CLINICAL RESEARCH ASSOCIATE CRA

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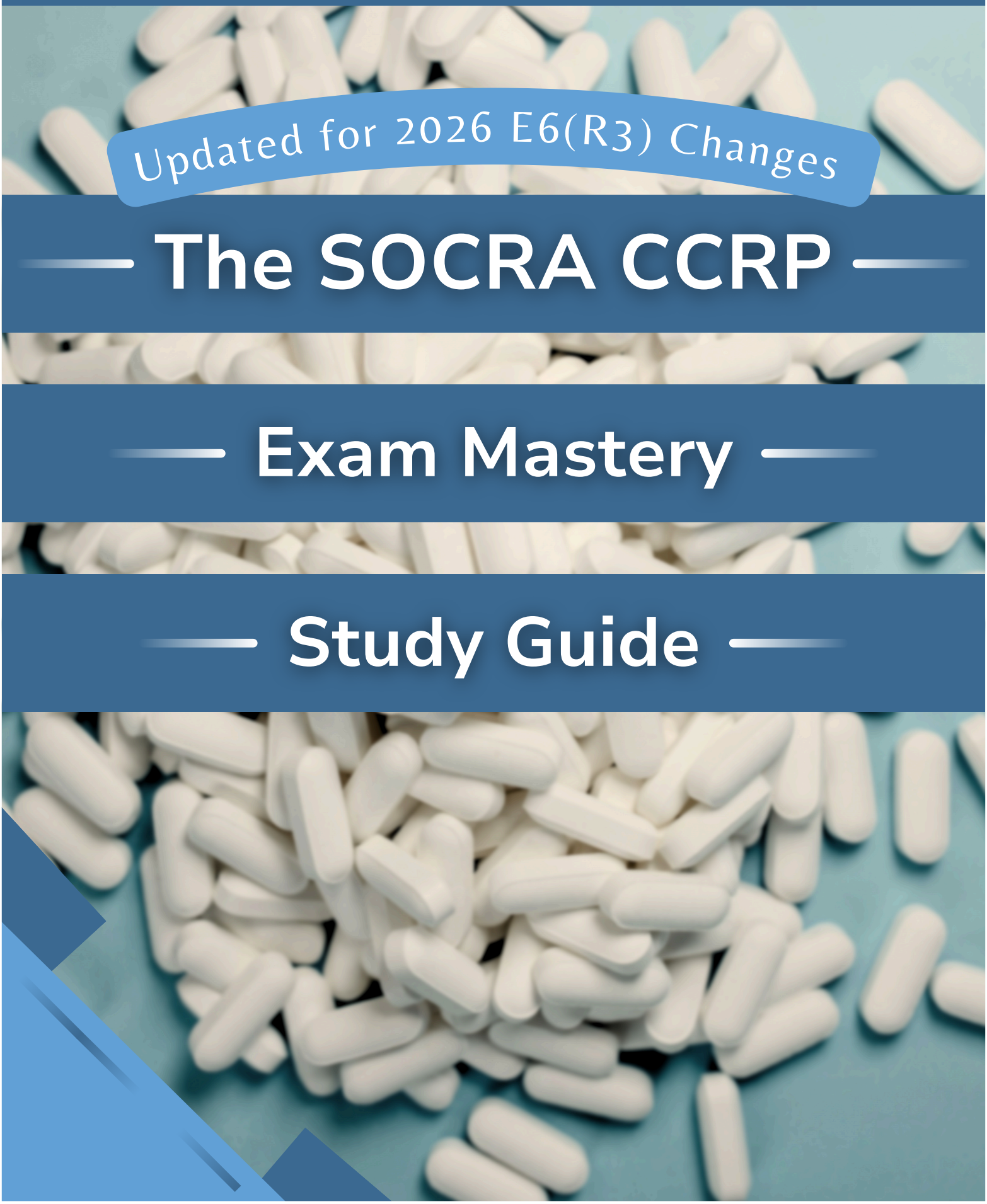

Updated for 2026 E6(R3) Changes

The SOCRA CCRP

Exam Mastery

Study Guide

TABLE OF CONTENTS

Table of Contents 1
Introduction 7
Disclaimer 9
The SOCRA CCRP Exam Application Process 10
Study Guide Outline 11
Three Subject Areas & Corresponding Percentages of Total Score 11
Additional Relevant Subject Areas 11
1. Research Study Start-Up (40%) 13
1.1 Coordinate the development of initial research study protocol 13
1.1.1 Roles and responsibilities of the sponsor, clinical investigator and IRB in determination the applicable regulatory pathway for a clinical study (e.g. IND, IDE) 13
1.1.2 Ethical concepts with foundations in: 13
1.1.3 Roles and responsibilities of the sponsor, clinical investigator and IRB in determining the applicable regulatory pathway for a clinical study (e.g. IND, IDE) 15
1.1.4 Roles and responsibilities of IRB/IEC review and approval of clinical studies including: 16
1.1.5 Development of protocols (including study design with consideration of methods to reduce bias, objectives, endpoints, data safety monitoring) 21
1.1.6 Roles and responsibility for protection of human subjects including: 31
1.2 Create or obtain research study documents (e.g., informed consent, essential documents, case report forms, financial disclosure statements) 37
1.2.1 Informed consent/assent process including development, content, review, approval 37
1.2.2 Submission (obtain approval) of informed consent documents to reviewing IRB/IEC- original 42
1.2.3 Informed consent essential and optional elements/information to be provided to subjects 43
1.2.4 Requirements for documentation and reporting financial disclosure for clinical investigators including: 43
1.2.5 Investigational product brochure / Investigator's brochure 45
1.2.6 IDE Significant Risk Determination 46
1.2.7 Regulatory requirements related to essential documents for clinical studies (IRB/IEC, sponsor and clinical sites) 46
1.2.8 Roles, responsibilities, and obligations of the sponsor 51
1.2.9 Roles, responsibilities, and obligations of the investigator 56
1.2.10 Delegation of duties 59
1.2.11 Investigational New Drug (IND) development and submission to applicable authorities 59
1.2.12 Investigational Device Exemption (IDE) development and submission to applicable authorities ... 59
1.2.13 IDE Significant Risk Determination 59

1.2.14 Regulatory requirement for protocol(s) and protocol related document(s) (e.g., informed consent) 60

1.2.15 Essential study related documents (paper/electronic) 60

1.2.16 Clinical investigator agreements (e.g., FDA Form 1572, investigator agreement) 62

1.3 Obtain research study approval from necessary stakeholders (e.g., IRB, research study sponsor, and relevant regulatory authorities) 62

1.3.1 Regulatory requirements for submission of protocol(s) to applicable authorities, sponsor and IRB/IEC 62

1.3.2 Regulatory requirement for protocol(s) and protocol related document(s) (e.g., informed consent documents, recruitment materials, safety reports, continuing review reports) development, review, and submission to reviewing authorities 63

1.4 Obtain research study product, related materials, equipment, tools, aids 64

1.4.1 Development of data collection tools (e.g., essential documents such as case report forms, product accountability logs, delegation logs) 64

1.4.2 Regulatory requirement for essential document development (electronic or paper based) 68

1.5 Select research study sites 68

1.5.1 Evaluating a clinical site to conduct a clinical study 68

1.6 Train research study staff members 69

1.6.1 Clinical site and personnel for qualifications to conduct a clinical study 69

1.6.2 Site/investigator training (GCP, investigational product, study, reporting requirements, compliance with protocol) 71

1.7 Evaluate research study's compliance with relevant local, state and provincial laws 73

1.7.1 Roles and responsibilities of the IRB/IEC for review and approval of study 73

1.7.2 Standard operating procedure development and implementation for the IRB/IEC 75

1.7.3 IRB / IEC membership requirements 75

1.7.4 IRB / IEC protocol review requirements 75

1.7.5 IRB / IEC protocol amendment review requirements 75

1.7.6 IRB / IEC expedited protocol review requirements 76

1.7.7 IRB evaluation of significant risk/non significant medical device study determination 76

1.7.8 Requirements for documentation of IRB/IEC meeting minutes, reviews and decisions 76

1.7.9 Communication of IRB/IEC decisions 76

1.7.10 Record retention for IRB/IEC documentation 76

1.7.11 Regulatory requirements for clinicaltrials.gov 76

1.7.12 Determine applicable requirements of regulatory agencies and any local (institution), state and provincial requirements 79

