SOCRA® SOURCE
FOR CLINICAL RESEARCH EXCELLENCE

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HIGHLIGHTS IN THIS ISSUE

QUALITY EDUCATION

PEER RECOGNITION

CLINICAL RESEARCH CERTIFICATION

SOCRA®
FOR CLINICAL RESEARCH EXCELLENCE

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SOCRA EDUCATION CALENDAR

November 2021
Clinical Site Coordinator / Manger and GCP Workshop
November 4 and 5, 2021 I New Orleans, LA

Clinical Research Professional Certification Preparation and GCP Virtual Review Course
November 10 and 11, 2021 I Virtual

FDA Clinical Trial Requirements, Regulations, Compliance and GCP Virtual Conference
November 16 to 18, 2021 I Virtual

FDA Sponsor-Investigator Virtual Conference
November 30 to December 2, 2021 I Virtual

December 2021
Clinical Research Monitoring and GCP Virtual Workshop
December 7 to 10, 2021 I Virtual

March 2022
FDA Clinical Trial Requirements, Regulations, Compliance and GCP Conference
March 20 and 21, 2022 I Newport Beach, CA

April 2022
Annual Device Research & Regulatory Conference
April 28 and 29, 2022 I Savanah, GA

May 2022
Clinical Research Nursing Conference
May 19 and 20, 2022 I Newport Beach, CA

www.socra.org/conferences-and-education/events-calendar

SOCRA SOURCE

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PRESIDENT'S MESSAGE

Abby Statler, PhD, MPH, MA, CCRP

Dear Colleagues.

SOCRA completed a very successful virtual annual conference in September. Our speakers addressed the many different areas of clinical research and discussed associated regulations, policies and procedures, and best practices. Our attendee participants had ample opportunity to "chat" with speakers and to have live / interactive Q&A following each presentation. I personally enjoyed moderating a lively and dynamic Q&A session after the open plenary. I do believe that the speakers enjoyed the technology as much as the attendees; thank you to everyone who contributed to this successful virtual event!

Our annual conference poster program presented a variety of content applicable to both clinical trial management and to clinical research science. Poster presenters shared some of the very newest concepts and interesting assessments and solutions related to issues involved in clinical research. Two poster presenters received special recognition for their work. They are:

- Nicole Stevens, PhD, CPT, CCRC, CPI, CCMA, Kathryn Allred, BS, CPT, and Charlotte Tuilevuka, BS, CPT, doTERRA International, for "A Multisensory Approach to Enhance Informed Consent and Improve Study Compliance."
- Xinmei Shi, MSc, CCRP, CCRA, National Cancer University Institute, Singapore, for "SARS-CoV-2 emitted in Respiratory Aerosols through Singing, Talking, Breathing."

We do thank our annual conference sponsors for their support and their commitment to clinical research education and development. Our sincere thanks and appreciation go to:

- Cenetron (Clinical Trial Logistics Solutions)
- IVY Brain Tumor Center (at the Barrow Neurological Institute)
- Matrix Clinical Trials (Decentralized Clinical Trial Solutions)
- Complion (Site eRegulatory Solutions)
- ClinEssentials (Resources and Tools for Clinical Research Professionals)

SOCRA continues to offer our certification program, "Certified Clinical Research Professional, CCRP," in a number of modalities for the convenience of our candidates. We are happy to provide a variety of safe testing options. In-person test centers were re-activated a while ago with every possible COVID appropriate precaution. At home, or anytime / anywhere remotely proctored testing has been available since early 2020, and in-person testing is once more available on a very limited basis and again, with a maximum of precaution.

You will find our calendar of education programs and conferences listed elsewhere in this journal, as SOCRA continues to offer our programs on-line with live and interactive technologies. Our attendees at virtual programs participate with speakers via video conferencing technologies that allow for comments and discussions/conversations with course leaders and with each other.

We do hope that you will take advantage of SOCRA education and certification programs to help enhance your contribution to the clinical research endeavor.

Sincerely,

Abby Statler, PhD, MPH, MA, CCRP
President, Society of Clinical Research Associates

SOCRA BOARD OF DIRECTORS

IRB Waiver or Alteration of Informed Consent for Clinical Investigations Involving No More Than Minimal Risk to Human Subjects

Guidance for Sponsors, Investigators, and Institutional Review Boards[1]

U.S. Department of Health and Human Services
Food and Drug Administration
July 2017

SOCRA SELF STUDY

I.INTRODUCTION

This document provides guidance to sponsors, investigators, and institutional review boards (IRBs) on enforcement of FDA regulations governing informed consent requirements for clinical investigations that involve no more than minimal risk[2] to human subjects. This guidance informs sponsors, investigators, IRBs and other interested parties that the FDA does not intend to object to an IRB waiving or altering informed consent requirements for certain minimal risk clinical investigations as described in Section IV of this guidance. In addition, FDA does not intend to object to a sponsor initiating, or an investigator conducting, a minimal risk clinical investigation for which an IRB waives or alters the informed consent requirements as described in Section IV of this guidance.

Over the years, FDA has received numerous inquiries from sponsors and investigators about conducting important minimal risk clinical investigations for which obtaining informed consent was not practicable. Many of these minimal risk clinical investigations did not proceed because FDA did not have the statutory authority to permit a waiver of informed consent for such investigations. As described in Section II of this document, an amendment to the Federal Food, Drug and Cosmetic Act (FD&C Act) has provided FDA with authority to permit an exception from informed consent for minimal risk clinical investigations when specific criteria are met. Since this amendment passed, FDA has received additional questions regarding requirements for informed consent in minimal risk clinical investigations. FDA believes this guidance will facilitate the conduct of certain minimal risk clinical investigations that are important to addressing significant public health needs without compromising the rights, safety, or welfare of human subjects. Although this guidance is immediately in effect, FDA will consider all comments received and will revise this guidance when appropriate.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word should in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

On December 13, 2016, the 21st Century Cures Act (Cures Act) (P.L. 114-255) was signed into law. Title III, section 3024 of the Cures Act amended sections 520(g)(3) and 505(i)(4) of the FD&C Act to provide FDA with the authority to permit an exception from informed consent requirements when the proposed clinical testing poses no more than minimal risk to the human subject and includes appropriate safeguards to protect the rights, safety, and welfare of the human subject. This statutory amendment became effective on December 13, 2016. FDA intends to promulgate regulations to reflect this statutory change, including appropriate human subject protection safeguards.

Currently, FDA's regulations governing the protection of human subjects (21 CFR parts 50 and 56) allow exception from the general requirements for informed consent only in life-threatening situations when certain conditions are met (21 CFR 50.23) or when the requirements for emergency research are met (21 CFR 50.24). This limitation in FDA's regulations stemmed from section 520(g)(3)(D) of the FD&C Act, relating to the investigational use of devices. Before the Cures Act amendments, this provision in the FD&C Act directed that FDA regulations require informed consent be obtained except where the investigator "determines in writing that there exists a life threatening situation involving the human subject of such testing which necessitates the use of such device" and it is not feasible to get the consent of the subject or the subject's representative.

The requirement in section 505(i) of the FD&C Act for informed consent for investigational use of drugs (including biologics) provided that FDA regulations must ensure informed consent is obtained "except where it is not feasible or it is contrary to the best interest of such human beings." In order to promote consistency across medical products, FDA adopted regulations reflecting the device standard for all medical product research.

In general, FDA's regulations governing the protection of human subjects conform to the requirements in the "Federal Policy for the Protection of Human Subjects" (the Common Rule), with a few exceptions because of differences in FDA's mission or statutory authority. The Common Rule, originally promulgated in 1991[3], sets forth requirements for the protection of human subjects involved in research that is conducted or supported by the Department of Health and Human Services (HHS) (see 45 CFR 46, Subpart A) and 15 other Federal departments and agencies. The purpose of the Common Rule is to promote uniformity, understanding, and compliance with human subject protections as well as to create a uniform body of regulations across the Federal departments and agencies.[4] FDA regulations and the Common Rule share the same definition for "minimal risk," but the Common Rule allows a waiver of informed consent for minimal risk research if specific criteria are met. As stated above, FDA's regulations currently do not include an exception from informed consent for minimal risk clinical investigations.[5]

III. DISCUSSION

The Common Rule standard has been adopted and successfully employed for decades by numerous other Federal agencies. The Common Rule permits an IRB to waive the requirements to obtain informed consent, or to allow changes to, or omission of, some or all elements of informed consent if the IRB finds and documents that: (1) the research involves no more than minimal risk to the subjects; (2) the waiver or alteration will not adversely affect the rights and welfare of the subjects; (3) the research could not practicably be carried out without the waiver or alteration; and (4) whenever appropriate, the subjects will be provided with additional pertinent information after participation. (45 CFR 46.116(d)).[6]

The Secretary's Advisory Committee on Human Research Protections (SACHRP) provided input on the issue of whether waiver of informed consent provisions for certain minimal risk clinical investigations would be appropriate and helpful to FDA-regulated research. On March 13, 2014, SACHRP considered this issue. Recognizing that harmonization

with the Common Rule would promote consistency and help to reduce confusion in the research community about when a waiver of informed consent may be permitted, while also facilitating certain FDA-regulated research, SACHRP recommended to the Secretary of HHS that FDA adopt the provisions for waiver of informed consent that exist under the Common Rule at 45 CRF 46.116(d). On October 26, 2016, SACHRP reiterated that recommendation to the Secretary.[7]

IV. IRB WAIVER OR ALTERATION OF INFORMED CONSENT

Waiver of informed consent for certain FDA-regulated minimal risk clinical investigations will facilitate investigators' ability to conduct studies that may contribute substantially to the development of products to diagnose or treat diseases or conditions, or address unmet medical needs. In light of the Cures Act amendment to the FD&C Act described above, FDA intends to revise its informed consent regulations to add this waiver or alteration under appropriate human subject protection safeguards to the two existing exceptions from informed consent (i.e., in life- threatening situations and for emergency research). However, until FDA promulgates these regulations, we do not intend to object to an IRB[8] approving a consent procedure that does not include, or that alters, some or all of the elements of informed consent set forth in 21 CFR 50.25, or waiving the requirements to obtain informed consent when the IRB finds and documents[9] that:

1. The clinical investigation involves no more than minimal risk (as defined in 21 CFR 50.3(k) or 56.102(i)) to the subjects;
2. The waiver or alteration will not adversely affect the rights and welfare of the subjects;
3. The clinical investigation could not practicably be carried out without the waiver or alteration; and
4. Whenever appropriate, the subjects will be provided with additional pertinent information after participation.

FDA does not intend to object to a sponsor initiating, or an investigator conducting, a minimal risk clinical investigation for which an IRB waives or alters the informed consent requirements as described above. FDA intends to withdraw this guidance after we promulgate regulations to permit a waiver or alteration of informed consent under appropriate human subject protection safeguards consistent with section 3024 of the Cures Act.

V. INQUIRIES ABOUT SPECIFIC CLINICAL INVESTIGATIONS

Sponsors, investigators and IRBs may contact FDA for questions about implementing the recommendations in this guidance for a specific clinical investigation. Questions should be directed to the appropriate Center contact listed below.

Center for Drug Evaluation and Research Ebla Ali Ibrahim
Office of Medical Policy Initiatives, Office of Medical Policy 301-796-2500 or 301-796-3691
Email: Ebla.Ali-Ibrahim@fda.hhs.gov

CITATIONS

[1] This guidance has been prepared by the Office of Good Clinical Practice, Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research and the Center for Devices and Radiological Health at the Food and Drug Administration.

[2] Minimal risk is defined in applicable FDA regulations as "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." (21 CFR 50.3(k), 56.102(i)).

[3] The Common Rule was recently revised to better protect human subjects involved in research, facilitate valuable research, and reduce burden, delay and ambiguity for investigators (82 FR 7149, January 19, 2017). The final rule that revised the Common Rule adopts an effective and general compliance date of January 19, 2018. References to the Common Rule in this document are to the pre-2018 requirements that are in effect at the time of issuance of this guidance.

[4] 80 FR 53931 at 53935, September 8, 2015.

[5] Note that this exception from the requirement to obtain informed consent differs from the waiver from the requirement for documentation of informed consent permitted under both the Common Rule and FDA regulations (45 CFR 46.117(c); 21 CFR 56.109(c)).

6 The final rule that recently revised the Common Rule (82 FR 7149, January 19, 2017) adds a fifth criterion (i.e., "if the research involves using identifiable private information or identifiable biospecimens, the research could not practicably be carried out without using such information or biospecimens in an identifiable format" (new 2018 requirement at 45 CFR 46.116(f)(3)(iii)). As FDA revises its regulations to harmonize to the extent appropriate and permissible with the Common Rule, we will consider including this new criterion in any waiver provision.

[7] SACHRP's recommendations are available at https://www.hhs.gov/ohrp/sachrp- committee/recommendations/2014-july-3-letter-attachment-c/index.html and https://www.hhs.gov/ohrp/sachrp- committee/recommendations/attachment-b-november-2-2016-letter/index.html.

8 An institutional review board (IRB) is defined in 21 CFR 56.102(g) and is subject to the requirements of 21 CFR part 56.

[9] An IRB is required to prepare and maintain adequate documentation of its activities, including actions taken by the IRB, under 21 CFR 56.115.

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2022

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SELF STUDY QUESTIONS

1. Waiver of informed consent for certain FDA-regulated minimal risk clinical investigations will facilitate investigators' ability to conduct studies that may contribute substantially to the development of products to _____.

a. diagnose diseases or conditions
b. treat diseases or conditions
c. address met medical needs
d. all of the above
e. a. and b.

2. Currently, the FDA's regulations governing the protection of human subjects (21 CFR parts 50 and 55) allow exception from the general requirements for informed consent only in life-threatening situations when certain conditions are met (21 CFR 50.23) or when the requirements for emergency research are met (21 CFR 50.24).

a. true
b. false

3. The FDA intends to withdraw this guidance after we promulgate regulations to permit waiver or alteration of informed consent under appropriate human subject protection safeguards consistent with _____.

a. Section 3023 of the Cures Act
b. Section 3024 of the Cures Act
c. Section 324 of the Cares Act
d. Section 3023 of the Cares Act

4. However, until FDA promulgates these regulations, we do not intend to object to an IRB approving a consent procedure that does not include, or that alters, some or all of the elements of informed consent set forth in 21 CFR 50.25, or waiving the requirements to obtain informed consent when the IRB finds and documents that:

a. The clinical investigation involves no more than minimal risk (as defined in 21 CFR 50.2(i) or 56.103(k)) to the subjects.
b. The waiver or alteration will not adversely affect the rights and welfare of the subjects.
c. The clinical investigation could not practicably be carried out without the waiver or alteration.
d. Whenever appropriate, the subjects will be provided with additional pertinent information after participation.
e. all of the above
f. b.-d.

5. SACHRP is an acronym for _____.

a. Secretary's Adult Committee on Human Research Protections
b. Secretary's Advisory Chairman on Human Research Protections
c. Secretary's Advisory Committee on Health Research Protections
d. Secretary's Advisory Committee on Human Research Protections

6. The Common Rule permits an IRB to waive the requirements to obtain informed consent, or to allow changes to, or omission of, some or all elements of informed consent if the IRB finds and documents that _____.

a. the research involves no more than minimal risk to the subjects
b. the waiver or alteration will not adversely affect the rights and welfare of the subjects
c. the research could not practicably be carried out without the waiver or alteration
d. all of the above

7. The Century Cures Act was signed into law on _____.

a. December 3, 2016
b. December 3, 2017
c. December 13, 2016
d. December 3, 2015

8. The FDA's guidance documents establish legally enforceable responsibilities.

a. true
b. false

9. This guidance informs _____ that the FDA does not intend to object to an IRB waiving or altering informed consent requirements for certain minimal risk clinical investigations as described in Section IV of this guidance.

a. sponsors
b. investigators
c. IRBs
d. other uninterested parties
e. a.–c.
f. all of the above

10. FD&C is an acronym for _____.

a. Federal Farm, Dairy and Cows Act
b. Federal Food, Drug and Consumer Act
c. Federal Food, Drug and Customer Act
d. Federal Food, Drug and Cosmetic Act

This self study qualifies for one hour of SOCRA CE (Continuing Education).
See answer key on page 22. Please retain this document for your CE record.

Name _____ Date _____

Sonja (Kasapinovic) Elsaid, MSc, CCRP

Using Results from Pharmaceutical Clinical Trials Beyond the NDA

Sonja (Kasapinovic) Elsaid, MSc, CCRP
Medical Affairs Consultant

Abstract: *Pharmaceutical companies use results obtained from Phase I to Phase III clinical trials in many ways other than to obtain New Drug Applications (NDA) and publish product monographs. This article describes several industry-initiated medical and commercial programs that use clinical trial results. These programs include medical education programs, advisory board meetings, medical ambassador programs, speaker tours, detail aids, patient focus groups, and educational initiatives. The article also describes how the pharmaceutical industry interacts with healthcare professionals, key opinion leaders, and patients. Understanding the uses of clinical trial results will enable clinical research professionals to extend their expertise beyond clinical operations.*

Conflict of interest declaration: The author has never been a direct employee of a pharmaceutical organization or owned any pharmaceutical-related stocks or bonds. The information in this article is shared for educational purposes only.

THE ORGANIZATIONAL STRUCTURE OF PHARMACEUTICAL COMPANIES

A pharmaceutical company's organizational structure depends on its size. Whereas smaller companies have fewer departments, and employees assume many job roles, employees in larger companies are more specialized.

Regardless of size, all pharmaceutical companies have leadership, support, and functional teams. The leadership is comprised of executive management and stakeholders. Support teams include the internal audit, human resources, information and technology, and finance departments. Functional teams encompass research and development, medical affairs, marketing and sales, reimbursement, manufacturing, and distribution. Pharmaceutical companies are typically matrix organizations in which the support teams provide service to the functional teams.

USE OF MEDICAL INFORMATION BY PHARMACEUTICAL COMPANIES

This article focuses on reviewing how clinical research data/ medical information derived from Phase I - III clinical trials is utilized by pharmaceutical, medical affairs, and commercial teams (marketing and sales) for education, marketing, and sales.

Clinical research professionals working in academia or industry

are most familiar with the roles and responsibilities of the pharmaceutical teams working in research and development, including:

- Drug discovery (discovering, synthesizing, and testing);
- Pre-clinical research (animal studies and toxicology studies);
- Clinical research;
- Review/approval processes related to clinical trials; and
- Post-approval activities (e.g., Phase IV clinical trials).

However, researchers may be less aware of what activities medical and commercial teams perform in a pharmaceutical organization.

Medical affairs teams are responsible for medical education, medical communications with healthcare workers, and clinical and scientific support to other pharmaceutical company divisions. Medical education departments primarily develop medical education programs for healthcare professionals. If a prescription drug has been launched in the market, medical education programs focus on delivering product-related medical information to physicians, who are the primary stakeholders. Medical communications staff comprise a team of scientists who interact with the prescribers. These scientists are also responsible for educating staff in other pharmaceutical departments, such as marketing directors and sales representatives.

Marketing and sales teams are responsible for product promotion to healthcare professionals and consumers/patients following product approval. Their primary role is to launch a product to the market and advertise it to healthcare professionals and consumers. Moreover, marketing and sales teams develop educational tools such as brochures and product information pamphlets for patients, and they are responsible for direct-to-consumer marketing. Direct-to-consumer marketing is permitted in the United States and New Zealand. An example of direct-to-consumer marketing is a prescription drug TV commercial for Celebrex, a non-steroidal anti-inflammatory drug indicated for pain and swelling from arthritis. Canada does not allow direct-to-consumer marketing.

The results of clinical research trials are typically published in peer-reviewed journals and product monographs. A product monograph is often referred to as a "drug bible" containing the results of pre-clinical drug studies, clinical drug trials, and drug toxicology data. The product monograph also contains prescribing guidelines, including drug indication(s) and dosage, and information on adverse drug reactions. Furthermore, the clinical data published in peer-reviewed journals and product monographs are used by medical affairs and marketing and sales teams for educational or promotional purposes.

REGULATION OF POST-APPROVAL PROGRAMS

Table 1 highlights post-approval programs in which clinical data is used. Research and development programs include Phase IV and investigator-initiated clinical trials. Academic research clinicians sometimes launch investigator-initiated clinical trials in collaboration with the pharmaceutical companies that manufacture the drug or device being researched in the trials. Other post-approval programs include:

- Investigator meetings;
- Recruitment and retention workshops;
- Study coordinator workshops to determine site feasibility; and
- Investigator workshops to gain insight into the patient population

Medical affairs and marketing and sales post-approval programs are also outlined in Table 1.

Regulation of post-approval programs varies by the type of program (Table 2). Research and development post-approval programs are regulated by the U.S. Food and Drug Administration, Health Canada, and institutional review boards (IRBs). These programs developed by medical affairs teams and marketing and sales must follow the Pharmaceutical Research & Manufacturers of America (PhRMA) Code on Interaction with Healthcare Professionals in the U.S. and the Rx&D (Research-Based Pharmaceutical Companies) Code of Ethical Practices in Canada. Medical affairs teams must follow accreditation guidelines set by medical societies to develop accredited continuing medical education (CME) programs.

The PhRMA Code on Interaction with Healthcare Professionals and Canada's Research Based Pharmaceutical Companies Rx&D Code of Ethical Practices specify how pharmaceutical companies should interact with healthcare professionals. Among such guidelines are that pharmaceutical companies should only share factual information derived from evidence-based research studies, and they should communicate only the information published in the peer-reviewed medical literature or product-related data from the product monograph. For instance, unapproved product

TABLE 1
EXAMPLES OF POST-APPROVAL PROGRAMS USING CLINICAL DATA

Research and development:

- Phase IV clinical trials
- Investigator-initiated clinical trials
- Investigator meetings
- Recruitment and retention workshops
- Study coordinator workshops to determine site feasibility
- Investigator workshops to gain insight into patient populations

Medical affairs:

- Publication planning initiatives:
  - Original/review articles
  - Posters
  - Abstracts
  - Conference activity
- Key opinion leader advocacy:
  - Advisory boards
  - Consults
- Medical science liaison tools and training
- Medical ambassador programs
- Accredited continuing medical education (CME) programs
- Non-accredited CME programs
- Conference symposia programs

Marketing and sales:

- Sales tools and training
- Leave-behinds and detail aids
- Patient education
- Boutique launches
- Mapping patient journeys
- Apps and other digital assets for patients
- Market research involving patients support groups or caregivers
- Patient association support
- Key practice leader development and engagement
- Conference booths

TABLE 2
REGULATION OF POST-APPROVAL PROGRAMS

Research and development post-approval programs:
- FDA
- Health Canada
- IRBs

Medical affairs post-approval programs:
- PhRMA Code on Interaction with Healthcare Professionals (U.S.)
- Rx&D Code of Ethical Practices (Canada)
- Accreditation guidelines by medical societies (U.S. and Canada)

Marketing and sales post-approval programs:
- PhRMA Code of Interaction with Healthcare Professionals (U.S.)
- Rx&D Code of Ethical Practices (Canada)
- Office of Prescription Drug Promotion (U.S.)
- Pharmaceutical Advertising Advisory Board (Canada)

indications should not be discussed.

Both the U.S. and Canadian guidelines specify how pharmaceutical companies should conduct advisory board meetings and distribute drug samples. Advisory boards consist of experts who advise pharmaceutical companies on a product/drug/device the company is manufacturing, and their integrity must remain sacrosanct. For example, drug samples should not be distributed at advisory board meetings, and sales representatives should not attend these meetings. Marketing and sales teams should follow advertising and labeling regulations pertaining to promotional materials, labeling, and advertising as established by either the U.S. FDA's Office of Prescription Drug Promotion or Health Canada. Such regulations and guidelines specify the content and the format of product promotional materials, product-related websites, interactive electronic programs, and electronic and paper-based detail aids, among other topics. The mission of the Office of Prescription Drug Promotion is: "To protect the public health by ensuring that prescription drug information is truthful, balanced, and accurately communicated." "This is accomplished through a comprehensive surveillance, enforcement, and education program and by fostering better communication of labeling and promotional information to both professionals and consumers."

Thus, any information that is not found in the product monograph should not be advertised.

There is a clear separation between medical and commercial programs. Medical programs are always developed by either research and development or medical affairs teams, whereas the marketing and sales always develop commercial programs and promotional materials. Research and development and medical affairs departments usually never attempt to sell drugs/products/devices to physicians. In most instances, if a physician asks a medical affairs scientist to provide a drug sample, then the medical affairs scientist will contact the sales representative, who will provide the sample.

