Welcome

Pilot 2022 Series Study Guide

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Resource/Reference Guidance Sheet

Terms/Acronyms/Abbreviations/Basics:

- **Advarra Glossary of Acronyms and Abbreviations:** https://www.advarra.com/blog/clinical-research-acronyms-abbreviations-know/
- **IMARC:** https://www.imarcresearch.com/blog/clinical-research-trial-acronyms
- **NIH Glossary of Common Terms:** https://www.nih.gov/health-information/nih-clinical-research-trials-you/glossary-common-terms
- **Clinicaltrials.gov**: Glossary of Common Site Terms https://clinicaltrials.gov/ct2/about-studies/glossary
- **NIH:** What Are Clinical Trials and Studies? https://clinicaltrials.gov/ct2/about-studies/learn
- **Clinicaltrials.gov:** Learn About Clinical Studies**:** https://clinicaltrials.gov/ct2/about-studies/learn
- **NIH:** The Basics: https://www.nih.gov/health-information/nih-clinical-research-trials-you/basics

Regulations/Guidance:

- **FDA 21 CFR**: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm
  - 21CFR Part 11: Electronic Records and Signatures
  - 21CFR Part 50: Protection of Human Subjects
  - 21CFR Part 54: Financial Disclosure of Clinical Investigators
  - 21CFR Part 56: Institutional Review Boards
  - 21CFR Part 312: Investigational New Drug Application
  - 21CFR Part 812: Investigational Device Exemption
- **ICH GCP E6 (R2)**:
  - https://www.fda.gov/media/93884/download
  - http://www.fda.gov/cder/guidance/959fnl.pdf
- **45CFR46**: https://www.hhs.gov/ohrp/regulations-and-policy/regulations/45-cfr-46/index.html

Ethical Principles:

- **Belmont Report:**
  - https://www.hhs.gov/ohrp/regulations-and-policy/belmont-report/index.html
  - http://www.hhs.gov/ohrp/humansubjects/guidance/belmont.htm

- **The Nuremberg Code:**
  - https://history.nih.gov/research/downloads/nuremberg.pdf
  - http://www.cirp.org/library/ethics/helsinki/
- **Declaration of Helsinki:**
  - https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/

Resource/Reference Guidance Sheet

Terms/Acronyms/Abbreviations/Basics:

- **Advarra Glossary of Acronyms and Abbreviations:** https://www.advarra.com/blog/clinical-research-acronyms-abbreviations-know/
- **IMARC:** https://www.imarcresearch.com/blog/clinical-research-trial-acronyms
- **NIH Glossary of Common Terms:** https://www.nih.gov/health-information/nih-clinical-research-trials-you/glossary-common-terms
- **Clinicaltrials.gov**: Glossary of Common Site Terms https://clinicaltrials.gov/ct2/about-studies/glossary
- **NIH:** What Are Clinical Trials and Studies? https://clinicaltrials.gov/ct2/about-studies/learn
- **Clinicaltrials.gov:** Learn About Clinical Studies**:** https://clinicaltrials.gov/ct2/about-studies/learn
- **NIH:** The Basics: https://www.nih.gov/health-information/nih-clinical-research-trials-you/basics

Regulations/Guidance:

- **FDA 21 CFR**: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm
  - 21CFR Part 11: Electronic Records and Signatures
  - 21CFR Part 50: Protection of Human Subjects
  - 21CFR Part 54: Financial Disclosure of Clinical Investigators
  - 21CFR Part 56: Institutional Review Boards
  - 21CFR Part 312: Investigational New Drug Application
  - 21CFR Part 812: Investigational Device Exemption
- **ICH GCP E6 (R2)**:
  - https://www.fda.gov/media/93884/download
  - http://www.fda.gov/cder/guidance/959fnl.pdf
- **45CFR46**: https://www.hhs.gov/ohrp/regulations-and-policy/regulations/45-cfr-46/index.html

Ethical Principles:

- **Belmont Report:**
  - https://www.hhs.gov/ohrp/regulations-and-policy/belmont-report/index.html
  - http://www.hhs.gov/ohrp/humansubjects/guidance/belmont.htm

- **The Nuremberg Code:**
  - https://history.nih.gov/research/downloads/nuremberg.pdf
  - http://www.cirp.org/library/ethics/helsinki/
- **Declaration of Helsinki:**
  - https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/

- **NIH:** http://history.nih.gov/laws/pdf/helsinki.pdf
- **HHS:** http://www.hhs.gov/ohrp/nhrpac/mtg12-00/h2000-1996.pdf
- **FDA Information Sheets:**
    - http://www.fda.gov/oc/ohrt/irbs/default.html

Articles:

- **Anatomy of a Great Clinical Research Coordinator:** https://acrpnet.org/2018/08/14/the-anatomy-of-a-great-clinical-research-coordinator/
- **imarc:** How to Properly Make a Correction to a Research Record: https://www.imarcresearch.com/blog/bid/345167/how-to-properly-make-a-correction-to-a-research-record
- **imarc:** What is Good Clinical Practice Today? https://www.imarcresearch.com/blog/good-clinical-practice-fundamentals

Additional resources:

- **Advarra Library:** https://www.advarra.com/resource-library/
- **ALCOA-C**
- **Center for Drug Evaluation and Research**: http://www.fda.gov/cder/regulatory/default.htm
- **Office of Human Subject Protection:** http://www.hhs.gov/ohrp/
- **Online Training Resources:**
    - http://www.hhs.gov/ohrp
    - http://nihtraining.com/cc/crt/indexvidoe/html
    - http://www.fda.gov/oc/gcp

SOCRA exam

- https://www.socra.org/certification/certification-program/introduction/
- https://www.socra.org/certification/ccrp-certification-exam/exam-outline/
- https://www.socra.org/certification/ccrp-certification-exam/candidate-eligibility/
- https://www.socra.org/certification/ccrp-certification-exam/preparing-for-the-exam/
- https://www.socra.org/assets/migrated/Certification/Candidate-Handbook-200805.pdf
- https://quizlet.com/15347048/socra-certification-exam-flash-cards/
- https://quizlet.com/class/4834454/
- https://www.proprofs.com/quiz-school/story.php?title=mtyzmtazmq0ytz
- https://www.brainscape.com/packs/socra-2020-14853217?origin=genome
- https://www.brainscape.com/packs/socra-ccrp-18783112?origin=genome
- https://www.brainscape.com/packs/socra-ccrp-2020-18626763?origin=genome
- https://www.brainscape.com/packs/socra-prep-15394464?origin=genome

ACRP exam:

- https://acrpnet.org/certifications/crc-certification/
- https://acrpnet.org/certifications/prep/ccrc-exam-prep/
- https://quizlet.com/307230511/acrp-ccrc-exam-prep-flash-cards/
- https://quizlet.com/class/3948653/
- https://quizlet.com/532172815/acrp-ccrc-exam-prep-questions-flash-cards/
- https://quizlet.com/307462346/acrp-ccrc-exam-flash-cards/
- https://quizlet.com/324512683/acrp-crc-prep-flash-cards/
- https://quizlet.com/535440613/acrp-ccraccrc-certification-exam-prep-flash-cards/
- https://quizlet.com/307055450/acrp-ich-flashcards-challenge-flash-cards/

Syllabus

Date	Topic	Materials
Materials to review before sessions begin		
	Reference for previously recorded power point presentation on the TN-CTSI website	**https://tnctsi.uthsc.edu/basic-research-training/**
	Handout of References	
	Vocabulary	**https://ichgcp.net/1-glossary** **https://www.fda.gov/patients/clinical-trials-what-patients-need-know/glossary-terms**
	Acronyms	**https://www.fda.gov/about-fda/fda-acronyms-abbreviations/acronyms-abbreviations-file-download**
	Confidentiality/HIPAA	**Research 102, session 5, https://mediaserver.uthsc.edu/uthscms/Play/e3f79a378af345499bae08951d0be48d1d**
	SOCRA exam overview	**https://www.socra.org/certification/ccrp-certification-exam/exam-overview/**
	SOCRA Preparation	**https://www.socra.org/certification/ccrp-certification-exam/preparation-resources/**
	ACRP Preparation	**https://acrpnet.org/certifications/prep/ccrc-exam-prep/**
	ACRP Certification Exam resources	**https://acrpnet.org/certifications/certification-resources/**

1/18/2022
DB
	1.Historical Events/Evolution of Regulations and HSP
	• Nuremburg Code
	• Belmont Report:
	• Declaration of Helsinki
	
	• **Phases and Types of Studies**
	  • Phases
	  • Types
	  • Study design
	  ○ Randomization
	  ○ Blinding
	  • Drug development
		Materials for Session 1:
		
		Handout/Reference Sheet:
		• **Timeline of Historical Events**
		• **Phases and Types of Studies**
		• **Graphics of Phases**
		• **Phases of Studies Comparison Chart**
		• **Blinding and Randomization Information Sheet**
		• **Drug Development Graphics**
		
		Webinar to View:
		• **Research 101, session 1, https://www.youtube.com/watch?v=6QXYpn8I26U**
		• **Research 102, session 2, https://tnctsi.uthsc.edu/basic-research-training/**
		
		Website/Article to review:
		• **NIH timeline: https://history.nih.gov/display/history/Human+Subjects+Timeline**
		• **Nuremburg Code: https://history.nih.gov/display/history/Nuremberg+Code**
		• **Belmont Report: https://history.nih.gov/display/history/Belmont+Report**
		• **Declaration of Helsinki: https://history.nih.gov/display/history/helsinki**
		• **Declaration of Helsinki: https://www.imarcresearch.com/blog/bid/361861/the-declaration-of-helsinki-1964**

Syllabus

		• **PRIM&R timeline of events: https://primr.org/resources/research-ethics-timeline** • **Drug development: https://www.fda.gov/patients/learn-about-drug-and-device-approvals/drug-development-process** • **Drug Development Process: https://www.fda.gov/drugs/cder-small-business-industry-assistance-sbia/new-drug-development-and-review-process** • **Study Design: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/drug-study-designs** • **Types of Studies: https://researchautism.org/five-basic-types-of-research-studies/** • **Blinding: https://toolbox.eupati.eu/resources/the-concept-of-blinding-in-clinical-trials/** • **Blinding: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2947122/** • **Randomization and Bias: https://www.cancer.gov/about-cancer/treatment/clinical-trials/what-are-trials/randomization** • **WHO: https://www.who.int/bulletin/archives/79(4)373.pdf** • **imarc article: https://www.imarcresearch.com/blog/bid/361861/the-declaration-of-helsinki-1964** **Worksheets:** • **Historical Events and Resulting Regulations/Guidance** • **Matching for Topics in this Session**
1/20 DB	**2. Ethics/Research Misconduct** •Definitions •Clinical Holds: Disqualification/Debarment •Sanctions Nuremburg Code Belmont Report: Declaration of Helsinki	**Materials for Session 2:** **Handout/Reference Sheet:** • **Ethics Definitions** • **Ethical Principles** • **Belmont Summary** • **Declaration of Helsinki Principles** • **Nuremburg Code Summary** • **Ethics/Misconduct Definitions** • **Ethical Scenarios** **Webinar to View:** • **Research 103, session 6, https://www.youtube.com/watch?v=0zVF-pJOkWQ** **Website to review:** • **Clinical Holds: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/use-clinical-holds-following-clinical-investigator-misconduct** • **Sanctions: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/clinical-investigator-regulatory-sanctions-information-sheet** • **Disqualification: Disqualification: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/clinical-investigator-administrative-actions-disqualification**

Syllabus

		Worksheets: • **Multiple-choice worksheet**
1/25 ML	**3.Regulations and Guidance** (1) Follow most restrictive regulation/guidance (2) Common Rule: 45 CFR 46 ○ Definitions ○ Engaged in Research ○ Human Subject ○ Subpart A ○ Subpart B ○ Subpart C ○ Subpart D ○ Federalwide Assurance (3) FDA Regulations: 21 CFR 50 ○ Vulnerable populations ○ Safeguards for children ○ Emergency use	**Materials for Session 3:** **Webinar to View:** • **Research 101, Session 3 https://tnctsi.uthsc.edu/basic-research-training/** **Websites to review:** • 45 CFR 46 | HHS.gov • **45 CFR 46, Common Rule: https://www.hhs.gov/ohrp/education-and-outreach/revised-common-rule/revised-common-rule-q-and-a/index.html** • **eCFR :: 21 CFR Part 50 -- Protection of Human Subjects** • **https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=11** • **Part 11, Electronic Records; Electronic Signatures - Scope and Application | FDA** • **Significant Differences in FDA and DHHS Regulations (hopkinsmedicine.org)** **Worksheets:** • **General Definitions for 45 CFR 46** • **General Definitions for 21 CFR 50** • **Definitions for Vulnerable Populations** • **Vulnerable Subjects Worksheet**
1/27 DB	**4.ICH GCP:** ○ ICH E6 (R2) ○ ICH E8 ○ IRB ○ IRB approval ○ Legally Authorized Representative ○ Investigator ○ Clinical Trial / Study ○ Human Subject ○ Protocol ○ Protocol Amendment ○ Sub-Investigator ○ Investigational Product	**Materials for Session 4:** **Handout/Reference Sheet:** • **ICH GCP E6 (r2) Coversheet** • **ICH GCP 13 Principles** **Webinar to View:** **Research 101, session 3: https://tnctsi.uthsc.edu/wp-content/uploads/sites/98/2020/10/R101-session3.pdf** **Website to review:** • **ICH E8: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/e8-general-considerations-clinical-trials** • **ICH guidelines: https://www.ich.org/page/efficacy-guidelines#8-1**

Syllabus

		• **ICH GCP E6 (R2): https://www.fda.gov/files/drugs/published/E6%28R2%29-Good-Clinical-Practice--Integrated-Addendum-to-ICH-E6%28R1%29.pdf** • **ICH GCP: https://www.fda.gov/media/93884/download** • **Article: The Importance of Good Clinical Practice Guidelines and its Role in Clinical Trials: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3097692/** **Worksheets:** • **ICH GCP E6 worksheet** • **ICH GCP E6 section 4 worksheet**
2/1 ML	**5. IRB/IEC** (1) Definitions (2) When is IRB review required (regulatory requirements) according to OHRP and FDA? Which of the federal regulations specifically describe the composition, operation and function of the IRB. For OHRP? FDA? (3) Responsibilities / Protocol review requirements ○ Benefit/risk ratio ○ Safety and Monitoring plan ○ Belmont-Justice/Beneficence/Respect for Persons (4) Define the IRB According to 45 CFR 46 Subpart A and the Act that created the IRB (5) Membership requirements. (6) Local vs. Non-local IRB review (7) Single IRB review (8) Transferring oversight (9) Authority (10) Approval	**Materials for Session 5:** **Websites to review:** • **2018 Requirements (2018 Common Rule) | HHS.gov** • **CFR - Code of Federal Regulations Title 21 (fda.gov)** • **https://www.fda.gov/regulatory-information/search-fda-guidance-documents/institutional-review-boards-frequently-asked-questions** • **Comparison of FDA and HHS Human Subject Protection Regulations | FDA** • **Using a Centralized IRB Review Process in Multicenter Clinical Trials | FDA** • **Expedited Review: Categories of Research that may be Reviewed Through an Expedited Review Procedure (1998) | HHS.gov** • **Continuing Review Guidance (2010) | HHS.gov** • **Considerations When Transferring Clinical Investigation Oversight to Another IRB | FDA** • **Institutional Review Board (IRB) Written Procedures: Guidance for Institutions and IRBs | HHS.gov** • **Lesson 2: What is Human Subjects Research? | HHS.gov** • **https://www.fda.gov/media/93884/download** **E6(R2) Good Clinical Practice: Integrated Addendum to ICH EG (R1)** **Worksheets:** • **IRB Definitions 45 CFR 46 Subpart A, 21 CFR 56, ICH G6(R2)** • **Institutional Review Board** • **ICH E6 Guidance for IRB**

	(11) Who the IRB communicates with- Sponsor/regulatory authorities/study team (12) IRB suspension/withdrawal/closure of study (13) Records and Reports ○ Record retention and documentation ○ Minute record requirements (14) Non-human subjects research (15) When may a study be exempted from IRB review according to the OHRP and FDA? (16) Exempt/Expedited/Full Board review Continuing Review, Limited IRB review ○ Disapproval of IRB compliance ○ Outcome letters ▫ Evaluation of IRB compliance ▫ Assessment of Severity/Causation/Outcome/Tx needed ▫ Documents to be submitted ○ Recruitment materials ○ ICF ○ Protocol ○ CRFs (17) Submission ○ Initial exempt, expedited, full board or limited review with essential documents. ○ Amendment/Modification/Revision ○ Continuing review / Progress reports ○ Safety Monitoring reports, DSMB or other annual reports	

Syllabus

	▫ Unblinding ▫ IP recall/notification of new AEs-revision to ICF ▫ Adverse Event Reporting, SUSAR's ▫ Reporting to PI/sponsor/CRO/IRB ▫ Onset/resolution dates ▫ Follow-up to resolution ▫ Relevant information in source docs and CRFs ○ Close-out/ outcome to sponsor (18) Regulatory Compliance ○ Local/state/federal laws ○ Privacy laws ○ Confidentiality	
2/3 DB	**6.Roles and Responsibilities** • PI/Investigator • Coordinator • Sponsor: PI as a sponsor • Relationships • IRB/IEC	**Materials for Session 6:** **Handout/Reference Sheet:** • **General Responsibilities of the Investigator** • **NIH delegation-responsibilities** • **FDA 1572 Form** • **Roles and Responsibilities Study Guide** **Webinar to View:** **Research 101, session 5: https://www.youtube.com/watch?v=qaueaCaQ7ts&t=43s** **Websites to review:** • **PI/Investigator: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/investigator-responsibilities-protecting-rights-safety-and-welfare-study-subjects** • **Sponsor: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/sponsor-responsibilities-safety-reporting-requirements-and-safety-assessment-ind-and** • **Relationships: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/sponsor-investigator-irb-interrelationship** • **IRB/IEC: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/irb-responsibilities-reviewing-qualifications-investigators-adequacy-research-sites-and**

Syllabus

2/8 and 2/10 DB/ML	**7. and 8. Study Start-up**
	• Steps for industry or non-industry sponsored studies
	• Feasibility for both site and sponsor
	• Screening tests before enrollment
	• Study protocol review
	  ○ Objectives/Purpose
	  ○ I/E
	  ○ Procedures
	  ○ Recruitment
	  ○ Statistical plan
	  ○ Feasibility
	• **SOPs**
	  ○ Site
	  ○ Knowledge of IRB/IEC's SOPs
	  ○ Sponsor
	• **Training**
	  ○ Communication
	  ○ IRB/study sites/study team/sponsor/regulatory authorities
	  ○ Retention plan
	  ○ I/E eligibility
	  ○ Protocol, read, compliance
	  ○ Study visits/procedures/assessments
	  ○ QA plan
	  ○ Script for documentation
	  ○ Data collection
	  ○ Procedures
	  ○ Safety
	  ○ GCP
		Materials for Session 7 and 8:
		
		Handout/Reference Sheet:
		• **Study Start-up reference sheet**
		• **NIH guideline-study-startup document**
		• **Study Start-up Tips**
		
		Webinar to View:
		• **Research 101, session 4, https://www.youtube.com/watch?v=l3WpEbbq8-Q&t=16s**
		• **Research 102, Session 4, https://mediaserver.uthsc.edu/uthscms/Play/077d365e7431487dae952a9e6e3f76d51d**
		
		Websites to review:
		• **SOCRA: https://www.socra.org/blog/developing-effective-study-start-up-processes/**
		• **NIDCR Study Start-up: https://www.nidcr.nih.gov/research/human-subjects-research/toolkit-and-education-materials/interventional-studies/planning-and-start-up**
		• **Screening tests before enrollment: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/screening-tests-prior-study-enrollment**
		• **Advarra article: https://info.advarra.com/rs/291-FFI-055/images/StudyActivationReport.pdf?aliId=eyJpIjoiVzBwdVRIeDZTUUJobDVBXC8iLCJ0IjoiZ0FMQ0I4VTZITkhNNGk3d1FkVFpWUT09In0%253D**

Syllabus

	○ IP	
2/15 and 2/17 DB	**9. and 10. Essential Documents/Documentation** ○ Paper ○ Electronic ○ DSMB ▪ Reports ▪ Roles/Responsibilities ○ Source documents-what are they-how to create ○ Maintenance/storage-length/location ○ Regulatory requirements ○ CRFs ○ Study visits/procedures/assessments ○ Test results/Abnormal results-responsibility ○ Documentation ▪ Continuing participation at each visit ▪ Discontinuation-reason ▪ Termination- reason ▪ Withdrawal-reason ○ Subject withdrawal ○ I/E ○ Enrollment documentation with ICF signing ○ Reports to sponsor ▪ Enrollment ▪ Safety reports ▪ Deviations ▪ Final report ○ Documentation by site (may need to be on own)- Quick Links ○ Subject education ○ Letter for PCP ○ Queries ▪ Develop/initiate/resolve ○ Questionnaires	**Materials for Session 9 and 10:** **Handout/Reference Sheet:** • **Good Documentation Best Practices** • **List of Essential Documents** • **Potential SOPS Needed** • **Regulatory Binder Best Practices** • **Regulatory Binder Set-up** • **Essential Documents Reference Sheet** • **SOP handout** **Webinar to View:** **Research 101, Session 7, https://www.youtube.com/watch?v=p3FnlY_PCyg&t=1345s** **Research 101, Session 8, https://www.youtube.com/watch?v=-PwU0ZwyHcw&t=3s** **Research 102, Session 4, https://mediaserver.uthsc.edu/uthscms/Play/077d365e7431487dae952a9e6e3f76d51d** **Websites to review:** • **Electronic: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/electronic-source-data-clinical-investigations** • **Subject withdrawal: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/data-retention-when-subjects-withdraw-fda-regulated-clinical-trials** • **1571/1572:https://www.fda.gov/regulatory-information/search-fda-guidance-documents/information-sheet-guidance-sponsors-clinical-investigators-and-irbs-frequently-asked-questions** **https://www.fda.gov/regulatory-information/search-fda-guidance-documents/frequently-asked-questions-statement-investigator-form-fda-1572** • **Certificate of Confidentiality: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/certificates-confidentiality** **Worksheets:** • **Regulatory Binder Tabs/Documents worksheet**

Syllabus

	○ Training documents ○ CAPA ○ Calibration/ maintenance of equipment ○ Record retention ○ Study team credentials ○ Paper/electronic/storage ○ CRFs ○ DOAL (Site source docs/worksheets) ○ Record Maintenance ○ Regulatory documents (under IRB) **Case report Forms** • Visit and worksheets/checklist • Tools/aids/summary of each visit • Schedule of events • Sponsor's CRFs cannot be used as a source doc unless identified in the protocol **Supplies** ▪ PI responsibilities ▪ Lab kits/expiration date ▪ Computers/equipment (EKG, etc./contract/negotiate?)	
2/22 DB	**11. Investigational Product** • Who can dispense • Investigator order • Documentation IP • PI responsibility/check dates • Package insert/IP brochure/Device instructions • IP accountability • IP documents: temp logs/distribution/return/destruction/ storage/shipping • Packaging/labeling: lot #s, etc. • IP compliance percentage/adherence rate/education/ re-education/ seek	**Materials for Session 11:** **Handout/Reference Sheet:** • **NIH IP Accountability Tool Summary Sheet** • **IP Accountability Reference Sheet** **Webinar to View:** • **Research 101, session 10, https://www.youtube.com/watch?v=PLVJeOYTEjo&t=7s** **Websites to review:** • **Article: imarc-Product Accountability-https://www.imarcresearch.com/blog/bid/259435/Product-Accountability-in-Clinical-Trials-Why-is-it-important** • **Charging for IP: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/charging-investigational-products**

Syllabus

	approval from sponsor for continuation vs terminate
	• Charging for IP
		• **FDA information sheet: Conduct of Clinical Trials of Medical Products During the COVID-19 Public Health Emergency https://www.fda.gov/media/136238/download**
		• **Emergency Use:**
		  ○ **https://www.fda.gov/regulatory-information/search-fda-guidance-documents/emergency-use-authorization-medical-products-and-related-authorities**
		  ○ **https://www.fda.gov/regulatory-information/search-fda-guidance-documents/emergency-use-investigational-drug-or-biologic**
		• **IND: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/investigational-new-drug-applications-inds-determining-whether-human-research-studies-can-be**
		• **Subjects enter a second institution: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/use-investigational-products-when-subjects-enter-second-institution**
		• **Off Label: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/label-and-investigational-use-marketed-drugs-biologics-and-medical-devices**
		
		Worksheets:
		• **IP Accountability Worksheet**

2/24 ML	**12. 21 CFR 312 and 21 CFR 812** IND/IDE ○ Forms ○ Application ○ Documents ○ Amendments **Emergency Research and Emergency use of a test article** • Medical Devices • Determination of risk (who makes determination): • Classes **HUD**	**Materials for Session 12:** **Websites to review:** • CFR - Code of Federal Regulations Title 21 (fda.gov) • https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRsearch.cfm?CFRPart=812 • https://www.fda.gov/regulatory-information/search-fda-guidance-documents/frequently-asked-questions-about-medical-devices • FDA-form-1571_r13_instructions_508_FINAL.pdf • Drugs@FDA Glossary of Terms | FDA • IND Application Procedures: Overview | FDA • IND Application Reporting: Protocol Amendments | FDA • IND Application Reporting: Annual Reports | FDA • IND Application Procedures: Clinical Hold | FDA • Treatment Use of Investigational Drugs | FDA • Recommended Tips for Creating an Orphan Drug Designation Application (fda.gov) • Safety Reporting Requirements for INDs and BA/BE Studies (fda.gov) • 3082FNL.PDF (fda.gov) • CFR - Code of Federal Regulations Title 21 (fda.gov) Section 807 • https://www.fda.gov/media/75459/download • How to Determine if Your Product is a Medical Device | FDA • CFR - Code of Federal Regulations Title 21 (fda.gov)

Syllabus

		• 510(k) Clearances | FDA • Premarket Notification 510(k) | FDA • Deciding When to Submit a 510(k) for a Change to an Existing Device - Guidance for Industry and Food and Drug Administration Staff (fda.gov) • IDE Application | FDA • Significant Risk and Nonsignificant Risk Medical Device Studies | FDA • Classify Your Medical Device | FDA • General Controls for Medical Devices | FDA • Expanded Access for Medical Devices | FDA • Regulatory Controls | FDA • Attachment E CDRH Final Guidance Cover Sheet (fda.gov) • Humanitarian Use Device (HUD) Designation Program | FDA Worksheets: • 21 CFR 312 Definition • 21 CFR 312 Worksheet • 21 CFR 812 Definition • 21 CFR 812 Worksheet • Forms Sponsor Investigator IND • Forms Sponsor Investigator IDE
3/1ML	**13. Recruitment** ○ Recruitment materials ○ Recruiting subjects ○ Subject payments **HIPAA regulations in clinical Research** **21 CFR 11** ○ Electronic Records: Electronic Signatures	**Materials for Session 13** **Webinars to review:** • **Research 102, Session 2** https://tnctsi.uthsc.edu/basic-research-training/ • **Research 102, Session 5** https://tnctsi.uthsc.edu/basic-research-training/ **Websites to review:** • **https://www.fda.gov/regulatory-information/search-fda-guidance-documents/recruiting-study-subjects** • **https://privacyruleandresearch.nih.gov/pdf/clin_research.pdf** • **https://www.hhs.gov/hipaa/for-professionals/special-topics/research/index.html** • **https://www.hhs.gov/hipaa/for-professionals/privacy/laws-regulations/index.html** • **https://www.hhs.gov/hipaa/for-professionals/privacy/guidance/health-information-of-deceased-individuals/index.html** • **https://www.hhs.gov/hipaa/index.html** • **eCFR :: 21 CFR Part 11 -- Electronic Records; Electronic Signatures** • **Part 11, Electronic Records; Electronic Signatures - Scope and Application | FDA**

Syllabus

		Worksheets: • **Recruiting Study Subjects** • **HIPAA Regulations in Clinical Research Worksheet** • **21 CFR 11**
3/3ML	**14. Safety and Compliance Reporting** (1) Clinicaltrials.gov submission/maintenance of information ○ Informed consent documents ○ Covered study definition (2) Safety Definitions ○ AEs ○ SAE ○ UADE ○ SUSAR (3) Medwatch reports (3500, 3500A, 3500B) ○ Safety reports from sponsor (4) Financial Disclosures 21 CFR 54 ○ FDA Form 3454 ○ FDA Form 3455	**Materials for Session 14** **Handout / Reference Sheets:** • **Adverse Event Reporting** • **Adverse Event Chart** **Webinars to Review:** • **Power Point Presentation Research 101, Session Nine** https://tnctsi.uthsc.edu/basic-research-training/ **Websites to review:** • **https://clinicaltrials.gov/** • **https://www.fda.gov/drugs/investigational-new-drug-ind-application/ind-application-reporting-safety-reports** • **https://www.fda.gov/files/drugs/published/Safety-Reporting-Requirements-for-INDs-%28Investigational-New-Drug-Applications%29-and-BA-BE-%28Bioavailability-Bioequivalence%29-Studies.pdf** • **https://www.fda.gov/medical-devices/investigational-device-exemption-ide/ide-reports** • **https://www.hhs.gov/ohrp/regulations-and-policy/guidance/reviewing-unanticipated-problems/index.html#Q1** • **https://database.ich.org/sites/default/files/E2A_Guideline.pdf** • **https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?fr=312.32** • **Information About Reporting Adverse Events to FDAs MedWatch Program | FDA** • **https://www.fda.gov/safety/medwatch-forms-fda-safety-reporting/instructions-completing-form-fda-3500** • **https://www.fda.gov/medical-devices/postmarket-requirements-devices/mandatory-reporting-requirements-manufacturers-importers-and-device-user-facilities** • **eCFR :: 21 CFR 314.80 -- Postmarketing reporting of adverse drug experiences.** • **CFR - Code of Federal Regulations Title 21 (fda.gov)** • **Financial Disclosures by Clinical Investigators | FDA** • **https://www.fda.gov/media/85293/download** **Financial Disclosures Guidance** **Worksheets:** • **Safety and Compliance Reporting** • **Safety Reporting Comparison between FDA and ICH** • **Forms Medwatch**

Syllabus

		• **Financial Disclosure 21 CFR 54**
3/8 and 3/10 ML	**15 and 16 Informed Consent** (1) Regulations ○ OHRP ○ FDA ○ ICH G6 (R2) (2) Consent (3) Assent (4) Decision making capabilities (5) Authorized representation/LAR (6) Signatures (7) Witnesses (8) Short Forms (9) Exculpatory language (10) Vulnerable subjects (11) Waiver/Alteration: (12) Emergency Research (13) Emergency Use of a Test Article (14) Copy to subject (15) Withdrawal /Termination/Discontinuation (16) Electronic ICF (17) FDA vs. DHHS regulations (18) Informed consent checklist	**Materials for Sessions 15 and 16:** **Handout / Reference Sheets:** • **Elements of Consent** **Webinars to Review:** • **Power Point Presentation Research 101, Session Six** • **Power Point Presentation Research 102, Session Six** **Basic Research Training – TN-CTSI (uthsc.edu)** **Websites to review:** • **45 CFR 46 | HHS.gov** • **CFR - Code of Federal Regulations Title 21 (fda.gov)** • **Informed Consent | FDA** • **Informed Consent Checklist (1998) | HHS.gov** • **https://www.fda.gov/regulatory-information/search-fda-guidance-documents/exculpatory-language-informed-consent** • **https://www.fda.gov/regulatory-information/search-fda-guidance-documents/irb-waiver-or-alteration-informed-consent-clinical-investigations-involving-no-more-minimal-risk** • **Additional Protections for Children | FDA** • **A Guide to Informed Consent | FDA** • **Research with Children FAQs | HHS.gov** • **Children: Information on Special Protections for Children as Research Subjects | HHS.gov** • **https://www.hhs.gov/ohrp/sachrp-committee/recommendations/2006-november-09-letter-attachment-a/index.html** • **Subpart C — Additional Protections Pertaining to Biomedical and Behavioral Research Involving Prisoners as Subjects | HHS.gov** • **Guidance on Approving Research Involving Prisoners (2000) | HHS.gov** • **download (fda.gov)** • **GCP Guidance** • **https://www.fda.gov/regulatory-information/search-fda-guidance-documents/exception-informed-consent-requirements-emergency-researchLAR** • **https://www.fda.gov/regulatory-information/search-fda-guidance-documents/use-electronic-informed-consent-clinical-investigations-questions-and-answers** **Worksheets:**

Syllabus

		• **Informed Consent Study Guide** • **ICH G6 Guidance for Informed Consent**
3/15 DB	**17.Monitoring/Auditing/Inspections** • Oversight: Preparation • Perform • FDA audit ○ Form 482/483 • IRB audit • Monitoring visit • CAPA	**Materials for Session 17** **Handout/Reference Sheet:** • **CAPA reference sheet** **Webinar to View:** • **Research 101, Session 11, https://www.youtube.com/watch?v=bybtMVF3PlY&t=4s** • **Research 102, Session 3 FDA Audits and Common Findings: https://mediaserver.uthsc.edu/uthscms/Play/d0c77f9a2fe84acc85c290ae3c28c5f31d** **Website to review:** • **SOCRA article: file:///C:/Users/dbran.UTHSC/Documents/SOCRA%20EXAM/16.%20Monitoring%20and%20Auditing/Resolving%20and%20Preventing%20Repetitive%20Problems%20in%20Clinical%20Trials%20-%20SoCRA.html** • **ACRP: https://acrpnet.org/resources/checklist-tasks-monitoring-visits/** • **FDA Inspections of Clinical Investigators: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/fda-inspections-clinical-investigators** • **Oversight of Clinical Investigations:https://www.fda.gov/regulatory-information/search-fda-guidance-documents/oversight-clinical-investigations-risk-based-approach-monitoring** • **What Should I Expect During an Inspection: https://www.fda.gov/industry/fda-basics-industry/what-should-i-expect-during-inspection** • **FDA Form 483 Frequently Asked Questions: https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/inspection-references/fda-form-483-frequently-asked-questions** • **FDA Inspection Readiness: Preparing for an Inspection: https://www.advarra.com/blog/fda-inspection-readiness-preparing-for-an-inspection/** • **Advara Article: https://www.advarra.com/blog/12-items-auditors-look-for/** • **FDA Bioresearch Monitoring Information: https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/compliance-actions-and-activities/fda-bioresearch-monitoring-information** **Worksheets:** • **Common Findings and Resolution Worksheet**
3/17 ML/DB	**18. Contracts and Agreements** **Study Closure** • Study close-out visit	**Materials for Session 18:** **Handout/Reference Sheet:** • Significant Differences Among OHRP, FDA and ICH GCP

Syllabus

	○ Essential docs-verification ○ Resolution of queries ○ IP accountability ○ QA/QC ○ IRB closure submission- outcome letter to sponsor ○ Final report to clinicaltrials.gov **Differences between FDA, OHRP and ICH**	• NIDCR Study Close-out Checklist **Webinars to Review:** • Power Point Presentation Research 103, Session Two Basic Research Training – TN-CTSI (uthsc.edu) **Website to review:** • https://www.clinicaltrialsarena.com/news/9-essential-components-of-a-clinical-trial-agreement-5885280-2/ • https://ccts.osu.edu/content/clinical-trial-agreement • Data Use Agreements | Research Data Management @Harvard • NIMH » Material Transfer Agreements (nih.gov) • https://www.fda.gov/medical-devices/investigational-device-exemption-ide/ide-responsibilities • Confidential Disclosure Agreements » Office of Clinical Research (OCR) » Clinical and Translational Science Institute » University of Florida (ufl.edu) • Establishing Indemnification in a Clinical Trial Agreement Requires Precise Language | 2019-01-14 | CenterWatch • https://research.cuanschutz.edu/crs/clinical-research-support/clinical-research-administration/clinicaltrials.gov-support/tips-of-the-week-archive/tip-of-the-week-april-2-2020/my-study-is-over.-how-do-i-close-my-clinicaltrials.gov-record • https://www.fda.gov/science-research/good-clinical-practice-educational-materials/comparison-fda-and-hhs-human-subject-protection-regulations **Worksheets:** • **Contracts and Agreements**

Session 1:

Historical Events, Evolution of Regulations, and Phases and Types of Studies

Timeline of Research Events

605 BC Book of Daniel Daniel tested the effects and benefits of a vegetarian diet. The study was conducted for 10 days. He only ate vegetables while the other subjects enjoyed the King's meat and wine. After ten days, they assessed who was healthier and determined it was Daniel.

1747 James Lind's Scurvy Experiment In one of the first clinical experiments in the history of medicine, Lind tested his theory regarding a cure for cure scurvy. Subjects in Lind's study included 12 affected sailors. He divided them into 6 groups. Each group received their regular diet with the addition of one of the following: Cider, sulfuric acid, vinegar, seawater, oranges and lemons, and a spicy paste with barley water. The group receiving the citrus fruit saw positive effects and began recovering immediately.

NIH traces its roots to 1887, when at the Marine Hospital Service (later to become U.S. Public Health Service) created a one-room laboratory. The Marine Hospital Service had been charged by Congress with examining arriving passengers on ships for symptoms diseases, such as, cholera and yellow fever, in an attempt to prevent epidemics.

1906 FDA Pure Food and Drug Act signed into law by President Theodore Roosevelt. The law prohibited products being sold for indications outside its labeling. It also prohibited unlawful food and drugs from being transportation across states.

1932-1972 The Tuskegee Syphilis Study The study was conducted by the U.S. Public Health Service and involved 600 low-income African-American males. 400 of the males were infected with syphilis and were not told about their disease. They were then followed for 40 years. They were given free medical examinations, but were not treated for syphilis when a proven cure (penicillin) became available in the 1950s. The study continued until 1972 with participants being denied treatment. The study was stopped in 1973 by the U.S. Department of Health, Education, and Welfare. In 1997, under pressure, President Clinton apologized to the study subjects and their families.

1937 Elixir Sulfanilamide Disaster S. E. Massengill Co.'s attempt to market Sulfanilamide to children, but instead became a mass poisoning of children. The chief chemist liquefied the drug by dissolving it in the toxic compound diethylene glycol. The company was made to pay a minimal fine for mislabeling the compound as this was the only penalty to serve under the 1906 Federal Food and Drugs Act.

1938 Federal Food, Drug, and Cosmetic Act. U.S. Congress passed the act to require proof of safety before the releasing new drugs.

1936-1945 Nazi Experiments Nazi doctors performed approximately 30 different experiments on concentration camp inmates. These were conducted without the consent of the inmates. They encountered extreme pain, disabilities and even death as a result of these studies. The experiments included studies/experiments involving the following: cold water, freezing, twins, treatment of wounds, poison, sterilization, bone transplantation, high altitude, air pressure, and exposure to chemical-warfare agents. These experiments were a total disregard for the human dignity.

1944 Multicenter Studies For the first time, trials were conducted at multi-centered sites using the same protocol. This allowed for a larger numbers of subjects to be included and a wider range of population groups to be studied.

Timeline of Research Events

1944-1974 Human Radiation Experiments. The U.S. government experimented on thousands of U.S. citizens without their knowledge that they were participating in an experiment to determine the effects of atomic radiation. The majority of subjects involved vulnerable populations.

1946 Nuremberg Doctor's Trial 23 German physicians and administrators were put on trial for their willing participation in war crimes and crimes against humanity.

1947 The Nuremberg Code This was the first international document which advocated voluntary participation and informed consent. This document was a result of the Nuremberg Doctor's Trial. The Nuremberg Code stated "The voluntary consent of the human subject is absolutely essential," that the benefits of research must outweigh the risks. In 1946 the United Nations adopted the document and it has been translated into over 500 languages.

1951 Henrietta Lacks Henrietta Lacks' was being treated for cervical cancer and tumor cells were taken from her without her knowledge. It was discovered that these cells could be kept alive in culture. Her cells would eventually become the HeLa (He for Henrietta and La for Lacks) immortal cell line. This cell line is currently and frequently utilized in biomedical research. These cells have been used to test the first polio vaccine, AIDS research, and cancer research, as well as, other scientific quests.

1953 First US Federal Policy for Protection of Human Subjects the NIH established a policy for the protection of human subjects. It required prior review by NIH, approval of all non-therapeutic research and all high-risk research, and informed consent of research subjects. The policy applied to almost all of the intramural NIH clinical research.

1956-1980 Willowbrook Experiments Researchers infected mentally disabled children with hepatitis at the Willowbrook State School. Subjects were then observed to record the progression of the disease. The New York Department of Health approved this study. Consent was obtained from parents, but the procedures were presented as vaccinations. In addition, there is evidence that only children enrolled in the study were admitted to the school (coercion).

1957-1961 Thalidomide was approved as a sedative in Europe in the late 1950's, but was not approved in the United States by the FDA. This drug was prescribed to pregnant women to control sleep and nausea, but taking this drug during pregnancy caused severe deformities in the fetus. The issue was that many patients did not know they were taking a drug that was not approved by the FDA and did not give informed consent. Deformities due to thalidomide affected approximately 12,000 babies.

Early 1960's Milgram Obedience Study Stanley Milgram, a Social psychology researcher, began a series of experiments at Yale after the Nuremberg trails. The trials made him want to examine the reason why the defendents justified their unethical actions by saying they were just following orders. He recruited subjects using deception; he called the experiments "a study of learning and memory," though he was really studying conditions of obedience and disobedience to authority.
https://www.simplypsychology.org/milgram.html

1962 Kefauver Amendments" to the Food, Drug and Cosmetic Act were passed into law to ensure drug efficacy and greater drug safety. For the first time, drug manufacturers were required to prove to FDA the effectiveness of their products before marketing them.

Timeline of Research Events

Thalidomide study a drug in Europe was allowed for use in the United States with waiver of clinical trials by FDA (1962). Those receiving drug were not warned that it was still 'experimental'. https://www.medicalnewstoday.com/articles/how-the-thalidomide-scandal-led-to-safer-drugs and https://www.mayoclinicproceedings.org/article/S0025-6196%2811%2962157-5/fulltext

1961-1962 Electric Shock Experiments Stanley Milgram conducted his experiments with electric shock. His experiments showed that people are willing to perform tasks that they previously considered to be morally wrong when being instructed to conduct the tasks by an authority figure.

1962 Kefauver-Harris Drug Amendment was a result of US Senate hearing following the use of the Thalidomide Drug. Manufacturers were required to provide proof of effectiveness of their drugs prior to approval. This amendment also required that side effects were to be reported.

1963 Jewish Chronic Disease Hospital Study At the Jewish Chronic Disease Hospital, NYC, chronically ill and debilitated patients were injected with live human cancer cells. The patients were not informed of this as it was believed the cancer cells would be rejected.

1964 World Medical Association, Helsinki Declaration governs international research ethics and defines rules for "research combined with clinical care" and "non-therapeutic research." The Declaration is the basis for Good Clinical Practices used today. The Declaration of Helsinki addresses the following: (1) Research with humans should be based on the results from laboratory and animal experimentation, (2) Research protocols should be reviewed by an independent committee prior to initiation, (3) Informed consent from research participants is necessary,(4) Research should be conducted by medically/scientifically qualified individuals and (5) Risks should not exceed benefits

1964 Henry Beecher published an article in N. Engl. J. Med. exposing 22 unethical studies/experiments, including the Tuskegee syphilis study and the Willowbrook hepatitis study. He reviewed biomedical research literature and showed that human subjects protections were violated in over 500 papers. His analysis was published in the New England Journal of Medicine and in two books.

1972 Zimbardo's Prison Stimulation Study involved Stanford University undergrads and made some of them guards and some of them prisoners in a mock underground dungeon for a planned two week stay. It was designed to study the psychology of prison life, but it had to be ended prematurely because of what the situation was doing to the college students who participated. In only a few days, subjects acting as guards became sadistic, and subjects playing the role of prisoners became depressed and showed signs of extreme psychological stress. The prisoners were also becoming quite mental. The experiment tells a story about psychological harm and informed consent, since the subjects did not know what they were getting into.

1974 National Research Act passed by Congress authorized federal agencies to develop human research regulations (45 CFR 46, 21 CFRs). IRB's were established and a National Commission for Protection of Human Subjects was established. It required that all human subject research be reviewed by an IRB/IEC to ensure human subject protections. Due to the publicity from the Tuskegee Syphilis Study, the National Research Act of 1974 was passed. The National Research Act created the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, which was charged to identify the basic ethical principles that should underlie the conduct of biomedical and behavioral research involving human subjects and to develop guidelines which should be followed to assure that such research is conducted in accordance with those principles. The Commission drafted the Belmont Report, a foundational document in for the ethics of human subjects research in the United States.

Timeline of Research Events

1978 The Belmont Report was published, based on the Presidentially commissioned work of MD Psychologists, Lawyers, and Biomedical and Behavioral Ethicists. This document proposed to go beyond "rules and regulations" and to proposed principles to use in judgments about protecting human subjects, (1) Respect for Persons, (2) Beneficence, and (3) Justice.

In Summary:

- Nazi atrocities in World War II drew attention to the lack of international standards on research with human subjects and led to the formulation of the Nuremberg Code.
- The thalidomide disaster led to the adoption of the "Kefauver Amendments" to the Food, Drug and Cosmetic Act, requiring drug manufacturers to prove to the FDA the effectiveness of their products before marketing them.
- The Declaration of Helsinki is the basis for Good Clinical Practices used today.
- The Tuskegee Syphilis Study is probably the worst case of unethical human subjects research in the history of the United States.
- The National Research Act codified the requirement that human subjects in research must be protected and **set the stage for the issuance of the Belmont Report**.

1974 FDA Bureau of Medical Devices and Diagnostic Products. Updated regulations were needed and the FDA created this Bureau to meet this need.

1976 Medical Device Amendment This amendment was signed by President Gerald Ford to increase FDA's authority over the production of medical devices.

1981 FDA Regulations Title 21 the Department of Health and Human Services (DHHS) and the Food and Drug Administration (FDA) issued regulations based on the Belmont Report. DHHS issued Code of Federal Regulations (CFR) Title 45 (public welfare), Part 46 (protection of human subjects). The FDA issued CFR Title 21 (food and drugs), Parts 50 (protection of human subjects) and 56 (Institutional Review Boards).

1981 Dr. John Darsee (Fabrication of data) conducted research at the University of Notre Dame (1966-70), Indiana University (1970-74), Emory University (1974-79), Harvard University, 1979. Colleagues became concerned about the accuracy of Darsee's results and an investigation found that Darsee had been altering dates on his laboratory work to make a few hours of work appear to be several weeks of data. It also concluded he had previously used false data between 1966 and 1970 at Notre Dame University. As a result of the investigation, Harvard University retracted 30 papers and abstracts in February, 1983 and Emory University retracted 52 papers and abstracts published between 1974 and 1979. https://onlineethics.org/cases/ethics-science-classroom/overly-ambitious-researchers-fabricating-data

1986 Robert Slutsky (Falsification of research records over a ten-year period) he conducted research at the University of California at San Diego and published 161 articles in 6 years. In 2 years, he was completing an article every 10 days, but included many different co-authors to mislead the editors of journals and cover up for what was later found to be falsified research. An investigation of 137 of his publications found that 77 were valid, 48 were questionable, and 12 were fraudulent.

1988 Steven Breuning Fabricated and falsified data in 24 papers. He was convicted of defrauding the federal government.

Timeline of Research Events

1989 Office of Scientific Integrity and the Office of Scientific Integrity Review These offices were created to investigate scientific misconduct and to amend the definition of misconduct.

1989 Responsible Conduct of Research Training Requirement of the NIH for all graduate students on training grants receive education on research training.

1990 International Conference on Harmonization Guidelines. Many European nations along with Japan and the United States began creating plans for global harmonization of regulatory requirements to reduce duplicate, time-consuming, and expensive procedures needed to market products internationally, while maintaining safeguards on quality, safety, and efficacy. This need led to the creation of the ICH guidelines in April of 1990.

1990 Safe Medical Devices Act Hospitals and health professionals were required to report safety incidents to the FDA and manufacturers regarding devices. The FDA under this act was able to recall devices and take other actions.

1991Common Rule (45 CFR Part 46) Set of ethics involving the protection of human subjects was adopted by 17 Federal agencies. The main elements of the Common Rule include: (1) requirements for assuring compliance by research institutions, (2) requirements for researchers obtaining and documenting informed consent, (3) requirements for Institutional Review Board (IRB) membership, function, operations, review of research, and record keeping, (4) additional protections for certain vulnerable research subjects-- pregnant women, prisoners, and children

1992 Office of Scientific Integrity and the Office of Scientific Integrity Review The two agencies became the Office of Research Integrity (ORI).

1993 MedWatch was launched by the FDA as a system designed to collect health professionals' reports of adverse events involving medical products. When safety hazards are detected, the FDA issues medical product safety alerts or orders product recalls, withdrawals, or labeling changes to protect the public health.

1994 Roger Poisson admits to fabricating and falsifying patient data in breast cancer clinical trials in order to qualify his patients to participate in research and have access to experimental treatments.

1994-1995 The Ryan Commission, convened by the NIH, holds meetings on scientific misconduct.

1994 Two scientists who worked at Philip Morris, Victor DeNobel and Paul Mele, testify before Congress about secret research on the addictive properties of nicotine. If the research had been made public, the FDA or Congress might have taken additional steps to regulate tobacco as a drug. Many states and individuals brought litigation against tobacco companies, which led to a $206 billion settlement between tobacco companies and 46 states. The scientific community also publishes more data on the dangers of second-hand smoke.

1996 HIPAA. The Health Insurance Portability and Accountability Act requires that patients be informed of how their protected health information will be stored and kept private when they participate in a research trial. President Bill Clinton signed this act into law in 1992, but the final HIPAA rule did not go into effect until 1996.

1996 The World Health Organization Guidelines for Good Clinical Practice. The guideline addresses justifications for a trial and protocol; protection of subjects; responsibilities of investigators, sponsors and monitors; assurance of data integrity and product accountability; and roles of regulatory authorities.

Timeline of Research Events

1998 The Vaccine-Autism Myth Andrew Wakefield published an article in the prestigious medical journal, *The Lancet*, falsely linking the MMR (measles, mumps and rubella) vaccine to autism. The article was eventually retracted by the co-authors and the journal. Wakefield was de-licensed by medical authorities for his deceit and "callous disregard" for children in his care. It took nearly two decades for the UK immunization rates to recover. By the end, UK families had experienced more than 12,000 cases of measles, hundreds of hospitalizations and at least three deaths.

1999 Jessie Gelsinger (Gene Therapy Study at University of Pennsylvania) Jessie Gelsinger (18 years old) dies while a participant in a human gene therapy experiment. He suffered from a rare x-linked genetic disease of the liver but did not suffer effects at the time he enrolled in a gene therapy study at a University to help others. He died four days after the research procedure. After his death, information revealed led Jesse's father to believe that Jesse nor his family were fully informed and aware of the risks involved in the study. The University failed to report previous experienced serious side effects from participants, the informed consent did not divulge known deaths and University financial conflicts of interest in the trial. Additionally, Jesse's had a high ammonia levels that should have excluded him from participating in the study. This generated the need for a heightened scrutiny of conflicts of interest in human subjects research, including institutional conflicts of interest. The Gelsinger family settled for an undisclosed amount of money.

1999 The NIH and the OHRP require all people conducting or overseeing human subjects research have some training in research ethics.

2000 Office of Human Research Protections (OHRP) Was elevated to the level of the US department of Health and Human services, replacing the NIH Office for protection

2000 The Office of Science and Technology Policy (OSTP) finalizes a federal definition of misconduct as "fabrication, falsification or plagiarism", but not "error honest error or differences. The policy is still not effective.

2000 ORI proposes mandatory training in responsible conduct of research for all researchers on PHS grants, including junior senior investigators, students, and technicians. Several scientific associations and universities oppose the policy as an unnecessary and un-funded mandate. The Bush Administration suspends the ORI proposal in 2001 on the grounds that the agency failed to follow proper procedures for proposing new government regulations. To ORI proposal is still in limbo.

2002 The NAS publishes Integrity in Scientific Research, which recommends that universities develop programs for education in responsible conduct of research (RCR) as well as policies and procedures to deal with research ethics.

2002 Jan Hendrik Schön was a researcher at Bell Labs conducting groundbreaking research in the field of electronics: superconductivity, molecular crystals, and molecular electronics. He was producing one paper every 8 days and was on the 'fast track' to a Nobel Prize.It was found Schön had fabricated or altered data at least 16 times between 1998 and 2001. Bell Labs terminated his employment and his doctorate was revoked by his alma mater in Germany.

2004 The EPA suspends the CHEERS study due to criticism from advocacy groups and members of Congress, who claimed that the study was intentionally exposing children to pesticides. The EPA revised its human subjects rules in response to a Congressional mandate to strengthen protections for children and pregnant or nursing women.

Timeline of Research Events

2004 The NIH and other agencies adopt the OSTP misconduct definition. The OSTP Policy defines "research misconduct" as "fabrication, falsification, or plagiarism in proposing, performing, or reviewing research, or in reporting research results". It also sets the legal threshold for proving charges of misconduct.

2004 Secretary's Advisory Committee on Human research Protection (SACHRP) provides expert advice and recommendations to the Secretary of HHS on issues pertaining to the protection of human subjects in research.

2005 In response criticism from Congress, the NIH revises its conflict of interest rules for intramural research. NIH researchers cannot hold stock in pharmaceutical or biotech companies or consult with these companies (and other affected entities) for pay.

2005 University of Vermont researcher Eric Poehlman admits to fabricating or falsifying data in 15 federal grants and 17 publications. https://ori.hhs.gov/press-release-dr-eric-t-poehlman

2010 The National Science Foundation (NSF) announces RCR training requirements for funded investigators, students, and trainees. The NIH expands and strengthens is RCR training requirements.

2010 While doing research on the Tuskegee Syphilis Study, Susan Reverby, Professor of Women's Studies at Wellesly College, uncovered documents concerning unethical research experiments on human subjects conducted by the US government in Guatemala from 1946 to 1948. The research involved intentionally infecting over 1300 subjects with venereal diseases to test the effectiveness of penicillin. Only 700 subjects were given penicillin and 83 died as a result of the study. The subjects were not informed that they were participating in an experiment.

2010 Lancet retracts a fraudulent paper, published in 1998 by Andrew Wakefield and colleagues, linking autism to the measles vaccine.

2011 The NIH and NSF revise their conflict of interest rules for funded research.

2011 The Office of Human Research Protections announces proposed changes to the Common Rule to enhance human subject protections and reduce investigator burden. The Common Rule has not been changed significantly since 1981.

2013 The NIH launches the reproducibility initiative in response to problems with the reproducibility of scientific research.

2017 17 federal agencies publish the Final Rule for revisions to the Common Rule. The Final Rule eliminates controversial provisions that would have required prior consent for all research involving human biological samples. The Trump Administration places a 60-day hold on the Final Rule, pending further action by the executive branch and Congress.

2021 Death of a Health Volunteer at Johns Hopkins a 24 year-old healthy female employee inhaled hexamethonium as a volunteer in a research study at Johns Hopkins Asthma and Allergy Center. Within days she became ill and died on June 2, 2001. It was discovered that the consent document failed to adequately describe the research procedures to be followed, or failed to identify procedures which were experimental, and failed to adequately describe the reasonably foreseeable risks and discomforts associated with the research. The researchers also failed to follow the approved research protocol. They also failed to report unanticipated problems in an initial subject and continued to involve additional subjects. The enrollment continued before the symptoms in the first subject were resolved and reported to the appropriate entities.

Phases and Types of Studies

PHASES of STUDIES:

Phase 0:

- Aren't widely used
- Purpose is to help speed up and streamline the drug approval process
- May help researchers find out if the drugs do what they're expected to do
- Used only a few small doses of a new drug in a few people
- Almost no chance the people in phase 0 trials will benefit
- Benefit will be for other people in the future
- Drug doses are low, there's also less risk to those in the trial
- Studies are very small, often with fewer than 15 people
- Drug is given only for a short time
- Not a required part of testing a new drug

Phase 1:

- Emphasis is on safety
- Tests an experimental treatment on a small group of often healthy people (20 to 80) to judge its safety and side effects and to find the correct drug dosage
- Ensure that the treatment is safe in humans and to determine how and where it distributes within the body
- Controlled
- Closely monitored
- Small group of healthy volunteers, up to a few dozen
- Usually the first that involve people for a new drug
- Performed to determine the metabolism and pharmacologic actions of the drug in humans
- Performed to determine the best/highest/route for the dose and schedule of a new study treatment that can be given safely without causing severe side effects
- High risk to benefit ratio
- Focus is to understand the side effects associated with increasing doses
- If possible to gain early evidence on pharmacological effectiveness
- Looks at the pharmacological aspect of the drug(how it works in healthy volunteers
- Safety is a main concern/focus
- Phase 1 oncology trials are likely to enroll subjects who have failed standard therapy
- Placebos (inactive treatments) are not used in phase I trials.

Phase 2:

- The emphasis in Phase II is on effectiveness
- Purpose is to determine the right dosage and effectiveness in treating that particular disease
- This phase aims to obtain preliminary data on whether the drug works in people who have a certain disease or condition
- Enrolls hundreds of subjects
- Evaluates the effectiveness of the drug for a particular indication in patients with the disease or condition under study
- This phase can last several years
- Determine the common short-term side effects and risks associate with the drug
- Designed to assess the efficacy of the intervention

- Collects side effects data
- Focus is to determine if the intervention is more effective than standard alternatives
- There are many different ways that a trial sponsor can conduct their trial, but the plan normally involves assigning participants to different treatment groups, where each group can receive different doses or delivery of the treatment.
- Normally, there is a "control group" that receives either the current standard of care, if another type of treatment is already available on the market for that disease, or a "placebo" treatment, such as a sugar pill or harmless injection that does not contain the treatment.
- The health of the group(s) of patients who received the different types of treatment is compared to the control groups.

Phase 3:

- Primarily focuses on determining whether the treatment would be safe and effective for a wide variety of people
- The plan normally involves assigning participants to treatment or control groups. There can be more than one treatment group, especially if the treatment involves a combination of drugs or different components. Again, there is a control group that receives either the current standard of care regiment or a placebo treatment
- Gathers more information about safety and effectiveness, studying different populations and different dosages, using the drug in combination with other drugs.
- The number of subjects usually ranges from several hundred to about 3,000 people
- If the FDA agrees that the trial results are positive, it will approve the experimental drug or device
- Most include a large number of patients, at least several hundred
- Are often conducted in many places across the country (or even around the world) at the same time
- More likely to be offered in local community hospitals and doctor's offices
- Placebos may be used in some phase III studies, but they're never used alone if there's a treatment available that works. Sometimes, a patient who is randomly assigned to the placebo for part of the study will at some point be offered the standard treatment as well
- Patients are watched closely for side effects, and treatment may be terminated if severe

Phase 4:

- After approval by the FDA and manufacturing of the drug Clinical Trial/Post-Market Surveillance/Report Adverse Events
- To obtain further information about the risks, benefits, and long-term effects, or to test the product in special patient populations
- Most likely to use a drug registry
- Does not require an IND
- Detection of rare side effects
- Detection of side effects associated with chronic/long-term use of the drug
- FDA approved drugs are often watched over a long period of time
- These studies may involve thousands of people
- Often the safest type of clinical trial because the treatment has already been studied
- Assesses safety over time
- May also look at other aspects of the treatment, such as quality of life or cost effectiveness
- Help researchers learn more about the treatment
- Takes place after the FDA approval

- A device or drug's effectiveness and safety are monitored in large, diverse populations. Sometimes, the side effects of a drug may not become clear until more people have taken it over a longer period of time.

STUDY TYPES:
2 Broad categories of research studies:
- Observational
- Interventional

SINGLE-BLIND CLINICAL TRIAL:
Trial in which the subject, but not the observer, does not know which of the possible treatments he/she is receiving

DOUBLE-BLIND CLINICAL TRIAL:
Trial in which neither the subject nor the observer know which treatment is being administered

TRIPLE-BLIND CLINICAL TRIAL:
Clinical trial in which the participating subject, the observer-researcher and the researcher who analyzes the data do not know which treatment is being received

CROSSOVER CLINICAL TRIAL:
Clinical trial in which each individual consecutively receives each of the treatments under study

UNICENTER/SINGLE Site CLINICAL TRIAL:
A trial carried out by a single researcher or research team in one hospital or another type of center

MULTICENTER CLINICAL TRIAL:
A trial carried out in two or more centers with the same protocol

PARALLEL CLINICAL TRIAL:
Clinical trial in which each group of patients receives a single treatment simultaneously

COMMUNITY TRIAL:
Clinical trial in which the elements allocated randomly are communities or populations, instead of individuals

PILOT STUDY:
Initial application, on a small scale, of a study protocol. The aim of checking whether the design is appropriate, establishing its viability or obtaining information to determine the sample size for the definitive study

OBSERVATIONAL STUDY:
The researcher does not determine the allocation of the subjects to each group, but simply records/observes what actually happens

OBSERVATIONAL DESCRIPTIVE STUDY:

This is carried out when little is known about the occurrence, natural history or determinants of a disease. Its objectives include estimating the frequency of a disease or attribute, the temporal trend in a particular population and elaborating or generating more specific etiological hypotheses

OBSERVATIONAL ANALYTICAL STUDY:

An analytical (etiological) study is carried out when enough information is known about the disease before the research, which means that a prior hypotheses already exist and these can be tested in the study. The objectives usually involve identifying risk factors for the disease, estimating the effect of exposure on the disease and therefore deducing possible strategic interventions

EXPERIMENTAL STUDY:

In epidemiology, controlled clinical trial or community trial with random distribution. The researcher manipulates the research conditions and randomly distributes the groups. The objective of experimental studies is to estimate the efficacy of a preventive, curative or rehabilitative intervention. The use of another active treatment or intervention as a comparative group is to examine the benefit/risk relation of the new treatment in a specific clinical situation. The control group may be: Untreated and its evolution monitored, or treated by other means and its evolution compared with another intervention

CROSS-SECTIONAL STUDIES:

These are studies in which the data of each subject represents essentially a moment of time.
This data may correspond to the presence, absence or different degrees of a characteristic or disease.
It consists of examining the relationship between different variables in a defined population at a specific moment in time. These designs do not permit the study of an alleged cause-effect relationship.
Cross-sectional studies are descriptive by definition. Epidemiological strategy in which observations of numerous factors at the same time are recorded and then a comparison is made between them. The presence or absence of a disease or other variables (or, if they are quantitative, their level) are determined in each subject. The analysis of the results can be made in two senses: by comparing all the variables in the individuals who suffer from the disease being studied, comparing them with those who do not suffer from it, or by comparing the prevalence of the disease in different subgroups of the population

Many people will be familiar with this kind of study. The classic type of cross-sectional study is the survey: A representative group of people – usually a random sample – are interviewed or examined in order to find out their opinions or facts. Because this data is collected only once, cross-sectional studies are relatively quick and inexpensive. They can provide information on things like the prevalence of a particular disease (how common it is). But they can't tell us anything about the cause of a disease or what the best treatment might be.

Cross-sectional studies can answer questions such as these:

- How tall are German men and women at age 20?
- How many people have cancer screening?

LONGITUDINAL STUDIES:

These are studies in which there is a time lapse between the different variables, so that a time sequence can be established between them. They can be both descriptive and analytical

In analytical studies, it should be taken into account whether the time sequence is from the cause to the outcome (experimental studies and cohort studies), or from the outcome to the cause (case-control studies). Any study not focused on an alleged cause-effect relationship, but whose data is used for purely descriptive purposes is considered descriptive. This type of study is useful for generating etiological hypotheses which should subsequently be contrasted with analytical studies. Any study which evaluates an alleged cause-effect relationship is considered analytical. The alleged causal agent may be a factor which is suspected of being able to lead etiologically to a disease or a treatment to prevent or improve a clinical situation

FEASIBILITY STUDY:
Preliminary study with the objective of determining whether a program, procedure or study protocol is practicable, as well as finding out data to help in determining the sample size for a definitive study

CROSSOVER STUDY:
In clinical trials and in cohort studies, the moving of subjects from the group they were in at the beginning of the observation to another group. In both types of design, the crossover is the cause of an estimation of the possible differences between the groups compared

ANALYTICAL STUDY:
Study designed to examine associations, with the final object usually of identifying or measuring the effects of risk factors or specific interventions on health. Analytical studies can be controlled clinical trials, cohort studies, case-control studies or cross-sectional studies

PROSPECTIVE STUDY:
Study in which the patients are included from the time the start of the study is decided

RETROSPECTIVE STUDY:
Study in which the data collected refers to events which have occurred

CASE-CONTROL STUDY:
This type of study identifies people with a disease (or another variable of interest) and compares them with an appropriate control group which does not have the disease. An examination is made, comparing the frequency of exposure to this or other factors between the cases and the controls. It is an analytical observational study which enables the cause-effect relationship to be followed. If the frequency of exposure or the cause is greater in the group of cases with the disease than in the control group, we can say that there is an association between the cause and effect. The measurement of the association which quantifies this association is called the “odds ratio“(OR). In medicine, a case-control study is a cross-sectional type of study which is used to research the etiology of a disease or a given result. Study in which people with a certain disease or symptom (cases) are compared with others who do not present the disease or symptom under study (controls), with regard to prior exposure to risk factors. This has been incorrectly called Retrospective Study. In a case-control study, a single disease but various risk factors or exposures are examined

Case-control studies compare people who have a certain medical condition with people who do not have the medical condition, but who are otherwise as similar as possible, for example in terms of their sex and age. Then the two groups are interviewed, or their medical files are analyzed, to find anything that might be risk factors for the disease. So case-control studies are generally retrospective.

Case-control studies are one way to gain knowledge about rare diseases. They are also not as expensive or time-consuming as RCTs or cohort studies. But it is often difficult to tell which people are the most similar to each other and should therefore be compared with each other. Because the researchers usually ask about past events, they are dependent on the participants' memories. But the people they interview might no longer remember whether they were, for instance, exposed to certain risk factors in the past.

Still, case-control studies can help to investigate the causes of a specific disease, and answer questions like these:

- Do HPV infections increase the risk of cervical cancer?
- Is the risk of sudden infant death syndrome ("cot death") increased by parents smoking at home?

Case-control studies are types of "observational studies."

COHORT STUDY:

In the Roman militia, a centuria was made up of 60 soldiers. Two centurias formed a manipulo. The manipulos could be made up of hastate (young, less experienced soldiers, spear throwers or those with swords or light weapons), principes (soldiers with several years of service and several campaigns) or triarii (veterans). At camps and during marches, they formed cohorts, made up of one manipulo of hastatis, one manipulo of principes and one centuria of triarii, that is, a total of 300 soldiers. Epidemiology adopted this term to refer to the idea of a simultaneous advancement, in time, of a group of individuals defined for possessing a common characteristic or group of characteristics. The common characteristic is usually exposure to a factor (environmental, pharmacological, occupational, etc). The term "cohort" is used to designate a group of subjects with a common characteristic or group of characteristics who are monitored over a period of time. A large number of cases (300 or more) is necessary. It is an observational, analytical and longitudinal study in which two cohorts differing with regard to the exposure to the factor under study are compared in order to assess a possible cause-effect relationship. Study in which people subjected to a certain exposure or treatment are compared with people who are not subjected or exposed. The word "cohort" (from the Latin dehors) means a company of soldiers. There are prospective cohort studies and retrospective cohort studies; this is why the term is not synonymous with "Prospective study"

A cohort is a group of people who are observed frequently over a period of many years – for instance, to determine how often a certain disease occurs. In a cohort study, two (or more) groups that are exposed to different things are compared with each other: For example, one group might smoke while the other doesn't. Or one group may be exposed to a hazardous substance at work, while the comparison group isn't. The researchers then observe how the health of the people in both groups develops over the course of several years, whether they become ill, and how many of them pass away. Cohort studies often include people who are healthy at the start of the study. Cohort studies can have a prospective (forward-looking) design or a retrospective (backward-looking) design. In a prospective study, the result that the researchers are interested in (such as a specific illness) has not yet occurred by the time the study starts. But the outcomes that they want to measure and other possible influential factors can be precisely defined beforehand. In a retrospective study, the result (the illness) has already occurred before the study starts, and the researchers look at the patient's history to find risk factors.