1.7.13 Data Safety Monitoring Board (DSMB) responsibilities 80

2. Research Study Implementation (50%) 81

2.1 Execute Research Strategy 81

2.1.1 Roles and responsibilities of IRB/IEC, sponsor and clinical investigator in the conduct of clinical research 81
2.1.2 Regulatory requirements to conduct a study in accordance with an investigational plan 84
2.1.3 Evaluating clinical site and personnel for ability to conduct a clinical study 85
2.1.4 Implementation of Standard Operating Procedures (SOPs) for: 86
2.1.5 Requirements for documentation, reporting and maintenance of financial disclosure for clinical investigators including: 87
2.1.6 Regulatory requirements for investigational site study reports and development and submission to reviewing authorities (e.g., progress reports, safety reports, final reports, protocol changes, protocol deviations) 87
2.1.7 Submission and review of protocol amendment(s) 92
2.1.8 Regulatory requirements for submission of protocol amendment(s) to applicable authorities, IRB/IEC 93
2.2 Assure regulatory compliance 94
2.2.1 Regulatory requirements for confidentiality of a research subject's information 94
2.3 Manage research study product (e.g., treatment, procedure, medication, medical device, questionnaire) 95
2.3.1 Sponsor's roles and responsibilities for investigational product accountability: 95
2.3.2 Clinical Investigator's roles and responsibilities related to receipt and distribution of investigational product and other supplies at study site 100
2.3.3 Regulatory requirements related to receipt and distribution of investigational product and other supplies at study site: 101
2.4 Identify, document & report research study anomalies 102
2.4.1 Sponsors and Clinical Investigator's roles and responsibilities for identification, documentation and reporting of unanticipated problems, unanticipated adverse device effects, adverse drug events, serious adverse events/effects. 102
2.4.2 Requirements for informing subjects of safety concerns and any relevant changes to the study 103
2.4.3 Subject safety issues –definitions, documentation, and reporting of adverse events, serious adverse events/serious adverse drug reactions, and unanticipated adverse device effects including the following: . 103
2.4.4 Documentation of serious adverse events/ serious adverse drug reactions, and unanticipated adverse device effects and relevant information in source documents and CRFs 105
2.4.5 Regulatory requirements for reporting serious adverse event/ serious adverse drug reaction, and unanticipated adverse device effects to Sponsor/CRO and IRB/IEC 105
2.4.6 Regulatory requirements for documenting reasons for subject discontinuation/termination 105
2.4.7 Regulatory requirements for documenting follow-up medical care for study subjects 106
2.4.8 Regulatory reporting and Medwatch [3500 and 3500A] requirements 107
2.4.9 Identification and reporting of research misconduct: 107
2.5 Manage subjects 108
2.5.1 Regulatory requirements for IRB review and approval of subject requirement materials 108
2.5.2 Subject Scheduling, Screening, Recruitment, and Retention including: 109

2.5.3 Regulatory requirements and ethical concepts related to protection of vulnerable subjects 110
2.5.4 Regulatory requirements related to source documentation (paper/electronic) –completion and review of 110
2.5.5 Source documentation and case report forms (CRFs) of subject participation in a study including: 111
2.6 Maintain the research study 112
2.6.1 Regulatory requirements for maintenance and retention of study related essential documents, sources documents and equipment including: 112
2.6.2 Regulatory requirements related to clinicaltrials.gov 113
2.6.3 Review of accuracy and completeness of site records including monitoring source documentation/case report forms: eligibility, product dosing and accountability, adverse events, study related visits and follow up care, and informed consent documentation..... 113
2.6.4 Preparation and follow-up for study site, IRB/IEC and sponsor regulatory agency inspections (including FDA Forms 482 and 483) 116
2.6.5 Knowledge of principles of Quality Assurance and Corrective and Preventive Action Plans (CAPA). 117
2.7 Communicate with research study stakeholders 121
2.7.1 Regulatory requirements for communication with IRB/IEC, sponsor, investigational site and regulatory authorities including:..... 121
2.7.2 IRB/IEC communication with sponsor, clinical investigator and regulatory authorities 124
2.7.3 Role and Responsibilities of Data Safety Monitoring Boards (DSMB) 124
2.7.4 Regulatory requirements related to study documentation (paper/electronic) -completion/review.. 124
2.7.5 Development and maintenance of accurate, current, and complete records relating to clinical studies..... 124
2.8 Perform / participate a research study audit..... 125
2.8.1 Regulatory requirements for maintenance and retention of study related essential documents, source documents..... 125
2.8.2 Quality Control and Quality Assurance..... 125
2.8.3 Preparation and follow-up for study site, IRB/IEC and sponsor regulatory agency inspections..... 125
3. Research Study Closure (10%) 126
3.1 Perform / participate a research study closeout visit 126
3.1.1 Study closeout visit 126
3.2 Develop & submit research study closure reports..... 127
3.2.1 Develop & submit closure report to IRB 127
3.2.2 Develop & submit final report to research study sponsor 128
3.2.3 Develop & submit final report to relevant regulatory authorities 128
3.2.4 Develop & submit final report to clinicaltrials.gov 128
3.2.5 Regulatory requirements for development and submission of study closure reports to IRB/IEC, sponsor and regulatory authorities:..... 129
3.2.6 Regulatory requirements related to clinical.trials.gov 129
3.3 Archive / retrieve research study records 130

3.3.1 Regulatory requirements for maintenance and retention of study related essential documents, source documents 130
4. Drug Development 131
4.1 Drug Discovery 131
4.2 Pre-Clinical Testing 131
4.3 Clinical Trials 131
4.3.1 Phase 0: Pharmacokinetics (PK) and Pharmacodynamics (PD) 132
4.3.2 Phase I: Safety 132
4.3.3 Phase II: Efficacy (Proof of Concept) 132
4.3.4 Phase III: Pivotal Studies 133
4.3.5 Phase IV: Post Marketing Surveillance 133
5. Medical Device & In-vitro Diagnostic Development 135
5.1 Medical Device Development 135
5.1.1 Class I: General Controls 135
5.1.2 Class II: General Controls + Special Controls 135
5.1.3 Class III: General Controls + Premarket Approval 135
5.1.4 Medical Device Clinical Trials 136
5.1.5 Significant Risk, Non-Significant Risk, and Exempt Studies 136
5.1.6 Differences between drug and medical device clinical trials 138
5.2 In-vitro Diagnostic Development 139
5.2.1 In-vitro diagnostic clinical trials 140
5.2.2 Number of clinical sites required 140
5.2.3 Informed Consent Waiver for Some In-Vitro Diagnostic Clinical Trials 140
5.2.4 Type of clinical evaluation needed 141
5.2.5 Level of on-site monitoring needed 141
6. FDA Inspections 142
6.1 Inspection of a sponsor/CRO 142
6.1.1 Personnel and organization 142
6.1.2 Selection of site/investigators and ongoing communication between sponsor and site 142
6.1.3 Study monitoring 143
6.1.4 Adverse event monitoring/reporting 143
6.1.5 Data handling/data verification 143
6.1.6 Control of investigational product(s) 143
6.1.7 Automated processes (electronic systems) 143
6.1.8 Record retention 143
6.1.9 After the inspection 143

6.2 Inspection of a clinical trial site 144
6.2.1 Preparation for the inspection 145
6.2.2 The day of the inspection 145
6.2.3 Personnel and organization 145
6.2.4 Facility 145
6.2.5 IRB approval 146
6.2.6 Protocol adherence 146
6.2.7 Documentation of informed consent 146
6.2.8 Data collection 146
6.2.9 investigational product accountability 146
6.2.10 Financial disclosure 146
6.2.11 Clinical trial oversight/monitoring 146
6.2.12 Electronic data 146
6.2.13 Adverse events 146
6.2.14 Record Retention 146
6.2.15 After the inspection 146
7. Tips from Reddit's r/clinicalresearch 148
7.1 Key topics to focus on 148
7.2 Topics requiring less study focus 148
7.3 Complete list of comments 149
8. Glossary of Terms 154
9. Practice Questions 161
10. Exam Day 172
10.1 Testing Options 172
10.2 Scheduling Your Exam 172
10.3 What to Bring to the Exam 172
10.4 What NOT to Bring / What's NOT Allowed 173
10.5 Before the Exam Begins 173
10.6 Exam Strategy: Maximizing Your Score 173
10.6.1 Time Management 173
10.6.2 Answering Strategies 174
10.6.3 During Your Review Pass 174
10.7 After the Exam 174
11. Last Words 175

INTRODUCTION

What This Guide Is

The SOCRA CCRP Exam Mastery Study Guide is a concentrated, exam-focused study resource designed to help you pass the SOCRA Certified Clinical Research Professional (CCRP) certification exam. It covers the full scope of the SOCRA exam outline - from research study start-up through implementation and closure - in a format that prioritizes what you actually need to know on exam day.

This guide is not a textbook. It is not an encyclopedia of clinical research. It is a focused study tool built around one goal: helping you walk into the exam confident and walk out certified.

