

Demonstrating Good Clinical Practice (GCP) Compliance in Research Through the Maintenance of Regulatory Documents

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Objectives

- **Define Good Clinical Practice**
- **Identify what Comprises Good Clinical Practice in the United States?**
- **Discuss the 13 Principles of ICH GCP Guidelines**
- **Determine Regulations to which your Institution is bound**
- **Determine Regulations Applicable to a specific Study**
- **Identify Regulatory Documents to Maintain**
- **Recognize the most common deficiencies in Regulatory Documentation**
- **Moving from Paper to a Digital Environment**



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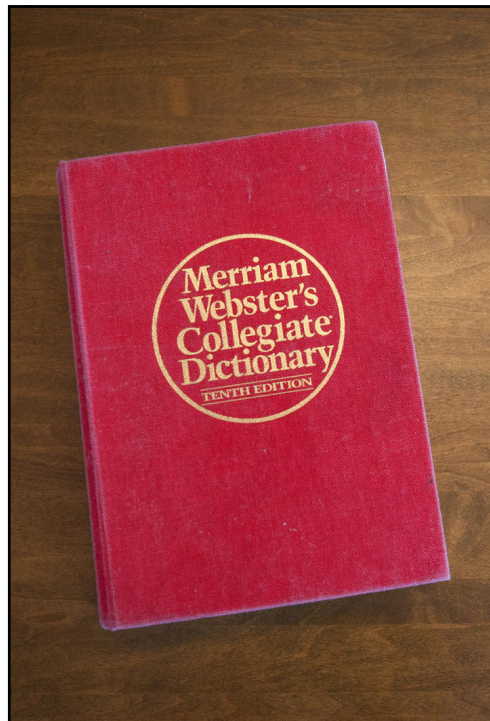
Good Clinical Practice (GCP)

A collection of Federal regulations, guidance, standards, and guidelines that together comprise the requirements and expectations of how clinical research is to be conducted ethically and with the rights and safety of the participants always placed first.



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Good Clinical Practice Defined

- Good Clinical Practice (GCP) is an **ethical** and **scientific quality** standard for the design, conduct, performance, monitoring, auditing, recording, analysis and reporting of clinical trials or studies that involve human subjects.
- Compliance with this standard provides assurances that the **rights, integrity and confidentiality** of the trial subjects are protected and the **data** and reported results are **credible and accurate**.

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Research Governing Bodies



- US Federal Agencies
 - Department of Health and Human Services (DHHS)
 - Office for Human Research Protections (OHRP)
 - Office of Research Integrity (ORI)
 - Food and Drug Administration (FDA)
 - National Institutes of Health (NIH)
 - Office of Management and Budget (OMB)
- State Laws
- International Standards
 - International Conference on Harmonisation (ICH)
- Accrediting Body
 - Association for the Accreditation of Human Research Protection Programs (AAHRPP)

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Primary Research Regulations in U.S. *Applicable to Sites Conducting Clinical Trials*

DHHS

- 45 CFR Part 46 "The Common Rule"

PHS

- 42 CFR Part 50, Subpart F: Promoting Objectivity in Research (Financial Conflicts of Interest)
- 42 CFR Part 93: Research Misconduct

FDA

- 21 CFR Part 11: Electronic Signatures
- 21 CFR Part 50: Informed Consent
- 21 CFR Part 54: Financial Disclosure
- 21 CFR Part 56: Institutional Review Boards
- 21 CFR Part 312: Investigational New Drug Application
- 21 CFR Part 812: Investigational Device Exemptions

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DHHS *aka* "The Common Rule" 45 CFR Part 46



- Federal policy for human subjects protection that applies to 17 federal agencies
- Outlines requirements for assuring institutional compliance
- Requirements for obtaining & documenting consent
- IRB membership, function, operations, review, record keeping
- Protection for vulnerable populations
 - Pregnant women, fetuses, prisoners, children

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Elements of a Good Research Study

Ethical

- Rights of subjects are protected
- Safety and well-being of subjects are protected

Scientific quality

- The data and reported results are credible and accurate
- = Following Good Clinical Practice (GCP) Guidelines, and...