Cohort studies are especially useful if you want to find out how common a medical condition is and which factors increase the risk of developing it. They can answer questions such as:

- How does high blood pressure affect heart health?
- Does smoking increase your risk of lung cancer?

For example, one famous long-term cohort study observed a group of 40,000 British doctors, many of whom smoked. It tracked how many doctors died over the years, and what they died of. The study showed that smoking caused a lot of deaths, and that people who smoked more were more likely to get ill and die.

Cohort studies are types of "observational studies."

RANDOMIZED CONTROLLED TRIAL: If you want to know how effective a treatment or diagnostic test is, randomized trials provide the most reliable answers. Because the effect of the treatment is often compared with "no treatment" (or a different treatment), they can also show what happens if you opt to not have the treatment or diagnostic test. When planning this type of study, a research question is stipulated first. This involves deciding what exactly should be tested and in what group of people. In order to be able to reliably assess how effective the treatment is, the following things also need to be determined before the study is started:

- How long the study should last
- How many participants are needed
- How the effect of the treatment should be measured

For instance, a medication used to treat menopause symptoms needs to be tested on a different group of people than a flu medicine. And a study on treatment for a stuffy nose may be much shorter than a study on a drug taken to prevent strokes. “Randomized” means divided into groups by chance. In RCTs participants are randomly assigned to one of two or more groups. Then one group receives the new drug A, for example, while the other group receives the conventional drug B or a placebo (dummy drug). Things like the appearance and taste of the drug and the placebo should be as similar as possible. Ideally, the assignment to the various groups is done "double blinded," meaning that neither the participants nor their doctors know who is in which group. The assignment to groups has to be random in order to make sure that only the effects of the medications are compared, and no other factors influence the results. If doctors decided themselves which patients should receive which treatment, they might – for instance – give the more promising drug to patients who have better chances of recovery. This would distort the results. Random allocation ensures that differences between the results of the two groups at the end of the study are actually due to the treatment and not something else.

Randomized controlled trials provide the best results when trying to find out if there is a cause-and-effect relationship. RCTs can answer questions such as these:

- Is the new drug A better than the standard treatment for medical condition X?
- Does regular physical activity speed up recovery after a slipped disk when compared to passive waiting?

QUALITATIVE STUDY: This type of study helps us understand, for instance, what it is like for people to live with a certain disease. Unlike other kinds of research, qualitative research does not rely on numbers and data. Instead, it is based on information collected by talking to people who have a particular medical condition and people close to them. Written documents and observations are used too. The information that is obtained is then analyzed and interpreted using a number of methods.

Qualitative studies can answer questions such as these:

- How do women experience a Cesarean section?
- What aspects of treatment are especially important to men who have prostate cancer?

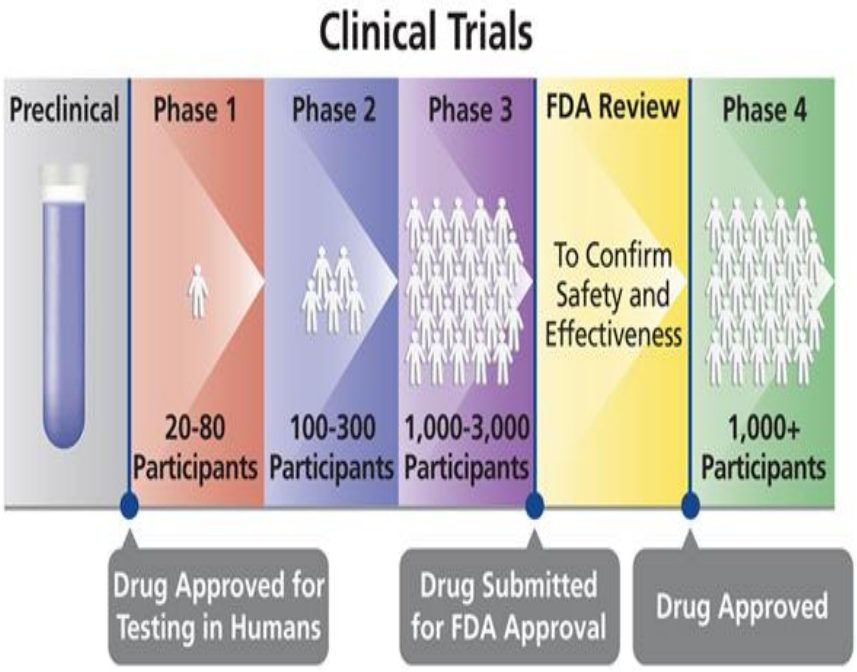
How reliable are the different types of studies?

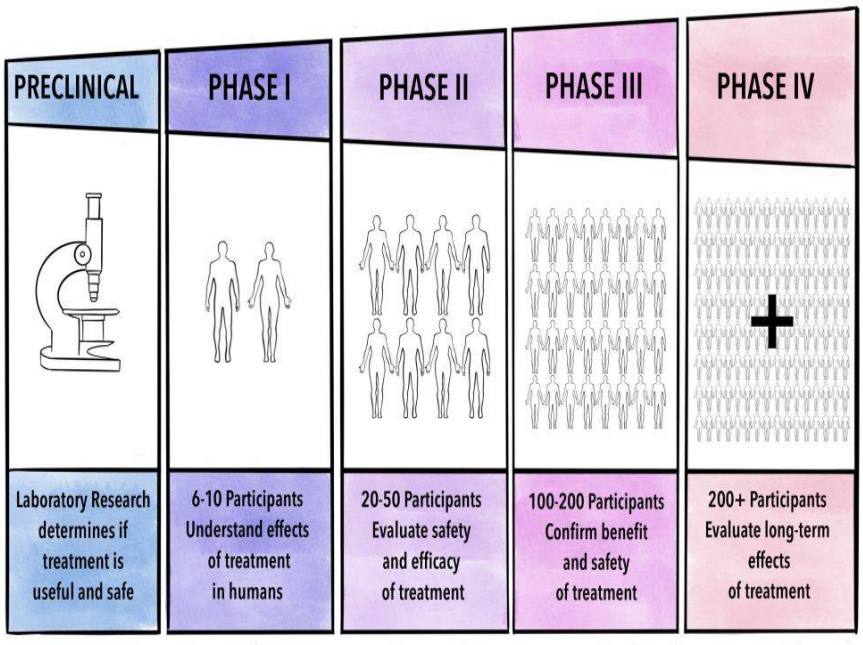
Each type of study has its advantages and disadvantages. It is always important to find out the following: Did the researchers select a study type that will actually allow them to find the answers they are looking for? You can't use a survey to find out what is causing a particular disease, for instance.

It is really only possible to draw reliable conclusions about cause and effect by using randomized controlled trials? Other types of studies usually only allow us to establish correlations (relationships where it isn't clear whether one thing is causing the other). For instance, data from a cohort study may show that people who eat more red meat develop bowel cancer more often than people who don't. This might suggest that eating red meat can increase your risk of getting bowel cancer. But people who eat a lot of red meat might also smoke more, drink more alcohol, or tend to be overweight. The influence of these and other possible risk factors can only be determined by comparing two equal-sized groups made up of randomly assigned participants.

That is why randomized controlled trials are usually the only suitable way to find out how effective a treatment is. Systematic reviews, which summarize multiple RCTs, are even better. In order to be good-quality, though, all studies and systematic reviews need to be designed properly and eliminate as many potential sources of error as possible.

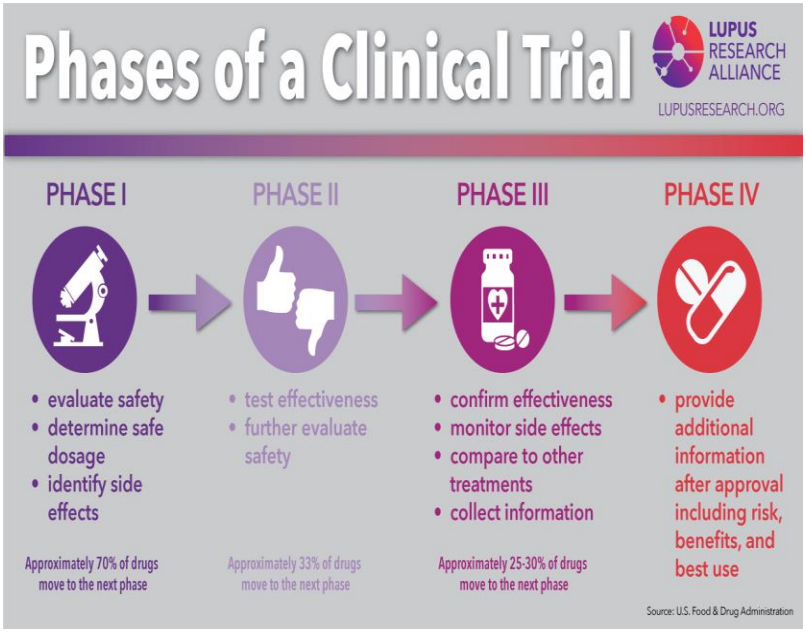
Abstracted from https://www.ncbi.nlm.nih.gov/books/NBK390304/


Clinical Trials
Preclinical
Phase 1
Phase 2
Phase 3
FDA Review
Phase 4
To Confirm Safety and Effectiveness
20-80 Participants
100-300 Participants
1,000-3,000 Participants
1,000+ Participants
Drug Approved for Testing in Humans
Drug Submitted for FDA Approval
Drug Approved


PRECLINICAL
PHASE I
PHASE II
PHASE III
PHASE IV
Laboratory Research determines if treatment is useful and safe
6-10 Participants Understand effects of treatment in humans
20-50 Participants Evaluate safety and efficacy of treatment
100-200 Participants Confirm benefit and safety of treatment
200+ Participants Evaluate long-term effects of treatment

Phases of a Clinical Trial

LUPUS RESEARCH ALLIANCE
LUPUSRESEARCH.ORG



Phases of Clinical Trials

Phase	Population	Study Design	Focus	Duration of treatment
0	1-15 people Aren't widely used	Sub-therapeutic dose	No safety or efficacy parameters	Single/micro dose Drug is given for a short time
1	Usually 20-80 healthy people Normal volunteers	Dose escalation to establish maximum tolerated dose	Safety and tolerability to determine the metabolism and pharmacologic actions	Short term, usually less than 30 days
2	200-300 volunteers with a targeted disease	Well-controlled, strict inclusion/exclusion criteria, most rigid study design, comparison between placebo and active controls	Comparison study, looking for effectiveness, efficacy, and safety (assess side effects) Determine the correct dose and effectiveness in treating a particular disease	Short term, usually less than 1 year, but can last several years
3	Several Hundred to several thousand	Eligibility is looser than Phase 2, multi-centered trials	Safety and efficacy, risk/benefit analysis, safety profiles Investigational vs placebo	Parallel, anticipated treatment Could last for years Often conducted in many places at the same time
4	All people on the treatment	Usually no study	Safety in large groups, patient satisfaction, additional safety data	Ongoing after FDA approval

Blinding and Randomization

Blinding

- Blinding or masking (the process of keeping the study group assignment hidden) is commonly used to reduce the risk of bias in clinical trials with two or more study groups
- the disguising of group distribution from one or more individuals involved in a clinical research study
- purpose: reduce the chance of bias
- maximizes the study result's validity
- keeping study participants, study team, and those collecting and analyzing clinical data unaware of the assigned treatment
- practice of keeping the name of the treatment hidden
- used to prevent conscious or unconscious bias in the design, conduct, and analysis of a clinical trial

Randomization

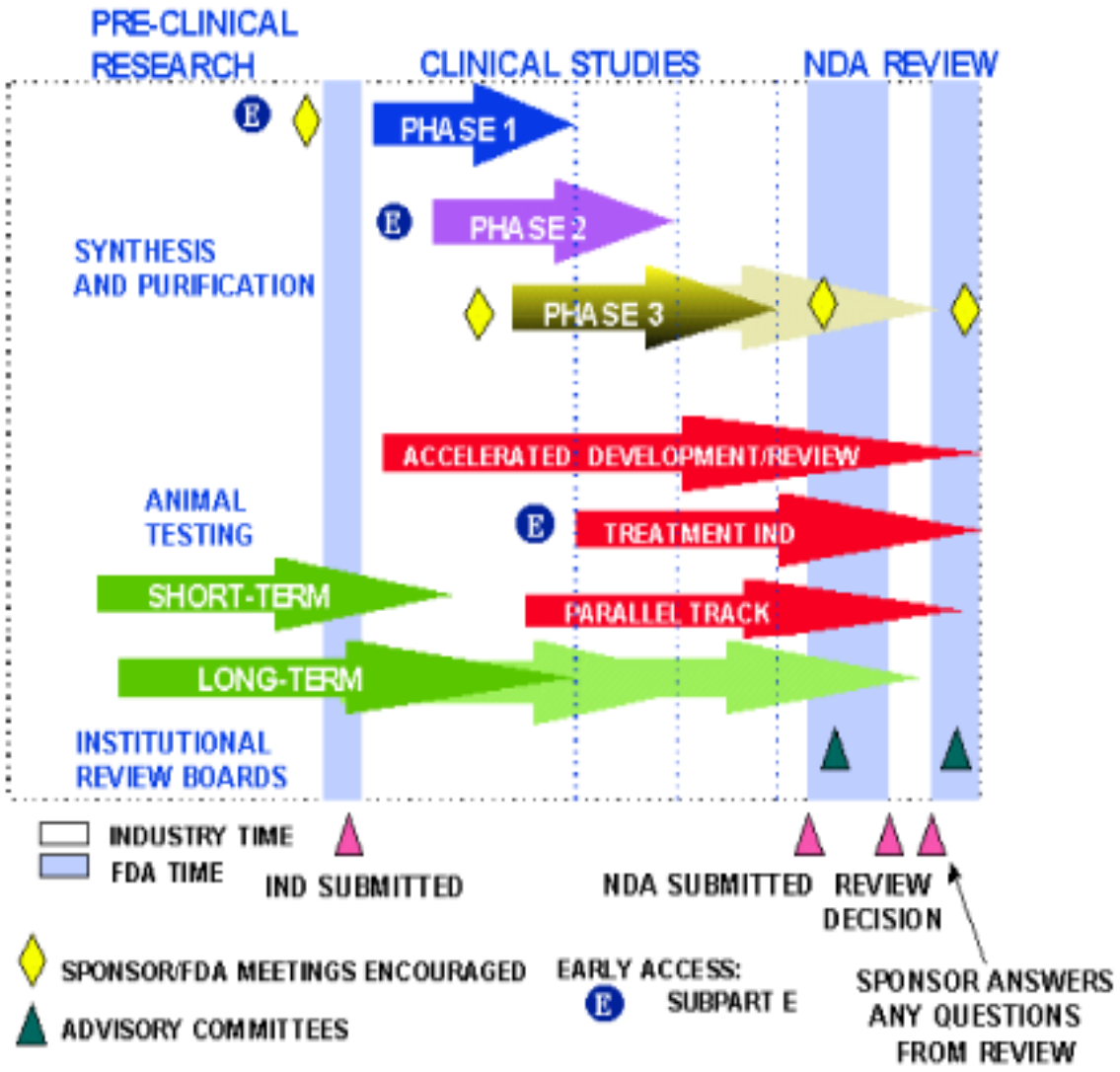
- process of assigning patients by chance to groups that receive different treatments
- helps prevent and reduce bias
- each participant has an equal chance of being assigned to any group

The parties involved in a clinical trial are all possible sources of bias, including:

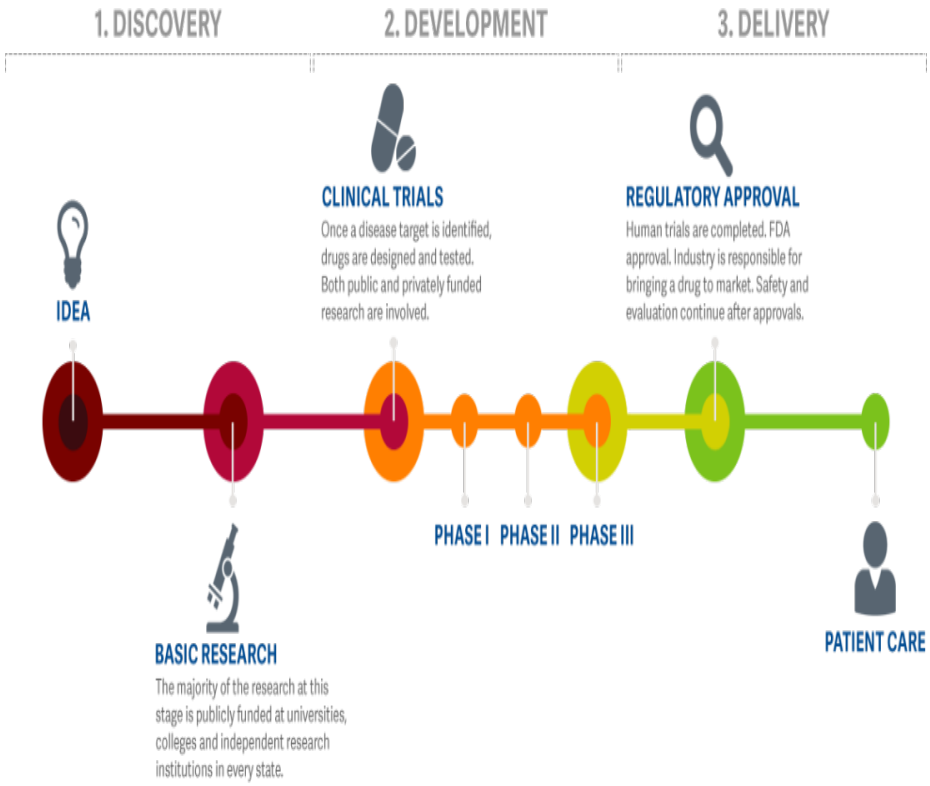
- The subject,
- The study team,
- The physician assessing the treatment,
- The team interpreting the results

All these parties can be blinded to ensure objectivity

https://www.dreamstime.com/illustration/drug-development.html



https://www.fda.gov/drugs/cder-small-business-industry-assistance-sbia/new-drug-development-and-review-process



https://www.gbs-cidp.org/support/resources/clinical-trials/

The Drug Research and Development Process

Discovery and origination of new compounds that become drug candidates	New compound efficacy and safety research	Confirmation of efficacy and safety in humans	Filing of new drug application with the Ministry of Health, Labour and Welfare (MHLW) and expert review	MHLW approval and listing in the National Health Insurance drug price list	Post-marketing check of safety and directions for use
1 Basic research 2-3 years	2 Non-clinical studies 3-5 years	3 Clinical studies 3-7 years	4 New drug application and review Approx. 1 year	5 Approval and launch	6 Post-marketing surveillance and clinical studies (Phase IV)

Phase I	Phase II	Phase III
Confirmation of safety, such as side effects, in a small number of healthy persons	Confirmation of effective, safe dosage and administration method in a small number of patients	Confirmation of efficacy and safety in comparison to existing medications in a large number of patients

Reference: "JPMA Guide," Japan Pharmaceutical Manufacturers Association

Historical Events and the Resulting Regulations/Guidance

1. The Elixir of Sulfanilamide Disaster → _____
2. Nuremburg Doctors Trial → _____
3. Thalidomide Tragedy → _____
4. Thalidomide Tragedy → _____
5. Tuskegee Experiment → _____
6. Penn's Gene Therapy → _____

_____A. Passed by Congress authorizing federal agencies to develop human research regulations (45 CFR 46, 21 CFRs). IRB's were established and a National Commission for Protection of Human Subjects was established. It required that all human subject research be reviewed by an IRB/IEC to ensure human subject protections

_____B. Signed into law by President Theodore Roosevelt. The law prohibited products being sold for indications outside its labeling. It also prohibited unlawful food and drugs from being transportation across states

_____C. Provided expert advice and recommendations to the Secretary of HHS on issues pertaining to the protection of human subjects in research

_____D. The study was conducted by the U.S. Public Health Service and involved 600 low-income African-American males. 400 of the males were infected with syphilis and were not told about their disease. They were then followed for 40 years. They were given free medical examinations, but were not treated for syphilis when a proven cure (penicillin) became available in the 1950s. The study continued until 1972 with participants being denied treatment. The study was stopped in 1973 by the U.S. Department of Health, Education, and Welfare. In 1997, under pressure, President Clinton apologized to the study subjects and their families

_____ E. manufacturer attempted to market a drug to children, but instead became a mass poisoning of children. The chief chemist liquefied the drug by dissolving it in the toxic compound diethylene glycol. The company was made to pay a minimal fine for mislabeling the compound as this was the only penalty to serve under the 1906 Federal Food and Drugs Act

_____ F. U.S. Congress passed the act to require proof of safety before the releasing new drugs

_____G. This guideline addresses justifications for a trial and protocol; protection of subjects; responsibilities of investigators, sponsors and monitors; assurance of data integrity and product accountability; and roles of regulatory authorities

_____ H. Doctors performed approximately 30 different experiments on concentration camp inmates. These were conducted without the consent of the inmates. They encountered extreme pain, disabilities and even death as a result of these studies. The experiments included studies/experiments involving the following: cold water, freezing, twins, treatment of wounds, poison, sterilization, bone transplantation, high altitude, air pressure, and exposure to chemical-warfare agents. These experiments were a total disregard for the human dignity

_____I. This office was elevated to the level of the US department of Health and Human services, replacing the NIH Office for Protection

_____J. This person was being treated for cervical cancer and tumor cells were taken from her without her knowledge. It was discovered that these cells could be kept alive in culture. Her cells would eventually become the HeLa immortal cell line. This cell line is currently and frequently utilized in biomedical research. These cells have been used to test the first polio vaccine, AIDS research, and cancer research, as well as, other scientific quests

signed into law by President Theodore Roosevelt. The law prohibited products being sold for indications outside its labeling. It also prohibited unlawful food and drugs from being transportation across states

_____ K. This document was published, based on the Presidentially commissioned work of MD Psychologists, Lawyers, and Biomedical and Behavioral Ethicists. This document proposed to go beyond "rules and regulations" and to proposed principles to use in judgments about protecting human subjects, (1) Respect for Persons, (2) Beneficence, and (3) Justice

_____ L. The Department of Health and Human Services (DHHS) and the Food and Drug Administration (FDA) issued regulations based on the Belmont Report. DHHS issued Code of Federal Regulations (CFR) Title 45 (public welfare), Part 46 (protection of human subjects). The FDA issued CFR Title 21 (food and drugs), Parts 50 (protection of human subjects) and 56 (Institutional Review Boards)

_____ M. Researchers infected mentally disabled children with hepatitis. Subjects were then observed to record the progression of the disease. The New York Department of Health approved this study. Consent was obtained from parents, but the procedures were presented as vaccinations. In addition, there is evidence that only children enrolled in the study were admitted to the school (coercion)

_____ N. Requirement of the NIH for all graduate students on training grants receive education on research training

_____ O. Trial in which neither the subject nor the observer know which treatment is being administered

_____ P. This was the first international document which advocated voluntary participation and informed consent. This document was a result of the Nuremberg Doctor's Trial. The Nuremberg Code stated "The voluntary consent of the human subject is absolutely essential," that the benefits of research must outweigh the risks. In 1946 the United Nations adopted the document and it has been translated into over 500 languages

_____ Q. Phase of a study that detects side effects associated with chronic/long-term use of the drug

_____ R. Set of ethics involving the protection of human subjects was adopted by 17 Federal agencies. The main elements of the Common Rule include: (1) requirements for assuring compliance by research institutions, (2) requirements for researchers obtaining and documenting informed consent, (3) requirements for Institutional Review Board (IRB) membership, function, operations, review of research, and record keeping, (4) additional protections for certain vulnerable research subjects-- pregnant women, prisoners, and children

_____ S. Preliminary study with the objective of determining whether a program, procedure or study protocol is practicable, as well as finding out data to help in determining the sample size for a definitive study

_____ T. This Act was passed into law to ensure drug efficacy and greater drug safety. For the first time, drug manufacturers were required to prove to FDA the effectiveness of their products before marketing them

_____ U. Type of study- Initial application, on a small scale, of a study protocol. The aim of checking whether the design is appropriate, establishing its viability or obtaining information to determine the sample size for the definitive study

_____ V. This system was launched by the FDA and was designed to collect health professionals' reports of adverse events involving medical products. When safety hazards are detected, the FDA issues medical product safety alerts or orders product recalls, withdrawals, or labeling changes to protect the public health

_____ W. A trial carried out in two or more centers with the same protocol

_____ X. governs international research ethics and defines rules for "research combined with clinical care" and "non-therapeutic research." The document is the basis for Good Clinical Practices used today. It addresses the following: (1) Research with humans should be based on the results from laboratory and animal experimentation, (2) Research protocols should be reviewed by an independent committee prior to initiation, (3) Informed consent from research participants is necessary,(4) Research should be conducted by medically/scientifically qualified individuals and (5) Risks should not exceed benefits

_____ Y. Clinical trial in which each group of patients receives a single treatment simultaneously

_____ Z. Designed to directly compare a study treatment to the usual treatment of the disease or condition, subjects are often randomly assigned to receive one of the 2or more treatments

_____ AA. A sedative was approved in Europe in the late 1950's, but was not approved in the United States by the FDA. This drug was prescribed to pregnant women to control sleep and nausea, but taking this drug during pregnancy caused severe deformities in the fetus. The issue was that many patients did not know they were taking a drug that was not approved by the FDA and did not give informed consent. Deformities due to thalidomide affected approximately 12,000 babies

_____ BB. The Phase of a study using only a few small doses of a new drug in a few people. Almost no chance the people in phase 0 trials will benefit

_____ CC. Requires all people conducting or overseeing human subjects research have some training in research ethics

_____ DD. Proposes mandatory training in responsible conduct of research for all researchers on PHS grants, including junior senior investigators, students, and technicians. Several scientific associations and universities oppose the policy as an unnecessary and un-funded mandate. The Bush Administration suspends the ORI proposal in 2001 on the grounds that the agency failed to follow proper procedures for proposing new government regulations. To ORI proposal is still in limbo

_____ EE. two (or more) groups that are exposed to different things are compared with each other in a study

_____ FF. The NIH and other agencies adopt the OSTP misconduct definition. The OSTP Policy defines "research misconduct" as "fabrication, falsification, or plagiarism in proposing, performing, or reviewing research, or in reporting research results". It also sets the legal threshold for proving charges of misconduct

_____ GG. Many European nations along with Japan and the United States began creating plans for global harmonization of regulatory requirements to reduce duplicate, time-consuming, and expensive procedures needed to market products internationally, while maintaining safeguards on quality, safety, and efficacy

_____ HH. Studies designed to look at efficacy and side effects

_____ II. The Office that announced proposed changes to the Common Rule to enhance human subject protections and reduce investigator burden

_____ JJ. Trial in which the subject, but not the observer, does not know which of the possible treatments he/she is receiving

_____ KK. Study in which the data collected refers to events which have occurred

_____ LL. The Act requires that patients be informed of how their protected health information will be stored and kept private when they participate in a research trial. President Bill Clinton signed this act into law in 1992, but the final rule did not go into effect until 1996

_____ MM. Primarily focuses on determining whether the treatment would be safe and effective for a wide variety of people

_____ NN. Gene Therapy Study at University of Pennsylvania) where an 18 years old dies while a participant in a human gene therapy experiment. He suffered from a rare x-linked genetic disease of the liver but did not suffer effects at the time he enrolled in a gene therapy study at a University to help others. He died four days after the research procedure. After his death, information revealed led his father to believe that he nor his family were fully informed and aware of the risks involved in the study. The University failed to report previous experienced serious side effects from participants, the informed consent did not divulge known deaths and University financial conflicts of interest in the trial. Additionally, he had a high ammonia levels that should have excluded him from participating in the study. This generated the need for a heightened scrutiny of conflicts of interest in human subjects research, including institutional conflicts of interest. The family settled for an undisclosed amount of money

_____ OO. Clinical trial in which each individual consecutively receives each of the treatments under study

_____ PP. Hospitals and health professionals were required to report safety incidents to the FDA and manufacturers regarding devices. The FDA under this act was able to recall devices and take other actions

_____ QQ. Performed to determine the best/highest/route for the dose and schedule of a new study treatment that can be given safely without causing severe side effects

_____ RR**.** These are studies in which there is a time lapse different between the variables, so that a time sequence can be established between them

_____ SS. Trials intended to determine the best dose and schedule of a study treatment. The focus of these trials is on understanding the side effects

Answer sheet for Matching

1. **1906 FDA Pure Food and Drug Act**
2. **1932-1972 The Tuskegee Syphilis Study**
3. **1937 Elixir Sulfanilamide Disaster**
4. **1938 Federal Food, Drug, and Cosmetic Act**
5. **Nazi Experiments**
6. **1947 The Nuremberg Code**
7. **1951 Henrietta Lacks**
8. **1956-1980 Willowbrook Experiments**
9. **1962 Kefauver-Harris Drug Amendment**
10. **1964 World Medical Association, Helsinki Declaration**
11. **1974 Congress passes the National Research Act**
12. **The Belmont Report 1979**
13. **1981 FDA Regulations Title 21**
14. **1989 Responsible Conduct of Research Training**
15. **1990 International Conference on Harmonization Guideline**
16. **1990 The Safe Medical Devices Act**
17. **1991 The Common Rule**
18. **1993 MedWatch**
19. **1996 HIPAA**
20. **1996 The World Health Organization Guidelines for Good Clinical Practice**
21. **Jessie Gelsinger**
22. **1999 The NIH and the OHRP**
23. **2000 ORI**
24. **2000 Office of Human Research Protections (OHRP)**
25. **2004 Secretary's Advisory Committee on Human research Protection (SACHRP)**
26. **2004 The NIH**
27. **2011 The Office of Human Research Protections**
28. **Open Clinical Trail**
29. **Single-blind Clinical Trial**
30. **Double-blind Clinical Trial**
31. **Crossover Clinical Trial**
32. **Multicenter Clinical Trial**
33. **Parallel Clinical Trial**
34. **Longitudinal descriptive studies**
35. **Experimental analytical studies**
36. **Pilot Study**
37. **Descriptive Study**
38. **Observational Study**
39. **Experimental Study**
40. **Cross-Sectional Study**
41. **Longitudinal Study**
42. **Feasibility Study**
43. **Analytical Study**
44. **Prospective Study**

Answer Sheet for Matching for Session 1 and 2

45. **Retrospective Study**
46. **Phase 0**
47. **1957-1961 Thalidomide**
48. **Phase 1**
49. **Phase 2**
50. **Phase 3**
51. **Phase 4**
52. **Case-Control Study**
53. **Cohort Study**

Session 2:

Ethics

Ethics:

- Moral principles that govern a person's behavior or how an activity is conducted
- The discipline dealing with what is good and bad, and with moral duty and obligation
- The basic concepts and fundamental principles of decent human conduct
- A system of moral principles
- Standards of right and wrong that prescribe what humans ought to do, usually in terms of rights, obligations, benefits to society, fairness, or specific virtues
- Provides guidelines for the responsible conduct of research
- Guides decision making
- Assists in dilemma resolution
- Based on a person's own values

The ethical principles involving research that researchers must adhere to are the principles of:

- **Justice, Beneficence, Non-maleficence, Accountability, Fidelity, and Autonomy**

The ethical principles aligned with doing a good job in any context should always be integrated when conducting research. Those principles include:

- **Honesty, Objectivity, Integrity, Carefulness, Openness, Credit, Responsibility, and Respect**

Ethical Obligations in Research

Adherence to responsible conduct of research (RCR) guidelines will help an investigator:

- Avoid departures from accepted ethical research practice and prevent the serious deviations that constitute research misconduct

Ethical Principles

Although codes, policies, and principles are very important and useful, like any set of rules, they do not cover every situation, they often conflict, and they require considerable interpretation. It is therefore important for researchers to learn how to interpret, assess, and apply various research rules and how to make decisions and to act ethically in various situations. The vast majority of decisions involve the straightforward application of ethical rules.

The following is a rough and general summary of some ethical principles that various codes address*:

Honesty

Strive for honesty in all scientific communications. Honestly report data, results, methods and procedures, and publication status. Do not fabricate, falsify, or misrepresent data. Do not deceive colleagues, research sponsors, or the public.

Objectivity

Strive to avoid bias in experimental design, data analysis, data interpretation, peer review, personnel decisions, grant writing, expert testimony, and other aspects of research where objectivity is expected or required. Avoid or minimize bias or self-deception. Disclose personal or financial interests that may affect research.

Integrity

Keep your promises and agreements; act with sincerity; strive for consistency of thought and action.

Carefulness

Avoid careless errors and negligence; carefully and critically examine your own work and the work of your peers. Keep good records of research activities, such as data collection, research design, and correspondence with agencies or journals.

Openness

Share data, results, ideas, tools, resources. Be open to criticism and new ideas.

Transparency

Disclose methods, materials, assumptions, analyses, and other information needed to evaluate your research.

Accountability

Take responsibility for your part in research and be prepared to give an account (i.e. an explanation or justification) of what you did on a research project and why.

Intellectual Property

Honor patents, copyrights, and other forms of intellectual property. Do not use unpublished data, methods, or results without permission. Give proper acknowledgement or credit for all contributions to research. Never plagiarize.

Responsible Publication

Publish in order to advance research and scholarship, not to advance just your own career. Avoid wasteful and duplicative publication.

Responsible Mentoring

Help to educate, mentor, and advise students. Promote their welfare and allow them to make their own decisions.

Respect for Colleagues

Respect your colleagues and treat them fairly.

Social Responsibility

Strive to promote social good and prevent or mitigate social harms through research, public education, and advocacy.

Competence

Maintain and improve your own professional competence and expertise through lifelong education and learning; take steps to promote competence in science as a whole.

Legality

Know and obey relevant laws and institutional and governmental policies.

Animal Care

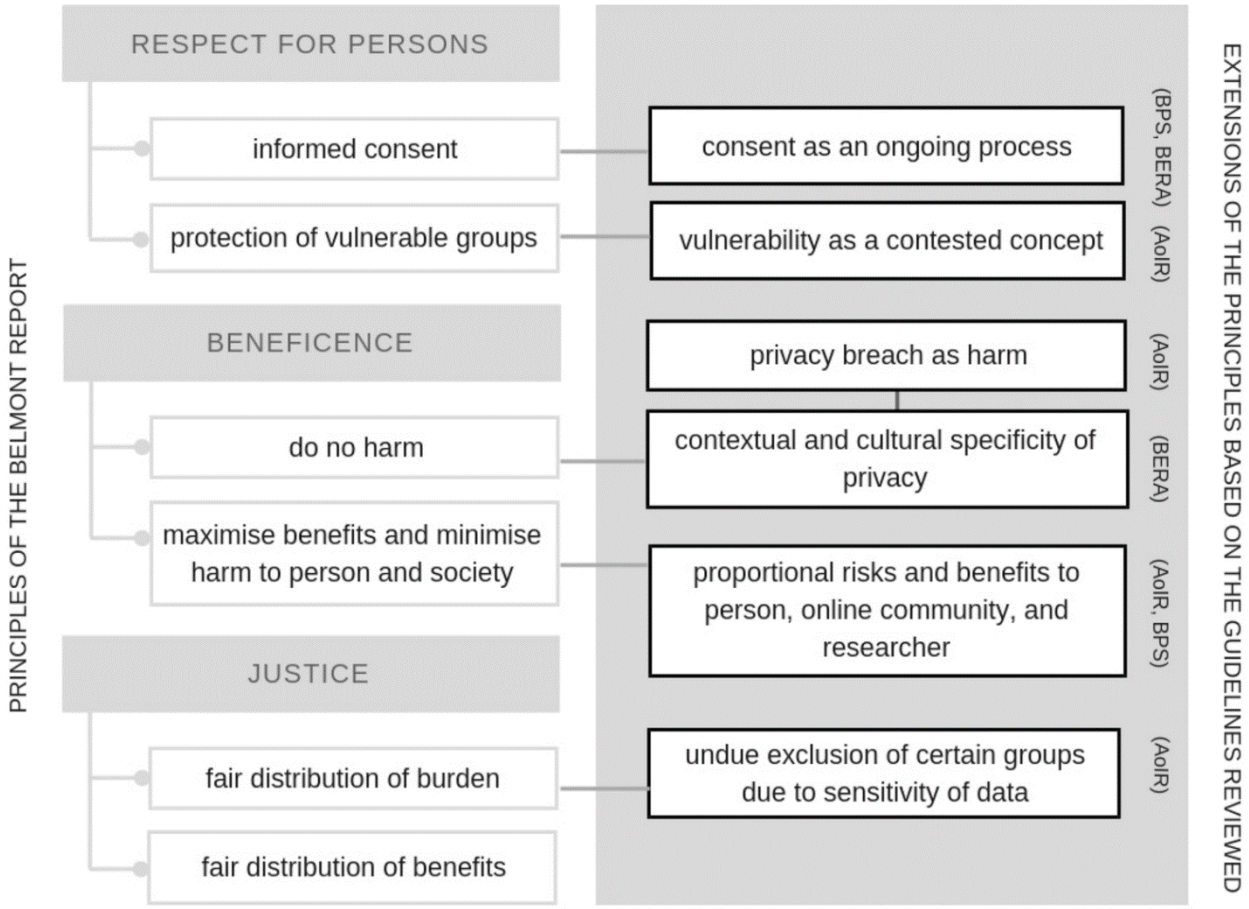
Show proper respect and care for animals when using them in research. Do not conduct unnecessary or poorly designed animal experiments.

Human Subjects Protection

When conducting research on human subjects, minimize harms and risks and maximize benefits; respect human dignity, privacy, and autonomy; take special precautions with vulnerable populations; and strive to distribute the benefits and burdens of research fairly.

The above was taken verbatim from https://www.niehs.nih.gov/research/resources/bioethics/whatis/index.cfm and was adapted from Shamoo A and Resnik D. 2015.Responsible Conduct of research, 3rd ed. (New York: Oxford: Oxford University Press).

Belmont Report



https://link.springer.com/article/10.1007/s10676-018-9495-z/figures/1

Declaration of Helsinki: Basic Principles

1. Conform to accepted scientific principles
2. Design formulated in experimental protocol, reviewed by IEC
3. Conducted by qualified and trained persons
4. Importance in proportion to inherent risk.
5. Assessment of risks vs. benefits
6. Safeguard subject's integrity (privacy)
7. Abstain unless hazards are predictable.
8. Preserve accuracy when publishing
9. Adequately inform or right to withdraw
10. Obtain true informed consent in writing
11. Reliance on legal guardian.
12. State compliance with Declaration

https://research.ucdavis.edu/wp-content/uploads/Declaration-of-Helsinki.pdf

The 10 Points of the Nuremberg Code

1. Participation must be voluntary, and subjects should have the capacity to give consent. Further, subjects should be fully informed of the purposes, nature, and duration of the experiment.
2. The research should yield results that are useful to society and that cannot be obtained in any other way.
3. The research should have a sound footing in animal research and be based on the natural history of the problem under study.
4. Steps should be taken in the research to avoid unnecessary physical or psychological harm to the subjects.
5. Research should not be conducted if there is reason to believe that death or disability will occur in the subjects.

The 10 Points of the Nuremberg Code

6. The risk involved in the research should be proportional to the benefits to be obtained.
7. Proper plans should be made and facilities provided to protect the subject from harm.
8. Research should be conducted by highly qualified scientists only.
9. The subject should have the freedom to withdraw at any time if he or she has reached the conclusion that continuing in the experiment is not possible.
10. The researcher must be prepared to discontinue the experiment if it becomes evident that continuing will be harmful to the subject.

The following provides the basis for the ethical principles for Human Subject Protection:

A. Belmont Report
B. Declaration of Helsinki
C. Nuremburg Code

The following addressed the need for Informed Consent:

A. Belmont Report
B. Declaration of Helsinki
C. Nuremburg Code

The ethical principles of the Belmont Report include which of the following? (Choose all that apply)

A. Respect
B. Knowledge
C. Beneficence
D. Protection
E. Justice

Which of the statements do not stand for justice?

A. Fairness in distribution
B. What is deserved
C. Each person receives a particular share according to merit

“Individuals should be treated as autonomous agents, and second, that persons with diminished autonomy are entitles to protection” is which of the basic ethical principles from the Belmont Report?

A. Respect
B. Knowledge
C. Beneficence
D. Protection
E. Justice

The experiment should be conducted only by scientifically qualified persons. The highest degree of skill and care should be required through all stages of the experiment of those who conduct or engage in the experiment.

A. Belmont Report
B. Declaration of Helsinki
C. Nuremburg Code

“The health of my patient will be my first consideration,” and the International Code of Medical Ethics declares that, “A physician shall act in the patient’s best interest when providing medical care.”. These statements are from which document?

D. Belmont Report
E. Declaration of Helsinki

F. Nuremburg Code

Two general rules of the Belmont Report have been formulated as complementary expressions of _____ actions. (1) do not harm and (2) maximize possible benefits and minimize possible harms.

A. Respect
B. Knowledge
C. Beneficence
D. Protection
E. Justice

According to this document, humane experimentation is justified only if its results benefit society and it is carried out in accord with basic principles that "satisfy moral, ethical, and legal concepts."

A. Belmont Report
B. Declaration of Helsinki
C. Nuremburg Code

Who ought to receive the benefits of research and bear its burdens/ This is a question of _____, in the sense of fairness in distribution or what is deserved."

A. Respect
B. Knowledge
C. Beneficence
D. Protection
E. Justice

What does respecting autonomy look like?

A. Asking other to make decisions for oneself
B. Using coercion to assist one in making a decision
C. Giving one merit to their opinions and choices

Medical research should be conducted in a manner that minimizes possible harm to the environment. This statement is from which document?

D. Belmont Report
E. Declaration of Helsinki
F. Nuremburg Code

The major themes of the Nuremburg Code were which of the following?

A. Voluntary consent, risk vs benefit, and research should be conducted by qualified staff
B. Voluntary consent, adequate knowledge, and research should be conducted by qualified staff
C. Voluntary consent, adequate knowledge, and justice

What beneficent actions are in the Belmont report?

A. Do no harm
B. Maximize benefits and harm
C. Minimize possible harms
D. Maximize benefits
E. A, B, C
F. A, C, D
G. All of the above

Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research. These statements are from which document?

A. Belmont Report
B. Declaration of Helsinki
C. Nuremburg Code

The commission that formulated the Belmont Report was created as part of the

A. National Research Act of 1974
B. National Researchers Act of 1974
C. National Research Act of 1975

The Declaration of Helsinki was written in what year?

A. 1965
B. 1964
C. 1963

The experiment should be so designed and based on the results of animal experimentation and a knowledge of the natural history of the disease or other problem under study that the anticipated results will justify the performance of the experiment.

A. Belmont Report
B. Declaration of Helsinki
C. Nuremburg Code

The Belmont Report addresses the difference between:

A. Risk/benefit ratio
B. Medical practice and research
C. Adequate knowledge and being uninformed

The experiment should be so designed and based on the results of animal experimentation and a knowledge of the natural history of the disease or other problem under study that the anticipated results will justify the performance of the experiment.

A. Belmont Report
B. Declaration of Helsinki
C. Nuremburg Code

Who is not an autonomous person?

A. One who is not capable of making their own decisions
B. One who makes their own decisions rather than being influenced by someone else
C. One who is self-governing
D. One who ha moral independence

What date was the Belmont report created:

A. 1976
B. 1978
C. 1979
D. 1980

The Declaration of Helsinki was formulated by the

A. World Health Association
B. World Medicine Association
C. World Medical Association

When assessing payments to subjects the ethical principles of the Belmont Report to consider would be:

A. Respect
B. Knowledge
C. Beneficence
D. Protection
E. Justice

The _____ advises treatment drug with comparator control whenever possible.

A. Belmont Report
B. Declaration of Helsinki
C. Nuremburg Code

Which action would show lack of respect for autonomy?

A. Repudiate a person's decision
B. Withhold information to make an informed decision
C. A and B
D. None of the above

In most cases of research involving human subjects, _____ demands that subjects enter into research voluntarily and with adequate information.

A. respect for persons
B. adequate Knowledge demonstrated by the study team
C. benefits over risk
D. protection of rights
E. justice

The major themes of the declaration of Helsinki included which of the following:

A. Physicians have a duty to protect subjects
B. Individuals take precedence over the interest of science
C. Research should be summarized in a protocol
D. Physicians should be aware of ethical, legal and regulatory requirements of research
E. A, B, and C
F. A, C, and D
G. All of the above

In what year was the Nuremburg Code written?

A. 1947
B. 1948
C. 1949

When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship. These statements are from which document?

A. Belmont Report
B. Declaration of Helsinki
C. Nuremburg Code

The _____ is the ethical framework cited in the ICH GCPs for conducting clinical trials.

A. Belmont Report
B. Declaration of Helsinki
C. Nuremburg Code

Misconduct

Types of Misconduct

- Research misconduct (falsification, omission, or fabrication of data, plagiarism)
- Misrepresenting research data
- Collaboration issues (authorship, ownership of data)
- Conflict of interest
- Involved in ethic violations through the wrong actions of other
- Confusion between research and routine care
- Coercion/undue influence
- Lack of data integrity

*** Honest mistakes/errors are not considered research misconduct ***

Taken from Office of Research Integrity:

Research misconduct means fabrication, falsification, or plagiarism in proposing, performing, or reviewing research, or in reporting research results

(a) **Fabrication** is making up data or results and recording or reporting them

(b) **Falsification** is manipulating research materials, equipment, or processes, or changing or omitting data or results such that the research is not accurately represented in the research record

(c) **Plagiarism** is the appropriation of another person's ideas, processes, results, or words without giving appropriate credit

(d) Research misconduct **does not include honest error or differences of opinion**

https://ori.hhs.gov/definition-research-misconduct

Ethics/Misconduct

The ethical principles involving research that researchers must adhere to are the principles of:

- **Justice, Beneficence, Non-maleficence, Accountability, Fidelity, and Autonomy**

The ethical principles aligned with doing a good job in any context should always be integrated when conducting research. Those principles include:

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Types of Misconduct

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- Coercion/undue influence
- Lack of data integrity

*** Honest mistakes/errors are not considered research misconduct ***

For discussion during the session if time allows

Subject Payment

Scenario: A 34 y/o female with low economic status is approached to participate in a Phase 1 drug study that offers a large amount of compensation. This potential participant could happily use the money to supplement her household expenses, such as groceries for her 2 children.

She has a history of some negative reaction to medications, none that have required intervention outside of stopping the drug. The study design includes 50% of the total payment ($600) until the last day of the 4 day treatment. Day 1-3 payment is $100 each day. Day 4- $300 payment.

- Are there undue Influences/Inducements to participate?
- Are the payment arrangements ethical?
- Effective informed consent vs coercion to participate due to payment?
- Retention method?
- How much remuneration is the right amount?

Randomization and Benefits

Scenario: A subject is participating in a oncology clinical trial. The clinical trial is a randomized, double-blinded, placebo-controlled study of an investigational oncology drug. Participation is to last two years.

After 6 months, one subject is not experiencing any signs of improvement and may be getting worse.

The subject asks the PI if he is in the treatment or placebo arm. He is requesting to be taken out of the trial if he is in the placebo arm. The PI believes the subject is in the placebo arm.

- What are the ethical dilemmas?
- What should the PI do?
- What would you do?

Assessment of Cognitive Abilities

Scenario: 27 y/o male patient who a PI indicates should be enrolled on a study. The PI assesses the potential subject as being able to consent for himself because his records show him to be an adult without the need of guardianship or a legal authorized representative.

The subject usually has his grandmother, whom he lives with, present for all appointments however, she is not present with him at this visit.

The coordinator assesses the cognitive ability of the potential subject and does not believe he has the appropriate understanding of the study to sign informed consent on his own behalf.

- Are the legal guidelines being met?
- Are the ethical concerns of the coordinator relevant?
- What courses of action should be taken?

Informed Consent

Scenario: A family is being approached to consent their 13 y/o child (age of assent) to a research study with no direct benefit to the patient. The study involves a few blood draws and an hour long MRI.

The patient is fluent in English and the parents seem to understand the majority of what is spoken; however, their native language is Spanish. On record they have refused the option to use an interpreter for standard-of-care medical issues. The PI, who is also the specialist caring for their son, is aware of this. The PI gives an abbreviated version of the study and explains the consent form and directs the coordinator to consent the subject and parents. The coordinator is present for the consent and feels that the parents are not understanding some of the details.

The parents agree to consent their child to the study. The patient does not want to participate, as he has had an MRI before which made him very upset and anxious and does not want to undergo multiple needlesticks.

- What are the factual concerns/have any policies been violated?
- How much weight should assent be given?
- What would you do?

Assessment of Cognitive Abilities

Scenario: The subject presents for visit 1 (day of enrollment) and you suspect he may have smoked some marijuana before presenting to the visit. He is alert and is comprehending the information regarding the study. He is able to answer questions appropriately and is able to describe in his own words what the study is about and study procedures that will be required during participation.

- What are the ethical dilemmas?
- What should the PI do?
- What would you do?

Session 3:

Regulations and Guidance

General Definitions for 45 CFR 46

Certification

Clinical trial

Human subject

Private information

Identifiable private information

Identifiable biospecimen

Intervention

Interaction

LAR

Minimal risk

Research

Minimal risk

General Definitions for 21 CFR 50

Clinical Investigation

Investigator

Sponsor

Sponsor Investigator

Human Subject

Test article

Minimal Risk

Definitions for Vulnerable Populations

Fetus

Neonate

Nonviable Neonate

Prisoner

Children

Assent

Permission

Parent

Guardian

Ward

Advocate

Vulnerable Subjects Worksheet

45 CFR 46, Subparts B, C, and D

45 CFR 46 Subpart B

Additional protections for pregnant women, fetuses and neonates

Pregnant women or fetuses may be involved in research when…

TURE or FASE

___Preclinical studies have been conducted and provide data for assessment potential risks

___Risks to the fetus are not greater than minimal and important medical knowledge can be obtained

___Risks to the fetus are caused by interventions that hold no prospect of benefit for the fetus or the woman

___The research holds out a benefit solely for the fetus and the investigator obtains consent from the pregnant woman only

___Individuals involved in the research provide an inducement to terminate a pregnancy but are not involved in determining viability of the neonate.

Neonates of uncertain viability or nonviable neonates may be involved in research if …

TRUE of FALSE

___Preclinical studies have been conducted and provide data for assessment risks

___Investigators have no part in determining the viability of the neonate

___The IRB determines that there is a prospect of improving the probability of survival of the neonate and that risk is minimized as much as possible

___Effective informed consent of both parents of a neonate with uncertain viability is obtained

___Nonviable neonates have vital functions artificially maintained

___There is a situation where neither parent is available, is incompetent or incapacitated, then effective informed consent of the LAR (of one or both parents) will suffice to involve a nonviable neonate in the research

45 CFR 46 Subpart C

Additional Protections for Prisoners in Research

List at least 2 additional requirements for the composition of the IRB and at least 4 additional requirements that must be satisfied by the IRB in order to review and approve research involving prisoners?

Biomedical or behavior research conducted or supported by DHHS may involve prisoners if…

TRUE or FALSE

___The institution certifies to the Secretary that the IRB has complied with all requirements under 45 CFR 46.304 and 305 for review and approval of research involving prisoners

___The research investigates the possible causes, effects and processes of incarceration or criminal behavior

___Research involving a reasonable probability of improving health or well being of prisoner subjects and requiring the assignment of prisoners to a control group who will not benefit from participation, must be reviewed by the Director of the FDA

45 CFR 46 Subpart D

Additional Protections for Children

List the regulatory risk categories that must be considered by the IRB when reviewing research that involves children.

Compare 45 CFR 46 Subpart D with 21 CFR 50 Subpart D

Biomedical or behavioral research conducted or supported by DHHS may involve children if…

TRUE or FALSE

___The sponsor determines whether and how assent must be documented

___Assent is a child's passive resignation to submit to a research intervention

___Parental permission must be obtained from both parents for research falling in the categories of .406 and .407 subsections of 45 CFR 46 Subpart D

___Wards of the State can be included in research approved under 45 CFR 46.406 or 407 only if the research is related to their status as wards or conducted in settings where the majority of children involved are not wards

Session 4

International Conference on Harmonization/ Good Clinical Practice

E6(R2) Good Clinical Practice: Integrated Addendum to ICH E6(R1)

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

March 2018
Procedural

OMB Control No. 0910-0843 Expiration Date 09/30/2020
See additional PRA statement in section 9 of this guidance.

GCP - 13 Principles

- **Ethics**
  Clinical trials should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with GCP and the applicable regulatory requirement(s).

- **Trial risk vs trial benefit**
  Before a trial is initiated, foreseeable risks and inconveniences should be weighed against the anticipated benefit for the individual trial subject and society. A trial should be initiated and continued only if the anticipated benefits justify the risks.

- **Trial participants**
  The rights, safety, and well-being of the trial subjects are the most important considerations and should prevail over interests of science and society.

- **Information on the Medicinal Product**
  The available non-clinical and clinical information on an Investigational Product should be adequate to support the proposed clinical trial.

- **Good quality trials**
  Clinical trials should be scientifically sound, and described in a clear, detailed protocol.

- **Compliance with the study protocol**
  A trial should be conducted in compliance with the protocol that has received prior institutional review board (IRB)/independent ethics committee (IEC) approval/favourable opinion.

- **Medical decisions**
  The medical care given to, and medical decisions made on behalf of, subjects should always be the responsibility of a qualified physician or, when appropriate, of a qualified dentist.

- **Trial staff**
  Each individual involved in conducting a trial should be qualified by education, training, and experience to perform his or her respective task(s).

- **Informed consent**
  Freely given informed consent should be obtained from every subject prior to clinical trial participation.

- **Clinical trial data**
  All clinical trial information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation and verification.

- **Confidentiality**
  The confidentiality of records that could identify subjects should be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).

- **Good Manufacturing Practice**
  Investigational products should be manufactured, handled, and stored in accordance with applicable good manufacturing practice (GMP). They should be used in accordance with the approved protocol.

- **Quality assurance**
  Systems with procedures that assure the quality of every aspect of the trial should be implemented.

ICH GCP E6 (R2) Worksheet

Section 1.0: Glossary

Please be familiar with all terms in the glossary

An _____ _____is a systematic and independent examination of trial-related activities and documents to determine whether the evaluated trial-related activities were conducted, and the data was recorded, analyzed, and accurately reported according to the protocol, sponsor's SOPs, good clinical practice, and the applicable regulatory requirements

_____ is the act of overseeing the progress of a clinical trial, and of ensuring that it is conducted, recorded, and reported in accordance with the protocol, SOPs, GCP, and the applicable regulatory requirements

A _____unique identifier assigned by the investigator to each trial subject to protect the subject's identity

_____ ____All those planned and systematic actions that are established to ensure that the trial is performed and the data is generated, documented (recorded), an reported in compliance with GCP and applicable regulatory requirements

The operational techniques and activities undertaken to verify that the requirements for the quality of the trial-related activities have been fulfilled is called _____ _____

___ _____ All information in original records and certifies copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with the treatment is known as an _____ _____

Documents that individually and collectively permit evaluation of the conduct of a study and the quality of the data produced are called _____ _____

_____A document that describes the objective(s), design, methodology, statistical considerations, and organization of the trial

A _____ _____ _____is an individual or juridical or other body authorized under applicable law to consent, on behalf of a prospective subject, to the subject's participation in the clinical trial

Detailed, written instructions to achieve uniformity of the performance of a specific function are known as _____ _____ _____

_____is the process of assigning trial subjects to treatment or control groups using an element of chance to determine the assignments in order to reduce bias

The physical and mental integrity of the subjects participating in a clinical trial is known as the ___ _____of trial subjects

Section 2.0: The Principles of ICH GCP

Clinical trials should be conducted in accordance with the ethical principles that have their origin in the _____, and are consistent with GCP and the applicable regulatory requirements

A trial should be initiated and continues only if the _____

The rights, safety, and well-being of the trial subjects are the most important considerations and should prevail over _____

The available _____ and _____ ____ information on an investigational product should be adequate to support the proposed clinical trial.

Clinical trials should be scientifically sound, and described in a clear,_____

A trial should be conducted in compliance with the _____ that has received prior IRB/IEC approval/favorable opinion

The medical care given to, and the medical decisions made on behalf of, subjects should always be the responsibility of a _____ _____or, when appropriate, of a qualified _____

Each individual involved in conducting a trial should be qualified by _____, _____ and _____ ___ to perform his or her respective task

Freely given informed consent should be obtained from every subject _____to clinical trial participation

All clinical trial information should be recorded, handled, and stored in a way that _____ its accurate reporting, interpretation, and verification

The confidentiality of records that could identify subjects should be _____, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirements

Investigational products should be manufactured, handled, and stored in accordance with applicable _____. They should be used in accordance with the approved _____

Systems with_____ that assure the_____of every aspect of the trial should be implemented

Section 3.0: Institutional Review Board/Independent Ethics Committee

An IRB/IEC should safeguard the rights, safety, and well-being of all trial subjects. Special attention should be paid to trials that may include_____

The IRB/IEC should consider the qualifications of the investigator for the proposed trial, as documented by a _____the IRB/IEC requests

The IRB/IEC should ensure that information regarding payment to subjects, _____, is set forth in the written informed consent form and any other written information to be provided to subjects. The way payment will be _____should be specified

The IRB/IEC should consist of a reasonable number of members, who collectively have the qualifications and experience to review and evaluate the science, medical aspects, and ethics of the proposed trial. It is recommended that the IRB/IEC should include:

(a) At least _____ members

(b) At least one member whose primary area of interest is in a _____ area

(c) At least one member who is independent of the _____

Only those IRB/IEC members who are independent of the investigator and the sponsor of the trial should _____ on a trial-related matter

The IRB/IEC should retain all relevant records (e.g., written procedures, membership lists, lists of occupations/affiliations of members, submitted documents, minutes of meetings, and correspondence) for a period of at least _____ years after completion of the trial and make them available upon request from the regulatory authority(ies)

Section 4.0: Investigator

Section 5.0: Sponsor

During_____, the sponsor should identify those processes and data that are critical to ensure human subject protection and the reliability of trial results

The sponsor should decide which risks to reduce and/or which risks to accept. The approach used to reduce risk to an _____should be proportionate to the _____of the risk

The sponsor should periodically review _____ to ascertain whether the implemented quality management activities remain effective and relevant, taking into account emerging knowledge and experience

The sponsor is responsible for implementing and maintaining quality assurance and quality control systems with _____ to ensure that trials are conducted and data are generated, documented (recorded), and reported in compliance with the _____

Agreements, made by the sponsor with the investigator/institution and any other parties involved with the clinical trial, should be in _____, as part of the protocol or in a separate agreement

A sponsor may transfer any or all of the sponsor's trial-related duties and functions to a _____, but the ultimate responsibility for the quality and integrity of the trial data always resides with the _____

Any trial-related duties and functions not specifically transferred to and assumed by a CRO are retained by the _____

If data are transformed during processing, it should always be possible to compare the _____ and observations with the _____

The sponsor specific essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period however if required by the _____

The sponsor should inform the investigator(s)/institution(s) in writing of the need for record retention and should notify the investigator(s)/institution(s) in writing when the trial related records are _____

Before entering an agreement with an investigator/institution to conduct a trial, the sponsor should provide the investigator(s)/institution(s) with the _____and an up-to-date _____ _____, and should provide sufficient time for the investigator/institution to review the protocol and the information provided

The sponsor should obtain the investigator's/institution's agreement:

(a) to conduct the trial in _____, with the applicable regulatory requirement(s) (see 4.1.3), and with the protocol agreed to by the sponsor and given approval/favorable opinion by the IRB/IEC (see 4.5.1);

(b) to comply with procedures for _____;

(c) to permit _____ (see 4.1.4) and

(d) to retain the trial related essential documents until _____(see 4.9.4 and 5.5.12)

The sponsor and the investigator/institution should sign _____, to confirm this agreement.

The sponsor should determine, for the _____(s), acceptable storage temperatures, storage conditions (e.g. protection from light), storage times, reconstitution fluids and procedures, and devices for product infusion, if any. The sponsor should inform _____ (e.g. monitors, investigators, pharmacists, storage managers) of these determinations.

The sponsor should not supply an investigator/institution with the investigational product(s) until the sponsor obtains _____ (e.g. approval/favorable opinion from IRB/IEC and regulatory authority(ies)).

Section 6.0: Clinical Trial Protocol and Protocol Amendment(s)

Know the information that should be included in a study protocol

Section 7.0: Investigator's Brochure

The Investigator's Brochure (IB) is a compilation of the _____ data on the investigational product(s) that are relevant to the study of the product(s) in human subjects.

Its purpose is to provide the investigators and others involved in the trial with the information to facilitate their understanding of the rationale for, and their compliance with, many key features of the

protocol, such as the dose, dose frequency/interval, methods of administration: and safety monitoring procedures.

The IB also provides insight to support the clinical management of the study subjects _____ the course of the clinical trial.

The information should be presented in a concise, simple, objective, balanced, and non-promotional form that enables a clinician, or potential investigator, to _____ it and make his/her own unbiased risk-benefit assessment of the appropriateness of the proposed trial.

For this reason, a _____ should generally participate in the editing of an IB, but the contents of the IB should be approved by the disciplines that generated the described data.

Section 8.0: Essential Documents for the Conduct of a Clinical Trial

These are discussed in the additional worksheet for this section

ICH GCP Guidelines
Section 4.0 Investigator

4.1 Investigator's Qualifications and Agreements

Guideline	Description	How is this documented to show compliance?
4.1.1	The investigator should be qualified by education, training, and experience to assume responsibility for the proper conduct of the trial, should meet all the qualifications specified by the applicable regulatory requirements and should provide evidence of such qualifications through up to date curriculum vitae and/or other relevant documentation requested by the sponsor/the IRB/IEC, and/or the regulatory authorities	
4.1.2	The investigator should be thoroughly familiar with the appropriate use of the investigational product(s), as described in the protocol, in the current Investigator's Brochure, in the product information and in other information sources provided by the sponsor.	
4.1.3	The investigator should be aware of, and should comply with, GCP and the applicable regulatory requirements.	
4.1.4	The investigator/institution should permit monitoring and auditing by the sponsor, and inspection by the appropriate regulatory authority(ies).	
4.1.5	The investigator should maintain a list of appropriately qualified persons to whom the investigator has delegated significant trial-related duties.	

4.2 Adequate Resources

Guideline	Description	How is this documented to show compliance?
4.2.1	The investigator should be able to demonstrate (e.g., based on retrospective data) a potential for recruiting the required number of suitable subjects within the agreed recruitment period.	
4.2.2	The investigator should have sufficient time to properly conduct and complete the trial within the agreed trial period.	
4.2.3	The investigator should have available an adequate number of qualified staff and adequate facilities for the foreseen duration of the trial to conduct the trial properly and safely.	
4.2.4	The investigator should ensure that all persons assisting with the trial are adequately informed about the protocol, the investigational product(s), and their trial-related duties and functions.	
4.2.5	The investigator is responsible for supervising any individual or party to whom the investigator delegates trial-related duties and functions conducted at the trial site.	
4.2.6	If the investigator/institution retains the services of any individual or party to perform trial related duties and functions, the investigator/institution should ensure this individual or party is qualified to perform those trial related duties and functions and should implement procedures to ensure the integrity of the trial-related duties and functions performed and any data generated.	

4.3 Medical Care of Trial Subjects

Guideline	Description	How is this documented to show compliance?
4.3.1	A qualified physician (or dentist, when appropriate), who is an investigator or a sub-investigator for the trial, should be responsible for all trial-related medical (or dental) decisions.	
4.3.2	During and following a subject's participation in a trial, the investigator/institution should ensure that adequate medical care is provided to a subject for any adverse events, including clinically significant laboratory values, related to the trial. The investigator/institution should inform a subject when medical care is needed for intercurrent illness(es) of which the investigator becomes aware.	
4.3.3	It is recommended that the investigator inform the subject's primary physician about the subject's participation in the trial if the subject has a primary physician and if the subject agrees to the primary physician being informed.	
4.3.4	Although a subject is not obliged to give his/her reason(s) for withdrawing prematurely from a trial, the investigator should make a reasonable effort to ascertain the reason(s), while fully respecting the subject's rights	

4.4 Communication with the IRB/IEC

Guidance	Description	How is this documented to show compliance?
4.4.1	Before initiating a trial, the investigator/institution should have written and dated approval/favorable opinion from the IRB/IEC for the trial protocol, written informed consent form, consent form updates, subject recruitment procedures (e.g., advertisements), and any other written information to be provided to subjects.	
4.4.2	As part of the investigator's/institution's written application to the IRB/IEC, the investigator/institution should provide the IRB/IEC with a current copy of the Investigator's Brochure. If the Investigator's Brochure is updated during the trial, the investigator/institution should supply a copy of the updated Investigator's Brochure to the IRB/IEC.	
4.4.3	During the trial the investigator/institution should provide to the IRB/IEC all documents subject to review.	

4.5 Compliance with the Protocol

Guidance	Description	How is this documented to show compliance?
4.5.1	The investigator/institution should conduct the trial in compliance with the protocol agreed to by the sponsor and, if required, by the regulatory authority(ies) and which was given approval/favorable opinion by the IRB/IEC. The investigator/institution and the sponsor should sign the protocol, or an alternative contract, to confirm agreement.	
4.5.2	The investigator should not implement any deviation from, or changes of the protocol without agreement by the sponsor and prior review and documented approval/favorable opinion from the IRB/IEC of an amendment, except where necessary to eliminate an immediate hazard(s) to trial subjects, or when the change(s) involves only logistical or administrative aspects of the trial (e.g., change in monitor(s), change of telephone number(s)).	
4.5.3	The investigator, or person designated by the investigator, should document and explain any deviation from the approved protocol.	
4.5.4	The investigator may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to trial subjects without prior IRB/IEC approval/favorable opinion. As soon as possible, the implemented deviation or change, the reasons for it, and, if appropriate, the proposed protocol amendment(s) should be submitted: (a) to the IRB/IEC for review and approval/favorable opinion, (b) to the sponsor for agreement and, if required, (c) to the regulatory authority(ies).	

4.6 Investigational Product

Guidance	Description	How is this documented to show compliance?
4.6.1	Responsibility for investigational product(s) accountability at the trial site(s) rests with the investigator/institution.	
4.6.2	Where allowed/required, the investigator/institution may/should assign some or all of the investigator's/institution's duties for investigational product(s) accountability at the trial site(s) to an appropriate pharmacist or another appropriate individual who is under the supervision of the investigator/institution.	
4.6.3	The investigator/institution and/or a pharmacist or other appropriate individual, who is designated by the investigator/institution, should maintain records of the product's delivery to the trial site, the inventory at the site, the use by each subject, and the return to the sponsor or alternative disposition of unused product(s). These records should include dates, quantities, batch/serial numbers, expiration dates (if applicable), and the unique code numbers assigned to the investigational product(s) and trial subjects. Investigators should maintain records that document adequately that the subjects were provided the doses specified by the protocol and reconcile all investigational product(s) received from the sponsor.	
4.6.4	The investigational product(s) should be stored as specified by the sponsor (see 5.13.2 and 5.14.3) and in accordance with applicable regulatory requirement(s).	

4.6.5	The investigator should ensure that the investigational product(s) are used only in accordance with the approved protocol.	
4.6.6	The investigator, or a person designated by the investigator/institution, should explain the correct use of the investigational product(s) to each subject and should check, at intervals appropriate for the trial, that each subject is following the instructions properly.	

4.7 Randomization Procedures and Unblinding

4.7	The investigator should follow the trial's randomization procedures, if any, and should ensure that the code is broken only in accordance with the protocol. If the trial is blinded, the investigator should promptly document and explain to the sponsor any premature unblinding (e.g., accidental unblinding, unblinding due to a serious adverse event) of the investigational product(s).	

