

# ES' SOCRA CCRP STUDY GUIDE

[www.ClinicalResearchAssociateCRA.com](http://www.ClinicalResearchAssociateCRA.com)

*Version: 1.5*

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**NOTE: Error messages above were due to chapter 2 -11 not being included in this sample chapter of the ES' SOCRA CCRP Study Guide**

# Introduction

My name is Ernie Sakchalathorn and I'm the guy behind [www.ClinicalResearchAssociateCRA.com](http://www.ClinicalResearchAssociateCRA.com). I have been in clinical research since 2007. My career started in academic science. After six years in an academic lab, I transitioned into clinical research, working as a Clinical Research Coordinator (CRC) at a hospital site for three years. From there, I progressed into a Clinical Research Associate (CRA) role at an in-vitro diagnostic sponsor company for 3.5 years, at several drug sponsor companies for 2 years, and at a CRO for 2.5 years. I'm currently a Sr. CRA at a medical device company, setting up and monitoring different trials in Diabetes population.

I was a Certified Clinical Research Coordinator (CCRC) through the Association of Clinical Research Professionals (ACRP) when I was a CRC in 2010. I have been a Certified Clinical Research Professional (CCRP) through the Society of Clinical Research Associates (SOCRA) since September 2013.

I compiled this ES' SOCRA CCRP Study Guide to help those who want to get Certified Clinical Research Professional (CCRP) certification through SOCRA. When I took the SOCRA CCRP exam in September 2013, I had a hard time studying for the exam in between my full time work schedule in the office and traveling to sites. The vast and dense information out there were cumbersome and not easy to understand. I needed summaries in bullet points to help break down the information. This Study Guide is exactly that. This Study Guide was compiled from the notes I took when I was studying. From these notes, I was able to pass the SOCRA CCRP exam with a score of 96% (I answered 130 questions correctly out of 135 questions total). The notes have been updated to fit the new exam outline for those taking the exam after June 1, 2014.

If you're new to the industry or you are planning to take the SOCRA CCRP exam, I'm here to help. Please shoot me any questions, comments, or suggestions anytime. Any post-exam feedback from those who used this Study Guide to prepare would be greatly appreciated.

Sincerely,

Ernie Sakchalathorn

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## Disclaimer

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SAMPLE

# 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).  
<https://www.socra.org/membership/applications-and-renewals/apply-for-new-membership/>
2. Register for CCRP certification exam (\$395 fee, must meet one of the eligibility options below and provide detailed CV/resume, verification of employment, and job description. See link below for more details)  
<https://www.socra.org/certification/ccrp-certification-exam/candidate-eligibility/>

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 <b>AND</b> 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) <b>AND</b> Hold an Associate's or Bachelor's Degree in a science, health science, pharmacy or related field <b>AND</b> 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.

SOCRA CCRP® Certification Application in paper format should be completed. Here is a link to the application: <https://www.socra.org/assets/Certification/Certification-ApplicationNewFooter150626.pdf>.

Completed application, supporting documentations, and fee can be sent via mail. Email scans can also be sent to [certification@socra.org](mailto:certification@socra.org). *Once an application is approved by SOCRA, no refunds will be issued.*

3. Enrollment confirmation letter and copy of the SOCRA Certification Program Reference Manual will be sent to the address on the application form.
4. Three weeks prior to the testing date, a VERIFICATION letter with details regarding the exam policies and location information. The applicant **MUST** bring this VERIFICATION letter and photo ID in order to be admitted to the examination site.
5. Attend and complete examination
6. Renew CCRP certification every three years (maintain membership during the three year period, \$350 fee)
  - a. Report 45 continuing education hours every three (3) years **AND**
  - b. Take the SOCRA Recertification Continuing Competence Learning Module

# ES' SOCRA CCRP Study Guide Outline

Below are the five subject areas and the percent of scored test items included in each area. This information is listed on SOCRA CCRP examination website:

<https://www.socra.org/certification/ccrp-certification-exam/exam-outline/>

This applies to exams to be held after June 1, 2014. This ES' SOCRA CCRP Study Guide has been updated to apply for those taking exams after June 1, 2014 under the new exam outline below.