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13 Principles of ICH Good Clinical Practice

Ethics

1. Ethical conduct of clinical trials

2. Benefits justify risks

3. Rights, safety, and well-being of subjects prevail

Protocol & Science

4. Nonclinical and clinical information supports the trial

5. Compliance with a scientifically sound, detailed protocol

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13 Principles of ICH Good Clinical Practice

Responsibilities

6. IRB/IEC approval prior to initiation

7. Medical care/decisions by qualified physician

8. Each individual is qualified (education, training, experience) to perform his/her tasks

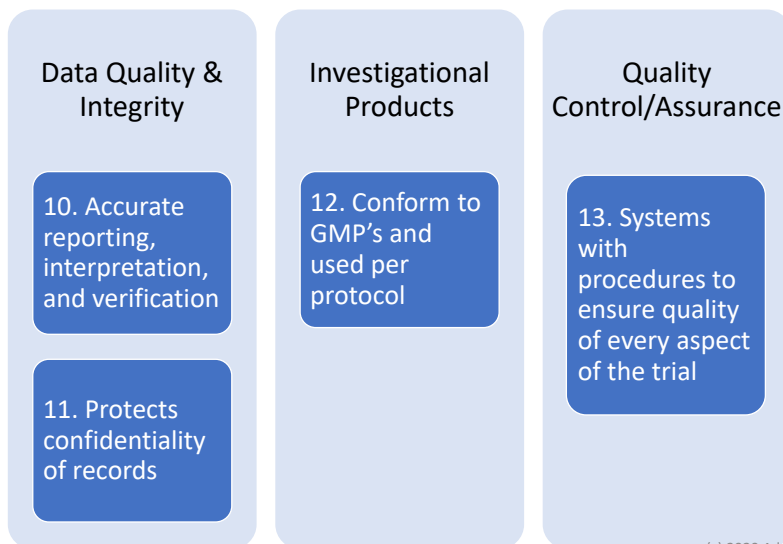
Informed Consent

9. Freely given informed consent from every subject prior to participation

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13 Principles of ICH Good Clinical Practice



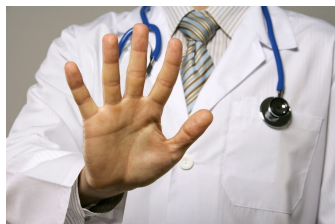
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Principal Investigator Responsibilities

“...usually one investigator is designated the “**principal investigator**” with overall responsibilities for the study. In every human subjects research study, investigators have certain responsibilities regarding the ethical treatment of human subjects.” DHHS

Supervise a clinical study in which some study tasks are delegated to employees or colleagues of the investigator or other third parties



Protect the rights, safety, and welfare of study subjects

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How Does HHS Ensure that Regulatory Requirements for Human Research are Met?



Through a system of IRB registration and assurances, HHS regulations require institutions to commit to compliance with 45 CFR part 46 (The Common Rule), before initiating participation in Federally funded or supported research involving human subjects.

- **IRB Registration**
- **Federalwide Assurance**

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Identifying the Regulations & Principles Your *Institution* is Bound to per Federalwide Assurance

The FWA application includes the following:

- Statement of Principles
 - The Belmont Report
 - The Declaration of Helsinki
 - Other
- Applicability
 - Federally conducted or supported (few exceptions)
 - Application **optional** for non-Federally funded research, as follows.
 - *The Common Rule of the HHS regulations at 45 CFR part 46*
 - *The Common Rule and Subparts B, C, and D*

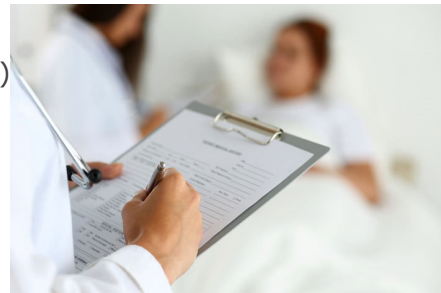


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Identifying the Regulations & Standards Applicable to an Individual Study

- Is the study Federally funded?
- Does the study include an investigational drug, device, or biologic?
- What regulations and standards does the protocol apply to the study?
- Clinical Trial Agreement (CTA)
- Policies & Procedures of other parties involved:
 - IRB of record (sometimes an external commercial IRB)
 - Contract Research Organization (CRO)
- Institutional Policies & Procedures



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Compliance with GCP Guidelines



i.e., the Paper Trail (or
Electronic Trail)..

Proving that we did so....



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Telling the Story....