4.8 Informed Consent of Trial Subjects

Guidance	Description	How is this documented to show compliance?
4.8.1	In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki. Prior to the beginning of the trial, the investigator should have the IRB/IEC's written approval/favorable opinion of the written informed consent form and any other written information to be provided to subjects.	
4.8.2	The written informed consent form and any other written information to be provided to subjects should be revised whenever important new information becomes available that may be relevant to the subject's consent. Any revised written informed consent form, and written information should receive the IRB/IEC's approval/favorable opinion in advance of use. The subject or the subject's legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the trial. The communication of this information should be documented.	
4.8.3	Neither the investigator, nor the trial staff, should coerce or unduly influence a subject to participate or to continue to participate in a trial.	
4.8.4	None of the oral and written information concerning the trial, including the written informed consent form, should contain any language that causes the subject or the subject's legally acceptable representative to waive or to appear to waive any legal rights, or that releases or appears to release the investigator, the institution, the sponsor, or their agents from liability for negligence.	

4.8.5	The investigator, or a person designated by the investigator, should fully inform the subject or, if the subject is unable to provide informed consent, the subject's legally acceptable representative, of all pertinent aspects of the trial including the written information and the approval/ favorable opinion by the IRB/IEC.	
4.8.6	The language used in the oral and written information about the trial, including the written informed consent form, should be as non-technical as practical and should be understandable to the subject or the subject's legally acceptable representative and the impartial witness, where applicable.	
4.8.7	Before informed consent may be obtained, the investigator, or a person designated by the investigator, should provide the subject or the subject's legally acceptable representative ample time and opportunity to inquire about details of the trial and to decide whether or not to participate in the trial. All questions about the trial should be answered to the satisfaction of the subject or the subject's legally acceptable representative.	
4.8.8	Prior to a subject's participation in the trial, the written informed consent form should be signed and personally dated by the subject or by the subject's legally acceptable representative, and by the person who conducted the informed consent discussion.	
4.8.9	If a subject is unable to read or if a legally acceptable representative is unable to read, an impartial witness should be present during the entire informed consent discussion. After the written informed consent form and any other written information to be provided to subjects, is read and explained to the subject or the subject's legally acceptable representative, and after the subject or the subject's legally acceptable representative has orally consented to the subject's participation in the trial and, if capable of doing so, has signed and personally dated the informed consent form, the witness should sign and personally date the consent form. By signing the consent form, the witness attests that the information in the consent form and any other written information was accurately explained to, and apparently understood by, the subject or the subject's legally acceptable representative, and that informed consent was freely given by the subject or the subject's legally acceptable representative.	
4.8.10	Both the informed consent discussion and the written informed consent form and any other written information to be provided to subjects should include explanations of the following: (a) That the trial involves research. (b) The purpose of the trial. (c) The trial treatment(s) and the probability for random assignment to each treatment. (d) The trial procedures to be followed, including all invasive procedures. (e) The subject's responsibilities. (f) Those aspects of the trial that are experimental. (g) The reasonably foreseeable risks or inconveniences to the subject and, when applicable, to an embryo, fetus, or nursing infant. (h) The reasonably expected benefits. When there is no intended clinical benefit to the subject, the subject should be made aware of this.	

	(i) The alternative procedure(s) or course(s) of treatment that may be available to the subject, and their important potential benefits and risks. (j) The compensation and/or treatment available to the subject in the event of trial-related injury. (k) The anticipated prorated payment, if any, to the subject for participating in the trial. (l) The anticipated expenses, if any, to the subject for participating in the trial. (m) That the subject's participation in the trial is voluntary and that the subject may refuse to participate or withdraw from the trial, at any time, without penalty or loss of benefits to which the subject is otherwise entitled. (n) That the monitor(s), the auditor(s), the IRB/IEC, and the regulatory authority(ies) will be granted direct access to the subject's original medical records for verification of clinical trial procedures and/or data, without violating the confidentiality of the subject, to the extent permitted by the applicable laws and regulations and that, by signing a written informed consent form, the subject or the subject's legally acceptable representative is authorizing such access. (o) That records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. If the results of the trial are published, the subject's identity will remain confidential. (p) That the subject or the subject's legally acceptable representative will be informed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the trial. (q) The person(s) to contact for further information regarding the trial and the rights of trial subjects, and whom to contact in the event of trial-related injury. (r) The foreseeable circumstances and/or reasons under which the subject's participation in the trial may be terminated. (s) The expected duration of the subject's participation in the trial. (t) The approximate number of subjects involved in the trial.	
4.8.11	Prior to participation in the trial, the subject or the subject's legally acceptable representative should receive a copy of the signed and dated written informed consent form and any other written information provided to the subjects. During a subject's participation in the trial, the subject or the subject's legally acceptable representative should receive a copy of the signed and dated consent form updates and a copy of any amendments to the written information provided to subjects.	
4.8.12	When a clinical trial (therapeutic or non-therapeutic) includes subjects who can only be enrolled in the trial with the consent of the subject's legally acceptable representative (e.g., minors, or patients with severe dementia), the subject should be informed about the trial to the extent compatible with the subject's understanding and, if capable, the subject should sign and personally date the written informed consent.	
4.8.13	Except as described in 4.8.14, a non-therapeutic trial (i.e. a trial in which there is no anticipated direct clinical benefit to the subject), should be conducted in	

	subjects who personally give consent and who sign and date the written informed consent form.	
4.8.14	Non-therapeutic trials may be conducted in subjects with consent of a legally acceptable representative provided the following conditions are fulfilled: (a) The objectives of the trial cannot be met by means of a trial in subjects who can give informed consent personally. (b) The foreseeable risks to the subjects are low. (c) The negative impact on the subject's well-being is minimized and low. (d) The trial is not prohibited by law. (e) The approval/favorable opinion of the IRB/IEC is expressly sought on the inclusion of such subjects, and the written approval/ favorable opinion covers this aspect. Such trials, unless an exception is justified, should be conducted in patients having a disease or condition for which the investigational product is intended. Subjects in these trials should be particularly closely monitored and should be withdrawn if they appear to be unduly distressed.	
4.8.15	In emergency situations, when prior consent of the subject is not possible, the consent of the subject's legally acceptable representative, if present, should be requested. When prior consent of the subject is not possible, and the subject's legally acceptable representative is not available, enrolment of the subject should require measures described in the protocol and/or elsewhere, with documented approval/favorable opinion by the IRB/IEC, to protect the rights, safety and well-being of the subject and to ensure compliance with applicable regulatory requirements. The subject or the subject's legally acceptable representative should be informed about the trial as soon as possible and consent to continue and other consent as appropriate (see 4.8.10) should be requested.	

4.9 Records and Reports

Guidance	Description	How is this documented to show compliance?
4.9.0	The investigator/institution should maintain adequate and accurate source documents and trial records that include all pertinent observations on each of the site's trial subjects. Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (e.g., via an audit trail).	
4.9.1	The investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor in the CRFs and in all required reports.	
4.9.2	Data reported on the CRF, that are derived from source documents, should be consistent with the source documents or the discrepancies should be explained.	

4.9.3	Any change or correction to a CRF should be dated, initialed, and explained (if necessary) and should not obscure the original entry (i.e. an audit trail should be maintained); this applies to both written and electronic changes or corrections Sponsors should provide guidance to investigators and/or the investigators' designated representatives on making such corrections. Sponsors should have written procedures to assure that changes or corrections in CRFs made by sponsor's designated representatives are documented, are necessary, and are endorsed by the investigator. The investigator should retain records of the changes and corrections.	
4.9.4	The investigator/institution should maintain the trial documents as specified in Essential Documents for the Conduct of a Clinical Trial and as required by the applicable regulatory requirement(s). The investigator/institution should take measures to prevent accidental or premature destruction of these documents.	
4.9.5	Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period however if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained	
4.9.6	The financial aspects of the trial should be documented in an agreement between the sponsor and the investigator/institution.	
4.9.7	Upon request of the monitor, auditor, IRB/IEC, or regulatory authority, the investigator/institution should make available for direct access all requested trial-related records.	

4.10 Progress Reports

Guidance	Description	How is this documented to show compliance?
4.10.1	The investigator should submit written summaries of the trial status to the IRB/IEC annually, or more frequently, if requested by the IRB/IEC.	
4.10.2	The investigator should promptly provide written reports to the sponsor, the IRB/IEC and, where applicable, the institution on any changes significantly affecting the conduct of the trial, and/or increasing the risk to subjects.	

4.11 Safety Reporting

Guidance	Description	How is this documented to show compliance?
4.11.1	All serious adverse events (SAEs) should be reported immediately to the sponsor except for those SAEs that the protocol or other document (e.g., Investigator's Brochure)	

	identifies as not needing immediate reporting. The immediate reports should be followed promptly by detailed, written reports. The immediate and follow-up reports should identify subjects by unique code numbers assigned to the trial subjects rather than by the subjects' names, personal identification numbers, and/or addresses. The investigator should also comply with the applicable regulatory requirement(s) related to the reporting of unexpected serious adverse drug reactions to the regulatory authority(ies) and the IRB/IEC.	
4.11.2	Adverse events and/or laboratory abnormalities identified in the protocol as critical to safety evaluations should be reported to the sponsor according to the reporting requirements and within the time periods specified by the sponsor in the protocol.	
4.11.3	For reported deaths, the investigator should supply the sponsor and the IRB/IEC with any additional requested information (e.g., autopsy reports and terminal medical reports).	

4.12 Premature Termination or Suspension of a Trial

* If the trial is prematurely terminated or suspended for any reason, the investigator/institution should promptly inform the trial subjects, should assure appropriate therapy and follow-up for the subjects, and, where required by the applicable regulatory requirement(s), should inform the regulatory authority(ies). In addition:

Guidance	Description	How is this documented to show compliance?
4.12.1	If the investigator terminates or suspends a trial without prior agreement of the sponsor, the investigator should inform the institution where applicable, and the investigator/institution should promptly inform the sponsor and the IRB/IEC,and should provide the sponsor and the IRB/IEC a detailed written explanation of the termination or suspension.	
4.12.2	If the sponsor terminates or suspends a trial (see 5.21), the investigator should promptly inform the institution where applicable and the investigator/institution should promptly inform the IRB/IEC and provide the IRB/IEC a detailed written explanation of the termination or suspension.	
4.12.3	If the IRB/IEC terminates or suspends its approval/favorable opinion of a trial (see 3.1.2 and 3.3.9), the investigator should inform the institution where applicable and the investigator/institution should promptly notify the sponsor and provide the sponsor with a detailed written explanation of the termination or suspension.	

4.13 Final Report(s) by Investigator

4.13	Upon completion of the trial, the investigator, where applicable, should inform the institution; the investigator/institution should provide the IRB/IEC with a summary of the trial's outcome, and the regulatory authority(ies) with any reports required.	

Session 5:

Institutional Review Board/ Independent Ethics Committee

IRB Definitions
45 CFR 46 Subpart A
21 CFR 56
ICH G6 (R2)

<u>45 CFR Subpart A</u>

IRB

IRB Approval

Exempt Research

Expedited Research

Full Board Research

Continuing Review

Limited IRB Review

Certification

Written or in writing

21 CFR 56

IRB / Approval

Institution

Clinical Investigation

Human Subject

Emergency Use of a test article

Sponsor

Sponsor Investigator

Test Article

ICH EG (R2)

IRB

IRB Approval

Legally Acceptable Representative

Investigator

Clinical Trials / Study

Human subject

Protocol

Protocol Amendment

Sub-Investigator

Investigational Product

Institutional Review Board Worksheet

According to the federal regulations, what is the charge of an IRB?

Which of the Federal Regulations specifically describe the composition, operation, and function of the Institutional Review Board? For OHRP? FDA?

List and compare OHRP and FDA requirements for the composition of the committee.

When is IRB review Required? According to OHRP? FDA?

When may a clinical investigation be exempted from IRB review according to OHRP? FDA?

Can OHRP or the FDA waiver the IRB review requirement?

What written procedures must an IRB have in place in order to accomplish its mandated function ? for OHRP? FDA?

List and compare OHRP and FDA requirements for IRB review of research?

Explain the Expedited Review procedures established by OHRP. FDA.

In order to approve research covered by OHRP regulations, the IRB shall determine that all of the following requirements are satisfied. List the criteria. List and compare FDA Requirements.

According to 45 CFR 46 Subpart A, explain how institutional review may be used in the approval of a research project. What about Title 21?

If an IRB suspends or terminates a research project, what actions must the IRB take to comply with the FDA regulations? OHRP?

What do the FDA regulations say regarding the review of Co-operative research? OHRP?

What records must an IRB prepare and maintain to comply with the OHRP regulations? FDA?

Who is responsible for the operation of the IRB? According to OHRP? FDA?

ICH E6(R2) Guidance for IRB

1. What is the first and most important responsibility of IRB / IEC review?

2. Under ICH E6(R2) 3.0 what documents does the guideline specifically require the IRB to review that are only generally referred to in the FDA regulations?

3. True or False

A. _____ ICH guidance allows for initial expediated review of certain studies presenting no more than minimal risk.

B. _____ ICH GCP requires the IRB to provide, when asked, copies of their written procedures and membership lists to investigators, sponsors or regulatory authorities.

C. _____ICH specifically requires that the sponsor and the investigator sign the study protocol.

D. _____There is no corresponding section in the FDA regulations for Ich guidance that states that payment to a subject should be prorated and not contingent upon completion of the trial.

Session 6:

Roles and Responsibilities

General Responsibilities of the Investigator

- Ultimately responsible even when delegating tasks
- Training of study team, assurance of their individual qualification to perform tasks
- Properly qualified to assume responsibility for conduct of the study
- Supervise a clinical study in which some study tasks are delegated to employees or colleagues of the investigator or other third parties
- Avoid coercion or undue influence
- Oversight of the study
- Ability to recruit in sufficient numbers and in timeframe given
- Obtain informed consent
- Record retention/Maintain adequate/essential documents, follow ALCOA-C
- Compliance with reporting requirements
- Conduct research in an ethical manner
- Fully inform subject/participant of all pertinent aspects of the trial
- Data collection
- Make records available to monitors, auditors and inspectors
- Submit reports as required
- Ensuring IRB review, approval, compliance and reporting requirements are met per 21CFR56
- Safety reporting
- Assurance of :
    - IRB review
    - Adequacy of Resources
        - Facility
        - qualified/sufficient number of study team members
        - time to conduct the study
- Adequate knowledge of the following:
    - Regulations and guidance
    - Protocol/study procedures
    - Investigational Product (IP) and its appropriate use, as applicable
- Ensure:
    - subject s' rights, safety, and well-being are protected
    - data integrity
    - regulatory compliance
    - IP accountability/dispensing, etc.

NIDCR National Institute of Dental and Craniofacial Research
National Institutes of Health

Tool Summary Sheet

Tool: Delegation of Responsibilities Log

Purpose: To record all study staff members' significant study-related duties.

Audience/User: Principal Investigators (PIs), Study Coordinators, other site staff, clinical monitor

Details: This log should provide a comprehensive list of study staff members and the duties that have been delegated to them by the Principal Investigator. It is required for both observational and interventional clinical research studies.

Best Practice Recommendations:

- List the names of study staff members and record the responsibilities that have been assigned to them using the Responsibilities Legend.
- Revise the Responsibilities Legend as needed to reflect study-specific needs, such as signing CRFs and reviewing/signing laboratory reports.
- Each study staff member listed should initial and sign to indicate understanding of the responsibilities assigned.
- The site PI should initial and date each line of the form as entries are recorded. The PI's signature at the bottom of each form is required at the conclusion of the study.
- Update the log as needed following any change in site study personnel.
- Number each page and maintain this log in the Essential Documents Binder, behind the 'Delegation of Responsibilities (DoR) Log' tab. (Synonyms for this binder include Investigator Binder, Regulatory Binder, Investigator Site File (ISF), and Study File.)
- Store pages in reverse chronological order, with the newest pages of the log placed at the front of the section.
- At the conclusion of the study, identify the final page of the log by checking the box in the footer.
- Remove this Tool Summary Sheet before use of the log.

Tool Revision History:

Version		
Number	**Date**	**Summary of Revisions Made:**
1.0	**05Feb2010**	**First approved version**
2.0	**02Mar2010**	**Removed automatic page numbering**
3.0	**04Jan2012**	**Added Tool Summary Sheet; minor updates to Responsibilities Legend**
4.0	**14Mar2012**	**Updated Tool Summary Sheet; added * cross-reference and Query Management to Responsibilities Legend; added check box to footer**

Delegation of Responsibilities Log

Investigator Name:	Protocol:	Site Number:

List staff to whom the Principal Investigator (PI) has delegated significant study-related duties.

Name	Responsibilities*	Initials	Signature	Start Date	End Date	PI Initials/Date

By initialing above, I, the PI, declare that during the conduct of the above study, I have delegated the following study-related activities:

*Responsibilities Legend		
1. Administer Consent	6. Randomize Subjects	11. Complete Study Forms
2. Screen Subjects	7. Dispense Study Drug	12. Provide Discharge Instructions
3. Obtain Medical History	8. Drug Accountability	13. Make Follow-up Phone Calls
4. Perform Physical Exam	9. Assess Adverse Events	14. Query Management
5. Determine Eligibility	10. Complete Source Documents	15.

Signature of Principal Investigator: _____ Date: _____

9. COMMITMENTS

I agree to conduct the study(ies) in accordance with the relevant, current protocol(s) and will only make changes in a protocol after notifying the sponsor, except when necessary to protect the safety, rights, or welfare of subjects.

I agree to personally conduct or supervise the described investigation(s).

I agree to inform any patients, or any persons used as controls, that the drugs are being used for investigational purposes and I will ensure that the requirements relating to obtaining informed consent in 21 CFR Part 50 and institutional review board (IRB) review and approval in 21 CFR Part 56 are met.

I agree to report to the sponsor adverse experiences that occur in the course of the investigation(s) in accordance with 21 CFR 312.64. I have read and understand the information in the investigator's brochure, including the potential risks and side effects of the drug.

I agree to ensure that all associates, colleagues, and employees assisting in the conduct of the study(ies) are informed about their obligations in meeting the above commitments.

I agree to maintain adequate and accurate records in accordance with 21 CFR 312.62 and to make those records available for inspection in accordance with 21 CFR 312.68.

I will ensure that an IRB that complies with the requirements of 21 CFR Part 56 will be responsible for the initial and continuing review and approval of the clinical investigation. I also agree to promptly report to the IRB all changes in the research activity and all unanticipated problems involving risks to human subjects or others. Additionally, I will not make any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to human subjects.

I agree to comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements in 21 CFR Part 312.

INSTRUCTIONS FOR COMPLETING FORM FDA 1572
STATEMENT OF INVESTIGATOR

1. Complete all sections. Provide a separate page if additional space is needed.
2. Provide curriculum vitae or other statement of qualifications as described in Section 2.
3. Provide protocol outline as described in Section 8.
4. Sign and date below.
5. FORWARD THE COMPLETED FORM AND OTHER DOCUMENTS BEING PROVIDED TO THE SPONSOR. The sponsor will incorporate this information along with other technical data into an Investigational New Drug Application (IND). INVESTIGATORS SHOULD NOT SEND THIS FORM DIRECTLY TO THE FOOD AND DRUG ADMINISTRATION.

10. DATE *(mm/dd/yyyy)*	11. SIGNATURE OF INVESTIGATOR Sign

(**WARNING**: A willfully false statement is a criminal offense. U.S.C. Title 18, Sec. 1001.)

Roles and Responsibilities

Be familiar with the Regulations and/or guidance where the roles and responsibilities of those conducting research are found

- 21 CFRs
- ICH GCP E6 (R2)

Be familiar with the roles/responsibilities of the following:

a. PI

b. Sub/Co-Investigator

c. Sponsor

d. IRB/IEC

e. Monitor

Session 7 and 8:

Study Start-Up

Notification of a Potential Trial

Sources:

- Contact by
  - Sponsor to site personnel/facility
  - CRO to site personnel/facility
  - Institution/Research Administration/Office to local department
  - Fellow researchers

2 Reasons for Initial Communication between a site and Sponsor/CRO:

1. Sponsor desires a research site to conduct their clinical trial
2. Site desires to pursue a study from a sponsor/CRO

During the initial contact between the site and sponsor/CRO, the following may occur:

Sponsors/CROs may reveal basic information regarding the clinical trial such as:

- Phase of the study
- Type of study
- Type of patients
- Enrollment goals
- Total # of sites to be recruited
- Time frames of enrollment/participation

Most sponsors/CROs are not willing to offer much more information regarding the clinical trial until mutual interest is confirmed and a CDA is signed.

Sponsor/CRO at the same time gathers from the potential site information such as:

- PI/Sub-Investigators research experience
- Personnel and their research experience
- Access to the subject population needed for the protocol

Protocol Feasibility Checklist:

The initial feasibility should begin immediately when receiving information on a new potential trial. Coordinators should have a role in the feasibility assessment.

Main Factors to consider are:

- Enrollment/Recruitment timeframe
- Subject population
- Protocol
- Study Procedures

- Staff/Resources
- Budget

Principal Investigator's Responsibilities:

- Participate in Ethical/Scientifically Relevant Research
- Provide Qualified Staffing
- Provide Adequate Facilities
- Satisfy Subject Recruitment Goals
- Medical Management of Trial Participants
- Ensure Protocol Compliance and Completion of Study Procedures
- Control the Investigational Product and Maintain Accountability

Contact between Sponsor/CRO and Site

Minimal Information re: potential trial

Begin Initial feasibility assessment

CDA Executed

Additional Information re: potential trial-such as: Protocol, budget, sample ICF, IB

Site should continue Feasibility assessment

Determine if your site can be successful with this clinical trial

Notify Sponsor/CRO of your decision

Sponsor/CRO would rather a site say no to a study that is not a good fit for them than accept to conduct the trial and not be successful. Being a successful site usually means repeat business.

Study Start-up:

- Infrastructure/Resources to support research project
  - Qualified/trained study team
  - Access to needed equipment

    - Ancillary departments support
    - Adequate space
- Budget
- Sufficient patient population
- Study billing procedures in place
- Signed and executed contract
- Clinicaltrials.gov registration
- Supplies/Investigational product has been received by study team, etc.
- Training completed
- Regulatory/Essential documents
- Visit worksheets/ Case report forms
- Calendar of events/study procedures
- Participant materials if needed

Approvals:

- Institution
- Department
- IRB

Pre-Trial Procedures:

Pre- Site Selection:

- Contact Sponsor/CRO to express interest in trial
- Negotiate CDA (To be negotiated by and signed by appropriate organizational signatory, not by PI alone)
- Receipt of Trial Information (Protocol Synopsis, Protocol, preliminary budget)
- Continue and complete feasibility review process of conducting the trial (Feasibility Checklist) and decide whether or not to proceed with the trial
- Site Visit by sponsor/CRO
    - Tour of facilities
    - Brief review of the protocol and IP
    - Review of site personnel and trial experience
    - Inspection of study product storage area, monitoring space

Post-Site Selection:

- Prepare and submit IRB application
- Prepare and submit other required regulatory/Essential Documents
    - Essential Documents

        - 1572
        - CV/Resumes
        - Licenses
        - Certifications
        - Delegation of Authority-Responsibilities outlined
        - Master log
        - Screening log
- Negotiate Clinical Trial/Study Agreement and Budget (To be negotiated by OCR and signed by appropriate organizational person and PI)
- Attend pre-trial initiation visit and/or investigator meetings
- Plan/Provide appropriate training to study team
    - Human Subject Protection
    - ICH GCPs
    - Conflict of Interest
    - HIPAA
    - FDA Regulations/guidance
    - Protocol
- Complete study set-up procedures
    - Regulatory Documents
    - Checklists
    - Logs/Spreadsheets
    - Regulatory Binder
    - Storage
    - Get organized
        - File as you receive information
        - Create additional binders if needed
    - Site Source Documents
    - Research chart/records
    - QA/QI plan
    - Recruitment/Advertising plan
        - IRB approval before use
        - Institutional approval/special wording
        - Budget
    - SOPs
    - Supplies
        - Pocket folders
        - Labels
        - Lab supplies if not provided by sponsor
    - Contact other departments for needed services and cost of procedures

Checklist for Training the Research Team

- **Overview of the Study**
- _____Read CDA/CTA/Budget
- _____Read 1572
- _____Read current version of the protocol
- _____Read current version of approved ICF
- _____Read all IRB approved materials for the study
- _____Discuss initiation of study, subject participation, enrollment period
- _____Discuss recruitment, enrollment, and consenting procedures
- _____Discuss roles of each study team member
- _____Discuss the study procedures to be performed at each visit
- _____Review procedures for obtaining, handling, shipping, and storage of specimens
- _____Verify study members possess the skills/credentials requires to perform their role
- _____Review forms to be used
- _____Discuss study product accountability, dispensing, and storage
- _____Discuss FDA regulations and ICH GCP guidelines to ensure compliance
- _____Discuss appropriate billing procedures
- _____Documents to read and be familiar with:
- Belmont Report
- Declaration of Helsinki
- Nuremburg Code
- FDA CFR
- ICH GCP Guidelines
- FDA Information Sheets
- Center for Drug Evaluation and Research
- Office for Human Subjects Protection

Training provided for each member of the study team should be documented.

This document does not contain all of the steps to start-up for all studies.

National Institute of Dental and Craniofacial Research

Tool Summary Sheet

Tool: Guideline: Study Start-up through Site Initiation Visit and Site Activation for Extramural Studies Requiring Additional NIDCR Oversight

Purpose: To clarify the Extramural study start-up process from protocol development through site initiation and activation. Explicitly included are studies requiring additional NIDCR oversight.

Audience/User: Lead Investigators and study team members of Extramural studies supported by the NIDCR, the Clinical Research Operations and Management Support team (CROMS), and Program Officials of the NIDCR

Details: This document identifies prerequisites for a) the scheduling of a site initiation visit and b) site activation (i.e., the authorization to begin subject recruitment). Also discussed are other study start-up recommendations. Useful tools are referenced.

Best Practice Recommendations:

- This guidance should be reviewed early in the protocol development process.
- Tools referenced in the guidance document should be reviewed early in the start-up process to determine those which are most useful and appropriate. Most tools are accompanied by a summary sheet that details the purpose of the tool, the audience for the tool, and best practices associated with the tool.
- Referenced tools are bolded, for convenience, and can be found on the CROMS website in the Clinical Tool Box section. Many are also located on the NIDCR's Toolkit for Clinical Researchers website.
- Clinical research tasks must be conducted in accordance with Good Clinical Practice (GCP) in order to ensure human subject safety and data integrity.

Tool Revision History:

Version		
Number	**Date**	**Summary of Revisions Made:**
1.0	23FEB2012	Approved version
2.0	19DEC2013	Updated to reflect current risk/oversight process and policy, and revised/added definitions and references to existing tools and templates.

Table of Contents

1 ABBREVIATIONS AND TERMINOLOGY

Ancillary Clinical Site (or Ancillary Clinical Study Site)	Physical site or location that may be an extension from the Clinical Site / Clinical Study Site (e.g., homes, schools, public locations) where subjects are seen for study purposes. Study personnel travel from a Clinical Site / Clinical Study Site to this ancillary site in order to perform some or all study procedures on subjects. Study personnel are not affiliated with or located at the ancillary site, but are affiliated with the Clinical Site / Clinical Study Site. Study documents, study product, and study materials are not maintained at the ancillary site; these usually travel with the study personnel and are maintained at the Clinical Site / Clinical Study Site.
CD	Consent document
Clinical Site (or Clinical Study Site)	Physical site or location where participant/subject records are maintained; often this is the location where participants/subjects are seen by study staff for study purposes and study procedures are performed, where study product or materials are maintained, and where data and regulatory records are stored. Study personnel are affiliated with the Clinical Site and operate in and from this location. (The term “Clinical Study Site” may be preferred for studies which include a dental or medical clinic and the use of the word “clinic” requires further definition.)
CRA	Clinical Research Associate. Monitor; person who monitors the progress of the investigation as well as sites participating in a clinical study and who is responsible for assessing study conduct in adherence with protocol requirements.
CRF	Case Report Form (term used to describe the set of data collection instruments of clinical trials). The term “data collection forms” is a common term for other clinical research, such as behavioral interventions, specimen collection studies, and observational studies.
Clinical Research	Patient-oriented research, including epidemiologic and behavioral studies, outcomes research, and health services research. Patient-oriented research is research conducted with human subjects (or on material of human origin such as tissues, specimens, and cognitive phenomena) in which a researcher directly interacts with human subjects. It includes research on mechanisms of human disease, therapeutic interventions, clinical trials, and development of new technologies, but does not include in vitro studies using human tissues not linked

	to a living individual. Studies falling under 45 CFR 46.101(b) (4) are not considered clinical research for purposes of this definition.
Clinical Trial evaluating a drug, device or biologic	A controlled study involving human subjects, designed to evaluate prospectively the safety and effectiveness of new drugs or devices [http://www.hhs.gov/ohrp/archive/irb/irb_chapter5.htm]. Drugs include any chemical compound that may be used on or administered to humans as an aid in the diagnosis, treatment, cure, mitigation, or prevention of disease or abnormal conditions. Testing of drugs in humans proceeds through different phases: Phase I: Testing in a small number of subjects (e.g., 20-80) to evaluate its safety, determine a safe dosage range, and identify side effects. Phase II: Study in a larger group of people (no more than several hundred) to determine preliminary efficacy for a particular indication and further evaluate safety by determining the common short-term side effects and risks associated with the drug. Phase III: Study in a larger number of subjects (from several hundred to several thousand) to confirm a drug's efficacy, to determine its safety, and to compare the intervention to commonly used treatments. Phase IV: Studies done after the drug has been marketed. These studies are designed to monitor the effectiveness of the approved intervention in the general population and to collect information about any adverse effects associated with widespread and long-term use. Devices encompass a broad range of medical products and product development stages may vary according to device. If NIDCR support is sought, discussion should begin with program and OCTOM at an early stage to outline NIDCR expectations. See Appendix D for details on behavioral interventions.
Clinical Trial evaluating a behavioral Intervention	A controlled study involving human subjects, designed to test a well-characterized behavioral intervention and evaluate prospectively the efficacy or effectiveness of the behavioral or psychosocial intervention on behavioral or social targets relevant to public health. "Behavioral intervention" is a broad term that describes an approach to preventing, maintaining or changing behavior of individuals or groups through the use of non-medical or non-pharmaceutical techniques. Behavioral intervention clinical trials proceed through different phases, typically called "stages" to distinguish them from drug or device trials:

	Stage I(a): Define the clinical problem of interest, and define the rationale for why the intervention is expected to address the problem, including identifying proposed mediators and moderators. The main product of this stage is a draft behavioral intervention that is described in sufficient detail – typically in an intervention manual – so that it can be delivered as intended. Stage I(b): Test the intervention for acceptability to the target population and to the intended interventionists, and test the feasibility of conducting an efficacy trial in subsequent stages. Stage II: Test the efficacy of an intervention, and further clarify variables that mediate and moderate the intervention's effects. Stage III: Prepare and/or adapt an efficacious intervention to be delivered in community (non-research) settings by the end-user interventionists in a sustainable way. Stage III is not meant to be a return to "black box" intervention research, but rather a systematic study of how an intervention can be delivered in a "real world" setting. Rigorous measurement of deviations from intervention fidelity, and of variables that might affect intervention delivery are expected in this stage.
CROMS	Clinical Research Operations and Management Support services. The term CROMS is used to identify the NIDCR contractor who provides operational and research services to Intramural and Extramural supported studies and infrastructure support to the Office of Clinical Trials Operations and Management (OCTOM).
CSOC	Clinical Study Oversight Committee. The CSOC is an independent group of experts that makes recommendations to NIDCR, and through NIDCR to the study investigators on clinical studies not involving an intervention. Such clinical research studies may be complex, involve risk or vulnerable populations, and may be observational, specimen collection, epidemiology or surveillance studies. The responsibilities of the CSOC are to 1) monitor human subject safety by reviewing and evaluating the accumulated study data, 2) evaluate study conduct and progress, and 3) make recommendations to NIDCR concerning the continuation, modification, or termination of the study. The CSOC considers study-specific data as well as relevant background information about the disease, procedures and progress of the study.
CToA	Clinical Terms of Award. A term and condition of grant/cooperative agreement awards, the purpose of which is to ensure that all clinical research and trials

	involving human subjects and conducted under grants and cooperative agreements supported by NIDCR are well designed, conducted with rigor, monitored commensurate with risk and complexity, and that the Institute is kept informed of study progress through reporting.
DCC	Data Coordinating Center (This may be CROMS or another group.) Synonym: data management center (DMC).
Device	An instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, or accessory, which is-- (1) recognized in the official National Formulary, or the United States Pharmacopeia, or any supplement to them, (2) intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or (3) intended to affect the structure or any function of the body of man or other animals, and which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of its primary intended purposes.
Drug	(A) articles recognized in the official United States Pharmacopoeia, official Homoeopathic Pharmacopoeia of the United States, or official National Formulary, or any supplement to any of them; and (B) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and (C) articles (other than food) intended to affect the structure or any function of the body of man or other animals; and (D) articles intended for use as a component of any articles specified in clause (A), (B), or (C).
DSMB	Data and Safety Monitoring Board. The DSMB is an independent group of experts that makes recommendations to NIDCR, and through NIDCR to the study investigators. The primary responsibilities of the DSMB are to 1) periodically review and evaluate the accumulated study data for participant safety, study conduct and progress, and, when appropriate, efficacy, and 2) make recommendations to NIDCR concerning the continuation, modification, or termination of the trial. The DSMB considers study-specific data as well as relevant background knowledge about the disease, test agent, or patient population under study.

FDA	Food and Drug Administration
GCP	Good Clinical Practice. From the International Conference on Harmonisation (ICH) guidance, GCP is a standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected.
ICH	International Conference on Harmonisation
IDE	Investigational Device Exemption
IND	Investigational New Drug application
IRB[1]	Institutional Review Board. An administrative body established to protect the rights and welfare of human research subjects recruited to participate in research activities conducted under the auspices of the organization with which it is affiliated. The Institutional Review Board has the authority to approve, require modifications in, or disapprove all research activities that fall within its jurisdiction.
ISM	Independent Safety Monitor. An ISM is a qualified clinician with relevant expertise whose primary responsibility is to provide independent safety monitoring in a timely fashion. This is accomplished by evaluation of adverse events, immediately after they occur, with follow-up through resolution or stabilization. The ISM evaluates individual and cumulative participant safety data when making recommendations regarding continuation of the study. An ISM could be the sole independent monitor for the study or may perform this role as a member of a DSMB. An ISM is appropriate as the sole independent safety monitor for small, early phase studies of short duration. DSMBs should consider the need to designate one or more members as ISM(s). In the case of DSMBs, the ISM focus may be directed at serious adverse events rather than all adverse events.
MOP	Manual of Procedures. A Manual of Procedures (MOP) is a handbook that guides a study's conduct and operations. The purpose of the MOP is to facilitate consistency in protocol implementation and data collection across participants and clinical sites.
OCTOM	NIDCR Office of Clinical Trials Operations and Management

PI	Principal Investigator. The lead investigator of the study. This PI may also be a site PI. This position may also be termed the "Study Director."
QMP	Quality Management Plan. The quality management plan describes the process designed to ensure compliance with human subject safety, quality and integrity of the data, and compliance with the protocol.
Site Activation	The point in time when all initial requirements have been satisfied and a site may begin to enroll subjects into the study. The NIDCR Program Official, assisted by CROMS and OCTOM, issues the approval for site activation.
Site Initiation Visit (SIV)	The on-site meeting designed to prepare the study team for conducting the study. The meeting includes (at a minimum) the PI, other investigators, site study coordinator, other site staff assuming study responsibilities, and data management representative. The Site Initiation Visit may also include NIDCR Program Official or representative, OCTOM representative, and a clinical monitor.
Site PI	Convenience term used to identify the lead principal investigator at a site. This term is created to differentiate the role of lead investigators at each clinical site (i.e., the Site PI) from the lead investigator of the study (i.e., the PI). One of the site PIs may also be the PI or Study Director of the study.
TMF	Trial Master File; the file that contains all of the key documents relating to a clinical study, usually maintained by the sponsor or sponsor representative (e.g., a Contract Research Organization [CRO]). This file contains "Essential Documents," defined as documents that individually and collectively permit evaluation of the conduct of a study and the quality of the data produced. Example of some content: IRB-approved protocols, consents, assents, advertisements; investigator curriculum vitae or list of qualifications; study team training log/documentation.

[1] verbatim definition from NIH Glossary of Terms

2 INTRODUCTION

Implementation and conduct of a clinical study can be a complex process that involves a team from various disciplines and multiple steps that are dependent on one another. This document offers guidance for navigating the clinical research study start-up and activation process. This

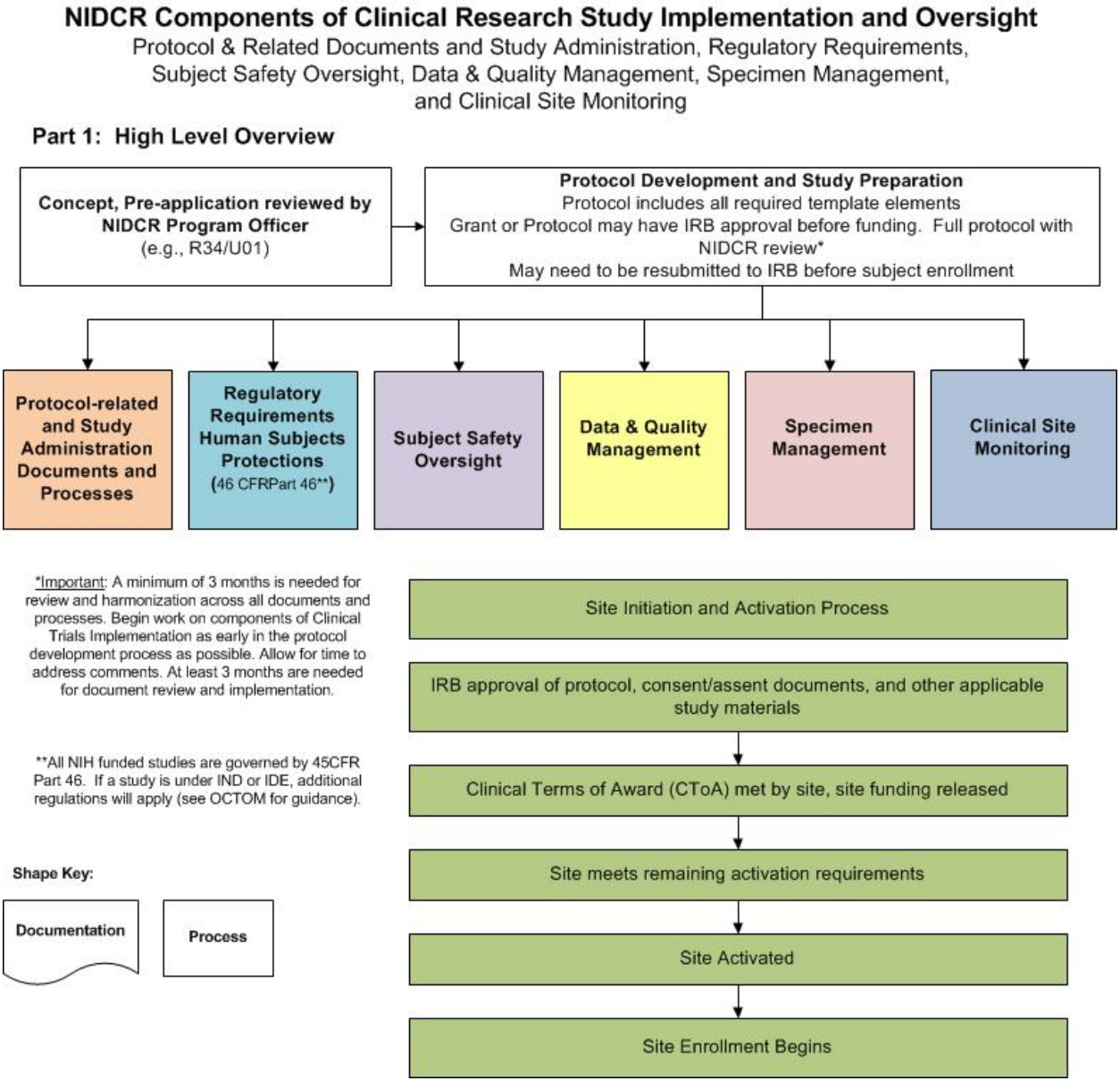
guide is for NIDCR Extramural clinical research studies that are determined to require additional oversight by the NIDCR Medical Monitor. Studies may require additional oversight because they are more than minimal risk to human subjects or have other characteristics that indicate a need for additional NIDCR oversight, (e.g., complex study design, vulnerable population, large sample size, high NIDCR profile, multi-center, large NIDCR investment of funds).

NIDCR receives clinical research study plans within a grant proposal. Clinical Terms of Award requires the clinical research study plan to be documented in a consolidated format to include applicable elements of a clinical protocol in accordance with the International Conference on Harmonisation's Guideline for Good Clinical Practice - ICH GCP E6, Section 6. NIDCR recommends the investigator use the relevant NIDCR protocol template to ensure all applicable elements of ICH are included in the protocol document.

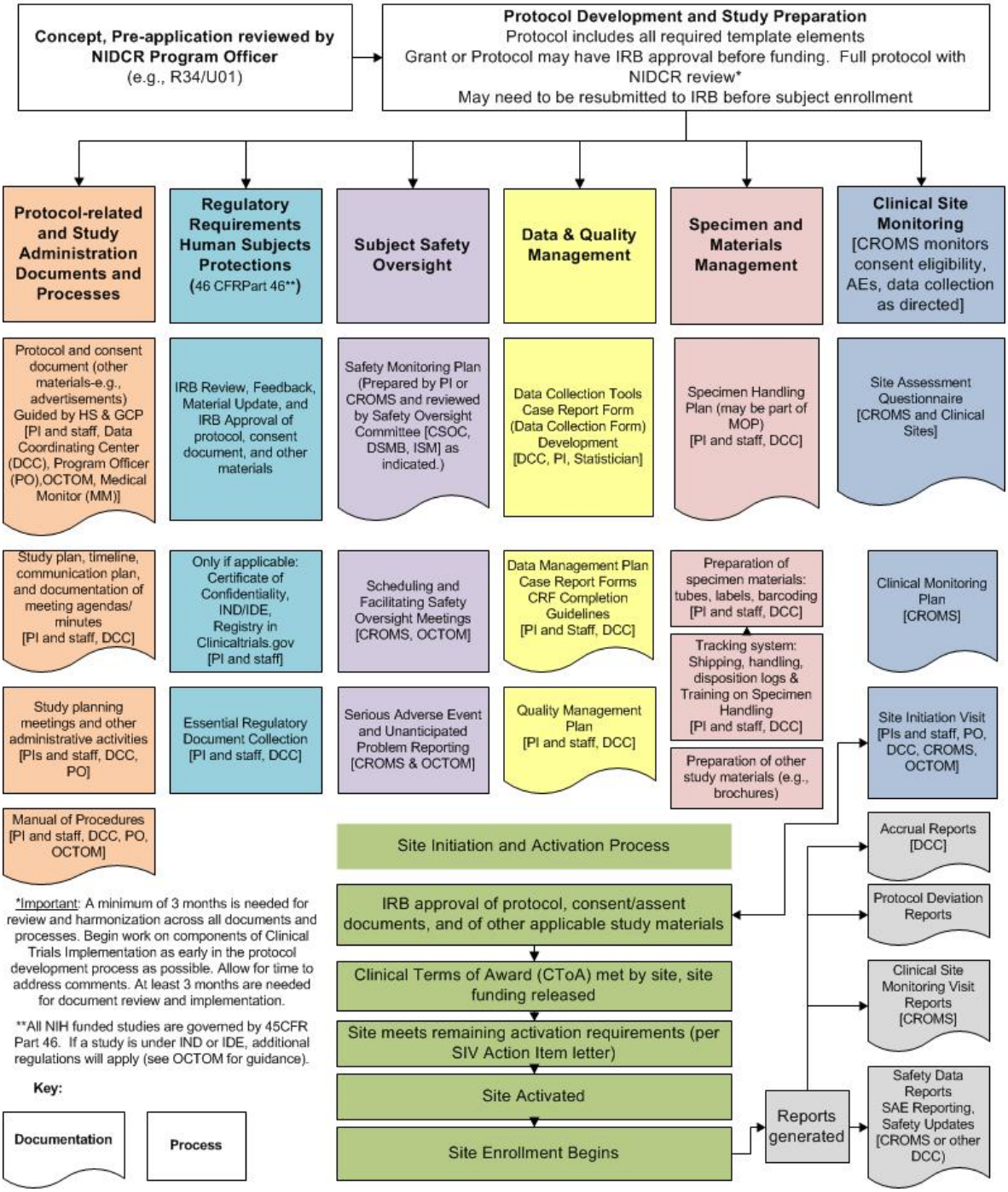
The start-up and activation process begins with the development of a clinical research study plan in the form a protocol. Other study documents such as consent and assent documents, data collection or case report forms, Manual of Procedures, checklists and logs will be helpful, if not already required, to implement a clinical study. To meet Human Subject Protections regulatory requirements and other applicable regulatory requirements, other documents including Institutional Review Board (IRB) approvals are required in accordance with ICH E6 Section 8. In order to have standardization of procedures across the study, adequate documentation is necessary. This guide will identify which documents and steps need to be completed to begin conduct of clinical research in compliance with Good Clinical Practice.

Figure 1 depicts both a simple and a more complex graphic of the components of Extramural clinical research study implementation and oversight, including the process for site initiation, CToA, and site activation.

Figure 1. Components of Extramural Clinical Research Study Implementation and Oversight



Part 2: Detailed View



3 PROTOCOL-RELATED AND STUDY ADMINISTRATION DOCUMENTS AND PROCESSES

3.1 Protocol and Consent/Assent Document Development, Review, and Internal Team Review and Approval

3.1.1 Protocol

For studies that include an intervention, prepare the protocol using the NIDCR Extramural **Clinical Trial (Interventional) Protocol Template.** For studies without an intervention, prepare the protocol using the NIDCR Extramural **Clinical Study (Observational) Protocol Template**. These templates provide thorough guidance on the required content.

Once the draft protocol has been written, it should be distributed to the study team for review and comment. The draft protocol review team should include one or more individuals in each of the following categories: NIDCR Program Official; Principal Investigator (PI); site study coordinator with logistical expertise; NIDCR Medical Monitor; Data Coordinating Center (DCC) study coordinator; statistician; data manager; and a representative from the Office of Clinical Trials Operations and Management (OCTOM).

The process for review and update of the protocol during this development stage should be specified early on. Identify the person(s) responsible for delivery of protocol drafts, for integration of comments from multiple sources into one version, and for version control; identify the process for distributing documents and reviewer comments; identify who and how decisions about protocol changes will be made; develop a communication plan that may include convening regularly scheduled meetings (e.g., teleconferences) with protocol reviewers to discuss proposed changes prior to implementation. Minutes from such meetings are critical to the update process.

Please refer to the **Version Control Guidelines** for the NIDCR prescribed version control process. In brief, draft documents should include both a version date and a version number. Versions prior to approval will begin with 0.1 and the number will be incremented with each new

draft; dates will be updated with the new issuance date. Please ensure that all document headers and footers are updated for each new draft.

To document the approval of all required reviewers for a protocol draft version to become final and ready for IRB submission, the study PI or team leader may initiate use of the **Extramural Clinical Protocol Approval Form**.

A separate process for authoring, tracking, and approving protocol amendments should also be established during study start-up. The Extramural Clinical Protocol Approval Form may also be used to approve amended protocols prior to IRB submission.

All tools referenced in this section (3.1.1) can be found in the Protocol section of the Clinical Tool Box.

3.1.2 Consent Documents (CD) and Assent Documents

Because the consent and assent documents are highly dependent on the content of the protocol, their development will begin in earnest as soon as the protocol procedures and study-associated risks are well described. The consent document (CD) should be prepared using both the Office of Human Research Protections (OHRP) guidance and local IRB requirements.

The CD review team is likely to be a subset of the protocol review team. At a minimum, the PI, site study coordinator, and DCC study coordinator or lead-site study coordinator should review the CD. Additionally, NIDCR staff will review the document and will communicate comments from NIDCR to the PI.

For multi-center studies, the PI may choose to distribute his/her CD to be used as a sample/starting point for other participating sites. Often individual IRBs have unique requirements for CDs, and it is likely that significant modifications of the initial CD template may be required. If there is any CD language that may not be modified, that language should be designated as such in the sample CD. In addition to the site review team, the CD should be reviewed by the Program Official and by the DCC or lead-site study coordinator who will ensure, among other things, that any required language has not been modified.

The **Consent Document Review Checklist** can be used to conduct a quality review of the CD; it will ensure that all required elements are included and that the CD is consistent with the protocol. See the Consent Documents folder of Clinical Tool Box.

Assent documents for minors and other subjects not able to provide consent will also be developed and reviewed as needed.

3.2 Other Reviews and Approvals of Protocol and Consent/Assent Documents

3.2.1 Scientific or Local Research Committee, Radiation or Other Therapeutic Review Committee

A clinical institution may require that the protocol and CD be reviewed by a scientific or other local research committee and/or a radiation or other therapeutic review committee. Often this review is conducted prior to the IRB and DSMB review.

3.2.2 NIDCR Safety Oversight Review

The purpose of the NIDCR safety oversight review is to independently assess the safety data (e.g., adverse events and unanticipated problems) as well as study progress (e.g., recruitment and enrollment), study conduct (e.g., protocol deviations), and key data elements determined on an individual study basis. All studies are assessed to determine the level of data and safety oversight required. Studies requiring additional oversight may be assigned to safety oversight committees (i.e., Data and Safety Monitoring Board [DSMB][2] or Clinical Study Oversight Committee [CSOC]) or to the Medical Monitor for both an initial protocol review and for ongoing reviews during the data collection portion of the studies.

Protocol and CD review should be completed by the designated DSMB/CSOC/Medical Monitor after the protocol team has completed their review and prior to site activation. The Program Official (PO) will provide the oversight-review-ready protocol and CD to OCTOM and the Medical Monitor. For protocols requiring committee review, an OCTOM representative will

[2] In rare instances, the Medical Monitor may determine that an Independent Safety Monitor (ISM) will provide oversight in addition to or in lieu of a DSMB. NIDCR can provide further information.

ensure that the protocol is added to the designated safety oversight committee docket for review at an upcoming meeting. Each DSMB or CSOC will be guided by a written charter.

It is best practice to submit the protocol and CD for a Safety Oversight review prior to submitting to the Institutional Review Board (IRB). In this way, any recommended changes can be implemented prior to submission of the documents to the IRB, thus reducing the likelihood of an extra IRB update cycle.

In addition to an initial review of the protocol and CD, the study will be scheduled for regular reviews (e.g., yearly) by the DSMB/CSOC/Medical Monitor. Following each review, the DSMB/CSOC/Medical Monitor will recommend to the NIDCR that the study either (1) continue as presented, (2) continue with modifications that the oversight committee will supply, or (3) be terminated for cause, with the cause specified. These recommendations are communicated in writing to NIDCR. NIDCR will convey accepted recommendations to the PI usually within one month.

3.2.3 IRB Review

Follow local IRB guidelines for creation and submission of materials.

For multi-site studies, it is conceivable that a site IRB, other than that of the lead-site, may recommend changes to the protocol that are not consistent with the protocol that has been accepted at other sites. In some instances, IRBs have asked that the protocol be put into the local IRB's template. It is not feasible or good practice to have different protocols at different sites for the same study; such cases will require further discussion with the study team. If the IRB continues to require a particular protocol change, then it will likely be necessary to amend the protocol at the other participating sites as well.

The protocol, CD, and other relevant study related materials must be approved by the site's IRB before that site is initiated.

3.3 Study Plan, Timeline, and Communication Plan

It is very important to establish a study plan that identifies all of the required activities that must be completed during the start-up process. The plan should also identify dependencies between

various activities so that the study team understands the impact of one set of activities on another.

3.3.1 Identify all Parties who will be Participating in the Study and Clarify the Responsibilities

Ensure that all study start-up activities are explicitly assigned. The **Task Distribution Checklist** can be used to support this goal (see the Project Management folder of Clinical Tool Box and the NIDCR's Toolkit for Clinical Researchers website). This spreadsheet includes a comprehensive list of research activities and a means to identify the relevant group responsible for each. It also affords the ability to differentiate subtask responsibilities (e.g., author vs. reviewer vs. approver).

In certain cases of an Investigational New Drug application (IND), the IND sponsor may wish to officially transfer some of the sponsor obligations. This requires that the transferred obligations are documented, the document is signed, and it is provided to the Food and Drug Administration (FDA) as part of the IND.

The **Delegation of Responsibilities Log** is used by a clinical site to specify the names of individuals who will be responsible for implementing specified protocol activities (see the Essential Documents section in the Clinical Tool Box and the NIDCR Toolkit). This document will be completed prior to site initiation.

3.3.2 Prepare Timeline or Start-up Tracking Tool

Once the full set of study activities is identified and the owner of each activity is established, a study start-up timeline or tracking tool should be prepared. There are several options for tools to support this effort. The **Countdown to Enrollment** is an Excel file that lists all of the study specific start-up activities along with the responsible parties and whether or not the activity is required a) before the first subject can be enrolled in the study; b) before the first subject can be enrolled at a specific site; or c) before an individual is permitted to engage in an activity (e.g., completion of randomization system training may be required prior to authorizing an individual to be able to use the randomization system to enroll a subject). The document also captures projected and actual dates of activity completion and denotes via comment the other activities

that are required prior to the completion of other activities. This tool is available in the Project Management folder of the Clinical Tool Box.

There are project management software programs available that support the development of a start-up timeline and Gantt chart including Microsoft Project. Other project management applications may also be used.

The study **Start-up Timeline Calculator** takes advantage of more widely available software (i.e., MS Excel) while simultaneously providing the opportunity to model activity dependencies. There is a simple version of this calculator that can be used to get a rough estimate of when enrollment can begin and a more complex calculator that can be used to create a detailed start-up timeline with dependencies. This tool is available in the Project Management folder of Clinical Tool Box and in the NIDCR Toolkit.

3.3.3 Conduct Regular Meetings during Start-up

Regular meetings with study staff, the PI, and the site PIs will facilitate study organization, communication, and tracking of progress toward initiation and activation. An OCTOM representative may participate in these meetings as well. The **Running Agenda and Meeting Minutes (RAMM)** document is an MS Excel file with multiple spreadsheets (see the Project Management folder of Clinical Tool Box and the NIDCR Toolkit). The document acts both as minutes from previous meetings and an agenda for the upcoming meeting. Additional pages of the spreadsheet capture study announcements, action items, and decisions. This one document retains items from all previous meetings, so that the one file is a complete archive for meeting minutes.

Regardless of the choice of start-up tracking tool (see Section 3.3.2), it is strongly recommended that the tool is prepared early in the start-up process, maintained vigorously during the process, and discussed regularly at team meetings, so that implications of missed target dates can be illuminated.

3.4 Manual of Procedures (MOP) or Other Study Process Documentation

A Manual of Procedures (MOP) is a handbook that guides a study's conduct and operations. It supplements the study protocol by detailing a study's organization, operational data definitions,

recruitment, screening, enrollment, randomization, intervention procedures and follow-up procedures, data collection methods, data flow, Case Report Forms (CRFs), and quality control procedures. The purpose of the MOP is to facilitate consistency in protocol implementation and data collection across participants and clinical sites. Procedures in the MOP should be followed with the same degree of vigor as those documented in the protocol. Use of the MOP increases the likelihood that the results of the study will be scientifically credible and provides reassurance that participant safety and scientific integrity are closely monitored.

A MOP or set of study-specific Standard Operating Procedures (SOPs) and other procedural documents should be prepared prior to site initiation. See the **Manual of Procedures Template** (in the Project Management folder of Clinical Tool Box and in the NIDCR Toolkit) for a template that includes detailed guidance for the content.

4 REGULATORY REQUIREMENTS

4.1 Institutional Review Board (IRB)

Each site will submit the final protocol, consent/assent documents, and other applicable materials to the governing IRB. IRB approval of materials is required for a) release of grant funds, via the Clinical Terms of Award process and b) site activation for enrollment. See Section 3.2.3 for additional details regarding IRB review.

4.2 Submission of Other Applications/Request/Information

4.2.1 Certificate of Confidentiality

Protocols that collect sensitive data may benefit from a certificate of confidentiality (see http://grants.nih.gov/grants/policy/coc/). According to the website, “Certificates of Confidentiality are issued by the National Institutes of Health (NIH) to protect identifiable research information from forced disclosure. They allow the investigator and others who have access to research records to refuse to disclose identifying information on research participants in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level. Certificates of Confidentiality may be granted for studies collecting information that, if disclosed, could have adverse consequences for subjects or damage their financial standing,

employability, insurability, or reputation. By protecting researchers and institutions from being compelled to disclose information that would identify research subjects, Certificates of Confidentiality help achieve the research objectives and promote participation in studies by assuring confidentiality and privacy to participants." Applications for a Certificate of Confidentiality are submitted to the NIDCR Certificate of Confidentiality Coordinator. The IRB approved CD must include a description of the protections and limitations of the Certificate of Confidentiality, including the circumstances in which the investigators plan to disclose voluntarily identifying information about research participants. Certificates from NIDCR generally take several weeks to be issued.

4.2.2 Investigational New Drug Application (IND) or Investigational Device Exemption (IDE)

If an IND or IDE is anticipated, early communication with the NIDCR Program Official, Medical Monitor, and OCTOM is highly recommended. The **IND Applicability Checklist** can be used to determine if an IND is needed (see the Regulatory folder of Clinical Tool Box and the NIDCR Toolkit).

For guidance on the IND application process, see: http://www.fda.gov/drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved/approvalapplications/investigationalnewdrugindapplication/default.htm.

Once an IND application has been submitted, you must plan for a minimum of 30 days before beginning the study. Often the FDA will require additional information after the initial review, which can further impact study start-up timelines.

4.2.3 ClinicalTrials.gov

The PI is responsible for registering applicable clinical trials into ClinicalTrials.gov prior to enrolling the first subject in the study. For more information see http://clinicaltrials.gov/.

4.3 Essential Documents

Per Good Clinical Practice (GCP), essential documents are those documents that "individually and collectively permit evaluation of the conduct of a study and the quality of the data

produced." Some essential documents should be filed only at the study site, others only in the sponsor (e.g., the IND holder, when applicable) files; the rest (the majority) should be maintained ultimately in both locations.

The **Essential Document Management Tool** clarifies the collection of these documents (see the Essential Documents folder of Clinical Tool Box). It provides both a recommended filing structure and references to relevant regulations and guidelines. Certain documents must be in place prior to site initiation and are identified in this tool.

Clinical sites can also use the **Extramural Essential Document Binder Tabs** to help organize the site files and clarify the required content of those files. (Synonyms for this binder include: Investigator Binder, Regulatory Binder, Investigational Site File (ISF) or Study Binder.) Two versions of these binder tabs are posted within the Essential Documents tab of Clinical Tool Box - one set that includes the instructions and sample documents, and one set that does not, for ease of printing.

Many of the site essential documents have corresponding templates available on the Clinical Tool Box page of the CROMS website and in the NIDCR Toolkit. These include, but are not limited to: **Site Screening and Enrollment Log**, **Training Log**, **Delegation of Responsibilities Log**, and a link to the **FDA 1572**. Please peruse these websites for the full list of available templates.

The site essential documents will either be reviewed prior to the site initiation visit, if CROMS is responsible for maintaining the Trial Master File, or they will be reviewed by CROMS and/or OCTOM during the site initiation visit. Files must be deemed complete by the DCC or CROMS prior to site activation.

5 SUBJECT SAFETY OVERSIGHT

5.1 Safety Monitoring Plan (SMP)

Clinical research studies must be monitored for safety and potential risk to the subject. Monitoring of participant/subject safety may be described in the protocol. A safety monitoring

plan will be prepared by the PI's designee or by CROMS, when appropriate. This plan must be reviewed and approved by the NIDCR Medical Monitor prior to site activation.

See Section 3.2.2 for further details of the Safety Oversight process.

In addition to Adverse Event (AE)/Serious Adverse Event (SAE) monitoring, the protocol and SMP should detail the process for monitoring and reporting Unanticipated Problems.

6 DATA AND QUALITY MANAGEMENT

6.1 Data Collection Tools

Study data must be initially captured using one or more of the following methods: on paper source documents, in electronic medical records or other electronic databases (e.g., central laboratory database), and/or in Electronic Data Capture (EDC) systems. Please note that GCP requires that the protocol describes instances when the EDC acts as the source document.

If paper CRFs are used, the DCC may provide support for initial data capture by providing source document templates. These are tools the site can use to create an initial data record that is able to be easily matched to the data collection instrument. Often these templates are created from the CRF. IMPORTANT NOTE: templates of this nature should only be used as the initial data record. If the data are captured elsewhere, they MUST NOT be transcribed onto source document templates. Each transcription increases the likelihood of a data error.

The Case Report Form will be designed to collect study related data in a manner that is practical and able to be easily rendered into an electronic database. Forms will be developed using Good Data Management Practices (GDMP), as established by the Society for Clinical Data Management, or using other best data management practices. The method for committing data to an electronic database should be determined during the start-up phase. Some studies may choose to use paper CRFs and to have a DCC enter the data into the database. Many EDCs permit immediate feedback of potential data errors, so they can be resolved in real time.

Sites that wish to create their own clinical database, or use support from a DCC, should use the **Data Management Considerations** document to confirm that they or the DCC have sufficient experience, adequate expertise, and appropriately validated software (see the Data

Management section of Clinical Tool Box and the NIDCR Toolkit). OCTOM can assist sites in determining experience, expertise, and appropriate software for the study. The CRF and data collection system should be in place prior to site initiation but must be in place prior to site activation.

6.2 Clinical Data Management Plan

A Clinical Data Management Plan (CDMP) is the document that summarizes the study's approach to handling the data. A CDMP includes, but is not limited to: a) a description of the system being used to handle the clinical data; b) a description of the validation plan (i.e., methods for confirming that data are correct, such as range checks, valid value checks, and data cross-checks); c) a description of how external data will be reviewed and integrated with the clinical database; and d) documentation of the resultant clinical database that will be available for analysis. All studies are required to prepare a CDMP. See the Data Management section of Clinical Tool Box and the NIDCR Toolkit for a **Clinical Data Management Plan Template**.

6.3 Statistical Analysis Planning

The protocol will contain sufficient statistical detail to describe the statistical analyses and the basis for any sample size and power calculations. A statistical analysis plan (SAP) may ultimately be prepared to elaborate on those protocol specifications. The SAP is not required prior to study start-up, but should be completed well in advance of database lock.

Statistical review of the CRF is another form of statistical planning. Review of the CRF by the study statistician ensures collection of the data that are necessary to support the protocol specified analyses. A statistical review of the protocol and CRF is necessary to ensure the study is appropriately designed and powered to meet its objectives.

6.4 Quality Management Plan (QMP)

Quality management is a process of checking clinical research records for completion, accuracy and logic. It is performed by clinical research site staff to identify and resolve problems found in

the conduct of their clinical research. This review and documentation of their findings and their plans to resolve and prevent problems is called a corrective and preventive action plan.

The quality management plan describes the process designed to ensure compliance with human subject safety, quality and integrity of the data, and compliance with the protocol. The NIDCR requests that a quality management plan be submitted to NIDCR for review and comment. OCTOM and CROMS can provide the site assistance with developing a quality management plan that is appropriate for the study design.

Quality Management tools are available in the Quality Management section of Clinical Tool Box and in the NIDCR Toolkit. Items include:

An Introduction to Site-Level Quality Management within the Clinical Research Process	A slide presentation, providing an overview of quality management (QM) and of these QM tools
Clinical Quality Management Plan (CQMP)Template	A template, including instructional and sample text, to be used to document the study/site specific approach to quality management
Quality Management of Clinical Research – Brief Overview	An overview of QM term definitions, activity examples, and available tools and templates
Quality Management Subject/Participant Data Review Tool	A checklist that can be used to conduct reviews of subject level data and processes
Quality Management Study-wide Review Tool	A checklist of study-level quality review activities
Quality Management Summary Report Template	A template to support the regular reporting of the quality review activities, as specified in the CQMP

7 SPECIMEN AND MATERIALS MANAGEMENT

7.1 Specimen Handling and Tracking

Studies that include specimen collection should ensure that the process for collection, handling, storage, and tracking is clearly established and documented. Often this documentation will be included as a section in the MOP or as a stand-alone Standard Operating Procedure.

7.2 Specimen and Other Materials

Materials necessary to conduct the protocol should be on-site prior to the initiation visit. CROMS and OCTOM will be responsible for verifying that all materials are available during the initiation visit. Materials could include specimen tubes and labels, packing and shipping materials, procedure equipment and supplies, paper CRFs (if applicable), and participant/subject informational or instructional material.

8 CLINICAL SITE MONITORING

8.1 Pre-Site Initiation Teleconference with OCTOM and CROMS

In order to help sites ensure that they are sufficiently prepared to begin participant enrollment, OCTOM, CROMS, and the Program Official may conduct a site initiation teleconference with the site PI and the study coordinator prior to the site initiation visit. Refer to the **Site Assessment Questionnaire** tool for samples of questions that may be asked of the study team during this teleconference (see the Clinical Monitoring folder of Clinical Tool Box and the NIDCR Toolkit). If this questionnaire is used, CROMS will pre-fill as much of it as possible to avoid unnecessary effort on the part of the clinical site. CROMS may request advance copies of key study documents for review (e.g., protocol, CD, MOP, CRF, study timeline) prior to the teleconference.

Teleconference discussions / questionnaire responses and review of the key study documents will guide the scheduling of the initiation visit.

CROMS has staff available to support sites with most aspects of the start-up and initiation process (e.g., familiarizing teams with available tools, supporting the establishment of timelines,

preparing for the site initiation visit). Requests for CROMS support should be directed to the study's Program Official, who will communicate with OCTOM.

8.2 Clinical Site Monitoring Plan (CMP)

Clinical site monitoring is performed by a site monitor to provide information to NIDCR on study progress and conduct to ensure the study is conducted, recorded, and reported in accordance with the protocol, Good Clinical Practice standards, and any applicable regulatory requirements.

When assigned clinical monitoring responsibilities by OCTOM, CROMS will prepare a clinical monitoring plan (CMP) for the study. The clinical research associate (CRA) is the individual from CROMS (or elsewhere, if so designated) who will be responsible for preparing the CMP and for conducting site monitoring visits. The CRA will tailor the **Clinical Monitoring Plan Template** to meet the needs of the study (see the Clinical Monitoring folder of Clinical Tool Box and the NIDCR Toolkit). The document will be approved by OCTOM, but approval is not required prior to site activation. If monitoring is performed by a group other than CROMS, the monitoring plan and visit reports must be submitted to the Program Official and OCTOM.

8.3 Site Initiation Visit (SIV)

The SIV is led by the site Principal Investigator and the site study team. Additional participants/attendees include the DCC team, the NIDCR Program Official, a representative of OCTOM, and the CROMS CRA. See Section 9.1 for additional details.

9 SITE INITIATION, CTOA, AND ACTIVATION

This section details the process for site initiation, meeting the CToA, and site activation. See Appendix B for a summary of items that are recommended or required at each step.

9.1 Site Initiation Visit (SIV)

When the Program Official and OCTOM determine that the site is sufficiently prepared to begin participant recruitment, CROMS will schedule an Initiation Visit to the site. The Site Initiation Visit (SIV) should be scheduled soon before the anticipated activation date so information discussed at the visit is retained by the site staff. If the study is not initiated at a site within 8

weeks of the Site Initiation Visit, appropriate material from the SIV will be reviewed again with the site staff. Participants will include the site PI, the CROMS study coordinator (if applicable) and/or the CROMS CRA, an OCTOM representative if needed, the Program Official, the site PI, all other relevant co-investigators, and site staff. Visits may be 1 or 2 days depending on the scope of the agenda. A **Site Initiation Visit Agenda Template** is available for study specific customization. Also available is an **annotated version of the SIV Agenda Template** which includes additional guidance about the meeting's content and conduct (see the Clinical Monitoring section of Clinical Tool Box and the NIDCR Toolkit [non-annotated only]). Please refer to this agenda for activities that will occur during the visit. In general, the meeting will include protocol review and detailed discussion of study implementation; MOP/study procedures review; data handling and electronic systems training; investigational product distribution and handling (if applicable); specimen processing, storage, and shipping procedures; safety reporting; clinical monitoring; good clinical practice training: sponsor and investigator responsibilities; and record retention. If the Essential Document files have not already been reviewed and approved prior to the visit, CROMS and OCTOM will review during the visit.