EXAMPLES OF MEDICAL PROGRAMS

There are many types of medical programs (Table 3), including non-accredited continuing medical education programs. For example, when a pharmaceutical organization recently delivered a satellite symposium to physicians, pharmacists, and

nurses during the European Conference on Oncology, they presented a slide deck to educate the attendees on prescribing a particular new oral chemotherapy agent to treat breast cancer. The program consisted of a didactic component and an interactive component to enhance delegate engagement. The didactic component included a presentation about the chemotherapy agent and metastatic breast cancer, whereas the interactive component enhanced the attendees' engagement.

The program outline was:

- Share your experience in managing metastatic breast cancer
- Introduction to metastatic breast cancer and oral cancer treatments
- Discuss the patient journey:
  - Diagnosis
  - Treatment selection
  - Dispensing and administration
  - Medicines management
  - Adverse event management
- Use digital pads to answer questions about patient cases.

The outline of the didactic component was:

- What is metastatic breast cancer?
- How is metastatic breast cancer diagnosed?
- How is metastatic breast cancer treated?
- What are the European treatment guidelines?
- What is the mechanism of action of the new oral chemotherapy drug?
- Phase III pivotal trial showing the efficacy of the new drug versus the standard of care
- Most common adverse events reported with the new drug.

Published results of the essential peer-reviewed Phase III pivotal clinical trial were shared during the didactic component.

Accredited continuing medical education programs are very similar to non-accredited programs in that they comprise both didactic and interactive, case-based components. However, the program must provide a balanced clinical research information overview in order to be approved by an accreditation body. In addition to sharing research information on the company's drug, the didactic components of accredited programs also include medical information on treatment/care standards and other new products. The clinical data on the company's product is usually compared to other products on the market. Sometimes treatments administered by other routes must be included. For example, if a pharmaceutical organization that developed an oral chemotherapy agent is putting together an accredited CME program, it might have to include radiation therapy information.

Accreditation is usually obtained from national medical specialty societies or universities,. A requirement for approval is demostrating the need for an accredited CME program. To do so, pharmaceutical companies typically conduct need assessments by distributing and collecting information from evaluation forms at medical meetings and conferences or disseminating healthcare professionals' surveys. Physicians are more likely to attend accredited CME programs because they receive credits for their participation. Accumulation of these CME credits is often necessary for maintaining their medical license or Maintenance of Certificate (MOC).

An example of an accredited continuing medical education program is a recent presentation designed to educate healthcare professionals about the proper use of radiopharmaceutical, radium-223 as a treatment method for metastatic

TABLE 3
TYPES OF MEDICAL PROGRAMS

- Non-accredited continuing medical education programs
- Accredited continuing medical education programs
- Medical ambassador programs
- Speaker tours
- Medical symposia at conferences
- Advisory board meetings
- Educational tools for healthcare workers

castration-resistant prostate cancer. The presentation included information on the St. Gallen Consensus Statement (treatment guidelines) and a Phase III double-blind clinical trial comparing the efficacy of radium-223 versus the placebo added to the standard of care treatments. The presentation also provided information on other clinical trials in order to provide a more balanced overview of medical treatment for metastatic-castration resistant prostate cancer. For example, a Phase III clinical trial's results comparing the efficacy and safety of two chemotherapy agents, namely cabazitaxel and docetaxel, were also presented.

Pharmaceutical companies often initiate medical ambassador programs to educate healthcare professionals and key opinion leaders on current treatments in a particular disease area. Such a program's final deliverable is typically a slide deck summarizing the information presented during a medical conference. Pharmaceutical companies recruit key opinion leaders/physician experts in the field and assign them to attend different conference sessions. These experts then decide which data presented during the conference would be included in the slide-deck. Once the slide deck is finalized, the physicians then share the slide-deck information with their local medical communities.

Speaker tours involve recruiting an influential expert in the medical field to develop and present an educational program to various medical communities across the country. A primary deliverable of such a program is a slide deck that includes a balanced overview of the disease of interest and available treatments. According to the PhRMA Code on Interaction with Healthcare Professionals in the U.S. and the Rx&D Code of Ethical Practices in Canada, pharmaceutical company teams should not develop such programs; rather, medical experts should be the ones to decide which information is included. However, pharmaceutical company representatives could be involved in organizing the logistics of the speaker tours.

Medical symposia are sessions sponsored by pharmaceutical companies that take place during a medical conference. These events are sometimes held at lunchtime/dinnertime and include a meal. A pharmaceutical company typically convenes a panel of three or four key opinion leaders who present the cutting-edge clinical trial data and discuss the implications of those findings to clinical practice. These key opinion leaders are usually clinical investigators leading the pharmaceutical company's Phase I, II, III, or investigator-initiated clinical trials testing the company's product/drug/device.

As is the case for accredited CME programs and speaker tours, pharmaceutical company members should not develop the content for a medical symposium. The teams can only be involved in organizational logistics such as the development of symposia booklets, invitations, evaluation forms, and signage.

EXAMPLES OF COMMERCIAL PROGRAMS

There are also many commercial programs designed to aid the marketing and sales of pharmaceutical products (Table 4). For example, detail aids are printed booklets, brochures, or electronic documents that help sales representatives share information with physicians about pharmaceutical products. Detail aids usually inform on:

- Efficacy;
- Tolerability ;
- Dosing and administration; and
- Clinical trial data supporting the manufacturer's claims from the product monograph.

Approval from the U.S. Office of Prescription Drug Promotion or the Canadian Pharmaceutical Advertising Advisory Board is generally required before disseminating detail aids.

Many sales representatives do not have a scientific background, and medical communication agencies or medical affairs teams develop tools to educate them about the product. The primary aim of such education is to facilitate the interaction between sales representatives and healthcare professionals. For example, an interactive visual aid delivered on an iPad could be used to educate sales reps and their clients (physicians) about a pharmaceutical product that is currently being marketed. The content of such a program would be very similar to that of a didactic presentation. For

example, it could also include a one-minute video of a key opinion leader discussing the product's clinical research findings.

Pharmaceutical companies conduct patient focus groups for various reasons, including facilitating care standards, understanding patient journey (as patients face disease-related challenges), and gaining feedback on clinical trials and marketing tools. Patient focus groups that facilitate care standards are often conducted when working with rare diseases and orphan drugs. For instance, it is imperative to know how long it would take for a patient with a rare disease to receive the proper diagnosis and treatment. Such information is often used to develop treatment algorithms to shorten diagnosis and treatment initiation times. Furthermore, pharmaceutical companies often conduct patient focus groups before developing informed consent forms to ensure that patients can easily understand them.

An example of a commercial program on a patient's journey through illness would include a presentation delivered to nurses, pharmacists, and physicians during a medical conference or a pharmaceutical organization-sponsored event. The content of such a presentation would include information on the disease, its diagnosis, treatment, medication dispensing, adverse events management, and long-term medication management. The section on diagnosis would indicate how long it took to make the diagnosis, who diagnosed the patient (physician, nurse, or a pharmacist), and what is the differential diagnosis. The presentation component on treatment selection would encompass the list of medications prescribed upon diagnosis, the success of that treatment, or if any medications needed to be changed. The dispensing section would discuss the instructions for adequate drug use patients should receive from their pharmacy. Adverse events management includes a list of side effects that patients experience while taking the medication, methods used for managing these side effects, and indications that the medication might need to be changed. Medication management discusses patient compliance.

TABLE 4
TYPES OF COMMERCIAL PROGRAMS

- Detail aids
- Sales representative tools
- Patient focus groups
- Maps of the patient journey through illness
- Patient brochures
- Patient newsletters
- Patient enrollment tools

Patient brochures and newsletters are often developed to inform about the patient's disease and available treatment options. Such tools aim to facilitate discussions of available treatments between patients and their physicians. Newsletters also often provide valuable information about disease management.

An example of a commercial initiative is a pharmaceutical company-sponsored blood pressure monitoring program and health and wellness e-bulletin, encouraging patients with high blood pressure and the prescribing physicians to choose a specific ACE inhibitor. Given that patients taking ACE inhibitors have low medication compliance, the program provided a free, automated blood pressure monitor designed to enhance patients' motivation to manage their condition and take their medications on time. The program also included educational materials for physicians, pharmacists, and patients, including a medication refill reminder for patients. Patients who attended the program also received monthly health and wellness e-bulletins.

Pharmaceutical companies organize advisory board meetings to gain insights into achieving optimal therapeutic goals with their products/medications/devices. Through these programs, executives

aim to learn from key opinion leaders about the challenges physicians and their patients face when managing a disease. Both medical and commercial teams initiate advisory board meetings. Pharmaceutical teams should follow the U.S. PhRMA Code on Interaction with Healthcare Professionals and the Canadian Rx&D Code of Ethical Practices when conducting advisory board meetings.

The best way to conduct advisory board meetings is to make them collaborative and interactive. Usually, the meeting agenda consists of a presentation describing clinical trial data for a product/drug/device, and pharmaceutical teams often present their product-related problem(s) for participants to solve. An example of a problem could be that the pharmaceutical drug is less prescribed than its competitor. In such a case, executives might be interested in knowing why their company's drug is less prescribed and devising measures to increase its use. The reason for not prescribing the drug might be the lack of clinical research evidence showing the superiority of the drug's efficacy compared to that of its competitor. To solve such a problem, the advisory board might recommend conducting an investigator-initiated, pivotal trial comparing the drug's efficacy versus that of the competing drug. A detailed report with strategic recommendations would then be developed based on the advisory board meeting.

EMPLOYMENT OPPORTUNITIES IN MEDICAL AND COMMERCIAL AFFAIRS

The diverse work of clinical research coordinators provides skills that translate into employment opportunities in medical and commercial affairs. In medical affairs, job opportunities include roles as medical science liaisons and medical advisors. Pharmaceutical company executives tend to appreciate coordinators' clinical research and patient-interaction skills, including their therapeutic area knowledge. Medical science liaisons' primary role is to establish and maintain peer-to-peer relationships with key opinion leaders at major academic institutions and clinics. By working in academia, clinical research coordinators have already developed and fostered these relationships, thereby making them good candidates for a medical science liaison role.

Within the medical education division, clinical research coordinators could become medical writers or medical education managers. Research coordinators often obtain medical writing skills when developing informed consent forms or study protocols. Medical education managers are responsible for developing the medical programs outlined in Table 3. Other employment opportunities in pharmaceutical organizations include medical program logistics managers and program organizers, who perform administrative tasks similar to those undertaken by coordinators, such as managing project timelines, budgets, and vendors.

Employment opportunities in commercial affairs include product management and sales. Product managers are responsible for developing commercial programs for a specific product/drug/device (see Table 4). They usually have backgrounds in science education combined with training in business administration. Pharmaceutical sales representatives have a primary role in promoting products to physicians, pharmacists, and/or nurse practitioners; thus, this role also requires building and fostering professional relationships with healthcare workers.

Patient engagement is another excellent job opportunity for clinical research coordinators. Patient engagement managers develop educational programs and provide resolutions to patient-based queries. Working with participants enrolled in clinical trials provides coordinators with the necessary experience for this job.

Marketing managers synthesize medical information and clinical research data to develop product promotional tools such as TV commercials, sales brochures, and drug advertisements.

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- BIMO Compliance and Enforcement

SELF STUDY ANSWER KEY

Information Sheet Guidance for Sponsors, Clinical Investigators, and IRBs

Frequently Asked Questions Statement of Investigator

(Form FDA 1572)

ANSWERS

1. e. a. and b. (page 4/Section IV)
2. b. false (page 2/Section II)
3. b. Section 3024 of the Cures Act (page 4/Section IV)
4. f. b.–d. (page 4/Section IV)
5. d. Secretary's Advisory Committee on Human Research Protections (page 3/Section III)
6. d. all of the above (page 3/Section III)
7. c. December 13, 2016 (page 2/Section II)
8. b. false (page 2/Section I)
9. e. a.–c. (page 1/Section I)
10. d. Federal Food, Drug, and Cosmetic Act (page 1/Section I)

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Vulnerable Participants: Challenges of Conducting Research Under Difficult Circumstances

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Abstract: *Researchers are often faced with difficult situations for which there are no easy solutions when conducting human research. There are many circumstances where research participants are vulnerable to coercion and dependent on others. They may have decreased autonomy due to developmental disabilities and cognitive impairments. This results in a violation of their freedom to choose whether to participate in research. This article provides an overview of vulnerability in clinical research, challenges in conducting research involving vulnerable populations, and strategies or additional protections for safeguarding vulnerable persons.*

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INTRODUCTION TO VULNERABLE POPULATIONS

Vulnerability in clinical research implies that an individual or group is at risk of harm associated with research procedures. It is necessary to identify those who are vulnerable and provide additional protections as needed.[1] Vulnerability can be absolute or context dependent. Some people are more at risk than others.

People are vulnerable when their ability to protect themselves is absent or diminished. [2,3] They are dependent upon others. For example, children are dependent upon their parents or caregivers and are therefore subject to increased risk of coercion.

There are many types of vulnerable people and populations. They may have a diminished capacity or may find themselves in situations in which they cannot make informed decisions. For example, patients in the emergency department may be unconscious or have an altered mental status. Vulnerable people do not have the capacity to make decisions and they depend upon others to make decisions for them.

Vulnerability is defined as "a status that generates a duty for researchers, review committees, and regulators to provide special protections."3 Researchers have a responsibility and must ensure that the rights of vulnerable populations are protected and that the decisions made for them are the best decisions for them.

HISTORICAL PERSPECTIVES ON RESEARCH CONDUCTED INVOLVING VULNERABLE POPULATIONS

High profile events in the past, where researchers might have

ignored basic ethical rules, have negatively influenced the public's perception of clinical research, resulting in a loss of credibility. Examples of unethical clinical research have included the Tuskegee Study of Untreated Syphilis in the Negro Male, sexually transmitted disease experiments in Guatemala, and the use of cells from Henrietta Lacks taken without her permission or the permission of her family (Table 1).

The Tuskegee Study of Untreated Syphilis in the Negro Male was conducted by the United States Public Health Service between 1932 and 1972, involving 400 African-American men in Macon County, Alabama. The participants had latent syphilis and were not offered treatment. The aims of the study included documenting the natural course of untreated syphilis in African-American men, and determining whether the disease had a different course in that particular race.

When penicillin became available as a treatment for syphilis in the 1940s, this treatment was withheld despite the fact that penicillin became the standard of care in 1947. In exchange for their participation, the subjects were given free meals, medical exams, and burial insurance. The researchers also promised participants that they would provide treatment for their "bad blood" which, in the end, they did not provide. The natural course of syphilis was followed until the subjects died.

This study continued for 40 years, until 1972. The men were enrolled without adequate information. Enrollment may not have been voluntary. Despite the availability of a treatment for syphilis, it was not provided to study participants. Fundamental ethical rules were violated in this study, which led to the establishment of the National Research Act in 1974. The purpose of this act was to ensure that basic ethical principles be followed when conducting biomedical and behavioral research on human subjects.

In addition, from 1946 to 1948, the U.S. Public Health Service conducted sexually transmitted disease-related experiments in Guatemala. At least 5,128 vulnerable people, including children, orphans, child and adult prostitutes, Guatemalan Indians, leprosy patients, mental patients, prisoners, and soldiers were included in this study. Researchers intentionally infected at least 1,308 of those individuals with syphilis, gonorrhea, and chancroid.[4] The study was conducted without the participants' informed consents.[5] The subjects did not enter the study voluntarily, nor did they receive adequate information to help them to decide whether to participate or not.

On another occasion, Henrietta Lacks died from cervical cancer at the age of 31 on October 4, 1951. Ms. Lacks' cells, however, did not die. Cells taken from her without permission ultimately became the immortal He-La cell line. There was no informed consent process invoked prior to her tissue being used in research.[6]

In 1966, Henry K. Beecher published "Ethics and Clinical Research" in the New England Journal of Medicine. The article listed 22 published medical studies in which participants were enrolled without their knowledge or approval. These were all serious issues concerning the violations of the rights of vulnerable populations. Research involving vulnerable populations requires scrutiny that requires much more rigor.

Investigators may harbor subconscious biases that impact research involving vulnerable populations. For example, in the Tuskegee Study, African American men were enrolled in a syphilis-related study in which treatment was withheld despite known benefits of treatment. In the Guatemalan sexually transmitted disease study, participants were inoculated with syphilis. Most of those subjects were very poor, and they were inoculated without their consent. On a different occasion, cancerous cells were obtained from Henrietta Lacks without her family's knowledge or consent. Subsequently, those cells were marketed as a liquid tumor and became known as HeLa Cells.

ETHICAL GUIDELINES AND FEDERAL REGULATIONS RELATED TO VULNERABLE POPULATIONS

Research involving vulnerable populations can be ethically challenging. Table 2 provides an overview of ethical guidelines and federal regulations

TABLE 1:
SELECTED UNETHICAL RESEARCH EXAMPLES

Tuskegee Study of Untreated Syphilis in the Negro Male:

- Conducted by the U.S. Public Health Service from 1932-1972
- 400 African-American men in Macon County, Ala. with latent or late syphilis
- Study aims:
  - Documenting the natural course of untreated syphilis in African-American men
  - Examining whether the disease had a different course according to race
- No treatment, even when penicillin became available in the 1940s
- Researchers promised treatment for "bad blood" in exchange for free meals, medical exams, and burial insurance. However, treatment was never provided.

Sexually-transmitted disease experiments, in Guatemala:

- Conducted by the U.S. Public Health Service from 1946-1948
- At least 5,128 vulnerable people were included without informed consent, including:
  - Children
  - Orphans
  - Child and adult prostitutes
  - Guatemalan Indians
  - Leprosy patients
  - Mentally ill patients
  - Prisoners
  - Soldiers
- At least 1,308 individuals were intentionally infected with syphilis, gonorrhea, and chancroid

Henrietta Lacks:

- Died from cervical cancer in 1951
- Cell samples were removed from her, without permission
- Cells became the immortal He-La cell line

addressing clinical research that involves vulnerable populations. The Belmont Report, 1979, provides an ethical foundation and guidelines for conducting research on humans. The fundamental principles are autonomy, beneficence, and justice. Autonomy is respect for the person. This means that people should enter the study voluntarily and with adequate information. Persons with diminished autonomy should receive additional protections. Beneficence means that the risks be reasonable in relation to the anticipated benefits. Researchers should maximize possible benefits and minimize possible harm. Justice requires that the benefits and burdens of research be equally distributed. No specific individuals or population should unfairly bear the burden of risks related to research procedures. Research should not target a specific vulnerable population for high-risk procedures or treatments. There should be a fair participant selection process. The research process itself may increase the vulnerability of the research participants, and this should be sought out and corrected, as needed.

While it can be risky to conduct research involving vulnerable populations, there may be many reasons to do so. If investigators do not enroll members of vulnerable populations in research, we might never know whether and how effective treatments might be for these people. For many

years, researchers protected vulnerable populations by excluding them from research. However, restricting their participation in research is not appropriate. The participation of members of any particular vulnerable group may be necessary in order to develop new treatments and prevention methods that could benefit them.[8]

Scientific necessity is essential to conducting any research involving members of any vulnerable population. For example, if a condition only affects children, the study must be conducted involving children. A condition that only affects premature babies can only be conducted with premature infants. The participation of children in research "is necessary to develop new treatments and prevention methods that will benefit children, and to protect children from untested potentially harmful practices."5 No member of any vulnerable population should be excluded from research if the research is deemed scientifically necessary.

The federal regulation governing federally-funded research is Title 45 CFR Part 46. Subpart A is the Basic Health and Human Services (HHS) Policy for Protection of Human Research Participants, and it is known as the Common Rule. Subparts B, C, and D provide additional protections for vulnerable populations as follows:

- Subpart B: Additional Protections for Pregnant Women, Human Fetuses, and Neonates Involved in Research
- Subpart C: Additional Protections Pertaining to Biomedical and Behavioral Research Involving Prisoners as Participants
- Subpart D: Additional Protections for Children Involved as Participants in Research.

Over the years, the Common Rule has been revised several times; whereas, the other subparts have not. The regulations do not define vulnerability. They merely give examples of vulnerable groups by pointing to different categories of potential research participants who need additional protections. The Common Rule states that: ''When some or all of the participants are likely to be vulnerable to coercion or undue influence… additional safeguards have been included in the study to protect the rights and welfare of these participants.''

The Declaration of Helsinki was developed in 1964 by the World Medical Association and has been revised seven times. It is an important statement emphasizing the ethical principles that guide medical research involving human participants. This establishes universal, minimum standards for ethically-conducted research.

The Declaration of Helsinki specifically considered protections for vulnerable groups by offering them a fair level of benefits. It also states that:
"Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group." "In addition, this group should stand to benefit from the knowledge, practices, or interventions that result from the research."

For example, if research involves prisoners, the research questions should be relevant to prisoners, and prisoners should benefit from that research.

VULNERABILITY AND VULNERABLE POPULATIONS

It is important to understand vulnerability in order to provide adequate protections tailored to specific circumstances or population. There must be a balance between the desire to perform research and the need to protect vulnerable populations. There are many vulnerable populations:

- Children and minors
- People with physical or mental disabilities
- Pregnant women
- Prisoners
- Disadvantaged people:
    - Low income
    - Undocumented individuals
- People prone to high-risk behavior
- People who are cognitively impaired or have diminished mental capacity
- Critically or terminally ill patients
- People with emergency situations
- Racial and ethnic minorities and other under-represented groups

There is research-induced vulnerability and there is

TABLE 2 :
ETHICAL GUIDELINES AND FEDERAL REGULATIONS RELATED TO VULNERABLE POPULATIONS

Belmont Report:

- Respect for persons:
  - Participation is voluntary
- Beneficence:
  - Risks are reasonable in relation to anticipated benefits
- Justice requires that the benefits and burdens of research are equitably distributed:
  - No single individual or population is exposed to risks of harm while other individuals or populations receive the benefits

Federal Regulations: 45 CFR 46, Common Rule:

- Subpart A: Basic HHS Policy for Protection of Human Research Participants
- Subpart B: Additional Protections for Pregnant Women, Human Fetuses and Neonates Involved in Research
- Subpart C: Additional Protections Pertaining to Biomedical and Behavioral Research Involving Prisoners as Participants
- Subpart D: Additional Protections for Children Involved as Participants in Research

Declaration of Helsinki:

- Vulnerable populations are only allowed if the research is:
  - Relevant to the group's health needs or priorities
  - Cannot be conducted in a non-vulnerable group
- Vulnerable populations should benefit from the research

situational vulnerability. (For examples of each category, see Table 3, below). Research participation may involve a risk of harm. A study could be poorly designed. Participants who are randomized to the placebo arm of a study may not receive adequate treatment. The Institutional Review Board (IRB) reviews studies to ensure that the rights and well-being of the participants are protected.

IRBs act as research gatekeepers and have a responsibility to safeguard and protect vulnerable populations. An IRB may require a full board review when the research involves a vulnerable population, depending on the risk involved. A pre-review screening process may be utilized by the IRB. In this process, a designated IRB member reviews each submission for completeness and compliance. This will ensure that the study is well designed and does not violate the rights of the participants. The pre-review process is also designed to ensure that no particular sub-group bears the burden or risks of the study.

It is important that consent is intelligible, informative, and voluntary. An inadequate informed consent document can introduce another type of research-induced vulnerability. Obtaining informed consent is an ongoing process throughout a study, not just a piece of paper that participants sign at the beginning of a study. It is predicated upon an interactive discussion or process. During the informed consent discussion, researchers must ensure that prospective participants receive adequate information that enables them to understand the study. It includes their rights, the risks and benefits of participating, and refers to possible compensation if they become injured during the study.

Another type of research-induced vulnerability occurs due to a possible misunderstanding of research risks and benefits. Although participation in research can be of benefit, sometimes there is no direct benefit to the participants themselves. However, participants may agree to participate in a study because it may benefit other people. In addition, parents may consent to a study because they perceive that the study will benefit their children. A transparent system is necessary, whereby the participants understand that there may be risks related to a study.

The informed consent document should not be at a higher-than-eighth-grade reading level. It should not contain jargon that participants cannot understand, and materials should not be presented in a way that participants cannot comprehend them. Participants whose primary language is not English should be provided with a consent document written in a language understandable to them.