## Five Subject Areas and Percent of Scored Test Items (Range) Included in Each Area

### 1. Ethical Principles/ Informed Consent/Safety (20% - 25%)

- Nuremberg Code
- Belmont Report
- Declaration of Helsinki
- Informed consent including development, content, review, approval, discussion, documentation and ongoing updates.
- Maintenance of informed consent documents an (paper/electronic)
- Abstracting/verification of information from medical records related to informed consent and safety reporting
- Vulnerable subjects
- Safety Reporting (adverse events, serious adverse drug experiences, unanticipated adverse device effects)
- Financial disclosure

### 2. Institutional Review Board/ Institutional Ethics Committee (IRB/IEC) Roles and Responsibilities (7% - 11%)

- Roles and Responsibilities roles, etc. of IRB/IEC
- Determination that the rights, welfare and safety of study subjects including vulnerable populations are protected
- Development and implementation of Standard Operating Procedures (SOPs)
- Membership
- Protocol review
- Significant Risk/Non Significant Medical Device study determination
- Documentation
- Development, maintenance of IRB/IEC related documents (paper/electronic)
- Record retention IRB/IEC

### 3. Clinical Trial Protocol and Protocol Amendments (4% - 8%)

1. Protocol development (including study design with considerations methods to reduce bias, objectives, endpoints, data safety monitoring)
2. Protocol Amendments

### 4. Investigator's Roles and Responsibilities (28% - 32%)

- Roles, responsibilities and obligations of the investigator



- Study conduct in accordance with investigational plan, investigator agreement and applicable regulations
- Protocol(s) and protocol related document(s) (i.e., informed consent documents, recruitment materials, safety reports, continuing reviews) development, review, and submission for reviewing authorities
- Recruitment, screening, enrollment, and retention of subjects
- Investigational product accountability at site (including training of subjects)
- Study visits and follow up care
- Investigational site source documentation
- Documentation/Reporting of study subject discontinuation
- Investigational site study related reports (i.e. progress reports, protocol changes, protocol deviations, final reports)
- Protocol(s) and protocol related document(s) (i.e., informed consent documents, recruitment materials, safety reports, continuing reviews) for reviewing authorities
- Source Documentation/Case Report Forms
- Maintenance of essential study related documents (paper/electronic)
- Abstracting/verification of Information from Medical Records
- Record retention requirements for clinical sites
- Investigational site corrective and preventative action plans (CAPA)

#### 5. Sponsor's Roles and Responsibilities (31% - 35%)

- Roles, responsibilities, and obligations of the sponsor
- Investigator/site qualifications
- Investigator Brochure
- Investigational site training, management, oversight and investigator compliance
- Protocol(s) and protocol related document(s) (i.e., informed consent documents, recruitment materials, safety reports, continuing reviews) development, review, and submission for reviewing authorities
- Site/investigator training (GCP, investigational product, study training, reporting requirements)
- Sponsor Investigational product accountability
- Standard Operating Procedures (SOPs)
- Regulatory documents (i.e. FDA Forms 1571, 1572, 3454, 3455, IND, IDE, Medwatch (3500 and 3500A), annual reports, safety reports, final reports)
- Study Plan
- Maintenance of essential study related documents (paper/electronic) for sponsors
- Development, verification, maintenance of electronic records and electronic record systems
- Monitoring including study coordination, record verification and quality assurance
- Abstracting-verification of Information from Medical Records
- Record retention (Sponsor)
- Sponsor corrective and preventative action plans (CAPA)

#### Additional Relevant Subject Areas

In addition to the above subject areas, this ES' SOCRA CCRP Study Guide will include additional relevant areas listed below. These additional relevant areas are from my experience in the clinical research industry. 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 that are not purely factual, but require industry experience to answer correctly.

## 6. Drug Development

- Drug discovery
- Pre-clinical testing
- Clinical trials (Phase 0, I, II, and III)
- Post market surveillance (Phase IV)

## 7. Medical Device (and In Vitro Diagnostic) Development

- Medical device classification (Class I, II, III)
- Medical device clinical Trials
- Difference between medical device and drug clinical trials
- In vitro diagnostic development

## 8. FDA Inspection

- Inspection of sponsor or CRO
- Inspection of clinical trial site

## 9. Case Studies

## 10. What to Do On Exam Date

## 11. Last Words

# 1. Ethical Principles/Informed Consent/Safety (20% - 25%)

Protection of human subjects is the main emphasis of current regulations and current clinical trial practices. SOCRA recognize this which reflects on the 20% - 25% weight (26 – 33 questions out of 130 graded questions) on this section.