A facilities tour is common and a review of other on-site study materials may be conducted.

CROMS will organize and guide the Site Initiation Visit when it holds responsibility for study management and other clinical services. If CROMS is not providing project management support for the study, the site PI will be responsible for the agenda and for guiding the visit.

CROMS will issue a visit report that details the findings from the visit. The report will include a list of action items and will clarify any items that remain outstanding and that must be completed prior to activation. The report will be reviewed by OCTOM, and the final version will be sent to the PI and site PI with a copy to the Program Official.

9.2 Clinical Terms of Award

The NIH responsibilities associated with clinical terms of award (CToA) are well documented in **NIDCR Clinical Terms of Award.** The Program Official tracks CToA in the electronic CToA system that is accessed via the CROMS website.

Awardees must comply with the Clinical Terms of Award which are incorporated into the Notice of Grant Award for grants and cooperative agreements that involve human subjects and meet the NIH definition of "clinical research."

Materials required to meet CToA include:

- IRB-approved clinical research protocol identified by protocol title, version number, and date, and including details of study design, proposed interventions, subject eligibility criteria, and plans for assessing, managing, and reporting adverse events and unanticipated problems.
- Documentation of IRB approval, citing the version number and date of the documents reviewed and approved.
- IRB approved consent document, identified by version number, date, or both.
- Plans for data and safety monitoring. This might be described in the protocol, be a separate procedural document, or be a charter of a safety oversight committee.

See the Clinical Terms of Award for detailed specifications of these requirements.

When CToA have been met, the Program Official will enter the information into the electronic CToA system. The system allows the Program Official to generate an email notification to the NIDCR Grants Management Branch that Clinical Terms of Award have been met. Grants Management will notify the institution's business official and principal investigator that funds may be drawn down from the payment system to support subject enrollment. The Program Official will complete the Site Activation Checklist (See section 9.3 and Appendix A) when the CToA have been met.

9.3 Site Activation

A site can be activated only after it has met CToA. See Appendix A for the Site Activation Checklist. This checklist will be prepared by CROMS with the Program Official, and used by the Program Official to determine when all additional requirements have been met for site activation. When all of these additional requirements have been met, CROMS will send the completed checklist to OCTOM for review. If all components of the Checklist are complete,

OCTOM will sign the form and recommend to the Program Official that the site may be activated. The Program Official will verify that CToA have been met and will approve the site for activation by signing the Checklist. The Program Official will send a Site Activation Notification letter (see Appendix C) to the site PI and will provide a copy of the memo and Checklist to CROMS for the study file.

For studies that involve a study product, a process must be established to ensure that the product is not released for use in the study until the site has been approved for activation.

10 APPENDICES

APPENDIX A: Protocol <#> EXTRAMURAL SITE ACTIVATION CHECKLIST

<PROTOCOL TITLE>

Site Name: **Site #:**

Protocol Version and Date:

Item	Date
1. IRB Approval Received for Protocol, Consent Form, and Other Applicable Documents	
2. NIDCR Safety Committee (e.g., CSOC, DSMB, DSMC) review complete or confirmation that no Safety Committee will be required	
3. Site Essential Document File Approved	
4. Case Report Forms Final	
5. Data Management System Ready for Data Entry and Clinical Data Management Plan Drafted	
6. Study Materials on Site *{Instruction: List types of required materials separately (e.g., specimen labels and tubes, questionnaires, supplies for procedures).}*	
7. Site Initiation Visit Completed • Trained on protocol, study procedures (MOP), electronic systems. (Note this requirement includes re-training, if site activation is more than 8 weeks after the site initiation visit.) • Facilities deemed acceptable	
8. Action Items from Site Initiation Visit Required for Site Activation Completed	
9. Study Specific Requirements Met *{Instruction: Update with relevant list.}*	
10. CToA Met and Notification of Award Sent	

APPENDIX A: Protocol <#> EXTRAMURAL SITE ACTIVATION CHECKLIST

<PROTOCOL TITLE>

Site Name: **Site #:**

Protocol Version and Date:

CROMS/DCC Representative Completing the Checklist — Date

Activation Recommended by <OCTOM Representative>, OCTOM — Date

Activation Approved by <NIDCR Program Official>, NIDCR[1] — Date

[1] Forward an electronic version of this document that includes all signatures to the CROMS representative for storage in the study file.

APPENDIX B: Requirements for CToA/Grant, Initiation, and Activation

Item	CToA/Grant	Initiation	Activation
IRB Approved Protocol	Required	Required	Required
IRB Approved Consent Document(s)	Required	Required	Required
IRB Approval of Study Materials	Not Required	Required	Required
Safety Oversight Committee Review of Protocol	Not Required	Recommended	Required
Manual of Procedures or Set of Study Specific Procedural Documents	Not Required	DRAFT Required	Required
Essential Document Packet Complete	Not Required	Required	Required
Essential Document Packet Approved by CROMS/OCTOM	Required	Not Required	Required
Safety Monitoring Plan	Required	DRAFT Required	Required
Case Report Forms	Not Required	Recommended	Required
Data Management System	Not Required	Recommended	Required
Clinical Data Management Plan	Not Required	Recommended	DRAFT Required
Quality Management Plan	Not Required	DRAFT Required	Required
Clinical Monitoring Plan	Not Required	Not Required	Recommended
Human Subjects Training	Required per Grant	Not Required	Required
IND or IDE[1]	Required	Required	Required
Targeted/Planned Enrollment Table (PHS 398)	Required per Grant	Not Required	Required
Approval of Recombinant DNA Advisory Committee and Institutional Biosafety Committee[1]	Required	Not Required	Required
Site Initiation Visit (SIV) Completed	Not Required	Not Required	Required
Completion of Action Items From SIV	Not Required	Not Applicable	Required
Study Drug Ready to be Dispensed[1]	Not Required	Not Required	Required[2]

[1]Only when applicable.

[2]Study drug may not be dispensed until after activation.

APPENDIX C: Site Activation Notification Template

TO: <Site Principal Investigator>

FROM: <Program Official>

SUBJECT: Site Activation: <Site>

PROTOCOL: <Protocol Number: Title>

DATE: <Date>

CC: OCTOM
<Grant PI>
<Other involved parties as determined by Program Official>

I am pleased that you will be conducting the above referenced study. This Site Activation Notification confirms that your protocol, consent, and IRB approvals have been received and have met NIDCR Clinical Terms of Award, and clinical operational systems are in place. Your site is now activated and may begin subject enrollment.

In the future, to help ensure subject safety and data integrity, please provide me with copies of documents related to all major changes, including protocol amendments, changes to the consent, termination or suspension of subject accrual, changes in IRB approval, IRB continuing review, changes in key study personnel, and any problems or issues that could affect the safety of subjects or integrity of the study.

Please let us know if you have any questions or concerns regarding the initiation or conduct of this study.

APPENDIX D: Clinical Trial Progression in Behavioral or Social Intervention Research

A controlled study involving human subjects, designed to test a well-characterized behavioral intervention and to evaluate prospectively the effect of the behavioral or psychosocial intervention on one or more aspects of public health. “Behavioral intervention” is a broad term that describes an approach to preventing, maintaining or changing behavior through the use of non-medical or non-pharmaceutical techniques. Examples of behavioral interventions include, but are not limited to: health education, health promotion, teaching skills, providing social support, resolving family conflict, screening and brief intervention for health behaviors, establishing reward systems for healthy behavior, changing organizational structure, and more. Behavioral interventions range in intensity (very brief to intensive), duration (a single session to sessions over the course of years), mode of delivery (in person, computer, other technology), and complexity (simple messages to sophisticated strategies). Behavioral intervention research proceeds through different phases, which are similar to phases of drug or device development. The behavioral intervention research field tends to describe these phases as “stages”, to identify the research as behavioral.

Stage 1a: Behavioral intervention development work begins in Stage 1a. During this early stage, findings from basic or clinical science about behavior, and/or clinical observations about behavior, are translated into a draft behavioral intervention, and the target population and/or interventionists provide feedback to ensure the intervention is acceptable and feasible.

During this stage, investigators should: define the clinical problem of interest (i.e., the theory or logic model of the problem), and define the rationale for why the intervention is expected to address the problem (i.e., the theory or logic model of change). Essential to defining the rationale for the intervention is a clear identification of proposed mediators and moderators. Mediators are intermediate variables targeted by the intervention that are causally related to a desired outcome. For instance, an intervention to improve oral health may involve improving nutrition. Presumably, the nutrition intervention improves oral health indirectly, by improving a mediating variable, such as eating behavior. Moderators are variables for which the relationship between the intervention and the desired outcome varies. In the above example, if the nutrition intervention led to greater oral health improvements for women than for men, sex/gender would be a moderator of the intervention-outcome relationship.

Activities appropriate for Stage 1a behavioral intervention development may include collection of qualitative data from stakeholders as an early check on the relevance and acceptability of the intervention, and iterative feedback between this data collection and further adaptations of the draft intervention manual. One product of this stage of research should be a draft behavioral intervention that is described in sufficient detail--typically in an intervention manual--so that it can be delivered as intended.

Another activity appropriate for Stage 1a research—and each subsequent stage--is testing the proposed rationale or theory for the intervention. During Stage 1a, testing the intervention rationale may take the form of highly-controlled, small-scale, lab-based tests. For instance, let's suppose that our nutrition intervention is expected to work by increasing the salience of healthy foods during meal times, which in turn increases choosing healthy foods. During Stage 1a, we could develop a psychometrically sound method for varying the salience of healthy foods, and then test our rationale by manipulating the salience of healthy foods, and measuring food choices. Testing the intervention rationale also may take other forms, such as in-depth case studies, within-subjects studies, time series studies, and more. Stage 1a activities may not involve analyses of statistical significance. However, if analyses involve tests of significance, adequate statistical power is expected.

Unlike other stages of behavioral intervention development that have analogous phases in drug or device development, Stage 1a is unique to behavioral intervention development research.

Stage 1b: Once a draft behavioral intervention manual is developed, the next stage involves testing the intervention for acceptability to the target population and to the intended interventionists, and testing the feasibility of conducting an efficacy trial in subsequent stages. Often, testing for acceptability and feasibility involves qualitative data collection rather than significance-testing using quantitative data. Some models of behavioral intervention development encourage investigators to conduct a small-scale, often under-powered, randomized clinical trial during this stage, in order to estimate the effect size of the draft intervention. The NIDCR model does not encourage under-powered randomized clinical trials. Instead, the NIDCR encourages investigators to ensure acceptability and feasibility in Stage 1b, typically using methods where statistical power and significance are not relevant. For instance, acceptability might be assessed by conducting focus groups with participants in the draft intervention. Feasibility of delivering the intervention might be assessed by tracking any problems that occur during initial delivery of the intervention to a small sample. Stage 1b activities may not involve analyses of statistical significance. However, if analyses involve tests of significance, adequate statistical power is expected.

The NIDCR views sufficiently-powered randomized clinical trials as appropriate for Stage 2 behavioral intervention research.

Stage 1b of behavioral intervention research is similar to Phase I in drug and device development.

Stage II: Once a behavioral intervention has been shown to be acceptable to the target population and interventionists, and has been shown to be feasible to deliver and test, Stage II research begins. The main goal of this stage is to identify causal relationships between the intervention and target outcomes. In other words, Stage II activities test the efficacy of an intervention, and further clarify variables that mediate and moderate the intervention's effects. Typically—but not always--an efficacy test involves

comparing the intervention to one or more control or comparison groups. If statistical analyses involve tests of significance, adequate statistical power is expected.

Clarifying mediators and moderators of a behavioral or social intervention may involve a variety of methods and study designs. Most experts in theory testing and in statistical mediation encourage certain considerations when studying mediation and moderation. Among these considerations are that hypothesized mediators and moderators: 1) are measured frequently enough to capture meaningful change; 2) are measured *before* target outcomes in order to establish temporal relationships; and 3) are measured in the experimental and comparison condition(s) to establish specificity of effects.

Strict controls are expected in Stage II behavioral intervention research. Whether conducted in a laboratory or community setting, or by researchers or community clinicians, Stage 2 research expects strict adherence to intervention fidelity, delivery by well-trained interventionists, a well-defined population, and sound measurement of outcomes and other variables.

Stage II behavioral intervention research is roughly analogous to Phases II and III in drug or device development.

Stage III: The purpose of Stage III research is to prepare and/or adapt an efficacious intervention to be delivered in community (non-research) settings by community interventionists in a sustainable way. Some models of behavioral intervention research call this stage “effectiveness research”, although the NIDCR draws an important distinction between typical effectiveness research and what we consider Stage III research. Specifically, we consider as vital to Stage III research rigorous measurement of deviations from fidelity, and of variables that might affect intervention delivery. Stage III is not meant to be a return to “black box” intervention research, but rather a systematic study of how an intervention can be delivered in a “real world setting”.

Examples of Stage III research activities include, but are not limited to: 1) comparing the adaptations community interventionists make to an efficacious intervention to accommodate different service delivery systems or specific populations; 2) adapting an efficacious intervention based on Stage II mediation and/or moderation analyses, and comparing the adapted version(s) to the standard intervention; 3) developing and testing methods of training and supervising community interventionists in an efficacious intervention; and 4) identifying organizational characteristics that facilitate delivery of an efficacious intervention.

Stage III behavioral intervention research is similar to Phase IV drug or device development in its attempt to meet the needs of the general population, and to continue to monitor limitations of an intervention’s effects.

Study Start-up Tips

Beginning with the first conversation regarding a potential research study and ends with the screening/ enrollment of the first subject.

To Do:

- Get organized
- Develop a checklist of procedures to be completed
- Create a contact list for the potential study
- Begin a regulatory binder
- Develop workflows and study start-up processes
- Identify who is responsible for each step
- Ensure everyone is aware of their role/responsibility and provide training
- Create a study-specific timeline
- Communicate the deadlines for the timeline to all parties involved
- Follow-up with involved parties frequently to ensure the timeline is followed as closely as possible
- Make sure everyone in study start-up is fully trained and understands their role

Steps:

- Discussion of potential study
- Feasibility
- Pre-study visit, possibly
- Site selection
- Budget/contract negotiations, execution
- Investigator meeting, possibly
- Submission of documents
- Study discussion with ancillary departments/other entities that will perform procedures
- Training
- Setting up accounts , as needed
- Initiation Visit
- IRB approval
- Site activation

Some of these steps will occur at the same time. They will not always occur in this particular order.

Some steps may be added or deleted for the particular study you are conducting.

Sessions 9 and 10

Essential Documents and Documentation

Good Documentation Best Practices

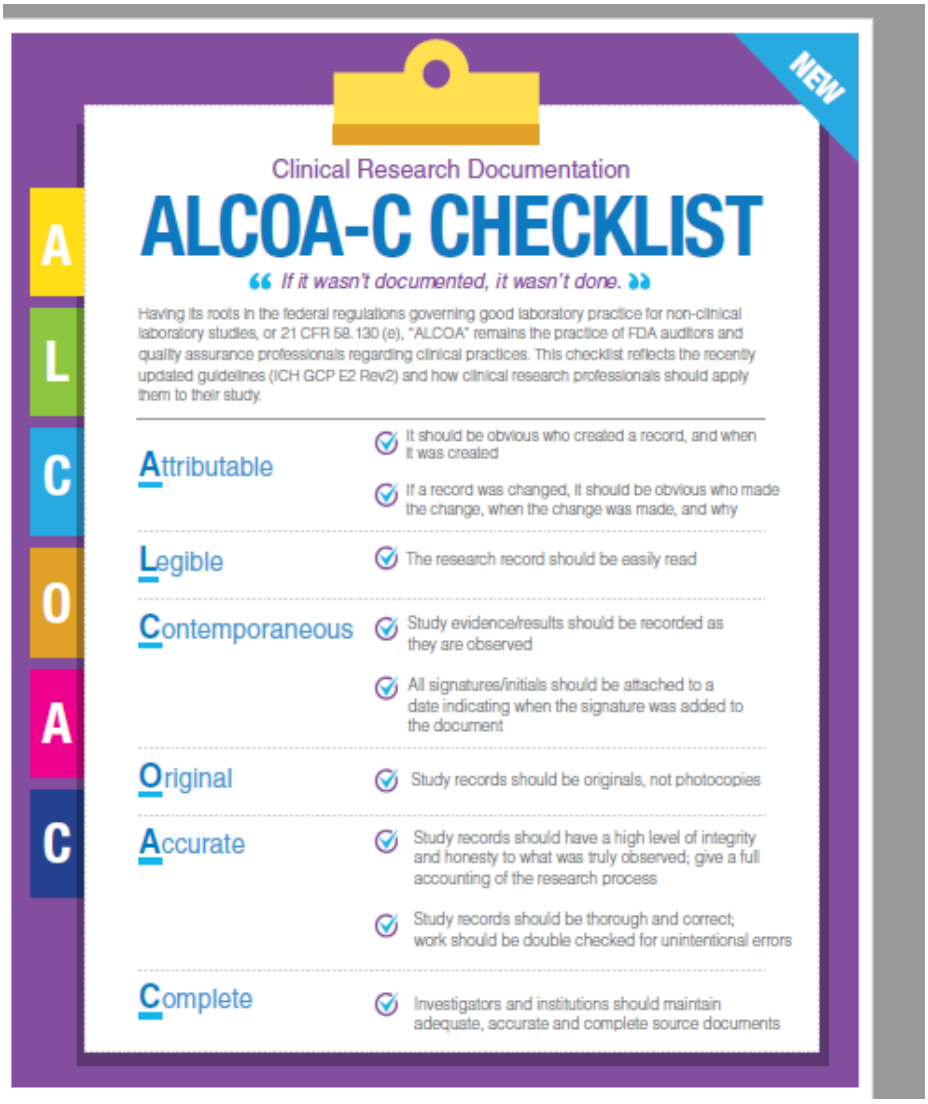
Best Practices:

- ✓ Follow ALCOA-C
    - Entries and changes to those entries should be made by authorized study team members as delegated by the PI
- ✓ Document ***what is*** - and ***what is not*** – ***done***
    - **What is not documented---Was not done!**
- ✓ Provide reasons for any missed information
- ✓ Use of indelible **blue** or **black** ink on paper forms
    - Reduces fading over time or smudging
    - No pencils, felt-tipped markers
- ✓ No back or future dating – use of current date when entries are made
- ✓ Do not use of "ditto" marks for repetitive data
- ✓ For any instrument printouts, adhere printout to chart with clear adhesive tape and include initials and date where the printout is attached
- ✓ Any printouts sent for data purposes need to be coded and de-identified of subject's health information. Maintain original source document
- ✓ Include reason for any missed information
- ✓ Be thorough and timely when documenting
- ✓ Perform quality checks
- ✓ Be Proactive when finding errors or omissions

Best Practices When Correcting Study Documentation

- ✓ *Errors happen*! Corrections are expected
- ✓ SLIDE rule for errors
- ✓ Single *line through incorrect information*,

- ✓ Make sure the original entry is not to obscured when the correction is made
- ✓ Include reason for any missed information
- ✓ Do not use “white out”
- ✓ Do not write over data (e.g. turning a 9 into a 0)
- ✓ Enter the **correct** information
- ✓ Initial and date when the corrections were made



ALCOA-C Checklist from imarc

Essential Documents for the Conduct of a Clinical Trial

Essential Documents:

- **Individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced**
- **Serve to demonstrate the compliance of the investigator, sponsor, and the monitor with the standards of Good Clinical Practice and with all applicable regulatory requirements**
- **Being filed in a timely manner can greatly assist in the successful management of a trial**
- **Usually audited and inspected as part of the process to confirm validity of the trial conduct and the integrity of the data collected**

Essential documents are grouped in three sections according to the stage of the trial:

- **Documents to have before the trial starts**
- **Documents to have during the clinical Conduct of the trial**
- **Documents to have after the completion or termination of the trial**

Documents used before the trial starts: (in alphabetical order)

- **Approval of institution where clinical trial is being conducted**
- **CDA (executed)**
- **Correspondence**
  - **PI/Site and Institution**
  - **PI/Site and Monitor**
  - **PI/Site and Sponsor/CRO**
  - **Internal**
- **Credentialing/ Certification documents**
  - **Key personnel**
- **CRFs (clean copy)**
  - **Questionnaires**
  - **Subject Diaries**
  - **Surveys**
- **CTA/CSA (executed)**
  - **Budget**
- **CV/Resume**

  - **Key personnel**
  - **PI**
  - **Sub/co-investigators**
- **Delegation of Authority log**
- **FDF (signed)**
  - **Key personnel**
- **Feasibility assessment**
- **IB/Device manual/Instructions/Drug insert**
- **ICF**
  - **All IRB approved versions**
- **IP accountability**
  - **Receipt**
  - **Shipping**
  - **Storage/Maintenance**
    - **Temperature logs**
  - **Decoding procedures for blinded trials**
  - **Dispensing Instructions**
    - **Randomization instructions**
- **IRB documentation**
  - **Advertisements**
  - **Approval**
  - **Correspondence**
  - **FWA/ Membership list**
  - **Subject information sheets/instruction**
  - **Submissions**
  - **DSMB Reports**
- **Laboratory documents**
  - **Certification**
  - **CLIA**
  - **CV/Resume/License of Laboratory Director**
  - **Normal Ranges**
  - **Laboratory manual/instructions**
    - **Obtaining/storing/shipping specimens**

- **Licenses**
  - **Key personnel**
- **Monitor's documentation**
  - **Initiation report**
  - **Sign-in sheet**
  - **Training**

- **Protocol**
  - **Signed signature page**
  - **All versions received at site**
- **SOPs/MOP/Written procedures**
- **Supplies**
  - **Dates**
  - **Receipt**
  - **Storage**
- **Training documentation**
  - **By Site— in services/meetings/written procedures**
  - **By sponsor/CRO----Site visit/initiation visit/online/investigator meetings**
- **1572/Device agreement (signed//dated)**

<u>Documents used during the Conduct of the trial:</u>

- **AE/SAE documentation (follow until resolution of the event)**
- **Approval of institution where clinical trial is being conducted**
- **Billing records/statements**
- **Case histories**
- **CRFs (completed and signed)**
  - **Completion instructions**
  - **Resolution to queries**
- **Correspondence**
  - **PI/Site and Institution**
  - **PI/Site and Monitor**
    - **Monitoring site visit results/letters**
  - **PI/Site and Sponsor/CRO**
  - **Internal**
  - **Subject/LAR**
- **DSMB reports**
- **IB**
  - **Submission to IRB**
  - **Training**
  - **Updates**
- **ICF**
  - **All IRB approved versions**
  - **All subject/LAR signed versions (original copy)**
  - **Continuing process**
- **IND Safety letters**
- **IP accountability**
  - **Dispensation documents**
  - **Shipping receipts**

  - **Storage and Maintenance**
  - **Subject compliance**
- **IRB documents**
  - **Amendments**
  - **Approvals**
  - **Audit/Monitoring reports**
  - **Continuing/Annual Review**
  - **Correspondence**
  - **Deviations/violations/exceptions**
  - **Revisions**
  - **Submissions**
- **Logs**
  - **Enrollment**
  - **Master**
  - **Randomization**
  - **Screening**
- **Notes-to-File**
- **Protocol**
  - **Amendments**
  - **Revisions**
  - **Versions**
- **QA/QI Process**
  - **Internal monitoring/auditing**
- **SOPs/MOP/Written procedures**
- **Source Documents**
- **Specimen log/retention**
- **Subject Records**
  - **Consults**
  - **Progress notes**
  - **Reports**
- **Supplies**
  - **Calibration logs**
  - **Dates**
  - **Receipt**
  - **Storage**
- **Subject Payments**
- **Training-Continuing process**
  - **Ongoing training needs to be documented—QA/QI system**
  - **By Site— in services/meetings/written procedures**
  - **By sponsor/CRO----Site visit/initiation visit/online/investigator meetings**
- **Updates for the following forms as necessary:**

- **Advertisements**
- **CV/license**
- **Delegation of Authority (PI to sign when change)**
- **FDF**
- **Laboratory documents**
- **Logs**
  - **Enrollment**
  - **Master**
  - **Monitor sign in log**
  - **Randomization**
  - **Screening**
- **Subject information sheets/instructions**
- **1572 updates**
  - **change in site, staff, facilities (such as labs)**

<u>Documents used at/after the completion /termination of the trial:</u>

- **Correspondence**
- **Close-out Visit documentation**
  - **Letter from sponsor re: pending closure**
  - **Letter of close out visit**
  - **Reconciliation of any unresolved issues**
- **IP Accountability**
  - **Destruction**
  - **Final reconciliation**
  - **Return**
- **IRB**
  - **Form 7**
  - **Institution**
- **Storage**
- **Supplies**
  - **Dates**
  - **Receipt**
  - **Return**
  - **Storage**

List of Possible Needed SOPs

- Training
- Development/Approval/Review of SOPs
- Responsibilities/Roles of Study Team
- Study Feasibility Assessment
- Informed Consent Process
- Protection of Subjects
- Conflict of Interest
- Subject Recruitment
- Misconduct
- SAEs/AEs
- IP Accountability
- Monitoring
- Study Closure
- Essential Documents
- Confidentiality

Regulatory Binder (RB): Best Practices and Resources

Alternative Names:

- **Investigator Site Files (ISF)**
- **Study Binder**
- **Master Trial File (MTF)**

Purpose:

- **Demonstrates compliance with ICH GCP compliance and applicable regulatory requirements**
- **Provide an organizational framework of study Essential Documents**
- **Evaluation of the conduct and data quality produced in a study project**
- **Permits evaluation/auditing of the conduct of a research study**

Location

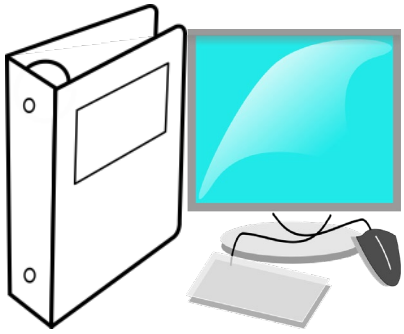
- **Paper or electronic format**
- **Locked office - accessible to research study team**
- **Single/or multiple binders/folders stored in same or other locations**
- **List other locations in binders, if other than primary site**
- **Place Note To File (NTF) in binder reference location for:**
    - **separate binder**
    - **electronic document and access**

Timeline for Essential Documents:

1. **BEFORE the study starts**
2. **DURING the conduct of the study**
3. **AFTER completion or termination of the study**

Best Practices:

- **Identify the key site personnel (KSPs) responsible for maintaining the Regulatory Binder**
  - **Ensure each member of the study team that is responsible for some aspect of maintaining the RB and essential documents is aware of their duties, are qualified, and are listed on the DOA/DOR/DOAL**
- **Establish the RB at the beginning of the study**
- **Store study documents in reverse chronological order**
- **Label each Regulatory Binder/electronic folder**
  - **Protocol identifier, PI name, study site, sponsor, as applicable**
- **Keep the binder current, up-to-date, and organized**
  - **Use tab/dividers for each section**
  - **Customize the binder to the needs of the specific protocol**
  - **Store items in reverse chronological order**
  - **File documents in a timely manner**
  - **Providing a thorough history of the study through documents**
- **Order the sections to facilitate easy referencing**
  - **File sections that most referenced in the front of the binder**
  - **Add/delete tabs as needed**
  - **Industry sponsored trials may have template binders to be used**
- **Subject specific information/documents are usually maintained separately from the Regulatory Binder in subject specific research records**
  - **Maintain subject confidentiality**
- **Store the binder in a safe and secure location at the investigator's site, accessible to appropriate study staff**
- **Never discard old versions**
- **Retain documents for maximum length of time stated by IRB/FDA/Sponsor, ect.**



- **Documents not stored in the RB should have a note (NTF)/memo indicating the location of where the documents will be maintained outside of the RB**
    - **All NTFs should always be dated and signed by the author and the PI when applicable**

Resources:

FDA **Code of Federal Regulations Title 21** (21 CFR 312)
https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRsearch.cfm?CFRPart=312

FDA **Code of Federal Regulations Title 21** (21 CFR 812)
https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=812

Common Rule: 45CFR 46:

https://www.hhs.gov/ohrp/regulations-and-policy/regulations/45-cfr-46/index.html

International Committee for Harmonization (ICH GCP) E6 (R2)

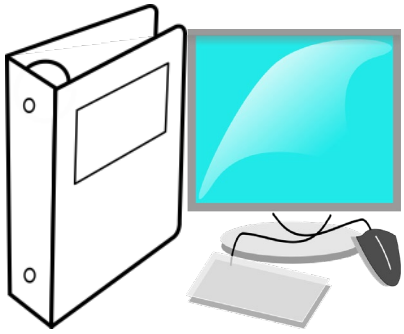
https://www.fda.gov/media/93884/download

NIH National Center for Complementary and Integrative Health – Essential Regulatory Documents Guidance and Binder Tabs

https://nccih.nih.gov/sites/nccam.nih.gov/files/CR-Toolbox/Regulatory_Binder_Guidance_and_Tabs_ver2_07-17-2015.docx

NIH National Center for Complementary and Integrative Health – Tool Summary Sheet
https://nccih.nih.gov/sites/nccam.nih.gov/files/CR-Toolbox/Regulatory_Binder_Checklist_ver3_07-17-2015.docx

NIH National Center for Complementary and Integrative Health – Clinical research Toolbox
https://nccih.nih.gov/grants/toolbox/pdfs



Regulatory Binder/Documents

Regulatory Binder:

- Documents compliance with the Regulations, Guidelines, Policies, and or Procedures
- Tells the story of study events
- Contains study specific information
- May contain different regulatory documents depending on the type of study you are conducting and the study Sponsor
- Should be tailored to meet the needs of the study
- Is often the first document reviewed during monitoring visits and audits
- May not contain all of the study documents in one binder
- Should be organized in a manner for easy access
- Provides a system to manage, organize, and store study documents

Most Sponsors will supply some type of Regulatory Binder; however, the Study Team should supplement the provided binder with all of the necessary study documents/sections.

Other Names for Regulatory Binder:

- Study Binder
- Investigator Binder
- Regulatory Files
- Study Files/Records

Purpose of Regulatory Binder:

- Organizes Essential Documents
- Means for easy access to study files
- Compiles study documents or reference to location in one place

Depending on the nature of your clinical trials, some sections may not be required and others may need to be added. There are not any Regulations that stipulate how the Regulatory binder should be organized; however, a Sponsor might have specific requirements.

The main goal is to organize study documents in a way so that files may be easily retrieved when needed.

The following Regulatory Binder sections are provided as a guide:

Monitoring
Monitoring/Site Visit log
CRA Correspondence
Site Response to Monitors' Letters/Findings

Delegation of Authority log

Contact Information
Sponsor/CRO Contacts
Site Contacts

Protocol
All Versions of Protocol
All Versions of Protocol Signature Page
Amendments

Master Log (keep in separate binder/location)

IRB (may be kept in separate binder/location due to volume)
All Correspondence
FWA Letter/Membership List (all past and current during trails period)
Initial Submission
- Protocol
- ICF
- Subject Information
- Investigator Brochure (IB)/Drug or Package Insert/Device Instruction
- Advertisements/Recruitment Materials
- PCP Letter

Revisions
- Protocol Amendments
- Revised ICF
- Subject Information
- IB/Drug Insert/Device Instruction
- Advertisements/Recruitment Materials
- PCP Letter

Continuations (at least on annual basis)
Submissions (Periodic)
- AEs
- SAEs
- DSMB Reports
- Study Results
- Protocol Deviations/Violations
- Advertisement/Recruitment Materials

Correspondence
- Proviso Letters
- Approval Letters
- Acknowledgement of Submitted AEs/SAEs

Audit Reports and Response
Final report/Closeout

Agreements (keep in separate binder/location)
CDA
CTA

Budget
Grant Application/Approval

Original Signed ICFs (may be kept in separate binder/location)
All Versions

AE/SAE (may be kept in separate binder/location due to volume)
AE/SAE Log
IND Letters
IRB Correspondence Regarding IND Letters

Study Team Credentials/Documents (all past and current during conduct of trial/ keep updated)
Professional License/Certification
Curriculum Vitae, Signed and Dated – usually updated every 2 years
Financial Disclosure Form
Documentation of HSP Training
Insurance (if required)
Dangerous Goods Training Certificate
Conflict of Interest
1572/1571 (may be kept in own tab)
HIPAA Training
Training (may be kept in separate binder/location)

- Formal
- In-service
- Educational Material

Laboratory
Reference Ranges/Normal Values
CV/License of Lab Director (past and current during conduct of trial)
CLIA/Accreditations
Equipment Validations (if required)

Correspondence
Site with Sponsor
Site with CRO
Site with Monitor (may be kept under Monitoring tab)
Site with Auditor/Inspector
Internal
Methods:

- Written
- Telephone conversations/Conference Calls
- Newsletters
- Note to File
- Fax
- E-mail

Investigational Product/Supplies
Investigator's Brochure
Drug Insert
Device Manual/Instructions
Accountability Log
Handling/Use Instructions
Shipment/Receipt Records
Dispensing/Return Records
Documentation of Dosing
Return/Disposal Records
Storage Records
Pharmacy Information/Correspondence
Emergency Code Break Procedures for Blinded Studies
Ordering Instructions/forms
Temperature Log (if requited)
Calibration Logs
Sample of Product Label
Training Manual

DSMB reports

Case Report Forms (completed) (may be kept in Subject's Research Record)

Extra Forms (may be kept in separate binder/location)
Clean Copy of CRFs and Sponsor's Instructions
Screening Log
Enrollment Log
Sponsor's ICF
Site Questionnaire
Sponsor Forms
Tissue/Specimen Log
Protocol Deviation/Exception/Violation Tracking Log

Queries (may be kept in separate binder/location)

Investigator Meeting
Agendas
Materials
Minutes

Miscellaneous (kept in separate binder/location)
SOPs
MOP
Subject Payment Request (keep in separate binder/location)
Subject Payment (Keep in separate binder/location)
Tracking Forms (keep in separate binder/location)

Notes-to-File
Used to explain missing documents
Used to explain discrepancies
Used to Identify the location of documents maintained outside of the Regulatory Binder
Need to be signed and dated
Contain Study Identifier

Resources:
http://www.partners.org/phsqi/vrb/files/index.html
ICH GCP E6 Guidance, Section 8

Best Practices to Follow:

- Filing essential documents in a timely manner can greatly assist in the successful management of a clinical trial
- If documents are maintained electronically, write a NTF/Memos indicating where they are maintained. If copied for review, obtain certified copied from IT/HIS department
- Maintain and update the Binder as necessary
- Add appropriate documents as they are received and or generated
- Keep organized and confidential
- Store in a secure, limited-access location
- Periodically review files for completeness
- File in reverse chronological order (most recent on top)
- If any Essential Document has a tab in the Regulatory Binder but is not maintained under that section, write NTF/Memos and explain where the documents are maintained
- Document all research related activities
- Document any missing or incomplete data
- Clarify any discrepancies
- Label each Binder for easy identification of documents contained

Disclaimer: This document contains information to be retained at the Investigator site. Regulatory binders may be organized in a different sequence from this format as long as all required Essential documents are maintained.

Tab	Documents (all versions) to be maintained in this Section
Current IRB approved protocol	
Current IRB approved ICF	
Signed ICFs	
Institutional review Board	
Study Team Credentials	
Training Documents	
Delegation Log	
Subject Logs	
Case Report Forms, Blank	
Case Report Forms, Completed	
Source Documents	
Investigational Product	
Laboratory	
Specimens	
Adverse Events	
Protocol Deviations	
Monitoring	
Correspondence	
Legal /Financial Documents	
Note to Files	

Essential documents:

documents which individually and collectively permit evaluation of the conduct of a study and the quality of the data produced. These documents serve to demonstrate the compliance of the investigator, sponsor, and monitor with the standards of GCP and with al applicable regulatory requirements

Purpose of Study Documentation:

- Verify that the subject's rights and welfare are protected
- Ensure integrity of the data
- Show compliance with the protocol, regulations, guidance, policies, and procedures
- Show compliance to the protocol/FDA regulation/ICH GCP guidance/SOPs, other regulatory requirements
- Demonstrate the subject's right, safety, and welfare was protected
- Validate a scientific valid and ethical study
- Document qualified personnel participated in the conduct of the clinical trial
- Provide documents for adequate auditing and monitoring
- Maintenance of current, complete, and accurate data collection

Good Documentation Practice:

- What is not documented---Was not done!
- Document what was done AND what was not done
- Include reason for any missed information
- Use black or dark blue ink
- Do not back or future date and entries
- Create and maintain documents
- Assure documentation is ALCOA-C compliant
- SLIDE rule for errors
- Be thorough and timely when documenting
- Perform quality checks
- Be Proactive when finding errors or omissions

Common Findings Related to Documentation/Essential Documents:

- Eligibility criteria could not be confirmed

- Discrepancies in records
- Missing pages or information
- AE/SAEs not captured/reported
- Incorrect/incomplete documentation
- Abnormal labs not assessed
- Visits not documented
- Phone calls not documented
- Re-training not documented
- ALCOA-C not followed

End Results of Poor Documentation:

- Shows lack of understanding of good documentation requirements
- Lost confidence in site, lack of integrity and credibility
- Affect the overall quality of data in question, resulting in the exclusion of data
- Averse affect on subject safety
- Wasted time of researchers and subjects if data can not be used
- Could lead to an IRB/NIH/FDA/Sponsor/Institution audit

Documents to maintain Before the Study Starts:

Trial Master File

Investigator brochure/Drug insert/Device manual

Signed Protocol

Sample Case Report Forms (CRFs)

IRB submitted documents and approvals

- Protocol
- Informed Consent Form
- Participant educational materials
- Advertisement materials

IRB Federal Wide Assurance (FWA)

IRB Membership

Study Team Credentials

- License/Certification
- Training Documents
- CV/Resume, signed/dated
- Signed Agreements

Contract Disclosure Form

Contract Trial Agreement

Budget

Data Use Agreement

Investigational Product (IP)

- Sample labels for IP
- Instructions
- Dispensing
- Storage
- Packaging
- Disposition
- Shipping records

Laboratory

- Normal Lab Values/Ranges
- Technical Procedures
- Laboratory Director CV/Resume/License
- Laboratory Certification/Accreditation

Participant List

Decoding Procedures for blinded trials

Sponsor Visits

Documents During the Conduct of the Trial:

Updates:

- Credentials
- Laboratory documents
- IRB submissions/approvals

- Protocol Amendments
- Investigator brochure/device manual
- ICF revisions
- Advertisements
- Subject information
- Continuing Review

IP Accountability

Signed Informed Consent Forms

Completed CRFs

- Documentation of CRF corrections

Monitoring Visits and Reports

Source Documentation to document compliance

- Protocol
- Regulations and Guidance
- Standard operating Procedures

Relevant Communications

- Letters
- Meeting Notes
- Phone calls
- Signature Sheet
- Record of retained body fluids/tissue samples
- Subject logs

Screening log

Identification code list (master log)

- Enrollment log

Adverse Events

- Evaluation
- Resolution
- Reporting

Documents After Completion the Trial:

IP Accountability

Completed master log

Audit Certificate

Final close-out monitoring report

IRB close-out

Standard Operating Procedures

Definition/Purpose of a SOP:

- ICH GCP defines a SOP as "detailed, written instructions to achieve uniformity of the performance of a specific function"
- Set of instructions describing a standardized procedure
- Intended to establish methods to be routinely followed
- Instrumental in developing a culture of compliance
- Provide standard instructions to improve efficiency
- Promote responsible conduct of research
- Defines processes and procedures
- Provides a process for the daily activities of clinical trials
- Define how employees perform duties
- Practices and work instructions
- Detail the regularly re-occurring work process
- Ensures the quality and consistency of procedures
- Reduces the number of mistakes
- Facilitate consistent conformance to ensure compliance with regulations/guidelines/policies/good clinical practices
- Assist study team to conduct clinical trials in an organized and consistent manner
- Help to achieve maximum safety and efficiency of performed tasks
- Clearly identify the roles and responsibilities of the research team
- Provide standard instructions
- Utilized as a training source
- Describes what task should be completed in the same way each time it is performed
- Assists in monitoring site performance/success

Why do we need SOPs?

Sponsors and Auditors are requesting research sites to demonstrate that they have policies and procedures in place to ensure site compliance with Federal Regulations and ICH GCP guidelines. Having SOPs will demonstrate your effort to maintain compliance with the regulations and guidelines.

Rules when developing SOPs:

- Use role/titles rather than names of specific people
- Where possible do not refer to specific elements of how tasks will be accomplished such as "by e-mail" , instead use "in writing", this allows flexibility

- Make sure the SOP is compliant with regulations/guidelines/policies
- Review periodically, update/revise as necessary (retain previous versions)
- Provide/Document training re: SOPs
- Use clear, concise language
- Develop internal review/approval process
- Establish consistent procedure for communication of SOPs to appropriate persons

Sample components to include when writing SOPs:

- Header
    - Institution/Department information
    - Title of SOP
    - Page _ of _
    - Approval information
        - Who approved by
        - Date of approval
        - Date first effective
        - Version date
- Purpose
- Background
- Scope
- Procedure
- Applicable Regulations/guidelines/policies
- Definitions
- Reference
- Attachments
    - flowchart
    - lists
    - tools, logs
- Revisions

Process for Writing SOPs

- Determine the task
- Lay out the steps currently used when completing the task
- Add details
- Test the steps/procedure/SOP

More comprehensive List of SOPs that may be needed

- 1st one to create—Developing, Disseminating, Maintaining, and Review of SOPs
- AE/SAE reporting
- Billing

- Budget Review and negotiations
- Conflict of Interest
- Credentialing and Certification of Research Personnel
- CRF completion
- Communication
- Data Queries
- Delegation of Authority
- Emergency procedures
- Essential Documents/Record Keeping
- HIPAA
- Informed Consent Process
- Inspection/Audit visit
- Investigational Product Accountability
- Investigator Meeting
- IRB Submissions
- Laboratory procedures
- Meetings
- Monitoring Visits
- Protocol deviations/violations
- Protocol Feasibility
- Pre-Study Qualification Visit
- QA/QI
- Regulatory Binder
- Roles/Responsibility of Research team
- Shipping/processing specimens
- Source Documentation
- Subject Medical Record
- Subject Research Record
- Steps to Conduct Clinical Trials
- Subject Recruitment/Screening/Enrollment/Retention
- Site Initiation Visit
- Study Closure
- Training
- Un-blinding Process

Comments from FDA audits

Your response is inadequate in that you failed to provide any new or revised policies and procedures (ICF)

- Please develop procedures that will prevent the above deviation from recurring in future studies (protocol deviation)
- Submit a copy of these procedures, along with documentation demonstrating staff training in these procedures (protocol deviation)
- In review of the SOP entitled “Standard Operating Procedure for eResearch Submissions”, there were no procedures detaining the methods used by your site to verify consistence of all elements between the informed consent form, protocol, investigator’s brochure and eResearch submission as noted in your promised corrective action
- You noted that your corrective action to prevent the recurrence of this finding included the development of new SOPs including “Obtaining Informed Consent”, Document Management and Storage”, and Patient Completion/Early Termination/Screen Failure”, and the education of your study team on these SOPs. These corrective actions appear adequate

Resources:

http://www.firstclinical.com/journal/

www.acrpnet.org

http://www.research.uky.edu/ori/human/SOPs_&_Policies.htm

http://www.researchadmin.iu.edu/Forms/human_subjects/IUB+Standard+Operating+Procedures

Session 11:

IP Accountability

National Center for Complementary and Integrative Health

Tool Summary Sheet

Tool: Investigational Product Accountability Log: Subject Record

Purpose: To document all study product disposition and accountability on the subject level.

Audience/User: Study Coordinators, Principal Investigators (PIs), pharmacy staff, other site staff, clinical monitor.

Details: This tracking log should provide a comprehensive list of all study product dispositions on the subject level. It is required for interventional clinical studies using a study product for research.

The set of columns are suggestions and can be customized to meet the needs of the study.

Best Practice Recommendations:

- Complete the log as study product is dispensed and/or received, to ensure completeness and accuracy of the data. A new line should be completed each time study product is dispensed and/or received.
- The “Subject Record” may be used to record dispensing and return of study product on the subject level. The associated “Stock Record” is a separate tool that may be used to record overall bulk study product supplies and accountability.
- In the "Quantity Dispensed and/or Received" column, use a “+“ before the number when receiving product; use a “-“ before the number when dispensing product. See the example provided within the log.
- In the “Balance Forward” column, use the diagonal line across the box to record the previous balance forward / the resulting balance (e.g., 600 / 500). See the example provided within the log.
- The log recorder should initial the line item as the information is entered.
- Create additional lines and pages as needed.
- For clinical studies that are not blinded, maintain this log in the Essential Documents Binder, behind the “Study Product Records” tab. (Synonyms for this binder include Investigator Binder, Regulatory Binder, Investigator Site File (ISF), and Study File.)
- For blinded clinical studies, it is recommended that study product accountability records be filed in a separate location (e.g., the research pharmacy), to maintain the blind.
- Number each page and store pages in reverse chronological order, with the newest pages of the log placed at the front of the section.
- At the conclusion of the study, identify the final page of the log by checking the box in the footer.
- Remove this Tool Summary Sheet before use of the log.

Tool Revision History:

Version		
Number	**Date**	**Summary of Revisions Made:**
1.0	24Apr2013	First approved version

Investigational Product Accountability Log: Subject Record

Name of Institution:	**Product Name:**
Investigator Name:	**Manufacturer:**
Protocol No.:	**Dose Form and Strength:**
Protocol Title:	**Dispensing Area:**

Line No.	Date	Subject ID Number	Subject's Initials	Dose	Quantity Dispensed and/or Received	Balance Forward / Balance	Lot No.	Recorder's Initials
Ex.	*15Feb2012*	*12345*	*ABC*	*10 mg*	*- 100 tabs*	*600* / *500*	*98765*	*JAD*
1.								
2.								
3.								
4.								
5.								
6.								
7.								
8.								
9.								
10.								

Check if final page of log: ☐

Investigational Product Accountability

What is IP Accountability?

- Inventory records document that IP was used only for study participants in accordance with the approved protocol

Who is responsible?

- Investigator
- Qualified study team members that have been delegated this task
- Sponsor/CRO
- Pharmacist

Why is IP accountability needed?

- Subject safety
- Documents the handling of the IP
- Identifies subjects who have received the IP/Ensure study participants receive the correct IP
- Document compliance with the protocol
- Verify data integrity

Result of poor IP accountability:

- Subject may incur a safety risk
- Loss of data/data integrity
- Negative monitoring/auditing reports
- Sponsor may place a “hold” on the study if non-compliance is severe

Documentation of the IP:

- Records/Essential Documents:
    - Receipt of the IP at the study site
    - Secured location of IP (locked/limited access)
    - Dispensing records
    - Return of IP from subject
    - Subject Compliance
    - Return to sponsor/CRO
    - Destruction
    - Storage
    - Expiration dates
    - Inventory
    - Temperature logs/excursions

What to document regarding the receipt of the IP at the site:

- Name of person receiving IP (qualified delegated personnel)
- Date of receipt
- Name of IP
- Lot #, expiration date, Batch/serial information/unique code (all that are applicable)
- Dosage
- Expiration date
- Quantity

What to document when dispensing IP

- Subject ID
- Name of IP
- Lot #, expiration date, Batch/serial information/unique code (all that are applicable)
- Dose
- Date dispensed
- Quantity
- Name of the person dispensing
- Subject instructions/education

What to document when returning IP

- Name of medication
- Lot #, expiration date, Batch/serial information/unique code (all that are applicable)
- Dose
- Date returned
- Quantity returned
- Name of the person receiving
- Compliance

What to document when destroying IP

- Name of medication
- Lot #, expiration date, Batch/serial information/unique code (all that are applicable)
- Dose
- Date destroyed
- Quantity destroyed
- Means of destruction
- Name/title/signature of the person destroying
- Name/title/signature of at least one witness

IP Worksheet

Define Investigational Product (IP)

Why is IP accountability important?

What is the impact of poor accountability?

Define rescue medication

Calculate IP compliance for the following scenario:

The subject's visit one occurred on March 1st and she was dispensed 100 tablets of investigational product. She is instructed to take 1 tablet daily, starting on March 1st and one on May 1st before her visit

She returns for Visit 2 on May 1st and returns 50 tablets

She should have taken 62 tablets.

What is her % of compliance?

What was taken/what should've been taken x100 = % compliance

What actions if any should you as the responsible study team member take?

IP Worksheet

Define Investigational Product (IP)

An investigational product may be **an unlicensed product or a licensed product when used or assembled** (formulated or packaged) differently from the approved form, when used for an unapproved indication, or when used to gain further information about an approved use.

The IP may be a drug, biologic, medical device, or combination product.

An investigational drug can also be called an experimental drug and is being studied to see:

- If your disease or medical condition improves while taking
- If the drug is safe and effective
- The desired dose
- What are the potential benefits and risks of taking the drug

Why is IP accountability important?

- Subject safety
- Documents the handling of the IP
- Identifies subjects who have received the IP/Ensure study participants receive the correct IP
- Document compliance with the protocol
- Verify data integrity

What is the impact of poor accountability?

- Subject may incur a safety risk
- Loss of data/data integrity
- Negative monitoring/auditing reports
- Sponsor may place a “hold” on the study if non-compliance is severe

Define rescue medication

Patients in some randomized clinical trials may start additional non-randomized medication because of an exacerbation of symptoms or insufficient therapeutic effect. Typically this rescue medication reduces the observed treatment effect in intention-to-treat analysis.
(https://pubmed.ncbi.nlm.nih.gov/11590628/)

Rescue medication also called **escape medication**; medicines identified in a study protocol as those that may be administered to the patients when the efficacy of the investigational medicinal product (IMP) is not satisfactory, or the effect of the IMP is too great and is likely to cause a adverse reactions (https://link.springer.com/chapter/10.1007%2F978-3-211-89836-9_1231)

Calculate IP compliance for the following scenario:

The subject's visit one occurred on March 1st and she was dispensed 100 tablets of investigational product. She is instructed to take 1 tablet daily, starting on March 1st and one on May 1st before her visit

She returns for Visit 2 on May 1st and returns 50 tablets

She should have taken 62 tablets.

What is her % of compliance? 81%

What was taken/what should've been taken x100 = % compliance

What actions if any should you as the responsible study team member take?

- Notify the PI
- Possibly notify the Sponsor/CRO representative
- Subject re-education
- Documentation of events

Session 12

21 CFR 312

21 CFR 812

21 CFR 312 Definition Worksheet

Drug

IND

Treatment IND

Orphan Drug

Parallel Track

Clinical Hold

NDA

aNDA

Sponsor

Sponsor—Investigators

Emergency Use IND

21 CFR 312 Worksheet

Note the table of contents for 21 CFR 312. How many subparts are there and what are the major areas addressed in the part of Title 21?

General Provisions

1. **Does 21 CFR 312 apply to all clinical investigations? If not, where does it not apply?**

2. **What are the labeling provisions for an investigational drug?**

3. **When may a subject be charged for receiving an investigational drug under and IND?**

IND

1. **What are the primary objectives of the FDA when reviewing an IND?**

2. **A sponsor is required to submit and annual report to the FDA reporting the status of the study for what purpose?**

3. **The FDA requires that an investigator brochure contain what information?**

HIPAA Regulation in Clinical Research Worksheet

To whom does the HIPAA Privacy Rule apply?

Who is considered a Business Associate?

Define Protected Health Information.

What are the common identifiers? (18)

Name two circumstances when a covered entity MUST disclose PHI?

What is de-identified data?

Under the regulations what criteria must be met to deem information "de-identified"?

What is a limited data set?

Define Personal representative under HIPAA.

What is the "minimum necessary" standard?

Name the nine elements that must be included in the HIPAA authorization agreement.

Under what circumstances can a HIPAA waiver of authorization be obtained?

Under HIPAA what are the Documentation and Record Retention requirements?

4. **A protocol must be provided in the IND and must contain 7 specific elements. List them.**

5. **If a sponsor intends to submit a new protocol not already covered by the IND, the sponsor must submit a protocol amendment to the FDA. The study can be initiated if two conditions are met What are they?**

6. **A sponsor has added a new investigator to take part in a previously submitted protocol. What action must the sponsor take to ship the investigational product to the investigator and initiate study participation?**

7. **When must a sponsor submit protocol amendments for a new protocol or a change in protocol? What about additional information about an investigator(s)?**

8. **Give one example of an information amendment_____.**

9. **How often would information amendments to an IND by submitted?**

10. **When is a sponsor required by the FDA to submit a written safety report to the agency and all participating investigators? What is the time frame in which the notification must be submitted?**

11. **When is a sponsor required to notify the FDA via telephone or facsimile of a safety report? What is the timeframe for reporting?**

12. **What is the purpose of an annual report and when must a sponsor submit an annual report to the FDA?**

13. **What must an annual report include?**

14. **What is treatment use of an investigational new drug? What is the purpose of a treatment IND?**

15. **What are the criteria for FDA approval of a treatment IND?**

16. **When is it necessary for a licensed practitioner to submit a treatment IND to the FDA?**

17. **When can treatment use of an investigational new drug begin?**

18. **What is "emergency use" of an investigational new drug? What action must the sponsor take after FDA approval of emergency use of the investigational new drug?**

19. **When can the sponsor withdraw an approved IND? If the withdrawal is due to safety concerns, what action must the sponsor take?**

20. **When does an IND go into effect?**

21. **When may the sponsor ship an investigational new drug to the investigators named in the IND?**

Administrative Action

1. **What is a clinical hold?**

2. **What major grounds can the FDA use to place a Phase I trial on clinical hold?**

   Phase II and III studies?

   Ongoing treatment protocol or treatment IND?

3. **What are two actions available to the FDA when there is not satisfactory resolution to the clinical hold status of an IND?**

4. **What is an "END of Phase II" meeting?**

5. **What is a "pre-NDA"? "pre-BLA" meeting?**

Sponsor and Investigator Responsibilities

1. **What is a Contract Research Organization (CRO)? What obligations may a sponsor delegate to the CRO?**

2. **Once the sponsor or (CRO) has identified an investigator for participation in an investigation, the sponsor is responsible for obtaining what major information (4 areas) from the investigator?**

3. **Familiarize yourself with the FDA Form 1572 "Statement of the Investigator". Outline the Investigator. Outline the investigator commitments proposed by this "contract" with the FDA.**

4. **The sponsor is responsible for selecting qualified investigators, collecting the FDA Form 1572, controlling the distribution of the investigational drug and selecting monitors to review the progress of the study. What are the sponsors monitoring obligations?**

5. **What information must the sponsor provide the investigator before the investigation begins? During the investigation?**

6. **What records must the sponsor maintain regarding the investigation and how long must the sponsor retain these records?**

7. **Regarding the control of the investigational drug, including controlled substances, what records does the FDA require the sponsor to make available for inspection?**

8. **According the 21 CFR 312.60-312.69, what are the responsibilities or the investigators?**

9. **When may the FDA disqualify an investigator form participating in a study?**

Expedited Development

In expedited development of drugs intended to treat life-threatening and severely debilitating illnesses, the FDA will honor, if possible, requests for early consultation meetings. Name two such meetings.

21 CFR 812 Definitions Worksheet

Define the following:

Medical Device

IDE

PMA

PreMarket Notification (PMN or 510(k)

Classes of Devices

Significant Risk

Insignificant Risk

Investigator Agreement


TN-CTSI CERTIFICATION EXAM
PREPARATION COURSE
Clinical Trials
UTHSC
TENNESSEE CLINICAL AND
TRANSLATIONAL SCIENCE INSTITUTE

HDE

HUD

UADE

21 CFR 812 Worksheet

The FDA places medical devices into one of three classes based on risk to the patient / subject or user and the level of control necessary to ensure the safety and effectiveness of the device. What are the general controls required of companies for all classes of devices?

Name the classes of devices and describe the controls required for each.

Who determines whether an investigational device is significant risk (SR) or non-significant risk (NDS) for a study?

What are the major differences in significant risk and non-significant risk device studies?

What must an IRB consider when determining whether a device study is significant risk or non-significant risk?

What is the difference in the IRB making a SR / NSR determination and "minimal risk"?

What is Emergency Use of an Unapproved Medical Device?

What are Pivotal Clinical Trials?

What is a 510(k) application (this information can be found in 21 CFR 807 Subpart E)?

When does a device modification require a 510k Notice?

What is a predicate device?

Define Substantial Equivalence?

How is substantial equivalence demonstrated?

Forms Worksheet

Sponsor / Investigator IND Study

Sponsor / IND Study	What	Who	When	CFR
FDA Form 1571				
FDA Form 1572				
IND Safety Reports 3500A				
IND Annual Report				
FDA Form 3454				
FDA Form 3455				
Final Report or Withdrawal				

Forms Worksheet

Sponsor / Investigator IDE Study

Sponsor / IDE Study	What	Who	When	CFR
Investigational Plan				21 CFR 812.25
Investigator Agreement				21 CFR 812.43
SRD Determination NSRD				21 CFR 812.66 21 CFR 812.2(1)(ii) 21 CFR 812.2.(b)
FDA Form 3454				21 CFR 54
FDA Form 3455				21 CFR 54

Forms Worksheet

Sponsor / Investigator IDE Study

IDE Annual Reports Final Report				21 CFR 812.150(b)(5)
IDE Safety Reports				21 CFR 812.150(b)(2) FDA Guidance for IDE Responsibilities

Session 13

Recruitment

HIPAA

21 CFR 11

Recruiting Study Subjects

Direct advertising that may be used to recruit potential subjects include:

Name three communications that are not considered recruitment tools and do not need to be reviewed by the IRB.

True or False:

_____The federal regulators expect that an IRB will review the methods and materials that investigators propose to use to recruit study subjects.

_____Listing of clinical trials on the internet do not require IRB review and approval as long as the format allows only basic trials information.

_____FDA considers direct advertising for study subjects to be a part of the enrollment process.

_____Receptionist's scripts to determine basic eligibility for a specific study must be reviewed and approved by the IRB.

21 CFR 11

1. **To what does 21 CFR Part 11 apply?**

2. **Define:**

   Audit Trail

   Biometrics

   Data Entry

   Digital Signature

   Electronic Record

   E-CFR

   Predicate Rules

   Source documents

   Software validation

3. **There are nine provisions that the FDA expects compliance and will enforce. What are they?**

4. **Does e-mail fall under Part 11 regulation? Justify you answer?**

5. **Describe Part 11 requirements for ensuring the authenticity, integrity, and confidentiality of electronic records.**

6. **Describe Part 11 requirements for electronic signatures.**

7. **Describe Part 11 requirements for passwords and/or identification codes.**

Session 14

Safety and Compliance Reporting

Safety and Compliance Reporting Worksheet

What are the following acronyms?

AE

SAE

UADE

SUSAR

Define Internal and External Adverse Events

<u>OHRP</u>

What are Unanticipated Problems Involving Risks to Subjects or Others per OHRP?

Per OHRP, when do you report an AE as an Unanticipated Problem?

What are the criteria tha must be met for an event to be considered serious?

Compare "serious" and "severe" as described in the regulations.

What are the timeframes for reporting an event to OHRP?

Evaluate and determine whether this example needs to be reported under 45 CRF 46.

1. **Example: An investigator is conducting a psychology study evaluating the factors that affect reaction times in response to auditory stimuli. In order to perform the reaction time measurement, subjects are placed in a small, windowless soundproof booth and asked to wear headphones. The IRB-approved protocol and informed consent document describes claustrophobic reactions as one of the risk of the research. The twentieth subject enrolled in the research experiences significant claustrophobia, resulting in the subject withdrawing from the research.**

2. **Example: The fifth subject enrolled in a phase 2, open-label, uncontrolled clinical study evaluating the safety and efficacy of a new oral agent administered daily for treatment of severe psoriasis unresponsive to FDA-approved treatments, develops severe hepatic failure complicated by encephalopathy one month after starting the oral agent. The known risk profile of the new oral agent prior to this event included mild elevation of serum liver enzymes in 10% of subjects receiving the agent during previous clinical studies, but there was not other history of subjects developing clinically significant liver disease. The investigators identify no other etiology for the liver failure in this subject and attribute it to the study.**

3. **An investigator conducting behavioral research collects individual identifiable sensitive information about illicit drug use and other illegal behaviors by surveying college students. The data are stored on a laptop computer without encryption, and the laptop computer is stolen from the investigator's car on the way home from work.**

FDA

Determine Investigator and sponsor responsibility for Managing AEs.

The investigator is responsible for:

The Sponsor is responsible for:

Investigators are required to report:

Sponsors are required to report:

IDE Safety Reporting:

Investigator Reporting Responsibility:

Sponsor Reporting Responsibility:

MedWatch:

What is MedWatch?

What form is used for MedWatch reporting?

Voluntary?

Mandatory?

Safety Reporting Comparison Between FDA and ICH

Definition	FDA	ICH
Adverse Event / Adverse Experience		
Suspected Adverse Reaction		
Unexpected Adverse Event / Unexpected Adverse Drug Reaction (ADR)		
Serious Adverse Event / Serious suspected Adverse Event / Serious Adverse Event or Serious Adverse Drug Reaction		.
Serious Unexpected Serious Adverse Reaction (**SUSAR)**		

Safety Reporting Comparison between FDA and ICH

ICH Definitions: Compare “serious” and “severe”:

Forms Worksheet
MedWatch Reporting Product Surveillance Program
Drugs, Devices and Biologic Safety Reports for Marketed Products

MedWatch Reporting Product Surveillance Program	What	Who	When	CFR
Form 3500 Voluntary reporting by health professionals, consumers, and patients				
Form 3500B Voluntary reporting by non-health professionals and consumers				
Form 3500A Mandatory Reporting for use by IND/IDE reporters, manufacturers, distributors, importer, user facilities personnel				

Financial Disclosure 21 CFR 54 Worksheet

1. **What is the purpose in the FDA requiring financial disclosure by clinical investigators?**

2. **Define:**

   Significant equity interest

   Proprietary interest

   Clinical Investigator

   Covered clinical study

   Significant payment of other sorts

   Applicant

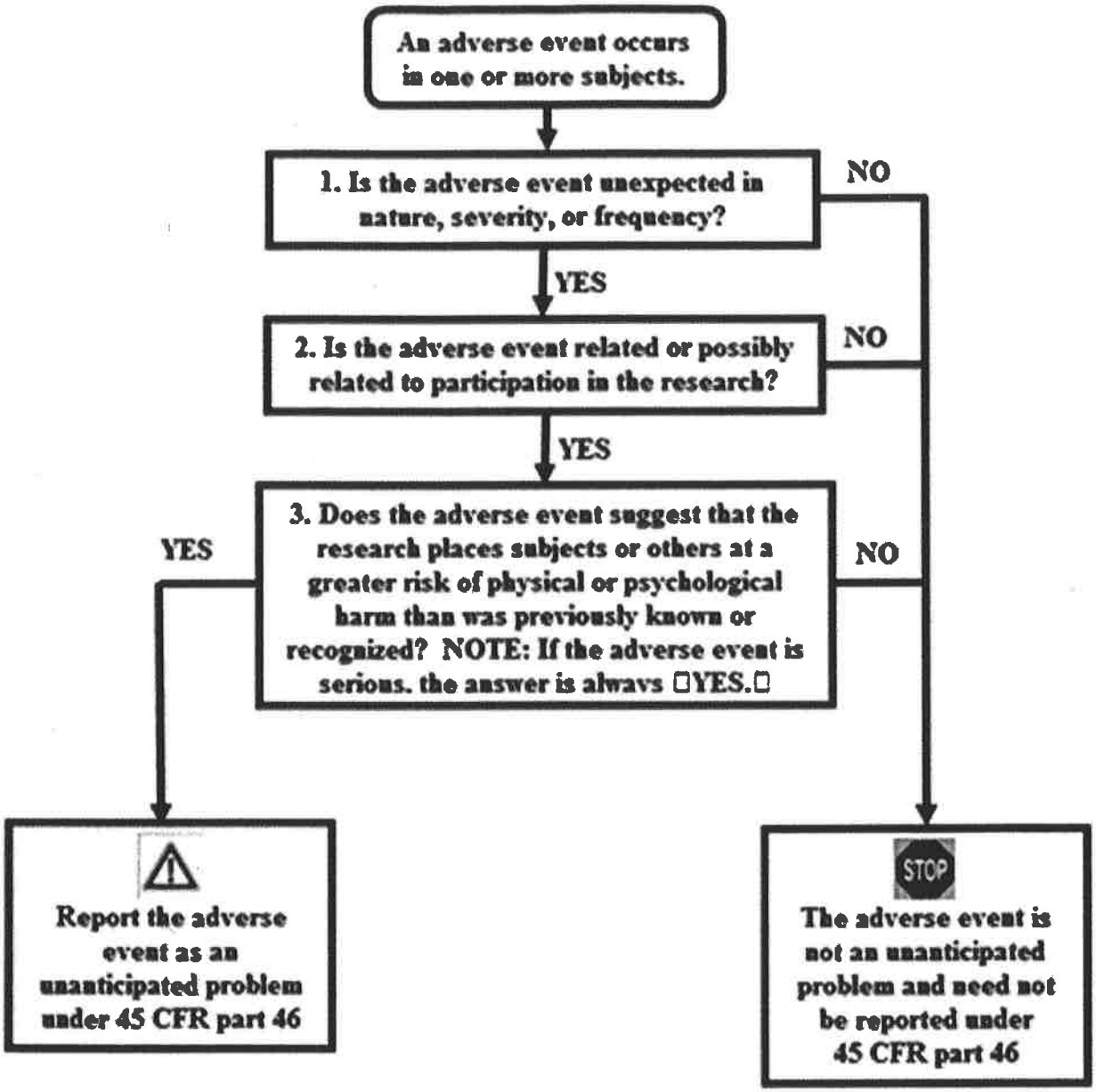
   Sponsor

3. **Explain the difference in “certification” and “disclosure”. What FDA forms are required?**

4. **To whom does the investigator submit the required financial information?**

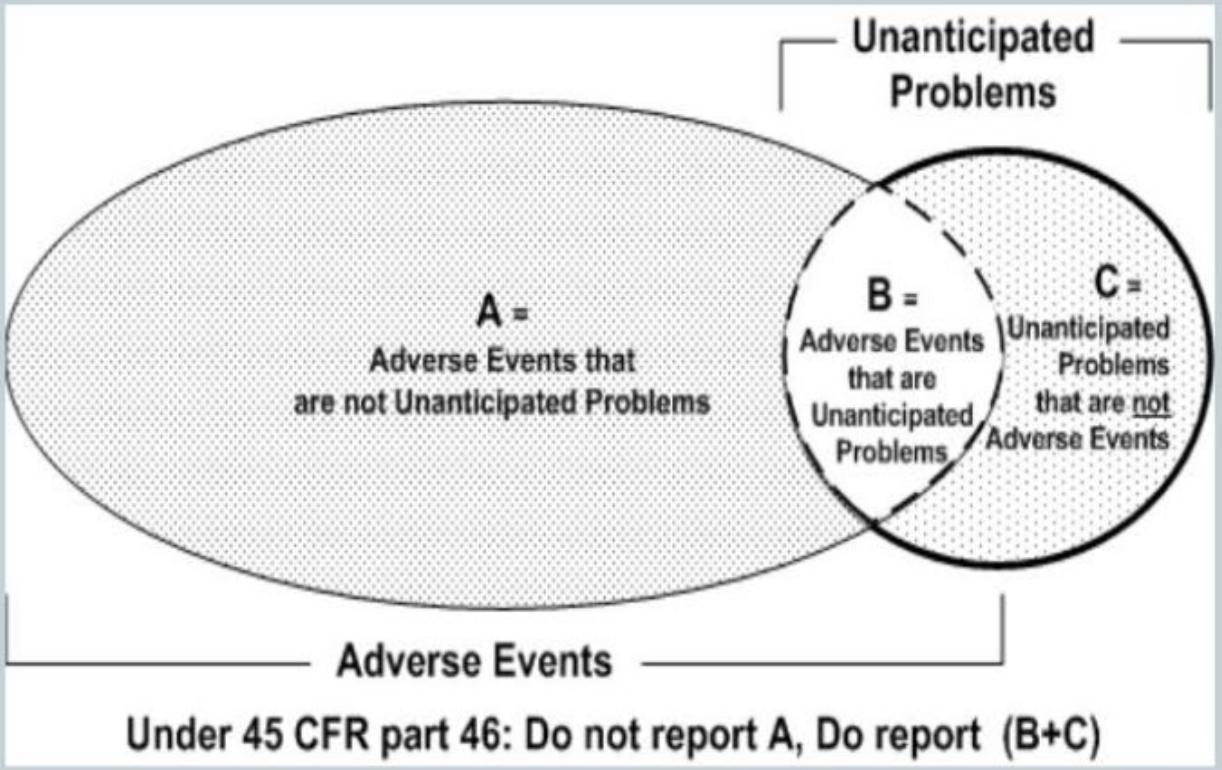
5. **When is the investigator required to provide updated information?**

6. **What are the recordkeeping and retention requirements?**


An adverse event occurs in one or more subjects.
1. Is the adverse event unexpected in nature, severity, or frequency?
NO
YES
2. Is the adverse event related or possibly related to participation in the research?
NO
YES
3. Does the adverse event suggest that the research places subjects or others at a greater risk of physical or psychological harm than was previously known or recognized? NOTE: If the adverse event is serious, the answer is always "YES."
YES
NO
Report the adverse event as an unanticipated problem under 45 CFR part 46
STOP
The adverse event is not an unanticipated problem and need not be reported under 45 CFR part 46

Adverse Events vs. Unanticipated Problems

The following Venn diagram summarizes the general relationship between adverse events and unanticipated problems:



Sessions 15 and 16

Informed Consent

Informed Consent Study Guide

1. **The general requirements for informed consent and documentation of informed consent are found in what federal regulations?**

2. **What are the conditions under which an investigator may seek legally effective informed consent?**

3. **List the basic elements of informed consent. What are the additional elements that must be included if appropriate?**

   Basic

   Additional

4. **Under 45 CFR 46, when may an IRB approve a consent procedure which does not include all the elements of informed consent or waive the requirement of informed consent?**

5. **For administration of an investigational product to a member of the armed forced involved in a particular military operation, only the President may waive the prior consent requirement. What are the three criteria that must be documented in order to waive the informed consent requirement in addition to the relevant FDA regulations?**

6. **For planned emergency research, who must review the regulatory criteria for exceptions form the informed consent requirement, document findings and provide to the IRB in order for the board to approve the exception for that study?**

7. **For planned emergency research, who must review the regulatory criteria for exceptions form the informed consent requirement, document findings and provide to the IRB in order for the board to approve the exception for that study?**

8. **When a clinical investigation involves children, OHRP and the FDA have implemented "Special Protections" for this population. Describe the four categories of clinical investigation outlined in the federal regulations for pediatric research.**

9. **What are the basic concepts that provide "special protections" for this population?**

10. **When can a clinical investigation proceed that is not approvable by the criteria governing research involving children?**

11. **Who determines whether the child (or children to be involved in a research study is capable of giving consent to participate?**

12. **When a child (or children) is capable of assenting, can the IRB waive the assent requirement?**

13. **In studies where there is greater than minimal risk and no prospect of direct benefit to an individual child subject, who must the investigator identify to give permission?**

14. How is assent to be obtained?

15. When can a child who is a ward of the State or other agency or institution be included in a clinical trial?

16. Can an individual serve as an advocate for more than once child?

17. Define Prisoner

18. When prisoners are involved in research, what provisions must the reviewing IRB meet?

19. **What procedure must the investigator take for selecting a control population for research involving prisoners?**

20. **What are the membership requirements of the IRB when prisoner research is being reviewed.**

21. **In research involving prisoners as subjects , what extra protection is required of the institution responsible for the conduct of the research?**

22. **In research involving pregnant women that holds prospect of benefit solely to the fetus, who must consent for the women's participation int the research? Is there any exception to this requirement?**

23. What is the consent criteria for research when for a non-viable neonate?

24. In research not otherwise approvable, from who must the IRB gain approval before the research involving pregnant women, fetuses or neonates can be initiated?