“Clinical research records have a far different intended use than have routine medical records. A research record must be capable of proving, to 3rd party medical and non-medical personnel that a study was conducted properly and the protocol was followed. This proof must withstand the test of time and be capable of reconstructing the entire trial long after it was completed and involved personnel have moved on.”

SoCRA Source, November 2009

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Essential Documents

- Demonstrate compliance with the standards of GCP applicable to your study (federal department or agency that governs the research)
- Permit evaluation of the conduct of the trial
- Permit evaluation of the quality of the data produced
- E6(R2) Good Clinical Practice: Integrated Addendum to ICH E6(R1), *Guidance for Industry*
 - *Section 8: Essential Documents for the Conduct of a Clinical Trial*

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Common Documents For ALL Clinical Trials

Protocol – All versions

Case Report Forms (CRFs) – All versions

IRB Documents

- IRB application & supporting documents
- IRB approvals, acknowledgements & other communication
- IRB membership roster with roles they fill
- Continuing Reviews and Reportable information

Consent Forms (if applicable) & HIPAA Authorizations

Study Personnel Training/Qualifications

- Delegation of Authority Log, Signature Log and/or Research Personnel Log
- Qualification documents
- All required training

Master Subject ID Log

ClinicalTrials.gov NCT #, if applicable



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Investigational New Drug (IND) Application FDA Forms and Documents

- FDA Form 1572 "Contract" between PI and the FDA
 - The statement of the investigator that he will abide by the federal guidelines set forth in the Code of Federal Regulations for the use of drugs in an investigational setting
 - Update each time there is a change of the information
- IND documentation (letter with IND # assignment)
- Financial Disclosure Form FDA Form 3455



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Investigational Device Exemption (IDE) FDA Forms and Documents

- Device studies obtain a signed agreement from the PI containing information (similar to that requested on the 1572)
- IDE documentation (FDA letter with IDE # assignment and CMS category) or exemption justification
- Financial Disclosure Form FDA Form 3455



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Drug/Device Required Records

- Investigational Product Accountability
 - Includes documentation of receipt
 - Documentation of dispensing, use or implanting
 - Documentation of destruction or return to sponsor/manufacturere
- Investigator's Brochure (IB or package insert) for IND studies
- Device Manual for IDE studies
 - Out of date versions should be kept behind the current version and clearly marked as outdated



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Sponsor Correspondence

Includes but is not limited to:

- Study updates
- Progress reports
- Safety updates/reports
- Amendments to protocol
- Reports of adverse events and protocol deviations
- Requests for protocol exceptions/waivers
- Monitor letters, reports, site initiation & close out letters



- Sponsor/CRO Letters, faxes, email, documented phone conversations
- Protocol training certifications
- Other funding agencies (NIH, GCRC)
- Email with project manager, annual reports to funding agency, summary reports to foundations

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ClinicalTrials.gov National Clinical Trial (NCT)

NIH U.S. National Library of Medicine

ClinicalTrials.gov

- The sponsor is the responsible party for registering in ClinicalTrials.gov
- For industry sponsored studies, obtain NCT # from the sponsor
- If investigator-initiated study, the investigator is responsible for registering. Save email correspondence from ClinicalTrials.gov informing you the project is published and documenting the NCT# assigned to the project

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Other Documents if Applicable

- Institutional Biosafety IBC (if applicable)
- Data Safety Monitoring Board/Committee (DSMB)
- Laboratory
- Hazardous Material Shipping
- Tracking Logs
- Notes to File



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Notes to File (NTF) Optional Document As Needed

Purpose:

- Used to explain discrepancies
- Identify locations of documents not in the file
- Mistakes
 - *corrective actions taken and whether the action worked*

Caution:

- Do not overuse - raises red flags to auditors



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Institutional Biosafety Committee (IBC)

- Cornerstone of institutional oversight of recombinant DNA research
- Responsible for reviewing and approving research that involves or utilizes:
 - Recombinant or synthetic nucleic acid molecules
 - Gene transfer
 - Viral vectors
 - Certain infectious agents, carcinogens
 - Biohazardous materials



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Data Safety Monitoring Board/Committee (DSMB) Correspondence

An independent committee set up specifically to monitor data throughout the duration of the study to determine if continuation of the study is appropriate scientifically and ethically.