## 1.1 Ethical Principles

Understanding and knowing the influential codes of ethics and the timeline will help us prepare for this section.

### 1.1.1 Nuremberg Code (1947)

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 in order to test possible antidotes. Many more examples of unethical treatments of prisoners were performed. At the end of World War II, the Nuremberg trials were conducted and the Nuremberg Code was established in 1947. Ten elements of human research conduct were given. The Nuremberg Code can be found at: <http://www.hhs.gov/ohrp/archive/nurcode.html>

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

1. *Voluntary informed consent is absolutely essential.*
2. *Research should yield 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. *Conducted only by scientifically qualified persons.*
9. *Subject can withdraw from the research at any time.*
10. *Researchers must be able to end the study if there is a 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 professional and governmental codes since the 1950s, including the Declaration of Helsinki in 1964.

### 1.1.2 Declaration of Helsinki (1964)

The Declaration of Helsinki was developed by the World Medical Association (WMA) in 1964 with basis from the principles of the Nuremberg Code. The Declaration laid out general principles that physicians should abide by when conducting research involving human subjects, including identifiable human material and data.

The Declaration is the first significant effort of the medical community to regulate itself. Since its release in 1964, revisions were made to improve the Declaration. Its current form can be found through this link: <http://www.wma.net/en/30publications/10policies/b3/index.html>. The Declaration set the stage for further creation and implementation of regulatory bodies and regulations.

### 1.1.3 Belmont Report (1979)

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. 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:

- **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.
- **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.
- **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.

#### ES' NOTES:

- Know the timeline of historical events  
*(Nuremberg Code 1947 → Declaration of Helsinki 1964 → Belmont Report 1979)*
- Know the 3 principles of the Belmont Report and their applications:
  1. **Respect for Person** = informed consent
  2. **Beneficence** = risk/benefit analysis
  3. **Justice** = appropriate selection of patients

## 1.2 Informed Consent

Informed consent is defined by the [ICH GCP guideline](#) as:

*A process by which a subject voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the subject's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.*

Two important words in the above definition are “voluntarily” and “informed.” The informed consenting process should ensure that potential participants understand all aspects involved in the research and able to decide freely whether or not to participate. Also, informed consent is a “process.” The process of consenting will be discussed in more detailed below.

### 1.2.1 Development

#### 1.2.1.1 Readability

Informed consent form should be written with the subjects in mind. It should be concise and easy to understand. It should contain technical and medical information in lay terms. **Sixth- to eight-grade** levels language should be used. The Flesch-Kincaid reading scale, under the spell-checking area in Microsoft Word, can be used to check reading level.

#### 1.2.1.2 Content

[21 CFR 50.25](#) lists the basic elements of informed consent:

- (1) A statement that the study involves research and
  - **Purposes;**
  - **Duration; and**
  - **Procedures** to be done and identification of any procedures which are experimental
- (2) A description of any reasonably foreseeable **risks or discomforts.**
- (3) A description of any **benefits.**
- (4) A disclosure of appropriate **alternative procedures** or courses of treatment.
- (5) A statement describing how the **confidentiality** of records will be maintained and 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.

[21 CFR 50.25](#) also lists additional elements of informed consent:

- (1) A statement that the particular treatment or procedure may involve **unforeseeable risks** to the subject.
- (2) Circumstances where the subject's **participation may be terminated by the investigator**.
- (3) Any **additional costs** to the subject.
- (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 will be provided to the subject.
- (6) The approximate **number of subjects** involved in the study.

For applicable clinical trials started on or after March 7, 2012, informed consent documents must also include a specific statement on trial's description on [www.ClinicalTrials.gov](http://www.ClinicalTrials.gov). This statement allows investigators to inform participants that trials information is available on [www.ClinicalTrials.gov](http://www.ClinicalTrials.gov).

The specific statement is:

*"A description of this clinical trial will be available on <http://www.ClinicalTrials.gov>, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time."*

In addition to above, some state law may require additional items to be included. For example, **California** requires that a **Patient Bill of Rights** be attached to all consent forms. Health Insurance Portability and Accountability Act (**HIPAA**) **form** are often attached to informed consent form as well.