ICH E6 Guidance for Informed Consent

1. **Which section of the ICH Guidelines contains the requirements for obtaining an informed decision to participate in the research?**

2. **When documenting informed consent, what additional requirement does ICH mandate?**

3. **Both FDA regulations and ICH guidance require the witness to be impartial and to be present if a subject (or LAR) is unable to read.**

   True or False

4. **ICH recommends that only subjects that can personally give consent and sign and date the consent form be included in a non-therapeutic trial. If the subject is unable to meet these conditions and the subjects' legally authorized representative must give consent, what other conditions must be met:**

5. **Define non-therapeutic trial.**

Post- Revision

8 Required Elements of Informed Consent

1.	Road	Research
2.	Runner	Risks
3.	Beats	Benefits
4.	A	Alternatives to treatment
5.	Crazy	Confidential
6.	Cartoon	Compensation
7.	Coyote	Contact person
8.	Vigorously	Voluntary
9.	Forever	Collection of identifiable information or specimens will or will not be used for future research (Future Use)

Nine Additional Elements of Informed Consent (as appropriate)

1.	U	Unforeseeable risks-subject or fetus
2.	T	Termination of participation
3.	Cheerleaders	Costs to subject
4.	Want	Withdrawal consequences
5.	Football	Findings that are new
6.	News	Number of subjects
7.	C	Commercial Profit
8.	D	Disclosure of Results
9.	G	Genome sequencing

Session 17:

Monitoring and Auditing

CAPA: Corrective and Preventive Action Plan

CAPA is a system/process for resolving quality issues and prevention of repeat occurrences

FDA's Definition of Corrective Action:

- The FDA indicates that corrective action plans are absolutely necessary to resolve problems and noncompliance in clinical investigations
- Corrective actions are those taken to resolve a problem and preventive actions are those actions that keep the problem from recurring
- Corrective action is action to eliminate the cause of a detected non-conformity or other undesirable situation
- There is a difference between correction and corrective action

CAPA Process:

- **IDENTIFY** the issue/event/deviation
- **EVALUATE** the extent of the issues and **ASSESS** the risk of harm for subjects
- **CORRECT** the issue: develop **REACTIVE** steps to correct the immediate problem
- **UNDERSTAND** the issue: **IDENTIFY** and **ANALYZE** the underlying cause(s) and extent of the problem(s)
- **DETERMINE** needed change/actions,
- **PREVENT** future issues/be **PROACTIVE**
- **DEVELOP/IMPLEMENT** the CAPA in a clear and concise manner
- **COMMUNICATE/REPORT/DISSEMINATE** information to appropriate persons/authorities, including training
- **EVALUATE** processes for effectiveness (this is never ending)
- **CLOSURE** of CAPA

Root cause Analysis (RCA):

- A root cause analysis (RCA) is the process of identifying and documenting the root cause and the downstream effect on the causal chain
- RCA should focus on identifying underlying problems that contribute to error rather than focusing on mistakes made by individuals

Writing the CAPA:

Once the root cause has been identified, the next step is to *develop a corrective and preventive action plan* to eliminate the root cause

From Emory University:

- CAPAs must be thorough (**SMART CAPA**)
- **Specific:** Compliant with regulations, addresses the full observation or root cause, accountable to named individual or role
- **Measurable:** Action can be measured to demonstrate whether it is adequate to address root cause
- **Achievable:** Addresses all implicated processes and levels
- **Realistic:** Plan can be carried out given resources, knowledge and expertise
- **Time-bound:** Assigned to a person or role who can accomplish action in a given time period, addresses urgency and criticality

Best Practices:

- Take responsibility for the error/event/issue
- Appropriately assess causes of the problem
- Should be written to explain an error and resolution to the issues in a forward thinking manner
- Should be signed/dates by the author and the PI
- Evaluate to ensure your CAPA works
- Document every step of your CAPA
- Should be maintained as an Essential Document in the Regulatory File
- Train staff on the new processes
- A CAPA should be written on department/institution form
- Make sure to DO WHAT YOU SAY YOU WILL DO

Dont's When Writing a CAPA:

- Don't promise corrective/preventive actions that could never realistically be carried out

Deficient CAPAs:

- Not addressing why the problem occurred
- Not providing enough detail when writing the CAPA
- Not outlining a timeframe of the corrective actions
- Not addressing how you will evaluate the implementation/effectiveness of the corrective actions
- Not developing SOPs when needed

- Not performing an adequate root cause analysis
- Not specifying the role/responsibilities of the PI when developing/implementing/evaluation the CAPA
- Not providing adequate documentation of the CAPA process

CAPA Format:

- Header
- Description of the Event/Issue
- Root Cause Analysis
- Immediate Action
- Planned Corrective Action
- Personnel Responsible for Ensuring the CAPA is Implemented
- Implementation with Dates
- Resolution
- Evaluation
- Comments
- Signatures/Dates
- Documentation of actions until the CAPA is closed
- Supporting documentation

Evaluation of the CAPA:

- CAPAs must be evaluated over time
- Effectiveness check is the final step of the CAPA process
- Ensure that the CAPA has addressed the root cause and that the problem has not recurred
- If the CAPA has not addressed the root cause, amend the CAPA as necessary
- Train on the process
- Implement the process
- Re-evaluate

Common Findings and Resolution Worksheet

1:Failure to Follow Investigational Plan *(51%)*

Includes:

- missing consent documents
- failure to perform protocol-required procedures
- missing documentation of required IRB review of study changes

Name processes that can be implemented to avoid this finding.

2: Inadequate and Inaccurate Records *(33%)*

Includes:

- record keeping, missing or incomplete subject record

Name processes that can be implemented to avoid this finding.

3: Inadequate Drug Accountability *(7%)*

Includes:

- the record keeping of drugs used in research
- absence or inadequacy of records on receipts, preparation, use, and/or disposition of the investigational drug/product

Name processes that can be implemented to avoid this finding.

4: Failure to Obtain and/or Document Subject Consent (5%)

Includes:

- missing consent documents
- omission of a description of required elements when obtaining consent

Name processes that can be implemented to avoid this finding.

5: Inadequate Informed Consent Form (4%)

Includes:

- missing communication about withdrawal and refusal to participate
- missing documentation showing subject receipt of information about their right to refuse to participate in any aspect of the study
- missing documentation that shows that subjects were informed of their right to withdraw without penalty

Name processes that can be implemented to avoid this finding.

Common Findings and Resolution Worksheet

1:Failure to Follow Investigational Plan *(51%)*

Includes:

- missing consent documents
- failure to perform protocol-required procedures
- missing documentation of required IRB review of study changes

Name processes that can be implemented to avoid this finding

- **Get organized**
- **Maintain all Essential Documents**
- **Create Visit checklists of all procedures to be performed at each visit**
- **Create and maintain an organized Regulatory Binder**
- **Training of all applicable study team members**
- **Re-training as needed**

2: Inadequate and Inaccurate Records *(33%)*

Includes:

- record keeping, missing or incomplete subject record

Name processes that can be implemented to avoid this finding

- **Get organized**
- **Maintain all Essential Documents**
- **Create and maintain subject binders/records**
- **Document events asap after occurrence**
- **Follow ACLOA-C**
- **Training of all applicable study team members**
- **Re-training as needed**

3: Inadequate Drug Accountability *(7%)*

Includes:

- the record keeping of drugs used in research
- absence or inadequacy of records on receipts, preparation, use, and/or disposition of the investigational drug/product

Name processes that can be implemented to avoid this finding

- **Maintain accurate Investigational Product Accountability records**
- **Keep IP accountability records/logs up-to-date at all times**
- **Document dispensing and return of IP to/from subject**
- **Training of all applicable study team members**
- **Re-training as needed**

4: Failure to Obtain and/or Document Subject Consent (5%)

Includes:

- missing consent documents
- omission of a description of required elements when obtaining consent

Name processes that can be implemented to avoid this finding

- **Get organized**
- **Maintain all Essential Documents**
- **Create a template/form to document the Informed Consent process**
- **Training of all applicable study team members**
- **Re-training as needed**

5: Inadequate Informed Consent Form (4%)

Includes:

- missing communication about withdrawal and refusal to participate
- missing documentation showing subject receipt of information about their right to refuse to participate in any aspect of the study
- missing documentation that shows that subjects were informed of their right to withdraw without penalty

Name processes that can be implemented to avoid this finding

- **Get organized**
- **Maintain all Essential Documents**
- **Maintain a subject screening/enrollment log**
- **Create a template/form to document the Informed Consent process**
- **Training of all applicable study team members**
- **Re-training as needed**

Session 18

Contracts and Agreements

Study Closure

Differences Between FDA OHRP and ICH

Contracts and Agreements Worksheet

Define:

Contract

Confidentiality Disclosure Agreement (CDA)

Material Transfer Agreement (MTA)

Clinical Trials Agreement (CTA)

Clinical Materials and Supplies Agreements (CSMA)

Memorandum of Understanding (MOU)

Data Use Agreement (DUA)

Investigator Agreements for drug trials and device trials

Indemnification / Liability

Tool Summary Sheet

Tool: Study Close-Out Checklist

Purpose: This document provides a checklist for site personnel to ensure that all necessary aspects of study closure and archival have been addressed.

Audience/User: Investigators and Study Coordinators may use this template as a starting point for customizing a protocol/study specific checklist for site closure activities.

Details: Prior to considering a study closed or archived, necessary steps must be completed to ensure all aspects of study components have been addressed. This checklist provides a reference point for closure status.

Best Practice Recommendations:

- Review this template and customize to the specific needs and requirements of the study. Close-Out activities may be updated as needed. Remove or mark as "not applicable" those elements that are not required.
- If the study is closing early, contact NIDCR for additional guidance.
- Text enclosed with <> is a placeholder for a specific detail (e.g., <protocol title>); replace as appropriate.
- In some instances documentation may not be available or complete. Acknowledge the absence or deficiency within the Comments section of the checklist to demonstrate awareness.

Tool Revision History:

Version Number	Version Date	Summary of Revisions Made:
1.0	21FEB2011	Approved version
2.0	03JUL2013	Clarified and added task listings; added note to contact NIDCR for guidance if the study is closing early

Study Close-Out Checklist

No.	*Task*	*Owner*	*Date Completed*	*Comments*
Case Report Forms (CRFs)/Source Documents				
1	Confirm that appropriate source documentation is present for all subjects			
2	Paper Studies: Confirm that all CRFs have been completed, collected, and the proper legible copies are present in study files Electronic Data Capture (EDC) Studies: Confirm that all electronic CRFs have been completed and submitted to the DCC, as applicable			
3	Paper Studies: Confirm that all data clarification forms (DCFs) and queries issued to date have been submitted to the DCC (CROMS), appropriately resolved, signed and dated by the investigator, and that signed and dated queries are filed with the corresponding CRF page or subject EDC Studies: Confirm that all electronic queries issued to date have been appropriately resolved, reviewed by the CRA/SC/DM as appropriate, and closed, where applicable			
4	EDC Studies: Ensure that all CRF pages requiring signature have been electronically signed and dated by the investigator			
Data Management				
Note: If the site is using a Data Coordinating Center (DCC), tasks 5-8 will be owned by the DCC.				
5	Confirm all data is entered into the database			
6	Ensure all queries have been issued, returned, and resolved			
7	Once all queries have been resolved, clean and QC the database			
8	Perform database lock			
Adverse Event, Unanticipated Problem, and Serious Adverse Event Reporting/Reconciliation				
9	Ensure that all AEs, UPs, and SAEs have been captured, followed, and resolved per protocol, and reported to the appropriate parties (Sponsor, IRB, and FDA, if applicable) according to protocol reporting requirements			
10	Confirm that all required follow-up documentation has been retrieved, communicated to appropriate parties, and is present in the study files			

Investigator Site Files				
11	Confirm that signed consent forms are on file for all subjects			
12	Reconcile study files with Trial Master File (TMF) list. For studies where the TMF is maintained at the lead site or by another DCC, ensure all required documents are present, including collection of all required documents from all Investigator Site Files, where appropriate. These can include, but are not limited to: • protocols and amendments • approved consent document templates • IRB approvals • study team licenses • study certification documentation and CVs • laboratory documentation • Manual of Procedures (MOP) • Standard Operating Procedures (SOPs)			
13	Ensure reporting of study closure to the IRB and receipt/filing of study closure confirmation in the investigator site files			
14	If study was terminated early, confirm notification of study termination has been sent to all enrolled subjects as appropriate*			
15	Confirm that all protocol deviations have been noted in source documentation and reported to the IRB as appropriate			
16	Consider appropriate storage of Quality Management (QM) reports / metrics			
17	Confirm NIDCR/sponsor requirements for record retention and notify NIDCR/sponsor when study files will be transferred to long term off-site storage			
Ensure the completeness of the following logs:				
18	Pre-Screening Log (*if applicable)*			
19	Subject Screening and Enrollment Log			
20	Monitoring Visit Log *(if applicable)*			
21	Delegation of Responsibilities Log			
22	Telephone Log			
23	Training Log			
24	Subject Code List			
25	Randomization Log *(if applicable)*			
26	Investigational Product Accountability Log: Stock Record *(if applicable)*			
27	Investigational Product Accountability Log: Subject Record *(if applicable)*			
28	Specimen Tracking Log *(if applicable)*			
29	Freezer/Refrigerator Temperature Logs *(if applicable)*			

Investigational Product				
30	Confirm that investigational product disposition forms and accountability records are complete and present for all subjects receiving study drug			
31	Confirm final disposition of investigational product was completed per MOP, site pharmacy protocol, supplier, and sponsor requirements			
Collected Laboratory Specimens (Samples)				
32	Confirm that all specimens have either been analyzed or stored for future use			
33	Ensure that specimens collected for future use have been adequately processed, labeled/de-identified, and stored			
34	Confirm site process for identification and disposition of future use specimens connected to subjects who withdraw consent or do not consent for their specimens to be saved			
35	Confirm destruction, per institutional policies, of specimens not identified for future analysis			
Analysis, Manuscripts, and Submissions/Publications				
36	Data analysis complete			
37	Primary manuscript finalized			
38	Results submitted to Pubmed and ClinicalTrials.gov *(as applicable)* Intramural Studies: Confirm that notification has been made to the Office of Protocol Services (OPS) for change in study status and update to ClinicalTrials.gov Extramural Studies: Confirm that the appropriate party has updated ClinicalTrials.gov with the update in study status			
39	Confirm final disposition of study supplies and any equipment provided for the study: <insert study-specific items>			

* Note: If the study is closing early, contact NIDCR for additional guidance.

Significant Differences Among OHRP, RDA and ICH GCP			
	45 CFR 46	21 CRF 50	ICH GCP
Research	Research means a systematic investigation, including research development, testing, and evaluation, designed to develop or contribute to generalizable knowledge. Activities that meet this definition constitute research for purposes of this policy, whether or not they are conducted or supported under a program that is considered research for other purposes. For example, some demonstration and service programs may include research activities. For purposes of this part, the following activities are deemed not to be research: Scholarly and journalistic activities, Public health surveillance activities, Collection and analysis of information, biospecimens, or records by or for a criminal justice agency, Authorized	HHS has defined *"research"* as a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to +++ generalizable knowledge.	Does not define

Resource: [Significant Differences in FDA and DHHS Regulations (hopkinsmedicine.org)]

	operational activities (as determined by each agency) in support of intelligence, homeland security, defense, or other national security missions.		
Human Subject	Human subject means a living individual about whom an investigator (whether professional or student) conducting research: (i) Obtains information or biospecimens through intervention or interaction with the individual, and, uses studies, or analyzes the information or biospecimens; or (ii) Obtains, uses, studies, analyzes, or generates identifiable private information or identifiable biospecimens.	*"Human subject"* means a living individual about whom an investigator (whether professional or student) conducting research obtains (1) data through intervention or interaction with the individual, or (2) identifiable private information.	Does not define
Regulations on Human Subject Research	45 CFR 46 Subparts A (Common Rule), B, C, and D	(some of the many applicable regulations) Part 50 (protection of human subjects): Subpart A (definitions), Subpart B (informed consent), Subpart D (children)	Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety, and well-being of trial subjects

Resource: [Significant Differences in FDA and DHHS Regulations (hopkinsmedicine.org)]

		Note: No subparts for prisoners or pregnant women/fetus/neonates Part 54 (financial disclosure by clinical investigators) Part 56 (Institutional Review Boards) Part 11 (Electronic Records, signatures) Part 312 (Investigational New Drug Application) Part 809 (In Vitro Diagnostic products for human use) Part 812 (Investigational Device Exemption)	are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical trial data are credible. Sections 1 through 7.
	Private information includes information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information	Does not define	2.11 The confidentiality of records that could identify subjects should be protected, respecting the privacy and confidentiality rules in

Resource: [Significant Differences in FDA and DHHS Regulations (hopkinsmedicine.org)]

Private Information	that has been provided for specific purposes by an individual and that the individual can reasonably expect will not be made public (e.g., a medical record). (5) Identifiable private information is private information for which the identity of the subject is or may readily be ascertained by the investigator or associated with the information. (6) An identifiable biospecimen is a biospecimen for which the identity of the subject is or may readily be ascertained by the investigator or associated with the biospecimen.		accordance with the applicable regulatory requirement(s) 4.8.10 Both the informed consent discussion and the written informed consent form and Contains Nonbinding Recommendations 20 any other written information to be provided to subjects should include explanations of the following: That records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. If the results of the trial are published, the subject's identity will remain confidential
Emergency Use: IRB Review	DHHS regulations state that they are not intended to limit the provision of emergency medical care. No special "emergency" IRB review procedure is provided.	FDA provides exemption from the prospective IRB review requirement for "emergency use" of test article in specific situations. FDA "Emergency Use" provides procedure for IRB clearance of investigational product use,	4.8.15 In emergency situations, when prior consent of the subject is not possible, the consent of the subject's legally acceptable representative, if present, should be requested. When prior consent of the subject is not possible, and the subject's legally acceptable representative is not available, enrollment of the

Resource: [Significant Differences in FDA and DHHS Regulations (hopkinsmedicine.org)]

		when possible, prior to use in emergency clinical setting.	subject should require measures described in the protocol and/or elsewhere, with documented approval/favorable opinion by the IRB/IEC, to protect the rights, safety and well-being of the subject and to ensure compliance with applicable regulatory requirements. The subject or the subject's legally acceptable representative should be informed about the trial as soon as possible and consent to continue and other consent as appropriate (see section 4.8.10) should be requested
Exempt Research	DHHS exempts certain categories of research and provides for a Secretarial waiver.	FDA provides for sponsors and sponsor-investigators to request a waiver of IRB review requirements (but not informed consent requirements). The FDA has a limited number of categories which are exempt (56.104/105)	Does not address
Waiver of IRB Review	DHHS has no provision for waiving IRB review for human subject research that is not exempt.	On the application of a sponsor or sponsor-investigator, the FDA may waive any of the requirements contained in these regulations, including the	Does not address

		requirement for IRB review, for specific research activities or for classes of research activities, otherwise covered by these regulations. 56.105	
Updating IRB membership	DHHS requires that the Institution submit IRB membership rosters to the OHRP and update any changes.	Effective July 14, 2009, 21 CFR 56.106 requires registration of each IRB in the U.S. that reviews clinical investigations. Registration is through the OHRP electronic IRB registration site.	Does not address
Waiver of Parent/ Guardian Permission in Minimal Risk Studies	45.404. For minimal risk studies involving children, the IRB may waive the requirement for consent if the research meets the criterial of 46.116(d) or is designed for conditions or a population for which parent / guardian permission is not a reasonable requirement to protect the subjects (examples include neglected and abused children).	Waiver of parental permission is not allowed for FDA regulated research.	Does not address
Waiver of Parent / Guardian Permission in studies posing more than minimal risk to subjects and offering direct benefit to children participating	45.405 For benefit studies with more than minimal risk involving children, the IRB may waive the requirement for consent if the research is designed for conditions or a population for which parent/guardian permission is not a reasonable	Waiver of parental permission is not allowed for FDA regulated research.	Does not address

Resource: [Significant Differences in FDA and DHHS Regulations (hopkinsmedicine.org)]

	requirement to protect the subjects (examples include neglected and abused children).		
Waiver of Parent / Guardian Permission in Studies –a minor increase over minimal risk and no benefit to children participants	45.406 For studies not offering the prospect of direct benefit and that involve only a minor increase over minimal risk involving children, the IRB may waive the requirement for consent ONLY if the research is designed for conditions or a population for which parent / guardian permission is not a reasonable requirement to protect the subjects (ex. Include neglected and abused children). If parental permission is sought, both parents must provide consent (some exceptions.)	Waiver of parental permission is not allowed for FDA regulated research.	Does not address
Date on consent forms	DHHS regulations do not explicitly require consent forms to be dated.	FDA explicitly requires that consent forms be dated as well as signed by the subject or the subject's legally authorized representative. 50.27(a)	Prior to participation in the trial, the subject or the subject's legally acceptable representative should receive a copy of the signed and dated written informed consent form and any other written information provided to the subjects. During a subject's participation in the trial, the subject or the subject's legally acceptable representative should receive a copy of the

Resource: [Significant Differences in FDA and DHHS Regulations (hopkinsmedicine.org)]

			signed and dated consent form updates and a copy of any amendments to the written information provided to subjects
Waiver of Documentation of Informed Consent	DHHS allows for waiver or alteration of the requirement for a signed informed consent document in certain minimal risk studies and when the principal risk is a breach of confidentiality.	FDA does not permit waiver of documentation. Obtaining informed consent is "deemed feasible" except in two situations (clinical emergency and emergency research. 21 CFR 50.23, 50.24.	Does not address
Waiver of Informed Consent / Consent not Required	Waiver permitted under 46.116(d) if: • The research involves minimal risk • The waiver will not adversely affect the rights and welfare of subjects • The research could not practicable be carried out w/out the waiver • Where appropriate, subjects will be provided w/ additional information	Exceptions to informed consent requirements 21 CFR 50.23: • Subject is confronted with life-threatening situation necessitating use of test article • Informed consent not possible because of an inability to communicate with, or obtain legally effective IC from the subject • No time to obtain consent from LAR • No alternative method of approved therapy	Does not address

Resource: Significant Differences in FDA and DHHS Regulations (hopkinsmedicine.org)

		available that provides equal or greater likelihood of saving subject's life • IRB approves emergency research without requiring IC. 21 CFR 50.24	
Costs of research	Informed consent document must include disclosure of any "additional costs to the subject that may result from participation in the research." 46.116(b)(3)	• Disclosure of "additional costs" in the IC document • Costs of IND product are not chargeable to the subject without FDA permission • Costs of IDE product are chargeable to the subject, and are controlled by regulation.	5.8.2 The sponsor's policies and procedures should address the costs of treatment of trial subjects in the event of trial-related injuries in accordance with the applicable regulatory requirement(s). The consent form should include: The anticipated expenses, if any, to the subject for participating in the trial.
Inspection of Study Records	DHHS reserves the right to inspect records of studies it funds at a reasonable time and in a reasonable manner; it does not require that subjects provide	FDA explicitly requires that subjects be informed that FDA may inspect the records of the study because FDA may occasionally examine a subject's	4.l.4 The investigator/institution should permit monitoring and auditing by the sponsor, and inspection by the appropriate regulatory authority(ies).

	informed consent for that inspection.	medical records when they pertain to the study. 50.25(a)(5)	
Responsibilities of Investigators	Defers to the IRB to determine competence of the investigators (s)	• Provides expectations and responsibilities (IND - 312.60; 812.100-110) • Form 1572 signed by IND holder	4.1.1 The investigator(s) should be qualified by education, training, and experience to assume responsibility for the proper conduct of the trial, should meet all the qualifications specified by the applicable regulatory requirement(s), and should provide evidence of such qualifications through up-to-date curriculum vitae and/or other relevant documentation requested by the sponsor, the IRB/IEC, and/or the regulatory authority(ies).
Record Retention Note: HIPAA requires records to be retained for up to 6 years after the last subjects has completed study activity	Records must be kept for 3 years after completion of research.	Specified recordkeeping and record retention (2 years after marketing application approved, investigation is discontinued.)	5.5.12 The sponsor should inform the investigator(s)/institution(s) in writing of the need for record retention and should notify the investigator(s)/institution(s) in writing when the trial-related records are no longer needed.
Problem and AE reporting	PI must report “any unanticipated problems involving risk to subjects or others” or “any serious or continuous non-compliance”	Drug: PI must report to sponsor “any adverse effect that may reasonably be regarded as caused by, or probably caused by, the drug”	4.11.1 All SAEs should be reported immediately to the sponsor except for those SAEs that the protocol or other document (e.g., Investigator's Brochure) identifies as not needing immediate reporting.

Resource: Significant Differences in FDA and DHHS Regulations (hopkinsmedicine.org)

		Device: PI must report "unanticipated adverse device effects" (812.150)	The immediate reports should be followed promptly by detailed, written reports. The immediate and follow-up reports should identify subjects by unique code numbers assigned to the trial subjects rather than by the subjects' names, personal identification numbers, and/or addresses. The investigator should also comply with the applicable regulatory requirement(s) related to the reporting of unexpected serious adverse drug reactions to the regulatory authority(ies) and the IRB/IEC.
Sanctions	DHHS regulations do not list sanctions; however, the OHRP may withdraw the assurance between the institution and the government, and prevent the conduct of federally sponsored research at that institution.	• FDA regulations provide sanctions for non-compliance with regulations. 56.120, 124. • The FDA had procedures for "disqualification" of a clinical investigator. (312.70, 812.119) • The FDA has a process of "debarment" which can prevent individual investigators from	4.12.3 If the IRB/IEC terminates or suspends its approval/favorable opinion of a trial (see sections 3.1.2 and 3.3.9), the investigator should inform the institution where applicable and the investigator/institution should promptly notify the sponsor and provide the sponsor with a detailed written explanation of the termination or suspension.

Resource: Significant Differences in FDA and DHHS Regulations (hopkinsmedicine.org)

		participating in FDA regulated research.	
Clinicaltrials.gov	No specific language in the consent form is required	For applicable clinical trials initiated on or after March 7, 2012, informed consent documents must be in compliance with the new requirement in 21 CFR § 50.25(c) and include a specific statement that refers to the trial's description on www.ClinicalTrials.gov.	No specific language is required.

Resource: [Significant Differences in FDA and DHHS Regulations (hopkinsmedicine.org)]

Miscellaneous Information

2.54 cm in 1 inches

1 cm to inches = 0.3937 inches

30 cm to inches = 11.81102 inches

75 cm to inches = 29.52756 inches

1 centimeter is equal to 0.39370079 inches, which is the conversion factor from centimeters to inches

1 oz = (1/16) lb = 0.0625 lb

1 pound (lb) is equal to 16 Ounces (oz).

1 lb = 453.59237 g

1 kg = 2.2 lb

The formula for calculating the IV flow rate (drip rate) is total volume (in mL) divided by time (in min), multiplied by the drop factor (in gtts/mL), which equals the IV flow rate in gtts/min.

The formula for the Drip Rate: Drip Rate = Volume (mL) Time (h)

Pill Count Adherence:

% adherence= Quantity dispensed – Quantity returned (remaining)

Prescribed # of pills X # days between the dispensing date and visit date

The number of pills expected to have been taken is calculated by multiplying the daily dose by the number of days since the date dispensed.

Successful adherence on pill counts is usually 85–100% of the pills taken during each follow-up period

The **Fahrenheit** temperature scale is named for German physicist Daniel Gabriel Fahrenheit and is the measurement of temperature commonly used by the United States (and its associated territories) and by several nations in the Caribbean. On the Fahrenheit scale, water freezes at 32°F and boils at 212°F (at sea level).

The **Celsius** temperature scale—originally called *centigrade* and later renamed for Swedish astronomer Anders Celsius—is used almost everywhere else in the world. On the Celsius scale, water freezes at 0°C and boils at 100°C (at sea level).

To convert temperatures in degrees Fahrenheit to Celsius, subtract 32 and multiply by .5556 (or 5/9).

- Example: (50°F - 32) x .5556 = 10°C

C° TO F°: CELSIUS TO FAHRENHEIT CONVERSION FORMULA
To convert temperatures in degrees Celsius to Fahrenheit, multiply by 1.8 (or 9/5) and add 32.

- Example: (30°C x 1.8) + 32 = 86°F

Answer Section

For all Sessions

Historical Events and the Resulting Regulations/Guidance

The Elixir of Sulfanilamide Disaster	→	**1938 Federal Food, Drug, and Cosmetic Act**
Nuremburg Doctors Trial	→	**Nuremburg Code**
Thalidomide Tragedy	→	**Declaration of Helsinki**
ThalidomideTragedy	→	**Kefauver Amendments to the Food, Drug, and Cosmetic Acts**
Tuskegee Experiment	→	**1974 National research Act**
Penn's gene Therapy	→	**Conflict of interest**

Timeline of Research Events

__11_A. Passed by Congress authorizing federal agencies to develop human research regulations (45 CFR 46, 21 CFRs). IRB's were established and a National Commission for Protection of Human Subjects was established. It required that all human subject research be reviewed by an IRB/IEC to ensure human subject protections

__1__B. Signed into law by President Theodore Roosevelt. The law prohibited products being sold for indications outside its labeling. It also prohibited unlawful food and drugs from being transportation across states

__25_C. Provided expert advice and recommendations to the Secretary of HHS on issues pertaining to the protection of human subjects in research

__2__D. The study was conducted by the U.S. Public Health Service and involved 600 low-income African-American males. 400 of the males were infected with syphilis and were not told about their disease. They were then followed for 40 years. They were given free medical examinations, but were not treated for syphilis when a proven cure (penicillin) became available in the 1950s. The study continued until 1972 with participants being denied treatment. The study was stopped in 1973 by the U.S. Department of Health, Education, and Welfare. In 1997, under pressure, President Clinton apologized to the study subjects and their families

__3__ E. manufacturer attempted to market a drug to children, but instead became a mass poisoning of children. The chief chemist liquefied the drug by dissolving it in the toxic compound diethylene glycol. The company was made to pay a minimal fine for mislabeling the compound as this was the only penalty to serve under the 1906 Federal Food and Drugs Act

__4___F. U.S. Congress passed the act to require proof of safety before the releasing new drugs

__20__G. This guideline addresses justifications for a trial and protocol; protection of subjects; responsibilities of investigators, sponsors and monitors; assurance of data integrity and product accountability; and roles of regulatory authorities

__5__ H. Doctors performed approximately 30 different experiments on concentration camp inmates. These were conducted without the consent of the inmates. They encountered extreme pain, disabilities and even death as a result of these studies. The experiments included studies/experiments involving the following: cold water, freezing, twins, treatment of wounds, poison, sterilization, bone transplantation, high altitude, air pressure, and exposure to chemical-warfare agents. These experiments were a total disregard for the human dignity

_24__I. This office was elevated to the level of the US department of Health and Human services, replacing the NIH Office for Protection

__7__J. This person was being treated for cervical cancer and tumor cells were taken from her without her knowledge. It was discovered that these cells could be kept alive in culture. Her cells would eventually become the HeLa immortal cell line. This cell line is currently and frequently utilized in biomedical research. These cells have been used to test the first polio vaccine, AIDS research, and cancer research, as well as, other scientific quests

Timeline of Research Events

signed into law by President Theodore Roosevelt. The law prohibited products being sold for indications outside its labeling. It also prohibited unlawful food and drugs from being transportation across states

__12__ K. This document was published, based on the Presidentially commissioned work of MD Psychologists, Lawyers, and Biomedical and Behavioral Ethicists. This document proposed to go beyond "rules and regulations" and to proposed principles to use in judgments about protecting human subjects, (1) Respect for Persons, (2) Beneficence, and (3) Justice

__13__ L. The Department of Health and Human Services (DHHS) and the Food and Drug Administration (FDA) issued regulations based on the Belmont Report. DHHS issued Code of Federal Regulations (CFR) Title 45 (public welfare), Part 46 (protection of human subjects). The FDA issued CFR Title 21 (food and drugs), Parts 50 (protection of human subjects) and 56 (Institutional Review Boards)

__8__M. Researchers infected mentally disabled children with hepatitis. Subjects were then observed to record the progression of the disease. The New York Department of Health approved this study. Consent was obtained from parents, but the procedures were presented as vaccinations. In addition, there is evidence that only children enrolled in the study were admitted to the school (coercion)

__14__ N. Requirement of the NIH for all graduate students on training grants receive education on research training

__30__O. Trial in which neither the subject nor the observer know which treatment is being administered

__6__P. This was the first international document which advocated voluntary participation and informed consent. This document was a result of the Nuremberg Doctor's Trial. The Nuremberg Code stated "The voluntary consent of the human subject is absolutely essential," that the benefits of research must outweigh the risks. In 1946 the United Nations adopted the document and it has been translated into over 500 languages

__51__ Q. Phase of a study that detects side effects associated with chronic/long-term use of the drug

__17__R. Set of ethics involving the protection of human subjects was adopted by 17 Federal agencies. The main elements of the Common Rule include: (1) requirements for assuring compliance by research institutions, (2) requirements for researchers obtaining and documenting informed consent, (3) requirements for Institutional Review Board (IRB) membership, function, operations, review of research, and record keeping, (4) additional protections for certain vulnerable research subjects-- pregnant women, prisoners, and children

_42__ S. Preliminary study with the objective of determining whether a program, procedure or study protocol is practicable, as well as finding out data to help in determining the sample size for a definitive study

__9__ T. This Act was passed into law to ensure drug efficacy and greater drug safety. For the first time, drug manufacturers were required to prove to FDA the effectiveness of their products before marketing them

Timeline of Research Events

_37__U. Type of study- Initial application, on a small scale, of a study protocol. The aim of checking whether the design is appropriate, establishing its viability or obtaining information to determine the sample size for the definitive study

__18_ V. This system was launched by the FDA and was designed to collect health professionals' reports of adverse events involving medical products. When safety hazards are detected, the FDA issues medical product safety alerts or orders product recalls, withdrawals, or labeling changes to protect the public health

__32_ W. A trial carried out in two or more centers with the same protocol

_10__X. governs international research ethics and defines rules for "research combined with clinical care" and "non-therapeutic research." The document is the basis for Good Clinical Practices used today. It addresses the following: (1) Research with humans should be based on the results from laboratory and animal experimentation, (2) Research protocols should be reviewed by an independent committee prior to initiation, (3) Informed consent from research participants is necessary,(4) Research should be conducted by medically/scientifically qualified individuals and (5) Risks should not exceed benefits

_33__Y. Clinical trial in which each group of patients receives a single treatment simultaneously

_36__ Z. Initial application, on a small scale, of a study protocol. The aim of checking whether the design is appropriate, establishing its viability or obtaining information to determine the sample size for the definitive study

__47_ AA. A sedative was approved in Europe in the late 1950's, but was not approved in the United States by the FDA. This drug was prescribed to pregnant women to control sleep and nausea, but taking this drug during pregnancy caused severe deformities in the fetus. The issue was that many patients did not know they were taking a drug that was not approved by the FDA and did not give informed consent. Deformities due to thalidomide affected approximately 12,000 babies

__46_BB. The Phase of a study using only a few small doses of a new drug in a few people. Almost no chance the people in phase 0 trials will benefit

_22__ CC. Requires all people conducting or overseeing human subjects research have some training in research ethics

__23_DD. Proposes mandatory training in responsible conduct of research for all researchers on PHS grants, including junior senior investigators, students, and technicians. Several scientific associations and universities oppose the policy as an unnecessary and un-funded mandate. The Bush Administration suspends the ORI proposal in 2001 on the grounds that the agency failed to follow proper procedures for proposing new government regulations. To ORI proposal is still in limbo

_53___ EE. two (or more) groups that are exposed to different things are compared with each other in a study

_26___ FF. The NIH and other agencies adopt the OSTP misconduct definition. The OSTP Policy defines "research misconduct" as "fabrication, falsification, or plagiarism in proposing, performing, or reviewing research, or in reporting research results". It also sets the legal threshold for proving charges of misconduct

Timeline of Research Events

_15__GG. Many European nations along with Japan and the United States began creating plans for global harmonization of regulatory requirements to reduce duplicate, time-consuming, and expensive procedures needed to market products internationally, while maintaining safeguards on quality, safety, and efficacy

50__HH. Studies designed to look at efficacy and side effects

_27__ II. The Office that announced proposed changes to the Common Rule to enhance human subject protections and reduce investigator burden

_29__ JJ. Trial in which the subject, but not the observer, does not know which of the possible treatments he/she is receiving

_45____KK. Study in which the data collected refers to events which have occurred

_19__LL. The Act requires that patients be informed of how their protected health information will be stored and kept private when they participate in a research trial. President Bill Clinton signed this act into law in 1992, but the final rule did not go into effect until 1996

_50__MM. Primarily focuses on determining whether the treatment would be safe and effective for a wide variety of people

_21__NN. Gene Therapy Study at University of Pennsylvania) where an 18 years old dies while a participant in a human gene therapy experiment. He suffered from a rare x-linked genetic disease of the liver but did not suffer effects at the time he enrolled in a gene therapy study at a University to help others. He died four days after the research procedure. After his death, information revealed led his father to believe that he nor his family were fully informed and aware of the risks involved in the study. The University failed to report previous experienced serious side effects from participants, the informed consent did not divulge known deaths and University financial conflicts of interest in the trial. Additionally, he had a high ammonia levels that should have excluded him from participating in the study. This generated the need for a heightened scrutiny of conflicts of interest in human subjects research, including institutional conflicts of interest. The family settled for an undisclosed amount of money

_**31**___OO. Clinical trial in which each individual consecutively receives each of the treatments under study

_16___PP. Hospitals and health professionals were required to report safety incidents to the FDA and manufacturers regarding devices. The FDA under this act was able to recall devices and take other actions

_48___QQ. Performed to determine the best/highest/route for the dose and schedule of a new study treatment that can be given safely without causing severe side effects

_41___ RR**.** These are studies in which there is a time lapse different between the variables, so that a time sequence can be established between them

_49____SS. Trials intended to determine the best dose and schedule of a study treatment. The focus of these trials is on understanding the side effects

The following provides the basis for the ethical principles for Human Subject Protection:

- **A. Belmont Report**
- **B. Declaration of Helsinki**
- **C. Nuremburg Code**

The following addressed the need for Informed Consent:

- **A. Belmont Report**
- **B. Declaration of Helsinki**
- **C. Nuremburg Code**

The ethical principles of the Belmont Report include which of the following? (Choose all that apply)

- **A. Respect**
- **B. Knowledge**
- **C. Beneficence**
- **D. Protection**
- **E. Justice**

Which of the statements do not stand for justice?

- **A. Fairness in distribution**
- **B. What is deserved**
- **C. Each person receives a particular share according to merit**

"Individuals should be treated as autonomous agents, and second, that persons with diminished autonomy are entitles to protection" is which of the basic ethical principles from the Belmont Report?

- **A. Respect**
- **B. Knowledge**
- **C. Beneficence**
- **D. Protection**
- **E. Justice**

The experiment should be conducted only by scientifically qualified persons. The highest degree of skill and care should be required through all stages of the experiment of those who conduct or engage in the experiment.

- **A. Belmont Report**
- **B. Declaration of Helsinki**
- **C. Nuremburg Code**

"The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act in the patient's best interest when providing medical care.". These statements are from which document?

D. **Belmont Report**
E. **Declaration of Helsinki**
F. **Nuremburg Code**

Two general rules of the Belmont Report have been formulated as complementary expressions of _____ actions. (1) do not harm and (2) maximize possible benefits and minimize possible harms.

A. **Respect**
B. **Knowledge**
C. **Beneficence**
D. **Protection**
E. **Justice**

According to this document, humane experimentation is justified only if its results benefit society and it is carried out in accord with basic principles that "satisfy moral, ethical, and legal concepts."

A. **Belmont Report**
B. **Declaration of Helsinki**
C. **Nuremburg Code**

Who ought to receive the benefits of research and bear its burdens/ This is a question of _____, in the sense of fairness in distribution or what is deserved."

A. **Respect**
B. **Knowledge**
C. **Beneficence**
D. **Protection**
E. **Justice**

What does respecting autonomy look like?

A. **Asking other to make decisions for oneself**
B. **Using coercion to assist one in making a decision**
C. **Giving one merit to their opinions and choices**

Medical research should be conducted in a manner that minimizes possible harm to the environment. This statement is from which document?

A. **Belmont Report**
B. **Declaration of Helsinki**
C. **Nuremburg Code**

The major themes of the Nuremburg Code were which of the following?

A. **Voluntary consent, risk vs benefit, and research should be conducted by qualified staff**

B. **Voluntary consent, adequate knowledge, and research should be conducted by qualified staff**
C. **Voluntary consent, adequate knowledge, and justice**

What beneficent actions are in the Belmont report?

A. **Do no harm**
B. **Maximize benefits and harm**
C. **Minimize possible harms**
D. **Maximize benefits**
E. **A, B, C**
F. **A, C, D**
G. **All of the above**

Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research. These statements are from which document?

A. **Belmont Report**
B. **Declaration of Helsinki**
C. **Nuremburg Code**

The commission that formulated the Belmont Report was created as part of the

A. **National Research Act of 1974**
B. **National Researchers Act of 1974**
C. **National Research Act of 1975**

The Declaration of Helsinki was written in what year?

A. **1965**
B. **1964**
C. **1963**

The Belmont Report addresses the difference between:

A. **Risk/benefit ratio**
B. **Medical practice and research**
C. **Adequate knowledge and being uninformed**

The experiment should be so designed and based on the results of animal experimentation and a knowledge of the natural history of the disease or other problem under study that the anticipated results will justify the performance of the experiment.

A. **Belmont Report**
B. **Declaration of Helsinki**

C. Nuremburg Code

Who is not an autonomous person?

A. One who is not capable of making their own decisions
B. One who makes their own decisions rather than being influenced by someone else
C. One who is self-governing
D. One who ha moral independence

What date was the Belmont report created:

A. 1976
B. 1978
C. 1979
D. 1980

The Declaration of Helsinki was formulated by the

A. World Health Association
B. World Medicine Association
C. World Medical Association

When assessing payments to subjects the ethical principles of the Belmont Report to consider would be:

A. Respect
B. Knowledge
C. Beneficence
D. Protection
E. Justice

The _____ advises treatment drug with comparator control whenever possible.

A. Belmont Report
B. Declaration of Helsinki
C. Nuremburg Code

Which action would show lack of respect for autonomy?

A. Repudiate a person's decision
B. Withhold information to make an informed decision
C. A and B
D. None of the above

In most cases of research involving human subjects, _____ demands that subjects enter into research voluntarily and with adequate information.

A. respect for persons
B. adequate Knowledge demonstrated by the study team
C. benefits over risk

D. protection of rights
E. justice

The major themes of the declaration of Helsinki included which of the following:

A. Physicians have a duty to protect subjects
B. Individuals take precedence over the interest of science
C. Research should be summarized in a protocol
D. Physicians should be aware of ethical, legal and regulatory requirements of research
E. A, B, and C
F. A, C, and D
G. All of the above

In what year was the Nuremburg Code written?

A. 1947
B. 1948
C. 1949

When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship. These statements are from which document?

A. Belmont Report
B. Declaration of Helsinki
C. Nuremburg Code

The _____ is the ethical framework cited in the ICH GCPs for conducting clinical trials.

A. Belmont Report
B. Declaration of Helsinki
C. Nuremburg Code

General Definitions for 45 CFR 46

With answers

Certification: Certification means the official notification by the institution to the supporting Federal department or agency component, in accordance with the requirements of a policy, that a research project or activity involving human subjects has been reviewed and approved by an IRB in accordance with an approved assurance.

Clinical trial: Clinical trial means research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of the interventions on biomedical or behavioral health-related outcomes.

Human subject: Human subject means a living individual about whom an investigator (whether professional or student) conducting research:

- Obtains information or biospecimens through intervention or interaction with the individual, and uses, studies, or analyzes the information or biospecimens; or
- Obtains, uses, studies, analyzes, or generates identifiable private information or identifiable biospecimens.

Private information: Private information includes information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information that has been provided for specific purposes by an individual and that the individual can reasonably expect will not be made public (e.g., a medical record).

Identifiable private information: Identifiable private information is private information for which the identity of the subject is or may readily be ascertained by the investigator or associated with the information.

Identifiable biospecimen: An identifiable biospecimen is a biospecimen for which the identity of the subject is or may readily be ascertained by the investigator or associated with the biospecimen.

Intervention: Intervention includes both physical procedures by which information or biospecimens are gathered (e.g., venipuncture) and manipulations of the subject or the subject's environment that are performed for research purposes.

Interaction: Interaction includes communication or interpersonal contact between investigator and subject.

LAR: (LAR) Legally authorized representative means an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research. If there is no applicable law addressing this issue, legally authorized representative means an individual recognized by institutional policy as acceptable for providing consent in the nonresearch context on behalf of the prospective subject to the subject's participation in the procedure(s) involved in the research.

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.

Research: Research means a systematic investigation, including research development, testing, and evaluation, designed to develop or contribute to generalizable knowledge. Activities that meet this definition constitute research for purposes of this policy, whether or not they are conducted or supported under a program that is considered research for other purposes. For example, some demonstration and service programs may include research activities.

General Definitions for 21 CFR 50

With answers

Clinical Investigation. Clinical investigation means any experiment that involves a test article and one or more human subjects and that either is subject to requirements for prior submission to the Food and Drug Administration under section 505(i) or 520(g) of the act, or is not subject to requirements for prior submission to the Food and Drug Administration under these sections of the act, but the results of which are intended to be submitted later to, or held for inspection by, the Food and Drug Administration as part of an application for a research or marketing permit. The term does not include experiments that are subject to the provisions of part 58 of this chapter, regarding nonclinical laboratory studies.

Investigator. Investigator means an individual who actually conducts a clinical investigation, i.e., under whose immediate direction the test article is administered or dispensed to, or used involving, a subject, or, in the event of an investigation conducted by a team of individuals, is the responsible leader of that team.

Sponsor. Sponsor means a person who initiates a clinical investigation, but who does not actually conduct the investigation, i.e., the test article is administered or dispensed to or used involving, a subject under the immediate direction of another individual. A person other than an individual (e.g., corporation or agency) that uses one or more of its own employees to conduct a clinical investigation it has initiated is considered to be a sponsor (not a sponsor-investigator), and the employees are considered to be investigators.

Sponsor Investigator. Sponsor-investigator means an individual who both initiates and actually conducts, alone or with others, a clinical investigation, i.e., under whose immediate direction the test article is administered or dispensed to, or used involving, a subject. The term does not include any person other than an individual, e.g., corporation or agency.

Human Subject. Human subject means an individual who is or becomes a participant in research, either as a recipient of the test article or as a control. A subject may be either a healthy human or a patient.

Test article. Test article means any drug (including a biological product for human use), medical device for human use, human food additive, color additive, electronic product, or any other article subject to regulation under the act or under sections 351 and 354-360F of the Public Health Service Act (42 U.S.C. 262 and 263b-263n).

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.

Definitions for Vulnerable Populations

With answers

Fetus: **Fetus means the product of conception from implantation until delivery**.

Neonate: **Neonate means a newborn.**

Nonviable Neonate: **Nonviable neonate means a neonate after delivery that, although living, is not viable.**

Prisoner**: *Prisoner* means any individual involuntarily confined or detained in a penal institution. The term is intended to encompass individuals sentenced to such an institution under a criminal or civil statute, individuals detained in other facilities by virtue of statutes or commitment procedures which provide alternatives to criminal prosecution or incarceration in a penal institution, and individuals detained pending arraignment, trial, or sentencing.**

Children: ***Children* are persons who have not attained the legal age for consent to treatments or procedures involved in the research, under the applicable law of the jurisdiction in which the research will be conducted.**

Assent: ***Assent* means a child's affirmative agreement to participate in research. Mere failure to object should not, absent affirmative agreement, be construed as assent.**

Permission: ***Permission* means the agreement of parent(s) or guardian to the participation of their child or ward in research.**

Parent: ***Parent* means a child's biological or adoptive parent.**

Guardian: ***Guardian* means an individual who is authorized under applicable State or local law to consent on behalf of a child to general medical care.**

Ward: **A person, usually a minor, under the care and control of a guardian appointed by their parents or a court.**

Advocate: **A person who publicly supports or recommends a particular cause or policy.**

Vulnerable Subjects Worksheet

45 CFR 46, Subparts B, C, and D

45 CFR 46 Subpart B

Additional protections for pregnant women, fetuses and neonates

Pregnant women or fetuses may be involved in research when…

TRUE or FALSE

True. Preclinical studies have been conducted and provide data for assessment of potential risks

True. Risks to the fetus are not greater than minimal and important medical knowledge can be obtained

False. Risks to the fetus are caused by interventions that hold no prospect of benefit for the fetus or the woman. ***The risk to the fetus is caused solely by interventions or procedures that hold out the prospect of direct benefit for the woman or the fetus; or, if there is no such prospect of benefit, the risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge which cannot be obtained by any other means***

False. The research holds out a benefit solely for the fetus and the investigator obtains consent from the pregnant woman only. ***The consent of the pregnant woman and the father is obtained in accord with the informed consent provisions of subpart A of this part, except that the father's consent need not be obtained if he is unable to consent because of unavailability, incompetence, or temporary incapacity or the pregnancy resulted from rape or incest.***

False. Individuals involved in the research provide an inducement to terminate a pregnancy but are not involved in determining viability of the neonate. ***Individuals or researchers have no involvement with the termination of the pregnancy or determining the viability of the neonate.***

Neonates of uncertain viability or nonviable neonates may be involved in research if …

TRUE of FALSE

True. Preclinical studies have been conducted and provide data for assessment risks

True. Investigators have no part in determining the viability of the neonate

True. The IRB determines that there is a prospect of improving the probability of survival of the neonate and that risk is minimized as much as possible

True. Effective informed consent of both parents of a neonate with uncertain viability is obtained unless there is unavailability, incompetence, or if the pregnancy resulted form rape or incest.

False. Nonviable neonates have vital functions artificially maintained. ***Neonates shall not have vital functions artificially maintained.***

45 CFR 46 Subpart C

Additional Protections for Prisoners in Research

List the 2 additional requirements for the composition of the IRB for review of prisoner research and at least 4 additional requirements that must be satisfied by the IRB in order to review and approve research involving prisoners?

IRB Requirements:

(a) A majority of the Board (exclusive of prisoner members) shall have no association with the prison(s) involved, apart from their membership on the Board.

(b) At least one member of the Board shall be a prisoner, or a prisoner representative with appropriate background and experience to serve in that capacity, except that where a particular research project is reviewed by more than one Board only one Board need satisfy this requirement.

Additional requirements:

(1) The research under review represents one of the categories of research permissible under §46.306(a)(2);

(2) Any possible advantages accruing to the prisoner through his or her participation in the research, when compared to the general living conditions, medical care, quality of food, amenities and opportunity for earnings in the prison, are not of such a magnitude that his or her ability to weigh the risks of the research against the value of such advantages in the limited choice environment of the prison is impaired;

(3) The risks involved in the research are commensurate with risks that would be accepted by nonprisoner volunteers;

(4) Procedures for the selection of subjects within the prison are fair to all prisoners and immune from arbitrary intervention by prison authorities or prisoners. Unless the principal investigator provides to the Board justification in writing for following some other procedures, control subjects must be selected randomly from the group of available prisoners who meet the characteristics needed for that particular research project;

(5) The information is presented in language which is understandable to the subject population;

(6) Adequate assurance exists that parole boards will not take into account a prisoner's participation in the research in making decisions regarding parole, and each prisoner is clearly informed in advance that participation in the research will have no effect on his or her parole; and

(7) Where the Board finds there may be a need for follow-up examination or care of participants after the end of their participation, adequate provision has been made for such examination or care, taking into account the varying lengths of individual prisoners' sentences, and for informing participants of this fact.

Biomedical or behavior research conducted or supported by DHHS may involve prisoners if…

TRUE or FALSE

True. The institution certifies to the Secretary that the IRB has complied with all requirements under 45 CFR 46.304 and 305 for review and approval of research involving prisoners

True. The research investigates the possible causes, effects and processes of incarceration or criminal behavior

False. Research involving a reasonable probability of improving health or well being of prisoner subjects and requiring the assignment of prisoners to a control group who will not benefit from participation, must be reviewed by the Director of the FDA .

Control subjects must be selected randomly from the group of available prisoners who meet the characteristics needed for that particular research project. ***The Secretary has consulted with appropriate experts --not the FDA.***

45 CFR 46 Subpart D

Additional Protections for Children

List the regulatory risk categories that must be considered by the IRB when reviewing research that involves children.

§46.404 Research not involving greater than minimal risk.

§46.405 Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects.

§46.406 Research involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition.

§46.407 Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children.

Compare 45 CFR 46 Subpart D with 21 CFR 50 Subpart D

Waiver of parental permission is not allowed for FDA regulated research.

Waiver of parental permission is allowed in OHRP regulations in some cases 45.404, 45.405 and 45.406 (examples include neglected and abused children)

Biomedical or behavioral research conducted or supported by DHHS may involve children if…

TRUE or FALSE

False. The sponsor determines whether and how assent must be documented. **The IRB determines whether and how assent must be obtained and documented.**

False. Assent is a child's passive resignation to submit to a research intervention ***Assent means a child's affirmative agreement to participate in research. Mere failure to object should not, absent affirmative agreement, be construed as assent.***

True. Parental permission must be obtained from both parents for research falling in the categories of .406 and .407 subsections of 45 CFR 46 Subpart D

Where research is covered by §§46.406 and 46.407 and permission is to be obtained from parents, both parents must give their permission unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child.

True. Wards of the State can be included in research approved under 45 CFR 46.406 or 407 only if the research is related to their status as wards or conducted in settings where the majority of children involved are not wards

ICG GCP E6 (R2) Worksheet

Section 1.0: Glossary

Please be familiar with all terms in the glossary

An ___audit___is a systematic and independent examination of trial-related activities and documents to determine whether the evaluated trial-related activities were conducted, and the data was recorded, analyzed, and accurately reported according to the protocol, sponsor's SOPs, good clinical practice, and the applicable regulatory requirements.

Monitoring___ is the act of overseeing the progress of a clinical trial, and of ensuring that it is conducted, recorded, and reported in accordance with the protocol, SOPs, GCP, and the applicable regulatory requirements

A subject identification code__unique identifier assigned by the investigator to each trial subject to protect the subject's identity

Quality Assurance__All those planned and systematic actions that are established to ensure that the trial is performed and the data is generated, documented (recorded), an reported in compliance with GCP and applicable regulatory requirements

The operational techniques and activities undertaken to verify that the requirements for the quality of the trial-related activities have been fulfilled is called __Quality Control

Source Data___ All information in original records and certifies copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with the treatment is known as an _Adverse Event_____

Documents that individually and collectively permit evaluation of the conduct of a study and the quality of the data produced are called ___Essential Documents___

Protocol___A document that describes the objective(s), design, methodology, statistical considerations, and organization of the trial

A legally authorized representative is an individual or juridical or other body authorized under applicable law to consent, on behalf of a prospective subject, to the subject's participation in the clinical trial

Detailed, written instructions to achieve uniformity of the performance of a specific function are known as standard operating procedures

Randomization is the process of assigning trial subjects to treatment or control groups using an element of chance to determine the assignments in order to reduce bias

The physical and mental integrity of the subjects participating in a clinical trial is known as the _well-being___ of trial subjects

Section 2.0: The Principles of ICH GCP

Clinical trials should be conducted in accordance with the ethical principles that have their origin in the __Declaration of Helsinki_, and are consistent with GCP and the applicable regulatory requirements

A trial should be initiated and continues only if the _anticipated benefits justify he risk.

The rights, safety, and well-being of the trial subjects are the most important considerations and should prevail over interests of science and society.

The available _nonclinical_and _clinical_ information on an investigational product should be adequate to support the proposed clinical trial.

Clinical trials should be scientifically sound, and described in a clear, detailed protocol.

A trial should be conducted in compliance with the __protocol_that has received prior IRB/IEC approval/favorable opinion

The medical care given to, and the medical decisions made on behalf of, subjects should always be the responsibility of a qualified _physician____ or, when appropriate, of a qualified __dentist_____

Each individual involved in conducting a trial should be qualified by __education___, _training_____, and __experience____ to perform his or her respective task

Freely given informed consent should be obtained from every subject prior to clinical trial participation

All clinical trial information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation, and verification

The confidentiality of records that could identify subjects should be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirements

Investigational products should be manufactured, handled, and stored in accordance with applicable good manufacturing practice. They should be used in accordance with the approved protocol

Systems with procedures that assure the quality of every aspect of the trial should be implemented

Section 3.0: Institutional Review Board/Independent Ethics Committee

An IRB/IEC should safeguard the rights, safety, and well-being of all trial subjects. Special attention should be paid to trials that may include vulnerable subjects.

The IRB/IEC should consider the qualifications of the investigator for the proposed trial, as documented by a current curriculum vitae and/or by any other relevant documentation the IRB/IEC requests.

The IRB/IEC should ensure that information regarding payment to subjects, including the methods, amounts, and schedule of payment to trial subjects, is set forth in the written informed consent form and any other written information to be provided to subjects. The way payment will be prorated should be specified.

The IRB/IEC should consist of a reasonable number of members, who collectively have the qualifications and experience to review and evaluate the science, medical aspects, and ethics of the proposed trial. It is recommended that the IRB/IEC should include:

(a) At least five members.

(b) At least one member whose primary area of interest is in a nonscientific area.

(c) At least one member who is independent of the institution/trial site.

Only those IRB/IEC members who are independent of the investigator and the sponsor of the trial should vote/provide opinion on a trial-related matter.

The IRB/IEC should retain all relevant records (e.g., written procedures, membership lists, lists of occupations/affiliations of members, submitted documents, minutes of meetings, and correspondence) for a period of at least 3 years after completion of the trial and make them available upon request from the regulatory authority(ies).

Section 4.0: Investigator

Section 5.0: Sponsor

During protocol development, the sponsor should identify those processes and data that are critical to ensure human subject protection and the reliability of trial results.

The sponsor should decide which risks to reduce and/or which risks to accept. The approach used to reduce risk to an acceptable level should be proportionate to the significance of the risk.

The sponsor should periodically review risk control measures to ascertain whether the implemented quality management activities remain effective and relevant, taking into account emerging knowledge and experience.

The sponsor is responsible for implementing and maintaining quality assurance and quality control systems with written SOPs to ensure that trials are conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirement(s).

Agreements, made by the sponsor with the investigator/institution and any other parties involved with the clinical trial, should be in writing, as part of the protocol or in a separate agreement.

A sponsor may transfer any or all of the sponsor's trial-related duties and functions to a CRO, but the ultimate responsibility for the quality and integrity of the trial data always resides with the sponsor.

Any trial-related duties and functions not specifically transferred to and assumed by a CRO are retained by the sponsor.

If data are transformed during processing, it should always be possible to compare the original data and observations with the processed data.

The sponsor specific essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period however if required by the applicable regulatory requirement(s) or if needed by the sponsor.

The sponsor should inform the investigator(s)/institution(s) in writing of the need for record retention and should notify the investigator(s)/institution(s) in writing when the trial related records are no longer needed.

Before entering an agreement with an investigator/institution to conduct a trial, the sponsor should provide the investigator(s)/institution(s) with the protocol and an up-to-date Investigator's Brochure, and should provide sufficient time for the investigator/institution to review the protocol and the information provided.

The sponsor should obtain the investigator's/institution's agreement:

(a) to conduct the trial in compliance with GCP, with the applicable regulatory requirement(s) (see 4.1.3), and with the protocol agreed to by the sponsor and given approval/favorable opinion by the IRB/IEC (see 4.5.1);

(b) to comply with procedures for data recording/reporting;

(c) to permit monitoring, auditing and inspection (see 4.1.4) and

(d) to retain the trial related essential documents until the sponsor informs the investigator/institution these documents are no longer needed (see 4.9.4 and 5.5.12).

The sponsor and the investigator/institution should sign the protocol, or an alternative document, to confirm this agreement.

The sponsor should determine, for the investigational product(s), acceptable storage temperatures, storage conditions (e.g. protection from light), storage times, reconstitution fluids and procedures, and devices for product infusion, if any. The sponsor should inform all involved parties (e.g. monitors, investigators, pharmacists, storage managers) of these determinations.

The sponsor should not supply an investigator/institution with the investigational product(s) until the sponsor obtains all required documentation (e.g. approval/favorable opinion from IRB/IEC and regulatory authority(ies)).

Section 6.0: Clinical Trial Protocol and Protocol Amendment(s)

Protocol title, protocol identifying number, and date. Any amendment(s) should also bear the amendment number(s) and date(s).

6.1.2 Name and address of the sponsor and monitor (if other than the sponsor).

6.1.3 Name and title of the person(s) authorized to sign the protocol and the protocol amendment(s) for the sponsor.

6.1.4 Name, title, address, and telephone number(s) of the sponsor's medical expert (or dentist when appropriate) for the trial.

6.1.5 Name and title of the investigator(s) who is (are) responsible for conducting the trial, and the address and telephone number(s) of the trial site(s).

6.1.6 Name, title, address, and telephone number(s) of the qualified physician (or dentist, if applicable), who is responsible for all trial-site related medical (or dental) decisions (if other than investigator).

6.1.7 Name(s) and address(es) of the clinical laboratory(ies) and other medical and/or technical department(s) and/or institutions involved in the trial. Contains Nonbinding Recommendations 40 6.2 Background Information

6.2.1 Name and description of the investigational product(s).

6.2.2 A summary of findings from nonclinical studies that potentially have clinical significance and from clinical trials that are relevant to the trial.

6.2.3 Summary of the known and potential risks and benefits, if any, to human subjects.

6.2.4 Description of and justification for the route of administration, dosage, dosage regimen, and treatment period(s).

6.2.5 A statement that the trial will be conducted in compliance with the protocol, GCP, and the applicable regulatory requirement(s).

6.2.6 Description of the population to be studied.

6.2.7 References to literature and data that are relevant to the trial and that provide background for the trial.

6.3 Trial Objectives and Purpose A detailed description of the objectives and the purpose of the trial.

6.4 Trial Design The scientific integrity of the trial and the credibility of the data from the trial depend substantially on the trial design. A description of the trial design should include:

6.4.1 A specific statement of the primary endpoints and the secondary endpoints, if any, to be measured during the trial.

6.4.2 A description of the type/design of trial to be conducted (e.g., double-blind, placebo-controlled, parallel design) and a schematic diagram of trial design, procedures, and stages.

6.4.3 A description of the measures taken to minimize/avoid bias, including: (a) Randomization (b) Blinding.

6.4.4 A description of the trial treatment(s) and the dosage and dosage regimen of the investigational product(s). Also include a description of the dosage form, packaging, and labelling of the investigational product(s).

6.4.5 The expected duration of subject participation, and a description of the sequence and duration of all trial periods, including follow-up, if any.

6.4.6 A description of the "stopping rules" or "discontinuation criteria" for individual Contains Nonbinding Recommendations 41 subjects, parts of trial, and entire trial.

6.4.7 Accountability procedures for the investigational product(s), including the placebo(s) and comparator(s), if any.

6.4.8 Maintenance of trial treatment randomization codes and procedures for breaking codes.

6.4.9 The identification of any data to be recorded directly on the CRFs (i.e., no prior written or electronic record of data), and to be considered to be source data.

6.5 Selection and Withdrawal of Subjects

6.5.1 Subject inclusion criteria.

6.5.2 Subject exclusion criteria.

6.5.3 Subject withdrawal criteria (i.e., terminating investigational product treatment/trial treatment) and procedures specifying: (a) When and how to withdraw subjects from the trial/investigational product treatment (b) The type and timing of the data to be collected for withdrawn subjects (c) Whether and how subjects are to be replaced (d) The follow-up for subjects withdrawn from investigational product treatment/trial treatment.