It is important that participants decide voluntarily and free of any coercion, concerning whether or not they agree to participate in a research study. The environment in the emergency department (ED) may pose special challenges regarding obtaining an informed consent. There may be time pressure to quickly enroll patients in research studies, and patients may not have adequate time to decide whether they want to participate in those studies. This may lead to research-induced vulnerability. Also, in the ED, enrollment is often time sensitive, and patients must be enrolled within a specified span of time. There may not be enough time to fully discuss the study, and the prospective participant may not fully understand the extent of the study's risks.

In the ED, patients who do not understand English well or are not sufficiently literate may be more likely to have research-induced vulnerability, as there may be less time to adequately explain the risks and benefits of studies to them. It is essential to present the consenting process to the participants in their own native language. In addition, patients who are in severe pain in the ED may not be able to make the right decision for themselves in order for them to decide if they really want to participate in any research studies. Additionally, in the ED, patients may have altered mental status, be intubated, be in shock, or be critically ill. Such patients cannot provide consent to participate in a study. There should be a mechanism to address this issue, to ensure that risks are minimized, and to ensure that the patients' rights are protected.

People under the "power of others" are in potentially vulnerable situations when requested by people in positions of power to participate in their studies. Examples of this may be patients of the clinician researcher and economically disadvantaged people who are in vulnerable positions because of their inherent situations. Conducting research that involves students or employees are other examples of power differentials that may lead to the vulnerability of study participants. Students and employees are hesitant to say "no" when asked to participate in a study by their teachers or supervisors. Students may be afraid of receiving a "bad grade" from their teachers if they refuse to participate in studies conducted by their teachers. Employees may be worried about being fired or being denied promotions if they refuse to be subjects in studies supervised by their employers. There is a need to have mechanisms in place to protect students and employees who decline to participate in studies directed by their teachers or bosses.

The physician-patient relationship is another example of unequal power. When a physician approaches his/her patient or the family of one of his/her patients concerning participation in a study, it may be difficult for the patient or the family to say "no." They may be worried about offending the physician, and consequently, they may not receive optimal care from the physician. The dependency of the patients and their families on their physicians may become higher if the patient's condition becomes worse. Indeed, they may have special medical or social needs, which may result in an increased vulnerability of the patient. Such a type of vulnerability must be recognized, and protections must be taken into consideration. It is important

that physicians put their patients' interests above their own research interests.

Payment to research participants could also influence their decision-making and compromise their ability to consent based on the risks and benefits of a study. Economically disadvantaged people may be unduly influenced to participate in a study that offers a seemingly expensive gift card as an excessive incentive to participate. There is a potential for undue influence by the researcher if an excessive amount of cash is offered to participate in a high-risk research project. IRBs should evaluate the ethical acceptability of protocols including the proposed method of payment, the timing of the payments, and the amount of the payments in the social context of the population that is being studied. How much is "too much?" The amount should be modest. It is also important to consider the motivation of the researcher for paying the participants. It is important that payment be viewed as reimbursement or compensation for the participants' time and inconvenience. It should not be an incentive to participate in a study or as compensation for research-related risk. IRBs should not approve research protocols unless the possibility of coercion or undue influence is minimized.

Vulnerability leads to fears about the possibility of the vulnerable population being exploited by the researchers for the researchers' benefit. People who are vulnerable are dependent on others and thus have decreased autonomy. A person's dependent status can be temporary or permanent. A person's status may change during a study. For example, if a patient who was enrolled in a study while unconscious regains consciousness, then consent should be obtained to determine if they remain willing to continue participating in the study.

TABLE 3:
TYPES OF VULNERABILITY

Research-induced vulnerability:

- Poorly-designed study
- Inadequate or biased consent discussion
- Misrepresentation of research risks and benefit
- Presented material is above the reading level of the prospective participant
- Material presented in a way that the potential participant cannot understand
- Undue pressure imposed by the investigator to quickly reach a decision

Situational vulnerability:

- Stressful situation (emergency department)
- Altered mental status/sedation
- Power differential (student or employee)
- Patients of physician-researcher
- Economically disadvantaged

Vulnerable populations are subject to coercion and being misled, mistreated, or otherwise taken advantage of. Vulnerability is context dependent. Exploitation is an unfair advantage whereby a researcher may offer expensive payments as incentives for study participation. Researchers should ensure fair payment benefits for study participants and avoid exploitation. IRBs should assess and ensure that participants are not exploited and can receive adequate protections.

PROTECTION AND INCLUSION OF VULNERABLE POPULATIONS

Researchers and research ethics committees should devise special protections or additional safeguards for groups considered vulnerable. This includes allowing no more than minimal risk for research procedures that offer no potential individual benefits for participants. Research involving vulnerable populations should only be performed when the research focuses on conditions that affect the particular group.

There is a need to re-think vulnerability. Patients with

TABLE 4:
CONDUCTING RESEARCH IN CHILDREN

- Appropriate balance of risk and benefit
- Three risk categories for children:
  - Minimal risk
  - Greater than minimal risk with a potential for direct benefit
  - Minor increment over minimal risk with no benefit but likely to yield generalizable knowledge about the minor's disorder or condition
- Additional regulatory review is required if the research is not in one of these categories
- Involvement in research is dictated by parental permission
- Children participate through an assent process
- The interest of the child must always prevail over the interests of science and society

critical illness or injuries may have situational vulnerability. When considering research that includes economically-disadvantaged individuals, the characteristics of the individual in the context of the study should be more pertinent to determining vulnerability than the fact that the participant is economically disadvantaged. For example, when conducting a study concerning patients with pulmonary edema, patients should be included because they have pulmonary edema and not because they are poor. Patients should not be taken advantage of because they are critically ill or poor. The risks and benefits should rather be made clear to patients and/or their families regardless of their socioeconomic status.

An ethical argument can be made for the inclusion of vulnerable populations in order to provide equitable access to the knowledge gained from research. If studies are not conducted involving vulnerable populations, there will be no data available to provide better treatment to such vulnerable people.

RESEARCH INVOLVING CHILDREN AND MINORS

Children differ in many ways from adults. In pediatrics, a saying that is often quoted is that "children are not just small adults." They are a uniquely vulnerable population. But there is an overwhelming need to test safety and efficacy of treatments in children. Children are examples of a vulnerable population addressed in federal regulations 45 CFR 46 Subpart D and in 21 CFR 50 Subpart D. Children are dependent upon their parents or caregivers due to their lack of maturity and their inability to make decisions. Hence, they are subject to the judgments and actions of others. Children comprise a wide range of ages, risks, and expectations, each of which challenges their individual autonomy. The challenge of conducting research with neonates is also different from that involved when research concerns adolescents.

An overview of research involving children is provided in Table 4. A stated scientific necessity must be proposed for research involving children. Also, appropriately balanced risks and potential benefits must be articulated. Children should be involved only if studies cannot be conducted on a different population. The risks to which children would be exposed must be very low if there is no prospect of direct therapeutic benefit to the enrolled children. These risks can be interpreted differently by different people and in different circumstances. For example, the pain from a blood draw is well tolerated by adults and adolescents. However, for some young children a blood draw may cause significant pain and anxiety. Children should not be harmed by being enrolled in a study either by exposure to excessive risks or by failing to get necessary health care. This is because the researchers may be withholding standard treatment in order to achieve the goals of their study.

The type of risk involved in a particular study dictates the type of protection that is required. There are three risk categories for children:

- Minimal risk
- Greater than minimal risk, and prospect of direct benefit
- Greater than minimal risk, and no prospect of direct benefit

The level of risk must be addressed by the investigator when designing a study. A study should only be approved if an IRB determines the risk to be justified by any anticipated benefit.

In order for children to be allowed to participate in research, the parents or guardians must provide permission, and the children should provide assent when appropriate. The IRB should determine if a child is capable of providing meaningful assent. The ability to assent is often presumed to occur around 7 or 8 years of age. According to 21 CFR 50.55 Section (c) (2): "The assent of the children is not a necessary condition for proceeding with the clinical investigation if the IRB determines: (1) that the capability of some or all of the children is so limited that they cannot reasonably be consulted, or (2) that the intervention or procedure involved in the clinical investigation holds out a prospect of direct benefit that is important to the health or well-being of the children and is available only in the context of the clinical investigation."

For these reasons and because of this regulation, a clinical investigator should avoid suggesting to children that they can make the participation decision when their parents can override a child's wishes.

The IRB should determine that adequate provisions are made for obtaining the assent of the child depending on the child's age. The author believes that the interests of the child must always prevail over the interests of science and knowledge.

Remuneration/reimbursement for participation is another challenge in research involving children. It should be age dependent. In general, young children should not be paid in dollars. For adolescents, the amount should not be excessive. The amount of the payment should be determined by the type of study, the age of the participant, and what the study involves. Payment can unduly influence decisions about research participation. An excessive amount can induce participants to enroll in a study in which they would otherwise not participate. Poorer populations may be more susceptible to inducements to decide against their own best interests. Sometimes a parent/guardian may demand that the child relinquish the payment to the adult. Sometimes a parent or guardian may coerce a child to assent because of the payment offer.

It is necessary to distinguish between reimbursements, compensations, and excessive payments:

Reimbursement is for expenses, such as travel expenses, parking costs, etc. Compensation is for the time and inconvenience involved in research participation, such as the parents taking off from work to bring the child to the study site. Excessive payment exceeds the reasonable amounts being given for reimbursement and compensation, and is obviously being given to induce the parents/guardians to enroll their child in a study.

Each child who participates in a research project should receive at least the standard of care if one exists. No child enrolled in research should receive inferior or inadequate treatment.

Children in foster care constitute a particularly vulnerable population with multiple medical, psychological, and social risks. Nationally, there are 542,000 children in foster care.[10, 11] Children in foster care may be vulnerable to exploitation, marginalization, powerlessness, oppression, and domination. Researchers must ensure that the rights and well-being of children in foster care are protected.

RESEARCH INVOLVING OTHER VULNERABLE POPULATIONS

Other vulnerable populations include pregnant women, prisoners, and undocumented individuals.

Traditionally, pregnant women have been excluded from drug development clinical trials. The exclusion criteria for virtually all drugs have included pregnant women. This has resulted in the lack of availability of FDA-approved treatments for pregnant women. In 1993, the U.S. Food and Drug Administration (FDA) withdrew restrictions on the participation of women in clinical trials. A few years later, in 1997, the FDA encouraged researchers to include women in clinical trials. Pregnant women are now covered as a vulnerable population under Title 45 CFR Part 46 Subpart B.

Prisoners are vulnerable because of enforcement of their diminished autonomy. There is increased risk of coercion

due to power imbalance, and prisoners are covered as a vulnerable population under Title 45 CFR Part 46 Subpart C. The prison population has increased from 1.96 million in 2002 to 2.2 million in 2018. It is therefore important that studies regarding the basic medical treatment for prisoners be conducted. However, if prisoners are involved in research, their rights and well-being should be protected. Additional regulations beyond the basic requirements for research with human subjects (45 CFR 46) are needed. It is important to determine that the proposed research falls within the permissible categories of research based on the risks and benefits of a study. Prisoners have the right to participate in research. Research involving prisoners must pose minimal risk to them. When reviewing research proposals involving prisoners, an IRB must have at least one prisoner advocate or representative. When they consider approving studies involving prisoners, IRB members should serve as advocates on behalf of the prisoners. Indeed, if a participant becomes a prisoner during a study, it is necessary to discuss how his/her rights will be protected.

Undocumented immigrants are particularly vulnerable because of their legal status, limited access to healthcare, and a limited English language proficiency. From a research perspective, undocumented individuals should have the same rights as members of the general population of the US. It could be beneficial to the undocumented immigrants themselves to participate in research. Latinos are the largest immigrant population in the United States, accounting for 17.6% of the total U.S. population. The vast majority of Latinos have legal status and are documented, and many of them have participated in research studies. Nevertheless, it would also be important to do certain types of research on undocumented members of this community in order to possibly benefit this particular community. However, undocumented individuals from many ethnicities may be reluctant to participate in research. They may be afraid that their undocumented status could be disclosed to government officials. That may, in turn, result in their being deported. Enrolling undocumented individuals in research may therefore be a challenging endeavor.

COGNITIVE VULNERABILITY

Research involving people who do not have the capacity to provide informed consent can also be a challenge. People with diminished capacity have cognitive vulnerability. Capacity is a functional determination and is an important indicator of an individual's ability to exercise their autonomy. This ability to provide consent can be impaired by many conditions. These may include psychiatric conditions and neurological disorders such as stroke, dementia, substance abuse, and head trauma. It is important to ensure that their rights are protected. Thus, a decision to include individuals with these disabilities in research studies should be made for the benefit of these participants.

CONCLUSIONS

All research should begin by considering the risks posed by the study design in order to determine additional safeguards required to protect vulnerable populations. Consideration of the targeted study population determines whether additional safeguards or protections are needed. When submitting a proposal to an IRB, researchers must consider and include in their plans how they will protect the rights and well-being of vulnerable populations involved in the research.

Recognition of the extent of vulnerability is imperative when developing regulations and guidelines for research. Including vulnerable populations in research requires special regulations. There is no reason to exclude vulnerable populations from research in so far as research may well serve to benefit a particular vulnerable group. However, researchers should be prepared to advocate on behalf of vulnerable patients by ensuring that the research is both of benefit to them and subjects them to minimal risk.

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CONFERENCE TOPICS

- Navigating the unique responsibilities and challenges of conducting clinical trials initiated and managed by Sponsor-Investigators
- The Sponsor-Investigator's relationships and reporting requirements with the IRB, CROs, Sub-Investigators and other research staff
- Study feasibility assessments and project management
- Proper study design for Sponsor-Investigator initiated research
- Building quality into clinical study design and management
- The Investigational New Drug (IND) and investigational device exemption (IDE) submission processes
- The Sponsor-Investigator's responsibilities for Clinicaltrials.gov reporting and FDA compliance actions regarding Clinicaltrials.gov
- Source Documentation requirements/responsibilities for Sponsor-Investigator clinical trials
- Training, delegation of tasks and operating procedures for executing study start-up
- Subject safety reporting responsibilities and related submission processes for Sponsor-Investigators
- The use of, and processes involved in risk-based monitoring
- Tools for FDA inspection preparedness

Marie-Pierre Desrosiers, MSc

Investigational Testing Authorizations for Medical Devices in Canada

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Abstract: *Canadians rely on safe and effective medical devices to maintain and improve their health and well-being. Investigational testing of medical devices in human subjects is a growing area for research and development in Canada. Understanding Health Canada's regulatory framework for investigational testing is important to facilitate access to investigational medical devices in Canada while ensuring the safety of research subjects. Health Canada is currently offering two regulatory pathways to obtain the authorization for investigational testing of medical devices: the Medical Devices Regulations and the Interim Order respecting clinical trials for medical devices and drugs relating to COVID-19. This article provides an overview of the regulatory requirements, policies and procedures for both regulatory pathways, including suggestions to avoid common avoidable deficiencies in the authorizations and minimize delays.*

Canadians rely on safe and effective medical devices to maintain and improve their health and well-being. Investigational testing of medical devices in human subjects is a growing area for research and development in Canada. Understanding Health Canada's regulatory framework for investigational testing is important to safeguard the protection of research subjects and also to facilitate the access to investigational medical devices in Canada.

At Health Canada, the Medical Devices Directorate (MDD) is responsible for reviewing and authorizing medical devices for human use in Canada. It consists of six offices and bureaus, including the Bureau of Investigational Testing, Special Access and Post-Market Surveillance (BISP) and the Bureau of Evaluation (BE) which are responsible for reviewing and authorizing medical devices used for investigational testing. The team includes scientific evaluators, medical officers, regulatory affairs officers, and project coordinators and managers, including experts in cardiovascular devices, musculoskeletal devices, in-vitro diagnostic devices, general and restorative devices, and digital health devices.

Before authorizing a medical device for investigational testing in Canada, MDD must verify that the device meets the requirements of the Food and Drugs Act (1) and its regulations. Currently, Health Canada is offering two regulatory pathways to obtain the authorization to import or sell a medical device for clinical testing:

1. Medical Devices Regulations (MDR), Part 3; (2)
2. Interim Order No 2 Respecting Clinical Trials for Medical Devices and Drugs Relating to COVID-19 (CT-IO) (3)

This article provides an overview of the regulatory requirements, policies and

procedures for both regulatory pathways, including suggestions to avoid common avoidable deficiencies in the authorization and minimize delays.

MEDICAL DEVICES REGULATIONS

Part 3 of the MDR set out the requirements related to investigational testing authorizations (ITAs) for the importation or sale of medical devices for investigational testing involving human subjects. The requirements vary depending on the risk classification of the medical device. In fact, Canada takes a risk-based approach to the regulation of medical devices and has four classes of devices: class I, II, III and IV. Class I devices present the lowest risk and Class IV devices present the highest risk. It is the manufacturer who is responsible for applying the rules set out in the regulations to determine the appropriate classification for their device in Canada. Health Canada has guidance documents to assist manufacturers to determine their device classification (4-7).

An ITA is not required to sell or import Class I medical devices for investigational testing but it is required for Class II, III, and IV medical devices. Although the MDR do not require manufacturers and importers to follow Good Clinical Practice for an ITA, Health Canada recommends that they conform to ISO 14155: Clinical Investigation of Medical Devices for Human Subjects—Good Clinical Practice (8), which addresses the design, conduct, recording, and reporting of clinical investigations.

ITA Applications

To obtain an ITA, an application must be submitted to Health Canada. The ITA application process is independent of the medical device license application and therefore, an authorization for investigational testing is not an assurance that the data will be considered to be sufficient to support a device license. There are no fees associated with applying for an ITA.

Health Canada's Guidance Document: Applications for Medical Device Investigational Testing Authorizations (9), provides more information on the ITA application process and related responsibilities. However, this guidance document, as well as the current article, is not applicable to in-vitro diagnostics devices (IVDDs). For more information on ITA applications for IVDDs, manufacturers and importers should refer to the guidance document titled Preparation of an Application for Investigational Testing – in vitro Diagnostics available on the Government of Canada website (10).

Who can apply?

Only the manufacturer or the importer of the device can submit a new ITA application. In other words, if the trial also involves an unlicensed device from another manufacturer or if an investigator wants to use an unlicensed device in a clinical trial, the manufacturer of that device is responsible for applying to obtain the authorization. Note that an investigator/clinician may act as a regulatory correspondent for the application, if authorized by the manufacturer.

When an ITA is required?

In general, an ITA is required when an unlicensed Class II, III, or IV medical device intended for use in a clinical investigation is imported, sold, or distributed (even if there is no monetary compensation) in Canada or when a licensed medical device is used as part of a manufacturer-sponsored study intended to generate data to support a new indication for use.

It is interpreted from the regulations that an ITA is not required for the following situations:

- There is no sale or distribution of the device (e.g., the manufacturer conducts an in-house product development study at its own facility where there is no distribution of the device)
- An investigator sponsors a clinical study (without manufacturer support) with a licensed device that is used outside of the licensed indications, and the data will not be used to support a new indication for use
- A product does not meet the definition of a "medical device"
- A post-market clinical investigation or marketing study uses a licensed medical device as indicated in the labelling.

The flowchart represented in Figure 1 provides guidance to help determine when an ITA is required.

What information needs to be submitted?

For an ITA application, a risk-based approach is followed and the level of information to be submitted in the application depends on the classification of the device. Table 1 provides an overview of the information that Health Canada expects to receive in the ITA application, based on the MDR and the Guidance document (2,9). For all devices, Health Canada requests information related to manufacturer/importer, device description, device labelling and a list of qualified investigators with the name(s) and address(es) of the institution(s), as well as the study protocol and informed consent form (ICF). Given their lower risk, class II devices are subject to reduced requirements and only this previously listed information needs to be submitted. For Class III and Class IV devices, which are higher risk devices, Health Canada requires additional information, such as the marketing history, pre-clinical testing, a risk assessment, results of previous studies, evidence of the investigator qualifications, a signed investigator agreement, and evidence of Research Ethics Board (REB) approval at each site. Generally, the applicant must provide evidence to demonstrate the safety and benefits of the device. Therefore, in all cases, the reviewer may find that the information submitted is not sufficient to complete the assessment and additional information may be requested. In this section, clarification on the following information is provided: device labelling, ethics approval and qualified investigator.

Device labelling

Section 86 of the MDR describes the labelling requirements. The intent of the label is to ensure that the device is only used under the study protocol. Along with the name of the device and the name and contact information of the manufacturer, the label must include a statement indicating that the device is an investigational device ("Investigational Device" and "Instrument de Recherche") and a statement indicating that the device is only to be used by qualified investigators ("To be Used by Qualified Investigators Only" and "Réservé uniquement à l'usage de chercheurs compétents"). Health Canada also accepts other statements that convey that meaning. Both statements must be available in English and in French. As well, they must be included on the device label, the operator's manual (or instructions for use), and the package label. For reusable devices, a label should be put directly on the device and/or displayed on the start-up screen of the graphical user interface.

REB approval

Written REB approval must be obtained before study initiation at each site. Evidence of REB approval is not required to be submitted to Health Canada for Class II devices but must be submitted for Class III and IV devices. Ideally, the REB approval should be submitted at the time of the ITA application submission. However, if REB approval is not available at the time the ITA application review has been completed, it may be possible for Health Canada to issue a Letter of Authorization, if the application meets the requirements stated in the Regulations. In this case, the REB approval letter must be submitted to Health Canada prior to initiation of the study. Site specific REB approved ICF and protocol document(s), clean and redlined version, should be submitted to Health Canada. Health Canada will issue a letter to acknowledge receipt of the REB approval letter(s).

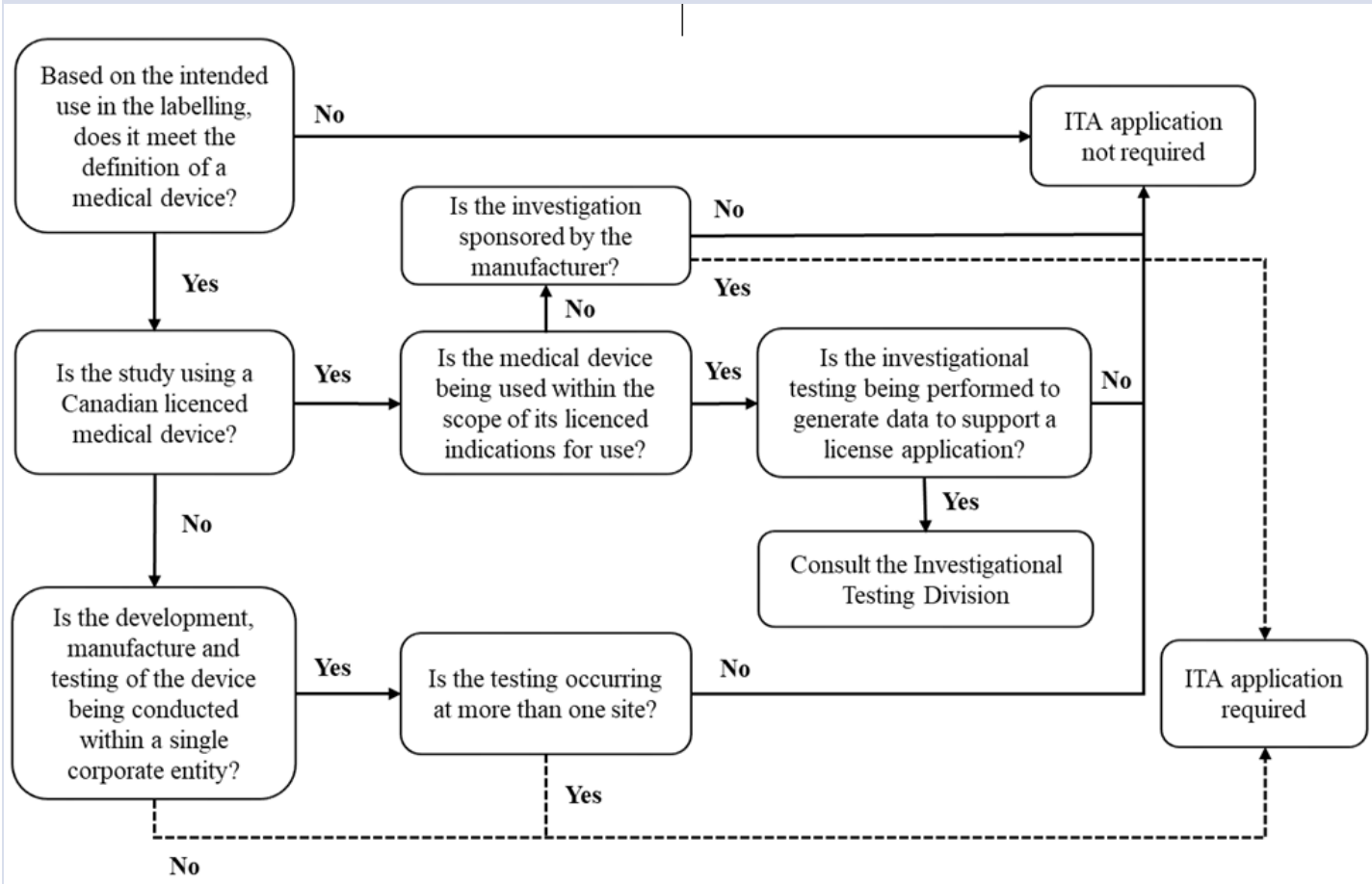
Qualified Investigators

For all device classes, the applicant must provide the name of the qualified investigator(s) who are actively involved in the use of the device within the clinical trial. To be listed as a qualified investigator, the investigator must be licensed to practice health care (i.e., health care professional) in the province. Also, the applicant must provide the name and address of the institution where the clinical trial will be conducted and/or where the device will be used.