#### ES' NOTES:

- Know the language level recommended for informed consent form: **6<sup>th</sup> - 8<sup>th</sup> Grade**
- Know the **8 basic** elements of informed consent form. Knowing the **6 additional elements** of informed consent form may be useful. However, they are less likely to be on the exam in my opinion.

### 1.2.2 Review and Approval of Informed Consent Form

The responsibility of informed consent form review and approval lies with the institutional review board (IRB) that oversees the clinical trial. Although a sample consent form may be provided by the sponsor,

many IRBs have their own standard language and/or a standard format of consent form to be used. The overseeing IRB has the final authority to approve / disapprove consent form to be used in the clinical trial under review.

### 1.2.3 Informed Consent Discussion and Documentation

It was mentioned earlier that informed consent is a “process.” This process should allow the sharing of information and answering questions and concerns, with the signing of the informed consent form afterward. The process may continue after the signature is obtained to ensure continued consent or when there is a change in research that required a new consent. There are two important points to remember regarding informed consenting:

1. No person can participate in clinical research without the person’s or the person’s legally authorized representative (LAR) consent ([21 CFR 50.20](#)); and
2. Documentation of informed consent is required ([21 CFR 50.27](#))

Two types of informed consent forms can be used: the short form and the long form.

#### 1.2.3.1 Short Form

[45 CFR 46.117\(b\) \(2\)](#) and [21 CFR 50.27\(b\) \(2\)](#) allow the use of a short form consent document. A short form is a document that states that the elements of informed consent have been presented orally to and understood by the participant or the participant’s LAR.

Four components are needed for a consent process using a short form:

1. A short form consent document;
2. An oral presentation of the required elements of informed consent;
3. An IRB approved written summary of what is to be said to the participant or the participant’s LAR; and
4. A witness must be present during the oral presentation.

What situation may an investigator use short form consent document?

Below are some examples.

Note: IRB approval of the short form consent document and written summary is needed prior to usage.

- When a potential subject does not understand English and the investigator does not have an IRB-approved consent document translated into appropriate language; and
- When the window of opportunity for a subject to benefit from research participation is brief, and the IRB finds that by use of short form consent document is appropriate

#### Documentation of Short Form Consent Document

- Subject or LAR signs the short form consent document;
- Witness signs both the short form consent document and written summary;
- The person obtaining the consent signs the written summary; and

- A copy of both the short form consent document and written summary are given to the subject or LAR.

### **1.2.3.2 Long Form**

The long form consent document is the **standard consent form** that lists all required elements of informed consent. The long form spells out in writing all that is orally presented when the short form is used. Long form consent document should be used whenever possible.

#### **Documentation of Long Form Consent Document**

- Subject or LAR signs and date two copies of the long form consent document (one copy for the subject or LAR, another copy for the person obtaining the consent); and
- Alternatively, subject or LAR signs and date one copy of the long form consent document. A copy is made and provided to the subject or LAR afterward

### **1.2.4 Ongoing Updates to Informed Consent Form**

The **IRB approval is needed** for all changes to the approved informed consent form. Handwritten revisions should not be made directly to the consent form that is being used to consent a subject. Once the IRB approves a revised consent form to replace a previous consent form, previous consent form can no longer be used. Depending on the type of changes made, re-consenting subjects who signed prior version of the informed consent form may be needed.

### **1.2.5 Maintenance of Informed Consent Form**

The **original signed informed consent form** should be kept with the study files and a copy given to the subject or the subject's LAR. If the subject or LAR requests an original copy, two original signing should be arranged (one for study file and one for subject or LAR). All signed informed consent forms for all subjects should be kept with the study files. This includes withdrawn subjects who changed their mind after signing the informed consent form. In general, paper version of informed consent form should be kept with the study files. Scanned electronic version may also be kept in addition to the required paper version. Refer to each overseeing IRB's policy regarding specific procedure on informed consent form maintenance.

### **1.2.6 Monitoring of Informed Consent Form**

Informed consent form serves as a proof of the subject's authorization to participate in clinical trial. Because of this, informed consent form review is one important focus area when FDA conducts an inspection at a clinical site. For both clinical research coordinator (CRC) and clinical research associate (CRA), monitoring of informed consent form is critical to ensure that appropriate documentation of informed consent is practiced.