6.6 Treatment of Subjects

6.6.1 The treatment(s) to be administered, including the name(s) of all the product(s), the dose(s), the dosing schedule(s), the route/mode(s) of administration, and the treatment period(s), including the follow-up period(s) for subjects for each investigational product treatment/trial treatment group/arm of the trial.

6.6.2 Medication(s)/treatment(s) permitted (including rescue medication) and not permitted before and/or during the trial.

6.6.3 Procedures for monitoring subject compliance.

6.7 Assessment of Efficacy 6.7.1 Specification of the efficacy parameters.

6.7.2 Methods and timing for assessing, recording, and analyzing efficacy parameters.

6.8 Assessment of Safety

6.8.1 Specification of safety parameters. Contains Nonbinding Recommendations 42

6.8.2 The methods and timing for assessing, recording, and analyzing safety parameters.

6.8.3 Procedures for eliciting reports of and for recording and reporting adverse event and intercurrent illnesses.

6.8.4 The type and duration of the follow-up of subjects after adverse events.

6.9 Statistics

6.9.1 A description of the statistical methods to be employed, including timing of any planned interim analysis(ses).

6.9.2 The number of subjects planned to be enrolled. In multicenter trials, the numbers of enrolled subjects projected for each trial site should be specified. Reason for choice of sample size, including reflections on (or calculations of) the power of the trial and clinical justification.

6.9.3 The level of significance to be used.

6.9.4 Criteria for the termination of the trial.

6.9.5 Procedure for accounting for missing, unused, and spurious data.

6.9.6 Procedures for reporting any deviation(s) from the original statistical plan (any deviation(s) from the original statistical plan should be described and justified in protocol and/or in the final report, as appropriate).

6.9.7 The selection of subjects to be included in the analyses (e.g., all randomized subjects, all dosed subjects, all eligible subjects, evaluable subjects).

6.10 Direct Access to Source Data/Documents The sponsor should ensure that it is specified in the protocol or other written agreement that the investigator(s)/institution(s) will permit trial-related monitoring, audits, IRB/IEC review, and regulatory inspection(s), providing direct access to source data/documents

6.11 QualityControl and QualityAssurance

6.12 Ethics Description of ethical considerations relating to the trial.

6.13 Data Handling and Recordkeeping

6.14 Financing and Insurance Financing and insurance if not addressed in a separate agreement.

6.1 5 Publication Policy Publication policy, if not addressed in a separate agreement. Contains Nonbinding Recommendations 43

6.16 Supplements (NOTE: Since the protocol and the clinical trial/study report are closely related, further relevant information can be found in the ICH Guidance for Structure and Content of Clinical Study Reports.)

Section 7.0: Investigator's Brochure

The Investigator's Brochure (IB) is a compilation of the clinical and nonclinical data on the investigational product(s) that are relevant to the study of the product(s) in human subjects.

Its purpose is to provide the investigators and others involved in the trial with the information to facilitate their understanding of the rationale for, and their compliance with, many key features of the protocol, such as the dose, dose frequency/interval, methods of administration: and safety monitoring procedures.

The IB also provides insight to support the clinical management of the study subjects during the course of the clinical trial.

The information should be presented in a concise, simple, objective, balanced, and non-promotional form that enables a clinician, or potential investigator, to understand it and make his/her own unbiased risk-benefit assessment of the appropriateness of the proposed trial.

For this reason, a medically qualified person should generally participate in the editing of an IB, but the contents of the IB should be approved by the disciplines that generated the described data.

Section 8.0: Essential Documents for the Conduct of a Clinical Trial

These are discussed in the additional worksheet for this section

ICH GCP Guidelines
Section 4.0 Investigator

4.1 Investigator's Qualifications and Agreements

Guideline	Description	How is this documented? Listings as applicable to the study
4.1.1	The investigator should be qualified by education, training, and experience to assume responsibility for the proper conduct of the trial, should meet all the qualifications specified by the applicable regulatory requirements and should provide evidence of such qualifications through up to date curriculum vitae and/or other relevant documentation requested by the sponsor/the IRB/IEC, and/or the regulatory authorities	Credentials: • CV/resume, current • Medical license • Certification • Training Log/documentation • Protocol Training documentation • GCP Training/CITI training
4.1.2	The investigator should be thoroughly familiar with the appropriate use of the investigational product(s), as described in the protocol, in the current Investigator's Brochure, in the product information and in other information sources provided by the sponsor.	Training Log/Documentation: • Protocol • IB/drug insert/device manual/pharmacy manual
4.1.3	The investigator should be aware of, and should comply with, GCP and the applicable regulatory requirements.	Training Log/Documentation: • FDA Regulations/ICH GCP Guidelines • 1572
4.1.4	The investigator/institution should permit monitoring and auditing by the sponsor, and inspection by the appropriate regulatory authority.	Monitoring Log Signed CTA with Monitoring Plan
4.1.5	The investigator should maintain a list of appropriately qualified persons to whom the investigator has delegated significant trial-related duties.	Delegation of Authority Log CV/Resume for study staff, licenses/certifications (as applicable)

4.2 Adequate Resources

Guideline	Description	How is this documented?
4.2.1	The investigator should be able to demonstrate (e.g., based on retrospective data) a potential for recruiting the required number of suitable subjects within the agreed recruitment period.	Study Feasibility Meeting/Questionnaire
4.2.2	The investigator should have sufficient time to properly conduct and complete the trial within the agreed trial period.	Study Feasibility Meeting/Questionnaire Documentation of current studies being conducted
4.2.3	The investigator should have available an adequate number of qualified staff and adequate facilities for the foreseen duration of the trial to conduct the trial properly and safely.	Study Feasibility Meeting/Questionnaire
4.2.4	The investigator should ensure that all persons assisting with the trial are adequately informed about the protocol, the investigational product(s), and their trial-related duties and functions.	Training Log
4.2.5	The investigator is responsible for supervising any individual or party to whom the investigator delegates trial-related duties and functions conducted at the trial site.	Training log DOAL Documentation of oversight
4.2.6	If the investigator/institution retains the services of any individual or party to perform trial related duties and functions, the investigator/institution should ensure this individual or party is qualified to perform those trial related duties and functions and should implement procedures to ensure the integrity of the trial-related duties and functions performed and any data generated.	Credentials Certifications Documentation of oversight of results

4.3 Medical Care of Trial Subjects

Guideline	Description	How is this documented?
4.3.1	A qualified physician (or dentist, when appropriate), who is an investigator or a sub-investigator for the trial, should be responsible for all trial-related medical (or dental) decisions.	Delegation of Authority Inclusion/Exclusion Worksheets signed by PI PI oversight-review of labs, test results, progress notes
4.3.2	During and following a subject's participation in a trial, the investigator/institution should ensure that adequate medical care is provided to a subject for any adverse events, including clinically significant laboratory values, related to the trial. The investigator/institution should inform a subject when medical care is needed for intercurrent illness(es) of which the investigator becomes aware.	AE/SAE Log and Documentation Reports of diagnostic tests/labs, per protocol Progress notes Medical Records, if applicable
4.3.3	It is recommended that the investigator inform the subject's primary physician about the subject's participation in the trial if the subject has a primary physician and if the subject agrees to the primary physician being informed.	PCP letter, if subject agrees
4.3.4	Although a subject is not obliged to give his/her reason(s) for withdrawing prematurely from a trial, the investigator should make a reasonable effort to ascertain the reason(s), while fully respecting the subject's rights	Contact subject via phone/mail, document accordingly

4.4 Communication with the IRB/IEC

Guidance	Description	How is this documented?
4.4.1	Before initiating a trial, the investigator/institution should have written and dated approval/favorable opinion from the IRB/IEC for the trial protocol, written informed consent form, consent form updates, subject recruitment procedures (e.g., advertisements), and any other written information to be provided to subjects.	Outcome Letter stating study is approved, approved consent forms, letter stating necessary protocol and forms are approved
4.4.2	As part of the investigator's/institution's written application to the IRB/IEC, the investigator/institution should provide the IRB/IEC with a current copy of the Investigator's Brochure. If the Investigator's Brochure is updated during the trial, the investigator/institution should supply a copy of the updated Investigator's Brochure to the IRB/IEC.	Application to IRB, including necessary documents needing approval
4.4.3	During the trial the investigator/institution should provide to the IRB/IEC all documents subject to review.	Amendments, progress reports, deviations, etc

4.5 Compliance with the Protocol

Guidance	Description	How is this documented?
4.5.1	The investigator/institution should conduct the trial in compliance with the protocol agreed to by the sponsor and, if required, by the regulatory authority(ies) and which was given approval/favorable opinion by the IRB/IEC. The investigator/institution and the sponsor should sign the protocol, or an alternative contract, to confirm agreement.	Signed 1572 Signed protocol signature page Clinical Trial Agreement (CTA) Source Documentation on all trial subjects, ALCOA-C Appointment calendars
4.5.2	The investigator should not implement any deviation from, or changes of the protocol without agreement by the sponsor and prior review and documented approval/favorable opinion from the IRB/IEC of an amendment, except where necessary to eliminate an immediate hazard(s) to trial subjects, or when the change(s) involves only logistical or administrative aspects of the trial (e.g., change in monitor(s), change of telephone number(s)).	Deviation Log Form 4, if applicable Appointment calendars
4.5.3	The investigator, or person designated by the investigator, should document and explain any deviation from the approved protocol.	Deviation Log
4.5.4	The investigator may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to trial subjects without prior IRB/IEC approval/favorable opinion. As soon as possible, the implemented deviation or change, the reasons for it, and, if appropriate, the proposed protocol amendment(s) should be submitted: (a) to the IRB/IEC for review and approval/favorable opinion, (b) to the sponsor for agreement and, if required, (c) to the regulatory authority(ies).	Deviation Log

4.6 Investigational Product

Guidance	Description	How is this documented?
4.6.1	Responsibility for investigational product(s) accountability at the trial site(s) rests with the investigator/institution.	IP Accountability Logs Drug Receipts/distribution/storage/destruction/return documentation
4.6.2	Where allowed/required, the investigator/institution may/should assign some or all of the investigator's/institution's duties for investigational product(s) accountability at the trial site(s) to an appropriate pharmacist or another appropriate individual who is under the supervision of the investigator/institution..	Delegation of Authority Training log
4.6.3	The investigator/institution and/or a pharmacist or other appropriate individual, who is designated by the investigator/institution, should maintain records of the product's delivery to the trial site, the inventory at the site, the use by each subject, and the return to the sponsor or alternative disposition of unused product(s). These records should include dates, quantities, batch/serial numbers, expiration dates (if applicable), and the unique code numbers assigned to the investigational product(s) and trial subjects. Investigators should maintain records that document adequately that the subjects were provided the doses specified by the protocol and reconcile all investigational product(s) received from the sponsor.	IP Accountability Logs Documentation of subject IP dispensing/instructions Drug Receipts/distribution/storage/destruction/return documentation
4.6.4	The investigational product(s) should be stored as specified by the sponsor (see 5.13.2 and 5.14.3) and in accordance with applicable regulatory requirement(s).	Temperature Log IP Accountability Logs Subject instructions documentation
4.6.5	The investigator should ensure that the investigational product(s) are used only in accordance with the approved protocol.	IP Accountability Logs
4.6.6	The investigator, or a person designated by the investigator/institution, should explain the correct use of the investigational product(s) to each subject and should	Source Documents

	check, at intervals appropriate for the trial, that each subject is following the instructions properly.	

4.7 Randomization Procedures and Unblinding

4.7	The investigator should follow the trial's randomization procedures, if any, and should ensure that the code is broken only in accordance with the protocol. If the trial is blinded, the investigator should promptly document and explain to the sponsor any premature unblinding (e.g., accidental unblinding, unblinding due to a serious adverse event) of the investigational product(s).	Documentation outlining notifications of the need to unblind Documentation of the steps taken in the unblinding process Documentation of events taken once the unblinding had occurred Documentation of subject events related to the need for unblinding

4.8 Informed Consent of Trial Subjects

Guidance	Description	How is this documented?
4.8.1	In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki. Prior to the beginning of the trial, the investigator should have the IRB/IEC's written approval/favorable opinion of the written informed consent form and any other written information to be provided to subjects.	ICF Log/Version Log
4.8.2	The written informed consent form and any other written information to be provided to subjects should be revised whenever important new information becomes available that may be relevant to the subject's consent. Any revised written informed consent form, and written information should receive the IRB/IEC's approval/favorable opinion in advance of use. The subject or the subject's legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the trial. The communication of this information should be documented.	Version, date on site source documents
4.8.3	Neither the investigator, nor the trial staff, should coerce or unduly influence a subject to participate or to continue to participate in a trial.	Site Source Documentation/Informed Consent Documentation
4.8.4	None of the oral and written information concerning the trial, including the written informed consent form, should contain any language that causes the subject or the subject's legally acceptable representative to waive or to appear to waive any	Site Source Documentation/Informed Consent Documentation

	legal rights, or that releases or appears to release the investigator, the institution, the sponsor, or their agents from liability for negligence.	
4.8.5	The investigator, or a person designated by the investigator, should fully inform the subject or, if the subject is unable to provide informed consent, the subject's legally acceptable representative, of all pertinent aspects of the trial including the written information and the approval/ favorable opinion by the IRB/IEC.	Site Source Documentation/Informed Consent Documentation
4.8.6	The language used in the oral and written information about the trial, including the written informed consent form, should be as non-technical as practical and should be understandable to the subject or the subject's legally acceptable representative and the impartial witness, where applicable.	Site Source Documentation/Informed Consent Documentation
4.8.7	Before informed consent may be obtained, the investigator, or a person designated by the investigator, should provide the subject or the subject's legally acceptable representative ample time and opportunity to inquire about details of the trial and to decide whether or not to participate in the trial. All questions about the trial should be answered to the satisfaction of the subject or the subject's legally acceptable representative.	Site Source Documentation/Informed Consent Documentation
4.8.8	Prior to a subject's participation in the trial, the written informed consent form should be signed and personally dated by the subject or by the subject's legally acceptable representative, and by the person who conducted the informed consent discussion.	Site Source Documentation/Informed Consent Documentation
4.8.9	If a subject is unable to read or if a legally acceptable representative is unable to read, an impartial witness should be present during the entire informed consent discussion. After the written informed consent form	Site Source Documentation/Informed Consent Documentation

	and any other written information to be provided to subjects, is read and explained to the subject or the subject's legally acceptable representative, and after the subject or the subject's legally acceptable representative has orally consented to the subject's participation in the trial and, if capable of doing so, has signed and personally dated the informed consent form, the witness should sign and personally date the consent form. By signing the consent form, the witness attests that the information in the consent form and any other written information was accurately explained to, and apparently understood by, the subject or the subject's legally acceptable representative, and that informed consent was freely given by the subject or the subject's legally acceptable representative.	
4.8.7	Before informed consent may be obtained, the investigator, or a person designated by the investigator, should provide the subject or the subject's legally acceptable representative ample time and opportunity to inquire about details of the trial and to decide whether or not to participate in the trial. All questions about the trial should be answered to the satisfaction of the subject or the subject's legally acceptable representative.	Site Source Documentation/Informed Consent Documentation
4.8.8	Prior to a subject's participation in the trial, the written informed consent form should be signed and personally dated by the subject or by the subject's legally acceptable representative, and by the person who conducted the informed consent discussion.	Site Source Documentation/Informed Consent Documentation
4.8.9	If a subject is unable to read or if a legally acceptable representative is unable to read, an impartial witness should be present during the entire informed consent discussion. After the written informed consent form	Site Source Documentation/Informed Consent Documentation

	and any other written information to be provided to subjects, is read and explained to the subject or the subject's legally acceptable representative, and after the subject or the subject's legally acceptable representative has orally consented to the subject's participation in the trial and, if capable of doing so, has signed and personally dated the informed consent form, the witness should sign and personally date the consent form. By signing the consent form, the witness attests that the information in the consent form and any other written information was accurately explained to, and apparently understood by, the subject or the subject's legally acceptable representative, and that informed consent was freely given by the subject or the subject's legally acceptable representative.	
4.8.10	Both the informed consent discussion and the written informed consent form and any other written information to be provided to subjects should include explanations of the following: (a) That the trial involves research. (b) The purpose of the trial. (c) The trial treatment(s) and the probability for random assignment to each treatment. (d) The trial procedures to be followed, including all invasive procedures. (e) The subject's responsibilities. (f) Those aspects of the trial that are experimental. (g) The reasonably foreseeable risks or inconveniences to the subject and, when applicable, to an embryo, fetus, or nursing infant. (h) The reasonably expected benefits. When there is no intended clinical benefit to the subject, the subject should be made aware of this.	Site Source Documentation/Informed Consent Documentation

	(i) The alternative procedure(s) or course(s) of treatment that may be available to the subject, and their important potential benefits and risks. (j) The compensation and/or treatment available to the subject in the event of trial-related injury. (k) The anticipated prorated payment, if any, to the subject for participating in the trial. (l) The anticipated expenses, if any, to the subject for participating in the trial. (m) That the subject's participation in the trial is voluntary and that the subject may refuse to participate or withdraw from the trial, at any time, without penalty or loss of benefits to which the subject is otherwise entitled. (n) That the monitor(s), the auditor(s), the IRB/IEC, and the regulatory authority(ies) will be granted direct access to the subject's original medical records for verification of clinical trial procedures and/or data, without violating the confidentiality of the subject, to the extent permitted by the applicable laws and regulations and that, by signing a written informed consent form, the subject or the subject's legally acceptable representative is authorizing such access. (o) That records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. If the results of the trial are published, the subject's identity will remain confidential. (p) That the subject or the subject's legally acceptable representative will be informed in a timely manner if information becomes available that	

	may be relevant to the subject's willingness to continue participation in the trial. (q) The person(s) to contact for further information regarding the trial and the rights of trial subjects, and whom to contact in the event of trial-related injury. (r) The foreseeable circumstances and/or reasons under which the subject's participation in the trial may be terminated. (s) The expected duration of the subject's participation in the trial. (t) The approximate number of subjects involved in the trial.	
4.8.11	Prior to participation in the trial, the subject or the subject's legally acceptable representative should receive a copy of the signed and dated written informed consent form and any other written information provided to the subjects. During a subject's participation in the trial, the subject or the subject's legally acceptable representative should receive a copy of the signed and dated consent form updates and a copy of any amendments to the written information provided to subjects.	Site Source Documentation/Informed Consent Documentation
4.8.12	When a clinical trial (therapeutic or non-therapeutic) includes subjects who can only be enrolled in the trial with the consent of the subject's legally acceptable representative (e.g., minors, or patients with severe dementia), the subject should be informed about the trial to the extent compatible with the subject's understanding and, if capable, the subject should sign and personally date the written informed consent.	Site Source Documentation/Informed Consent Documentation
4.8.13	Except as described in 4.8.14, a non-therapeutic trial (i.e. a trial in which there is no anticipated direct clinical benefit to the subject), should be conducted	Site Source Documentation/Informed Consent Documentation

	in subjects who personally give consent and who sign and date the written informed consent form.	
4.8.14	Non-therapeutic trials may be conducted in subjects with consent of a legally acceptable representative provided the following conditions are fulfilled: (a) The objectives of the trial cannot be met by means of a trial in subjects who can give informed consent personally. (b) The foreseeable risks to the subjects are low. (c) The negative impact on the subject's well-being is minimized and low. (d) The trial is not prohibited by law. (e) The approval/favorable opinion of the IRB/IEC is expressly sought on the inclusion of such subjects, and the written approval/ favorable opinion covers this aspect. Such trials, unless an exception is justified, should be conducted in patients having a disease or condition for which the investigational product is intended. Subjects in these trials should be particularly closely monitored and should be withdrawn if they appear to be unduly distressed.	Site Source Documentation/Informed Consent Documentation
4.8.15	In emergency situations, when prior consent of the subject is not possible, the consent of the subject's legally acceptable representative, if present, should be requested. When prior consent of the subject is not possible, and the subject's legally acceptable representative is not available, enrolment of the subject should require measures described in the protocol and/or elsewhere, with documented approval/favorable opinion by the IRB/IEC, to protect the rights, safety and well-being of the subject and to ensure compliance with applicable regulatory requirements. The subject or the subject's legally	Site Source Documentation/Informed Consent Documentation

	acceptable representative should be informed about the trial as soon as possible and consent to continue and other consent as appropriate (see 4.8.10) should be requested.	

4.9 Records and Reports

Guidance	Description	How is this documented?
4.9.0	The investigator/institution should maintain adequate and accurate source documents and trial records that include all pertinent observations on each of the site's trial subjects. Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (e.g., via an audit trail).	Essential and Source documents Documentation of visits ALCOA-C
4.9.1	The investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor in the CRFs and in all required reports.	Source Documentation on all subjects, ALCOA-C CRF documentation
4.9.2	Data reported on the CRF, that are derived from source documents, should be consistent with the source documents or the discrepancies should be explained.	Source Documentation on all subjects, ALCOA-C Notes to File Progress notes
4.9.3	Any change or correction to a CRF should be dated, initialed, and explained (if necessary) and should not obscure the original entry (i.e. an audit trail should be maintained); this applies to both written and electronic changes or corrections Sponsors should provide guidance to investigators and/or the investigators' designated representatives on making such corrections. Sponsors should have written procedures to assure that changes or corrections in CRFs made by sponsor's designated representatives are documented, are necessary, and are	Source Documentation on all subjects, ALCOA-C Notes to File Progress notes

	endorsed by the investigator. The investigator should retain records of the changes and corrections.	
4.9.4	The investigator/institution should maintain the trial documents as specified in Essential Documents for the Conduct of a Clinical Trial and as required by the applicable regulatory requirement(s). The investigator/institution should take measures to prevent accidental or premature destruction of these documents.	Regulatory Binder, up to date with all essential documents
4.9.5	Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period however if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained	
4.9.6	The financial aspects of the trial should be documented in an agreement between the sponsor and the investigator/institution.	Clinical Trial Agreement
4.9.7	Upon request of the monitor, auditor, IRB/IEC, or regulatory authority, the investigator/institution should make available for direct access all requested trial-related records.	Documentation of visit on the monitoring log FDA Audit-maintain records of any requested/copied materials

4.10 Progress Reports

Guidance	Description	How is this documented?
4.10.1	The investigator should submit written summaries of the trial status to the IRB/IEC annually, or more frequently, if requested by the IRB/IEC.	IRB Submissions
4.10.2	The investigator should promptly provide written reports to the sponsor, the IRB/IEC and, where applicable, the institution on any changes significantly affecting the conduct of the trial, and/or increasing the risk to subjects.	IRB submissions

4.11 Safety Reporting

Guidance	Description	How is this documented?
4.11.1	All serious adverse events (SAEs) should be reported immediately to the sponsor except for those SAEs that the protocol or other document (e.g., Investigator's Brochure) identifies as not needing immediate reporting. The immediate reports should be followed promptly by detailed, written reports. The immediate and follow-up reports should identify subjects by unique code numbers assigned to the trial subjects rather than by the subjects' names, personal identification numbers, and/or addresses. The investigator should also comply with the applicable regulatory requirement(s) related to the reporting of unexpected serious adverse drug reactions to the regulatory authority(ies) and the IRB/IEC.	SAE/AE Logs and Documentation Concomitant medication logs Diaries, if applicable Progress notes
4.11.2	Adverse events and/or laboratory abnormalities identified in the protocol as critical to safety evaluations should be reported to the sponsor according to the reporting requirements and within the time periods specified by the sponsor in the protocol.	SAE/AE Logs and Documentation

4.11.3	For reported deaths, the investigator should supply the sponsor and the IRB/IEC with any additional requested information (e.g., autopsy reports and terminal medical reports).	SAE/AE Logs and Documentation

4.12 Premature Termination or Suspension of a Trial

* If the trial is prematurely terminated or suspended for any reason, the investigator/institution should promptly inform the trial subjects, should assure appropriate therapy and follow-up for the subjects, and, where required by the applicable regulatory requirement(s), should inform the regulatory authority(ies). In addition:

Guidance	Description	How is this documented?
4.12.1	If the investigator terminates or suspends a trial without prior agreement of the sponsor, the investigator should inform the institution where applicable, and the investigator/institution should promptly inform the sponsor and the IRB/IEC, and should provide the sponsor and the IRB/IEC a detailed written explanation of the termination or suspension.	IRB/institution/IRB/subject notification
4.12.2	If the sponsor terminates or suspends a trial (see 5.21), the investigator should promptly inform the institution where applicable and the investigator/institution should promptly inform the IRB/IEC and provide the IRB/IEC a detailed written explanation of the termination or suspension.	IRB/institution/subject notification
4.12.3	If the IRB/IEC terminates or suspends its approval/favorable opinion of a trial (see 3.1.2 and 3.3.9), the investigator should inform the institution where applicable and the investigator/institution should promptly notify the sponsor and provide the sponsor with a detailed written explanation of the termination or suspension.	Notify the institution/subjects/sponsor

4.13 Final Report(s) by Investigator

4.13	Upon completion of the trial, the investigator, where applicable, should inform the institution; the investigator/institution should provide the IRB/IEC with a summary of the trial's outcome, and the regulatory authority(ies) with any reports required.	Close-out form submitted to the IRB Storage of the essential Documents for the appropriate time outlined in the regulations/guidance/CTA Notify the sponsor/IRB (if applicable) of a change in storage location as necessary

IRB Definitions with Answers
45 CFR 46 Subpart A
21 CFR 56
ICH G6(R2)

DEFINE:

45 CFR 46 Subpart A

IRB. IRB means an institutional review board established in accord with and for the purposes expressed in this policy.

IRB Approval. IRB approval means the determination of the IRB that the research has been reviewed and may be conducted at an institution within the constraints set forth by the IRB and by other institutional and federal requirements.

Exempt Research: Federal regulations provide for exemption from IRB oversight for certain kinds of research involving minimal risk. OHRP policy guidance requires that the determination that a study qualifies for exempt status be made by an entity other than the investigator.

(1) Research, conducted in established or commonly accepted educational settings, that specifically involves normal educational practices that are NOT likely to adversely impact students' opportunity to learn required educational content OR the assessment of educators who provide instruction. This includes most research on regular and special education instructional strategies, and research on the effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods.

(2) Research that ONLY includes interactions involving educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, OR observation of public behavior (including visual or auditory recording), if at least ONE of the following criteria is met:

(i) The information obtained is recorded by the investigator in such a manner that the identity of the human subjects CANNOT readily be ascertained, directly or through identifiers linked to the subjects; **OR**

(ii) Any disclosure of the human subjects' responses outside the research would NOT reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, educational advancement, or reputation; **OR**

(iii) The information obtained is recorded by the investigator in such a manner that the identity of the human subjects can readily be ascertained, directly or through identifiers linked to the subjects, AND an IRB conducts a limited IRB review.

(3) Research involving benign behavioral interventions in conjunction with the collection of information from an adult subject through verbal or written responses (including data entry) or audiovisual recording if the subject prospectively agrees to the intervention and information collection AND at least ONE of the following criteria is met:

(A) The information obtained is recorded by the investigator in such a manner that the identity of the human subjects CANNOT readily be ascertained, directly or through identifiers linked to the subjects; **OR**

(B) Any disclosure of the human subjects' responses outside the research would NOT reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, educational advancement, or reputation; **OR**

(C) The information obtained is recorded by the investigator in such a manner that the identity of the human subjects can readily be ascertained, directly or through identifiers linked to the subjects, AND an IRB conducts a limited IRB review...

(4) Secondary research uses of identifiable private information or identifiable biospecimens, for which consent is NOT required, if at least ONE of the following criteria is met:

(i) The identifiable private information or identifiable biospecimens are publicly available; **OR**

(ii) Information, which may include information about biospecimens, is recorded by the investigator in such a manner that the identity of the human subjects CANNOT readily be ascertained directly or through identifiers linked to the subjects, the investigator DOES NOT contact the subjects, AND the investigator will not re-identify subjects; **OR**

(iii) The research involves ONLY information collection and analysis involving the investigator's use of identifiable health information when that use is regulated under the HIPAA Privacy regulations.

(iv) The research is conducted by, or on behalf of, a Federal department or agency using government-generated or government-collected information obtained for nonresearch activities, if the research generates identifiable private information that is or will be maintained on information technology that is subject to and in compliance with section 208(b) of the E-Government Act of 2002, 44 U.S.C. 3501 note, if all of the identifiable private information collected, used, or generated as part of the activity will be maintained in systems of records subject to the Privacy Act of 1974, 5 U.S.C. 552a, and, if applicable, the information used in the research was collected subject to the Paperwork Reduction Act of 1995, 44 U.S.C. 3501 et seq.

(5) Research and demonstration projects, which are conducted or supported by or subject to the approval of the department or agency heads (or the approval of the heads of bureaus or other subordinate agencies that have been delegated authority to conduct the research and demonstration projects), and which are designed to study, evaluate, or otherwise examine: i. public benefit or service programs

(6) Taste and food quality evaluation and consumer acceptance studies:

(i) If wholesome foods without additives are consumed, or

(ii) If a food is consumed that contains a food ingredient at or below the level and for a use found to be safe, or agricultural chemical or environmental contaminant at or below the level found to be safe, by the Food and Drug Administration or approved by the Environmental Protection Agency or the Food Safety and Inspection Service of the U.S. Department of Agriculture.

(7) Storage or maintenance for secondary research for which broad consent is required: Storage or maintenance of identifiable private information or identifiable biospecimens for potential secondary research use if an IRB conducts a limited IRB review and makes the determinations required by §46.111(a)(8).

(8) Secondary research for which broad consent is required: Research involving the use of identifiable private information or identifiable biospecimens for secondary research use, if the following criteria are met:

(i) Broad consent for the storage, maintenance, and secondary research use of the identifiable private information or identifiable biospecimens was obtained in accordance with §46.116(a)(1) through (4), (a)(6), and (d);
(ii) Documentation of informed consent or waiver of documentation of consent was obtained in accordance with §46.117;
(iii) An IRB conducts a limited IRB review and makes the determination required by §46.111(a)(7) and makes the determination that the research to be conducted is within the scope of the broad consent referenced in paragraph (d)(8)(i) of this section; and
(iv) The investigator does not include returning individual research results to subjects as part of the study plan. This provision does not prevent an investigator from abiding by any legal requirements to return individual research results.

Expedited Research: Research activities that (1) present no more than minimal risk to human subjects, and (2) involve only procedures listed in one or more of the following categories:

1. Clinical studies of drugs and medical devices only when condition (a) or (b) is met.

    a. (a) Research on drugs for which an investigational new drug application (21 CFR Part 312) is not required. (Note: Research on marketed drugs that significantly increases the risks or decreases the acceptability of the risks associated with the use of the product is not eligible for expedited review.)

    b. Research on medical devices for which (i) an investigational device exemption application (21 CFR Part 812) is not required; or (ii) the medical device is cleared/approved for marketing and the medical device is being used in accordance with its cleared/approved labeling.

2. Collection of blood samples by finger stick, heel stick, ear stick, or venipuncture as follows:

a. (a) from healthy, nonpregnant adults who weigh at least 110 pounds. For these subjects, the amounts drawn may not exceed 550 ml in an 8 week period and collection may not occur more frequently than 2 times per week; or

b. from other adults and children [2], considering the age, weight, and health of the subjects, the collection procedure, the amount of blood to be collected, and the frequency with which it will be collected. For these subjects, the amount drawn may not exceed the lesser of 50 ml or 3 ml per kg in an 8 week period and collection may not occur more frequently than 2 times per week.

3. Prospective collection of biological specimens for research purposes by noninvasive means. Examples: (a) hair and nail clippings in a nondisfiguring manner; (b) deciduous teeth at time of exfoliation or if routine patient care indicates a need for extraction; (c) permanent teeth if routine patient care indicates a need for extraction; (d) excreta and external secretions (including sweat); (e) uncannulated saliva collected either in an unstimulated fashion or stimulated by chewing gumbase or wax or by applying a dilute citric solution to the tongue; (f) placenta removed at delivery; (g) amniotic fluid obtained at the time of rupture of the membrane prior to or during labor; (h) supra- and subgingival dental plaque and calculus, provided the collection procedure is not more invasive than routine prophylactic scaling of the teeth and the process is accomplished in accordance with accepted prophylactic techniques; (i) mucosal and skin cells collected by buccal scraping or swab, skin swab, or mouth washings; (j) sputum collected after saline mist nebulization.

4. Collection of data through noninvasive procedures (not involving general anesthesia or sedation) routinely employed in clinical practice, excluding procedures involving x-rays or microwaves. Where medical devices are employed, they must be cleared/approved for marketing. (Studies intended to evaluate the safety and effectiveness of the medical device are not generally eligible for expedited review, including studies of cleared medical devices for new indications.)
   Examples: (a) physical sensors that are applied either to the surface of the body or at a distance and do not involve input of significant amounts of energy into the subject or an invasion of the subject=s privacy; (b) weighing or testing sensory acuity; (c) magnetic resonance imaging; (d) electrocardiography, electroencephalography, thermography, detection of naturally occurring radioactivity, electroretinography, ultrasound, diagnostic infrared imaging, doppler blood flow, and echocardiography; (e) moderate exercise, muscular strength testing, body composition assessment, and flexibility testing where appropriate given the age, weight, and health of the individual.

5. Research involving materials (data, documents, records, or specimens) that have been collected, or will be collected solely for nonresearch purposes (such as medical treatment or diagnosis). (NOTE: Some research in this category may be exempt from the HHS regulations for the protection of human subjects. 45 CFR 46.101(b)(4). This listing refers only to research that is not exempt.)

6. Collection of data from voice, video, digital, or image recordings made for research purposes.

7. Research on individual or group characteristics or behavior (including, but not limited to, research on perception, cognition, motivation, identity, language, communication, cultural beliefs or practices, and social behavior) or research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance methodologies. (NOTE: Some research in this category may be exempt from the HHS regulations for the protection of human subjects. 45 CFR 46.101(b)(2) and (b)(3). This listing refers only to research that is not exempt.)

8. Continuing review of research previously approved by the convened IRB as follows:

    a. where (i) the research is permanently closed to the enrollment of new subjects; (ii) all subjects have completed all research-related interventions; and (iii) the research remains active only for long-term follow-up of subjects; or

    b. where no subjects have been enrolled and no additional risks have been identified; or

    c. where the remaining research activities are limited to data analysis.

9. Continuing review of research, not conducted under an investigational new drug application or investigational device exemption where categories two (2) through eight (8) do not apply but the IRB has determined and documented at a convened meeting that the research involves no greater than minimal risk and no additional risks have been identified.

Full Board review:

Full board review usually involves research that is greater than minimal risk but also includes minimal risk research that does not meet one or more of the Expedited Review Categories**.**

Continuing Review HHS and FDA regulations for the protection of human subjects require that IRBs create procedures for conducting continuing review of previously approved research and for reporting its findings to investigators and the institution. Continuing review must be substantive and meaningful. The IRB is responsible for determining that the criteria for initial approval of research studies are still satisfied at the time of continuing review.

Limited IRB Review. Limited IRB review is a process that is required only for certain exemptions, and does not require an IRB to consider all of the IRB approval criteria in §46.111. In limited IRB review, the IRB must determine that certain conditions, which are specified in the regulations, are met. Limited IRB review may be done via the expedited review mechanism, that is, by the Chair or an experienced IRB member designated by the Chair (although it can also be conducted by the full IRB). Continuing review is not required.

Certification. Certification means the official notification by the institution to the supporting Federal department or agency component, in accordance with the requirements of this policy, that a research

project or activity involving human subjects has been reviewed and approved by an IRB in accordance with an approved assurance.

Written or in writing. Written, or in writing, for purposes of this part, refers to writing on a tangible medium (e.g., paper) or in an electronic format.

Institution. Institution means any public or private entity, or department or agency (including federal, state, and other agencies).

21 CFR 56

IRB / Approval
Institutional review board (IRB) means any board, committee, or other group formally designated by an institution to review biomedical research involving humans as subjects, to approve the initiation of and conduct periodic review of such research. The term has the same meaning as the phrase institutional review committee as used in section 520(g) of the act.

Institution
Institution means any public or private entity or agency (including Federal, State, and other agencies). The word facility as used in section 520(g) of the act is deemed to be synonymous with the term institution for purposes of this part.

Clinical Investigation
Clinical investigation means any experiment that involves a test article and one or more human subjects and that either is subject to requirements for prior submission to the Food and Drug Administration under section 505(i) or 520(g) of the act, or is not subject to requirements for prior submission to the Food and Drug Administration under these sections of the act, but the results of which are intended to be submitted later to, or held for inspection by, the Food and Drug Administration as part of an application for a research or marketing permit. The term does not include experiments that are subject to the provisions of part 58 of this chapter, regarding nonclinical laboratory studies.

Human Subject
Human subject means an individual who is or becomes a participant in research, either as a recipient of the test article or as a control. A subject may be either a healthy human or a patient.

Emergency Use of a test article
Use of a test article on a human subject in a life-threatening situation in which no standard acceptable treatment is available and in which there is not sufficient time to obtain IRB approval (21 CFR 56.102(d)

Sponsor
Sponsor means a person who initiates a clinical investigation, but who does not actually conduct the investigation, i.e., the test article is administered or dispensed to or used involving, a subject under the immediate direction of another individual. A person other than an individual (e.g., corporation or agency) that uses one or more of its own employees to conduct a clinical investigation it has initiated is considered to be a sponsor (not a sponsor-investigator), and the employees are considered to be investigators.

Sponsor Investigator
Sponsor-investigator means an individual who both initiates and actually conducts, alone or with others, a clinical investigation, i.e., under whose immediate direction the test article is administered or dispensed to, or used involving, a subject. The term does not include any person other than an individual, e.g., corporation or agency.

Test Article
Test article means any drug (including a biological product for human use), medical device for human use, human food additive, color additive, electronic product, or any other article subject to regulation under the act or under sections 351 and 354-360F of the Public Health Service Act (42 U.S.C. 262 and 263b-263n).

ICH E6(R2) Definitions

IRB
An independent body constituted of medical, scientific, and nonscientific members, whose responsibility is to ensure the protection of the rights, safety and well-being of human subjects involved in a trial by, among other things, reviewing, approving, and providing continuing review of trial protocols and amendments and of the methods and material to be used in obtaining and documenting informed consent of the trial subjects.

IRB Approval
The affirmative decision of the IRB that the clinical trial has been reviewed and may be conducted at the institution site within the constraints set forth by the IRB, the institution, good clinical practice (GCP), and the applicable regulatory requirements.

Legally Acceptable Representative
An individual or juridical or other body authorized under applicable law to consent, on behalf of a prospective subject, to the subject's participation in the clinical trial.

Investigator
A person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a Contains Nonbinding Recommendations 7 team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator. (See also Subinvestigator.)

Clinical Trial / Study
Any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of an investigational product(s), and/or to identify any adverse reactions to an investigational product(s), and/or to study absorption, distribution, metabolism, and excretion of an investigational product(s) with the object of ascertaining its safety and/or efficacy. The terms clinical trial and clinical study are synonymous.

Human Subject
Not defined

Protocol
A document that describes the objective(s), design, methodology, statistical considerations, and organization of a trial. The protocol usually also gives the background and rationale for the trial, but these could be provided in other protocol referenced documents. Throughout the ICH GCP Guidance, the term protocol refers to protocol and protocol amendments.

Protocol Amendment
A written description of a change(s) to or formal clarification of a protocol.

Sub-Investigator
Any individual member of the clinical trial team designated and supervised by the investigator at a trial site to perform critical trial-related procedures and/or to make important trial-related decisions (e.g., associates, residents, research fellows). See also Investigator.

Investigational Product
A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use.

Institutional Review Board Worksheet with Answers

According to the federal regulations, what is the charge of an IRB?

In accordance with FDA regulations, an IRB has the authority to approve, require modifications in (to secure approval), or disapprove research. This group review serves an important role in the protection of the rights and welfare of human research subjects.

Which of the Federal Regulations specifically describe the composition, operation, and function of the Institutional Review Board? For OHRP? FDA?

OHRP
45 CRF 46 Subpart A

FDA
21 CFR 56

List and compare OHRP and FDA requirements for the composition of the committee.

OHRP

Each IRB shall have at least five members, with varying backgrounds to promote complete and adequate review of research activities commonly conducted by the institution.

Each IRB shall include at least one member whose primary concerns are in scientific areas and at least one member whose primary concerns are in nonscientific areas.

Each IRB shall include at least one member who is not otherwise affiliated with the institution and who is not part of the immediate family of a person who is affiliated with the institution.

No IRB may have a member participate in the IRB's initial or continuing review of any project in which the member has a conflicting interest, except to provide information requested by the IRB.

An IRB may, in its discretion, invite individuals with competence in special areas to assist in the review of issues that require expertise beyond or in addition to that available on the IRB. These individuals may not vote with the IRB.

FDA

Each IRB shall have at least five members, with varying backgrounds to promote complete and adequate review of research activities commonly conducted by the institution.

Every nondiscriminatory effort will be made to ensure that no IRB consists entirely of men or entirely of women, including the institution's consideration of qualified persons of both sexes, so long as no selection is made to the IRB on the basis of gender. No IRB may consist entirely of members of one profession.

Each IRB shall include at least one member whose primary concerns are in the scientific area and at least one member whose primary concerns are in nonscientific areas.

Each IRB shall include at least one member who is not otherwise affiliated with the institution and who is not part of the immediate family of a person who is affiliated with the institution.

No IRB may have a member participate in the IRB's initial or continuing review of any project in which the member has a conflicting interest, except to provide information requested by the IRB.

An IRB may, in its discretion, invite individuals with competence in special areas to assist in the review of complex issues which require expertise beyond or in addition to that available on the IRB. These individuals may not vote with the IRB.

When is IRB review Required? According to OHRP? FDA?

OHRP

Except as detailed in § 46.104 (exempt research), this policy applies to all research involving human subjects conducted, supported, or otherwise subject to regulation by any Federal department or agency that takes appropriate administrative action to make the policy applicable to such research. This includes research conducted by Federal civilian employees or military personnel, except that each department or agency head may adopt such procedural modifications as may be appropriate from an administrative standpoint. It also includes research conducted, supported, or otherwise subject to regulation by the Federal Government outside the United States. Institutions that are engaged in research described in this paragraph and institutional review boards (IRBs) reviewing research that is subject to this policy must comply with this policy.

FDA

Except as provided in §§ 56.104 and 56.105 (exempt and waiver), any clinical investigation which must meet the requirements for prior submission (as required in parts 312, 812, and 813) to the Food and Drug Administration shall not be initiated unless that investigation has been reviewed and approved by, and remains subject to continuing review by, an IRB meeting the requirements of this part.

(b) Except as provided in §§ 56.104 and 56.105, the Food and Drug Administration may decide not to consider in support of an application for a research or marketing permit any data or information that has been derived from a clinical investigation that has not been approved by, and that was not subject to initial and continuing review by, an IRB meeting the requirements of this part. The determination that a clinical investigation may not be considered in support of an application for a research or marketing

permit does not, however, relieve the applicant for such a permit of any obligation under any other applicable regulations to submit the results of the investigation to the Food and Drug Administration.

(c) Compliance with these regulations will in no way render inapplicable pertinent Federal, State, or local laws or regulations.

When may a clinical investigation be exempted from IRB review according to OHRP? FDA?

OHRP

The following categories of human subjects research are exempt from this policy:

(1) Research, conducted in established or commonly accepted educational settings, that specifically involves normal educational practices that are not likely to adversely impact students' opportunity to learn required educational content or the assessment of educators who provide instruction. This includes most research on regular and special education instructional strategies, and research on the effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods.

(2) Research that only includes interactions involving educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public behavior (including visual or auditory recording) if at least one of the following criteria is met:

(i) The information obtained is recorded by the investigator in such a manner that the identity of the human subjects cannot readily be ascertained, directly or through identifiers linked to the subjects;

(ii) Any disclosure of the human subjects' responses outside the research would not reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, educational advancement, or reputation; or

(iii) The information obtained is recorded by the investigator in such a manner that the identity of the human subjects can readily be ascertained, directly or through identifiers linked to the subjects, and an IRB conducts a limited IRB review to make the determination required by § 46.111(a)(7).

(3)

(i) Research involving benign behavioral interventions in conjunction with the collection of information from an adult subject through verbal or written responses (including data entry) or audiovisual recording if the subject prospectively agrees to the intervention and information collection and at least one of the following criteria is met:

(A) The information obtained is recorded by the investigator in such a manner that the identity of the human subjects cannot readily be ascertained, directly or through identifiers linked to the subjects;

(B) Any disclosure of the human subjects' responses outside the research would not reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, educational advancement, or reputation; or

(C) The information obtained is recorded by the investigator in such a manner that the identity of the human subjects can readily be ascertained, directly or through identifiers linked to the subjects, and an IRB conducts a limited IRB review to make the determination required by § 46.111(a)(7).

(ii) For the purpose of this provision, benign behavioral interventions are brief in duration, harmless, painless, not physically invasive, not likely to have a significant adverse lasting impact on the subjects, and the investigator has no reason to think the subjects will find the interventions offensive or embarrassing. Provided all such criteria are met, examples of such benign behavioral interventions would include having the subjects play an online game, having them solve puzzles under various noise conditions, or having them decide how to allocate a nominal amount of received cash between themselves and someone else.

(iii) If the research involves deceiving the subjects regarding the nature or purposes of the research, this exemption is not applicable unless the subject authorizes the deception through a prospective agreement to participate in research in circumstances in which the subject is informed that he or she will be unaware of or misled regarding the nature or purposes of the research.

(4) Secondary research for which consent is not required: Secondary research uses of identifiable private information or identifiable biospecimens, if at least one of the following criteria is met:

(i) The identifiable private information or identifiable biospecimens are publicly available;

(ii) Information, which may include information about biospecimens, is recorded by the investigator in such a manner that the identity of the human subjects cannot readily be ascertained directly or through identifiers linked to the subjects, the investigator does not contact the subjects, and the investigator will not re-identify subjects;

(iii) The research involves only information collection and analysis involving the investigator's use of identifiable health information when that use is regulated under 45 CFR parts 160 and 164, subparts A and E, for the purposes of “health care operations” or “research” as those terms are defined at 45 CFR 164.501 or for “public health activities and purposes” as described under 45 CFR 164.512(b); or

(iv) The research is conducted by, or on behalf of, a Federal department or agency using government-generated or government-collected information obtained for nonresearch activities, if the research generates identifiable private information that is or will be maintained on information technology that is subject to and in compliance with section 208(b) of the E-Government Act of 2002, 44 U.S.C. 3501 note, if all of the identifiable private information collected, used, or generated as part of the activity will be maintained in systems of records subject to the Privacy Act of 1974, 5 U.S.C. 552a, and, if applicable, the information used in the research was collected subject to the Paperwork Reduction Act of 1995, 44 U.S.C. 3501 *et seq.*

(5) Research and demonstration projects that are conducted or supported by a Federal department or agency, or otherwise subject to the approval of department or agency heads (or the approval of the heads of bureaus or other subordinate agencies that have been delegated authority to conduct the research and demonstration projects), and that are designed to study, evaluate, improve, or otherwise examine public benefit or service programs, including procedures for obtaining benefits or services under those programs, possible changes in or alternatives to those programs or procedures, or possible changes in methods or levels of payment for benefits or services under those programs. Such projects include, but are not limited to, internal studies by Federal employees, and studies under contracts or consulting arrangements, cooperative agreements, or grants. Exempt projects also include waivers of otherwise mandatory requirements using authorities such as sections 1115 and 1115A of the Social Security Act, as amended.

(i) Each Federal department or agency conducting or supporting the research and demonstration projects must establish, on a publicly accessible Federal Web site or in such other manner as the department or agency head may determine, a list of the research and demonstration projects that the Federal department or agency conducts or supports under this provision. The research or demonstration project must be published on this list prior to commencing the research involving human subjects.

(ii) [Reserved]

(6) Taste and food quality evaluation and consumer acceptance studies:

(i) If wholesome foods without additives are consumed, or

(ii) If a food is consumed that contains a food ingredient at or below the level and for a use found to be safe, or agricultural chemical or environmental contaminant at or below the level found to be safe, by the Food and Drug Administration or approved by the Environmental Protection Agency or the Food Safety and Inspection Service of the U.S. Department of Agriculture.

(7) Storage or maintenance for secondary research for which broad consent is required: Storage or maintenance of identifiable private information or identifiable biospecimens for potential secondary research use if an IRB conducts a limited IRB review and makes the determinations required by § 46.111(a)(8).

(8) Secondary research for which broad consent is required: Research involving the use of identifiable private information or identifiable biospecimens for secondary research use, if the following criteria are met:

(i) Broad consent for the storage, maintenance, and secondary research use of the identifiable private information or identifiable biospecimens was obtained in accordance with § 46.116(a)(1) through (4), (a)(6), and (d);

(ii) Documentation of informed consent or waiver of documentation of consent was obtained in accordance with § 46.117;

(iii) An IRB conducts a limited IRB review and makes the determination required by § 46.111(a)(7) and makes the determination that the research to be conducted is within the scope of the broad consent referenced in paragraph (d)(8)(i) of this section; and

(iv) The investigator does not include returning individual research results to subjects as part of the study plan. This provision does not prevent an investigator from abiding by any legal requirements to return individual research results.

FDA

The following categories of clinical investigations are exempt from the requirements of this part for IRB review:

(a) Any investigation which commenced before July 27, 1981 and was subject to requirements for IRB review under FDA regulations before that date, provided that the investigation remains subject to review of an IRB which meets the FDA requirements in effect before July 27, 1981.

(b) Any investigation commenced before July 27, 1981 and was not otherwise subject to requirements for IRB review under Food and Drug Administration regulations before that date.

(c) Emergency use of a test article, provided that such emergency use is reported to the IRB within 5 working days. Any subsequent use of the test article at the institution is subject to IRB review.

(d) Taste and food quality evaluations and consumer acceptance studies, if wholesome foods without additives are consumed or if a food is consumed that contains a food ingredient at or below the level and for a use found to be safe, or agricultural, chemical, or environmental contaminant at or below the level found to be safe, by the Food and Drug Administration or approved by the Environmental Protection Agency or the Food Safety and Inspection Service of the U.S. Department of Agriculture.

Can OHRP or the FDA waive the IRB review requirement?

FDA

Sec. 56.105 Waiver of IRB requirement.

On the application of a sponsor or sponsor-investigator, the Food and Drug Administration may waive any of the requirements contained in these regulations, including the requirements for IRB review, for specific research activities or for classes of research activities, otherwise covered by these regulations.

OHRP

46.101 (i)

Unless otherwise required by law, department or agency heads may waive the applicability of some or all of the provisions of this policy to specific research activities or classes of research activities otherwise

covered by this policy, provided the alternative procedures to be followed are consistent with the principles of the Belmont Report.[63] Except when otherwise required by statute or Executive Order, the department or agency head shall forward advance notices of these actions to the Office for Human Research Protections, Department of Health and Human Services (HHS), or any successor office, or to the equivalent office within the appropriate Federal department or agency, and shall also publish them in the Federal Register or in such other manner as provided in department or agency procedures. The waiver notice must include a statement that identifies the conditions under which the waiver will be applied and a justification as to why the waiver is appropriate for the research, including how the decision is consistent with the principles of the Belmont Report.

What written procedures must an IRB have in place in order to accomplish its mandated function? for OHRP? FDA?

OHRP

Establish and follow written procedures for:

(i) Conducting its initial and continuing review of research and for reporting its findings and actions to the investigator and the institution;

(ii) Determining which projects require review more often than annually and which projects need verification from sources other than the investigators that no material changes have occurred since previous IRB review; and

(iii) Ensuring prompt reporting to the IRB of proposed changes in a research activity, and for ensuring that investigators will conduct the research activity in accordance with the terms of the IRB approval until any proposed changes have been reviewed and approved by the IRB, except when necessary to eliminate apparent immediate hazards to the subject.

Establish and follow written procedures for ensuring prompt reporting to the IRB; appropriate institutional officials; the department or agency head; and the Office for Human Research Protections, HHS, or any successor office, or the equivalent office within the appropriate Federal department or agency of

(i) Any unanticipated problems involving risks to subjects or others or any serious or continuing noncompliance with this policy or the requirements or determinations of the IRB; and

(ii) Any suspension or termination of IRB approval.

FDA

In order to fulfill the requirements of these regulations, each IRB shall:

(a) Follow written procedures:

(1) For conducting its initial and continuing review of research and for reporting its findings and actions to the investigator and the institution;

(2) for determining which projects require review more often than annually and which projects need verification from sources other than the investigator that no material changes have occurred since previous IRB review;

(3) for ensuring prompt reporting to the IRB of changes in research activity; and

(4) for ensuring that changes in approved research, during the period for which IRB approval has already been given, may not be initiated without IRB review and approval except where necessary to eliminate apparent immediate hazards to the human subjects.

(b) Follow written procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, and the Food and Drug Administration of:

(1) Any unanticipated problems involving risks to human subjects or others;

(2) any instance of serious or continuing noncompliance with these regulations or the requirements or determinations of the IRB; or

(3) any suspension or termination of IRB approval.

In order to approve research covered by OHRP regulations, the IRB shall determine that all of the following requirements are satisfied. List the criteria. List and compare FDA Requirements.

<u>OHRP</u>

(a) In order to approve research covered by this policy the IRB shall determine that all of the following requirements are satisfied:

1) Risks to subjects are minimized:

> (i) By using procedures that are consistent with sound research design and that do not unnecessarily expose subjects to risk, and
> (ii) Whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes.

(2) Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result. In evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the research (as distinguished from risks and benefits of therapies subjects would receive even if not participating in the research). The IRB should not consider possible long-range effects of applying knowledge gained in the research (e.g., the possible effects of the research on public policy) as among those research risks that fall within the purview of its responsibility.

(3) Selection of subjects is equitable. In making this assessment the IRB should take into account the purposes of the research and the setting in which the research will be conducted. The IRB should be particularly cognizant of the special problems of research that involves a category of subjects who are vulnerable to coercion or undue influence, such as children, prisoners, individuals with impaired decision-making capacity, or economically or educationally disadvantaged persons.

(4) Informed consent will be sought from each prospective subject or the subject's legally authorized representative, in accordance with, and to the extent required by, §46.116.

(5) Informed consent will be appropriately documented or appropriately waived in accordance with §46.117.

(6) When appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects.

(7) When appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.

> (i) The Secretary of HHS will, after consultation with the Office of Management and Budget's privacy office and other Federal departments and agencies that have adopted this policy, issue guidance to assist IRBs in assessing what provisions are adequate to protect the privacy of subjects and to maintain the confidentiality of data.
> (ii) [Reserved.]

(8) For purposes of conducting the limited IRB review required by §46.104(d)(7)), the IRB need not make the determinations at paragraphs (a)(1) through (7) of this section, and shall make the following determinations:

> (i) Broad consent for storage, maintenance, and secondary research use of identifiable private information or identifiable biospecimens is obtained in accordance with the requirements of §46.116(a)(1)-(4), (a)(6), and (d);
> (ii) Broad consent is appropriately documented or waiver of documentation is appropriate, in accordance with §46.117; and
> (iii) If there is a change made for research purposes in the way the identifiable private information or identifiable biospecimens are stored or maintained, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.

(b) When some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as children, prisoners, individuals with impaired decision-making capacity, or economically or educationally disadvantaged persons, additional safeguards have been included in the study to protect the rights and welfare of these subjects.

FDA

(a) In order to approve research covered by these regulations the IRB shall determine that all of the following requirements are satisfied:

(1) Risks to subjects are minimized: (i) By using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk, and (ii) whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes.

(2) Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may be expected to result. In evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the research (as distinguished from risks and benefits of therapies that subjects would receive even if not participating in the research). The IRB should not consider possible long-range effects of applying knowledge gained in the research (for example, the possible effects of the research on public policy) as among those research risks that fall within the purview of its responsibility.

(3) Selection of subjects is equitable. In making this assessment the IRB should take into account the purposes of the research and the setting in which the research will be conducted and should be particularly cognizant of the special problems of research involving vulnerable populations, such as children, prisoners, pregnant women, handicapped, or mentally disabled persons, or economically or educationally disadvantaged persons.

(4) Informed consent will be sought from each prospective subject or the subject's legally authorized representative, in accordance with and to the extent required by part 50.

(5) Informed consent will be appropriately documented, in accordance with and to the extent required by § 50.27.

(6) Where appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects.

(7) Where appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.

(b) When some or all of the subjects, such as children, prisoners, pregnant women, handicapped, or mentally disabled persons, or economically or educationally disadvantaged persons, are likely to be vulnerable to coercion or undue influence additional safeguards have been included in the study to protect the rights and welfare of these subjects.

(c) In order to approve research in which some or all of the subjects are children, an IRB must determine that all research is in compliance with part 50, subpart D of this chapter.

If an IRB suspends or terminates a research project, what actions must the IRB take to comply with the FDA regulations? OHRP?

FDA

An IRB shall have authority to suspend or terminate approval of research that is not being conducted in accordance with the IRB's requirements or that has been associated with unexpected serious harm to subjects. Any suspension or termination of approval shall include a statement of the reasons for the

IRB's action and shall be reported promptly to the investigator, appropriate institutional officials, and the Food and Drug Administration.

OHRP

An IRB shall have authority to suspend or terminate approval of research that is not being conducted in accordance with the IRB's requirements or that has been associated with unexpected serious harm to subjects. Any suspension or termination of approval shall include a statement of the reasons for the IRB's action and shall be reported promptly to the investigator, appropriate institutional officials, and the department or agency head.

What do the FDA regulations say regarding the review of Co-operative research? OHRP?

The Food and Drug Administration (FDA) and Department of Health and Human Services (HHS) regulations permit institutions involved in multi-institutional studies to use reasonable methods of joint or cooperative review [21 CFR 56.114 and 45 CFR 46.114, respectively]

FDA
21 CFR § 56.114 - **Cooperative research**. § 56.114 Cooperative research. In complying with these regulations, institutions involved in multi-institutional studies may use joint review, reliance upon the review of another qualified IRB, or similar arrangements aimed at avoidance of duplication of effort.

OHRP

The revised **Common Rule** (i.e., the 2018 Requirements) requires at 45 CFR 46.114 (b) that all institutions located in the United States that are engaged in cooperative research conducted or supported by a Common Rule department or agency rely upon approval by a single IRB for the portion of the research that is conducted in the United States.

What records must an IRB prepare and maintain to comply with the OHRP regulations? FDA?

OHRP

(a) An institution, or when appropriate an IRB, shall prepare and maintain adequate documentation of IRB activities, including the following:

(1) Copies of all research proposals reviewed, scientific evaluations, if any, that accompany the proposals, approved sample consent forms, progress reports submitted by investigators, and reports of injuries to subjects.

(2) Minutes of IRB meetings, which shall be in sufficient detail to show attendance at the meetings; actions taken by the IRB; the vote on these actions including the number of members voting for, against, and abstaining; the basis for requiring changes in or disapproving research; and a written summary of the discussion of controverted issues and their resolution.

(3) Records of continuing review activities, including the rationale for conducting continuing review of research that otherwise would not require continuing review as described in § 46.109(f)(1).

(4) Copies of all correspondence between the IRB and the investigators.

(5) A list of IRB members in the same detail as described in § 46.108(a)(2).

(6) Written procedures for the IRB in the same detail as described in § 46.108(a)(3) and (4).

(7) Statements of significant new findings provided to subjects, as required by § 46.116(c)(5).

(8) The rationale for an expedited reviewer's determination under § 46.110(b)(1)(i) that research appearing on the expedited review list described in § 46.110(a) is more than minimal risk.

(9) Documentation specifying the responsibilities that an institution and an organization operating an IRB each will undertake to ensure compliance with the requirements of this policy, as described in § 46.103(e).

(b) The records required by this policy shall be retained for at least 3 years, and records relating to research that is conducted shall be retained for at least 3 years after completion of the research. The institution or IRB may maintain the records in printed form, or electronically. All records shall be accessible for inspection and copying by authorized representatives of the Federal department or agency at reasonable times and in a reasonable manner.

FDA

(a) An institution, or where appropriate an IRB, shall prepare and maintain adequate documentation of IRB activities, including the following:

(1) Copies of all research proposals reviewed, scientific evaluations, if any, that accompany the proposals, approved sample consent documents, progress reports submitted by investigators, and reports of injuries to subjects.

(2) Minutes of IRB meetings which shall be in sufficient detail to show attendance at the meetings; actions taken by the IRB; the vote on these actions including the number of members voting for, against, and abstaining; the basis for requiring changes in or disapproving research; and a written summary of the discussion of controverted issues and their resolution.

(3) Records of continuing review activities.

(4) Copies of all correspondence between the IRB and the investigators.

(5) A list of IRB members identified by name; earned degrees; representative capacity; indications of experience such as board certifications, licenses, etc., sufficient to describe each member's chief anticipated contributions to IRB deliberations; and any employment or other relationship between each member and the institution; for example: full-time employee, part-time employee, a member of governing panel or board, stockholder, paid or unpaid consultant.

(6) Written procedures for the IRB as required by § 56.108 (a) and (b).

(7) Statements of significant new findings provided to subjects, as required by § 50.25.

(b) The records required by this regulation shall be retained for at least 3 years after completion of the research, and the records shall be accessible for inspection and copying by authorized representatives of the Food and Drug Administration at reasonable times and in a reasonable manner.

(c) The Food and Drug Administration may refuse to consider a clinical investigation in support of an application for a research or marketing permit if the institution or the IRB that reviewed the investigation refuses to allow an inspection under this section.

Who is responsible for the operation of the IRB? According to OHRP? FDA?

FDA

The parent institution is presumed to be responsible for the operation of an IRB, and the Food and Drug Administration will ordinarily direct any administrative action under this subpart against the institution. However, depending on the evidence of responsibility for deficiencies, determined during the investigation, the Food and Drug Administration may restrict its administrative actions to the IRB or to a component of the parent institution determined to be responsible for formal designation of the IRB.

OHRP

The Institution bears full responsibility for all research involving human subjects covered under its Assurance. For all HHS-conducted or supported research, all of the requirements of the HHS Regulations at 45 CFR Part 46, Subpart A, as well as Subparts B through E, must be met.

ICH E6(R2) Guidance for IRB

With Answers

1. **What is the first and most important responsibility of IRB / IEC review?**

   An IRB/IEC should safeguard the rights, safety, and well-being of all trial subjects. Special attention should be paid to trials that may include vulnerable subjects

2. **Under ICH E6(R2) 3.0 what documents does the guideline specifically require the IRB to review that are only generally referred to in the FDA regulations?**

   ICH

   Trial protocol(s)/amendment(s), written informed consent form(s) and consent form updates that the investigator proposes for use in the trial, subject recruitment procedures (e.g., advertisements), written information to be provided to subjects, Investigator's Brochure (IB), available safety information, information about payments and compensation available to subjects, the investigator's current curriculum vitae and/or other documentation evidencing qualifications, and any other documents that the IRB/IEC may need to fulfil its responsibilities.

   FDA

   Copies of all research proposals reviewed, scientific evaluations, if any, that accompany the proposals, approved sample consent documents, progress reports submitted by investigators, and reports of injuries to subjects.

3. **True or False**

   A. **FALSE** ICH guidance allows for initial expedited review of certain studies presenting no more than minimal risk.

   The ICH E6 Guideline for Good Clinical Practice is written primarily for research that requires full board review at a convened meeting. Expedited review (i.e., review conducted by the IRB chairperson or designee) is mentioned only as it relates to "minor changes" to a protocol that has already received full board approval.

   3.3.5 Providing, according to the applicable regulatory requirements, expedited review and approval/favorable opinion of minor change(s) in ongoing trials that have the approval/favorable opinion of the IRB/IEC.

B. **TRUE** ICH GCP requires the IRB to provide, when asked, copies of their written procedures and membership lists to investigators, sponsors or regulatory authorities.

3.4 Records The IRB/IEC should retain all relevant records (e.g., written procedures, membership lists, lists of occupations/affiliations of members, submitted documents, minutes of meetings, and correspondence) for a period of at least 3 years after completion of the trial and make them available upon request from the regulatory authority(ies). The IRB/IEC may be asked by investigators, sponsors or regulatory authorities to provide its written procedures and membership lists.

C. **TRUE** ICH specifically requires that the sponsor and the investigator sign the study protocol.

4.5.1 The investigator/institution should conduct the trial in compliance with the protocol agreed to by the sponsor and, if required, by the regulatory authority(ies), and which was given approval/favorable opinion by the IRB/IEC. The investigator/institution and the sponsor should sign the protocol, or an alternative contract, to confirm agreement.

D. **TRUE** There is no corresponding section in the FDA regulations for ICH guidance that states that payment to a subject should be prorated and not contingent upon completion of the trial.

3.1.8 The IRB/IEC should review both the amount and method of payment to subjects to assure that neither presents problems of coercion or undue influence on the trial subjects. Payments to a subject should be prorated and not wholly contingent on completion of the trial by the subject.

There is no statement in 21 CFR 50 regarding payment to subjects.

Tab	Documents (all versions) to be maintained in this Section
Current IRB approved protocol	
Current IRB approved ICF	
Signed ICFs	
Institutional review Board	• **<u>IRB Submissions</u>** **Initial/Ongoing** **Continuing** **Revision** **Amendment** **Termination** • **<u>Including all versions of the following:</u>** **Protocol with signature page** **ICF** **Recruitment materials** **Blank CRFs** **Participant educational/study informational materials** **Reportable events (protocol deviations/ unanticipated problems/ SAEs/New information)** **Data Safety Monitoring Board Reports/Other Sponsor reports** **Correspondence with the IRB** **<u>Including:</u>** **Approval letters** **Proviso letters** **PI responses to IRB** **IRB notices of upcoming expiration dates** **Request for corrected IRB letter** **IRB stamped approved documents** **IRB Membership Roster (Maintain from date of first submission to close out of the study (all 4 boards if UTHSC)** **IRB FWA**
Study Team Credentials	• **Curriculum vitae (CVs)/resume/bio sketch for the Principal Investigator/ sub-or co-investigator(s) and key study personnel (KSP) for the study** • **Financial Disclosure Forms** • **Clinical professional licensure/certification (dental, medical, nursing, pharmacy, etc.) for all KSP**

Training Documents	• **Human Subject Protection** • **ICH GCP E6 (R2)** • **FDA regulations** • **45CFR46** • **Declaration of Helsinki** • **Nuremburg Code** • **Institution specific training** • **Protocol/procedures/IP** • **In-services** • **Study related meetings** • **IATA** • **SOPs/MOPs** • **Site Initiation Visit**
Delegation Log	
Subject Logs	• Master log • Screening/Enrollment log
Case Report Forms, Blank	
Case Report Forms, Completed	
Source Documents	
Investigational Product	• **Current Investigational brochure, package insert, or device manual, all versions** • **Investigational brochure, package insert, or device manual, all versions** • **Sample of product label** • **Documentation of study product shipment/receipt/dispensing/return/disposal** • **Current Investigational brochure, package insert, or device manual, all versions** • **Investigational brochure, package insert, or device manual, all versions** • **Sample of product label** • **Documentation of study product shipment/receipt/dispensing/return/disposal** • **Instructions for IP handling** • **Temperature log, when applicable** • **Storage/maintenance instructions**

	• **Unblinding procedures, as applicable** • **IP Accountability Log/Dispense record to subject**
Laboratory	• **Copy of laboratory certification and accreditations** • **Laboratory normal reference ranges/values for procedures included in the protocol** • **Certification of analysis/reliability of tests performed, when requested** • **Copy of Laboratory Director's license and CV (current within 2 years)**
Specimens	• **Shipping/Receipt documentation** • **Storage temperature logs**
Adverse Events	
Protocol Deviations	• **Maintain a protocol deviation log** • **Corrective Action Preventive Action (CAPA), as applicable for each deviation**
Monitoring	• **Monitoring reports/letters** • **Monitoring Log**
Correspondence	**Significant e-mails/faxes/letters/electronic documents, meeting notes, phone calls from the following:** • **Sponsor** • **Contract Research Organization (CROs)** • **Monitor** • **IRB (prefer to keep this correspondence with the IRB section)** • **Study Team**
Legal /Financial Documents	• **FDA** • **Contracts** • **Budgets** • **Subject payments** • **Letter of Understanding/Confidentiality Agreement** • **Data Sharing Agreement** • **Material transfer Agreement** • **Signed agreements between parties (i.e., sponsor/CRO/Institution investigators)**
Note to Files	

IP Worksheet

Define Investigational Product (IP)

An investigational product may be **an unlicensed product or a licensed product when used or assembled** (formulated or packaged) differently from the approved form, when used for an unapproved indication, or when used to gain further information about an approved use.