What Makes This Guide Different

- **Aligned to the SOCRA exam outline**
  Every section follows the official SOCRA exam content outline, so you can study by section number and know exactly where you are in relation to the exam.
- **Updated for ICH GCP E6(R3**
  SOCRA updated its exam content to reflect ICH GCP E6(R3) beginning January 1, 2026. This guide covers all E6(R3) concepts - Quality Management Systems, risk-proportionate monitoring, quality by design, eConsent, decentralized trials, and the media-neutral approach. All E6(R3) content is clearly labeled with **E6(R3) Update** or **E6(R3) Note** markers throughout.
- **Author's Notes throughout**
  Practical, exam-focused callouts from the authors that tell you what to prioritize, what to memorize, and what the exam is most likely to test. These are based on real clinical research experience and feedback from candidates who have taken the exam.
- **Real exam intelligence from Reddit**
  Section 7 contains crowdsourced insights from actual SOCRA CCRP exam-takers on Reddit's r/clinicalresearch - including which topics are most heavily tested, which topics require less focus, and what the exam experience is actually like. No other study guide offers this.
- **30 practice questions with explanations**
  Scenario-based questions matching the actual exam format, covering the most heavily tested topics. Each question includes a detailed explanation of why the correct answer is right and why the others are wrong.
- **Written by clinical research professionals**
  This guide combines regulatory knowledge with practical industry experience from multiple perspectives.

How to Use This Guide

If you have 6+ weeks before your exam:

1. Read the guide cover to cover, focusing on understanding concepts rather than memorizing details.
2. Pay special attention to the **Author's Notes** - these highlight the most testable content.
3. After your first read-through, review Section 7 (Reddit Tips) to calibrate your study priorities.

4. On your second pass, focus on the areas Reddit test-takers say are most heavily tested: reporting timelines, sponsor vs. investigator responsibilities, record retention, informed consent, and electronic systems.
5. Use the practice questions (Section 9) as a self-assessment. Review the explanations for any questions you get wrong.
6. In the final week, review the Glossary (Section 8).

If you have 2–4 weeks before your exam:

1. Start with Section 7 (Reddit Tips) to understand what's most heavily tested.
2. Focus your reading on Sections 1 and 2 (which together account for 90% of the exam).
3. Prioritize the Author's Notes and E6(R3) Update sections.
4. Create flashcards for reporting timelines, record retention periods, and key definitions.
5. Review the practice questions and use your results to identify remaining weak areas.

If you have less than 2 weeks:

1. Read the Reddit Tips (Section 7) and the Author's Notes throughout the guide.
2. Memorize reporting timelines, record retention requirements, and sponsor vs. investigator responsibilities.
3. Review the Glossary and all E6(R3) Update sections.
4. Complete the practice questions.

About the Authors

This study guide was originally created by **Ernie Sakchalathorn, CCRP** - the founder of ClinicalResearchAssociateCRA.com and a clinical research professional since 2007. Ernie passed the SOCRA CCRP exam with a 96% score and brings both CRC and CRA perspectives from his career in drug, medical device, and in vitro diagnostic clinical trials.

Kenyatta Cosby, MD serves as Senior Editor. Dr. Cosby is a Physician Scientist based in the Rockville, Maryland region with extensive clinical and biomedical research experience. He completed his medical education at Howard University College of Medicine and his post-doctoral training at Johns Hopkins University School of Medicine and the National Institutes of Health. Dr. Cosby is known for managing an NIH-based clinical trial whose results were published in Nature Medicine and featured in the New York Times. He has published research in numerous scientific journals including Circulation, Blood, and the Journal of the American College of Cardiology, and has written extensively for the pharmaceutical industry.

We Want Your Feedback

Your comments and post-exam feedback make this guide better for everyone. If you have suggestions, corrections, or want to share your exam experience, please email info@clinicalresearchassociatecra.com. We read every message and use your feedback to improve future editions.

DISCLAIMER

The information contained within The SOCRA CCRP Exam Mastery Study Guide is for informational purposes only. It is to be used as a study tool for the SOCRA CCRP exam.

Summaries, methods of study, and tips are only recommendations from the authors, and reading the information in The SOCRA CCRP Exam Mastery Study Guide does not guarantee a passing score on the SOCRA CCRP exam.

This study guide is not an all-inclusive resource. The authors have made reasonable efforts to provide current and accurate information to readers. The authors will not be held liable for any unintentional errors or omissions that may be found.

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THE SOCRA CCRP EXAM APPLICATION PROCESS

Below are the steps for a CRA to be certified CCRP through SOCRA:

1. Become a SOCRA member ($75 annual membership fee)
2. **Register for CCRP certification exam** ($395 fee for members, $450 for non-members), must meet one of the eligibility options below and provide detailed CV/resume, verification of employment, and job description. Click here for more details.

Category	Description
1	• Have two years of experience as a full-time clinical research professional (or have 3,500 hours part-time) during the last five years
2	• Hold a degree in clinical research from an associate, undergraduate, or graduate degree program ***AND*** • Have completed a minimum of one year of full-time experience (or 1,750 hours part-time) during the past two years as a clinical research professional
3	• Hold an undergraduate or graduate certificate in clinical research with a curriculum of no less than 12 semester (credit) hours or totaling a minimum of 144 credit hours from an academic institution of higher learning (community college, college or university) ***AND*** • Hold an associate or bachelor's degree in a science, health science, pharmacy or related field ***AND*** • Have completed a minimum of one year of full-time experience (or 1750 hours part-time) during the past two years as a clinical research professional.

3. **Take and pass the CCRP certification exam** (year-round testing through Prometric)
4. **Renew your CCRP certification every 3 years** (maintain membership during the 3 year period). This costs $350 for three years, which includes three years of complimentary SOCRA membership. This means you no longer need to pay separate annual membership fees during your certification period. A payment installment option is also available.
5. **Report 45 continuing education hours** every three (3) years; ***AND***
6. **Complete the Continuing Competence Learning Module**: this is an online, self-paced exercise intended to ensure that CCRPs are maintaining their knowledge and understanding related to changes affecting clinical research.

STUDY GUIDE OUTLINE

Below are the three subject areas and the percentages of scored test items included in each area. This information is listed on the SOCRA website.

THREE SUBJECT AREAS & CORRESPONDING PERCENTAGES OF TOTAL SCORE

1. **Research Study Start-Up (40%) – Approximately 40 questions**
    1. Coordinate the development of initial research study protocol
    2. Create or obtain research study documents (e.g., informed consent, essential documents, case report forms, financial disclosure statements)
    3. Obtain research study approval from necessary stakeholders (i.e., IRB, research study sponsor, and relevant regulatory authorities)
    4. Obtain research study product, related materials, equipment, tools and aids
    5. Select research study sites
    6. Train research study staff members
    7. Evaluate research study's compliance with relevant local, state and provincial laws

2. **Research Study Implementation (50%) – Approximately 50 questions**
    1. Execute research study in accordance with the protocol
    2. Assure regulatory compliance
    3. Manage research study product (e.g., treatment, procedure, medication, medical device, questionnaire)
    4. Identify, document & report research study anomalies
    5. Manage subjects
    6. Maintain the research study
    7. Communicate with research study stakeholders
    8. Perform/participate a research study audit

3. **Research Study Closure (10%) – Approximately 10 questions**
    1. Perform/participate a research study closeout visit
    2. Develop & submit research study closure reports
    3. Archive/retrieve research study records

ADDITIONAL RELEVANT SUBJECT AREAS

In addition to the above subject areas, The SOCRA CCRP Exam Mastery Study Guide will include additional relevant areas listed below. These additional topics are from the professional clinical research experience of Ernie Sakchalathorn, CCRP, the founder of ClinicalResearchAssociateCRA.com and the author of the original study guide titled ES' SOCRA CCRP Study Guide.

The SOCRA CCRP exam evaluates not only knowledge of the regulations, but industry experience as well. Thus, these additional relevant areas are critical to prepare you for test questions whose answers may not explicitly stated in regulatory documentation, but may require industry experience to answer correctly.

4. **Drug Development**
    1. Drug discovery
    2. Pre-clinical testing
    3. Clinical trials (Phase 0, I, II, and III)
    4. Post market surveillance (Phase IV)

5. **Medical Device (and In Vitro Diagnostic) Development**
    1. Medical device classification (Class I, II, III)
    2. Medical device clinical Trials
    3. Difference between medical device and drug clinical trials
    4. In vitro diagnostic development

6. **FDA Inspection**
    1. Inspection of sponsor or CRO
    2. Inspection of clinical trial site

7. **Tips from Reddit r/clinicalresearch**

8. **Glossary of Terms**

9. **Practice Questions**

10. **Exam Day**

11. **Last Words**

1. RESEARCH STUDY START-UP (40%)

Study start-up is the first and important step in conducting clinical research. This section includes regulatory requirements of IRB/IEC, sponsors and investigators related duties/task related to study start up. SOCRA recognizes the importance of this step, which is reflected in the 40% weight of test questions focused on this section.