When reviewing the informed consent forms, a CRC or CRA should ensure that:

- The subject signed the most recent IRB approved version;
- The subject signature is present in addition to the subject's name;
- The subject dated for him/herself and the date is correct (verify against date of visit and date/time of study procedure on medical records);



- An error was corrected by drawing a signal line through the error; and
- All pages of the informed consent document are present

**ES' NOTES:**

- Know the differences between short and long informed consent form and their use
- Know the details for informed consent form monitoring

## 1.3 Safety Assurance & FDA Reporting of Adverse Events / Vulnerable Subjects / Financial Disclosure

### 1.3.1 Source Data Verification/Review Related To Informed Consent and Safety Reporting

Source Data Verification (SDV) is the process where data within the case report form (CRF) or other data collection systems are compared to the original source of information to confirm data accuracy.

Source data review (SDR) is a review of source documentation to check quality, review protocol compliance, and ensure compliance. SDV and SDR are important areas of focus when a clinical research associate (CRA) conducts site monitoring visits. This is to ensure subjects' protection and that information and the results of the trial are being recorded properly and accurately. Source documents may include medical charts, laboratory and radiology reports, subject's diaries, and pharmacy records. Below are areas where source data verification / review can be performed:

#### 1.3.1.1 Informed Consent Verification

In addition to the items listed in [section 1.2.6 Monitoring of Informed Consent Form](#) above, below are some additional items to consider when reviewing / verifying information on the consent form against source information:

- Compare the date that the subject signed the informed consent form against the study procedures dates. The date on the informed consent form must be either the same or an earlier date (i.e. subject authorized his/her participation prior to receiving study procedures).

#### 1.3.1.2 Case Report Form (CRF) Verification

Case report form (CRF) is a paper or electronic document designed to record all of the protocol required information to be reported to the sponsor. Data recorded onto CRF should follow protocol specifications. The data recorded are from source documents and thus, should match with source documents. Below are some consideration when reviewing / verifying information on the CRF:

- Compare the data recorded on the CRF against the data from the source documents.
- In the circumstances where source data were entered directly onto the CRF, signature or initial of the person recording and date should be recorded.

#### 1.3.1.3 Safety Reporting of Adverse Events (AEs) and Serious Adverse Events (SAEs)

An adverse event (AE) or experience is symptom, sign, illness, or untoward experience (including a clinically significant abnormal laboratory finding) that develops or worsens during the course of the

study, whether or not the event is considered related to study treatment. All AEs, whether or not related to study treatment, must be fully and completely documented on the AE page of the CRF and in the patient's medical records. Below are some considerations when reviewing / verifying AEs on the CRF:

- Ensure that all AEs are recorded on both the CRF and in the patient's medical records;
- Review AE records and reports whether protocol procedures are followed; and
- Check that responsible person (investigator or designee) had assessed AEs for seriousness, causality, and expectedness.

A **serious adverse events (SAE)** - or serious adverse reaction - is any untoward medical occurrence that can occur at any dose that:

- Results in death;
- Is life threatening (IE, the patient was at immediate risk of death at the time of the event);
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity (i.e. a substantial disruption of the patient's ability to carry out normal life functions); and
- Is a congenital anomaly/birth defect

#### SAE Reporting Requirement

[21 CFR 312.64](#) requires that an investigator **immediately** reports to the sponsor any serious adverse event (SAE), whether or not considered drug related, and must include an assessment of whether there is a reasonable possibility that the drug caused the event. [21 CFR 312.32](#) requires that the sponsor then must notify FDA and all participating investigators of potential serious risks, as soon as possible, but in no case later than **15 calendar days** after the sponsor determines that the information qualifies for reporting as:

- (i) **Serious and unexpected suspected adverse reaction** (i.e. SAEs);
- (ii) **Findings from other studies** (epidemiological studies, pooled analysis of multiple studies, or clinical studies that suggest a significant risk in humans exposed to the drug);
- (iii) **Findings from animal or in-vitro testing** (reports of mutagenicity, teratogenicity, or carcinogenicity, or reports of significant organ toxicity at or near the expected human exposure); and
- (iv) **Increased rate of occurrence of serious suspected adverse reactions**

For medical device clinical trials, an **unanticipated adverse device effect (UADE)** 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 812.3](#)).

