




PARTICIPANT HANDOUT
GCP Refresher and GCP/GCDMP Trends in the CTN

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CTN WEB SEMINAR SERIES
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Learning Objectives

- Review principles and regulatory requirements for Good Clinical Practice (GCP).
- Discuss staff roles and responsibilities, protocol compliance, and other criteria for conducting quality trials.
- Examine best practices, examples of GCP non-compliance, and corrective actions for protocol or procedural deviations.
- Identify significant GCP and Good Clinical Data Management Practice (GCDMP) trends in the CTN, such as, informed consent, safety, documentation, drug management, and data management.

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GOOD CLINICAL PRACTICE FOR RESEARCH

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What is GCP?



- Good Clinical Practices: An international ethical and scientific quality standard for the:
 - Design
 - Conduct, performance, monitoring
 - Recording, auditing and
 - Analysis and reporting of...Research Studies involving Human Subjects

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What is GCDMP?



- Good clinical data management practice (GCDMP)
- The current industry standards for clinical data management that consist of best business practice and acceptable regulatory standards
- In all phases of clinical trials, clinical and laboratory information must be collected and converted to digital form for analysis and reporting purposes



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What are Research Studies involving Human Subjects?



- Many types of human research—
 - Clinical trials for medical products
 - Laboratory studies on tissue samples
 - Epidemiological research studies
 - Behavioral research studies
 - Marketing research studies
- All types benefit from use of GCP



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Where GCP is applied?



- Private industry, NIH, CDC, government, research institutions, private practice
- Internationally adopted standards
- Formalized by regulations that vary in only minor ways between countries
- Expected to be used universally



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Why GCP?

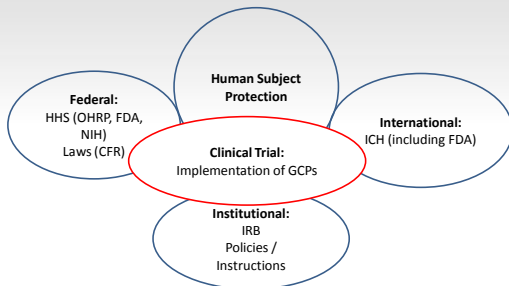


- Assurance to public
- Protection of rights, safety and well-being of trial subjects
- Credible data based on scientific quality standards



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Entities involved in human research protection



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ICH GCP Highlights—1



- Ethical principles paramount
- Risk-benefit assessment expected
- Individual subject rights & safety to prevail over other interests
- Scientifically sound & detailed protocol



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ICH GCP Highlights—2



- IRB/Ethical committee approval
- Medical care by qualified physician
- All staff qualified for duties



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ICH GCP Highlights—3



- Informed consent for each subject
- Subject confidentiality protected
- All data recorded, handled & stored to allow accurate reporting, interpretation and verification



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ICH GCP Highlights—4



- Investigational products (IP) prepared in accordance with GMP
- IP maintained according to approved protocol and study Operations Manual
- Site level systems with procedures implemented to assure quality of all aspects of trial



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Adoption of GCP Principles



- Governments and government agencies (FDA, Health Canada, EU, etc.)
- Industry, e.g., Pharmaceutical Research and Manufacturers of America (PhRMA) and individual manufacturers
- Contract Research Organizations (CROs)
- Professional societies (clinical, regulatory, medical)



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How do we “Do” GCP?



- Develop and use written, standard procedures
 - Investigators
 - Sponsors
 - Monitors and Auditors
 - Data managers and IT staff
 - Statisticians
 - Regulatory authorities



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More on doing GCP—1



- Plan clinical trials carefully
 - Provide adequate detailed instructions in protocol and study manuals
 - Incorporate guidance from regulators and standards organizations
 - Be precise with inclusion/exclusion criteria
 - Clarify safety and efficacy endpoints



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More on doing GCP—2



- Select qualified investigators and staff
 - Inform and train investigators
 - Qualified, adequately trained, and committed to quality research
 - Communication with sponsor is essential
 - Must follow protocol and SOPs



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More on doing GCP—3



- Documentation important
 - Consent
 - Study procedures
 - Adverse event reporting
 - Entering study data on time
 - Annual IRB reviews and keeping IRB up to date on changes
 - Keeping staff and study subjects informed of trial progress



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More on doing GCP—4



- Sponsor's broad obligations
 - ❑ Quality assurance and quality control
 - ❑ Investigator's Brochure
 - ❑ Manufacturing test article under GMP
 - ❑ Regulatory approvals to proceed
 - ❑ Monitoring, auditing study progress
 - ❑ Reports to investigators, regulators

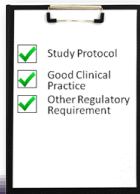


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Quality Assurance (QA)



- Planned, systematic activities conducted to ensure that a trial is performed and that trial data are generated, documented, and reported in compliance with the protocol and with GCP and all other applicable regulatory requirement(s)



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Performing Quality Assurance (QA)



- QA is the responsibility of every member of the research team. The role of QA staff is to support and assist members of the research team in adhering to high quality standards.
- Internal and External QA



Who is responsible for quality assurance?