1.1 COORDINATE THE DEVELOPMENT OF INITIAL RESEARCH STUDY PROTOCOL

- ✓ Determine if a research study design involves human subjects
- ✓ Develop Standard Operating Procedures (SOPs) for sponsors, clinical investigators, and IRBs
- ✓ Coordinate the expedited review of research study protocol
- ✓ Coordinate the development of emergency use research study protocol
- ✓ Coordinate the development of a research study protocol involving vulnerable subjects
- ✓ Coordinate the development of a research study protocol involving investigational products (e.g., pharmaceutical, biologic or device)

KNOWLEDGE OF:

1.1.1 Roles and responsibilities of the sponsor, clinical investigator and IRB in determination the applicable regulatory pathway for a clinical study (e.g. IND, IDE)

Whether it be drug, medical device, or in-vitro diagnostic clinical study, the regulatory pathway depends on the stage of the development. In general, pre-clinical testing (e.g., animal testing) is required to ensure preliminary safety and efficacy of the candidate. Pre-clinical testing can be conducted by the sponsor and/or clinical investigator without the need to notify the FDA provided that no human subjects are involved.

If pre-clinical testing shows promising results and the sponsor and/or clinical investigator would like to go on to conduct human testing, FDA notification is required.

- For new drugs, an IND application to the FDA is needed prior to conducting a clinical study on human subject.
- For medical devices and in-vitro diagnostics, an IDE application to the FDA is needed prior to conducting a clinical study on human subjects.

IND and IDE applications will be described in more detail in later sections of this study guide.

1.1.2 Ethical concepts with foundations in:

1.1.2.1 Nuremburg Code

During World War II, some German physicians conducted unethical experiments on concentration camp prisoners without their consent. Prisoners were subjected to inhumane treatments such as exposure to mustard gas to test possible antidotes. Many more examples of unethical treatment of prisoners were performed.

At the end of World War II, the Nuremberg trials were conducted, and the Nuremberg Code was established in 1947. The Nuremberg Code contains ten elements of conduct for research on human subjects.

Note: More information about the Nuremberg Code can be found at http://www.hhs.gov/ohrp/archive/nurcode.html

Below are summaries (not the actual text) of these 10 points:

1. Voluntary informed consent is absolutely essential.
2. Research should yield a benefit to society.
3. Research should be based on prior animal work.
4. Avoid all unnecessary physical and mental suffering and injury.
5. Research in which death or disabling injury is expected should not be conducted.
6. The risks should be justified by the anticipated benefits.
7. Proper preparations and adequate facilities should be provided to prevent injury, disability, or death.
8. Research should be conducted only by scientifically qualified people.
9. The subject has the right to withdraw from the research at any time.
10. Researchers must be able to end the study if there is probable cause to believe that continuation of the experiment will cause injury, disability, or death.

The Nuremberg Code was the first set of principles outlining professional ethics for clinical research. The Code has been the model for many professionals.

1.1.2.2 Belmont Report

In 1974, the U.S. Congress passed the National Research Act which established the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. The National Commission was tasked to compose a set of standard principles for all human subject research. This led to the Belmont Report, which was published in 1979 by the National Commission.

Note: The full text of the Belmont Report can be found at http://www.hhs.gov/ohrp/humansubjects/guidance/belmont.html

The three core principles of the Belmont Report are:

1. **Respect for Persons**
   This principle states that individuals are autonomous human beings and that they must be allowed to choose for themselves. Individuals with diminished autonomy must be afforded special protections. Informed consent and protection of vulnerable subjects are the results of this principle.

2. **Beneficence**
   This principle states the philosophy of "do no harm." The goal of research should be to maximizing benefits from the research while minimizing risks to the subjects.

3. **Justice**
   This principle requires equality in research conduct. Research design must ensure that burdens and benefits are shared fairly. One group should not assume greater research risks for the benefit of another group. Fair procedures and outcomes in the selection of subjects must be in place.

1.1.2.3 Declaration of Helsinki

The Declaration of Helsinki was developed by the World Medical Association (WMA) in 1964 with a basis in the principles of the Nuremberg Code. The Declaration laid out general principles that physicians

b. any instances of serious or continuing noncompliance with regulations or requirements
c. any suspension or termination of IRB approval for the research

In addition to the above, the IRB should develop a documentation system when standard operating procedures (SOPs) are written, approved, and used.

1.1.3.1.2 For Sponsors

The ICH GCP E6(R3) guideline states the requirement for standard operating procedures (SOPs) for sponsors as:

> *"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)."*

SOPs are required as part of the sponsor's quality assurance (QA) and quality control (QC) system to ensure proper conduct of the trial following the protocol, GCP, and appropriate regulations. We will discuss QA and QC in a later section of this study guide.

Note: An auditor will likely request to review sponsor's SOPs during an inspection to evaluate the sponsor's process to ensure proper clinical trial conduct. SOPs should be regularly maintained and updated with effective date and version.

1.1.3.1.3 For Clinical Trial Sites

The ICH GCP E6(R3) guideline states that:

> *"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."*

To demonstrate that all personnel are trained in trial-related duties and functions above, a clinical research site will need to develop standard operating procedures (SOPs) for different duties and functions. Some examples of the trial-related duties and functions requiring SOPs are:

1. Obtaining informed consent procedures
2. Subject recruitment procedures
3. Reporting of adverse events (AEs) / serious adverse events (SAEs)
4. Dispensing investigational products
5. Record retention procedures

1.1.4 Roles and responsibilities of IRB/IEC review and approval of clinical studies including:

1.1.4.1 Emergency use of a research product

21 CFR 56.102(d) defines emergency use as:

> *"Emergency use means the 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."*

Under 21 CFR 56.102(d), life-threatening covers both life-threatening and severely debilitating as defined below.

- **Life-threatening**
  Life-threatening means diseases or conditions where the likelihood of death is high unless the course of the disease is interrupted and diseases or conditions with potentially fatal outcomes, where the end point of clinical trial analysis is survival. The criteria for life-threatening do not require the condition to be immediately life-threatening or to immediately result in death. Rather, the subjects must be in a life-threatening situation requiring intervention before review at a convened meeting of the IRB is feasible.

- **Severely debilitating**
  Severely debilitating means diseases or conditions that cause major irreversible morbidity. Examples of severely debilitating conditions include blindness, loss of arm, leg, hand or foot, loss of hearing, paralysis, or stroke.

1.1.4.1.1 For drugs or biologics

Emergency use of an unapproved investigational drug or biologic requires an IND. The physician must contact the manufacturer and determine if the drug or biologic can be made available for the emergency use under the company's IND.

In an emergency that does not allow time for submission of an IND, the FDA may authorize shipment of the test article in advance of the IND submission. The physician must contact the FDA by telephone or other rapid communication means – see 21 CFR 312.310(d).

1.1.4.1.2 For medical devices

Emergency use of an unapproved device may occur before an IDE is approved. The physician should contact the device sponsor to obtain the emergency use of the device.

The sponsor must notify the FDA of the emergency use within five (5) days through a submission of an IDE Report describing the details of the case and the patient protection measures that were followed.

Below are the criteria needed for an emergency use of an unapproved device:

1. Life-threatening or serious disease or condition
2. No alternative
3. No time to obtain FDA approval

1.1.4.1.3 IRB approval exemption

21 CFR 56.104(c) allows the emergency use of an unapproved drug without prior review and approval by the IRB. It allows for one (1) emergency use of a test article in a single patient without prospective IRB review and approval of a test article, provided that the emergency use is reported to the IRB within five (5) days of the use. Any subsequent use of the test article at the institution is subject to prospective IRB review.

> **Note:** For emergency use of the test article on a second patient, in which the only obstacle to treatment is that the IRB has not had sufficient time to convene a meeting to review the issue, subsequent emergency use should not be withheld for the purpose of gaining IRB approval.

1.1.4.1.4 Informed consent

Consent will be sought and documented from the patient or the patient's legally authorized representative, unless the criteria for the exception to the requirement for consent are met (see Informed Consent Exemption below)

1.1.4.1.5 Informed consent exemption

21 CFR 50.23(c) allows for exemption from the use of informed consent if the following conditions are met (in writing):

1. The human subject is confronted by a life-threatening situation necessitating the use of the test article.
2. Informed consent cannot be obtained from the subject because of an inability to communicate with or obtain legally effective consent from the subject.
3. Time is not sufficient to obtain consent from the subject's legal representative.
4. There is no alternative method of approved or generally recognized therapy available that provides an equal or greater likelihood of saving the life of the subject.
5. Within five (5) working days after the use of the article, the emergency use must be reviewed and evaluated in writing by a physician who is not participating in the clinical investigation.

After an emergency use, regardless of whether informed consent was obtained or not, the physician must submit a written statement of the above five conditions to the IRB within five (5) working days after the use of the test article – see 21CFR56.104(c).

1.1.4.2 Expedited review clinical studies

21 CFR 56.110 allows minimal risk research to be reviewed and approved by the IRB under an expedited review process. Minimal risk research must meet the minimal risk definition defined under 21 CFR 56.102(i) as:

> *"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."*

An IRB may use the expedited review process if either or both of the following is met:

1. Some or all of the research involves no more than minimal risk
2. There are minor changes in previously approved research during the approval period (of 1 year or less)

Expedited review procedure allows for review by the IRB chairperson or by one or more experienced reviewers designated by the IRB chairperson. The reviewers may exercise all the authorities of the IRB. However, the reviewers may not disapprove of the research. Disapproval of research can only be done with the non-expedited review procedure – see 21 CFR 56.108(c).