How to submit the ITA application?

The applicant should follow Health Canada's electronic submission process, which includes a cover letter, executive summary, table of contents, and the New ITA Application Form (available at: https://www.canada.ca/en/health-canada/services/drugs-health-products/medical-devices/application-information/forms.html) with the required records based on the class of the device. The manufacturer or importer

FIGURE 1. DETERMINING WHEN AN ITA APPLICATION IS REQUIRED



must sign and complete the application form. Health Canada requires submission of the ITA application in an editable electronic format and will only accept non-eCTD electronic-only format (11). All submissions should be emailed to devicelicensing-homologationinstruments@hc-sc.gc.ca.

When one device is used in multiple studies, a separate ITA application is required for each study protocol. In this case, when the device information remains unchanged in the different ITA applications, a cross-reference should be used and the information may be submitted only once. If multiple devices from different manufacturers are used in the same study protocol, each manufacturer must submit a separate ITA application, listing only its device on the ITA Application Form; the other ITA applications should be referenced.

If an unlicensed device is used in a drug study, both an ITA application for the device and a Clinical Trial Application (CTA) for the drug are required. Both applications must be authorized before the clinical trial can start in Canada. If a drug-device combination is tested, either an ITA application or a CTA is required, depending on the principal mechanism of action of the combination product (12).

ITA application review process

Figure 2 provides an overview of the ITA review process at Health Canada. First, new ITA applications are screened for administrative and technical content to ensure that the applicable regulatory requirements as they pertain to the submission and labelling requirements have

TABLE 2:
POST-ITA REQUIREMENTS

OBLIGATIONS	REFERENCES
Record keeping	MDR Section 81
Advertising	MDR Section 87
Distribution records	MDR Section 88 (a) (referring to sections 52 to 56)
Complaint handling	MDR Section 88 (b) (referring to sections 57 and 58)
Reports of incidents	MDR Section 88 (c) (referring to sections 59 to 61.1) MDR section 81 (k) (v)
Recalls	MDR Section 88 (d) (referring to sections 63 to 65.1)
Implant registration	MDR Section 88 (e) (referring to sections 66 to 68)
Serious risk of injury to human	MDR Section 88.1 (referring to subsections 61.2(2) and (3) and section 61.3)
Quality management system	Guidance document, section 2.4.2
Requests for revisions to an ITA	Guidance document, section 2.5
Notification: cancellation of an ITA	Guidance document, section 2.6
Notification: discontinuance, resumption and completion of study.	Guidance document, section 2.8

been addressed. If regulatory deficiencies are identified, a Screening Deficiency Letter is issued which details the missing information. The applicant has 15 days to provide the missing information.

If the information is complete, a Screening Acceptance letter will be issued and the review process will be initiated. The review period for new ITA application is 30 days from when a complete application is received by Health Canada. This duration is an estimated review target and not default deadlines that result in automatic authorization.

Once the review has been initiated at Health Canada, approval from the Investigational Testing Division Manager should be sought before the applicant submits un-solicited new or updated information (e.g. multinational study protocol revised per FDA request).

After the review is complete, if it was found that any information is missing from the application or if discrepancies were noted, Health Canada will send a request for additional information. The applicant must submit a complete response within 60 days. When the information submitted in support of the ITA is deemed to satisfy the requirements of the MDR, Health Canada will issue an authorization.

What are the obligations and responsibilities of the ITA holder?

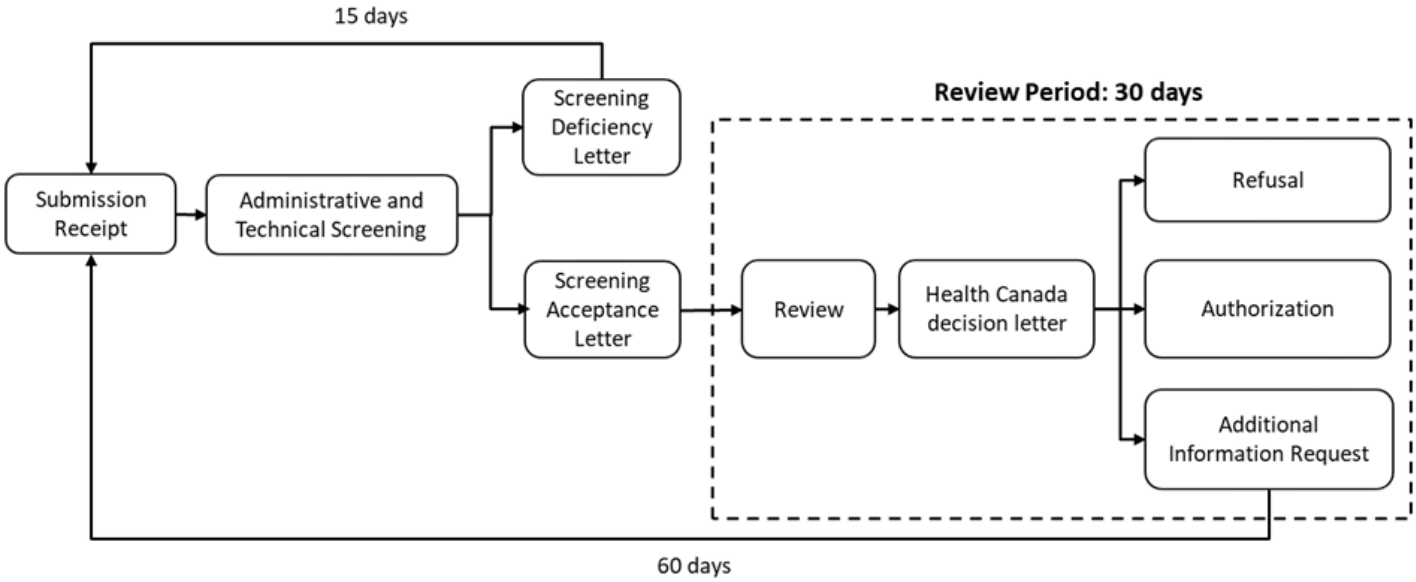
Once the ITA has been issued by Health Canada, it is expected that the ITA holder (i.e. manufacturer or importer) fulfill some obligations and responsibilities. Table 2 presents a list of the obligations and responsibilities, as described in the MDR and in the guidance document. A summary and clarifications for the requirements surrounding incident reporting, records keeping, revisions to an ITA and notification of study closure are provided below.

Incident Reporting

Section 88 (c) of the MDR describes the requirements with respect to reports on incidents. This section refers to sections 59 to 61.1 of the MDR.
Based on section 59 of the MDR, an incident is reportable if:

- it relates to a failure of the device or a deterioration in its effectiveness or any inadequacy in its labelling or in its directions for use, and

FIGURE 2. ITA REVIEW PROCESS OVERVIEW



- has led to the death or serious deterioration in the state of health of a patient, user or other person, or could do so if it were to recur.

In brief, manufacturers and importers shall report incidents involving a medical device that is sold (authorized for sale) in Canada when the incident:

- Occurs within Canada
- Occurs outside Canada for a Class I medical device
- Meet the criteria of reportable incidents

If a death or serious deterioration in the state of the health of a patient, user or other person has occurred because of an incident, a report must be submitted to Health Canada within 10 calendar days after becoming aware of the incident. If a death or serious deterioration in the state of the health did not occur as a result of the incident, but the incident could cause death or serious deterioration if it were to recur, then a report must be submitted to Health Canada within 30 calendar days.

On the other hand, based on section 81 (k)(v) of the MDR, investigators must report a reportable incident to Health Canada and the manufacturer or importer within 72 hours after becoming aware of the incident (Health Canada Medical device problem report form for health care professionals available at: https://hpr-rps.hres.ca/side-effects-reporting-form.php?form=medical_devices&lang=en).

Records keeping

The ITA holder must possess the appropriate records as indicated under Section 81 of the MDR. Although the risk-based approach does not require the applicant to submit all information (Class II devices) or to obtain an authorization (Class I devices), there is a requirement to possess all of the information for all device classes.

ITA revisions

Following the issuance of the ITA, an ITA holder may submit a request for a revised ITA to address changes made to the device, study protocol and/or informed consent form, or institutional information. A list of changes that would require a revised authorization is included in the ITA Application Guidance document (9) but some example of changes would include additional sites, increased number of devices and/or subjects or device changes. In the event where substantial study and/or device changes

introduce new risks, a new ITA application would be required. An ITA holder should refer to the Health Canada Guidance for the Interpretation of Significant Change of a Medical Device (13) to determine whether the device change is considered to be significant or not.

A revised ITA application must include:

- Cover letter and/or executive summary which clearly describe the revisions being requested
- Application form for the revised ITA (available at: https://www.canada.ca/en/health-canada/services/drugs-health-products/medical-devices/application-information/forms.html)
- Redlined and clean copies of the revised documents
- Tabular summary of changes with justification for any non-administrative changes
- Evidence of REB approval for Class III or IV devices (if not available at the time the revised ITA application review has been completed, the REB approval letter must be submitted to Health Canada prior to initiation of the study).

Notification of study closure

The ITA holder must inform Health Canada when a study is completed, suspended, or discontinued. Health Canada recommends submitting a copy of the final study report for completed studies. If the study is suspended or discontinued, the ITA holder must inform Health Canada and provide reasons for this action, clarify if safety concerns were involved in this decision, and include a summary of the study outcomes and adverse events, if applicable. Upon study closure, reusable devices and unused devices should be returned to the manufacturer or importer.

INTERIM ORDER NO. 2 RESPECTING CLINICAL TRIALS FOR MEDICAL DEVICES AND DRUGS RELATING TO COVID-19

During the COVID-19 pandemic, Health Canada needed to be flexible and provide access to clinical trials while ensuring patient safety. On May 23, 2020, the Ministry of Health approved the Interim Order Respecting Clinical Trials for Medical Devices and Drugs Relating to COVID-19 (14), hereafter called the Clinical Trial Interim Order (CT-IO). Although a COVID-19 medical device clinical trial may be authorized under the MDR, the CT-IO provides an alternative authorization pathway for COVID-19 medical devices (not applicable to Class I devices). As interim orders are temporary, action was needed to ensure that the interim order authorizations, obligations, and oversight continued for trials already authorized and for the pathway to remain available for new clinical trials for COVID-19 drugs and medical devices; therefore, a CT-IO #2 was created in May 2021 to extend this regulation (3).

Under the CT-IO, applicants are exempt from requiring an authorization under the MDR and instead apply for a Clinical Trial Authorization (CTA) under modified requirements which introduce new benefits, including:

- Authorization of the medical device and the clinical trial across its entire lifecycle
- Expanded range of applicants who are able to apply beyond manufacturers and importers
- Enhanced means to obtain informed consent to allow for remote and non-written consent when appropriate to facilitate virtual trials and infection control
- Allows Health Canada to suspend or cancel part or the entire trial.
- Expedited review timeline

Although there are no set review deadlines, COVID-19-related trials are prioritized and internal guidelines call for a review to be completed within 14 days. The shortened timelines could allow COVID-19-related trials to begin sooner.

There is no required format for the submission; however, Health Canada requests that the cover letter clearly indicate the direct use of the device in relation to COVID-19. The applicant should submit the application form and all supporting documentation as outlined in the interim order guidance document, (15).

Like the MDR, the CT-IO follows a risk-based approach where the level of required information is lower for Class II devices than for Class III and IV devices. Many requirements from the MDR Part 3 are the same as in the interim order, but some requirements were modified.

A new requirement in the CT-IO is the submission

TABLE 1
REQUESTED INFORMATION FOR THE ITA APPLICATION

Records (MDR Part 3, 81)	Submission Requirements		Summary description of the information to be provided (but not limited to)
	Class II	Class III / IV	
a) Manufacturer / importer information	√	√	Complete name and address of the device manufacturer and importer, if applicable.
b) Device and identifier information	√	√	Name of the device and the device identifiers, as they appear on the label, including any component, part or accessory that is part of the device. Risk classification of the device. Number of units of each device requested
c) Detailed device description, materials	√	√	Description of the device, hardware and software components and materials used in its construction and packaging.
d) Details of features, design and medical purpose (design philosophy		√	Description of features of the device that permit it to be used for the medical conditions and purposes for which it will be sold by the manufacturer (design philosophy and performance specifications) Indications for Use and/or intended use, as proposed by the manufacturer.
e) Marketing history		√	Details on the regulatory status in other jurisdictions, volume of sales, summary of reported problems, recalls. Also include previously licensed IT/SAP in Canada.
f) Risk assessment		√	Analysis and evaluation of the risks inherent in the use of the device and the measures adopted to reduce these risks to acceptable levels for the purpose of conducting the investigational testing.
i) previous testing;		√	Results from any previous studies including verification and validation studies: device design (e.g. mechanical, electrical); performance; shelf life; sterilization; bioburden, pyrogenicity; software; packaging stability; and biocompatibility. Animal studies, clinical studies A list of standards and Declaration of Conformity to a recognized standard may be sufficient to replace detailed pre-market information.
ii) Alternative therapies;		√	Description of the methods currently used to diagnose or treat the medical conditions that are the subject of the proposed investigational testing.
iii) precautions /contraindications		√	Information respecting any cautions, warnings, contra-indications and possible adverse events associated with the use of the device.
g) Qualified investigator information and their qualifications	√	√	For all devices: name of the qualified investigator(s) For Class III and IV devices: the curriculum vitae for each qualified investigator(s).
h) Institution information	√	√	Name, address and contact information of each institution where the testing is proposed to be conducted.
Evidence of REB approval		√	REB approval letter at each site confirming that the trial can be conducted at the site and the approval of the study documents.

TABLE 1
REQUESTED INFORMATION FOR THE ITA APPLICATION

i) Protocol and Informed Consent Form	√	√	Study protocol and ICF documents with date and version number. For Class III and IV devices: Investigator Brochure
j) Device label	√	√	Includes the device label, package labels, instructions for use, operator's manual, training manual and all advertising brochures intended to be used with the device.
k) Written undertaking from each qualified investigator		√	Signed investigator agreement for each investigator to be listed on the authorization.

of an attestation of the implementation of documented procedures for distribution records, complaint handling, incident reporting, and recalls. For Class III and IV devices, evidence of REB approval is not required, however, the applicant must submit the name and contact information of the REB responsible to review and approve the study, if known at the time of the submission.

The CT-IO provides a detailed list of information which must be included in the device labelling. The labelling includes the package label and the directions for use. The information on the label must be in English and in French. If a package label is too small to display all of the required information, it can be included in the directions for use.

Post-authorization reporting requirements for changes have been reduced to decrease administrative burden on sponsors. The application holder is required to submit a request for an amendment to the authorization if there are significant changes to any information submitted in the application. An amendment is not required for the addition or removal of an institution where the trial is being conducted or a change to the qualified investigators. These changes can be implemented immediately; however, the applicant must keep records of such changes on file.

Like the Part 3 of the MDR, the Interim Order requires the authorization holder to maintain all records and report medical device incidents, recalls, and study discontinuation to Health Canada. Applicants should refer to the Interim Order and corresponding guidance document for more details (3,15).

COMMON AVOIDABLE DEFICIENCIES

To facilitate a timely review and avoid unnecessary delays, it is important that the applicant submit an authorization package that contains complete, accurate and consistent information. Table 3 highlights common avoidable deficiencies in applications seen by Health Canada and suggestions for avoiding these deficiencies.

Health Canada sometimes receives application forms that are missing information on the anticipated study duration, number of devices to be authorized, or number of Canadian subjects.

Manufacturers and importers should accurately complete all sections of the application form. A complete marketing history should be provided, including Special Access requests and previous ITAs or Clinical Trial Authorizations. The informed consent form should include potential risks and benefits and treatment alternatives, as well as statements indicating that the device is investigational. It is recommended that applicants refer to the standard ISO 14155 (8), which provides guidance on what to include in an informed consent form. Also, test reports submitted to provide evidence of safety and effectiveness must be signed and describe methods, acceptance criteria, results, and any deviations.

For the device description, if the investigational device is modified from a licensed device or used under a previously

issued ITA, the applicant should cross-reference this previously approved device and specify if changes have been made. If so, a comparison of the similarities and differences should be provided in tabular form.

The device label must include the investigational statements, as set out by Section 86 of the MDR, in English and in French. For reusable devices, the investigational statements should be on the device in addition to packaging and instructions for use. The instructions for use, the user manual, and the package insert should also be submitted as part of the device labelling documentations.

Finally, common deficiencies also occur in the list of qualified investigators and REB approval. In the list of qualified investigators, the applicant should ensure that each qualified investigator identified is licensed to practice healthcare in his/her province and that only the qualified investigator(s) actively involved in the use of the device be provided.

When evidence of REB approval is required (Class III and IV devices), the applicant should include the REB letter(s) which reference to the most current protocol and informed consent form. If there are any discrepancies, justification must be provided.

CONCLUSIONS

Health Canada currently offers two regulatory pathways to obtain authorization for investigational medical devices in clinical trials. The MDR pathway governs the authorization for sale or importation of medical devices for investigational testing. A new temporary pathway authorized the importation and sale of medical devices related to COVID-19 for investigational testing; this pathway allows for expedited reviews of COVID-19-related devices for investigational testing using reduced requirements for authorizations. For both pathways, an authorization is required for Class II, III, and IV medical devices. Each pathway has specific risk-based requirements that must be met before an authorization can be issued. To avoid delays, the application must be complete, and contain consistent and sufficient information to support the safety and benefits of the device as required by the regulations.

Health Canada is working to modernize the clinical trial regulations for all the product lines, including medical devices, and therefore, changes to the MDR are expected. The overall intent of the modernization initiative is to encourage clinical trials in Canada by creating an environment that supports innovative trials. The aim is to provide consistency, greater flexibility, and remove the unnecessary regulatory burden, while still maintaining the proper regulatory oversight that is proportionate with the risks, to ensure patient safety. As part of the modernization project, Health Canada envisions to incorporate some of the agile concepts introduced through the COVID-19 Clinical Trial Interim Order. This new framework will be developed based on the lessons learned from the pandemic but also informed through discussions and questions that we receive from stakeholders (consultation session took place May – July 2021). Canadians will have the opportunity to provide comments on the regulatory proposal during the Canada Gazette, Part I, public comment period.

TABLE 3
COMMON AVOIDABLE DEFICIENCIES IN APPLICATIONS

Common Avoidable Deficiencies	Tips and Tricks
Device description	• Clearly describe differences for modifications from the licensed device or previously issued ITA
Device label	• Provide the device label, instructions for use, user manual, and package insert • The name of the legal manufacturer and the name of the device must be consistent with the information found on the device labelling. • Provide a sample of the label with the investigational statements: ○ In English and French • For reusable devices, put the investigational statements on the device, packaging, and instructions for use
Marketing History	• Provide complete marketing history (include Special Access requests, previous ITAs or clinical trial authorizations elsewhere – for subject device or predicate)
Informed Consent Form (ICF)	• Include potential risks and benefits (even if none directly to the patient) and alternative treatment options • Include a statement indicating that the device is investigational • Refer to ISO 14155 • For clinical trials involving subjects <18 years old, submit a copy of the parent ICF, the assent form and/or participant consent form.
Incomplete application – missing information: • Anticipated study duration • Number of devices to be authorized • Number of Canadian subjects	• Accurately complete the Application Form and make sure that all fields are completed.
Number of devices	• If there are multiple independent components, include the number for each
List of qualified investigators	• Ensure each qualified investigator is licensed to practice healthcare in his/her province • Provide the name of the qualified investigators who are actively involved in the use of the device.
Test reports not signed or missing results	• Submit signed test reports that describe methods, acceptance criteria, results, and any deviations
REB approval (when required): Date and/or version included on the protocol and ICF does not correspond with the REB letter	• Submit REB letter(s) which reference the most current protocol and informed consent form (or justifications for discrepancies, if applicable) – For Class III and IV devices only.
Inconsistent information between the Application Form, study documents and other documents submitted in the application.	• Maintain consistency in study documents and other documents submitted in the application.

TABLE 4
COMMON CLINICAL INVESTIGATOR INSPECTIONAL OBSERVATIONS

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Mike M. Rashti

Investigator/Investigational Site Responsibilities

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Abstract: *The successful completion of clinical studies in support of New Drug Applications requires clinical investigators and investigational sites to fulfill their responsibilities, including complying with Good Clinical Practice (GCP). This article describes these responsibilities and explains how to prepare for an inspection by the U.S. Food and Drug Administration (FDA) and address deficiencies. The most common deficiencies observed during FDA inspections are highlighted, along with how to avoid them and maintain compliance with GCP.*

Disclosure: The author has no relevant financial relationship in relation to this article.

THE BIORESEARCH MONITORING PROGRAM

The FDA initiated the Bioresearch Monitoring (BIMO) program to:
help ensure the protection of the rights, safety, and welfare of human research subjects involved in FDA-regulated clinical trials, to verify the accuracy and reliability of clinical trial data submitted to FDA in support of research or marketing applications, and to assess compliance with statutory requirements and FDA's regulations governing the conduct of clinical trials.

Accordingly, a BIMO program inspection has three parts:

- protecting the rights, safety, and welfare of human research subjects;
- verifying the accuracy and reliability of research submitted on FDA-regulated products; and
- assessing the clinical investigator's compliance.

Inspection assignments are issued by the FDA's six centers:

- Center for Drug Evaluation and Research;
- Center for Biologics Evaluation and Research;
- Center for Devices and Radiological Health;
- Center for Veterinary Medicine;
- Center for Food Safety and Nutrition; and
- Center for Tobacco Products.

At the end of an FDA BIMO program clinical investigator inspection, it is far better to receive a handshake from the FDA investigator than an FDA Form 483, which may result in a Warning Letter.

CLINICAL INVESTIGATOR COMMITMENTS FOR DRUGS

General Responsibilities of Investigators (21 CFR 312.60) requires the clinical investigator to ensure:
that an investigation is conducted according to the signed investigator statement, the investigational plan, and applicable regulations; for protecting the rights, safety, and welfare of subjects under the investigator's care; for the control of drugs under investigation; and for provisions of 21CFR part 50.
Table 1 provides a brief overview of FDA Form 1572 (Statement of Investigator). FDA Form 1572 is straightforward,

TABLE 1:
FORM FDA 1572 (STATEMENT OF INVESTIGATOR)

1. Name and address of the clinical investigator
2. Education, training, and experience that qualify the clinical investigator as an expert in the clinical investigation of the drug for the use under investigation (CV)
3. Name and address of any medical school, hospital, or other research facility where the clinical investigation(s) will be conducted
4. Name and address of any clinical laboratory facilities to be used in the study
5. Name and address of the institutional review board (IRB) that is responsible for review and approval of the study(ies)
6. Names of sub-investigators (if not applicable, enter "none")
7. Name and code number, if any, of the protocol(s) in the IND for the study(ies) to be conducted by the investigator

starting with the name and address of the clinical investigator. Under education, training, and experience, "CV" should be checked, and the CV must be up to date. The name and address where the clinical investigation(s) will be conducted is next, followed by the name and address of all clinical laboratory facilities to be used in the study. The fifth item is the name and address of the institutional review board (IRB) that is responsible for review and approval of the study(ies). The IRB can be institutional or central. Any sub-investigators must also be listed. The last item is the name and code number, if applicable, of the protocol(s) in the Investigational New Drug (IND) Application for the study(ies) to be conducted by the clinical investigator.