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Performing Quality Assurance (QA)



- Monitoring verifies
 - Rights and well-being of human participants are protected
 - Reported trial data are accurate, complete, and verifiable
 - The trial is conducted in compliance with the currently approved protocol (including any amendments), as well as with GCP and all other applicable regulatory requirement(s)
- In general, on-site monitoring is required before, during, and after completion of a trial



Performing Quality Assurance (QA)



- All CTN studies undergo QA monitoring by the CCC
 - Initiation, Interim, and Close-out visits
 - File reports with the CTP, the local Node, NIDA and the Lead Investigator as required
 - Detailed Monitors' responsibilities
 - ICH GCP 5.18.4
- Good monitoring is not the enemy of good research; it protects our participants and research

More on doing GCP—5



- Essential documents maintained by Investigator/Research Site
 - Keeping documents together
 - Preparing for sponsor visits
 - Preparing for an FDA audit (if applicable)
 - Closing out a study
 - Maintaining study documents after conclusion of a study



More on doing GCP—6



- Objectivity in research
 - Recognizing and reducing bias
 - Disclosing potential conflicts of interest
 - Independent monitoring boards



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More on doing GCP—7



- Training of investigators and staff
 - Study-specific procedures, tests
 - Data recording methods



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GCP at Home and On the Road



- US requirements under Title 21 of the Code of Federal Regulations (CFR):
 - 312 (INDs for drugs and biologics)
 - 812 (IDEs for medical devices)
 - 50 (Protection of human subjects)
 - 54 (Financial disclosures)
 - 56 (IRBs)
 - Also 45 CFR 46 (the “Common Rule”)
- Everywhere, the ICH Guidelines for GCP



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GCP for Research—Conclusions



- Broad applicability of GCP
- Ethical standards paramount
- Protections against unreasonable risks
- Assures confidentiality of study participants
- Quality in study design, data, and conclusions
- Data useful for marketing approvals
- Creates new and expanded treatment indications

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GCP Take-home Messages



- Prepare & follow written procedures
- Follow the protocol
- Safety rules
- Maintain confidentiality
- Integrity of research data crucial
- Know your Investigator responsibilities

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APPLYING GCP

GCP Scenario 1



FOR AUDIENCE PARTICIPATION...

- The research trial required negative Hep A and B prior to randomization. An investigator must sign laboratory reports for each participant prior to randomization.
- Protocol monitor noted that the lab results for 3 randomized participants had not been signed by an investigator as required by the protocol.
- What next?

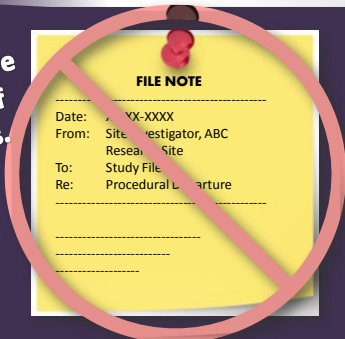
TYPE YOUR ANSWERS IN CHAT

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Note to File (NTF)



Avoid excessive use of NTFs.



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GCP Scenario 2




FOR AUDIENCE PARTICIPATION...

- The research study's MOP outlines procedures for performing informed consent and documenting the process.
- The protocol monitor discovered that there was no documentation of the informed consent process in 3 participant charts.
- What next?

TYPE YOUR ANSWERS IN CHAT

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Questions? Use the Chat



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GOOD CLINICAL DATA MANAGEMENT PRACTICES



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Research Misconduct

- Definition
 - **Fraud:** intentional deception
 - **Misconduct:** intentional wrongdoing
 - **Falsification** of data, either through omission (failing to reveal data) or commission (altering or fabricating data)



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Research Misconduct



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Research Misconduct



- Examples –
 - Inadequate records:
 - Creating source documents for missed assessments
 - Throwing away source documents for assessments that are supposed to be direct data entry
 - Failure to report data (e.g., knowledge of an AE that a coordinator assumes is unrelated)
 - Backdating review of eligibility criteria
 - Assuming result/answer

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EDC - Issues





- Sharing username and password access
 - Compromises our ability to track data entry and maintain 21 CFR part 11 compliance
 - Each person using EDC must be certified and have their own ID
 - Even applies to ePro
 - Compromises integrity of "self-report" assessment



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EDC – Issues







www.iwaysoftware.com/go/dataquality

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EDC - Issues



- Source Documents
 - Initial point of collection for study data
 - Note when direct data entry is required vs. paper source docs
 - Even a sticky note can become a source document



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APPLYING GCDMP



GCDMP Scenario 1



FOR AUDIENCE PARTICIPATION...