An IRB that uses an expedited review procedure must keep all IRB members informed of research proposals approved under the expedited review procedure.

1.1.4.3 Significant risk determination for medical device clinical studies

For a medical device study, the regulatory pathway is different depending on the risk classification of the device. Regardless of the regulatory approval route a medical device will go through (510(k), PMA, etc.),

an Investigational Device Exemption (IDE) may be needed for an investigational device to be used in a clinical study to evaluate safety and effectiveness.

Three types of medical device studies are listed under the Investigational Device Exemptions (IDE) regulation – see 21 CFR 812.

1. Significant risk (SR)
2. Non-significant risk (NSR)
3. Exempt studies

The overseeing IRB will need to determine which devices pose significant, non-significant risk, or are exempt from the IDE requirement. Below is a description of significant risk, non-significant risk, and exempt studies.

1.1.4.3.1 Significant Risk (SR)

21 CFR 812.3(m) defines a significant risk (SR) medical device as 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, safety, or welfare of a subject.

1.1.4.3.2 Non-significant Risk (NSR)

A non-significant risk device is an investigational device that does not meet the SR requirement above. NSR device studies should not be confused with "minimal risk" studies.

Minimal risk studies are studies that meet the definition in 21 CFR 56.102(i) where an "expedited review" procedure (21 CFR 56.110) can be used in IRB approval. Some NSR studies may qualify as minimal risk and the IRB may review those studies under its expedited review procedures.

1.1.4.3.3 Differences between SR & NSR device studies

Significant Risk (SR) Studies	Non-significant Risk (NSR) Studies
• Follow all IDE regulations according to 21 CFR 812 • Have IDE application approved by FDA prior to study start	• Follow abbreviated requirements according to 21 CFR 812.2(b) • Do not need to have IDE application approved by FDA • Sponsors and IRBs do not have to report to FDA prior to study start

1.1.4.3.4 Exempt studies

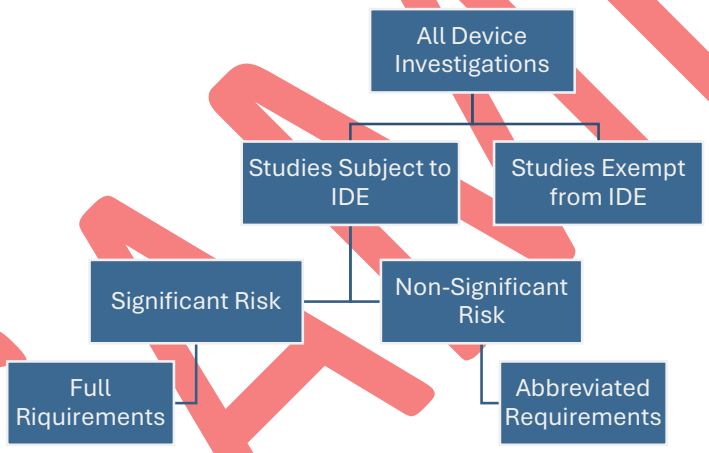
According to FDA 21 CFR 812.2(c), an IDE exempt study involves:

1. A device in commercial distribution on or before May 28, 1976.

2. A device that FDA deemed substantially equivalent to a device in criteria 1 above, and that is used following indications in the labeling FDA reviewed under subpart E of part 807 in determining substantial equivalence.
3. A diagnostic device, if the sponsor complies with applicable requirements in 809.10(c) and if the testing:
    a. Is noninvasive
    b. Does not require an invasive sampling procedure that presents significant risk
    c. Does not by design or intention introduce energy into a subject, and
    d. Is not used as a diagnostic procedure without confirmation of the diagnosis by another, medically established diagnostic product or procedure.
4. A device undergoing consumer preference testing, testing of a modification, or testing of a combination of two or more devices in commercial distribution, if the testing is not for the purpose of determining safety or effectiveness and does not put subjects at risk.
5. A device intended solely for veterinary use.
6. A device shipped solely for research on or with laboratory animals and labeled in accordance with 21 CFR 812.5(c).
7. A custom device as defined in 21 CFR 812.3(b), unless the device is being used to determine safety or effectiveness for commercial distribution.

1.1.4.3.5 Clinical study pathways for SR, NSR, & IDE exempt devices

Below is a diagram summarizing specific clinical study pathways for significant risk, non-significant risk, and IDE exempt devices.



For both SR and NSR device studies, IRB approval prior to conducting clinical trials and continuing review by the IRB is required. Informed consent must also be obtained for either type of study following 21 CFR 50.

Sponsors are responsible for making the initial determination whether the device under study is SR or NSR and present it to the Institutional Review Board (IRB). FDA may also be available to help the sponsor, clinical investigator, IRB in determining the risk of the device.

SR studies must meet the full IDE requirements under 21 CFR 812. SR studies are first submitted to the FDA for review and approval of the IDE application, and then to the IRB.

NSR studies need to meet the abbreviated IDE requirements under 21 CFR 812.2(b). NSR studies do not require an IDE during initial IRB application submission. IRB will determine whether it considers the device to be SR or NSR.

- If the IRB determines that the device is SR, then the IRB will request that the sponsor submit an IDE application to the FDA. Written approval obtained from the FDA will be needed before the research can start.
- If the IRB determines that the device is NSR, the study may proceed after IRB approval following the abbreviated IDE regulations without the need for further FDA review and approval.

Note: Please refer to Section 5. Medical Device & In-vitro Diagnostic Development for more information.

Author's Notes:
1. Know the definition of minimal risk research and its expedited review process
2. Know the definitions of significant risk (SR) and non-significant risk (NSR) device studies
3. Know the differences between SR and NSR devices (see table above)

1.1.5 Development of protocols (including study design with consideration of methods to reduce bias, objectives, endpoints, data safety monitoring)

The clinical trial protocol is a document that contains all relevant information for the conduct of the trial. ICH GCP E6(R3) guideline describes a protocol as:

> *"A document that describes the objective(s), design, methodology, statistical considerations, and organization of a trial."*

E6(R3) Update - Quality by Design in Protocol Development:

ICH GCP E6(R3) introduces the principle of quality by design into the protocol development process. This means that sponsors should prospectively identify factors that are critical to quality (CtQ) during the design phase, including factors critical to participant safety, data reliability, and the ability to answer the trial's key questions, and build appropriate controls into the protocol from the start.

Under E6(R3), protocol development is no longer just about defining the study procedures and endpoints. It also involves:

- Identifying risks that could affect trial quality and participant safety
- Defining what data and processes are critical to the trial's objectives
- Designing proportionate approaches to monitoring, data collection, and oversight based on those risks
- Considering the participant's perspective, including trial burden and accessibility

This approach is closely aligned with ICH E8(R1) (General Considerations for Clinical Studies), which E6(R3) explicitly references. E8(R1) emphasizes that quality should be considered at the earliest stages of trial planning.

Author's Notes:
Know that E6(R3) emphasizes identifying "critical to quality" (CtQ) factors during protocol development. This is a shift from the E6(R2) approach, which focused more on what the protocol should contain rather than how quality should be designed into it. The key concept is this: quality is planned in, not inspected in.

21 CFR 312.53(c)(3) gives a list of items that a clinical protocol should contain for different drug trial phases:

1. Phase 1 investigations
    a. a general outline of the planned investigation
    b. the estimated duration of the study
    c. the maximum number of subjects that will be involved.

2. Phase 2 or 3 investigations
    a. an outline of the study protocol
    b. an approximation of the number of subjects to be treated with the drug
    c. and the number to be employed as controls, if any;
    d. the clinical uses to be investigated;
    e. characteristics of subjects by age, sex, and condition;
    f. the kind of clinical observations and laboratory tests to be conducted;
    g. the estimated duration of the study;
    h. and copies or a description of case report forms to be used.

Although 21 CFR 312.53 contains its own list of protocol items, the ICH GCP E6(R3) guideline gives a more complete list and description of items needed for a protocol. In this section, we will go through protocol items that the ICH GCP E6(R3) guideline recommends.

We also cover protocol sections that are not on the ICH GCP E6(R3) guideline, but are still commonly used in the industry. These sections will have the words "commonly used" after the section name.

1.1.5.1 General information (ICH GCP recommended)

General information outlined below should be included in the protocol title page and general information pages:

- Protocol title
- Protocol number
- Date
- Name and address of the sponsor and monitor
- Name and title of the person(s) authorized to sign the protocol
- Name, title, address, and phone number(s) of the sponsor's medical expert for the trial
- Name and title of the investigator(s) and the address and contact information of the site(s)
- Name, title, address, and contact information of a physician who is responsible for medical decisions (if other than investigator)
- Name(s) and address(es) of the clinical laboratory(ies) and other medical and/or technical departments(s)

1.1.5.2 Protocol summary (commonly used)

The protocol summary provides an overview of the study. It is commonly placed in the front of the protocol right after the title page and general information pages. The summary should provide enough information about the study in 2-3 pages.