The following documents should be kept on file:

- Reports
- Interim findings
- General correspondence

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Laboratory Certifications for Labs Performing Specimen Testing

- Lab
 - Documents competency of facility to perform required test and support reliability of results
 - Central and local labs
- College of American Pathologist (CAP) or Commission on Laboratory Accreditation (COLA)
- Clinical Laboratory Improvement Amendments (CLIA)
- Laboratory License, if applicable per State
- Lab Director's CV
- Normal Lab Values/Reference Ranges



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Training on Proper Packaging & Shipment of Biospecimens

- The shipment of hazardous materials
- Category B Biological Specimens
- Sites that don't use lab personnel to package/ship
- Regulations protect the shippers, the carriers, the environment, and the recipients
- Failure to comply with the regulations can result in substantial fines and/or jail terms



Department of Transportation (DOT)

- <http://www.phmsa.dot.gov/hazmat>

International Air Transportation Association (IATA) Certification

- <http://www.iata.org/index.htm>

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Logs

- Additional optional logs that may not be required can be useful to capture information
- Examples include:
 - Subject Screening/Enrollment Log (De-Ident)
 - AE/SAE Tracking Log
 - Protocol Deviation/Violation Log
 - Equipment Calibration Log
 - Storage Temperature Monitoring Log
- Sponsors usually provide the tracking logs that they require to record and document the study activity



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Business Documents

Not GCP Regulatory Documents
File Separately

- Budget
- Medicare Coverage Analysis
- CDA (Confidentiality Disclosure Agreement)
- CTA (Clinical Trial Agreement)
- DUA (Data Use Agreement) or MTA (Materials Transfer Agreement) if applicable
- Conflict of Interest Disclosure
 - *Significant Financial Interests*
 - *Management Plans*



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Source Data & Subject Binders

Each subject should have the following on file:

- Original signed informed consent/assent/HIPAA Authorization Forms or waiver
 - May retain in separate binder
- Case report forms, completed and signed by PI
- Randomization Assignment
- Completed questionnaires
- Adverse Events (AEs)



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Quality of Source Data

- All source data should be **transparent**
- **Transparency** can be accomplished by applying the **ALCOA-C Standard** to your source data
- The quality of your data can be measured by applying the **ALCOA-C test** to your source data
- Any changes to source data should:
 - Be traceable
 - Not obscure the original entry
 - Be explained if necessary (e.g., via an audit trail)



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Apply The ALCOA-C Standard to all Source Data

- **A** = Attributable (to person collecting & recording the data)
- **L** = Legible
- **C** = Contemporaneous (existing, occurring, or originating during the same time)
- **O** = Original (1st recording)
- **A** = Accurate
- **C** = Complete

EXCELLENT



AVERAGE



POOR



EMA (European Medicines Agency) has added: Enduring, Available & Accessible, Consistent, Credible, and Corroborated

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Demonstrating Investigator Oversight

Supervision

- Responsible for the study team and the appropriate delegation of tasks
- Interaction and communication with the study team (meetings, etc.)

Protection of research subjects

- Determine eligibility for trial participation
- Ensure adequate medical care is provided
- SAEs: Particularly causality, relation to IP, & severity
- Reviewing labs, ECGs, CRFs, and notes regarding pertinent issues with either a subject or the study as a whole



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Informed Consent Regulations

- **FDA 21 CFR 50.25**
Elements of IC
- **FDA 21 CFR 50.27 (a)**
Documentation of IC
- **DHHS 45 CFR 46.116**
General Requirements for IC
- **DHHS 45 CFR 46.117**
Documentation of IC



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Informed Consent Required Per Federal Regulations

Per DHHS: "...no investigator may involve a human being as a subject in research covered by this policy unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative."

DHHS 45 CFR 46.116

Per the FDA regulations: "...no investigator may involve a human being as a subject in research covered by these regulations unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative."

FDA 21 CFR 50.20



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Documentation of Informed Consent What do the Federal Regulations Say?

"...The case history for each individual shall document that informed consent was obtained prior to participation in the study." FDA 21 CFR 312.62 (b)

- Document either the time IC was obtained and the time that the study procedures began, or simply include a statement in your documentation, such as; "no study procedures began prior to obtaining informed consent".
- The FDA states, "*The case history*" should contain documentation of the informed consent process. The document itself is not enough, the IC process must be documented as well.



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Documentation of Informed Consent What do the Federal Regulations Say?