The IP may be a drug, biologic, medical device, or combination product.

An investigational drug can also be called an experimental drug and is being studied to see:

- If your disease or medical condition improves while taking
- If the drug is safe and effective
- The desired dose
- What are the potential benefits and risks of taking the drug

Why is IP accountability important?

- Subject safety
- Documents the handling of the IP
- Identifies subjects who have received the IP/Ensure study participants receive the correct IP
- Document compliance with the protocol
- Verify data integrity

What is the impact of poor accountability?

- Subject may incur a safety risk
- Loss of data/data integrity
- Negative monitoring/auditing reports
- Sponsor may place a “hold” on the study if non-compliance is severe

Define rescue medication

Patients in some randomized clinical trials may start additional non-randomized medication because of an exacerbation of symptoms or insufficient therapeutic effect. Typically this rescue medication reduces the observed treatment effect in intention-to-treat analysis.
(https://pubmed.ncbi.nlm.nih.gov/11590628/)

Rescue medication also called **escape medication**; medicines identified in a study protocol as those that may be administered to the patients when the efficacy of the investigational medicinal product (IMP) is not satisfactory, or the effect of the IMP is too great and is likely to cause a adverse reactions (https://link.springer.com/chapter/10.1007%2F978-3-211-89836-9_1231)

Calculate IP compliance for the following scenario:

The subject's visit one occurred on March 1st and she was dispensed 100 tablets of investigational product. She is instructed to take 1 tablet daily, starting on March 1st and one on May 1st before her visit

She returns for Visit 2 on May 1st and returns 50 tablets

She should have taken 62 tablets.

What is her % of compliance? 81%

What was taken/what should've been taken x100 = % compliance

What actions if any should you as the responsible study team member take?

- Notify the PI
- Possibly notify the Sponsor/CRO representative
- Subject re-education
- Documentation of events

21 CFR 312 Definition Worksheet

With Answers

1. Drug

A drug is defined as:

- A substance recognized by an official pharmacopoeia or formulary.
- A substance intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease.
- A substance (other than food) intended to affect the structure or any function of the body.
- A substance intended for use as a component of a medicine but not a device or a component, part or accessory of a device.
- Biological products are included within this definition and are generally covered by the same laws and regulations, but differences exist regarding their manufacturing processes (chemical process versus biological process.)

2. IND

Investigational New Drug

Investigational new drug means a new drug or biological drug that is used in a clinical investigation. The term also includes a biological product that is used in vitro for diagnostic purposes. The terms "investigational drug" and "investigational new drug" are deemed to be synonymous for purposes of this part.

3. Treatment IND

The treatment IND [21 CFR 312.34 and 312.35] is a mechanism for providing eligible subjects with investigational drugs for the treatment of serious and life-threatening illnesses for which there are no satisfactory alternative treatments. A treatment IND may be granted after sufficient data have been collected to show that the drug "may be effective" and does not have unreasonable risks. Because data related to safety and side effects are collected, treatment INDs also serve to expand the body of knowledge about the drug.

4. Orphan Drug

Drugs (includes biologics) for the prevention, diagnosis, or treatment of diseases or conditions affecting fewer than 200,000 persons in the US

OR – Drugs that will not be profitable within 7 years following approval by the FDA

5. Parallel Track

The Agency's Parallel Track policy [57 FR 13250] permits wider access to promising new drugs for AIDS/HIV related diseases under a separate "expanded access" protocol that "parallels" the controlled clinical trials that are essential to establish the safety and effectiveness of new drugs. It provides an administrative system that expands the availability of drugs for treating AIDS/HIV. These studies require prospective IRB review and informed consent.

6. Clinical Hold

A clinical hold is an order issued by FDA to the sponsor to delay a proposed clinical investigation or to suspend an ongoing investigation. The clinical hold order may apply to one or more of the investigations covered by an IND. When a proposed study is placed on clinical hold, subjects may not be given the investigational drug. When an ongoing study is placed on clinical hold, no new subjects may be recruited to the study and placed on the investigational drug; patients already in the study should be taken off therapy involving the investigational drug unless specifically permitted by FDA in the interest of patient safety.

7. NDA

New Drug Application (NDA)
When the sponsor of a new drug believes that enough evidence on the drug's safety and effectiveness has been obtained to meet FDA's requirements for marketing approval, the sponsor submits to FDA a new drug application (NDA). The application must contain data from specific technical viewpoints for review, including chemistry, pharmacology, medical, biopharmaceutics, and statistics. If the NDA is approved, the product may be marketed in the United States. For internal tracking purposes, all NDA's are assigned an NDA number.

8. ANDA

Abbreviated New Drug Application (ANDA)
An Abbreviated New Drug Application (ANDA) contains data that, when submitted to FDA's Center for Drug Evaluation and Research, Office of Generic Drugs, provides for the review and ultimate approval of a generic drug product. Generic drug applications are called "abbreviated" because they are generally not required to include preclinical (animal) and clinical (human) data to establish safety and effectiveness. Instead, a generic applicant must scientifically demonstrate that its product is

bioequivalent (i.e., performs in the same manner as the innovator drug). Once approved, an applicant may manufacture and market the generic drug product to provide a safe, effective, low cost alternative to the American public.

9. Sponsor

Sponsor means a person who takes responsibility for and initiates a clinical investigation. The sponsor may be an individual or pharmaceutical company, governmental agency, academic institution, private organization, or other organization. The sponsor does not actually conduct the investigation unless the sponsor is a sponsor-investigator. A person other than an individual that uses one or more of its own employees to conduct an investigation that it has initiated is a sponsor, not a sponsor-investigator, and the employees are investigators.

10. Sponsor-Investigators

Sponsor-Investigator means an individual who both initiates and conducts an investigation, and under whose immediate direction the investigational drug is administered or dispensed. The term does not include any person other than an individual. The requirements applicable to a sponsor-investigator under this part include both those applicable to an investigator and a sponsor.

11. Emergency Use IND

The need for an investigational drug may arise in an emergency situation that does not allow time for submission of an IND in the usual manner. In such cases, FDA may authorize shipment of the drug for a specified use [21 CFR 312.36]. Such authorization is usually conditioned upon the sponsor filing an appropriate application as soon as practicable. Prospective IRB review is required unless the conditions for exemption are met [21 CFR 56.104(c) and 56.102(d)]. Informed consent is required unless the conditions for exception are met [21 CFR 50.23].

21 CFR 312 Worksheet with Answers

Note the table of contents for 21 CFR 312. How many subparts are there and what are the major areas addressed in the part of Title 21?

Subpart A—General Provisions
Subpart B—Investigational New Drug application (IND)
Subpart C—Administrative Actions
Subpart D—Responsibilities of Sponsors and Investigators
Subpart E - Drugs Intended to Treat Life-threatening and Severely-debilitating Illnesses
Subpart F - Miscellaneous
Subpart G - Drugs for Investigational Use in Laboratory Research Animals or In Vitro Tests
Subpart H [Reserved]
Subpart I - Expanded Access to Investigational Drugs for Treatment Use

General Provisions

1. Does 21 CFR 312 apply to all clinical investigations? If not, where does it not apply?

(a) Applicability. Except as provided in this section, this part applies to all clinical investigations of products that are subject to section 505 of the Federal Food, Drug, and Cosmetic Act or to the licensing provisions of the Public Health Service Act (58 Stat. 632, as amended (42 U.S.C. 201 et seq.)).
(b) Exemptions.
(1) The clinical investigation of a drug product that is lawfully marketed in the United States is exempt from the requirements of this part if all the following apply:
(i) The investigation is not intended to be reported to FDA as a well-controlled study in support of a new indication for use nor intended to be used to support any other significant change in the labeling for the drug;
(ii) If the drug that is undergoing investigation is lawfully marketed as a prescription drug product, the investigation is not intended to support a significant change in the advertising for the product;
(iii) The investigation does not involve a route of administration or dosage level or use in a patient population or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product;
(iv) The investigation is conducted in compliance with the requirements for institutional review set forth in part 56 and with the requirements for informed consent set forth in part 50; and
(v) The investigation is conducted in compliance with the requirements of § 312.7.
(2)
(i) A clinical investigation involving an in vitro diagnostic biological product listed in paragraph (b)(2)(ii) of this section is exempt from the requirements of this part if (a) it is intended to be used in a diagnostic procedure that confirms the diagnosis made by another, medically established, diagnostic product or procedure and (b) it is shipped in compliance with § 312.160.

(ii) In accordance with paragraph (b)(2)(i) of this section, the following products are exempt from the requirements of this part: (a) blood grouping serum; (b) reagent red blood cells; and (c) anti-human globulin.

(3) A drug intended solely for tests in vitro or in laboratory research animals is exempt from the requirements of this part if shipped in accordance with § 312.160.

(4) FDA will not accept an application for an investigation that is exempt under the provisions of paragraph (b)(1) of this section.

(5) A clinical investigation involving use of a placebo is exempt from the requirements of this part if the investigation does not otherwise require submission of an IND.

(6) A clinical investigation involving an exception from informed consent under § 50.24 of this chapter is not exempt from the requirements of this part.

(c) Bioavailability studies. The applicability of this part to in vivo bioavailability studies in humans is subject to the provisions of § 320.31.

(d) Unlabeled indication. This part does not apply to the use in the practice of medicine for an unlabeled indication of a new drug product approved under part 314 or of a licensed biological product.

(e) Guidance. FDA may, on its own initiative, issue guidance on the applicability of this part to particular investigational uses of drugs. On request, FDA will advise on the applicability of this part to a planned clinical investigation.

[52 FR 8831, Mar. 19, 1987, as amended at 61 FR 51529, Oct. 2, 1996; 64 FR 401, Jan. 5, 1999]

2. What are the labeling provisions for an investigational drug?

(a) The immediate package of an investigational new drug intended for human use shall bear a label with the statement "Caution: New Drug - Limited by Federal (or United States) law to investigational use."

(b) The label or labeling of an investigational new drug shall not bear any statement that is false or misleading in any particular and shall not represent that the investigational new drug is safe or effective for the purposes for which it is being investigated.

(c) The appropriate FDA Center Director, according to the procedures set forth in §§ 201.26 or 610.68 of this chapter, may grant an exception or alternative to the provision in paragraph (a) of this section, to the extent that this provision is not explicitly required by statute, for specified lots, batches, or other units of a human drug product that is or will be included in the Strategic National Stockpile.

[52 FR 8831, Mar. 19, 1987, as amended at 72 FR 73599, Dec. 28, 2007]

3. When may a subject be charged for receiving an investigational drug under and IND?

(a) General criteria for charging.

(1) A sponsor must meet the applicable requirements in paragraph (b) of this section for charging in a clinical trial or paragraph (c) of this section for charging for expanded access to an investigational drug for treatment use under subpart I of this part, except that sponsors need not fulfill the requirements in this section to charge for an approved drug obtained from another entity not affiliated with the sponsor for use as part of the clinical trial evaluation (e.g., in a clinical trial of a new use of the approved drug, for use of the approved drug as an active control).

(2) A sponsor must justify the amount to be charged in accordance with paragraph (d) of this section.

(3) A sponsor must obtain prior written authorization from FDA to charge for an investigational drug.

(4) FDA will withdraw authorization to charge if it determines that charging is interfering with the development of a drug for marketing approval or that the criteria for the authorization are no longer being met.

(b) Charging in a clinical trial –

(1) Charging for a sponsor's drug. A sponsor who wishes to charge for its investigational drug, including investigational use of its approved drug, must:

(i) Provide evidence that the drug has a potential clinical benefit that, if demonstrated in the clinical investigations, would provide a significant advantage over available products in the diagnosis, treatment, mitigation, or prevention of a disease or condition;

(ii) Demonstrate that the data to be obtained from the clinical trial would be essential to establishing that the drug is effective or safe for the purpose of obtaining initial approval of a drug, or would support a significant change in the labeling of an approved drug (e.g., new indication, inclusion of comparative safety information); and

(iii) Demonstrate that the clinical trial could not be conducted without charging because the cost of the drug is extraordinary to the sponsor. The cost may be extraordinary due to manufacturing complexity, scarcity of a natural resource, the large quantity of drug needed (e.g., due to the size or duration of the trial), or some combination of these or other extraordinary circumstances (e.g., resources available to a sponsor).

(2) Duration of charging in a clinical trial. Unless FDA specifies a shorter period, charging may continue for the length of the clinical trial.

(c) Charging for expanded access to investigational drug for treatment use.

(1) A sponsor who wishes to charge for expanded access to an investigational drug for treatment use under subpart I of this part must provide reasonable assurance that charging will not interfere with developing the drug for marketing approval.

(2) For expanded access under § 312.320 (treatment IND or treatment protocol), such assurance must include:

(i) Evidence of sufficient enrollment in any ongoing clinical trial(s) needed for marketing approval to reasonably assure FDA that the trial(s) will be successfully completed as planned;

(ii) Evidence of adequate progress in the development of the drug for marketing approval; and

(iii) Information submitted under the general investigational plan (§ 312.23(a)(3)(iv)) specifying the drug development milestones the sponsor plans to meet in the next year.

(3) The authorization to charge is limited to the number of patients authorized to receive the drug under the treatment use, if there is a limitation.

(4) Unless FDA specifies a shorter period, charging for expanded access to an investigational drug for treatment use under subpart I of this part may continue for 1 year from the time of FDA authorization. A sponsor may request that FDA reauthorize charging for additional periods.

(d) Costs recoverable when charging for an investigational drug.

(1) A sponsor may recover only the direct costs of making its investigational drug available.

(i) Direct costs are costs incurred by a sponsor that can be specifically and exclusively attributed to providing the drug for the investigational use for which FDA has authorized cost recovery. Direct costs include costs per unit to manufacture the drug (e.g., raw materials, labor, and nonreusable supplies and equipment used to manufacture the quantity of drug needed for the use for which charging is authorized) or costs to acquire the drug from another manufacturing source, and direct costs to ship and handle (e.g., store) the drug.

(ii) Indirect costs include costs incurred primarily to produce the drug for commercial sale (e.g., costs for facilities and equipment used to manufacture the supply of investigational drug, but that are primarily intended to produce large quantities of drug for eventual commercial sale) and research

and development, administrative, labor, or other costs that would be incurred even if the clinical trial or treatment use for which charging is authorized did not occur.

(2) For expanded access to an investigational drug for treatment use under §§ 312.315 (intermediate-size patient populations) and 312.320 (treatment IND or treatment protocol), in addition to the direct costs described in paragraph (d)(1)(i) of this section, a sponsor may recover the costs of monitoring the expanded access IND or protocol, complying with IND reporting requirements, and other administrative costs directly associated with the expanded access IND.

(3) To support its calculation for cost recovery, a sponsor must provide supporting documentation to show that the calculation is consistent with the requirements of paragraphs (d)(1) and, if applicable, (d)(2) of this section. The documentation must be accompanied by a statement that an independent certified public accountant has reviewed and approved the calculations.

[74 FR 40899, Aug. 13, 2009]

IND

1. What are the primary objectives of the FDA when reviewing an IND?

FDA's primary objectives in reviewing an IND are, in all phases of the investigation, to assure the safety and rights of subjects, and, in Phase 2 and 3, to help assure that the quality of the scientific evaluation of drugs is adequate to permit an evaluation of the drug's effectiveness and safety. Therefore, although FDA's review of Phase 1 submissions will focus on assessing the safety of Phase 1 investigations, FDA's review of Phases 2 and 3 submissions will also include an assessment of the scientific quality of the clinical investigations and the likelihood that the investigations will yield data capable of meeting statutory standards for marketing approval.

2. A sponsor is required to submit and annual report to the FDA reporting the status of the study for what purpose?

To report the progress of the investigation to include:

(a) Individual study information. A brief summary of the status of each study in progress and each study completed during the previous year. The summary is required to include the following information for each study:

(1) The title of the study (with any appropriate study identifiers such as protocol number), its purpose, a brief statement identifying the patient population, and a statement as to whether the study is completed.

(2) The total number of subjects initially planned for inclusion in the study; the number entered into the study to date, tabulated by age group, gender, and race; the number whose participation in the study was completed as planned; and the number who dropped out of the study for any reason.

(3) If the study has been completed, or if interim results are known, a brief description of any available study results.

(b) Summary information. Information obtained during the previous year's clinical and nonclinical investigations, including:

(1) A narrative or tabular summary showing the most frequent and most serious adverse experiences by body system.

(2) A summary of all IND safety reports submitted during the past year.

(3) A list of subjects who died during participation in the investigation, with the cause of death for each subject.
(4) A list of subjects who dropped out during the course of the investigation in association with any adverse experience, whether or not thought to be drug related.
(5) A brief description of what, if anything, was obtained that is pertinent to an understanding of the drug's actions, including, for example, information about dose response, information from controlled trials, and information about bioavailability.
(6) A list of the preclinical studies (including animal studies) completed or in progress during the past year and a summary of the major preclinical findings.
(7) A summary of any significant manufacturing or microbiological changes made during the past year.

(c) A description of the general investigational plan for the coming year to replace that submitted 1 year earlier. The general investigational plan shall contain the information required under § 312.23(a)(3)(iv).
(d) If the investigator brochure has been revised, a description of the revision and a copy of the new brochure.
(e) A description of any significant Phase 1 protocol modifications made during the previous year and not previously reported to the IND in a protocol amendment.
(f) A brief summary of significant foreign marketing developments with the drug during the past year, such as approval of marketing in any country or withdrawal or suspension from marketing in any country.
(g) If desired by the sponsor, a log of any outstanding business with respect to the IND for which the sponsor requests or expects a reply, comment, or meeting.
[52 FR 8831, Mar. 19, 1987, as amended at 52 FR 23031, June 17, 1987; 63 FR 6862, Feb. 11, 1998; 67 FR 9585, Mar. 4, 2002]

3. The FDA requires that an investigator brochure contain what information?

(i) A brief description of the drug substance and the formulation, including the structural formula, if known.
(ii) A summary of the pharmacological and toxicological effects of the drug in animals and, to the extent known, in humans.
(iii) A summary of the pharmacokinetics and biological disposition of the drug in animals and, if known, in humans.
(iv) A summary of information relating to safety and effectiveness in humans obtained from prior clinical studies. (Reprints of published articles on such studies may be appended when useful.)
(v) A description of possible risks and side effects to be anticipated on the basis of prior experience with the drug under investigation or with related drugs, and of precautions or special monitoring to be done as part of the investigational use of the drug.

4. A protocol must be provided in the IND and must contain 7 specific elements. List them.

(a) A statement of the objectives and purpose of the study.
(b) The name and address and a statement of the qualifications (curriculum vitae or other statement of qualifications) of each investigator, and the name of each subinvestigator (e.g., research fellow, resident) working under the supervision of the investigator; the name and address of the research facilities to be used; and the name and address of each reviewing Institutional Review Board.

(c) The criteria for patient selection and for exclusion of patients and an estimate of the number of patients to be studied.
(d) A description of the design of the study, including the kind of control group to be used, if any, and a description of methods to be used to minimize bias on the part of subjects, investigators, and analysts.
(e) The method for determining the dose(s) to be administered, the planned maximum dosage, and the duration of individual patient exposure to the drug.
(f) A description of the observations and measurements to be made to fulfill the objectives of the study.
(g) A description of clinical procedures, laboratory tests, or other measures to be taken to monitor the effects of the drug in human subjects and to minimize risk.

5. **If a sponsor intends to submit a new protocol not already covered by the IND, the sponsor must submit a protocol amendment to the FDA. The study can be initiated if two conditions are met What are they?**

Whenever a sponsor intends to conduct a study that is not covered by a protocol already contained in the IND, the sponsor shall submit to FDA a protocol amendment containing the protocol for the study. Such study may begin provided two conditions are met: (1) The sponsor has submitted the protocol to FDA for its review; and (2) the protocol has been approved by the Institutional Review Board (IRB) with responsibility for review and approval of the study in accordance with the requirements of part 56. The sponsor may comply with these two conditions in either order.

6. **A sponsor has added a new investigator to take part in a previously submitted protocol. What action must the sponsor take to ship the investigational product to the investigator and initiate study participation?**

A sponsor shall submit a protocol amendment when a new investigator is added to carry out a previously submitted protocol, except that a protocol amendment is not required when a licensed practitioner is added in the case of a treatment protocol under § 312.315 or § 312.320. Once the investigator is added to the study, the investigational drug may be shipped to the investigator and the investigator may begin participating in the study. The sponsor shall notify FDA of the new investigator within 30 days of the investigator being added.

7. **When must a sponsor submit protocol amendments for a new protocol or a change in protocol? What about additional information about an investigator(s)?**

A sponsor of an IND application is expected to submit a protocol amendment in cases when there are changes in the existing protocol that significantly affect safety of subjects, scope of the investigation, or scientific quality of the study. Such amendment should contain a brief description of the change and reference (date and number) to the submission that contained the original protocol.

A sponsor of an IND application is expected to submit a protocol amendment when a new investigator is added to carry out a previously submitted protocol. The amendment should include the investigator's name, the qualifications to conduct the investigation, and any reference to the previously submitted protocol, if relevant. FDA should be notified within 30 days of the investigator being added.

8. Give one example of an information amendment_____.

- Any increase in drug dosage or duration of exposure of individual subjects to the drug beyond that described in the current protocol, or any significant increase in the number of subjects under study.
- Any significant change in the design of a protocol (such as the addition or elimination of a control group).
- Addition of a new test or procedure intended to improve monitoring for, or reduce the risk of, a side effect or adverse event; or elimination of a test intended to monitor safety.

9. How often would information amendments to an IND by submitted?

When submitted. A sponsor shall submit a protocol amendment for a new protocol or a change in protocol before its implementation. Protocol amendments to add a new investigator or to provide additional information about investigators may be grouped and submitted at 30-day intervals. When several submissions of new protocols or protocol changes are anticipated during a short period, the sponsor is encouraged, to the extent feasible, to include these all in a single submission.

10. When is a sponsor required by the FDA to submit a written safety report to the agency and all participating investigators? What is the time frame in which the notification must be submitted?

Mandatory Safety Reporting

- ***Initial reporting:*** IND application sponsor must report any suspected adverse reaction or adverse reaction to study treatment that is both serious and unexpected.

  Unexpected serious suspected adverse reactions and observations from animal studies suggesting significant risk to human subjects must be reported to FDA as soon as possible but no later than within **15 calendar days** following the sponsor's initial receipt of the information.

  Unexpected fatal or life-threatening suspected adverse reactions represent especially important safety information and must be reported to FDA as soon as possible but no later than **7 calendar days** following the sponsor's initial receipt of the information.

- ***Follow-up reporting:*** Any relevant additional information obtained by the sponsor that pertains to a previously submitted IND safety report must be submitted as a Follow-up IND Safety Report. Such report should be submitted without delay, as soon as the information is available but no later than 15 calendar days after the sponsor receives the information.

11. When is a sponsor required to notify the FDA via telephone or facsimile of a safety report? What is the time frame for reporting?

The FDA recommends that sponsors submit 7-day IND safety reports electronically in eCTD (Electronic Common Technical Document) format. If the IND is not in eCTD format, other means of rapid communication (e.g., telephone, facsimile transmission, email) may be used.

12. What is the purpose of an annual report and when must a sponsor submit an annual report to the FDA?

IND application sponsors are expected to submit brief reports of the progress of the investigations conducted under their respective IND application within 60 days of the anniversary date that the application went into effect.

13. What must an annual report include?

- A brief summary of the status of each study in progress and each study completed during the previous year to include titles of the study, total number of subjects, any study results
- Summary information regarding serious adverse experience, IND safety reports, list of subjects who died during participation, list of subjects who dropped out, a brief description of the understanding of the drugs actions, a list of the preclinical studies, and a summary of any significant manufacturing or microbiological changes.
- General investigational plans for the coming year
- Revision of the Investigator's Brochure
- A description of any significant Phase 1 protocol modifications
- Update on foreign marketing developments
- A log of outstanding business

14. What is treatment use of an investigational new drug? What is the purpose of a treatment IND?

The treatment IND [21 CFR 312.34 and 312.35] is a mechanism for providing eligible subjects with investigational drugs for the treatment of serious and life-threatening illnesses for which there are no satisfactory alternative treatments. A treatment IND may be granted after sufficient data have been collected to show that the drug "may be effective" and does not have unreasonable risks. Because data related to safety and side effects are collected, treatment INDs also serve to expand the body of knowledge about the drug.

15. What are the criteria for FDA approval of a treatment IND?

(1) The patient or patients to be treated have a serious or immediately life-threatening disease or condition, and there is no comparable or satisfactory alternative therapy to diagnose, monitor, or treat the disease or condition;

(2) The potential patient benefit justifies the potential risks of the treatment use and those potential risks are not unreasonable in the context of the disease or condition to be treated; and

(3) Providing the investigational drug for the requested use will not interfere with the initiation, conduct, or completion of clinical investigations that could support marketing approval of the expanded access use or otherwise compromise the potential development of the expanded access use.

16. When is it necessary for a licensed practitioner to submit a treatment IND to the FDA?

For use in expanded access to Investigational drugs for treatment use in Individual patients, including for emergency use.

17. When can treatment use of an investigational new drug begin?

An expanded access IND goes into effect 30 days after FDA receives the IND or on earlier notification by FDA that the expanded access use may begin.

A licensed physician may satisfy the submission requirements by obtaining from the sponsor permission for FDA to refer to any information in the IND that would be needed to support the expanded access request (right of reference) and by providing any other required information not contained in the IND (usually only the information specific to the individual patient).

18. What is "emergency use" of an investigational new drug? What action must the sponsor take after FDA approval of emergency use of the investigational new drug?

The need for an investigational drug may arise in an emergency situation that does not allow time for submission of an IND in the usual manner. In such cases, FDA may authorize shipment of the drug for a specified use [21 CFR 312.36]. Such authorization is usually conditioned upon the sponsor filing an appropriate application as soon as practicable. Prospective IRB review is required unless the conditions for exemption are met [21 CFR 56.104(c) and 56.102(d)]. Informed consent is required unless the conditions for exception are met [21 CFR 50.23].

19. When can the sponsor withdraw an approved IND? If the withdrawal is due to safety concerns, what action must the sponsor take?

(a) At any time a sponsor may withdraw an effective IND without prejudice.

(b) If an IND is withdrawn, FDA shall be so notified, all clinical investigations conducted under the IND shall be ended, all current investigators notified, and all stocks of the drug returned to the sponsor or otherwise disposed of at the request of the sponsor in accordance with § 312.59.

(c) If an IND is withdrawn because of a safety reason, the sponsor shall promptly so inform FDA, all participating investigators, and all reviewing Institutional Review Boards, together with the reasons for such withdrawal.

20. When does an IND go into effect?

An IND application may go into effect:

- 30 days after FDA receives the application, unless FDA notifies the sponsor that the investigations described in the application are subject to a Clinical Hold; or
- on earlier notification by FDA that the clinical investigations in the IND may begin.

21. When may the sponsor ship an investigational new drug to the investigators named in the IND?

Once an IND application is in effect, a drug manufacturer may ship the investigational new drug to the investigator(s) named in the application. An investigator may not administer an investigational new drug to human subjects until the IND application goes into effect.

Administrative Action

1. What is a clinical hold?

A clinical hold is an order issued by FDA to the sponsor of an IND application to delay a proposed clinical investigation or to suspend an ongoing investigation. All or some of the investigations conducted under an IND application may be placed on clinical hold.

2. What major grounds can the FDA use to place a Phase I trial on clinical hold?

- Human subjects are or would be exposed to an unreasonable and significant risk of illness or injury; or
- The clinical investigators named in the IND are not qualified by reason of their scientific training and experience to conduct the investigation described in the IND; or
- The investigator brochure is misleading, erroneous, or materially incomplete; or
- The IND application does not contain sufficient information needed to assess the risks to subjects of the proposed studies; or
- The IND application is for the study of an investigational drug intended to treat a life-threatening disease or condition that affects both genders, and men or women with reproductive potential who have the disease or condition being studied are excluded from eligibility because of a risk of reproductive toxicity (i.e., affecting reproductive organs) or developmental toxicity (i.e., affecting potential offspring).

  However, this criterion does **not** apply to circumstances when: (1) proposed studies are pertinent only to one gender, (2) proposed studies are conducted in subjects who do not have the disease or condition for which the drug is being studied (e.g., some studies in healthy volunteers), (3) another study that does not exclude members of the other gender with

reproductive potential is being conducted concurrently, has been conducted, or will take place with the same investigational product within a reasonable time agreed upon by FDA.

Phase II and III studies?

- Any of the conditions described above as for Phase 1 investigations; or
- The plan or protocol for the investigation is clearly deficient in design to meet its stated objectives

Ongoing treatment protocol or treatment IND?

- The pertinent Criteria for permitting the expanded access use to begin are not satisfied; or
- The expanded access IND application or expanded access protocol does not comply with the requirements for Expanded Access submissions.

3. **What are two actions available to the FDA when there is not satisfactory resolution to the clinical hold status of an IND?**
   - The study is allowed to proceed with specific restrictions not proposed by the applicant (i.e., a partial hold),
   - The study is informed that studies under the IND may still not proceed.

4. **What is an "END of Phase II" meeting?**

   The purpose of an end-of-phase 2 meeting is to determine the safety of proceeding to Phase 3, to evaluate the Phase 3 plan and protocols and the adequacy of current studies and plans to assess pediatric safety and effectiveness, and to identify any additional information necessary to support a marketing application for the uses under investigation.

5. **What is a "pre-NDA"? "pre-BLA" meeting?**
   "Pre-NDA" and "pre-BLA" meetings. FDA has found that delays associated with the initial review of a marketing application may be reduced by exchanges of information about a proposed marketing application. The primary purpose of this kind of exchange is to uncover any major unresolved problems, to identify those studies that the sponsor is relying on as adequate and well-controlled to establish the drug's effectiveness, to identify the status of ongoing or needed studies adequate to assess pediatric safety and effectiveness, to acquaint FDA reviewers with the general information to be submitted in the marketing application (including technical information), to discuss appropriate

methods for statistical analysis of the data, and to discuss the best approach to the presentation and formatting of data in the marketing application. Arrangements for such a meeting are to be initiated by the sponsor with the division responsible for review of the IND. To permit FDA to provide the sponsor with the most useful advice on preparing a marketing application, the sponsor should submit to FDA's reviewing division at least 1 month in advance of the meeting the following information:
(i) A brief summary of the clinical studies to be submitted in the application.
(ii) A proposed format for organizing the submission, including methods for presenting the data.
(iii) Information on the status of needed or ongoing pediatric studies.
(iv) Any other information for discussion at the meeting.

Sponsor and Investigator Responsibilities

1. **What is a Contract Research Organization (CRO)? What obligations may a sponsor delegate to the CRO?**
   Contract research organization means a person that assumes, as an independent contractor with the sponsor, one or more of the obligations of a sponsor, e.g., design of a protocol, selection or monitoring of investigations, evaluation of reports, and preparation of materials to be submitted to the Food and Drug Administration.

2. **Once the sponsor or (CRO) has identified an investigator for participation in an investigation, the sponsor is responsible for obtaining what major information (4 areas) from the investigator?**

   A signed investigator statement (Form FDA-1572)
   Curriculum vitae
   Clinical protocol
   Financial disclosure information

3. **Familiarize yourself with the FDA Form 1572 "Statement of the Investigator". Outline the investigator commitments proposed by this "contract" with the FDA.**

   - A commitment by the investigator that he or she:

   (*a*) Will conduct the study(ies) in accordance with the relevant, current protocol(s) and will only make changes in a protocol after notifying the sponsor, except when necessary to protect the safety, the rights, or welfare of subjects;

   (*b*) Will comply with all requirements regarding the obligations of clinical investigators and all other pertinent requirements in this part;

(*c*) Will personally conduct or supervise the described investigation(s);

(*d*) Will inform any potential subjects that the drugs are being used for investigational purposes and will ensure that the requirements relating to obtaining informed consent (21 CFR part 50) and institutional review board review and approval (21 CFR part 56) are met;

(*e*) Will report to the sponsor adverse experiences that occur in the course of the investigation(s) in accordance with § 312.64;

(*f*) Has read and understands the information in the investigator's brochure, including the potential risks and side effects of the drug; and

(*g*) Will ensure that all associates, colleagues, and employees assisting in the conduct of the study(ies) are informed about their obligations in meeting the above commitments.

- A commitment by the investigator that, for an investigation subject to an institutional review requirement under part 56, an IRB that complies with the requirements of that part will be responsible for the initial and continuing review and approval of the clinical investigation and that the investigator will promptly report to the IRB all changes in the research activity and all unanticipated problems involving risks to human subjects or others, and will not make any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to the human subjects.

- A list of the names of the subinvestigators (e.g., research fellows, residents) who will be assisting the investigator in the conduct of the investigation(s).

4. The sponsor is responsible for selecting qualified investigators, collecting the FDA Form 1572, controlling the distribution of the investigational drug and selecting monitors to review the progress of the study. What are the sponsors monitoring obligations?

(a)The sponsor shall monitor the progress of all clinical investigations being conducted under its IND.

(b) A sponsor who discovers that an investigator is not complying with the signed agreement (Form FDA-1572), the general investigational plan, or the requirements of this part or other applicable parts shall promptly either secure compliance or discontinue shipments of the investigational new drug to the investigator and end the investigator's participation in the investigation. If the investigator's participation in the investigation is ended, the sponsor shall require that the investigator dispose of or return the investigational drug in accordance with the requirements of § 312.59 and shall notify FDA.

(c) The sponsor shall review and evaluate the evidence relating to the safety and effectiveness of the drug as it is obtained from the investigator. The sponsors shall make such reports to FDA regarding information relevant to the safety of the drug as are required under § 312.32. The

sponsor shall make annual reports on the progress of the investigation in accordance with § 312.33.

(d) A sponsor who determines that its investigational drug presents an unreasonable and significant risk to subjects shall discontinue those investigations that present the risk, notify FDA, all institutional review boards, and all investigators who have at any time participated in the investigation of the discontinuance, assure the disposition of all stocks of the drug outstanding as required by § 312.59, and furnish FDA with a full report of the sponsor's actions. The sponsor shall discontinue the investigation as soon as possible, and in no event later than 5 working days after making the determination that the investigation should be discontinued. Upon request, FDA will confer with a sponsor on the need to discontinue an investigation.

5. What information must the sponsor provide the investigator before the investigation begins? During the investigation?

(a) Before the investigation begins, a sponsor (other than a sponsor-investigator) shall give each participating clinical investigator an investigator brochure containing the information described in § 312.23(a)(5).

(b) The sponsor shall, as the overall investigation proceeds, keep each participating investigator informed of new observations discovered by or reported to the sponsor on the drug, particularly with respect to adverse effects and safe use. Such information may be distributed to investigators by means of periodically revised investigator brochures, reprints or published studies, reports or letters to clinical investigators, or other appropriate means. Important safety information is required to be relayed to investigators in accordance with § 312.32.

6. What records must the sponsor maintain regarding the investigation and how long must the sponsor retain these records?

A sponsor shall maintain adequate records showing the receipt, shipment, or other disposition of the investigational drug. These records are required to include, as appropriate, the name of the investigator to whom the drug is shipped, and the date, quantity, and batch or code mark of each such shipment.

(b) A sponsor shall maintain complete and accurate records showing any financial interest in § 54.4(a)(3)(i), (a)(3)(ii), (a)(3)(iii), and (a)(3)(iv) of this chapter paid to clinical investigators by the sponsor of the covered study. A sponsor shall also maintain complete and accurate records concerning all other financial interests of investigators subject to part 54 of this chapter.

(c) A sponsor shall retain the records and reports required by this part for 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 and FDA has been so notified.

(d) A sponsor shall retain reserve samples of any test article and reference standard identified in, and used in any of the bioequivalence or bioavailability studies described in, § 320.38 or § 320.63 of this

chapter, and release the reserve samples to FDA upon request, in accordance with, and for the period specified in § 320.38.

7. Regarding the control of the investigational drug, including controlled substances, what records does the FDA require the sponsor to make available for inspection?

(a) FDA inspection. A sponsor shall upon request from any properly authorized officer or employee of the Food and Drug Administration, at reasonable times, permit such officer or employee to have access to and copy and verify any records and reports relating to a clinical investigation conducted under this part. Upon written request by FDA, the sponsor shall submit the records or reports (or copies of them) to FDA. The sponsor shall discontinue shipments of the drug to any investigator who has failed to maintain or make available records or reports of the investigation as required by this part.

(b) ***Controlled substances.*** If an investigational new drug is a substance listed in any schedule of the Controlled Substances Act (21 U.S.C. 801; 21 CFR part 1308), records concerning shipment, delivery, receipt, and disposition of the drug, which are required to be kept under this part or other applicable parts of this chapter shall, upon the request of a properly authorized employee of the Drug Enforcement Administration of the U.S. Department of Justice, be made available by the investigator or sponsor to whom the request is made, for inspection and copying. In addition, the sponsor shall assure that adequate precautions are taken, including storage of the investigational drug in a securely locked, substantially constructed cabinet, or other securely locked, substantially constructed enclosure, access to which is limited, to prevent theft or diversion of the substance into illegal channels of distribution.

8. According the 21 CFR 312.60-312.69, what are the responsibilities or the investigators?

An investigator is responsible for ensuring that an investigation is conducted according to the signed investigator statement, the investigational plan, and applicable regulations; for protecting the rights, safety, and welfare of subjects under the investigator's care; and for the control of drugs under investigation. An investigator shall, in accordance with the provisions of part 50 of this chapter, obtain the informed consent of each human subject to whom the drug is administered, except as provided in §§ 50.23 or 50.24 of this chapter. Additional specific responsibilities of clinical investigators are set forth in this part and in parts 50 and 56 of this chapter.

If the investigational drug is subject to the Controlled Substances Act, the investigator shall take adequate precautions, including storage of the investigational drug in a securely locked, substantially constructed cabinet, or other securely locked, substantially constructed enclosure, access to which is limited, to prevent theft or diversion of the substance into illegal channels of distribution.

9. When may the FDA disqualify an investigator form participating in a study?

If FDA has information indicating that an investigator (including a sponsor-investigator) has repeatedly or deliberately failed to comply with the requirements of this part, part 50 or part 56 of this chapter, or has repeatedly or deliberately submitted to FDA or to the sponsor false information in any required report.

Expedited Development

In expedited development of drugs intended to treat life-threatening and severely debilitating illnesses, the FDA will honor, if possible, requests for early consultation meetings. Name two such meetings.

For products intended to treat life-threatening or severely-debilitating illnesses, sponsors may request to meet with FDA-reviewing officials early in the drug development process to review and reach agreement on the design of necessary preclinical and clinical studies. Where appropriate, FDA will invite to such meetings one or more outside expert scientific consultants or advisory committee members. To the extent FDA resources permit, agency reviewing officials will honor requests for such meetings

(a) ***Pre-investigational new drug (IND) meetings.*** Prior to the submission of the initial IND, the sponsor may request a meeting with FDA-reviewing officials. The primary purpose of this meeting is to review and reach agreement on the design of animal studies needed to initiate human testing. The meeting may also provide an opportunity for discussing the scope and design of phase 1 testing, plans for studying the drug product in pediatric populations, and the best approach for presentation and formatting of data in the IND.

(b) ***End-of-phase 1 meetings.*** When data from phase 1 clinical testing are available, the sponsor may again request a meeting with FDA-reviewing officials. The primary purpose of this meeting is to review and reach agreement on the design of phase 2 controlled clinical trials, with the goal that such testing will be adequate to provide sufficient data on the drug's safety and effectiveness to support a decision on its approvability for marketing, and to discuss the need for, as well as the design and timing of, studies of the drug in pediatric patients. For drugs for life-threatening diseases, FDA will provide its best judgment, at that time, whether pediatric studies will be required and whether their submission will be deferred until after approval. The procedures outlined in § 312.47(b)(1) with respect to end-of-phase 2 conferences, including documentation of agreements reached, would also be used for end-of-phase 1 meetings.

21 CFR 812 Worksheet with answers

Define the following:

Medical Device

Per Section 201(h) of the Food, Drug, and Cosmetic Act, a device is:
An instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including a component part, or accessory which is:

1. recognized in the official National Formulary, or the United States Pharmacopoeia, or any supplement to them,
2. intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or
3. intended to affect the structure or any function of the body of man or other animals, and which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and

which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of its primary intended purposes. The term "device" does not include software functions excluded pursuant to section 520(o).

IDE

IDE refers to the regulations under 21 CFR 812. An approved IDE means that the IRB (and FDA for significant risk devices) has approved the sponsor's study application and all the requirements under 21 CFR 812 are met.

PMA

Premarket approval (PMA) is the FDA process of scientific and regulatory review to evaluate the safety and effectiveness of Class III medical devices. Class III devices are those that support or sustain human life, are of substantial importance in preventing impairment of human health, or which present a potential, unreasonable risk of illness or injury.

PreMarket Notification (PMN or 510(k)

510(k) refers to the type of submission to FDA described under 21 CFR 807 Subpart E in which the applicant must establish that their device is substantially equivalent to a legally marketed device. This type of submission is used for most Class II devices and some Class I devices.

Classes of Devices

Federal law (Federal Food, Drug, and Cosmetic Act, section 513), established the risk-based device classification system for medical devices. Each device is assigned to one of three regulatory classes: Class I, Class II or Class III, based on the level of control necessary to provide reasonable assurance of its safety and effectiveness. For information related to device classification, please refer to "Classify Your Medical Device."

As device class increases from Class I, to Class II to Class III, the regulatory controls also increase, with Class I devices subject to the least regulatory control, and Class III devices subject to the most stringent regulatory control.

The regulatory controls for each device class include:

- Class I (low to moderate risk): general controls
- Class II (moderate to high risk): general controls and Special Controls
- Class III (high risk): general controls and Premarket Approval (PMA)

Examples of Class I Devices:

- Electric Toothbrush
- Tongue Depressor
- Oxygen Mask
- Reusable Surgical Scalpel
- Bandages
- Hospital Beds
- Non-electric wheelchair

Examples of Class II Medical Devices:

- Catheters
- Blood Pressure Cuffs
- Pregnancy Test Kits
- Syringes
- Blood Transfusion Kits
- Contact Lenses
- Surgical Gloves

- Absorbable Sutures

Examples of Class III Medical Devices:

- Breast implants
- Pacemakers
- Defibrillators
- High-frequency ventilators
- Cochlear implants
- Fetal blood sampling monitors
- Implanted prosthetics

Significant Risk

Significant risk device means an investigational device that:

(1) Is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject;

(2) Is purported or represented to be for a use in supporting or sustaining human life and presents a potential for serious risk to the health, safety, or welfare of a subject;

(3) Is for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health and presents a potential for serious risk to the health, safety, or welfare of a subject; or

(4) Otherwise presents a potential for serious risk to the health, safety, or welfare of a subject.

Insignificant Risk

An NSR device study is one that does not meet the definition for an SR device study.

Investigator Agreement

A sponsor shall obtain from each participating investigator a signed agreement that includes:

(1) The investigator's curriculum vitae.

(2) Where applicable, a statement of the investigator's relevant experience, including the dates, location, extent, and type of experience.

(3) If the investigator was involved in an investigation or other research that was terminated, an explanation of the circumstances that led to termination.

(4) A statement of the investigator's commitment to:

(i) Conduct the investigation in accordance with the agreement, the investigational plan, this part and other applicable FDA regulations, and conditions of approval imposed by the reviewing IRB or FDA;

(ii) Supervise all testing of the device involving human subjects; and

(iii) Ensure that the requirements for obtaining informed consent are met.

(5) Sufficient accurate financial disclosure information to allow the sponsor to submit a complete and accurate certification or disclosure statement as required under part 54 of this chapter. The sponsor shall obtain a commitment from the clinical investigator to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year following completion of the study. This information shall not be submitted in an investigational device exemption application, but shall be submitted in any marketing application involving the device.

HDE

Humanitarian Device Exemption (HDE) provides is a possible route to market medical devices that may help people with a rare diseases or conditions. This database includes devices with HDE approval, and includes the approval order, Summary of Safety and Probable Benefit, and labeling for the approved device.

HUD

The Humanitarian Use Device or HUD program was established in 1990 with passage of the Safe Medical Devices Act and creates an alternative pathway for getting market approval for medical devices that may help people with rare diseases or conditions. As defined by 21 CFR 814.3(n), and updated by the 21st Century Cures Act, a HUD is a “medical device intended to benefit patients in the treatment or diagnosis of a disease or condition that affects or is manifested in not more than 8,000 individuals in the United States per year.”

UADE

Unanticipated adverse device effect is any serious adverse effect on health or safety, any life-threatening problem or death caused by, or associated with a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the application; or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

21 CFR 812 Worksheet

With Answers

The FDA places medical devices into one of three classes based on risk to the patient / subject or user and the level of control necessary to ensure the safety and effectiveness of the device. What are the general controls required of companies for all classes of devices?

- General Controls are the basic authorities of the Medical Device Amendments that provide the FDA with the means of regulating devices to ensure their safety and effectiveness.
- General Controls apply to all three classes of medical devices; however, they are the only level of controls that apply to Class I devices.
- Class I devices are not intended to be:
    1. For use in supporting or sustaining life;
    2. Of importance in preventing impairment to human life; and may not
    3. Present a potential unreasonable risk of illness or injury
- General Controls include the provisions of the Act pertaining to:
    1. Adulteration;
    2. Misbranding;
    3. Device registration and listing;
    4. Premarket notification;
    5. Banned devices;
    6. Notification and repair, replacement, and refund;
    7. Records and reports;
    8. Restricted devices; and
    9. Good Manufacturing Practices.

Name the classes of devices and describe the controls required for each.

Device Class and Regulatory Controls

1. Class I General Controls (as above)
2. Class II General Controls and Special Controls

    Special controls are usually device-specific and include:
    - Performance standards
    - Postmarket surveillance
    - Patient registries
    - Special labeling requirements

- Premarket data requirements
- Guidelines

3. Class III General Controls and Premarket Approval

Under federal law, class III devices are subject to approval of a Premarket Approval Application (PMA).

Who determines whether an investigational device is significant risk (SR) or non-significant risk (NDS) for a study?

Sponsors are responsible for making the initial risk determination and presenting it to the IRB. FDA is also available to help the sponsor, clinical investigator, and IRB in making the risk determination.2 Unless FDA has already made a risk determination for the study, the IRB must review the sponsor's SR or NSR determination for every investigational medical device study reviewed and modify the determination if the IRB disagrees with the sponsor. If FDA has already made the SR or NSR determination for the study, the agency's determination is final.

What are the major differences in significant risk and non-significant risk device studies?

Significant Risk (SR) Device Studies

- SR device studies must follow all the IDE regulations at 21 CFR 812.
- SR device studies must have an IDE application approved by FDA before they may proceed.

Nonsignificant Risk (NSR) Device Studies

NSR device studies must follow the abbreviated requirements at 21 CFR 812.2(b).

These abbreviated requirements address labeling, IRB approval, informed consent, monitoring, records, reports, and prohibition against promotion. However, there is no need to make progress reports or final reports to FDA.

NSR device studies do not have to have an IDE application approved by FDA.

Sponsors and IRBs do not have to report the IRB approval of an NSR device study to FDA. This means that an IRB may approve an NSR device study and an investigator may conduct the study without FDA knowing about it.

An IRB's NSR determination is important because the IRB serves as the FDA's surrogate for review, approval, and continuing review of the NSR device studies. An NSR device study may start at the institution as soon as the IRB reviews and approves the study and without prior approval by FDA.

What must an IRB consider when determining whether a device study is significant risk or non-significant risk?

- IRBs should have standard operating procedures that explain how the IRB makes SR and NSR determinations and that the decision should be documented. FDA considers this determination to be part of the IRB's responsibilities for conducting its initial review of a study. (See 21 CFR 56.108)
- IRBs should make the SR or NSR determination about a study by reviewing relevant information at a convened meeting. This information includes the description of the device, reports of prior investigations conducted with the device, the proposed investigational plan, and subject selection criteria. The sponsor should provide the IRB with a risk assessment and the rationale used in making its SR or NSR determination.
- An IRB may agree or disagree with the sponsor's initial NSR assessment.
- If the IRB determines the study is NSR, the IRB may approve the study using the criteria at 21 CFR 56.111. The study may begin without submission of an IDE application to FDA.
- If the IRB disagrees with the sponsor's NSR assessment and decides the study is SR, the IRB must tell the clinical investigator, and where appropriate, the sponsor. (See 21 CFR 812.66) Contains Nonbinding Recommendations 6
- An IRB may approve the study as an SR device study, but the study may not begin until FDA approves the sponsor's IDE application.
- To facilitate the IRB's review of the study, an IRB may ask the sponsor for proof (i.e., a copy of FDA's approval or conditional approval letter) that an SR study has an FDA-approved IDE application.
- The IRB should document its SR/NSR determination in the IRB meeting minutes.

What is the difference in the IRB making a SR / NSR determination and "minimal risk"?

IRBs should not confuse their responsibility to make an SR/NSR determination for a device study with the concept of "minimal risk." "Minimal Risk" is a term used in the IRB regulations in part to identify certain studies that IRBs may approve through an expedited review procedure. For a device study to be eligible for expedited review, it must be an NSR study AND present no more than minimal risk to the subject. (See 21 CFR 56.110)

IRBs should not confuse their responsibility to review and approve research for conduct at a clinical site with the SR/NSR determination. IRBs make the SR/NSR determination before the IRB conducts its review of the study under Part 56. The judgment about whether a study poses a significant risk or nonsignificant risk is based on the significance of the potential harm that may result from participation in the study, including the use of the device; whereas Contains Nonbinding Recommendations 8 the IRB's decision to approve a study for implementation is based on the study's risk-benefit assessment.

What is Emergency Use of an Unapproved Medical Device?

Emergency use is when there is a need to use a device that has not received the FDA's approval or clearance in an emergency. Expanded access to an investigational device under the emergency use mechanism is intended to provide patients and physicians with access to investigational devices to address immediately life-threatening situations when there is no available alternative and no time to use existing procedures to obtain FDA approval. Emergency use may apply if the device is being studied in clinical trials under an investigational device exemption (IDE) such as when a physician who is not part of the IDE clinical study wishes to use the device to treat a patient in an immediately life-threatening situation. An IDE allows an investigational device to be used in a clinical study in order to collect safety and effectiveness data. Emergency use may also apply if there is no IDE or ongoing clinical studies for the device.

Criteria for Emergency Use

- The patient has a life-threatening condition that needs immediate treatment;
- No generally acceptable alternative treatment for the condition exists; and
- Because of the immediate need to use the device, there is no time to use existing procedures to obtain FDA approval for the use.

Is FDA approval required prior to Emergency Use?

No. If all of the above criteria are met, an unapproved device may be used in an emergency situation without prior approval by the FDA.

The FDA expects the physician to make the determination that the patient's circumstances meet the above criteria, to assess the potential for benefit from the use of the unapproved device, and to have substantial reason to believe that benefits will exist. In the event that a device is used in circumstances meeting the criteria listed above, the physician should follow as many patient protection procedures as possible. Such patient protection procedures include obtaining:

1. Informed consent from the patient or a legal representative;
2. Clearance from the institution as specified by their policies;
3. Concurrence of the Institutional Review Board (IRB) chairperson;
4. An independent assessment from an uninvolved physician; and
5. Authorization from the device manufacturer.

Do I need to report Emergency Use to the FDA?

Yes. If there is an IDE for the device, the IDE sponsor must notify the FDA of the emergency use within 5 days through submission of an IDE Report (§812.35(a)(2)). This follow-up report should include a summary of the conditions constituting the emergency, the patient protection measures that were followed, and patient outcome information.

If no IDE exists, the physician should submit to the FDA a follow-up report within 5 days on the use of the device including: a description of device used, details of the case, and the patient protection measures that were followed.

What are Pivotal Clinical Trials?

Medical devices can undergo three general stages of clinical development. These stages may be extremely dependent on each other and doing a thorough evaluation in one stage can make the next stage much more straightforward. To begin, medical devices may undergo an exploratory clinical stage. In this stage, the limitations and advantages of the medical device are evaluated. This stage includes first-in-human studies and feasibility studies. The next stage, the pivotal stage, is used to develop the information necessary to evaluate the safety and effectiveness of the device for the identified intended use. It usually consists of one or more pivotal studies. Finally, devices undergo a post-market stage which can include an additional study or studies for better understanding of device safety, such as rare adverse events and long-term effectiveness.

A medical device pivotal study is a definitive study in which evidence is gathered to support the safety and effectiveness evaluation of the medical device for its intended use. Evidence from one or more pivotal clinical studies generally serves as the primary basis for the determination of reasonable assurance of safety and effectiveness of the medical device of a pre-market approval application (PMA) and FDA's overall benefit-risk determination. In some cases, a PMA may include multiple studies designed to answer different scientific questions

What is a 510(k) application (premarket notification) (this information can be found in 21 CFR 807 Subpart E)?

Section 510(k) of the Food, Drug and Cosmetic Act requires device manufacturers who must register, to notify FDA of their intent to market a medical device at least 90 days in advance. This is known as Premarket Notification - also called PMN or 510(k). This allows FDA to determine whether the device is equivalent to a device already placed into one of the three classification categories. Thus, "new" devices (not in commercial distribution prior to May 28, 1976) that have not been classified can be properly identified. Specifically, medical device manufacturers are required to submit a premarket notification if they intend to introduce a device into commercial distribution for the first time or reintroduce a device that will be significantly changed or modified to the extent that its safety or effectiveness could be affected. Such change or modification could relate to the design, material, chemical composition, energy source, manufacturing process, or intended use.

When does a device modification require a 510k Notice?

Changes made with intent to significantly affect safety or effectiveness of a device – If a manufacturer modifies their device with the intent to significantly affect the safety or effectiveness of the device (for example, to significantly improve clinical outcomes, to mitigate a known risk, in response to adverse events, etc.), submission of a new 510(k) is likely required. A change intended to significantly affect the safety or effectiveness of the device is considered to be a change that "could significantly affect the safety or effectiveness of the device" and thus requires submission of a new 510(k) regardless of the considerations outlined below. Changes that are not intended to significantly affect the safety or effectiveness of a device, however, should still be evaluated to determine whether the change could significantly affect device safety or effectiveness.

What is a predicate device?

In the US FDA premarket notification or 510k approval, predicate medical device is a term that is frequently used. A medical device legally marketed in the US and can be used as a point of comparison to prove the performance and safety of the medical device that is seeking marketing clearance from the FDA is known as a predicate medical device.

Define Substantial Equivalence?

A 510(k) requires demonstration of substantial equivalence to another legally U.S. marketed device. Substantial equivalence means that the new device is as safe and effective as the predicate.

How is substantial equivalence demonstrated?

A device is substantially equivalent if, in comparison to a predicate it:

- has the same intended use as the predicate; **and**
- has the same technological characteristics as the predicate;
  or
- has the same intended use as the predicate; **and**
- has different technological characteristics and does not raise different questions of safety and effectiveness; **and**
- the information submitted to FDA demonstrates that the device is as safe and effective as the legally marketed device.

Forms Worksheet
Sponsor / Investigator / IND Study
With answers

Sponsor / IND Study	What	Who	When	CFR
FDA Form 1571	Investigational New Drug application	The sponsor is the person who takes responsibility for and initiates a clinical investigation. The sponsor may be an individual, pharmaceutical company, governmental agency, academic institution, private organization or other organization	Prior to the date the submission is being submitted to the FDA.	21 CFR 312.23
FDA Form 1572	Statement of Investigator Form required for clinical trials involving investigational drugs and biologics	Investigators and sub-investigators	The sponsor must obtain a completed and signed 1572 before permitting the investigator to begin participation in the clinical investigation.	21 CFR 312.53(c)
IND Annual Report	IND application sponsors are expected to submit brief reports of the progress of the investigations conducted under their respective IND application	Application sponsors	Within 60 days of the anniversary date that the application went into effect.	21 CFR 312.33
FDA Form 3454	Certification: Financial Interests and Arrangements of Clinical Investigators	Sponsor / applicant of the study	Prior to the start of a study	21 CFR 54
FDA Form 3455	Disclosure: Financial Interests and Arrangements of Clinical Investigators	Sponsor / applicant of the study	Prior to the start of a study	21 CFR 54
Final report or withdrawal	Withdrawal of the IND application upon completion of the clinical study (studies) of the investigational drug	Sponsor / applicant of the study	At the time that all clinical studies of the investigational drug have been completed, and no future studies are planned, the Sponsor of the IND application should notify the FDA, in writing, that the IND is being withdrawn or terminated.	21 CFR 312.38

Forms Worksheet

Sponsor / Investigator / IDE Study

With answers

Sponsor / IDE Study	What	Who	When	CFR
Investigational Plan	An overview of the study which includes the purpose, protocol, risk analysis, description of device, monitoring procedures, labeling, consent materials, IRB information, other institutions, and any additional records and reports.	Sponsor or applicant	With the application to the FDA	21 CFR 812.25
Investigator Agreement	A signed agreement between the sponsor and the investigator	A sponsor shall obtain from each participating investigator a signed agreement that includes: (1) The investigator's curriculum vitae. (2) Where applicable, a statement of the investigator's relevant experience, including the dates, location, extent, and type of experience. (3) If the investigator was involved in an investigation or other research that was terminated, an explanation of the circumstances that led to termination. (4) A statement of the investigator's commitment to:	Prior to the start of a study	21 CFR 812.43

Forms Worksheet

Sponsor / Investigator / IDE Study

With answers

		(i) Conduct the investigation in accordance with the agreement, the investigational plan, this part and other applicable FDA regulations, and conditions of approval imposed by the reviewing IRB or FDA; (ii) Supervise all testing of the device involving human subjects; and (iii) Ensure that the requirements for obtaining informed consent are met. (5) Sufficient accurate financial disclosure information to allow the sponsor to submit a complete and accurate certification or disclosure statement as required under part 54 of this chapter. The sponsor shall obtain a commitment from the clinical investigator to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year following completion of the study. This information shall not be		

Forms Worksheet

Sponsor / Investigator / IDE Study

With answers

		submitted in an investigational device exemption application, but shall be submitted in any marketing application involving the device.		
SRD Determination NSRD	Under 21 CFR 812.3(m), an SR device means an investigational device that: • Is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject; • Is purported or represented to be for use supporting or sustaining human life and presents a potential for serious risk to the health, safety, or welfare of a subject; • Is for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health and presents a potential for serious risk to the health, safety, or welfare of a subject; or • Otherwise presents a potential for serious risk to the health,	Sponsors are responsible for making the initial risk determination and presenting it to the IRB. FDA is also available to help the sponsor, clinical investigator, and IRB in making the risk determination. Unless FDA has already made a risk determination for the study, the IRB must review the sponsor's SR or NSR determination for every investigational medical device study reviewed and modify the determination if the IRB disagrees with the sponsor. I		21 CFR 812.66 21 CFR 812.2(1)(ii) 21 CFR 812.2.(b)

Forms Worksheet

Sponsor / Investigator / IDE Study

With answers

	safety, or welfare of a subject. An NSR device study is one that does not meet the definition for an SR device study.			
FDA Form 3454	Certification: Financial Interests and Arrangements of Clinical Investigators	Sponsor / applicant of the study	Prior to the start of a study	21 CFR 54
FDA Form 3455	Disclosure: Financial Interests and Arrangements of Clinical Investigators	Sponsor / applicant of the study	Prior to the start of a study	21 CFR 54
IDE Annual Reports IDA Final Report	Status and program reports for the IDE application	Sponsor or applicant	Progress reports. At regular intervals, and at least yearly, a sponsor shall submit progress reports to all reviewing IRB's. In the case of a significant risk device, a sponsor shall also submit progress reports to FDA. A sponsor of a treatment IDE shall submit semi-annual progress reports to all reviewing IRB's and FDA in accordance with § 812.36(f) and annual reports in accordance with this section.	21 CFR 812.150(b)(5)

Forms Worksheet

Sponsor / Investigator / IDE Study

With answers

			In the case of a significant risk device, the sponsor shall notify FDA within 30 working days of the completion or termination of the investigation and shall submit a final report to FDA and all reviewing the IRB's and participating investigators within 6 months after completion or termination. In the case of a device that is not a significant risk device, the sponsor shall submit a final report to all reviewing IRB's within 6 months after termination or completion.	
IDE Safety Reports	Ongoing safety reports and communication from the sponsor to all parties involved in the safety and welfare of subjects	Investigator, Sponsor or applicant	An investigator shall submit to the sponsor and to the reviewing IRB a report of any unanticipated adverse device effect occurring during an investigation as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect.	21 CFR 812.150(b)(2) FDA Guidance for IDE Responsibilities

Forms Worksheet

Sponsor / Investigator / IDE Study

With answers

			A sponsor who conducts an evaluation of an unanticipated adverse device effect under § 812.46(b) shall report the results of such evaluation to FDA and to all reviewing IRB's and participating investigators within 10 working days after the sponsor first receives notice of the effect. Thereafter the sponsor shall submit such additional reports concerning the effect as FDA requests. A sponsor who determines that an unanticipated adverse device effect presents an unreasonable risk to subjects shall terminate all investigations or parts of investigations presenting that risk as soon as possible. Termination shall occur not later than 5 working days after the sponsor makes this determination and not later	

Forms Worksheet

Sponsor / Investigator / IDE Study

With answers

			than 15 working days after the sponsor first received notice of the effect.	

Recruiting Study Subjects

Direct advertising that may be used to recruit potential subjects include:

Direct advertising for research subjects, i.e., advertising that is intended to be seen or heard by prospective subjects to solicit their participation in a study, is not in and of itself, an objectionable practice. Direct advertising includes, but is not necessarily limited to: newspaper, radio, TV, bulletin boards, posters, and flyers that are intended for prospective subjects.

Name three communications that are not considered recruitment tools and do not need to be reviewed by the IRB.

(1) communications intended to be seen or heard by health professionals, such as "dear doctor" letters and doctor-to-doctor letters (even when soliciting for study subjects), (2) news stories and (3) publicity intended for other audiences, such as financial page advertisements directed toward prospective investors.

True or False:

TRUE. The federal regulators expect that an IRB will review the methods and materials that investigators propose to use to recruit study subjects.

An IRB is required to ensure that appropriate safeguards exist to protect the rights and welfare of research subjects and this include review of the methods and material that investigators propose to used to recruit subjects.

TRUE. Listing of clinical trials on the internet do not require IRB review and approval as long as the format allows only basic trials information.

IRB review and approval of listings of clinical trials on the internet would provide no additional safeguard and is not required when the system format limits the information provided to basic trial information, such as: the title; purpose of the study; protocol summary; basic eligibility criteria; study site location(s); and how to contact the site for further information. Examples of clinical trial listing services that do not require prospective IRB approval include the National Cancer Institute's cancer clinical trial listing (PDQ) and the government-sponsored AIDS Clinical Trials Information Service (ACTIS). However, when the opportunity to add additional descriptive information is not precluded by the data base system, IRB review and approval may assure that the additional information does not promise or imply a certainty of cure or other benefit beyond what is contained in the protocol and the informed consent document.

TRUE. FDA considers direct advertising for study subjects to be a part of the enrollment process.

FDA considers direct advertising for study subjects to be the start of the informed consent and subject selection process. Advertisements should be reviewed and approved by the IRB as part of the package for initial review.

TRUE. Receptionist's scripts to determine basic eligibility for a specific study must be reviewed and approved by the IRB.

The first contact prospective study subjects make is often with a receptionist who follows a script to determine basic eligibility for the specific study. The IRB should assure the procedures followed adequately protect the rights and welfare of the prospective subjects.

HIPAA Regulation in Clinical Research Worksheet

To whom does the HIPAA Privacy Rule apply?

The HIPAA Rules apply to **covered entities and business associates**.

Individuals, organizations, and agencies that meet the definition of a **covered entity** under HIPAA must comply with the Rules' requirements to protect the privacy and security of health information and must provide individuals with certain rights with respect to their health information.

The HIPAA Privacy Rule protects the individually identifiable health information for the living and about a decedent for 50 years following the date of death of the individual.

Who is considered a Business Associate?

A "business associate" is a person or entity that performs certain functions or activities that involve the use or disclosure of protected health information on behalf of, or provides services to, a covered entity. A member of the covered entity's workforce is not a business associate. A covered health care provider, health plan, or health care clearinghouse can be a business associate of another covered entity. The Privacy Rule lists some of the functions or activities, as well as the particular services, that make a person or entity a business associate, if the activity or service involves the use or disclosure of protected health information. The types of functions or activities that may make a person or entity a business associate include payment or health care operations activities, as well as other functions or activities regulated by the Administrative Simplification Rules.

Business associate functions and activities include: claims processing or administration; data analysis, processing or administration; utilization review; quality assurance; billing; benefit management; practice management; and repricing. Business associate services are: legal; actuarial; accounting; consulting; data aggregation; management; administrative; accreditation; and financial. See the definition of "business associate" at 45 CFR 160.103.

Define Protected Health Information.

Protected health information "Relates to the past, present, or future physical or mental health or condition of an individual; the provision of health care to an individual; or the past, present, or future payment for the provision of health care to an individual" that is:

- Transmitted by electronic media;
- Maintained in electronic media; or

- Transmitted or maintained in any other form or medium.

What are the common identifiers? (18)

1. Names (Full or last name and initial)
2. All geographical identifiers smaller than a state, except for the initial three digits of a zip code if, according to the current publicly available data from the U.S. Bureau of the Census: the geographic unit formed by combining all zip codes with the same three initial digits contains more than 20,000 people; and the initial three digits of a zip code for all such geographic units containing 20,000 or fewer people is changed to 000
3. Dates (other than year) directly related to an individual
4. Phone Numbers
5. Fax numbers
6. Email addresses
7. Social Security numbers
8. Medical record numbers
9. Health insurance beneficiary numbers
10. Account numbers
11. Certificate/license numbers
12. Vehicle identifiers (including serial numbers and license plate numbers)
13. Device identifiers and serial numbers;
14. Web Uniform Resource Locators (URLs)
15. Internet Protocol (IP) address numbers
16. Biometric identifiers, including finger, retinal and voice prints
17. Full face photographic images and any comparable images
18. Any other unique identifying number, characteristic, or code except the unique code assigned by the investigator to code the data

Name two circumstances when a covered entity MUST disclose PHI?

A covered entity must disclose protected health information in only two situations: (a) to individuals (or their personal representatives) specifically when they request access to, or an accounting of disclosures of, their protected health information; and (b) to HHS when it is undertaking a compliance investigation or review or enforcement action.

What is de-identified data?

Health information that does not identify an individual and with respect to which there is no reasonable basis to believe that the information can be used to identify an individual is not individually identifiable health information.

Under the regulations what criteria must be met to deem information "de-identified"

Two methods to achieve de-identification in accordance with the HIPAA Privacy Rule.