Below are the items that go into the protocol summary:

- Protocol title (same as in the title page)
- Study objective

- Population
- Study design
- Study treatment description, dose, route, dose regimen, and duration
- Study procedures
- Study duration
- Inclusion / exclusion criteria
- No. of subjects
- Endpoints (primary, secondary, exploratory, etc.)
- Statistical methods

1.1.5.3 Table of contents (commonly used)

A detailed table of contents should be included in the protocol to allow for easy document navigation.

1.1.5.4 Background information (ICH GCP recommended)

Background information should bring the reader up to speed on the product and findings in previous studies. Background information should contain the following:

- Name and description of the investigational product(s)
- Findings from nonclinical studies that have clinical significance
- Findings from clinical trials that are relevant
- Known and potential risks and benefits, if any, to human subject
- Description of and justification for the route of administration, dosage, dosage regimen, and treatment period(s);
- A statement that the trial will be conducted in compliance with the protocol, GCP and the applicable regulatory requirement(s)
- Description of the population to be studied
- References to literature and data that are relevant to the trial, and that provide background for the trial

1.1.5.5 Trial objectives & purpose (ICH GCP recommended)

The ICH GCP E6(R3) guideline specifies that the protocol should contain a detailed description of the study objectives and the purpose of the trial. This is crucial as it sets the foundation for all other aspects of the study design and conduct.

The protocol must also justify the rationale for conducting the trial based on current scientific evidence. This involves explaining why the study is necessary, what it intends to prove or disprove, and how this contributes to existing knowledge or clinical practice.

Objectives should be specifically stated and can be categorized as primary and secondary objectives:

- The primary objective typically focuses on the main question the study seeks to answer, often related to the efficacy of an intervention.
- Secondary objectives may explore additional effects, long-term outcomes, or specific mechanisms.

1.1.5.6 Trial design (ICH GCP recommended)

The scientific validity of a given clinical trial depends largely on the thoughts and consideration that go into the design of the trial. Before we go into the items ICH GCP E6(R3) guidance recommends for this

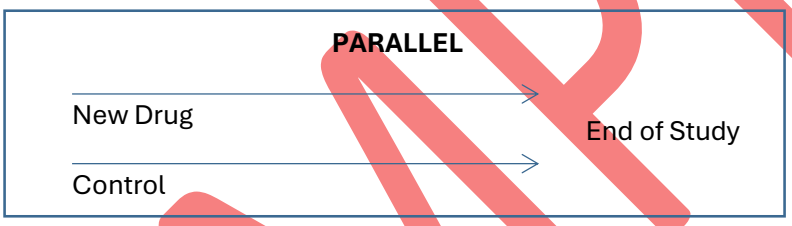
section, there are other topics that we should deeply cover first. These include common study design, sample size, method to reduce bias, and control groups. These topics are further discussed below.

1.1.5.6.1 Common study design types

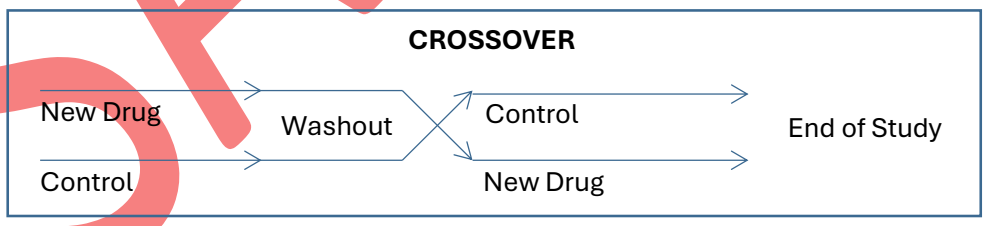
There are different study designs for different type of studies (prospective, retrospective, case control, effectiveness, etc.). We won't go into detail on these different types of studies, as it's beyond the scope of the SOCRA CCRP exam. However, the one area we should focus on is prospective study that is commonly used in evaluating a new drug or medical device.

A prospective study involves taking a group of subjects and evaluating them over a set time period. In our case, a new drug or device is given to subjects and measurements/tests are done over time to evaluate the safety and effectiveness of the intervention. The two most used designs for a prospective study are the parallel and crossover designs.

1. **Parallel**
   This is commonly used to compare a new treatment against a control group. In a parallel study, each subject is assigned to a study arm or group (either a new treatment or a control). Two or more study arms are common. The subjects in each arm are then monitored in parallel. At the end of study, the results from each arm are then compared against each other. Below is a schematic diagram of parallel study.



2. **Crossover**
   In a crossover study, two or more treatments are given sequentially to the same subject. A crossover study starts off like a parallel study in that each subject gets assigned into a treatment arm. At a pre-determined point in time, the subject is then switched into another treatment arm. Usually, a washout period occurs prior to the switch to allow time for the subject's body to return to pre-treatment status. The benefit of a crossover study is that each subject can serve as their own control. Often, less subjects are required in a crossover study.



1.1.5.6.2 Sample size

The sample size for a trial is usually determined by a statistician. To do this, a statistician uses prior findings and assumptions to evaluate:

- The magnitude of the drug or device effect (effect size) expected between the treatment arms. This is the difference in what you expect to see with the new drug or device vs. comparator (placebo or other treatment). This is often hard to determine for a Phase II trial as there is not much information available until after the trial is completed. An educated guess from prior

experience or findings is often used. The results of the Phase II trial is then used to determine the effect size for the Phase III trial.

- The variability of the outcome. This is similar to effect size in that the variability is also often determined by an educated guess using data from prior work or best known experience.

- The probability of observing the effect (statistical power of the test). Using the effect size and variability, the statistician can then calculate the different sample sizes needed for different levels of statistical power. Usually, more subjects are needed to meet higher levels of statistical power. For example, a given study may need 200 subjects to show the effect at 80% statistical power and 300 subjects to show the effect at 90% power.

1.1.5.6.3 Methods of reducing bias

Bias in the context of clinical trials is the tendency to give preference or partiality that prevents objective results to be obtained. As there is usually greater interest in proving that a new drug works than in proving it doesn't work, biases in clinical trials often lead to results that show an exaggerated impact of the drug or device being tested. Below are some methods used to reduce bias in clinical trials:

Blinding

Blinding is a method where personnel involved in the trial are intentionally blinded from knowing the treatment assignment of each subject. Without the knowledge of assigned treatment arms, preferential treatment cannot be given. Thus, each subject should theoretically be treated in the same manner. Blinding can be done by making the treatment look the same. If that is not possible, a third party not involved in the trial can administer the treatment. Below are some common blinding practices:

- **Triple blind** is when the sponsor, investigator and staff, and the subjects are blinded
- **Double blind** is when the investigator and staff and subjects are blinded
- **Single blind** is when the subjects are blinded
- **Open label** is when no blinding is done

Randomization

Randomization is a method where subjects are randomly assigned into different treatment arms. This helps reduce bias by ensuring that no subjects get preferential treatment in their assignment to an arm. Randomization also helps ensure that the blinding is maintained, as the investigator & staff cannot make guesses on treatment assignment.

Randomization is often done in blocks. For example, if the trial plans to enroll 50 total subjects into 2 groups (new drug vs. control), 5 blocks of 10 subjects can be randomly assigned. Each block of 10 will contains 5 subjects taking new drug and 5 subjects taking control.

The value in using block assignment is that it ensures even subject distribution in case the study needs to be terminated early. In the example above, if the study ends after 20 subjects have been enrolled, we will have 10 subjects taking new drug and 10 subjects taking control. If no block assignment is used, the distribution of subjects will be random and may not be equally distributed when the study is terminated.

Author's Notes:
Know the two most used methods for reducing bias in clinical trials:
- Blinding
- Randomization

1.1.5.6.4 Control groups

In clinical trial, subjects are usually assigned into a new treatment or a control group. Control groups are groups that the performance of the new treatment will be compared against. Control group can be:

- **Placebo**
  A placebo is a mock treatment that exactly mimics the new treatment in appearance and administering procedure. Placebos can look exactly like the new drug, but they contain inert substances that have no therapeutic benefit (e.g. a sugar pill). A placebo is used to minimize any psychological effects of the subject being in the trial. It also gives us data on baseline adverse events that occur through the normal course of the disease.

  Placebo usage is common. However, in cases where withholding standard treatment would be unethical (e.g. where standard treatment is known to be effective against the disease), a placebo should not be used as a control.

- **Standard care**
  Standard care should be used in cases where placebo usage would be unethical. Standard care can be existing drugs or treatments that are currently used in clinical care. The study would then compare the effects of the new drug or treatment against the current drug or treatment.

- **Historical control**
  Historical control may be used in cases where the other control options are not available or practical. Historical control may be prior data from similar patients with the same disease. It can also be data from the same patient in a crossover study.

  The level of similarity between patients in the historical control and the current treatment group is important. Higher similarity between the two comparison groups would strengthen the validity of a study using historical control.