## UADE Reporting Requirement

[21 CFR 812.150](#) requires that an investigator submits to the sponsor and to the reviewing IRB a report of any unanticipated adverse device effect (UADE) 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. After the sponsor first receives notice of a UADE from the investigator, a sponsor shall then report the results of such evaluation to FDA and to all reviewing IRB's and participating investigators within [10 working days](#).

As both SAE and UADE are critical to the health and safety of the subject, principal investigator, CRC, and CRA overseeing the clinical trial should ensure that above requirements for SAE and UADE reporting are properly followed.

### ES' NOTES:

- Know SAE and UADE reporting requirements  
SAE in drug trial: [immediately](#) for investigator and [15 calendar days](#) for sponsor  
UADE in medical device trial: [10 working days](#) for both investigator and sponsor

## 1.3.2 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 children.

### 1.3.2.1 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:

- 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.
- 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.
- Any risk is the least possible for achieving the objectives of the research.
- The consent is obtained in accord with the required informed consent provisions of [45 CFR 46 Subpart A](#).
- If the research may only benefit the fetus, consent from the pregnant woman and the father is needed. 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.

- (f) Each individual providing consent is fully informed on the potential impact of the research on the fetus or neonate.
- (g) For children who are pregnant, assent and permission are obtained in accord with [45 CFR 46 Subpart D](#).
- (h) No inducements, monetary or otherwise, will be offered to terminate a pregnancy.
- (i) 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
- (j) Individuals engaged in the research will have no part in determining the viability of a neonate.

#### Points To Consider When Considering 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?
4. Is the risk to the fetus the least possible?
5. Will the mother be fully informed of the potential risk to the fetus and of alternative treatments and their risks and benefits?
6. Is the father's consent required?

#### 1.3.2.2 Children

[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 [[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 [[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 [[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 [[45 CFR 46.407](#)].

### Consent and Assent Requirement

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 subject.

### 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** ([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.

### Points To Consider When Considering 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.

#### ES' NOTES:

- Know consent and assent requirement for research involving children
  - o Parental consent from one or both parents or LAR is required
  - o Child assent may be required as determined by the overseeing IRB

### 1.3.3 Financial Disclosure

[21 CFR 54](#) describes financial disclosure required by clinical investigators. The regulation requires sponsors/manufacture to certify the absence of certain financial interests and arrangements that could impact the reliability of clinical trial data. If there are financial interests involved, steps taken to minimize the potential for bias ([21 CFR 54.4\(a\)](#)) should be given to FDA. A sponsor is required to obtain financial information from investigator before the conduct of the clinical trial. A sponsor may provide investigator's financial disclosure via:

1. A certification that no financial interests exists ([FDA Form 3454](#), Certification)
2. Complete disclosure statement using [FDA Form 3455](#), Disclosure Statement
3. Certification that financial disclosure was not obtained after sponsor's due diligence (option 3 on [FDA Form 3454](#))

#### 1.3.3.1 Disclosable Financial Interests and Arrangements

Below is a list of disclosable financial interests and arrangements. Note that the dollar amounts that trigger reporting are the combined financial interests of the investigator, spouse, and dependent children.

1. Any compensation made to the investigator by any sponsor where the value of compensation could be affected by study outcome.

2. A proprietary interest in the tested product such as a patent, trademark, copyright or licensing agreement.
3. Any equity interest in any sponsor of the clinical study (i.e., stock, stock options, or other financial interest) whose value may not be readily determined during the time of the study conduct and for one year afterward.
4. Any stock in any sponsor of the clinical study that exceeds \$50,000 in value held during the time of the study conduct and for one year afterward.
5. Significant payments of other sorts (SPOOS) in the amount of \$25,000 or more from the sponsor of the study to the investigator or the investigator's institution during the time of the study and for one year afterward. This excludes the costs of conducting the clinical study involved or other clinical studies.

### ***1.3.3.2 What is the Time Period Where Financial Disclosure is Required?***

The regulation requires that investigators provide information on financial interests and arrangements **during the course of the study** and for **one year after completion** of the study (21 CFR 54.4(b)). “During the course of the study” means the time from the date the clinical investigator entered into an agreement with the sponsor to conduct the study until the completion of the study. Completion of the study is when all study subjects have been enrolled and follow-up of primary endpoint data on all subjects has been completed.

#### **ES' NOTES:**

- Know the time period where financial disclosure is needed
  - o During the course of the study and
  - o One (1) year after completion

The sample materials end here.

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