The author often sees mistakes on FDA Form 1572 when conducting mock inspections to help clinical investigators and investigational sites prepare for inspections. In addition, clinical investigators often sign the form without reading it. Signing the form means that the clinical investigator agrees to:

- conduct the study according to the protocol;
- personally conduct/ supervise the study;
- ensure proper informed consent and IRB review;
- report adverse experiences to the sponsor;
- ensure that associates know their obligations;
- maintain adequate and accurate records;
- ensure that an IRB complies with 21 CFR 312.60, 21CFR part 50, and 21 CFR part 56 and does initial and continuing review;
- promptly report to the IRB all changes in research activity; and
- know and comply with the requirements in 21 CFR 312.
- The author inspected one investigational site where about 30% of the subjects consented after they were given the first dose of the study drug. This is not allowed.

Recordkeeping is very important. Changes that must be reported to the IRB include notification that a sub-investigator has left the investigational site.

RESPONSIBILITIES OF THE CLINICAL INVESTIGATOR

The investigational site is comprised of the clinical investigator, the clinical research coordinator, and the entire research staff. For research purposes, the investigational site should be prepared as if every day is an FDA inspection.

The investigational site must know the regulations, protocol, and study documents and have adequate communication with the sponsor or contract research organization (CRO) and the IRB. Additionally, the site must have all of the regulatory binders, case report forms (CRFs), and source documents available for the FDA investigator. The regulatory binder should be organized from the start of the study in order to shorten the length of the inspection.

The sponsor or CRO should train the investigational site; such training should include the investigator's meeting. The investigator's meeting and the initial monitoring visit are different. The clinical investigator will learn much more at the investigator's meeting than at the initial monitoring visit.

The clinical investigator should know:

- GCP (Good Clinical Practice);
- 21 CFR Part 50: Protection of Human Subjects;
- 21 CFR Part 54: Financial Disclosure by Clinical Investigators;
- 21 CFR Part 56: Institutional Review Boards;
- 21 CFR Part 312: Investigational New Drug Application or 21 CFR Part 812: Investigational Device Exemptions; and
- FDA Compliance Program Guidance Manual for Clinical Investigators 7348.811.

When conducting a clinical investigator inspection, the FDA investigator follows the Compliance Program Guidance Manual for Clinical Investigators, which is available online on the FDA's website. Clinical investigators should also be familiar with this manual.

HOW FDA SELECTS CLINICAL RESEARCH SITES FOR INSPECTIONS

Clinical investigators always want to know why they were selected for an inspection. Reasons for being selected include conducting a pivotal study, being a high enroller, and being different than other investigational sites (for example, if a pivotal study had 10 clinical research sites, and nine of the sites had problems including serious adverse events, the FDA will inspect the one site that had no serious adverse events or data that were too clean). The FDA will inspect sites that have many more problems than other sites in the study. The FDA will also inspect sites based upon issues raised by the sponsor or complaints from an employee or another company. Once in a while, the FDA inspects an ongoing study in order to assess a compliance issue at the investigational site.

BIMO assignments are assigned by one of the centers rather than being issued by the FDA District Offices. There are two types of inspections: routine and directed. Routine inspections are normal inspections of pivotal studies pending New Drug Application (NDA) review, whereas directed (for cause) inspections are conducted due to suspicion of false or fraudulent data, data that appear unrealistic or are perfect, or when the sponsor alerts the agency of serious problems.

A routine inspection takes an average of five days, with a typical range of three to seven days. The author's shortest inspection was one day and his longest inspection was three weeks. A directed inspection may take at least seven days.

Table 2 provides an overview of inspection activities. When the FDA investigator receives an assignment from a center, he/she calls the clinical investigator or clinical research coordinator to announce the inspection. It usually takes some time to find the right department and reach the clinical investigator or clinical research coordinator. The FDA investigator explains the reason for the inspection, provides the NDA number and the protocol number, and asks for the relevant documents. The FDA investigator will also set a date, time, and location to meet with the clinical investigator and the clinical research coordinator, and if possible, with the entire staff.

The clinical investigator or clinical research coordinator should never claim that the investigational site does not have time for the inspection. He/she should provide a suitable room for the FDA investigator to work and make available:

- all of the source documents for the study;
- all of the CRFs or eCRFs related to the study; and
- the regulatory binder(s).

During the opening interview, the FDA investigator will present his/her credentials and the Notice of Inspection (FDA Form 482). The FDA investigator will interview staff, and in cases when the clinical research site is part of a large facility, he/she will walk through the facility, see their equipment, visit their laboratory, and so forth. The investigational site should be clean and orderly, and it should not have any expired investigational drugs.

The investigational drug should be stored as per the protocol.

TABLE 2:
INSPECTION ACTIVITIES

- Announce inspection (phone)
  - Provide date, time, and location to meet the clinical investigator and the study coordinator
- Opening interview
- Review of:
  - Regulatory binders
  - Source documents
  - Case report forms
  - Informed consent forms
  - Administrative records
  - Drug storage and records
- Exit interview

During an inspection for a vaccine study, the author found that the protocol required the vaccine to be stored in a -40-degree C freezer; however, the investigational site's freezer was only -20 degrees C. The staff argued that a -40-degree freezer is the same as a-20-degree freezer; however, the protocol required a -40-degree freezer.

The FDA investigator will review the regulatory binders, source documents, CRFs, informed consent forms, administrative records, and drug storage and records. The informed consent forms must be the original forms. Administrative records are the communication between the clinical research site and the sponsor and communication between the clinical research site and the IRB. Drug storage and records include drugs received, drugs used, and drugs returned or destroyed by the site.

If the investigational site uses electronic CRFs (eCRFs) or electronic data capture, then there may be problems making the eCRFs available to the FDA investigator. The site must either provide media with the records or a computer and an operator with access to the necessary records.

At the conclusion of an inspection, the FDA investigator conducts an exit interview with the clinical investigator, during which the FDA investigator will discuss any inspection findings. He/she may issue an FDA Form 483 (Inspectional Observations), which documents deviations from federal regulations for clinical investigators. If there is only one item, the FDA investigator may simply discuss it with the clinical investigator rather than issuing an FDA Form 483. The clinical investigator has the right to respond to each item in the FDA Form 483 either verbally or in writing.

POST-INSPECTION ACTIVITIES

There are three compliance classifications for clinical investigator inspections:

- No Action Indicated (NAI):
  - The clinical research site is in compliance
- Voluntary Action Indicated (VAI):
  - Voluntary correction(s) required and marginal compliance
- Official Action Indicated (OAI):
  - Serious non-compliance requiring regulatory or administrative action. An OAI classification may result in a Warning Letter.

After completing the inspection, the FDA investigator has between 7 and 30 days to write the Establishment Inspection Report and send it to the center that assigned the inspection. The center reviews the Establishment Inspection Report and classifies the inspection. The center then sends a letter to the clinical investigator and the FDA district office.

CRITICAL ISSUES AND COMMON DEFICIENCIES AT INVESTIGATIONAL SITES

Critical issues reviewed during an FDA inspection are:

- subjects meeting all inclusion/exclusion criteria;
- having a diagnosis for every subject;
- documenting drug administration;
- having raw data available for the inspection;
- having IRB approval for all significant stages of the study; and
- having proper informed consent for every subject prior to study enrollment.

Table 3 highlights common deficiencies found in clinical investigator inspections, some of which are illustrated below in citations in FDA Form 483s.
Under protocol non-adherence, deficiencies in inclusion/exclusion criteria resulted in the following finding on an FDA Form 483:
Five of 21 subjects (#s 02-04, 06, and 08) who entered into the study were ineligible based on failure to meet protocol inclusion/exclusion criteria:
They were ineligible based on their positive HBsAg test results which required exclusion from entry.

The above deficiency occurred in 25% of the investigational site's subjects.
Another FDA Form 483 on protocol non-adherence was issued for not dosing the subjects on time:
The protocol treatment plan was not followed in that subjects 002, 004 and 005 received the first and second doses 10 days apart and not 8 days apart according to the protocol.

Failure to report concomitant therapy is another common deficiency. An example of an FDA Form 483 related to this issue is:
Concomitant medications were not reported in the case report forms for the first 2 weeks for subjects # 002, and 004 (This was documented in their patient charts).
Under failure to maintain adequate accurate records, one FDA Form 483 cited lack of supporting documentation for entries found in the CRFs:
Source documents could not be found for the subjects # 005 and 007.
The investigational site should have a good explanation as to why the source documents were not available.
The CRF and the patient chart should match. Another FDA Form 483 cited source documents that revealed that the CRFs were inaccurate:
The case report form for subject #001 indicates that the subject was taken off study drug at 1400 hours on 1/11/10. Nurse's notes, dated 1/11/10, state that this subject was taken off study drug at 1300 hrs.
The author would not have cited the above on an FDA Form 483; this could have been a discussion item.

Failure to report adverse events (AEs) is another common deficiency. One FDA Form 483 stated:
Adverse events were not reported to the sponsor: Patient # 003 was treated with study drug. This patient reported symptoms of easy fatigability, nausea and vomiting when admitted to the hospital on 12/24/11. There is no documentation that this serious adverse event was reported to the sponsor.

There is a difference between adverse events (AEs) and serious AEs (SAEs). Admission to the hospital changes the AE to an SAE. Every protocol defines SAEs, which are:

- death;
- life-threatening condition;
- hospitalization (initial or prolonged);
- disability;
- congenital anomaly; and
- required intervention to prevent permanent impairment or damage.

Drug accountability is straightforward. No investigational site should ever have inadequate drug accountability. Under inadequate drug accountability, one FDA Form 483 stated:
Records for drug accountability are inadequate in that they do not show dates the study article was received, nor is there any documentation of the final disposition of the study article.

Informed consent should be properly documented, signed, and dated.

TABLE 3:
COMMON DEFICIENCIES IN CLINICAL INVESTIGATOR INSPECTIONS

- Protocol non-adherence
- Failure to report concomitant therapy
- Inadequate and inaccurate records
- Failure to report adverse events
- Inadequate drug accountability
- IRB problems
- Informed consent issues

TABLE 4:
POSSIBLE OUTCOMES OF FDA INSPECTIONS

- Untitled correspondence (most common outcome)
- Invalidation of the study
- Delayed NDA approval or disapproval of the study
- Warning letter
- Consent agreement
- Disqualification of clinical investigator
- Prosecution of clinical investigator and/or site staff

WARNING LETTERS AND POSSIBLE OUTCOMES OF FDA INSPECTIONS

An inspection classification of OAI results in a Warning Letter, which typically begins with:
You failed to conduct the clinical investigations according to the investigational plan [21 CFR 312.60].
About 60% of the time, the Warning Letter cites 21 CFR 312.60. One warning letter stated:
Regarding Protocol [xx]. Of nine subjects randomized in Protocol [xx] three subjects met exclusionary criteria, but were not excluded from the study. The details for these subjects are described below:
The exclusionary criteria were age, concomitant medications, and laboratory test values.

A Warning Letter gives the clinical investigator 15 working days to respond:
Within fifteen (15) working days of your receipt of this letter, you should notify this office in writing of the actions you have taken or will be taking to prevent similar violations in the future. Failure to adequately and promptly explain the violations noted above may result in regulatory action without further notice.
Warning Letters are publicly available on the FDA's website. The responses should be adequate to reduce the consequences.

Table 4 outlines possible outcomes of an FDA inspection. Untitled correspondence is the most common outcome. The study can also be invalidated or the NDA can have approval delayed or be disapproved. The FDA could issue a Warning Letter or a consent agreement. Disqualification of the clinical investigator is another possible outcome. It takes about two years from issuing a Warning Letter to disqualification of a clinical investigator.

Also, the FDA has prosecuted clinical investigators and investigational site staff. Site staff members have been prosecuted for changing or falsifying data or for creating fraudulent data. Clinical investigators and their staff should be honest and as clear as possible.

CONCLUSION

Clinical investigators, clinical research coordinators, and other investigational site staff should know what to expect during an FDA inspection. The FDA usually provides five days' notice before an inspection; however, the investigator can arrive with no notice. Clinical investigators and their staff should be aware of the common types of deficiencies found during inspections and the possible outcomes of an FDA inspection (NAI, VAI, and OAI). The inspection report will be sent to the clinical investigator; however, FDA Form 483s and inspection reports are also publicly available through a freedom of information (FOI) request. Clinical investigators' documents should be organized, and the site should be ready for an inspection at any time.

Preparing for the FDA inspection is crucial. Table 5 highlights the dos and don'ts of inspection behavior. Over the course of 25 years, the author has conducted many inspections and seen that no two inspections are the same. Clinical investigators and investigational site staff should always be polite and pleasant to the FDA investigator, including providing a heated room for him/her in the winter and an air-conditioned room in the summer.

The regulatory binder should be well-organized. The clinical investigator should show interest by dropping in daily to ask how the inspection is going and attending the end-of-inspection meeting. The clinical

investigator and investigational site staff should never argue with the FDA. Even if they are correct, the FDA will win. They should not make inappropriate comments, such as asking how the inspection was or if they passed the inspection, as a center can change the FDA investigator's suggested classification.

Documentation of everything related to the study is crucial. Clinical investigators and investigational site staff should have a telephone log documenting communication with subjects. Sites should use memos sparingly, as having too many memos to file may indicate that the site needs help. The author inspected one investigational site that had more than an inch of memos to file. When asked about this, the clinical investigator blamed clinical research coordinator turnover; however, the clinical investigator signed FDA Form 1572 and is responsible for the study regardless of staff turnover.

It is important to be honest with the FDA investigator. The fewer mistakes the clinical investigator and investigational site staff make and the more prepared and organized they are, the sooner the FDA investigator will leave the site. Being prepared and organized also makes it more likely that the inspection will end with a handshake.

TABLE 5:
DOS AND DON'TS DURING AN FDA INSPECTION

Do:

- Provide a comfortable room for the FDA investigator to work in
- Provide a well-organized regulatory binder
- Show some interest by dropping in daily
- Have a telephone log
- Document everything
- Use memos to the file sparingly

Don't:

- Argue with the FDA investigator
- Make inappropriate comments

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Adrian Granobles, MS, CCRP

Checking the Eligibility Checklist

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Abstract: *Clinical research sites must have a process in place to verify the eligibility of patients to participate in clinical trials. This article reviews the three stages of eligibility, namely development, verification, and documentation, and the role of the eligibility checklist in this process. Barriers to verifying eligibility and recommendations for resolving them and for balancing conflicting needs are described. The way that Memorial Sloan Kettering Cancer Center oversees the management of eligibility confirmation and the resources implemented to ensure that appropriate eligibility management is maintained are also discussed.*

Disclosures: The author has no conflicts of interest related to this article.

OVERVIEW OF ELIGIBILITY

Most institutions use an eligibility checklist document to ensure eligibility verification. Also known as an inclusion/exclusion checklist or inclusion/exclusion criteria checklist, the eligibility checklist is one of three main documents used during enrollment in a clinical trial along with the protocol and the informed consent form. The protocol and the informed consent form, which are the most commonly used documents, are required. The protocol is the main source for the background, purpose, and management of a study, whereas the informed consent form is used to convey potential risks and benefits and confirm the patient's agreement to participate in the study. The eligibility checklist is an important tool that can serve as a source document to confirm a participant's qualification for a study.

Confirming eligibility serves two main purposes. First, it ensures participants' safety. The second purpose is to define the study population and ensure that the appropriate participants are enrolled in studies so that results will be interpretable.

Establishing the inclusion/exclusion criteria is a standard practice to ensure the safety of participants in clinical research trials. The inclusion criteria define the key features that the investigator(s) will be using to answer the research questions. The eligibility criteria describe characteristics that must be shared by all participants. Ultimately, the eligibility criteria are necessary to protect the scientific integrity of the clinical trial and ensure that accurate and meaningful results are achieved.

The eligibility checklist serves two purposes. It can indicate that source documentation for the inclusion/exclusion criteria exists somewhere else in the medical record. The eligibility checklist can also serve as a source document for one or multiple inclusion/exclusion

criteria that are not documented elsewhere. For criteria that do not involve judgement or interpretation (e.g., laboratory values, age, etc.) the checklist would not be considered the primary source document because the original recording of the information is elsewhere in the medical record.

BARRIERS TO ELIGIBILITY

If the eligibility criteria are too strict, then enrollment in the clinical trial will be lower because fewer patients will qualify. The results of the study will be limited to a smaller population rather than a potentially more diverse patient population that will ultimately receive the drug or treatment. Other enrollment barriers related to eligibility include restrictions by insurance companies on enrollment in clinical trials or assumptions made by clinicians that prevent them from considering some patients for certain studies.

If the barriers are considered in advance, then researchers can potentially address them during the development of the eligibility criteria. For example, if a drug is not metabolized by the liver, then mild abnormalities in liver function tests that would otherwise exclude patients could be permitted. Expanding the age limit will enable more patients to participate.

Among the many other barriers to enrollment in clinical trials, some can be addressed by modifying the inclusion/exclusion criteria, whereas others are beyond that scope. However, researchers can open studies to a larger population by considering common barriers while developing eligibility criteria.

RECOMMENDATIONS FOR EXPANDING CLINICAL TRIAL ELIGIBILITY

The American Society of Clinical Oncology (ASCO) and Friends of Cancer Research collaborated with the U.S. Food and Drug Administration to present the Modernizing Eligibility Criteria Project. Friends of Cancer Research is a group of clinicians and other stakeholders from various institutions across the United States.

The Modernizing Eligibility Criteria Project's goal was to evaluate clinical trial eligibility criteria so that they do not unnecessarily restrict access to clinical trials. The working group provided recommendations for a more rational approach to determining inclusion/exclusion criteria (Table 1). This more rational approach helps to expand the number and diversity of participants in clinical trials.

The working group recommended including pediatric patients when there is a strong scientific rationale for doing so as well as cancer patients with HIV infection who are otherwise healthy and at low risk of AIDS. The group also recommended using a standard method for the creatine clearance to validate the renal function and other tests to evaluate hepatic function. Other recommendations are to include patients with prior or concurrent malignancies when the risk for interference with the drug and recurrence is low and not to include ejection fraction values in the inclusion/exclusion criteria if the therapy is known to not pose cardiac risk.

Based upon these recommendations, the National Cancer Institute (NCI) now asks researchers of clinical trials to make efforts to address eligibility issues by working to broaden the criteria for all studies funded by the NCI. Thus, researchers are encouraged to relax the use of upper age limits in clinical trials involving adults and allow people with cancer who are HIV-positive to enroll in clinical trials.

The working group also assessed the risks and benefits of expanded eligibility (Table 2). The top risks include adverse events and safety issues. As clinical trials include new groups of patients who have never been given the study

TABLE 1:
RECOMMENDATIONS OF THE MODERNIZING ELIGIBILITY CRITERIA PROJECT

- Relax age limits
- Include HIV-positive participants
- Optimize organ dysfunction tests
- Include participants with prior malignancies
- Remove cardiac dysfunction assessments

TABLE 2:
RISKS AND BENEFITS OF EXPANDED ELIGIBILITY

- Expanded eligibility risks:
  - Variability of outcome (need larger sample size)
  - Safety concerns may require separate cohorts or analysis
  - Complicates attribution of adverse events
  - Increased costs associated with additional cohorts
  - Potential for additional procedures for increased safety monitoring
  - Additional resources required

- Expanded eligibility benefits: Variability of outcome (need larger sample size)
  - Earlier access to investigational agents
  - More complete safety and efficacy data
  - Earlier identification of drugs that may not be effective
  - Generalizable to "real-world" patients
  - Faster accrual
  - Efficacy in understudied population could differentiate between drugs of the same class

Source: Friends of Cancer Research Annual Meeting, November 2016

drug, researchers will have to be hypervigilant. Expanding eligibility will also increase the resources required to manage clinical trials. Top benefits of expanded eligibility include earlier access to investigational agents and shorter clinical trials. By increasing the number of participants, accrual in clinical trials will be faster and the endpoints will be met much quicker. Being more inclusive will also lead to more complete safety and efficacy data.

Finding the right balance between expanded eligibility and ensuring participant safety is key to the success of the above recommendations. Because the new NCI eligibility criteria were only recently implemented, it will take some time to see any impact and be able to evaluate the results.

Other changes to the inclusion/exclusion criteria are coming soon. The ASCO and Friends of Cancer Research are continually meeting and addressing additional eligibility issues. Some of these issues include the amount of treatment and permissible concomitant medications that patients can have before entering a clinical trial, both of which are major barriers for cancer patients.

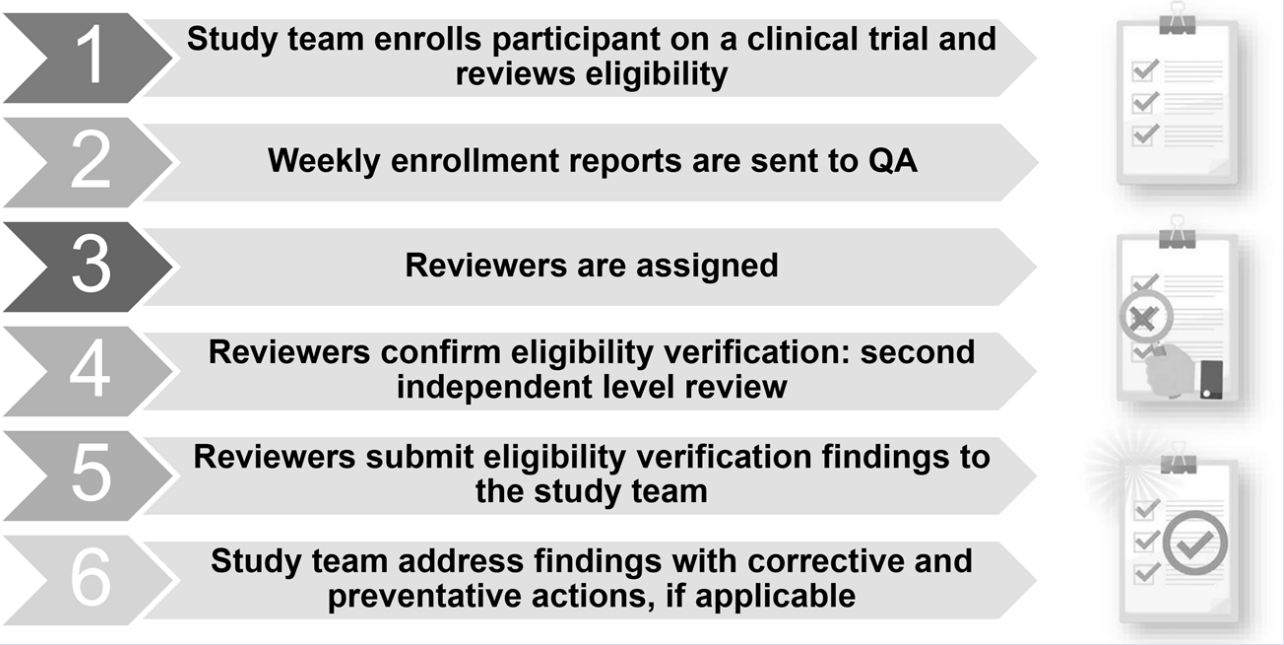
Clinical trial enrollment is a complex issue. Ongoing critical assessment of eligibility criteria is essential to achieving the right balance between expanded eligibility and ensuring participant safety. As less restrictive eligibility criteria translate into study conclusions that are more relevant to a broader patient population, researchers can make faster progress in discovering new targeted cancer treatments and immunotherapies.

Although there are many benefits to patients of expanded eligibility in clinical trials, the impact of this on study teams and data management must also be considered. For example, on just one study with expanded eligibility, the number of participants the study team sees may increase from one to five participants per month.

MEMORIAL SLOAN KETTERING CANCER CENTER ELIGIBILITY CHECKLIST MANAGEMENT AND INITIATIVES

Memorial Sloan Kettering Cancer Center has always recognized the importance of verifying eligibility during enrollment in clinical trials. The center has instituted different approaches to ensure adequate eligibility verification throughout the years. Based on these experiences, the center

TABLE 3:
MEMORIAL SLOAN KETTERING CANCER CENTER ELIGIBILITY CHECKLIST VERIFICATION PROCESS



has seen the need to have its regulatory and quality assurance (QA) units work closely with the study teams to identify gaps/risks in eligibility verification.