1.1.5.6.5 ICH GCP guideline recommendations

Below are the items recommended by the ICH GCP E6(R3) guidance specifically for the trial design section of the clinical trial protocol.

- Primary endpoints and the secondary endpoints, if any, to be measured during the trial;
- 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;
- The measures taken to minimize/avoid bias, including:
  - Randomization
  - Blinding
- Trial treatment(s) and the dosage and dosage regimen of the investigational product(s). Also, include a description of the dosage form, packaging, and labeling of the investigational product(s);
- Expected duration of subject participation, and a description of the sequence and duration of all trial periods, including follow-up, if any;
- A description of the "stopping rules" or "discontinuation criteria" for individual subjects, parts of trial and entire trial;
- Accountability procedures for the investigational product(s), including the placebo(s) and comparator(s), if any;
- Maintenance of trial treatment randomization codes and procedures for breaking codes; and

- 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 as source data.

E6(R3) Note - Decentralized & Hybrid Trial Design:

E6(R3) formally recognizes decentralized clinical trial (DCT) designs, where some or all trial activities occur outside the traditional clinical site. If a protocol includes decentralized elements, the trial design section should address:

- Which activities will be conducted remotely vs. on-site
- How remote data collection will be managed (e.g., wearable devices, electronic patient-reported outcomes, telehealth visits)
- How informed consent will be obtained if using electronic consent (eConsent) processes
- How investigational product will be managed if shipped directly to participants
- How participant safety will be monitored in a decentralized setting

Not all trials will include decentralized elements, but awareness of these design options is increasingly important for clinical research professionals.

1.1.5.7 Selection and withdrawal of subjects (ICH GCP recommended)

Study population and the number of subjects to be enrolled should be described in this section. Withdrawal criteria may also be included. Below are the items ICH GCP E6(R3) guideline recommends for this section:

- Inclusion criteria;
- Exclusion criteria; and
- Withdrawal criteria (i.e. terminating investigational product treatment/trial treatment) and procedures specifying:
  - When and how to withdraw subjects from the trial/investigational product treatment
  - The type and timing of the data to be collected for withdrawn subjects
  - Whether and how subjects are to be replaced
  - The follow-up for subjects withdrawn from investigational product treatment/trial treatment

1.1.5.8 Treatment of subjects (ICH GCP recommended)

This section should describe specific treatment(s) to be administered. Below are the items recommended by the ICH GCP E6(R3) guidance:

- The treatment(s) to be administered, including the name(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);
- Medication(s)/treatment(s) permitted and not permitted before and/or during the trial; and
- Procedures for monitoring subject compliance.

In addition, below are some common topics that may also go into this section:

- Investigational product storage and accountability and
- Return or destruction of investigational product

1.1.5.9 Description of study procedures (commonly used)

ICH GCP E6(R3) guidance recommends sections that include assessment of efficacy and safety. The description of these sections can be incorporated into a study procedures section that is commonly used in the industry. An example of a commonly used table that summarizes study procedures / activities is shown below. Also below are some common study procedures.

- Screening procedures
  - Screening/enrollment identification numbers
  - Informed consent
  - Demographics
  - Medical history
  - Screening tests
- Efficacy procedures
  - Tests for efficacy (e.g. viral load for HIV drug)
- Safety procedures
  - Physical examination
  - Vital signs
  - Clinical laboratory tests
  - Previous / concomitant medications
  - Electrocardiograms (ECG)
  - Adverse event (AE) assessments
  - Pharmacokinetics (PK) Procedures

Example Study Schedule of Activities Table

	In-hospital Stay				Follow-up Visit
Days	**Observation Period**	**Study Day 1**	**Study Day 2**	**Study Day 3**	**Study Day 7**
Hours	**-6 to 0**	**0-23**	**24-47**	**48-72**	
Informed consent	✓				
Inclusion/exclusion criteria review	✓				
Demographics / Medical history	✓				
Screening test	✓				
Physical exam	✓	✓	✓	✓	✓
Vital signs	✓	✓	✓	✓	✓
Previous/concomitant medications	✓	✓	✓	✓	✓
Randomization	✓				
Study drug administration		✓	✓	✓	
Clinical laboratory test / ECG	✓	✓	✓	✓	✓
Efficacy test		✓	✓	✓	✓
Adverse event assessments	✓	✓	✓	✓	✓
PK blood draw		✓	✓	✓	
Drug accountability		✓	✓	✓	

1.1.5.10 Data and Safety Monitoring Plan (DSMP) and Data Safety Monitoring Board (DSMB) (commonly used)

A Data and Safety Monitoring Plan (DSMP) is a plan that is used to ensure the safety of the subjects. Validity of the data is also a part of the DSMP.

A Data Safety Monitoring Board (DSMB) is a group of experts that reviews research data to ensure subject safety and data validity following the plan described in DSMP. The DSMB is also known as Data Monitoring Committee (DMC). During the DSMB review of trial data, the DSMB may invite the principal investigator (PI) or designee to provide information on study conduct, present data, or respond to questions. The DSMB may also request any data in its assessment and may review unblinded data.

If required, a DSMP and DSMB section should be included in the protocol. This section should describe:

- Procedures for DSMB to oversee the trial progress and the safety of subjects;
- Plans for DSMB to assure data accuracy and protocol compliance; and
- How the DSMB will review the reporting of unanticipated problems involving risks to subjects op adverse events to the IRB, FDA, sponsor, appropriate authorities, etc.

Author's Notes:
Know the definitions and basic functions of the DSMP and DSMB.

1.1.5.11 Adverse events (AEs) (commonly used)

An Adverse Events (AEs) section can either be incorporated into the study procedures section (see Section 1.1.5.10 Description of study procedures) or described explicitly under its own section. The ICH GCP E6(R3) guidance recommends that this section includes:

- Specification of safety parameters
  - Example: An adverse event or experience is defined as any symptom, sign, illness, or untoward experience (including a clinically significant abnormal laboratory finding) that develops or worsens during the study, whether the event is considered related to the study drug.
- Methods and timing for assessing, recording, and analyzing safety parameters.
  - Example: A description of the adverse event's relationship to the study drug (unrelated, unlikely, possible, probable, and definite) and adverse event severity (mild, moderate, severe, life threatening, and death).
  - Example: A description of serious adverse events (SAEs) and SAE reporting rules.
- Procedures for eliciting reports of and for recording and reporting adverse events and intercurrent illnesses.
- Type and duration of the follow-up of subjects after adverse events.

1.1.5.12 Statistics and statistical plan (ICH GCP recommended)

A statistical planning section should be described in the protocol based on calculations and plans from a statistician. ICH GCP E6(R3) guidance recommends the statistics section to include:

- Statistical methods to be employed, including timing of any planned interim analysis;
- Number of subjects planned to be enrolled;
- Level of statistical significance to be used;
- Criteria for the termination of the trial;
- Procedure for accounting for missing, unused, and spurious data;
- Procedures for reporting any deviation(s) from the original statistical plan;
- The selection of subjects to be included in the analyses (e.g. all randomized subjects, all dosed subjects, all eligible subjects, and evaluable subjects).

1.1.5.13 Data quality assurance (commonly used)

This section should describe procedures to be performed to ensure the accuracy and quality of the data. Below are some items that can be incorporated into this section:

- Data recording, handling, and record keeping;
- Study monitoring;
- Auditing and direct access to source data/documents

E6(R3) Update — Risk-Proportionate Quality Management:

Under E6(R3), data quality assurance goes beyond traditional monitoring and auditing. The guideline expects sponsors to implement a **quality management system (QMS)** that includes:

- Prospective identification of risks to critical data and processes
- Risk-proportionate monitoring plans (focusing resources on what matters most to participant safety and data reliability)
- Use of centralized monitoring techniques to detect data trends and signals across sites
- Ongoing evaluation and adaptation of quality controls throughout the trial lifecycle

The protocol's data quality assurance section should reflect this risk-proportionate approach by describing how critical data and processes will be identified and how monitoring intensity will be calibrated to risk.

The protocol should include a statement that permits trial-related monitoring, audits, IRB/IEC review, and regulatory inspection(s), providing direct access to source data/documents.

1.1.5.14 Administrative considerations (commonly used)

This section contains administrative or other topics that may be included in the protocol. Below are some items that may be included in this section:

- Ethical assurance for protection of human rights;
- Publication rights; and
- Financing and insurance.

1.1.5.15 References (commonly used)

This section plays a crucial role in providing the scientific and regulatory foundation for the study. Here's what should be included to ensure that this section is comprehensive and useful:

- Relevant literature
- Previous study results
- Regulatory guidelines (FDA, EMA, or ICH)
- Safety information
- Meta-analyses and systematic reviews
- Patents and proprietary information
- Statistical methods
- Ethical principles

Each reference should be presented in a consistent format that includes the author(s), title of the article, journal name, volume, page numbers, and year of publication. This allows reviewers and others involved

in the trial to access and verify the sources easily, ensuring transparency and credibility of the trial's foundation.