The first is the "Expert Determination" method:

(b) *Implementation specifications: requirements for de-identification of protected health information.* A covered entity may determine that health information is not individually identifiable health information only if:
(1) A person with appropriate knowledge of and experience with generally accepted statistical and scientific principles and methods for rendering information not individually identifiable:
(i) Applying such principles and methods, determines that the risk is very small that the information could be used, alone or in combination with other reasonably available information, by an anticipated recipient to identify an individual who is a subject of the information; and
(ii) Documents the methods and results of the analysis that justify such determination; or

The second is the "Safe Harbor" method:

(2)(i) The following identifiers of the individual or of relatives, employers, or household members of the individual, are removed:

(A) Names

(B) All geographic subdivisions smaller than a state, including street address, city, county, precinct, ZIP code, and their equivalent geocodes, except for the initial three digits of the ZIP code if, according to the current publicly available data from the Bureau of the Census:
(1) The geographic unit formed by combining all ZIP codes with the same three initial digits contains more than 20,000 people; and
(2) The initial three digits of a ZIP code for all such geographic units containing 20,000 or fewer people is changed to 000

(C) All elements of dates (except year) for dates that are directly related to an individual, including birth date, admission date, discharge date, death date, and all ages over 89 and all elements of dates (including year) indicative of such age, except that such ages and elements may be aggregated into a single category of age 90 or older

(D) Telephone numbers

(L) Vehicle identifiers and serial numbers, including license plate numbers

(E) Fax numbers

(M) Device identifiers and serial numbers

(F) Email addresses

(N) Web Universal Resource Locators (URLs)

(G) Social security numbers

(O) Internet Protocol (IP) addresses

(H) Medical record numbers

(P) Biometric identifiers, including finger and voice prints

(I) Health plan beneficiary numbers

(Q) Full-face photographs and any comparable images

(J) Account numbers

(R) Any other unique identifying number, characteristic, or code, except as permitted by paragraph (c) of this section [Paragraph (c) is presented below in the section "Re-identification"]; and

(K) Certificate/license numbers

What is a limited data set?

A limited data set under HIPAA is a set of identifiable healthcare information that the HIPAA Privacy Rule permits covered entities to share with certain entities for research purposes, public health activities, and healthcare operations without obtaining prior authorization from patients, if certain conditions are met.

In contrast to de-identified protected health information, which is no longer classed as PHI under HIPAA Rules, a limited data set under HIPAA is still identifiable protected information. Therefore it is still subject to HIPAA Privacy Rule regulations.

A HIPAA limited data set can only be shared with entities that have signed a data use agreement with the covered entity. The data use agreement allows the covered entity to obtain satisfactory assurances that the PHI will only be used for specific purposes, that the PHI will not be disclosed by the entity with which it is shared, and that the requirements of the HIPAA Privacy Rule will be followed.

Under HIPAA Rules, a limited data set cannot contain any of the following information:

- Names
- Street addresses or postal address information with the exception of town/city, state and zip code
- Phone/Fax numbers
- E-mail addresses
- Social Security numbers
- Medical records numbers
- Health plan beneficiary numbers
- Other account numbers
- Certificate and license numbers
- Vehicle identifiers and serial numbers, including license plates
- Device identifiers and serial numbers
- URLs and IP addresses
- Biometric identifiers such as fingerprints, retinal scans and voice prints
- Full face photos and comparable images

So town/city state and zip codes are allowed along with dates.

Define Personal representative under HIPAA.

The personal representative stands in the shoes of the individual and has the ability to act for the individual and exercise the individual's rights.

In general, the scope of the personal representative's authority to act for the individual under the Privacy Rule derives from his or her authority under applicable law to make health care decisions for the individual.

What is the "minimum necessary" standard?

The HIPAA "Minimum Necessary" standard requires **all HIPAA covered entities and business associates** to restrict the uses and disclosures of protected health information (PHI) to the minimum amount necessary to achieve the purpose for which it is being used, requested, or disclosed.

Name the elements that must be included in the HIPAA authorization agreement.

The authorization form must be written in plain language to ensure it can be easily understood and as a minimum, must contain the following elements:

- Specific and meaningful information, including a description, of the information that will be used or disclosed
- The name (or other specific identification) of the person or class of persons authorized to make the requested use or disclosure
- The name(s) or other specific identification of the person or class of persons to whom information will be disclosed
- A description of the purpose of the requested use or disclosure. In cases where a statement of the purpose is not provided, "at the request of the individual" is sufficient
- A specific time frame for the authorization including an expiration date. In the case of uses and disclosures related to research, "at the end of the study" can be used or 'none' in the case of the creation of a research database or research repository
- A date and signature from the individual giving the authorization. If the authorization is being given by an individual's authorized representative, a description of the person's authority to act on behalf of the individual must be detailed.

Under what circumstances can a HIPAA waiver of authorization be obtained?

The following three criteria must be satisfied for an IRB or Privacy Board to approve a waiver of authorization under the Privacy Rule:

1. The use or disclosure of protected health information involves no more than a minimal risk to the privacy of individuals, based on, at least, the presence of the following elements:
    - an adequate plan to protect the identifiers from improper use and disclosure;
    - an adequate plan to destroy the identifiers at the earliest opportunity consistent with conduct of the research, unless there is a health or research justification for retaining the identifiers or such retention is otherwise required by law; and
    - adequate written assurances that the protected health information will not be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the research project, or for other research for which the use or disclosure of protected health information would be permitted by this subpart;

2. The research could not practicably be conducted without the waiver or alteration; and

3. The research could not practicably be conducted without access to and use of the protected health information.

Under HIPAA what are the Documentation and Record Retention requirements?

The authorization document itself is subject to HIPAA retention laws, which means it must be retained for six years. However, if the document is part of the patient´s medical record, it is subject to the state´s medical record retention requirements – which could be longer. Furthermore, if the covered entity operates in a state in which the Statute of Limitations for private rights of action exceeds six years, it will be necessary to retain the document until the Statute of Limitations has expired.

21 CFR 11 with answers

1. **To what does 21 CFR Part 11 apply?**

   This part applies to records in electronic form that are created, modified, maintained, archived, retrieved, or transmitted, under any records requirements set forth in agency regulations. This part also applies to electronic records submitted to the agency under requirements of the Federal Food, Drug, and Cosmetic Act and the Public Health Service Act, even if such records are not specifically identified in agency regulations. However, this part does not apply to paper records that are, or have been, transmitted by electronic means.

2. **Define:**

   Audit Trail
   An audit trail (also called audit log) is a security-relevant chronological record, set of records, and/or destination and source of records that provide documentary evidence of the sequence of activities that have affected at any time a specific operation, procedure, event, or device.

   Biometrics
   Biometrics means a method of verifying an individual's identity based on measurement of the individual's physical feature(s) or repeatable action(s) where those features and/or actions are both unique to that individual and measurable.

   Data Entry
   Data entry is **the** inputting of data or information into a computer using input devices**,** such as a keyboard, scanner, disk, and voice.

   Digital Signature
   Digital signature means an electronic signature based upon cryptographic methods of originator authentication, computed by using a set of rules and a set of parameters such that the identity of the signer and the integrity of the data can be verified.

   Electronic Record
   Electronic record means any combination of text, graphics, data, audio, pictorial, or other information representation in digital form that is created, modified, maintained, archived, retrieved, or distributed by a computer system.

E-CFR

An E-CFR (electronic case report form) is a software system used to collect information (data) in research studies.

Predicate Rules

A predicate rule is any FDA regulation that requires a company to maintain certain records and submit specific information to the agency as part of compliance. Although predicate rules originally applied to paper records with handwritten signatures, due to Part 11 they are also applicable to electronic records and signatures used for compliance purposes.

Part 11 requirements are not meant to replace or override other existing FDA regulations pertaining to signatures and records. They are simply a modern extension of the requirements for records and signatures that must be met by companies that use digital systems to manage compliance-related processes and activities.

Source documents

Source means the original source of the data and can be paper or electronic. Some examples of source documents are: Informed Consent Forms, Medical History, Subject Diary, Outpatient Medical Chart, Various Logs / Hospital Charts, Laboratory, MRI or any other reports, Hospital records, Clinical and office charts, Laboratory notes, Subjects' diaries or evaluation checklists, Pharmacy dispensing records, Recorded data from automated instruments, Microfiches, Photographic negatives, Microfilm or magnetic media, X-rays, Subject files, Records of pharmacy, laboratories and other departments involved in the clinical trial**.**

Software validation

Software Validation is a process of **evaluating software product**, so as to ensure that the software meets the pre-defined and specified business requirements as well as the end users/customers' demands and expectations.

3. There are nine provisions that the FDA expects compliance and will enforce. What are they?

- limiting system access to authorized individuals
- use of operational system checks
- use of authority checks
- use of device checks
- determination that persons who develop, maintain, or use electronic systems have the education, training, and experience to perform their assigned tasks
- establishment of and adherence to written policies that hold individuals accountable for actions initiated under their electronic signatures
- appropriate controls over systems documentation
- controls for open systems corresponding to controls for closed systems bulleted above (§ 11.30)
- requirements related to electronic signatures (e.g., §§ 11.50, 11.70, 11.100, 11.200, and 11.300)

4. **Does e-mail fall under Part 11 regulation? Justify you answer?**
   11.1 (b) states: This part applies to records in electronic form that are created, modified, maintained, archived, retrieved, or transmitted, under any records requirements set forth in agency regulations. This part also applies to electronic records submitted to the agency under requirements of the Federal Food, Drug, and Cosmetic Act and the Public Health Service Act, even if such records are not specifically identified in agency regulations. However, this part does not apply to paper records that are, or have been, transmitted by electronic means.

   However, If a file was created electronically and sent by email, then 21 CFR 11 would apply.

5. **Describe Part 11 requirements for ensuring the authenticity, integrity, and confidentiality of electronic records.**

   Closed systems:

   Persons who use closed systems to create, modify, maintain, or transmit electronic records shall employ procedures and controls designed to ensure the authenticity, integrity, and, when appropriate, the confidentiality of electronic records, and to ensure that the signer cannot readily repudiate the signed record as not genuine. Such procedures and controls shall include the following:

   (a) Validation of systems to ensure accuracy, reliability, consistent intended performance, and the ability to discern invalid or altered records.

   (b) The ability to generate accurate and complete copies of records in both human readable and electronic form suitable for inspection, review, and copying by the agency. Persons should contact the agency if there are any questions regarding the ability of the agency to perform such review and copying of the electronic records.

   (c) Protection of records to enable their accurate and ready retrieval throughout the records retention period.

   (d) Limiting system access to authorized individuals.

   (e) Use of secure, computer-generated, time-stamped audit trails to independently record the date and time of operator entries and actions that create, modify, or delete electronic records. Record changes shall not obscure previously recorded information. Such audit trail documentation shall be retained for a period at least as long as that required for the subject electronic records and shall be available for agency review and copying.

   (f) Use of operational system checks to enforce permitted sequencing of steps and events, as appropriate.

(g) Use of authority checks to ensure that only authorized individuals can use the system, electronically sign a record, access the operation or computer system input or output device, alter a record, or perform the operation at hand.

(h) Use of device (e.g., terminal) checks to determine, as appropriate, the validity of the source of data input or operational instruction.

(i) Determination that persons who develop, maintain, or use electronic record/electronic signature systems have the education, training, and experience to perform their assigned tasks.

(j) The establishment of, and adherence to, written policies that hold individuals accountable and responsible for actions initiated under their electronic signatures, in order to deter record and signature falsification.

(k) Use of appropriate controls over systems documentation including:

(1) Adequate controls over the distribution of, access to, and use of documentation for system operation and maintenance.

(2) Revision and change control procedures to maintain an audit trail that documents time-sequenced development and modification of systems documentation.

Open systems:

Persons who use open systems to create, modify, maintain, or transmit electronic records shall employ procedures and controls designed to ensure the authenticity, integrity, and, as appropriate, the confidentiality of electronic records from the point of their creation to the point of their receipt. Such procedures and controls shall include those identified in § 11.10, as appropriate, and additional measures such as document encryption and use of appropriate digital signature standards to ensure, as necessary under the circumstances, record authenticity, integrity, and confidentiality.

6. Describe Part 11 requirements for electronic signatures.

Signed electronic records shall contain information associated with the signing that clearly indicates all of the following:

(1) The printed name of the signer;

(2) The date and time when the signature was executed; and

(3) The meaning (such as review, approval, responsibility, or authorship) associated with the signature.

Each electronic signature shall be unique to one individual and shall not be reused by, or reassigned to, anyone else.

Before an organization establishes, assigns, certifies, or otherwise sanctions an individual's electronic signature, or any element of such electronic signature, the organization shall verify the identity of the individual.

Persons using electronic signatures shall, prior to or at the time of such use, certify to the agency that the electronic signatures in their system, used on or after August 20, 1997, are intended to be the legally binding equivalent of traditional handwritten signatures.

7. Describe Part 11 requirements for passwords and/or identification codes.

Persons who use electronic signatures based upon use of identification codes in combination with passwords shall employ controls to ensure their security and integrity. Such controls shall include:

(a) Maintaining the uniqueness of each combined identification code and password, such that no two individuals have the same combination of identification code and password.

(b) Ensuring that identification code and password issuances are periodically checked, recalled, or revised (e.g., to cover such events as password aging).

(c) Following loss management procedures to electronically deauthorize lost, stolen, missing, or otherwise potentially compromised tokens, cards, and other devices that bear or generate identification code or password information, and to issue temporary or permanent replacements using suitable, rigorous controls.

(d) Use of transaction safeguards to prevent unauthorized use of passwords and/or identification codes, and to detect and report in an immediate and urgent manner any attempts at their unauthorized use to the system security unit, and, as appropriate, to organizational management.

(e) Initial and periodic testing of devices, such as tokens or cards, that bear or generate identification code or password information to ensure that they function properly and have not been altered in an unauthorized manner.

Safety and Compliance Reporting Worksheet with answers

What are the following acronyms?

AE

Adverse Event

SAE

Serious Adverse Event

UADE

Unanticipated Adverse Device Effect

SUSAR

Suspected Unexpected Serious Adverse Reaction

Define Internal and External Adverse Events

External adverse event: From the perspective of one particular institution engaged in a multicenter clinical trial, *external adverse events* are those adverse events experienced by subjects enrolled by investigators at other institutions engaged in the clinical trial.

Internal adverse event: From the perspective of one particular institution engaged in a multicenter clinical trial, *internal adverse events* are those adverse events experienced by subjects enrolled by the investigator(s) at that institution. In the context of a single-center clinical trial, all adverse events would be considered *internal adverse events.*

OHRP

What are Unanticipated Problems Involving Risks to Subjects or Others per OHRP?

The phrase "unanticipated problems involving risks to subjects or others" is found but not defined in the HHS regulations at 45 CFR part 46. OHRP considers *unanticipated problems*, in general, to include any incident, experience, or outcome that meets **all** of the following criteria:

1. unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;

2. related or possibly related to participation in the research (in this guidance document, *possibly related* means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and

3. suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized

Per OHRP, when do you report an AE as an Unanticipated Problem?

The HHS regulations at 45 CFR part 46 do not define or use the term *adverse event*, nor is there a common definition of this term across government and non-government entities. In this guidance document, the term *adverse event* in general is used very broadly and includes any event meeting the following definition:

Any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research (modified from the definition of adverse events in the 1996 International Conference on Harmonization E-6 Guidelines for Good Clinical Practice).

The key question regarding a particular adverse event is whether it meets the three criteria and therefore represents an unanticipated problem. To determine whether an adverse event is an unanticipated problem, the following questions should be asked:

- Is the adverse event unexpected?

- Is the adverse event related or possibly related to participation in the research?

- Does the adverse event suggest that the research places subjects or others at a greater risk of harm than was previously known or recognized?

If the answer to **all three questions** is *yes,* then the adverse event is an unanticipated problem and must be reported to appropriate entities under the HHS regulations at 45 CFR 46.103(a) and 46.103(b)(5).

What are the criteria that must be met for an event to be considered serious?

1. results in death;

2. is life-threatening (places the subject at immediate risk of death from the event as it occurred);

3. results in inpatient hospitalization or prolongation of existing hospitalization;

4. results in a persistent or significant disability/incapacity;

5. results in a congenital anomaly/birth defect; or

6. based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition (examples of such events include allergic bronchospasm requiring intensive treatment in the emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse).

Compare "serious" and "severe" as described in the regulations.

There is often a lot of confusion about the difference between a severe adverse event and a serious adverse event. Severity is a grading. Adverse Events (AEs) can be classified as mild, moderate or severe. An AE can be severe without being a Serious Adverse Event.
A Serious Adverse Event (SAE) is an adverse event that meets one of the following criteria:

- results in death
- is life-threatening
- requires inpatient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect

A SAE can be graded as mild, moderate or severe. It is most common for SAEs to fall into the severe grading category but it is not always the case.
When classifying an AE, first work out if it meets the SAE criteria. Then work out the grading. If you follow this order, it should be much clearer.

What are the timeframes for reporting an event to OHRP?

The HHS regulations at 46.103(b)(5) require written procedures for ensuring *prompt* reporting of unanticipated problems to the IRB, appropriate institutional officials, any supporting department or agency head (or designee), and OHRP. The purpose of prompt reporting is to ensure that appropriate steps are taken in a timely manner to protect other subjects from avoidable harm.

The regulations do not define *prompt*. The appropriate time frame for satisfying the requirement for prompt reporting will vary depending on the specific nature of the unanticipated problem, the nature of the research associated with the problem, and the entity to which reports are to be submitted. For

example, an unanticipated problem that resulted in a subject's death or was potentially life-threatening generally should be reported to the IRB within a shorter time frame than other unanticipated problems that were not life-threatening. Therefore, OHRP recommends the following guidelines in order to satisfy the requirement for *prompt* reporting:

1. Unanticipated problems that are serious adverse events should be reported to the IRB within 1 week of the investigator becoming aware of the event.

2. Any other unanticipated problem should be reported to the IRB within 2 weeks of the investigator becoming aware of the problem.

3. All unanticipated problems should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and OHRP within one month of the IRB's receipt of the report of the problem from the investigator.

Evaluate and determine whether this example needs to be reported under 45 CRF 46.

1. **Example: An investigator is conducting a psychology study evaluating the factors that affect reaction times in response to auditory stimuli. In order to perform the reaction time measurement, subjects are placed in a small, windowless soundproof booth and asked to wear headphones. The IRB-approved protocol and informed consent document describes claustrophobic reactions as one of the risk of the research. The twentieth subject enrolled in the research experiences significant claustrophobia, resulting in the subject withdrawing from the research.**

This is not a reportable event because the claustrophobia is expected and was described in the informed consent document.

2. **Example: The fifth subject enrolled in a phase 2, open-label, uncontrolled clinical study evaluating the safety and efficacy of a new oral agent administered daily for treatment of severe psoriasis unresponsive to FDA-approved treatments, develops severe hepatic failure complicated by encephalopathy one month after starting the oral agent. The known risk profile of the new oral agent prior to this event included mild elevation of serum liver enzymes in 10% of subjects receiving the agent during previous clinical studies, but there was no other history of subjects developing clinically significant liver disease. The investigators identify no other etiology for the liver failure in this subject and attribute it to the study.**

This is a reportable event because the event is unexpected, potentially related to the oral agent and could place others at risk.

3. **An investigator conducting behavioral research collects individual identifiable sensitive information about illicit drug use and other illegal behaviors by surveying college students. The**

data are stored on a laptop computer without encryption, and the laptop computer is stolen from the investigator's car on the way home from work.

This is a reportable event because the event is unexpected, related to the study, and places subjects at risk.

FDA

Determine Investigator and sponsor responsibility for Managing AEs.

The investigator is responsible for:

Safety reports. An investigator must immediately report to the sponsor any serious adverse event, whether or not considered drug related, including those listed in the protocol or investigator brochure and must include an assessment of whether there is a reasonable possibility that the drug caused the event. Study endpoints that are serious adverse events (e.g., all-cause mortality) must be reported in accordance with the protocol unless there is evidence suggesting a causal relationship between the drug and the event (e.g., death from anaphylaxis). In that case, the investigator must immediately report the event to the sponsor. The investigator must record nonserious adverse events and report them to the sponsor according to the timetable for reporting specified in the protocol.

The Sponsor is responsible for:

The sponsor is responsible for safety surveillance and a plan should include

• Clearly defined roles and responsibilities of the entities and participating individuals that have responsibility for any or all of following: reviewing, analyzing, and making decisions regarding IND safety reporting

• A plan for regular review of SAEs and other important safety information, with unblinding as necessary for interpretation

• A process for aggregate safety reviews

Investigators are required to report:

Adverse events according to IRB and sponsor policies.

Sponsors are required to report:

The sponsor must submit each IND safety report in a narrative format or on FDA Form 3500A or in an electronic format that FDA can process, review, and archive. FDA will periodically issue guidance on how to provide the electronic submission (e.g., method of transmission, media, file formats, preparation and organization of files).

Unexpected fatal or life-threatening suspected adverse reaction reports. The sponsor must also notify FDA of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible but in no case later than 7 calendar days after the sponsor's initial receipt of the information.

The time frame for submitting an IND safety report to FDA and all participating investigators is 1195 as soon as possible but no later than 15 calendar days after the sponsor determines that the 1196 suspected adverse reaction or other information qualifies for reporting (§ 312.32(c)(1)). T

Unexpected fatal or life-threatening suspected adverse reactions represent especially important 1227 safety information and must be reported more rapidly to FDA (§ 312.32(c)(2)). The requirement 1228 for reporting any unexpected fatal or life-threatening suspected adverse reaction to FDA is as 1229 soon as possible but no later than 7 calendar days after the sponsor's initial receipt of the 26 For details on obtaining a secure email account with FDA, visit https://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/d efault.htm. Contains Nonbinding Recommendations Draft — Not for Implementation 30 1230 information (§ 312.32(c)(2)). If the safety report submitted within 7 calendar days is complete, 1231 an additional submission within 15 calendar days from day zero is not required.

If the IND is not in eCTD 1185 format, other means of rapid communication (e.g., telephone, fax, email) may be used.

IDE Safety Reporting:

Investigator Reporting Responsibility:

The investigator must submit to the sponsor and the reviewing IRB a report of any unanticipated adverse device effect as soon as possible but no later than 10 working days after the investigator first learns of the effect.

Sponsor Reporting Responsibility:

The sponsor must report the results of an evaluation of an unanticipated adverse device effect to FDA and all reviewing IRBs and investigators within 10 working days after the sponsor first receives notice of the adverse effect.

MedWatch:

What is MedWatch?

MedWatch, the FDA's medical product safety reporting program for health professionals, patients and consumers.

MedWatch receives reports from the public and when appropriate, publishes safety alerts for FDA-regulated products such as:

- **Prescription and over-the-counter medicines**
- **Biologics** such as blood components, blood/plasma derivatives and gene therapies.
- **Medical devices** such as hearing aids breast pumps, and pacemakers.
- **Combination products** such as pre-filled drug syringe, metered-dose inhalers and nasal spray.
- **Special nutritional products** such as dietary supplements, medical foods and infant formulas.
- **Cosmetics** such as moisturizers, makeup, shampoos, hair dyes and tattoos.
- **Food** such as beverages and ingredients added to foods.

What form is used for MedWatch reporting?

Voluntary?

Reporting can be done through our online reporting portal or by downloading, completing and then submitting FDA Form 3500 (health professional) or 3500B (consumer/patient) to MedWatch:The FDA Safety Information and Adverse Event Reporting Program,

Mandatory?

FDA Form 3500 a is used for mandatory reporting by IND reporters, manufacturers, distributors, importers, user facilities personnel.

Safety Reporting comparison Between FDA and ICH

Definition	FDA	ICH
Adverse Event / Adverse Experience	**Adverse event or Adverse Experience** means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.	**Adverse Event (or Adverse Experience)** Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.
Suspected Adverse Reaction	**Suspected adverse reaction** means any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, 'reasonable possibility' means there is evidence to suggest a causal relationship between the drug and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than an adverse reaction.	Many terms and scales are in use to describe the degree of causality (attributability) between a medicinal product and an event, such as certainly, definitely, probably, possibly or likely related or not related. Phrases such as "plausible relationship," "suspected causality," or "causal relationship cannot be ruled out" are also invoked to describe cause and effect. However, there is currently no standard international nomenclature. The expression "reasonable causal relationship" is meant to convey in general that there are facts (evidence) or arguments to suggest a causal relationship.
Unexpected Adverse Event / Unexpected Adverse Drug Reaction (ADR)	An **adverse event or suspected adverse reaction is considered "unexpected"** if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information	**An unexpected adverse drug reaction**, the nature or severity of which is not consistent with the applicable product information (e.g., Investigator's Brochure for an unapproved investigational medicinal product).

	described in the general investigational plan or elsewhere in the current application, as amended. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the investigator brochure referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the investigator brochure listed only cerebral vascular accidents. "Unexpected," as used in this definition, also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation	And **Unexpected Adverse Reaction** would be an event more specific or more severe than described in the Investigator's Brochure would be considered "unexpected". Those described in the IB would be **Suspected.**
Serious Adverse Event / Serious suspected Adverse Event / Serious Adverse Event or Serious Adverse Drug Reaction	**An adverse event or suspected adverse reaction is considered "serious"** if, in the view of either the investigator or sponsor, it results in any of the following outcomes: Death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical	A **Serious Adverse Event or Serious Adverse Drug Reaction** is any untoward medical occurrence that at any dose: * results in death, * is life-threatening, NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe. * requires inpatient hospitalisation or prolongation of existing hospitalisation, * results in persistent or significant disability/incapacity, or * is a congenital anomaly/birth defect.

	judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse. Note that the definition of "serious" differs slightly from the ICH E2A guidance7 (i.e., FDA definition uses "and" rather than "or" in the sentence "Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition"). We will accept application of either the FDA definition (i.e., "and") or the ICH E2A guidance criteria (i.e., "or") in determining the seriousness of an event.	

Serious Unexpected Serious Adverse Reaction (**SUSAR)**	Adverse Events that meet all three criteria are reported to FDA (SUSAR): – Serious (S) – Unexpected (U) – Suspected Adverse Reactions (SAR) • Fatal or life-threatening SUSAR should be reported to FDA no later than 7 days • Others SUSAR should be reported to FDA no later than 15 days	

ICH Definitions: Compare “serious” and “severe”:

To ensure no confusion or misunderstanding of the difference between the terms "serious" and "severe," which are not synonymous, the following note of clarification is provided: The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as "serious," which is based on patient/event outcome or action criteria usually associated with events that pose a threat to a patient's life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations. After reviewing the various regulatory and other definitions in use or under discussion elsewhere, the following definition is believed to encompass the spirit and meaning of them all: A serious adverse event (experience) or reaction is any untoward medical occurrence that at any dose: * results in death, * is life-threatening, NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe. * requires inpatient hospitalisation or prolongation of existing hospitalisation, * results in persistent or significant disability/incapacity, or * is a congenital anomaly/birth defect.

Forms Worksheet
MedWatch Reporting Product Surveillance Program
Drugs, Devices and Biologic Safety Reports for Marketed Products

MedWatch Reporting Product Surveillance Program	What	Who	When	CFR
Form 3500 Voluntary reporting by health professionals, consumers, and patients	Report a serious adverse event, product quality problem, product use error, or therapeutic inequivalence/failure that you suspect is associated with the use of an FDA-regulated drug, biologic, medical device, dietary supplement or cosmetic You can also report suspected counterfeit medical products to FDA through MedWatch	FDA	Problem is identified	21 CFR 314.80 21 CFR 803
Form 3500B Voluntary reporting by non-health professionals and consumers	Same as for 3500	FDA	Problem is identified	21 CFR 314.80 21 CFR 803

Forms Worksheet
MedWatch Reporting Product Surveillance Program
Drugs, Devices and Biologic Safety Reports for Marketed Products

Form 3500A Mandatory Reporting for use by IND/IDE reporters, manufacturers, distributors, importer, user facilities personnel	Can be for Pre – or Post marketing reports IND-Mandatory serious adverse event [SAE} reports	FDA	See Chart Below for mandatory device reporting	21 CFR 314.80 21 CFR 803

Forms Worksheet
MedWatch Reporting Product Surveillance Program
Drugs, Devices and Biologic Safety Reports for Marketed Products

Summary of Mandatory Reporting Requirements for Manufacturers and Importers

REPORTER	WHAT TO REPORT	REPORT FORM #	TO WHOM	WHEN
Manufacturers	30 day reports of deaths, serious injuries and malfunctions	Form FDA 3500A *	FDA	Within 30 calendar days of becoming aware of an event
	5-day reports for an event designated by FDA or an event that requires remedial action to prevent an unreasonable risk of substantial harm to the public health	Form FDA 3500A *	FDA	Within 5 work days of becoming aware of an event
Importers	Reports of deaths and serious injuries	Form FDA 3500A *	FDA and the manufacturer	Within 30 calendar days of becoming aware of an event
	Reports of malfunctions	Form FDA 3500A *	Manufacturer	Within 30 calendar days of becoming aware of an event

Financial Disclosure 21 CFR 54 Worksheet

With answers

1. **What is the purpose in the FDA requiring financial disclosure by clinical investigators?**

   FDA may consider clinical studies inadequate and the data inadequate if, among other things, appropriate steps have not been taken in the design, conduct, reporting, and analysis of the studies to minimize bias. One potential source of bias in clinical studies is a financial interest of the clinical investigator in the outcome of the study because of the way payment is arranged (e.g., a royalty) or because the investigator has a proprietary interest in the product (e.g., a patent) or because the investigator has an equity interest in the sponsor of the covered study.

2. **Define:**

   Significant equity interest

   Significant equity interest in the sponsor of a covered study means any ownership interest, stock options, or other financial interest whose value cannot be readily determined through reference to public prices (generally, interests in a nonpublicly traded corporation), or any equity interest in a publicly traded corporation that **exceeds $50,000 during the time the clinical investigator is carrying out the study and for 1 year following completion of the study.**

   Proprietary interest

   Proprietary interest in the tested product means property or other financial interest in the product including, but not limited to, a patent, trademark, copyright or licensing agreement.

   Clinical Investigator

   Clinical investigator means only a listed or identified investigator or subinvestigator who is directly involved in the treatment or evaluation of research subjects. The term also includes the spouse and each dependent child of the investigator.

   Covered clinical study

   Covered clinical study means any study of a drug or device in humans submitted in a marketing application or reclassification petition subject to this part that the applicant or FDA relies on to establish that the product is effective (including studies that show equivalence to an effective

product) or any study in which a single investigator makes a significant contribution to the demonstration of safety. This would, in general, not include phase l tolerance studies or pharmacokinetic studies, most clinical pharmacology studies (unless they are critical to an efficacy determination), large open safety studies conducted at multiple sites, treatment protocols, and parallel track protocols (an administrative system that parallels controlled clinical trials and expands the availability of drugs for treating AIDS/HIV). An applicant may consult with FDA as to which clinical studies constitute "covered clinical studies" for purposes of complying with financial disclosure requirements.

Significant payment of other sorts

Significant payments of other sorts means payments made by the sponsor of a covered study to the investigator or the institution to support activities of the investigator that have a **monetary value of more than $25,000,** exclusive of the costs of conducting the clinical study or other clinical studies, (e.g., a grant to fund ongoing research, compensation in the form of equipment or retainers for ongoing consultation or honoraria) during the time the clinical investigator is carrying out the study and for 1 year following the completion of the study.

Applicant

Applicant means the party who submits a marketing application to FDA for approval of a drug, device, or biologic product. The applicant is responsible for submitting the appropriate certification and disclosure statements required in this part.

Sponsor

Sponsor of the covered clinical study means the party supporting a particular study at the time it was carried out.

3. Explain the difference in "certification" and "disclosure". What FDA forms are required?

Certification: The applicant covered by this section shall submit for all clinical investigators to whom the certification applies, a completed Form FDA 3454 attesting to the absence of financial interests and arrangements.

Disclosure Statement: For any clinical investigator for whom the applicant does not submit the certification, the applicant shall submit a completed Form FDA 3455 disclosing completely and accurately the following:

- Any financial arrangement entered into between the sponsor of the covered study and the clinical investigator involved in the conduct of a covered clinical trial, whereby the value of the compensation to the clinical investigator for conducting the study could be influenced by the outcome of the study;
- Any significant payments of other sorts from the sponsor of the covered study, such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria;

- Any proprietary interest in the tested product held by any clinical investigator involved in a study;
- Any significant equity interest in the sponsor of the covered study held by any clinical investigator involved in any clinical study; and
- Any steps taken to minimize the potential for bias resulting from any of the disclosed arrangements, interests, or payments.

4. To whom does the investigator submit the required financial information?

The clinical investigator shall provide to the sponsor of the covered study sufficient accurate financial information to allow the sponsor to submit complete and accurate certification or disclosure statements as required.

5. When is the investigator required to provide updated information?

The investigator shall promptly update this information if any relevant changes occur in the course of the investigation or for 1 year following completion of the study.

6. What are the recordkeeping and retention requirements?

For any application submitted for a covered product, an applicant shall retain records for 2 years after the date of approval of the application.

Informed Consent Study Guide

1. **The general requirements for informed consent and documentation of informed consent are found in what federal regulations?**

   45 CFR 46.116 OHRP
   21 CFR 50.20 FDA

2. **What are the conditions under which an investigator may seek legally effective informed consent?**

   45 CFR 46.116 OHRP

   (1) Before involving a human subject in research covered by this policy, an investigator shall obtain the legally effective informed consent of the subject or the subject's legally authorized representative.

   (2) An investigator shall seek informed consent only under circumstances that provide the prospective subject or the legally authorized representative sufficient opportunity to discuss and consider whether or not to participate and that minimize the possibility of coercion or undue influence.

   (3) The information that is given to the subject or the legally authorized representative shall be in language understandable to the subject or the legally authorized representative.

   (4) The prospective subject or the legally authorized representative must be provided with the information that a reasonable person would want to have in order to make an informed decision about whether to participate, and an opportunity to discuss that information.

   (5) Except for broad consent:

   (i) Informed consent must begin with a concise and focused presentation of the key information that is most likely to assist a prospective subject or legally authorized representative in understanding the reasons why one might or might not want to participate in the research. This part of the informed consent must be organized and presented in a way that facilitates comprehension.

   (ii) Informed consent as a whole must present information in sufficient detail relating to the research, and must be organized and presented in a way that does not merely provide lists of isolated facts, but rather facilitates the prospective subject's or legally authorized representative's understanding of the reasons why one might or might not want to participate.

(6) No informed consent may include any exculpatory language through which the subject or the legally authorized representative is made to waive or appear to waive any of the subject's legal rights, or releases or appears to release the investigator, the sponsor, the institution, or its agents from liability for negligence.

21 CFR 50.20 FDA

An investigator shall seek such consent only under circumstances that provide the prospective subject or the representative sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence. The information that is given to the subject or the representative shall be in language understandable to the subject or the representative. No informed consent, whether oral or written, may include any exculpatory language through which the subject or the representative is made to waive or appear to waive any of the subject's legal rights, or releases or appears to release the investigator, the sponsor, the institution, or its agents from liability for negligence.

3. List the basic elements of informed consent. What are the additional elements that must be included if appropriate?

OHRP

Basic

(1) A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures that are experimental;

(2) A description of any reasonably foreseeable risks or discomforts to the subject;

(3) A description of any benefits to the subject or to others that may reasonably be expected from the research;

(4) A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject;

(5) A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained;

(6) For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained;

(7) An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject;

(8) A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled; and

(9) One of the following statements about any research that involves the collection of identifiable private information or identifiable biospecimens:

(i) A statement that identifiers might be removed from the identifiable private information or identifiable biospecimens and that, after such removal, the information or biospecimens could be used for future research studies or distributed to another investigator for future research studies without additional informed consent from the subject or the legally authorized representative, if this might be a possibility; or
(ii) A statement that the subject's information or biospecimens collected as part of the research, even if identifiers are removed, will not be used or distributed for future research studies.

Additional

One or more of the following elements of information, when appropriate, shall also be provided to each subject or the legally authorized representative:

(1) A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant) that are currently unforeseeable;

(2) Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's or the legally authorized representative's consent;

(3) Any additional costs to the subject that may result from participation in the research;

(4) The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject;

(5) A statement that significant new findings developed during the course of the research that may relate to the subject's willingness to continue participation will be provided to the subject;

(6) The approximate number of subjects involved in the study;

(7) A statement that the subject's biospecimens (even if identifiers are removed) may be used for commercial profit and whether the subject will or will not share in this commercial profit;

(8) A statement regarding whether clinically relevant research results, including individual research results, will be disclosed to subjects, and if so, under what conditions; and

(9) For research involving biospecimens, whether the research will (if known) or might include whole genome sequencing (i.e., sequencing of a human germline or somatic specimen with the intent to generate the genome or exome sequence of that specimen).

Additional elements regarding broad consent for the storage, maintenance and secondary research use of identifiable private information or identifiable biospecimens.

- A general description of the types of research that may be conducted with the identifiable private information or identifiable biospecimens. This description must include sufficient information such that a reasonable person would expect that the broad consent would permit the types of research conducted;

- A description of the identifiable private information or identifiable biospecimens that might be used in research, whether sharing of identifiable private information or identifiable biospecimens might occur, and the types of institutions or researchers that might conduct research with the identifiable private information or identifiable biospecimens;

- A description of the period of time that the identifiable private information or identifiable biospecimens may be stored and maintained (which period of time could be indefinite), and a description of the period of time that the identifiable private information or identifiable biospecimens may be used for research purposes (which period of time could be indefinite);

- Unless the subject or legally authorized representative will be provided details about specific research studies, a statement that they will not be informed of the details of any specific research studies that might be conducted using the subject's identifiable private information or identifiable biospecimens, including the purposes of the research, and that they might have chosen not to consent to some of those specific research studies;

- Unless it is known that clinically relevant research results, including individual research results, will be disclosed to the subject in all circumstances, a statement that such results may not be disclosed to the subject; and

- An explanation of whom to contact for answers to questions about the subject's rights and about storage and use of the subject's identifiable private information or identifiable biospecimens, and whom to contact in the event of a research-related harm.

FDA

(1) A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental.

(2) A description of any reasonably foreseeable risks or discomforts to the subject.

(3) A description of any benefits to the subject or to others which may reasonably be expected from the research.

(4) A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject.

(5) A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained and that notes the possibility that the Food and Drug Administration may inspect the records.

(6) For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained.

(7) An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject.

(8) A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and that the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

Additional elements of informed consent. When appropriate, one or more of the following elements of information shall also be provided to each subject:

(1) A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant) which are currently unforeseeable.

(2) Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent.

(3) Any additional costs to the subject that may result from participation in the research.

(4) The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject.

(5) A statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation will be provided to the subject.

(6) The approximate number of subjects involved in the study.

4. Under 45 CFR 46, when may an IRB approve a consent procedure which does not include all the elements of informed consent or waive the requirement of informed consent?

Requirements for waiver and alteration. In order for an IRB to waive or alter consent as described in this subsection, the IRB must find and document that:

- The research involves no more than minimal risk to the subjects;
- The research could not practicably be carried out without the requested waiver or alteration;
- If the research involves using identifiable private information or identifiable biospecimens, the research could not practicably be carried out without using such information or biospecimens in an identifiable format;
- The waiver or alteration will not adversely affect the rights and welfare of the subjects; and

- Whenever appropriate, the subjects or legally authorized representatives will be provided with additional pertinent information after participation.

What about 21 CFR 50?

Exception from general requirements. Emergency use of a test article

(a) The obtaining of informed consent shall be deemed feasible unless, before use of the test article both the investigator and a physician who is not otherwise participating in the clinical investigation certify in writing all of the following:

(b) The human subject is confronted by a life-threatening situation necessitating the use of the test article.

(c) Informed consent cannot be obtained from the subject because of an inability to communicate with, or obtain legally effective consent from, the subject.

(d) Time is not sufficient to obtain consent from the subject's legal representative.

(e) There is available no alternative method of approved or generally recognized therapy that provides an equal or greater likelihood of saving the life of the subject.

(f) If immediate use of the test article is, in the investigator's opinion, required to preserve the life of the subject, and time is not sufficient to obtain the independent determination required in paragraph (a) of this section in advance of using the test article, the determinations of the clinical investigator shall be made and, within 5 working days after the use of the article, be reviewed and evaluated in writing by a physician who is not participating in the clinical investigation.

(g) The documentation required in paragraph (a) or (b) of this section shall be submitted to the IRB within 5 working days after the use of the test article.

(h)(1) Under 10 U.S.C. 1107(f) the President may waive the prior consent requirement for the administration of an investigational new drug to a member of the armed forces in connection with the member's participation in a particular military operation.

5. **For administration of an investigational product to a member of the armed forced involved in a particular military operation, only the President may waive the prior consent requirement. What are the three criteria that must be documented in order to waive the informed consent requirement in addition to the relevant FDA regulations?**

21 CFR 23 FDA
A) The context in which the investigational drug will be administered, e.g., the setting or whether it will be self-administered or it will be administered by a health professional;

(B) The nature of the disease or condition for which the preventive or therapeutic treatment is intended; and
(C) To the extent there are existing data or information available, information on conditions that could alter the effects of the investigational drug.

6. **For planned emergency research, who must review the regulatory criteria for exceptions form the informed consent requirement, document findings and provide to the IRB in order for the board to approve the exception for that study?**

   The IRB responsible for the review, approval, and continuing review of the clinical investigation described in this section may approve that investigation without requiring that informed consent of all research subjects be obtained if the IRB (with the concurrence of a licensed physician who is a member of or consultant to the IRB and who is not otherwise participating in the clinical investigation)

7. **In documenting the informed consent, explain the FDA requirement when the elements** of informed consent have been presented orally.

   FDA

   A short form written consent document stating that the elements of informed consent required by § 50.25 have been presented orally to the subject or the subject's legally authorized representative. When this method is used, there shall be a witness to the oral presentation. Also, the IRB shall approve a written summary of what is to be said to the subject or the representative. Only the short form itself is to be signed by the subject or the representative. However, the witness shall sign both the short form and a copy of the summary, and the person actually obtaining the consent shall sign a copy of the summary. A copy of the summary shall be given to the subject or the representative in addition to a copy of the short form.

   OHRP

   A short form written informed consent form stating that the elements of informed consent required by §46.116 have been presented orally to the subject or the subject's legally authorized representative, and that the key information required by §46.116(a)(5)(i) was presented first to the subject, before other information, if any, was provided. The IRB shall approve a written summary of what is to be said to the subject or the legally authorized representative. When this method is used, there shall be a witness to the oral presentation. Only the short form itself is to be signed by the subject or the subject's legally authorized representative. However, the witness shall sign both the short form and a copy of the summary, and the person actually obtaining consent shall sign a copy of the summary. A copy of the summary shall be given to the subject or the subject's legally authorized representative, in addition to a copy of the short form.

Both OHRP and FDA

- Short form: Signed by Subject or Representative and Witness
- Consent summary: Signed by Witness
- Copy of summary: Signed by Witness and Person obtaining consent
- Copy of the short form and the summary to be given to subject or the representative

8. When a clinical investigation involves children, OHRP and the FDA have implemented "Special Protections" for this population. Describe the four categories of clinical investigation outlined in the federal regulations for pediatric research.

OHRP

45 CFR 46.404 Research not involving greater than minimal risk to the children.

45 CFR 46.405- Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual child subjects involved in the research.

(a) The risk represents a minor increase over minimal risk;
(b) The intervention or procedure presents experiences to subjects that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations;
(c) The intervention or procedure is likely to yield generalizable knowledge about the subjects' disorder or condition that is of vital importance for the understanding or amelioration of the subjects' disorder or condition; and
(d) Adequate provisions are made for soliciting the assent of the children and permission of their parents or guardians as set forth in § 50.55.

45 CFR 46.406- Research involving greater than minimal risk and no prospect of direct benefit to the individual child subjects involved in the research, but likely to yield generalizable knowledge about the subject's disorder or condition.

45 CFR 46.407- Research that the IRB believes does not meet the conditions of 45 CFR 46.404, 46.405, or 46.406, but finds that the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children.

FDA

21 CFR 50.51 Clinical investigations not involving greater than minimal risk.

Any clinical investigation within the scope described in §§ 50.1 and 56.101 of this chapter in which no greater than minimal risk to children is presented may involve children as subjects only if the IRB finds that:

(a) No greater than minimal risk to children is presented; and

(b) Adequate provisions are made for soliciting the assent of the children and the permission of their parents or guardians as set forth in § 50.55.

21 CFR 50.52 Clinical investigations involving greater than minimal risk but presenting the prospect of direct benefit to individual subjects.

Any clinical investigation in which more than minimal risk to children is presented by an intervention or procedure that holds out the prospect of direct benefit for the individual subject, or by a monitoring procedure that is likely to contribute to the subject's well-being, may involve children as subjects only if the IRB finds that:

(a) The risk is justified by the anticipated benefit to the subjects;

(b) The relation of the anticipated benefit to the risk is at least as favorable to the subjects as that presented by available alternative approaches; and

(c) Adequate provisions are made for soliciting the assent of the children and permission of their parents or guardians as set forth in § 50.55.

21 CFR 50.53 Clinical investigations involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subjects' disorder or condition.

Any clinical investigation within the scope described in §§ 50.1 and 56.101 of this chapter in which more than minimal risk to children is presented by an intervention or procedure that does not hold out the prospect of direct benefit for the individual subject, or by a monitoring procedure that is not likely to contribute to the well-being of the subject, may involve children as subjects only if the IRB finds that:

(a) The risk represents a minor increase over minimal risk;

(b) The intervention or procedure presents experiences to subjects that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations;

(c) The intervention or procedure is likely to yield generalizable knowledge about the subjects' disorder or condition that is of vital importance for the understanding or amelioration of the subjects' disorder or condition; and

(d) Adequate provisions are made for soliciting the assent of the children and permission of their parents or guardians as set forth in § 50.55.

21 CFR 50.54 Clinical investigations not otherwise approvable that present an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children.

If an IRB does not believe that a clinical investigation within the scope described in §§ 50.1 and 56.101 of this chapter and involving children as subjects meets the requirements of § 50.51, § 50.52, or § 50.53, the clinical investigation may proceed only if:

(a) The IRB finds that the clinical investigation presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children; and

(b) The Commissioner of Food and Drugs, after consultation with a panel of experts in pertinent disciplines (for example: science, medicine, education, ethics, law) and following opportunity for public review and comment, determines either:

(1) That the clinical investigation in fact satisfies the conditions of § 50.51, § 50.52, or § 50.53, as applicable, or

(2) That the following conditions are met:

(i) The clinical investigation presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children;

(ii) The clinical investigation will be conducted in accordance with sound ethical principles; and

(iii) Adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians as set forth in § 50.55.

9. What are the basic concepts that provide "special protections" for this population?

OHRP

When reviewing research with children as subjects, in addition to ensuring adherence to the general regulatory requirements of 45 CFR part 46, Subpart A, the IRB also must consider the potential benefits, risks, and discomforts of the research to children and assess the justification for their inclusion in the research. In assessing the risks and potential benefits, the IRB should consider the circumstances of the children to be enrolled in the study-for example their health status, age, and ability to understand what is involved in the research-as well as potential benefits to subjects, other children with the same disease or condition, or society as a whole.

10. When can a clinical investigation proceed that is not approvable by the criteria governing research involving children?

FDA has charged the Commissioner with determining whether such a clinical investigation can proceed. The Commissioner is to consult with a panel of experts. FDA anticipates that this panel may include an advisory committee supplemented, if needed, by appropriate experts. This provision also provides for public review and comment on the Commissioner's pending decision.

11. Who determines whether the child (or children to be involved in a research study is capable of giving consent to participate?

OHRP

45 CFR 46. 408

the IRB shall determine that adequate provisions are made for soliciting the assent of the children, when in the judgment of the IRB the children are capable of providing assent. In determining whether children are capable of assenting, the IRB shall take into account the ages, maturity, and psychological state of the children involved. This judgment may be made for all children to be involved in research under a particular protocol, or for each child, as the IRB deems appropriate. If the IRB determines that the capability of some or all of the children is so limited that they cannot reasonably be consulted or that the intervention or procedure involved in the research holds out a prospect of direct benefit that is important to the health or well-being of the children and is available only in the context of the research, the assent of the children is not a necessary condition for proceeding with the research. Even where the IRB determines that the subjects are capable of assenting, the IRB may still waive the assent requirement under circumstances in which consent may be waived in accord with §46.116 of Subpart A.

FDA

Section 50.55(b) states that in making this determination, an IRB must take into account the ages, maturity, and psychological state of the children involved. An IRB may make this determination for each individual child to be involved in the clinical investigation or for all children under a particular protocol.

12. When a child (or children) is capable of assenting, can the IRB waive the assent requirement?

OHRP

Even where the IRB determines that the subjects are capable of assenting, the IRB may still waive the assent requirement under circumstances in which consent may be waived in accord with §46.116 of Subpart A.

1. (i) The research involves no more than minimal risk to the subjects;
   (ii) The research could not practicably be carried out without the requested waiver or alteration;
   (iii) If the research involves using identifiable private information or identifiable biospecimens, the research could not practicably be carried out without using such information or biospecimens in an identifiable format;
   (iv) The waiver or alteration will not adversely affect the rights and welfare of the subjects; and
   (v) Whenever appropriate, the subjects or legally authorized representatives will be provided with additional pertinent information after participation.

FDA 21 CFR 50

FDA has adopted in Sec. 50.55 the provisions of 45 CFR 46.408 of HHS subpart D, describing when assent may be waived. Even in cases where an IRB determines waiver of assent is necessary, FDA regulations require the permission of parents or guardians to the extent informed consent is required in part 50. Documentation of permission must be consistent with the documentation required for informed consent at Sec. 50.27. Section 50.55(a) allows an IRB to make a judgment as to whether children are capable of providing assent. Section 50.55(b) states that in making this determination, an IRB must take into account the ages, maturity, and psychological state of the children involved. An IRB may make this determination for each individual child to be involved in the clinical investigation or for all children under a particular protocol. FDA has made format changes in adopting 45 CFR 46.408 to clarify the conditions for waiving the assent requirement. Section 50.55(c) states that assent is not a necessary condition for proceeding with a clinical investigation if the IRB determines:

(1) That the capability of some or all of the children is so limited that they cannot reasonably be consulted, or

(2) that the intervention or procedure involved in the clinical investigation presents a prospect of direct benefit that is important to the health or well-being of the children and is available only in the context of the clinical investigation.

Section 50.55(d) states that even where an IRB determines the children are capable of assenting, the IRB may still waive the assent requirement if:

(1) The clinical investigation involves no more than minimal risk to the subjects,

(2) the waiver will not adversely affect the rights and welfare of the subjects,

(3) the clinical investigation could not practicably be carried out without the waiver, and

(4) when appropriate, the children will be provided with additional pertinent information after participation. Section 50.55(g) provides that when an IRB determines that assent is required, the IRB must determine whether and how assent must be documented. FDA solicits comments on how to ensure that age-appropriate explanations are provided to children.

When the IRB determines that assent is required, it must also determine whether and how assent must be documented.

13. In studies where there is greater than minimal risk and no prospect of direct benefit to an individual child subject, who must the investigator identify to give permission?

Where parental permission is to be obtained, the IRB may find that the permission of one parent is sufficient for clinical investigations to be conducted under § 50.51 or § 50.52.

Where clinical investigations are covered by § 50.53 or § 50.54 and permission is to be obtained from parents, both parents must give their permission unless one parent is deceased, unknown, incompetent,

or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child.

14. How is assent to be obtained?

OHRP

"Assent" means a child's affirmative agreement to participate in research. Mere failure to object should not, absent affirmative agreement, be construed as assent. (45 CFR 46.402(b)).

This means the child must actively show his or her willingness to participate in the research, rather than just complying with directions to participate and not resisting in any way. When judging whether children are capable of assent, the Institutional Review Board (IRB) is charged with taking into account the ages, maturity, and psychological state of the children involved. The IRB has the discretion to judge children's capacity to assent for all of the children to be involved in a proposed research activity, or on an individual basis.

FDA

FDA's regulation, like the HHS regulation, defines assent as a child's affirmative agreement to participate in research. FDA's definition also states that mere failure to object to participation in clinical investigations should not, absent affirmative agreement, be considered assent.

15. When can a child who is a ward of the State or other agency or institution be included in a clinical trial?

§46.409 Wards.

(a) Children who are wards of the state or any other agency, institution, or entity can be included in research approved under §46.406 (more than minimal risk with no prospect of direct benefit) or §46.407 (Research that the IRB believes does not meet the conditions of 45 CFR 46.404, 46.405, or 46.406, but finds that the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children) only if such research is:

(1) Related to their status as wards; or

(2) Conducted in schools, camps, hospitals, institutions, or similar settings in which the majority of children involved as subjects are not wards.

(b) If the research is approved under paragraph (a) of this section, the IRB shall require appointment of an advocate for each child who is a ward, in addition to any other individual acting on behalf of the child as guardian or in loco parentis. One individual may serve as advocate for more than one child. The advocate shall be an individual who has the background and experience to act in, and agrees to act in,

the best interests of the child for the duration of the child's participation in the research and who is not associated in any way (except in the role as advocate or member of the IRB) with the research, the investigator(s), or the guardian organization.

The HHS regulations do not require that the protections at 45 CFR 46.409 be applied to §46.404 and §46.405 level research. However the regulations at 45 CFR 46.111 (b) permits the IRB to consider any "additional safeguards" for vulnerable populations (including wards) they deem appropriate. Essentially, this recommendation suggests to IRBs that they consider applying the protections described under 45 CFR 46.409 to §46.404 and §46.405 level research if they feel it is appropriate.

16. Can an individual serve as an advocate for more than once child?

Yes

17. Define Prisoner

OHRP

Prisoner means any individual involuntarily confined or detained in a penal institution. The term is intended to encompass individuals sentenced to such an institution under a criminal or civil statute, individuals detained in other facilities by virtue of statutes or commitment procedures which provide alternatives to criminal prosecution or incarceration in a penal institution, and individuals detained pending arraignment, trial, or sentencing.

18. When prisoners are involved in research, what provisions must the reviewing IRB meet?

§46.305 Additional duties of the Institutional Review Boards where prisoners are involved.

(1) The research under review represents one of the categories of research permissible under §46.306(a)(2);

(2) Any possible advantages accruing to the prisoner through his or her participation in the research, when compared to the general living conditions, medical care, quality of food, amenities and opportunity for earnings in the prison, are not of such a magnitude that his or her ability to weigh the risks of the research against the value of such advantages in the limited choice environment of the prison is impaired;

(3) The risks involved in the research are commensurate with risks that would be accepted by nonprisoner volunteers;

(4) Procedures for the selection of subjects within the prison are fair to all prisoners and immune from arbitrary intervention by prison authorities or prisoners. Unless the principal investigator provides to the Board justification in writing for following some other procedures, control subjects must be selected

randomly from the group of available prisoners who meet the characteristics needed for that particular research project;

(5) The information is presented in language which is understandable to the subject population;

(6) Adequate assurance exists that parole boards will not take into account a prisoner's participation in the research in making decisions regarding parole, and each prisoner is clearly informed in advance that participation in the research will have no effect on his or her parole; and

(7) Where the Board finds there may be a need for follow-up examination or care of participants after the end of their participation, adequate provision has been made for such examination or care, taking into account the varying lengths of individual prisoners' sentences, and for informing participants of this fact.

§46.306(a)(2);

(1) The institution responsible for the conduct of the research has certified to the Secretary that the Institutional Review Board has approved the research under §46.305 of this subpart; an

(2) In the judgment of the Secretary the proposed research involves solely the following:

(i) Study of the possible causes, effects, and processes of incarceration, and of criminal behavior, provided that the study presents no more than minimal risk and no more than inconvenience to the subjects;
(ii) Study of prisons as institutional structures or of prisoners asincarcerated persons, provided that the study presents no more than minimal risk and no more than inconvenience to the subjects;

(iii) Research on conditions particularly affecting prisoners as a class (for example, vaccine trials and other research on hepatitis which is much more prevalent in prisons than elsewhere; and research on social and psychological problems such as alcoholism, drug addiction, and sexual assaults) provided that the study may proceed only after the Secretary has consulted with appropriate experts including experts in penology, medicine, and ethics, and published notice, in the FEDERAL REGISTER, of his intent to approve such research; or

(iv) Research on practices, both innovative and accepted, which have the intent and reasonable probability of improving the health or well-being of the subject. In cases in which those studies require the assignment of prisoners in a manner consistent with protocols approved by the IRB to control groups which may not benefit from the research, the study may proceed only after the Secretary has consulted with appropriate experts, including experts in penology, medicine, and ethics, and published notice, in the FEDERAL REGISTER, of the intent to approve such research.

19. What procedure must the investigator take for selecting a control population for research involving prisoners?

Control subjects must be selected randomly from the group of available prisoners who meet the characteristics needed for that particular research project.

20. What are the membership requirements of the IRB when prisoner research is being reviewed.

(a) A majority of the Board (exclusive of prisoner members) shall have no association with the prison(s) involved, apart from their membership on the Board.

(b) At least one member of the Board shall be a prisoner, or a prisoner representative with appropriate background and experience to serve in that capacity, except that where a particular research project is reviewed by more than one Board only one Board need satisfy this requirement.

21. In research involving prisoners as subjects, what extra protection is required of the institution responsible for the conduct of the research?

For research conducted or supported by DHHS to involve prisoners, two actions must occur: (1) the IRB must certify to the Secretary (OPRR) that it has reviewed and approved the research under 45 CFR 46.305; and (2) the Secretary (OPRR) must determine that the proposed research falls within one of the categories of permissible research specified in 45 CFR 46.306(a)(2).

22. In research involving pregnant women that holds prospect of benefit solely to the fetus, who must consent for the women's participation int the research? Is there any exception to this requirement?

If the research holds out the prospect of direct benefit solely to the fetus then the consent of the pregnant woman and the father is obtained in accord with the informed consent provisions of subpart A of 45 CFR 45, except that the father's consent need not be obtained if he is unable to consent because of unavailability, incompetence, or temporary incapacity or the pregnancy resulted from rape or incest.

23. What is the consent criteria for research when for a non-viable neonate?

The legally effective informed consent of either parent of the neonate or, if neither parent is able to consent because of unavailability, incompetence, or temporary incapacity, the legally effective informed consent of either parent's legally authorized representative is obtained in accord with subpart A of this part, except that the consent of the father or his legally authorized representative need not be obtained if the pregnancy resulted from rape or incest.

24. In research not otherwise approvable, from who must the IRB gain approval before the research involving pregnant women, fetuses or neonates can be initiated?

45 CFR 46.207

The Secretary, after consultation with a panel of experts in pertinent disciplines (for example: science, medicine, ethics, law) and following opportunity for public review and comment, including a public meeting announced in the FEDERAL REGISTER, has determined either:

(1) That the research in fact satisfies the conditions of §46.204, as applicable; or

(2) The following:

(i) The research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of pregnant women, fetuses or neonates;
(ii) The research will be conducted in accord with sound ethical principles; and
(iii) Informed consent will be obtained in accord with the informed consent provisions of subpart A and other applicable subparts of this part.

ICH E6 Guidance for Informed Consent
With answers

1. **Which section of the ICH Guidelines contains the requirements for obtaining an informed decision to participate in the research?**

   Section 4.8

2. **When documenting informed consent, what additional requirement does ICH mandate?**

   4.8.11 Prior to participation in the trial, the subject or the subject's legally acceptable representative should receive a copy of the signed and dated written informed consent form and any other written information provided to the subjects. During a subject's participation in the trial, the subject or the subject's legally acceptable representative should **receive a copy of the signed and dated consent form** updates and a copy of any amendments to the written information provided to subjects.

3. **Both FDA regulations and ICH guidance require the witness to be impartial and to be present if a subject (or LAR) is unable to read.**

   True.

   4.8.9 If a subject is unable to read or if a legally acceptable representative is unable to read, an impartial witness should be present during the entire informed consent discussion. After the written informed consent form and any other written information to be provided to subjects, is read and explained to the subject or the subject's legally acceptable representative, and after the subject or the subject's legally acceptable representative has orally consented to the subject's participation in the trial and, if capable of doing so, has signed and personally dated the informed consent form, the witness should sign and personally date the consent form. By signing the consent form, the witness attests that the information in the consent form and any other written information was accurately explained to, and apparently understood by, the subject or the subject's legally acceptable representative, and that informed consent was freely given by the subject or the subject's legally acceptable representative

4. **ICH recommends that only subjects that can personally give consent and sign and date the consent form be included in a non-therapeutic trial. If the subject is unable to meet these conditions and the subjects' legally authorized representative must give consent, what other conditions must be met:**

   4.8.14 Nontherapeutic trials may be conducted in subjects with consent of a legally acceptable representative provided the following conditions are fulfilled: (a) The objectives of the trial

cannot be met by means of a trial in subjects who can give informed consent personally. (b) The foreseeable risks to the subjects are low. (c) The negative impact on the subject's well-being is minimized and low. (d) The trial is not prohibited by law. (e) The approval/favorable opinion of the IRB/IEC is expressly sought on the inclusion of such subjects, and the written approval/ favorable opinion covers this aspect. Such trials, unless an exception is justified, should be conducted in patients having a disease or condition for which the investigational product is intended. Subjects in these trials should be particularly closely monitored and should be withdrawn if they appear to be unduly distressed.

5. **Define non-therapeutic trial.**
   A trial in which there is no anticipated direct clinical benefit to the subject

Common Findings and Resolution Worksheet

1:Failure to Follow Investigational Plan *(51%)*

Includes:

- missing consent documents
- failure to perform protocol-required procedures
- missing documentation of required IRB review of study changes

Name processes that can be implemented to avoid this finding

- **Get organized**
- **Maintain all Essential Documents**
- **Create Visit checklists of all procedures to be performed at each visit**
- **Create and maintain an organized Regulatory Binder**
- **Training of all applicable study team members**
- **Re-training as needed**

2: Inadequate and Inaccurate Records *(33%)*

Includes:

- record keeping, missing or incomplete subject record

Name processes that can be implemented to avoid this finding

- **Get organized**
- **Maintain all Essential Documents**
- **Create and maintain subject binders/records**
- **Document events asap after occurrence**
- **Follow ACLOA-C**
- **Training of all applicable study team members**
- **Re-training as needed**

3: Inadequate Drug Accountability *(7%)*

Includes:

- the record keeping of drugs used in research
- absence or inadequacy of records on receipts, preparation, use, and/or disposition of the investigational drug/product

Name processes that can be implemented to avoid this finding

- **Maintain accurate Investigational Product Accountability records**
- **Keep IP accountability records/logs up-to-date at all times**
- **Document dispensing and return of IP to/from subject**
- **Training of all applicable study team members**
- **Re-training as needed**

4: Failure to Obtain and/or Document Subject Consent (5%)

Includes:

- missing consent documents
- omission of a description of required elements when obtaining consent

Name processes that can be implemented to avoid this finding

- **Get organized**
- **Maintain all Essential Documents**
- **Create a template/form to document the Informed Consent process**
- **Training of all applicable study team members**
- **Re-training as needed**

5: Inadequate Informed Consent Form (4%)

Includes:

- missing communication about withdrawal and refusal to participate
- missing documentation showing subject receipt of information about their right to refuse to participate in any aspect of the study
- missing documentation that shows that subjects were informed of their right to withdraw without penalty

Name processes that can be implemented to avoid this finding

- **Get organized**
- **Maintain all Essential Documents**
- **Maintain a subject screening/enrollment log**
- **Create a template/form to document the Informed Consent process**
- **Training of all applicable study team members**
- **Re-training as needed**

Contracts and Agreements Worksheet with Answers

Define:

Contract

A contract is an agreement that obligates all parties to do or not do certain act(s).

Confidentiality Disclosure Agreement (CDA)

A Confidential Disclosure Agreement (CDA), also known as a non-disclosure agreement (NDA), is a legal contract between at least two parties that outlines confidential material, knowledge, or information that the parties wish to share with one another for certain purposes, but wish to restrict access to, or by, third parties.

Material Transfer Agreement (MTA)

An MTA (or Material Transfer Agreement) is a mechanism to facilitate the free transfer of proprietary materials and/or information between scientists and other institutions, whether they are for-profit or non-profit institutions. MTAs are used when the following circumstances obtain:

1. The receiving party wishes to obtain proprietary material and/or information to use for his/her own research purposes.
2. No research collaboration between the parties is planned.
3. Neither rights in intellectual property nor rights for commercial purposes may be granted under this type of agreement.
4. The agreement clearly sets forth the terms and conditions under which the recipient of the material and/or information, provided by either party, may use it.

Clinical Trials Agreement (CTA)

A CTA is an agreement negotiated between entities who decide it is to their mutual benefit to cooperate in the conduct of a clinical research protocol. The agreement addresses the responsibilities and obligations of the parties in the conduct of the study as well as the handling of intellectual property and proprietary information.

Clinical Materials and Supplies Agreements (CSMA)

A CMSA is a type of CTA. A CMSA is used when a company/investigator is only providing the test article and receiving data (for example, clinical trial reports and/or SAS datasets) and not involved in the clinical trial.

Memorandum of Understanding (MOU)

An MOU is a non-binding agreement that outlines how parties intend to collaborate on a series of related projects.

Data Use Agreement

The transfer of data between organizations is common in the research community. When the data is confidential, proprietary, or otherwise considered sensitive, the organization providing the data ("Provider") will often require that the organization receiving the data ("Recipient") enter into a written contract to outline the terms and conditions of the data transfer. Such a contract is usually referred to as a **Data Use Agreement (DUA)**, although it may also be referred to as a License Agreement, Confidentiality Agreement, Non-Disclosure Agreement, Memorandum of Understanding, Memorandum of Agreement, or other names if these agreements include data sharing or data transfer requirements.

Investigator agreement for drug trials and device trials

Drug Trials 21 CFR 312.53

A signed investigator statement (Form FDA-1572) containing:

(i) The name and address of the investigator;

(ii) The name and code number, if any, of the protocol(s) in the IND identifying the study(ies) to be conducted by the investigator;

(iii) The name and address of any medical school, hospital, or other research facility where the clinical investigation(s) will be conducted;

(iv) The name and address of any clinical laboratory facilities to be used in the study;

(v) The name and address of the IRB that is responsible for review and approval of the study(ies);

(vi) A commitment by the investigator that he or she:

(a) Will conduct the study(ies) in accordance with the relevant, current protocol(s) and will only make changes in a protocol after notifying the sponsor, except when necessary to protect the safety, the rights, or welfare of subjects;

(b) Will comply with all requirements regarding the obligations of clinical investigators and all other pertinent requirements in this part;

(c) Will personally conduct or supervise the described investigation(s);

(d) Will inform any potential subjects that the drugs are being used for investigational purposes and will ensure that the requirements relating to obtaining informed consent (21 CFR part 50) and institutional review board review and approval (21 CFR part 56) are met;

(e) Will report to the sponsor adverse experiences that occur in the course of the investigation(s) in accordance with § 312.64;

(f) Has read and understands the information in the investigator's brochure, including the potential risks and side effects of the drug; and

(g) Will ensure that all associates, colleagues, and employees assisting in the conduct of the study(ies) are informed about their obligations in meeting the above commitments.

(vii) A commitment by the investigator that, for an investigation subject to an institutional review requirement under part 56, an IRB that complies with the requirements of that part will be responsible for the initial and continuing review and approval of the clinical investigation and that the investigator will promptly report to the IRB all changes in the research activity and all unanticipated problems involving risks to human subjects or others, and will not make any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to the human subjects.

(viii) A list of the names of the subinvestigators (e.g., research fellows, residents) who will be assisting the investigator in the conduct of the investigation(s).

<u>Device trials 21 CFR 812</u>

A sponsor must obtain a signed agreement from each participating investigator that includes:

- the investigator's curriculum vitae,
- a statement of the investigator's relevant experience, including the dates, location, extent, and type of experience, where applicable,
- an explanation of the circumstances that led to termination of a study if the investigator was involved in an investigation or other research that was terminated,
- a statement of the investigator's commitment to:
    - conduct the investigation in accordance with the agreement, the investigational plan, the IDE and other applicable FDA regulations, and conditions of approval imposed by the reviewing IRB or FDA,
    - supervise all testing of the device involving human subjects. and
    - ensure that the requirements for obtaining informed consent are met.
- sufficient accurate financial disclosure information to allow the sponsor to submit a complete and accurate certification or disclosure statement as required under 21 CFR 54, Financial Disclosure by Clinical Investigators. The sponsor shall also obtain a commitment from the clinical

investigator to promptly update this information if any relevant changes occur during the course of the investigation and for one year following completion of the study. (The financial certification or disclosure is submitted in the PMA or Premarket Notification 510(k) application. It should not be submitted in the IDE application.)

Indemnification / Liability

Indemnification is a contractual agreement between the parties whereby one party, the indemnifying party, agrees to protect the other party, the indemnified party, against harms or losses brought by a third party that the indemnified party may incur. It's important to understand that indemnification protects the indemnified party against third-party claims that are brought against it, not claims by the indemnifying party against the indemnified party.