The current approach has a two-level validation process: initial validation is done by the clinician/study team member completing the form, and the second review is conducted by a member of the quality assurance department. The quality assurance department's approach to verifying eligibility triages findings and rapidly communicates with the study teams to request corrective and preventive actions (CAPAs) or regulatory corrections.

Memorial Sloan Kettering Cancer Center has moved from a limited review of 100% of all registrations to a risk-based monitoring (RBM) approach in which a percentage of all registrations are randomly selected for a more in-depth review. The goal is to focus on the process in addition to the individual participant. This change has led to an increase in oversight of the entire portfolio of clinical trials.

The volume of participants in clinical trials at Memorial Sloan Kettering Cancer Center continues to increase each year. It is important to dedicate adequate resources to enforcing proper eligibility checklist management. The author's department, Clinical Research Quality Assurance, developed a real-time participant eligibility verification process to ensure that clinical trial registrations are conducted in compliance with regulations and act as an independent reviewing group separate from the study teams. Implementing the new eligibility checklist verification program led to discovering ways to improve this important quality assurance process.

The purpose of the eligibility checklist verification program is to:

- ensure that participants are eligible when registered to a protocol;
- ensure the eligibility checklist accurately captures the protocol's inclusion and exclusion criteria; and
- ensure that the related source documentation is available in the electronic medical record (EMR) and is being appropriately managed.

Achieving these goals ensures that ineligible participants are

not enrolled in clinical trials and exposed to unnecessary risks.

THE ELIGIBILITY CHECKLIST VERIFICATION PROCESS

The previous eligibility checklist verification process at Memorial Sloan Kettering Cancer Center was labor intensive and prone to data loss. It used Excel spreadsheets that were shared with one user at a time. The new process includes a centralized database that has reduced transfer errors and standardized the data used for reporting. Data fields are directly uploaded from another system, which reduces time and effort.

Transferring the management of reviews to REDCap has streamlined the work. REDCap is an internet-based meta-data-driven electronic data capture software designed for research. Using REDCap provides access to query reports for faster analysis and allows multiple users to use the database at the same time.

REDCap allows Memorial Sloan Kettering Cancer Center to make immediate changes to the interface and the data fields as needed to adjust for new complex scenarios that require changing the way that certain questions are asked. If clinical research leaders request that certain data points be collected, then the system can be updated in real time to include these new requests.

Table 3 provides a simplified overview of the eligibility checklist verification process. The process begins with the study team enrolling a participant in a clinical trial and reviewing the participant's eligibility. The system used to register participants then sends a weekly enrollment report with a randomized sample of new participants to the quality assurance department for an independent review. The reviewers are assigned and perform a second level review (after the study team) of the eligibility checklist. The reviewers then submit their findings to the study teams. Finally, the study team addresses all findings and provides a CAPA, as applicable.

It is important to set clear expectations when communicating with study teams, especially if reviewers are requesting a response to eligibility review findings. The eligibility checklist verification process uses timelines based

TABLE 4:
RESULTS OF THE MEMORIAL SLOAN KETTERING CANCER CENTER ELIGIBILITY CHECKLIST VERIFICATION PROCESS

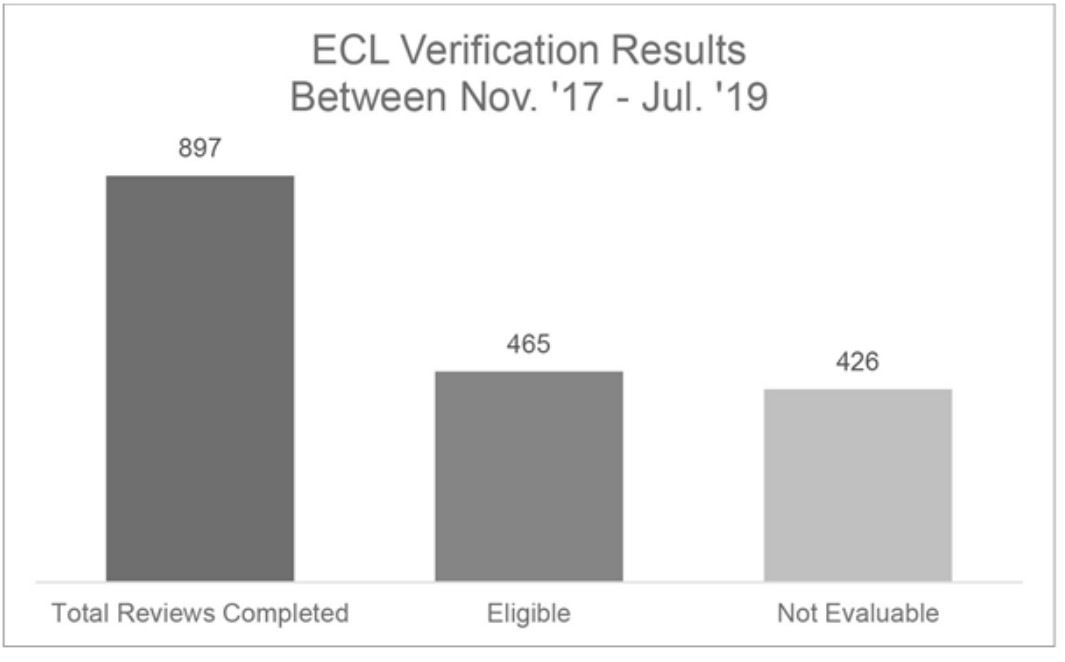
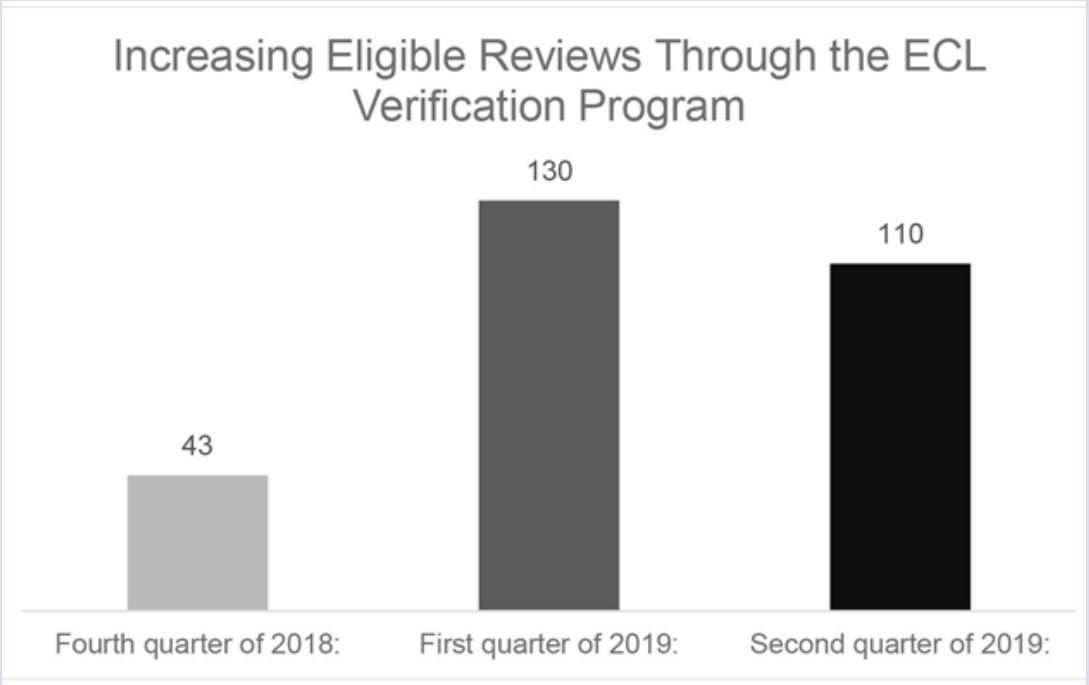


TABLE 5:
RESULTS OF THE MEMORIAL SLOAN KETTERING CANCER CENTER ELIGIBILITY CHECKLIST VERIFICATION PROCESS



on the type of finding: five days for reporting categories that are associated with not-evaluable findings and three days for findings of not-eligible. A response to non-evaluable related findings is not typically critical or urgent because participants' qualifications are not in question. Examples of this situation include errors in the eligibility checklist template or missing source documents in the EMR at the time of review.

Due to the risk of not-eligible findings, study teams must respond within a shorter period of time (three days). Examples of not-eligible findings include the use of the wrong eligibility checklist version, the use of the wrong informed consent form version, or questions about eligibility. Once the quality assurance department receives a response from the study team and determines that the response is satisfactory, the case is closed.

RETROSPECTIVE DEVIATIONS AND CAPAS

Eligibility checklist verification findings can lead study teams to submit retrospective deviations and CAPAs. Findings that involve registration and informed consent procedures not being followed can impact previously enrolled and future participants. Awareness of these issues and using CAPAs to resolve them are necessary.

For example, if the study team used the wrong eligibility checklist version, then this could impact qualification of participants. In this case, quick action is required. The quality assurance department must communicate with the study team to determine why the issue occurred and develop a preventive action plan so that the issue does not affect future participants. It is also necessary to determine the impact on previous participants who were enrolled using the wrong eligibility checklist version and take the appropriate corrective action.

RESULTS OF THE ELIGIBILITY CHECKLIST VERIFICATION PROCESS

The eligibility checklist verification process at Memorial Sloan Kettering Cancer Center has provided important information about quality and the eligibility processes (Table 4). Between November 2017 and July 2019, the quality assurance department completed the review of 897 eligibility checklists. The results were:

- 465 eligible clinical trial participants

- 426 non-evaluable participants – ECL and/or source document not evaluable in the EMR at the time of review, so eligibility could not be validated by reviewer

The goal is to increase the number of clinical trial participants for whom eligibility has been validated. The quality assurance department reviews the data collected through this program on a monthly basis to ensure quality control. Every quarter, the quality assurance department reviews trends and compares results to track progress and identify areas for improvement.

Between the fourth quarter of 2018 and the first two quarters of 2019 (Table 5), data showed an increase in the number of participants resulting as eligible after being reviewed through the eligibility checklist verification program. In the fourth quarter of 2018, just 43 participants resulted as eligible through the eligibility checklist verification program, whereas during the first two quarters of 2019, the number of eligible participants had increased to 130 and 110, respectively. The eligibility checklist verification program may have influenced the latter eligible results by re-educating study teams with proper compliance in the earlier quarters.

When the ECL and/or source documents are not evaluable in the EMR at the time of review, they result in non-evaluable. These results are reviewed with the study team, and findings are addressed to ensure that they ultimately meet all eligible validations.

The eligibility checklist verification program has indicated areas for improvement in three categories (Table 6). The first area for improvement is appropriately and completely filling out the eligibility checklist. Study teams do not consistently answer all questions fully and clearly.

Developing and updating the eligibility checklist document to accurately reflect the inclusion and exclusion criteria is another area for improvement. In some cases, a study's eligibility checklist template is missing an inclusion or exclusion criterion. Missing even one criterion can have a critical impact on whether a patient is eligible for a clinical trial. The protocol's inclusion/exclusion criteria are best taken without edit from the clinical protocol.

The third area for improvement is ensuring the timely and complete upload of the eligibility checklist and associated source documents into the EMR. Improvements to workflows, policies and processes are being made to timely submit source documents into the EMR.

CONCLUSION

Centralizing and streamlining the eligibility checklist verification process are key to the success of Memorial Sloan Kettering Cancer Center's eligibility checklist verification program. Using REDCap has enabled the quality assurance department to increase the collection of meaningful data as well as ensure timely data analysis and implementation of process improvement. Continuous communication with study teams on issues discovered throughout the verification process has improved education and ensured consistency and compliance with eligibility practices.

TABLE 6:
RESULTS OF THE MEMORIAL SLOAN KETTERING CANCER CENTER ELIGIBILITY CHECKLIST VERIFICATION PROCESS

Identification of areas of improvement:

- Appropriately and completely filling out the eligibility checklist
- Developing and updating the eligibility checklist to accurately reflect inclusion and exclusion criteria
- Uploading the eligibility checklist and associated source documents into the EMR within the required timeframe

Heather Tudor, DrPH, CCRP, RHIA

Importance of Quality Research: A Review of Quality Tools and Ideas for Incorporation

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Abstract: *Quality improvement is crucial to enhancing clinical research by identifying errors or potential errors and fixing processes to prevent those errors from reoccurring. This article describes quality methodologies and management tools and how they can be used to improve various aspects of clinical research programs.*

HISTORY OF QUALITY IMPROVEMENT

In the 1950s, Dr. W. Edwards Deming helped change the manufacturing industry in Japan. Starting in the 1960s, the rest of the world began paying attention to his work.[1] Even today, Deming's teachings continue to influence organizations.

When clinical research professionals feel like a failure or are haunted by mistakes, they should remember this quote from Deming: "A bad system will beat a good person every time."[2] His point is that problems in processes cause errors, not problems with people.

Clinical research is full of processes, which usually can be improved. For example, when a healthcare organization receives a new study, there are processes to start the study, send the study for review by the institutional review board (IRB), enroll subjects, move subjects through the study, and close out the study.

A process is a series of actions or steps taken in a specific order to achieve a particular end. Whatever the process is, specific steps must be taken in order to achieve the same result every time. In clinical research, problems or errors occur when steps in the process are missed or performed out of order.

THE START OF QUALITY

Quality starts with developing standardized work, which serves as the foundation for process improvement. Several tools can be used to help establish standardized work. Some organizations begin by creating a flowchart. They then develop a procedure based on the flowchart. A simple checklist can also be used to create standardized work.

For example, Sally constantly forgets to place a copy of the informed consent form (ICF) in the subject's chart and write consent notes after a subject has consented. Sally's director wants to improve the process but is unsure of how to do this. When Sally is asked about this problem, she typically says that she gets called to do other things and simply forgets.

The director sets a goal for Sally to have 100% of consent notes on subjects at the end of every week. Sally improves but does not reach 100%. Without

TABLE 1:
THE PDSA MODEL

Plan:
- Plan the implementation

Do:
- Implement the plan

Study:
- Study the plan

Act:
- Make changes as needed

a standardized process with specific steps in a particular order, Sally and her boss will likely not determine the root cause of the problem so that Sally's performance can improve.

Sally decides to create a checklist to help her remember to place a copy of the ICF in the subject's chart and write consent notes after consent. She writes down her process for consenting subjects and thinks about all the tasks that she must accomplish:

- Step 1: Consenting the subject;
- Step 2: Collecting the signature of the patient (research subject);
- Step 3: Making a copy of the signed ICF for the patient (research subject);
- Step 4: Putting the ICF in a folder with a business card for the patient (research subject);
- Step 5: Scanning the copy of the ICF and ensuring that it gets placed in the subject's chart; and
- Step 6: Writing the consent note.

The checklist gives Sally a foundation for ensuring that she is performing each step. The order helps maintain consistency so that she and all other study coordinators will perform the task in the same way.

Now that the foundation has been laid, Sally's director can see if there is a problem that needs improvement.

PDSA AND FOCUS PDSA QUALITY IMPROVEMENT METHODS

Once the foundation for standardized work has been laid, then areas for improvement can be identified.
In the 1940s, Walter Shewhart developed a method to review a manufacturing process and identify areas for improvement.[3] He compared this process to the scientific method: developing a hypothesis and then carrying out an experiment to test the hypothesis.[3]

Deming, studied under Shewhart and built off his model to develop the Plan, Do, Study, Act (PDSA) cycle (Table 1). This model serves as the foundation for the majority of process improvement methodologies and is often used for improving healthcare processes. In the early 1980s, the Hospital Corporation of America (HCA) improved upon the PDSA model by introducing the FOCUS PDSA model.[4]

Going back to the foundation of standardized work, once processes have been standardized, the team can begin to collect data and look for areas to be improved.

FIND A PROBLEM TO IMPROVE

The first step in the PDSA process is to identify a gap that needs improvement and quantify the gap. The goal cannot simply be to increase or decrease something; it must be quantifiable. It is important to graphically show the current state of the process, the desired state, and the gap. Losing weight is a good example of a quantifiable process. The person knows his/her current weight and ideal weight. Subtracting the ideal weight from the current weight shows the gap for quality improvement efforts.

Next, the problem statement is written. The problem statement should include who will be working on the problem, what will be improved when this will be done, and the desired improvement.

Along with investigating problems that have occurred, it is necessary to track near-misses that could have caused a problem but did not because they were caught before the

error occurred. Near-misses do not get the attention they should and can lead to bigger problems if not tracked and dealt with. For example, in one study, a subject was supposed to get FOLFOX for chemotherapy. However, when the coordinator double-checked, they realized that one of the drugs used to make FOLFOX was left off the cocktail. The order was taken to the physician and was corrected before the error occurred.

ORGANIZE A TEAM

The next step is to organize the team. A smaller team of 3–5 people is often better than a larger team. Your team should include people who can contribute knowledge to help solve the problem.

CLARIFY CURRENT KNOWLEDGE

After your team is organized, the next step is to clarify what is known about the problem. This is an essential part of the quality improvement process. Unless complete data and information about the error are collected, it will not be possible to solve the problem. During this step, the team needs to clearly understand the entire process, including knowing who performs each task and how the tasks are related to each other.

Before measuring the process and collecting the data, the current state of the process must be mapped out. Observing the process and taking notes on what is actually occurring in the process is recommended, as this is more effective than merely listening to what people say should be happening during the process. Mapping out the process allows areas that need improvement to be identified. Tools that can be used during this step in the process are flowcharts, swim lanes, and spreadsheets. A graphical representation of steps in the process, a flowchart is especially helpful if the foundation of standardized work has not already been laid. A swim lane diagram is similar to a flowchart; however, the work is divided into "lanes" according to who performs each step in the process. Spreadsheets can be used to collect quantifiable data.

It is important to fully understand what data are necessary to collect and ensure that good and accurate data are collected. If garbage data are collected, the next step will result in garbage data being interpreted. Once the data have been collected, the team needs to identify one area of focus that is having the most negative overall impact on the problem.

UNDERSTAND ROOT CAUSES

The fourth step in the process is understanding the root causes of the problem. This is done by analyzing the data collected in step three (Clarify Current Knowledge) to look for areas of variation and determine the root cause of the problem.

First, teams will brainstorm and develop a list of all possible causes of the problem. Then the team can conduct interviews to determine whether the causes are occurring. Anything that is not a potential cause must be eliminated from the list.

Lastly, the team will narrow down the list and look at each identified cause to determine the likelihood of impact on the problem. The team can use a fishbone diagram and a five whys analysis to display the brainstorming session results and help identify possible root causes of the problem.

TABLE 2:
THE LEAN METHOD

Method:

- Identify areas of waste
- Determine whether each task:
- adds value
- is necessary non-value added
- is pure waste

Tools:

- Flowchart/process map
- Fishbone diagram
- Spaghetti diagrams
- 5S

TABLE 3:
THE LEAN PDSA MODEL

Plan:
- Clarify the problem
- Break down the problem
- Set the target
- Analyze the root cause
- Develop countermeasures

Do:
- See countermeasures through

Study:
- Monitor both results and processes

Act:
- Standardize successful processes

In a fishbone or a cause-and-effect diagram, the problem stated is placed on the head of the fishbone. All of the possible causes of the problem are placed on the spine of the fish. The possible causes are grouped into major categories such as methods, equipment, people, materials, and environment.

A five whys analysis involves further breaking down the problem to determine the driving force behind it by continually asking why the problem occurred. It may not be necessary to ask why five times. The goal is to keep asking why until the reason has been determined or the problem is found to be beyond the team's control.

Some teams work backward through the five whys using what is called a "therefore check." Using this tool, the team starts at the bottom and states the answer to why the problem occurred followed by "therefore" and work their way back up. The therefore check allows teams to double-check whether they have thought through all of the potential driving forces behind the problem.

The following example illustrates the five whys with a therefore check tool. Sally opens a baseline kit for a breast biopsy. She realizes that items are missing from the kit, so she has to open another baseline kit to collect all of the supplies she needs. Sally is using multiple kits for one test. This is wasteful and something that should be improved.

The why questions for this problem are:
- Why are multiple kits being used?
  - Because Sally was not aware there were items missing from the first kit.
- Why was Sally not aware that there were items missing from the first kit?
  - Because Sally assumed the kit was quality control-checked prior to being sent to the clinical research site.

At this point, the team would stop using the five whys tool because quality control of the kits is beyond the team's control.

The therefore check starts at the bottom. The kit was not quality control-checked, therefore, items were missing from the kit. Therefore, Sally had to open multiple kits. The therefore check allows the team to ensure that they have double-checked their understanding of the cause of the problem.

SELECT AN IMPROVEMENT

In the last step of FOCUS, the team selects a process for improvement. Once the team has identified the problem, they can begin to identify potential countermeasures to solve the problem. Discussing the problem with others who have encountered the same problem can help identify possible solutions. When selecting an improvement, the team should include staff members who the change will impact.

All of the potential solutions should be put into a decision matrix. A ranking system should be developed to rank each potential solution by the critical elements for evaluation. Each possible solution should be evaluated for each element and ranked accordingly. The solution

with the highest-ranking should be implemented first.

There are two key things to remember when making selections using a decision matrix. First, when choosing potential solutions, the solution should not involve causing work in other areas. Second, if a solution is implemented and is not effective, the team can return to the matrix and try another solution; you do not have to start over.

Once the team has identified an appropriate solution, they move on to the PDSA cycle.

PLAN

During the planning phase, the team should develop a plan along with the timeline that will be used to implement the selected solution.

A GANTT chart, which allows the team to show the tasks that need to be completed against the timeframe they need to complete, can be used to plan implementation. For each task in the GANTT chart, the team can provide the start time, the duration, and the completion time. The chart can be color-coded to help identify who is responsible for performing each task.

DO

After the team has developed the plan, it is time to implement the solution in the plan. This is the do phase.

CHECK (STUDY AND ACT)

After implementing the solution, the next step is to study it. This is when the team determines whether implementing the solution has improved the process and quantifies the improvement. Data must again be collected to ensure that the solution is helping to meet the improvement targets. Depending on what the team learns from the study phase, the team may decide to either stay the course or make necessary adjustments.

FOCUS PDSA serves as the foundation for other quality management methods. Other popular quality improvement methods that are used in healthcare are Lean, Six Sigma, and lean Six Sigma.

THE LEAN QUALITY IMPROVEMENT METHOD

Table 2 provides an overview of Lean, which was born in the manufacturing industry, specifically Toyota manufacturing. The Toyota Motor Company was established in Japan by Kiichiro Toyoda in the 1930s.5 By 1950, Kiichiro and his cousin had implemented the jidoka ("automation with a human touch") and just-in-time concepts into the Toyota Motor Company.[5] Later, with the help of Taiichi Ohno, the Toyota production system was developed.[5]

The term "Lean" derives from a 1988 article by John Krafcik in which Krafcik discussed two different types of production systems: a buffered production system and a lean production system.6 According to Krafcik, buffered organizations kept a large inventory on hand in case there were defects in the inventory, the equipment broke down, or just to have extra quantity on hand.[6] Lean organizations, such as the Toyota Motor Company, kept their inventory levels low to help reduce costs; therefore, problems with quality were quickly detected and flushed out of the system. [5, 6]

In truth, the Toyota Production System (TPS) and Lean are not the same thing.[7] Rather, lean is an interpretation of the TPS.7 The main goal of Lean is to identify and reduce areas of waste.[7] As part of Lean, each task within a process needs to be evaluated to determine if the task:

- adds value to the process;
- is necessary to the process but does not add value; or
- is pure waste.[7]

Aspects that add value are typically things that the customer for which is willing to pay. In clinical research, for example, getting a treatment adds value. Something that is necessary but non-value added might be billing the sponsor for completed research items. Pure waste might be something like printing copies of the informed consent form in case the computer system goes down.

Lean identifies seven areas of waste:

1. inventory;
2. waiting;
3. defects;
4. over-production;
5. motion;
6. transportation; and
7. over-processing.

Having too much inventory on hand is wasteful. Clinical research sites often have too much inventory in study supply kits. The author remembers

constantly breaking down expired kits that had never been used.

Waiting on a physician for a signature, for a patient to be roomed, or anything else that typically requires a wait is wasteful, as are defects. Defects are errors that cause rework. For example, if a subject was consented with the wrong version of the informed consent form, then someone has to go back and re-consent that subject.