1.1.5.16 Appendices (commonly used)

Information that may be too complex for the body of the protocol can be placed in appendices. This may include details and results from previous trials, more description on the facilities available at the site, investigator's biography, etc.

1.1.6 Roles and responsibility for protection of human subjects including:

E6(R3) Update — Participant-Centered Protections:

While the federal regulations governing human subjects protection (45 CFR 46) have not changed, ICH GCP E6(R3) introduces a stronger emphasis on **participant-centered** trial conduct. Key additions include:

- **Participant perspective in trial design**
  E6(R3) expects sponsors and investigators to consider the participant's experience when designing trials — including trial burden, visit schedules, and accessibility of trial activities.
- **Meaningful informed consent**
  E6(R3) emphasizes that the informed consent process should be meaningful and ensure genuine understanding, not just compliance with documentation requirements. This includes supporting the use of technology (such as multimedia or interactive tools) to enhance participant comprehension.
- **Ongoing consent**
  E6(R3) reinforces the concept that consent is an ongoing process, not a one-time event. Participants should be kept informed of any new information that might affect their willingness to continue.
- **Diversity and inclusion**
  While not a prescriptive requirement, E6(R3) acknowledges the importance of designing trials that are accessible to diverse populations.

  These E6(R3) principles complement — but do not replace — the federal regulations (45 CFR 46, 21 CFR 50/56) that continue to govern human subjects protection in the United States.

1.1.6.1 Safeguards for children in clinical trials

45 CFR 46 Subpart D describes regulations to protect children participating in clinical research. Children are those who have not attained the legal age for consent to involvement in research. In the United States, state and local law determine the legal age of adulthood. In general, 18 years of age is the legal age of adulthood, but this can vary from state to state.

The federal regulations require IRBs to classify research involving children into one of four categories below:

1. Research not involving greater than minimal risk – see 45 CFR 46.404.
2. Research involving greater than minimal risk, but may provide direct benefit to an individual subject. Research in this category is approvable provided:
   a. The risk is justified by the potential benefit to the subject; and
   b. The relationship of risk to benefit is at least as favorable as any available alternative approach - see 45 CFR 46.405.

3. Research involving greater than minimal risk with no potential benefit to individual subjects, but may yield generalizable knowledge about the subject's disorder or condition. Research in this category is approvable provided:
    a. The risk represents a minor increase over minimal risk;
    b. The intervention or procedure presents experiences to subjects that are reasonably comparable to his/her clinical care; and
    c. The intervention or procedure is likely to yield generalizable knowledge for the understanding or treatment of the subject's disorder or condition – see 45 CFR 46.406.
4. Research that is not otherwise approvable, but which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children. The overseeing IRB must find that the research presents an opportunity to further the understanding, prevention, or alleviation of a significant problem affecting the health and welfare of children. The research must also be done with sound ethical principles - see 45 CFR 46.407.

1.1.6.1.1 Consent & assent requirements

When children or minors are involved in research, consent from one or both parent or legally authorized representative (LAR) is required. The overseeing IRB will determine whether informed consent from one or both parents is needed in response to the risk to the subjects involved. In addition, an assent of the child may be required. There is no requirement of specific age where assent must be sought, however, the overseeing IRB should determine assent requirement while considering the following factors:

- The nature of the research;
- Child's age, status, and condition; and
- Whether all or some of the children are capable of assenting to participation

> **Note:** If a child reaches the legal age of consent while enrolled in a study, unless the IRB determines that the requirements for obtaining informed consent can be waived (45 CFR 46.116(d)), the child, who is now an adult should be re-consent for ongoing continuation in research. This is because prior parental permission and child assent are not equivalent to informed consent for the now-adult.

1.1.6.1.2 Wards of the State

Children who are wards of the State or any other institution are further protected under federal regulations. These additional protections (in addition to IRB oversight, parental consent, and child assent) include:

- When research involves greater than minimal risk with no direct benefit to subjects, the research must be either related to the children status as wards or be conducted in settings where majority of children involved are not wards – see 45 CFR 46.409; and

- In addition to the any other individual acting on behalf of the child, the IRB must require appointment of an advocate to give consent to participate in clinical trial and protect the child's interest.

1.1.6.1.3 Points to consider for clinical research involving children

1. Is there direct benefit to the individual child participant? If so, are there alternative means to achieve the benefit?
2. Is there potential risk to the individual child participant? If so, what are the safeguards needed to minimize the risk?

3. Does the study involve placebo or controls that may place the child at greater risk by withholding from potential therapeutic interventions?
4. Have appropriate studies been done on animals, adults, or older children?
5. What is the legal age in the state the trial will be conducted? Can a child give assent? If so, at what age?
6. What legal limits are there on the right of parents to consent on behalf of their children?
7. Is permission of both parents needed? If one of the parents is not available, what are the acceptable reasons?
8. How will assurance be made to ensure that parents' permission for their children's participation is free from coercion, exploitation, and undue expectation?
9. How will the child's dignity and rights as a person be preserved? How will sensitive topics be handles? This may include topics such as child abuse or adolescent related topics such as confidentiality, sexual practices, drug use, etc.

Author's Notes:
Know consent and assent requirements for research involving children:
1. Parental consent from one or both parents or LAR is required
2. Child assent may be required as determined by the overseeing IRB

1.1.6.2 Protection of vulnerable subjects

Federal regulations require that IRB pay special attention when overseeing clinical trials that involve vulnerable subject population. This may include pregnant women, children, prisoners, mentally disabled persons, or economically - or educationally - disadvantaged persons. For this discussion, we will focus on clinical trials that involve pregnant women and prisoners.

1.1.6.2.1 Pregnant women

45 CFR 46 Subpart B describes regulations for participation of pregnant women in clinical trials. Pregnant women or fetuses may be involved in clinical research if all of the following conditions are met:

1. Where scientifically appropriate, with available preclinical data from pregnant animals and clinical data on non-pregnant women assessing potential risks to pregnant women and fetuses.
2. The risk to the fetus may result in 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. In addition, the important biomedical knowledge cannot be obtained by any other means.
3. Any risk is the least possible for achieving the objectives of the research.
4. The consent is obtained in accord with the required informed consent provisions of 45 CFR 46 Subpart A.
5. If the research may only benefit the fetus, consent from the pregnant woman and the father is needed. The father's consent needs not be obtained if he is unable to consent because of unavailability, incompetence, or temporary incapacity or the pregnancy resulted from rape or incest.
6. Everyone providing consent is fully informed on the potential impact of the research on the fetus or neonate.
7. For children who are pregnant, assent and permission are obtained in accord with 45 CFR 46 Subpart D.
8. No inducements, monetary or otherwise, will be offered to terminate a pregnancy.
9. Individuals engaged in the research will have no part in any decisions as to the timing, method, or procedures used to terminate a pregnancy; and

10. Individuals engaged in the research will have no part in determining the viability of a neonate.

Points to consider when for clinical research involving pregnant women

1. Is there a reason to include or exclude pregnant women?
2. Have appropriate studies on animals and non-pregnant women been done?
3. Is any special monitoring of the informed consent process needed? Is the risk to the fetus the least possible?
4. Will the mother be fully informed of the potential risk to the fetus and of alternative treatments and their risks and benefits?
5. Is the father's consent required?

1.1.6.2.2 Prisoners

45 CFR 46 Subpart C defines a prisoner as:

> *"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."*

To provided further protection for prisoner population, 45 CFR 46.304 requires the Institutional Review Boards overseeing research that involved prisoners to have:

1. 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.
2. 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.

In addition, 45 CFR 46 Subpart C (46.305) also requires 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 45 CFR 46 Subpart C (46.306(a)(2)), see next section below;
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 non-prisoner 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.

45 CFR 46 Subpart C (46.306) - Permitted research involving prisoners

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; and
2. In the judgment of the Secretary the proposed research involves solely the following:
    a. 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;
    b. Study of prisons as institutional structures or of prisoners as incarcerated persons, provided that the study presents no more than minimal risk and no more than inconvenience to the subjects;
    c. 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
    d. 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 his intent to approve such research.

Author's Notes:
Research involving prisoners is strict in terms of IRB requirements and the types of studies allowed. We covered parts of vulnerable population (children, pregnant women, and prisoners) in the above sections, but mentally disabled persons, or economically - or educationally - disadvantaged persons/populations are beyond the scope of this study guide.

1.1.6.3 Emergency use research

Refer to section 1.1.4.1 Emergency use of a research product. To protect human subjects in the situation where an emergency use of a research product is needed:

1. Informed consent should be sought if possible (unless exception criteria listed in 21 CFR 50.23(c) are met – see 1.1.4.1 Emergency use of a research product for more details).

2. IRB notification should be made if possible (unless exemption in 21 CFR 56.104(c) is met). If no reporting to the IRB was made prior to emergency usage, IRB reporting must be made within 5 days of the usage 21 CFR 56.104(c).