- Protocol monitor discovered missing source documents for vitals and an EDC questionnaire.
- Site Coordinator stated that these entries were done via direct data entry.
- What next?

MULTIPLE CHOICE

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GCDMP Scenario 1



CHOOSE THE BEST ANSWER...

- Re-create the source document
- Indicate on progress note assessment was done via direct data entry

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Paper First vs. Direct Data Entry



- Verify requirements for Source Documents or Direct Data Entry for each assessment
 - Do not create a paper source document if direct data entry was used
- Verify data source (RA interview, Participant self-report, Medical record abstraction)
- eCRF should match paper source document


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GCDMP Scenario 2

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FOR AUDIENCE PARTICIPATION...

Urine Drug Screening – Recording Results



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GCDMP Scenario 2

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- Data entry UDS results recording.

UDS results from paper source:

1st Urine Drug Screen Results	Drug Name (Abbreviation)	Negative	Positive	Invalid
5	Benzodiazepine (BZO)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Amphetamine (AMP)	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>
	Marijuana (THC)	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>
	Methamphetamine (MET)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

UDS results in EDC:

5	1st Urine Drug Screen Result(s):	Negative	Positive	Invalid
	Benzodiazepines (BZO)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Amphetamine (AMP)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Marijuana (THC)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	Methamphetamine (MET)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

What next? 50

GCDMP Scenario 2


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CHOOSE THE BEST ANSWER...

- Assume missing was a negative result
 - “Remember” it being negative
 - Fix source document to match EDC
- Remove value in AdvantageEDC and submit Missing Value Exception Request

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GCDMP Scenario 3



FOR AUDIENCE PARTICIPATION...

- In this research study, a Substance Use Assessment is direct data entry into EDC.
- At the end of the day, an RA discovered that this assessment was not recorded in EDC for a participant whose visit concluded early morning.


INFORMATION ABOUT THE ASSESSMENT

- The assessment is an RA-administered interview.
- Based on other assessments conducted with this participant, the RA knows that the participant did not use any substances.
- What next?

MULTIPLE CHOICE

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GCDMP Scenario 3





CHOOSE THE BEST RESPONSE...

- Complete assessment in EDC with data indicating "no substance use"
- Submit Missing Form Exception Request

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GCDMP Scenario 4





Please note that **GCDMP Scenario 4** was slightly modified after the live webinar to clarify the condition presented.

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GCDMP Scenario 4



Protocol requirement:

14.4.5 Reportable Adverse Events and Serious Adverse Events

Adverse Events

For the purpose of this study, the following AEs will not require reporting in the data system but will be captured in the source documentation as medically indicated:

- Grade 1 (mild) and unrelated adverse events
- This would typically include physical events such as headache, cold, etc., that were considered not reasonably associated with the use of the study drug/intervention.

Scenario: Participant presents with mild acid reflux.

Is this AE reportable in EDC? YES or NO

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WRAPPING IT UP!

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Take Home Messages...



- Ongoing Training and Documentation
- Reference provided materials
 - Study MOP
 - AdvantageEDC User's Guide/Data Management Handbook
- Ask questions!
 - Manuals may need to be updated to be clearer
- Bad data = useless study = waste of taxpayer money

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References



- International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). (2015). E6 Good Clinical Practice. Retrieved from <http://www.ich.org/products/guidelines.html>.
- U.S. Food and Drug Administration. (n.d.). FDA's Electronic Reading Room – Warning Letters. Retrieved from <http://www.accessdata.fda.gov/scripts/warningletters/wSearchResult.cfm?office=Center%20for%20Drug%20Evaluation%20and%20Research>.

Questions / Comments

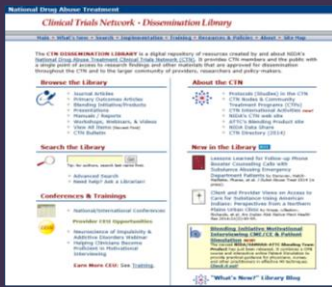


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Next topic...
Preparing for Closeout of Studies and Sites
Wednesday, April 29, 2015
12-1:30 pm ET

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