available O2 supply. • Nataluzimab/Placebo 300mg in 100 mL .09% NaCl (order from pharmacy). • 100 mL bag 0.9% NaCl for 40 mL post- infusion flush.	• Central Laboratory Kit • Central Laboratory Kit for Pharmacogenetic Sample • Courier Contact Information • Supply IP • Accelerometer Patient Teaching Handout • Fed-Ex Envelope for mailing accelerometer • Labels for ordering study drug from pharmacy • Patient Post – Infusion Discharge Instructions.

Protocol # Site # XXX IRB # XXX Primary Investigator: Dr.	**Study Logo or Name**	Subject Initials: _____ Subject #: _____ Visit Date: _____

Screening Visit Guidelines

Checklist:

____ Informed Consent

____ Review of Eligibility Criteria

____ Medical History

____ MS / MS Treatment History

____ Concomitant Meds

____ Vital Signs, Height and Weight

____ Physical Exam

____ 12 lead ECG

____ Neurological Exam and EDSS entered in Trial Slate

____ Serum Pregnancy Test for Women of Childbearing Potential

____ Contact ALMAC / IXRS to register screen visit and obtain screening number

____ Blood and urine sample

____ Eligibility Screening Form [ESF] completed

____ Visit 2 / Baseline MRI (scheduled at least 10 days prior to the Baseline visit)

____ In Matrix

____Check In/Out in EPIC