Over-production is producing too much of something. An example of overproduction is making five copies of all of the IRB-approved informed consent forms as soon as approval is received simply so you do not have to print a copy in a rush. Not only is this an example of waste, having extra ICFs on hand could also cause issues because someone could accidentally take and use the wrong version, resulting in a defect.

Excessive motion or movement of people and transportation of materials can be wasteful. For example, if a study coordinator has an office that is not centrally located to make it easy for the physician to see research subjects, then extra steps and time will be required to walk back and forth to see subjects.

Transportation is movement of materials that do not add value to the customer, such as a pharmacy that holds a research drug in an area far from the treatment area.

Processing that does not add value to the customer is over-processing, which is wasteful. For example, vital signs are taken after the patient checks in. Then the patient decides to enroll in a research study. Following informed consent, vital signs are taken again. This does not add value to the customer.

Some healthcare organizations add an eighth area of waste: non-utilization of human talent. Talent within the organization should be used effectively and efficiently.

BUILDING ON THE FOUNDATION OF LEAN

The foundations for Lean and the TPS are similar to the FOCUS PDSA model. Standardization is necessary before any processes can be improved. Next, Lean and the TPS system apply a principle called *Kaizen*, which means continuous quality improvement. *Kaizen* enables organizations to always be continually improving and striving towards their ideal state of zero defects.

Lean is much like many other quality improvement models in that it implements identifiable changes and sustains them using the PDSA cycle as the basis for improvement.[8]

Table 3 provides an overview of lean's eight-step PDSA problem-solving process. The main differences between Lean and FOCUS PDSA are in the first three steps. Lean does not cover organizing a team but rather focuses on the data and letting the data lead to the correct problem to target.

Lean's eight steps start with clarifying the problem, which is very similar to the "F" in the FOCUS model, when the ideal state, current state, and gap are identified. Step two is to break down the problem, which is similar to "C" in the FOCUS model, when the data are collected and analyzed to determine the areas that are the biggest contributors to the problem. Step three is setting the target goal for improvement. This is an extension of the "C" in the FOCUS model. Step four, identifying root causes, is very similar to the "U" in the FOCUS model. Step five, develop countermeasures, is analogous to the "S" in the FOCUS model.

The last three steps in the lean problem-solving process are similar to "Do," "Study," and "Act" in FOCUS PDSA:

- See countermeasures through
- Monitor both results and processes
- Standardize successful processes.

Quality improvement tools are interchangeable across the various methodologies. Many of the tools used with FOCUS PDSA and Lean are similar to each other. For example, Lean uses flowcharts, process maps, and fishbone diagrams. However, Lean also uses spaghetti diagrams and 5S. A spaghetti diagram visualizes an item's path through a process, which can help organizations identify excess motion. Such diagrams can be used to redefine the workspace to be centered around the human

movement, such as locating the study coordinator in a place that is central to the work that is being done.

5S IN LEAN

5S is a lean tool that applies basic housekeeping and organizational principles to processes: sift, sweep, sort, sanitize, and sustain. Organizations can use 5S to reduce excess products and expired or obsolete items to improve the organization of work.

Sifting entails separating the essential materials from the non-essential ones, and sweeping eliminates all of those non-essential items from the work area. Sorting is organizing the remaining essential items in the work area so that everything has a place and a label. One focus of the TPS is ensuring that everything has a place and is marked. Sanitizing means cleaning up the work area and establishing a schedule for regular cleaning. Sustaining is probably the most difficult "S"; it refers to ensuring that the cycle of sifting, sweeping, sorting, and sanitizing is continued following the re-organization.

Lean uses many other tools to evaluate a process and identify areas of waste and improvement, including storyboards, which are called A-3s. The A-3 tool is named after the size of the paper used for the storyboard: an 11" by 17" sheet of paper.

THE SIX SIGMA QUALITY IMPROVEMENT METHOD

The goal of Six Sigma is to reduce variation in a process through statistical analysis (Table 4). Because statistical processes drive Six Sigma, the normal distribution curve is used to explain the process. The goal is to drive out variation so that any deviations will fall greater than six standard deviations away from the mean, or about 3.4 defects per every million products produced. If the process were consenting patients, then the goal would be just three errors per one million patients. That would be impressive.

Six Sigma uses a five-step approach to problem-solving: define, measure, analyze, improve, and control (DMAIC) is used for a new process, whereas define, measure, analyze, design, and verify (DMADV) is used for an old process. The two approaches are similar. This article covers the DMAIC process.

The PDSA cycle provides a foundation for the various steps within the performance improvement cycle used with Six Sigma. There is some overlap between the improve and control phrases.

In the define phase, the problem is identified, the project goals are set, and the customer's requirements are identified. In the measure phase, data are collected to examine the process and quantify the problem. In the analysis phase, the root causes of the problem are identified, followed by the improve phase, when the identified cause from the previous step is addressed and countermeasures are implemented and studied to ensure they are effective. In the control phase, the countermeasures are continually studied. The process is adjusted as needed and to make future improvements.

Because Six Sigma focuses on statistical analysis, many graphs and charts are used in order to help analyze the data. Tools for Six Sigma include Pareto charts and control charts. These tools can also be used with Lean or

TABLE 4: THE SIX SIGMA METHOD

Method
- Reduce variation
- Goal – 3.4 defects per million

5-step approach:
- DMAIC – new process
- DMADV – existing process

Plan:
- Define
- Measure
- Analyze

Do:
- Improve

Study:
- Improve
- Control

Act:
- Control

PDSA in some situations.

The Pareto Principle states that about 80% of the effects come from 20% of the causes (or inputs) for many events. Identifying those causes can help eliminate about 80% of the effects that are contributing to that problem. Pareto charts are appropriate in trying to determine the frequency or causes of problems. They can also be used to try to determine the most significant cause of the problem.

For example, say that the team wants to determine why people are not typically participating in research studies. The team sends out a survey to patients asking them about the reasons they do not participate. The data are collected and analyzed, and the reasons are organized in order from the most common reason to the least common reason for not participating. The ordered reasons are put into a bar chart. Next, the team determines how much each reason contributes to the overall problem, assigning each reason a percentage. The finding is that being afraid to participate in research contributes to about 40% of the problem. When side effects are added, these two reasons contribute to about 79% of the problem. Adding in time, the three reasons contribute to about 88% of the problem. As the Pareto Principle states, the majority of the reasons for non-participation come from a few reasons.

A control chart is used to study changes in a process over time. For example, if the team wants to standardize the amount of time required to send a study through the IRB, then the first step is to determine the average time for this process. The team collects data on the last 20 studies that were sent to that IRB. They review the submission and approval dates to determine the average number of days required for IRB approval.

Next, the team must determine the variation. This task involves using the data to calculate a couple of control limits. The upper control limit is two standard deviations from the mean, and the lower control limit is two standard deviations from the mean in the other direction.

Typically, the goal is to standardize the process, in this case, the process for sending something through the IRB and then continuously evaluating how long the process is taking when each new study is sent through the IRB. The goal is that the control limits would become tighter over time as processes become standardized. Whenever the process goes beyond the upper or lower control limit, the team should stop and investigate what happened.

Lean focuses on driving out waste and standardizing processes to improve quality while improving the quality that is passed on to the customer, whereas Six Sigma focuses on reducing process variation and improving control. Together, these two methods are a powerful tool to identify and prevent defects, drive out waste, promote standardization, and always ensure that quality is passed on to the customer.

Often during our work, when filing a deviation, we merely try to determine why problems occur. All too often, finding out why is the end of the process. We do not always fix the problem, thereby leading it to reoccur. Deming states that finding the problem does not mean that the process has been improved.9 Finding the problem is only half the battle.9 The ultimate goal is to fix the process so that problems can be mitigated.9

THE END GOAL OF QUALITY IMPROVEMENT

The end goal of quality improvement is to identify the error or the potential error in a process and fix the process so that error does not reoccur. Teams must continually improve every aspect of a research program and strive to reach the ideal state of zero errors or defects.

When one project is completed, another priority area for improvement should be identified. However, it is important to be aware that changing one process to fix a problem might cause other problems to occur in other areas. The new problems should be promptly identified and mitigated.

Lastly, clinical research sites must create a culture that fosters staff development. Such a culture includes open lines of communication so that staff members are

comfortable bringing problems to management's attention instead of hiding them. As Deming asserted, "Problems in our processes cause errors, not bad employees." If employees feel that they will be blamed for errors, then they will not mention them and problems will never be fixed. Table 5 presents resources related to quality improvement in research.

TABLE 5:
RESOURCES ON QUALITY IMPROVEMENT IN RESEARCH

1 - The W. Edwards Deming Institute. Deming the Man. https://deming.org/deming-the-man/. Accessed 6/29/21.

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3 - Moen RD and Norman CL. Circling Back: Clearing up the Myths about the Deming Cycle and Seeing How It Keeps Improving. Basic Quality. 2010. http://www.apiweb.org/circling-back.pdf. Accessed 6/29/21.

4 - Jones & Bartlett Learning, LLC. Continuous Quality Improvement Using Plan, Do, Study/Check, Act (PDSA/PDCA) and Quality Improvement Tools. http://samples.jblearning.com/9780763795368/95368_CH01_001_030.pdf. Accessed 6/29/21.

5 - Toyota. Toyota Production System. https://global.toyota/en/company/vision-and-philosophy/production-system/. Accessed 6/29/21.

6 - Krafcik JF. Triumph of the Lean Production System. Massachusetts Institute of Technology. Sloan Management Review. 1988;30(1). https://www.lean.org/downloads/MITSloan.pdf. Accessed 6/29/21.

7 - Keown D. Toyota Production System Overview. University of Kentucky Canvas LMS – MFS 526. Accessed Fall 2019.

8 - Scoville R, Little K. Comparing Lean and Quality Improvement. IHI White Paper. Cambridge, Massachusetts: Institute for Healthcare Improvement; 2014. (Available at ihi.org)

9 - The W. Edwards Deming Institute. W. Edwards Deming: The 14 Points. https://www.youtube.com/watch?v=tsF-8u-V4j4. Accessed 6/29/21.

10 - American Society for Quality. Quality Resources. https://asq.org/quality-resources. Accessed 6/29/21.

SOCRA
FOR CLINICAL RESEARCH EXCELLENCE

LIVE + INTERACTIVE + VIRTUAL

SOCIETY OF CLINICAL RESEARCH ASSOCIATES

PREPARE FOR THE CCRP EXAM VIRTUALLY

UPCOMING COURSE DATE

CCRP CERTIFICATION PREP + GCP VIRTUAL REVIEW COURSE

NOVEMBER 10 AND 11, 2021
JANUARY 19 AND 20, 2022
FEBRUARY 23 AND 24, 2022
APRIL 6 AND 7, 2022

ADDITIONAL COURSE DATES COMING SOON!

The purpose of this interactive virtual workshop is to assist the participant in preparing for the CCRP certification examination through a GCP review. This course will review the concepts identified in the CCRP Certification Examination Content Outline, as well as the Standards of Practice including the ICH Guidelines and FDA Regulations that govern clinical research practice.

IN REVIEW

30TH ANNUAL CONFERENCE

DISSEMINATING KNOWLEDGE TO ENHANCE CLINICAL RESEARCH INNOVATION





QUINCY BYRDSONG, ED.D, CCRP, CIP
SOCRA President
Vice Provost for Health Affairs, Lipscomb University

ABBY STATLER, PHD, MPH, MA, CCRP,
Incoming SOCRA President
Director, Research Quality and Safety, Dartmouth-Hitchcock Medical Center

ERIC PITTMAN, MBA
Program Division Director, Bioresearch Monitoring, West, Office of Regulatory Affairs, FDA

GIANNA MCMILLAN, DBE
Faculty and Program Administrator, Loyola Marymount University

ALICIA WRIGHT, MS, CCRP
Research Programs Manager, Vanderbilt University Medical Center

2021 PRESIDENT'S AWARD

George D'Addamio, PhD, MS, BS
President, PharmConsult Inc.
2021 President's Award Recipient

2020 CHAPTER SPECIAL RECOGNITION AWARD

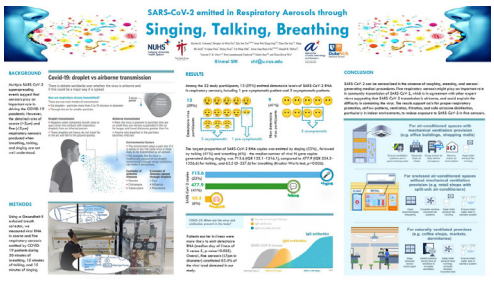
Wendy Lloyd, BA, LPN, CCRP
Senior Clinical Quality Research Analyst, Vanderbilt Medical Center

2020 POSTER PROGRAM SPECIAL RECOGNITION AWARD

CLINICAL RESEARCH MANAGEMENT CATEGORY

SARS-COV-2 PARTICLES CAN BE AEROSOLISED WHEN TALKING AND SIGNING

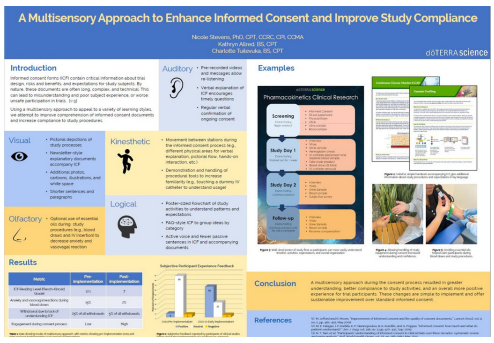
Author: Xinmei Shi, CCRP, CCRA
National Cancer University Institute, Singapore



CLINICAL TRIALS CATEGORY

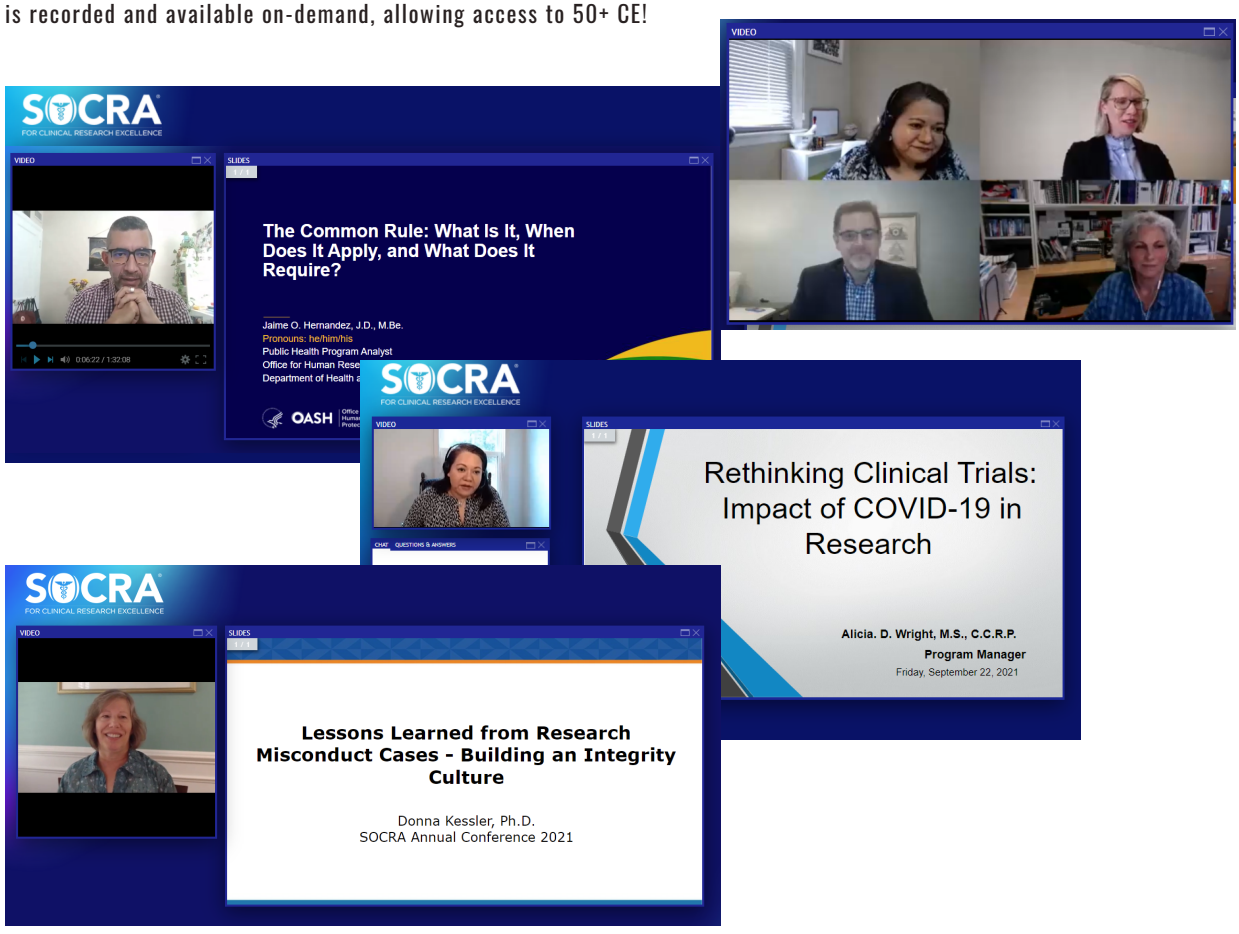
A MULTISENSORY APPROACH TO ENHANCE INFORMED CONSENT AND IMPROVE STUDY COMPLIANCE

Author: Nicole Stevens, PhD, MS, BA, CCRP, CPT, CPI, CCRC, doTerra International



THIS YEAR'S 2021 ANNUAL CONFERENCE WAS AGAIN UNPRECEDENTED.

The 2021 Annual Conference was a dynamic, interactive virtual program, with enhanced educational networking and collaborative opportunities. Thank you for joining us as we offered a program that helped the global clinical research community come together and work toward safe, efficient and quality clinical research. This four day virtual conference offered current information, tools, best practices, and training to assure that you're up-to-date and compliant in your clinical research practice. The program featured live opening and closing plenary sessions, 6 educational tracks with on-demand content and live Q+A, a peer-driven poster program and award competition, plus sponsor opportunities. All content is recorded and available on-demand, allowing access to 50+ CE!



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2021 POSTER PROGRAM WINNER

XINMEI SHI, MSC, CCRP, CCRA

SARS-COV-2 Particles can be Aerosolised when Talking and Signing

Xinmei Shi, MSc, CCRA, CCRP,
Research Manager,
National Cancer University Institute,
Singapore

Background:
Multiple SARS-CoV-2 superspreading events suggest that aerosols play an important role in driving the COVID-19 pandemic. To better understand how airborne SARS-CoV-2 transmission occurs, we sought to determine viral loads within coarse (>5μm) and fine (≤5μm) respiratory aerosols produced when breathing, talking, and singing.

Methods:
Using a G-II exhaled breath collector, we measured viral RNA in coarse and fine respiratory aerosols emitted by COVID-19 patients during 30 minutes of breathing, 15 minutes of talking, and 15 minutes of singing.

Results:
Thirteen participants (59%) emitted detectable levels of SARS-CoV-2 RNA in respiratory aerosols, including 3 asymptomatic and 1 presymptomatic patient. Viral loads ranged from 63–5,821 N gene copies per expiratory activity per participant, with high person-to-person variation. Patients earlier in illness were more likely to emit detectable RNA. Two participants, sampled on day 3 of illness, accounted for 52% of the total viral load. Overall, 94% of SARS-CoV-2 RNA copies were emitted by talking and singing. Interestingly, 7 participants emitted more virus from talking than singing. Overall, fine aerosols constituted 85% of the viral load detected in our study. Virus cultures were negative.

Conclusions:
Fine aerosols produced by talking and singing contain more SARS-CoV-2 copies than coarse aerosols and may play a significant role in SARS- CoV-2 transmission. Exposure to fine aerosols, especially indoors, should be mitigated. Isolating viable SARS-CoV-2 from respiratory aerosol samples remains challenging, and whether this can be more easily accomplished for emerging SARS-CoV-2 variants is an urgent enquiry necessitating larger- scale studies.

2021 POSTER PROGRAM WINNER

NICOLE STEVENS, PHD, MS, BA, CCRP, CPT, CPI, CCRC

A Multisensory Approach to Enhance Informed Consent and Improve Study Compliance

Nicole Stevens, PhD, MS, BA, CCRP, CPT, CPI, CCRC,
doTerra International

Purpose: Informed consent forms are a critical part of ethical human subjects research. However, their length and complexity often render these documents unintelligible to prospective clinical research participants [1]. Although improvements are being made to help volunteers realize the risks, benefits, design and outcomes of a study, adequate understanding may be as low as 50% [2], [3]. Additional approaches must be investigated for improving participant comprehension of informed consent documents and increasing compliance in clinical research.

Methods: Using tools that appeal to different learning styles, we implemented the following enhancements to the standard informed consent process:

1) For visual learners
   - Infographic handouts going into greater detail on the processes that would be used during the trial.
   - Additional photos, illustrations, and cartoons in the informed consent document.
2) For auditory learners
   - Verbal presentation of the informed consent document explained in lay terms.
   - Recorded presentations of procedures and demonstrations that can be replayed at leisure.
3) For kinesthetic learners
   - Tactile, interactive presentation of procedural items (e.g. handling an IV catheter to better understand size and placement).
   - Movement through stations during the informed consent process.
4) For logical learners
   - Q&A format on informed consent document to group information by concept and contribute to logical flow.
   - Poster-sized flowchart of the steps involved in each stage of research, including expectations for the participant.
5) General tools
   - Olfactory association using essential oils for calming or focus during informed consent presentation.
   - Reminders and interactive tools on mobile devices.

Results: Following implementation of these tools during and after the informed consent process, participant withdrawal due to lack of understanding was reduced to nearly zero. Subjective feedback from participants indicated good comprehension of study details and more positive perception of participation. The costs involved in implementing these tools was minimal compared to costs associated with participant withdrawal and protracted recruitment.

Conclusion: Over the course of several trials, our research team confirmed that using multisensory tools of presentation, discussion, and interaction throughout the study has led to better understanding of informed consent documents, fewer withdrawals, greater compliance to study procedures, and more complete datasets. These benefits greatly outweigh the up-front investment of staff time in implementing these tools. A multisensory approach in presenting informed consent information and encouraging participant compliance can result in higher quality clinical research and overall better participant experience.

SOCRA - CHAPTER PROGRAM

The purpose of the SOCRA chapter program is to provide a cost free forum under which members can learn, exchange information, grow professionally in clinical research, acquire CE for SOCRA CCRP re-certification, and build strong foundations for successful clinical research outcomes.

A SOCRA chapter's membership consists of current members of SOCRA who are located within a non-exclusive geographic area defined by the local chapter. Volunteer members within a chapter develop and participate in continuing education projects and programs related to clinical research that benefit clinical research professionals and other parties who might be interested in clinical research.

The following is our list of chapters and chapter contacts. If you are interested in starting a chapter in your area, please contact the SOCRA office.

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CCRP® CERTIFICATION PROGRAM
for Clinical Research Professionals

Statement of Purpose

SOCRA established the Certification Program for Clinical Research Professionals in order to create an internationally accepted standard of knowledge, education, and experience by which clinical research professionals will be recognized by the clinical research community. Those individuals so recognized may use the "Certified Clinical Research Professional" or "CCRP®" designation.

Definition of a Clinical Research Professional

A clinical research professional's (CRP) practice is guided by the principles of Good Clinical Practice (GCP) (ICH E6 and FDA regulations).

A CRP may function as a clinical investigator, sub-investigator, clinical researcher, research nurse, pharmacist, administrator, coordinator, consultant, data manager, quality assurance manager, regulatory affairs manager or educator in clinical trial management.

The duties of a CRP may include data collection, analysis, or monitoring; case management of protocol participants; recruitment and enrollment of human subjects; protection of subjects and subjects' rights; development of informed consent documents; preparation of adverse event experience reports; construction or monitoring of case report forms; maintenance of drug accountability records; development of grants and budgets; preparation of reports; educating other healthcare professionals, patients or families about clinical trials; protocol development; program administration; or research program audit.

A CRP would not include professionals working exclusively under Good Laboratory Practice (GLP) and/or Good Manufacturing Practice (GMP) regulations.