21 CFR 50.27 (a): "...informed consent shall be documented by the use of a written consent form approved by the IRB and *signed and dated* by the subject or the subject's legally authorized representative at the time of consent. *A copy shall be given to the person signing the form.*"

- The subject or LAR must date their own signature (no one should enter the date for them)
- Document that a copy was given to the subject



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Documentation of IC What Should be Included?

- **FDA guidance and information sheets describe a best practice of including additional information in the documentation of the IC process.**

- Potential risks and benefits were explained
- Inclusion and exclusion criteria were reviewed
- The subject was given adequate time to review the IC document
- The subjects questions were answered to their satisfaction
- The subject verbalized understanding



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Informed Consent Documentation Best Practice

- **Include a contextual statement in the documentation regarding exactly how and when the consenting process occurred.**
 - [Informed Consent Documentation Checklist](#)
 - Writing or typing a narrative statement
- If utilizing an IC checklist, it is best to add "comment" lines to add additional information unique to each consenting conversation in order to individualize it.
- Narrative statements may be entered in a progress note, the EMR, or other appropriate source.



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Sponsor-Investigator Added Responsibilities

- An individual who both initiates (Principal Investigator) and conducts a clinical investigation and under whose immediate direction the investigational drug or device is being administered or dispensed at all study sites (Sponsor).
- Have both Investigator & Sponsor responsibilities as identified in the FDA regulations.

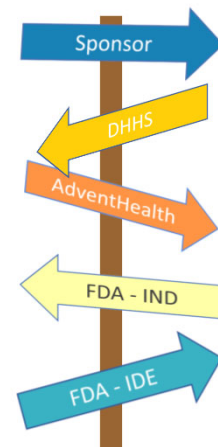


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Record Retention

- DHHS 45 CFR 46.117
 - Signed informed consent form
 - **At least three years** after completion of the research
- Institutional policy and state law
 - Seven years
- Sponsor requirements
Additional requirements depending on the language in the clinical trial agreement (CTA), and the study closeout letter



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Record Retention – FDA Regulations

- IND research
 - Records and reports
 - **2 years after a marketing application is approved for the drug; or if an application is not approved for the drug, until 2 years after shipment and delivery of the drug for investigational use is discontinued**
- IDE research

Maintain the records "for a period of 2 years after the latter of the following two dates: The date on which the investigation is terminated or completed, or the date that the records are no longer required for purposes of supporting a premarket approval application or a notice of completion of a product development protocol.



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Most Common Deficiencies in Regulatory Documentation

- **Documentation of Informed Consent**
- **Training & Qualification Documents**
 - GCP Training certificates
 - Protocol specific training
 - CVs and licenses
- **Documentation of Investigator Oversight**
- **Investigational Product Accountability**
- **Tracking Logs**
- **Missing Documents**
 - Sponsor/CRO correspondence
 - IRB Rosters



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Potential Areas of Non-Compliance Involving Informed Consent

Maintain the original signed IC document in the study files.

Use Valid Consent Forms:

- Make certain the current IRB approved consent form is used
- Electronically stamped ICF noting the "Date of IRB approval" and expiration date, if applicable

Ensure the person obtaining IC is qualified to do so, an IRB approved research team member listed on the Delegation of Authority Log, and delegated the task of obtaining IC.



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Potential Areas of Non-Compliance Involving Informed Consent

Ensure there is documentation of the informed consent process.

Ensure the subject or LAR signing the IC, dates their signature themselves and initials every page.

If a LAR signs, ensure they state their relationship to the subject.

The person obtaining consent should sign/date the same day.

Ensure the documentation demonstrates that IC was obtained prior to any study related activities.



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Moving from Paper to a Digital Environment



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Implementing an eRegulatory Application

Advantages

- **Remote availability for Researchers, staff, and Sponsor/CRO partners**
- **Facilitates standardized processes**
- **Efficiencies gained**
 - Filing is faster/easier
 - Electronic signature capability
 - Link or Share central documents needed for multiple study master files (training documents, laboratory documents, IRB rosters, etc.)
- **Increased security**
 - Can limit access, audit trails
- **Savings on Storage Expenses and Space**

Challenges

- **Time needed to convert documents to an electronic format**
- **Training**
- **Slow adaptation by some users**
- **Difficulty with frequently changed "living" documents**
- **Potential for a hybrid system initially due to legacy studies maintained in paper and newer studies maintained electronically**

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Questions

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Thank You!



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