Examination Content

The CCRP® certification examination is organized into five major content areas derived from the 2012 SOCRA Job/Task Analysis. The examination content outline provides a detailed description of the content areas including topic areas and knowledge domains. Each question on the exam is based on the content outline. To prepare for the exam, a candidate should study the detailed outline and consider the knowledge, skills, and abilities needed to perform the duties of a CRP. Satisfactory completion of the CCRP certification examination indicates that the candidate has met all the eligibility criteria and has demonstrated knowledge of the key duties/tasks of a CRP.

The questions assess understanding and application, not just the ability to recall facts. Some questions are based on scenarios and case studies that relate to clinical research practice. The case studies and scenarios are intended to evaluate a candidate's ability to abstract information and do not require clinical (medical) experience.

Each test question has only one correct answer. Each question is weighted equally, and there is no penalty for an incorrect answer. Therefore, it is advantageous to answer all questions.

The CCRP certification examination consists of 130 multiple choice questions. Thirty (30) of these questions are "beta test" questions and will not affect the candidate's score (unscored). These items are not identified to the candidate. The number of scored items on the exam is 100.

The passing score is determined by a panel of experts using the "Modified Angoff Method." In order to achieve a passing score, candidates must correctly answer 72 of the 100 scored questions.

Examination Validation

The exam is statistically and psychometrically validated by independent consultants. The Certification Committee evaluates the results from statistical/psychometric evaluations and updates the exam as needed.

The examination pass/fail score, or "cut score", is statistically determined by a panel of experts using the "Modified Angoff Method." The "cut score" is validated after a review of the psychometric testing analysis.

Three Content Areas & Percent of Scored Items in Each Area

1	**Research Study Start-Up** - Regulatory Requirements of IRB/IEC, sponsors and investigators related duties/task related to study start up	40%
2	**Research Study Implementation** - Regulatory Requirement of IRB/IEC, sponsors and investigators related duties/task related to conduct of the study	45%
3	**Research Study Closure** - Regulatory Requirement of IRB/IEC, sponsors and investigators related duties/task related to study close out and record maintenance	15%

*an extended version of the outline can be downloaded at socra.org/certification

Preparing for the Exam

Certification Program Reference Manual

The CCRP Certification Program Reference Manual is made available to the applicant once the application has been approved. The reference manual is intended to assist with preparation for the CCRP Certification Examination. In addition to program policies and procedures and sample questions, the manual contains:

- 21 Code of Federal Regulations: Parts 11, 50, 56, 312, 812
- 45 Code of Federal Regulations: Part 46
- FDA regulatory forms: 482, 483, 1572, 3454, 3455, 3500, 3500A
- The Belmont Report
- The Nuremberg Code
- The Declaration of Helsinki
- The ICH GCP Guideline for Good Clinical Practice (E6)
- The ICH Clinical Safety Data Management: Definitions and Standards for Expedited Reporting (E2A)

Clinical Research Professional Certification Preparation and GCP Review Course*

This optional one-day course is offered throughout the year. Organizations may schedule this course at their facility if a minimum of 20 attendees is guaranteed. Details may be found at www.socra.org/conferences-and-education.

*The content of this course has been developed by a SOCRA education committee, independently from the certification program. The certification program does not control or dictate the content of this program.

Applying to the Exam

How to Apply

Applicants should thoroughly review all of the information provided in the Certification section of the website. Before submitting an application packet, applicants must review the eligibility requirements, application procedures, and certification program policies and procedures. The application must support the required work experience. If experience spans multiple positions, each position must be substantiated through submitted documentation and references. A completed Certification Application Portfolio must be forwarded to the SOCRA administrative office a minimum of six weeks prior to the test date. Upon approval, the applicant will receive a letter of acceptance and a link to the CCRP Certification Program Reference Manual. Fees are refunded only if the application is unsuccessful.

Choosing and Exam Site / Date

Visit www.socra.org/certification to view the current exam schedule. Enrollment in specific exam venues may be limited due to room size and enrollment may be closed prior to the registration deadline. Complete applications must be received by the SOCRA office a minimum of six weeks prior to the testing date. Early registration will help secure a space at the preferred venue.

Applicants Having Special Needs

Applicants having special needs including physical, sensory, or learning needs, should contact the SOCRA administrative office to discuss testing requirements and accommodations.

Application Portfolio

The applicant must submit the following:

- **Certification Application:** A completed certification application.
- **Resume / CV:** The applicant's resume or CV documenting their employment and education in clinical research.
- **Verification of Employment:** A letter of reference, on organizational letterhead signed by a supervisor or human resources representative, documenting position titles, dates of employment and Full-or Part-time status.
- **Job Description:** The applicant's official job description issued by the institution or employer.
- **Signed Ethics Statement**

Note: For applicants applying under Category 2 or 3, appropriate documentation (including transcripts) and a completed Form 1011 (Category 2) or Form 1022 (Category 3) must be included.

Please visit **www.socra.org/certification** for details

Payment Options

1. **Payment in Full** (3 years of certification, includes complimentary membership)

Non-member: $450 (includes 3 years complimentary SOCRA membership)	Current Member: $395 (includes 3 years complimentary SOCRA membership)

2. **3 year Installment Plan**

Non-member: $300 initial payment* ($100 in years 2 & 3)**	Current Member: $250 initial payment* ($100 in years 2 & 3)**
Total = $500	**Total = $450**

Computer Based Testing (CBT): Addition $115
Paper & Pencil Retest Fee: $200
CBT Retest Fee: $275

*includes a complimentary SOCRA membership upon successful completion of exam
**includes complimentary SOCRA membership upon successful completion of exam

Candidate Eligibility

The applicant must work under Good Clinical Practice (GCP) guidelines, and with IRB/IEC/REB-approved (or specifically exempted) protocols. The applicant's documented experience must fall within one of the following categories:

2 years of full-time experience* as a Clinical Research Professional within the past five years

*equal to 3500 part-time hours

OR

1 year of full-time experience* as a Clinical Research Professional within the past two years

*equal to 1750 part-time hours

and

Degree in "Clinical Research" from an Associate, Undergraduate or Graduate Degree Program*

OR

and

Undergraduate or Graduate Certificate in "Clinical Research"

and

Associate or Bachelor Degree in a science, health science, pharmacy or related field

***Degree and Certificate Programs must meet requirements. Visit www.socra.org/certification for more details.**

Maintaining Your Certification

The CCRP credential is awarded in three year increments. Certification of Clinical Research Professionals by SOCRA is based on a continuing process of professional experience and education.

This program is intended to provide recognition and validation of the continued professional growth of the individual CCRP®.

Continuing Education (CE) Requirement

Certificants must complete 45 hours of CE during their three-year certification period. The breakdown of CE that may be claimed within each CE category follows:

Clinical Research Operations / Regulatory → Minimum of 22 CE hours must be claimed (no maximum)

\+

Therapeutic / Professional Area → NO minimum

\+

Recertification Continuing Competence Learning Module → 1 CE hour may be claimed

= Total of 45 CE hours per 3-year certification period

Only educational hours may be claimed for CE; candidates may not claim CE credit for work hours.

Recertification / Certification Renewal

To maintain active certification status, certificants must apply for renewal of certification every three years. Those wishing to renew their CCRP certification must successfully complete an online regulatory learning module and provide documentation of 45 hours of validated CE credit. The fee for re-certification for three years is currently $350. An installment payment plan is available at $200, $100, $100 over three years for a total of $400.

As you know, SOCRA strives to promote individual recognition and continuing excellence in the ethical and operational conduct of clinical trials through the CCRP certification program. We truly appreciate your accomplishment as a CCRP and your continued maintenance of the CCRP credential.

We have been able to maintain our fees for recertification for the CCRP credential at the same levels for the past 15 years. However, due to current interpretations of applicable law, the Certification Committee has updated the requirements and subsequently adjusted the fee structure for CCRP recertification.

Under the revised system, certified clinical research professionals receive complimentary SOCRA membership for their term of certification. Certified clinical research professionals thereby still:

- have access to the SOCRA journal
- have access to CITI's GCP and Human Research Protections on-line modules (10 hours of no cost CE)
- receive SOCRA CE certificates when attending SOCRA Chapter meetings (at no cost)

When applying for recertification you will now have two options. You can be assured that the committee has minimized the cost impact of both options. Please note that complimentary SOCRA membership is included in both options.

Option 1: Payment in Full for a three year recertification term = $350 for three years (includes complimentary SOCRA membership for all three years)

Option 2: Installment Plan over three years: $200 initial payment for one year, $100 for year two and $100 for year three = $400 total (includes complimentary annual SOCRA membership as each installment is received)

SOCRA ONLINE EDUCATION OPPORTUNITIES

SOCRA offers online courses that are intended to provide access to training and continuing education that will promote quality clinical research, protect the welfare of research participants and improve global health. A quiz following the presentation will summarize the topic and evaluate your understanding of the material. Please see below for information regarding CE, CNE and CME. Each course, including viewing presentation and post-test, should take 1 hour.

Courses led by: Harvey Arbit, PharmD, MBA, RAC, CCRP & James Simmer BSN, MBA

Course registration fee - **Member $35 (Non-member $110 includes one year membership)**

CME AND CNE OFFERED!

cGMP for Investigational New Drugs (IND) in Phase I Clinical Trials

All drugs manufactured for use in clinical trials must comply with Good Manufacturing Practices. Drugs for Phase I clinical studies must comply with statutory CGMP. Drugs for human use must not be adulterated. The manufacturer must assure the drug is safe and has the identity, strength, quality, and purity which it is represented to possess. The FDA's guidance document covering this topic will be discussed.

Learning Objective: At the completion of the webinar, participants should be able to:

- Discuss the FDA's guidance document covering cGMP for clinical trials

What You Should Know Before the FDA Arrives

This course will discuss the steps involved in an FDA inspection and will address best practices in responding to FDA questions. The faculty will discuss what the FDA is instructed to look for when conducting an inspection and review recommendations regarding what to do after the inspection. The FDA's Compliance Program Guidance Manuals will be explained.

Learning Objectives: At the completion of the webinar, participants should be able to:

1. Discuss the steps of an FDA audit
2. Discuss how to respond to FDA questions
3. Have an understanding of the FDA's Compliance Program Manuals
4. Understand what the FDA auditor is looking for
5. Discuss how to review recommendations from the FDA after an Audit

IND / IDE Assistance in an Academic Health Center Why Provide IND/IDE Assistance?

Why provide IND/IDE assistance? This course will discuss program start up and program successes.

Learning Objective: At the completion of the webinar, participants should be able to:

- Discuss IND/IDE program start up and program success

Risk Based Monitoring (RBM) from the Site Perspective

This course will discuss the definition and rationale for RBM, it will also demonstrate how it will be implemented by Sponsors and what the downstream affects will be to sites. Lastly, the course will provide insight what sites need to do to best prepare for this new monitoring paradigm.

Learning Objectives: At the completion of the webinar, participants should be able to:

1. Understand the rationale for changing the fundamentals of the monitoring process
2. Describe what is Risk Based Monitoring
3. Recognize how Risk Base Monitoring will affect the Site
4. Identify current Site processes that will need to be altered to accommodate Risk Based Monitoring

Informed Consent: It Really Is a Process

Informed consent is a key process in clinical research. Regulations must be followed. Guidance documents provide FDA's current thinking on this topic.

This is a 60 minute internet media player video of a voice over slide show. A quiz concluding the presentation will summarize the topic and evaluate your understanding of the material.

Learning Objectives: At the completion of the webinar, participants should be able to:

1. Describe the required and additional elements of the informed consent form
2. Understand special considerations and vulnerable populations
3. Describe the responsibilities of the IRB, investigator, sponsor, and research subject

SOCRA designates this educational activity for a maximum of 1 Continuing Education Credit for SOCRA CE, CME, and CNE.
SOCRA designates this enduring material for a maximum of 1 AMA PRA Category 1 Credit(s)™. Physicians should claim only the credit commensurate with the extent of their participation in the activity. CME for Physicians: The Society of Clinical Research Associates is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.
CNE for Nurses: Society of Clinical Research Associates is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center's Commission on Accreditation.

https://www.socra.org/conferences-and-education/clinical-research-courses-online/

ADDITIONAL ONLINE OPPORTUNITIES

FREE FOR MEMBERS!

Course registration fee - **Member: Free (Non-member $75, includes one year membership)**

Part 1: Informed Consent for Research - Operationalizing the Process

Speaker: Laura Holtz, MS, CCRP

This talk will review the new common rule definition of vulnerable subjects including "individuals with impaired decision making ability." It will discuss why inclusion of this vulnerable population is needed in research studies, especially for diseases such as Alzheimer's research. Finally, it will review the ethical guidelines and discuss practical strategies for obtaining informed consent for subjects who may lack decision making capacity.

Learning Objectives: At the completion of the webinar, participants should be able to:

1. Discuss the requirements for Informed Consent and HIPAA authorization for human subjects research.
2. Recognize vulnerable populations and discuss ethical considerations and appropriate mechanisms for obtaining informed consent.
3. Discuss strategies to ensure high-quality, high understanding in informed consent discussions.

Part 2: Informed Consent for Research - The Importance of Quality for Understanding Decision-Making

Speaker: Laura Holtz, MS, CCRP

This presentation will review the new common rule definition of vulnerable subjects including "individuals with impaired decision making ability." It will discuss why inclusion of this vulnerable population is needed in research studies, especially for diseases such as Alzheimer's research. Finally, it will review the ethical guidelines and discuss practical strategies for obtaining informed consent for subjects who may lack decision making capacity.subjects who may lack decision making capacity.

Learning Objectives: At the completion of the webinar, participants should be able to:

1. Discuss the requirements for Informed Consent and HIPAA authorization for human subjects research.
2. Recognize vulnerable populations and discuss ethical considerations and appropriate mechanisms for obtaining informed consent.
3. Discuss strategies to ensure high-quality, high understanding in informed consent discussions.

A Primer on Clinical Research

Speaker: Patricia Beers Block, MDEd, BS, BS, CCRP

In this presentation the speaker will introduce different practices and principles for how new medicals products are identified as safe and effective, and ultimately introduced into the marketplace. How clinical research came to be and how professionals deal with proving that products are safe and effective will be presented. Lastly, the speaker will discuss the evolving research approaches used today.

Learning Objectives: At the completion of the webinar, participants should be able to:

1. Discuss how new medical products might help to identify and mitigate the impact of COVID-19 on our health
2. Discuss different practices and principles for how products are identified as safe and effective for humans
3. Discuss how new products are introduced into the marketplace

Sponsor Responsibilities

Speaker: Amy Jo Jenkins, MS, CCRP

This presentation will provide an overview of the sponsor responsibilities for conducting clinical research. The presentation will address sponsor responsibilities for regulatory submissions, site selection, documentation, and monitoring. Safety and regulatory reporting will also be discussed. As clinical trials expand throughout the globe, it is important to understand the regulatory and ethical responsibilities of the Sponsor.

Learning Objectives: At the completion of the webinar, participants should be able to:

1. Describe sponsor responsibilities for conducting clinical research
2. Discuss responsibilities for regulatory submissions, site selection, documentation and monitoring
3. Discuss safety and regulatory reporting

Institutional Review Boards (IRB)

Speaker: Mtonya Hunter, MBA, CCRP

This presentation will provide a basic overview of the regulatory requirements and responsibilities for an Institutional Review Board (IRB) review for Human Subjects Protection. Usual business practices for most IRBs will be discussed including the required members of an IRB, required documentation that must be submitted to an IRB, and the types of IRB reviews.

Learning Objectives: At the completion of the webinar, participants should be able to:

1. Understand the role of the IRB
2. Discuss what documentation needs to be submitted to the IRB
3. Discuss the different types of IRB reviews

SOCRA Virtual Clinical Research Monitoring and GCP Conference for Monitors, Site Coordinators and Auditors

DECEMBER 7 TO 10, 2021 I VIRTUAL

Workshop registration fee - $430 (Non-Member $510- includes one year's membership)

Clinical Research Monitoring is an evolving practice. The purpose of this 4-day workshop is to assist Research Site Coordinators, Quality Assurance Auditors, and CRAs/Monitors in improving their skills and their understanding of the roles and responsibilities of the Clinical Research Associate/Monitor. Although designed with all research professionals in mind, this program is ideal for Research Study Coordinators who want to improve the understanding of their responsibilities and interactions with their Clinical Research Monitors, and for Monitors/Auditors/Project Managers with 0-5 years monitoring experience who want to increase their knowledge and understanding of monitoring responsibilities.

This interactive virtual workshop will be facilitated by clinical research professionals with a wealth of industry experience. Information will be presented and discussed regarding monitoring clinical trials according to FDA Regulations and International Conference on Harmonisation (ICH) guidelines as well as practical procedures and site / sponsor / CRO relationships.

Learning Objectives - The attendee should be able to:

- Describe the role of monitoring in clinical research
- Discuss the basic principles of Good Clinical Practice; International Conference on Harmonisation GCP guidance; Investigator's responsibilities; Sponsor's responsibilities; Monitor's responsibilities; record retention; and basic requirements for conducting studies in Canada
- Describe the investigator recruitment process, identify key selection criteria, and discuss the conduct of a site selection visit
- Within the historical perspective of the Nuremberg Code, the Declaration of Helsinki, and the Belmont Report, discuss the objectives of regulations pertaining to Institutional Review Boards and financial disclosure
- Discuss regulatory requirements and ethical considerations involved in the informed consent process as well as the informed consent document
- Describe the activities involved in study initiation including budget and contract negotiation; planning and conducting investigator meetings; investigator selection; the conduct of study initiation visits; and preparing the site for study participation
- Assess the collection and evaluation of research data for completeness, compliance, and accuracy through periodic monitoring visits; discuss reporting and follow-up correspondence
- Compare and contrast the auditing and monitoring functions; describe the objectives of auditing; describe FDA inspections and how to prepare for them; review FDA warning letters
- Discuss mechanisms to implement and assure the quality of the processes and deliverables involved in clinical research
- Describe the essential elements of planning and preparing for and conducting a site closeout visit; site follow-up; and final documents for closure
- Describe site management techniques to manage expectations, facilitate site interactions, and improve subject recruitment and study conduct
- Discuss additional investigator responsibilities and monitoring of investigator-initiated studies

SOCRA designates this educational activity for a maximum of 15.0 Continuing Education Credits for SOCRA CE and Nurse CNE.

SOCRA designates this live activity for a maximum of 15.0 AMA PRA Category 1 Credit(s)™.

Physicians should claim only the credit commensurate with the extent of their participation in the activity.

CME for Physicians: The Society of Clinical Research Associates is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

CNE for Nurses: Society of Clinical Research Associates is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center's Commission on Accreditation.

SOCRA Course Series 200

SOCRA Virtual Advanced Site Management Workshop:
Finance and Productivity Enhanced Business Practices for Clinical Research Programs

ADDITIONAL COURSE DATES COMING SOON

Workshop registration fee - $475 (Non-Member $550- includes one year's membership)

Goal: The Society of Clinical Research Associates (SOCRA) recognizes the continuing need for education for Clinical Research Professionals responsible for the activities at the research site or institution. The topic of financial practices and business processes continues to be a challenge for clinical research sites. The purpose of this workshop is to assist Site Managers, Site Coordinators, and Research Associates in improving their skills and their understanding of the practical financial and business tasks related to clinical research. This workshop will focus on providing tools and techniques that the participants can immediately utilize to benefit their clinical research programs.

Objective: This 3 day interactive virtual workshop will assist Site Managers, Site Coordinators, and Research Associates in improving their skills and their understanding of the practical financial and business tasks related to clinical research. This workshop will focus on providing tools and techniques that the participants can immediately utilize to benefit their clinical research programs.

Learning Objectives - The attendee should be able to:

- Describe the role of financial management in medical research
- Discuss current trends in the clinical research industry
- Discuss the foundational principles required to build a profitable research site
- Explain effective processes for implementing billing systems and assuring billing compliance including relevant CMS (Centers for Medicare & Medicaid Services) billing regulations
- Demonstrate an ability to conduct billing analysis on research protocols
- Describe techniques for assessing study costs and reviewing sponsor budgets
- Describe tools to assist in clinical trial budget negotiation
- Demonstrate an ability to calculate the complete cost of a research study
- Demonstrate an ability to understand the contract negotiation process
- Discuss revenue recognition models and tools
- Describe methods for assessing study performance and revenue positions and for enhancing cash flow
- Describe methods for managing research program accounts receivable and business office reporting requirements
- Discuss issues and challenges related to managing expenses at the clinical research site
- Describe methods of calculating the profitability of a clinical research program
- Demonstrate an ability to develop a research budget
- Demonstrate an ability to use spreadsheets in managing financial aspects of clinical trials
- Describe issues related to reporting the results of a research program to executive management

SOCRA designates this educational activity for a maximum of 13.25 Continuing Education Credits for SOCRA CE, Nurse CNE, and Physician CME.
SOCRA designates this live activity for a maximum of 13.25 AMA PRA Category 1 Credit(s)™.
Physicians should claim only the credit commensurate with the extent of their participation in the activity.

CME for Physicians: The Society of Clinical Research Associates is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.
CNE for Nurses: Society of Clinical Research Associates is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center's Commission on Accreditation.

SOCRA Course Series 650

SOCRA Virtual Clinical Research Professional Certification Preparation and GCP Review Course

NOVEMBER 10 AND 11, 2021
JANUARY 19 AND 20, 2022
FEBRUARY 23 AND 24, 2022
APRIL 6 AND 7, 2022

Workshop registration fee - $295 (Non-Member $370- includes one year's membership)

Goal: The Society of Clinical Research Associates (SOCRA) recognizes Certified Clinical Resear`ch Professionals (CCRPs) as clinical researchers who meet an internationally accepted standard of knowledge, education and experience. The purpose of this workshop is to assist the participant in preparing for the SOCRA examination for the Certified Clinical Research Professional examination and to review regulations, policies, and procedures appropriate to the clinical research environment.

Objective: This interactive virtual workshop will be facilitated by clinical research professionals with a combined industry experience of more than 20 years. The goal will be accomplished through lecture, discussion and practical application. Information will be presented and discussed regarding the conduct of clinical trials; regulatory guidelines regarding IRB oversight and human research protections; ethical issues in clinical research; and workshops will stress the ability to follow directions and practices related to abstracting information and completing case report forms and other records.

Learning Objectives - The attendee should be able to:

- Discuss the basic requirements necessary to meet the demands of a CRP in clinical practice
- Discuss the basic components of compliance - Law, regulation, guidance, policy and procedure
- Explain the drug/biologic development process
- Describe the device development process
- Outline concepts for Good Clinical Practices (GCP)
- Explain the elements of informed consent
- Describe the membership and reporting requirements of IRBs
- Explain rules relating to financial disclosure
- Discuss the basic rules of study design
- Explain the rules and reporting requirements for adverse events and serious adverse events
- Explain study closure procedures and record retention guidelines
- Outline the reasons for monitoring, audits and site visits
- Explain the Food and Drug Administration rules, regulations, and guidelines on research
- Discuss the importance of investigational drug accountability
- Demonstrate and describe how to read clinical reports and records
- Discuss Quality Assurance including monitoring and auditing
- Explain issues that would constitute clinical fraud

Course Overview

Discussion and Explanation of Ethical Issues in Clinical Research

- Nuremberg Code
- Declaration of Helsinki
- Code of Federal Regulations (CFR)
- Belmont Report
- International Conference on
- Harmonisation (ICH) - Guidelines for Good Clinical Practice
- Informed Consent
- Disclosure of clinical information
- Clinical Fraud

Practice Test

- (Intended to affirm information discussed)

Explanation of IRBs, IECs, and Associated Regulations

- Initial review, changes and
- continuing review

SAEs/ADRs

- Reporting requirements
- Forms
- Investigational New Drugs

Ability to Follow Directions

- Test Schedules / Study Parameters
- Dose Calculations

Abstracting Information

- Reading charts and clinical reports
- Eligibility Criteria

Conduct of Clinical Trials

- Pre-study activities
- Sponsors and research
- Responsibility of the Investigator
- Study design, phases and blinding
- Protocol Development
- Investigational Drugs, Devices, Therapeutics and procedures
- Records retention
- Study Closure
- SAEs
- Monitoring and GCPs
- Informed consent
- Forms completion
- Audits and site visits

SOCRA designates this educational activity for a maximum of 7.5 Continuing Education Credits for SOCRA CE, Nurse CNE, and Physician CME.

SOCRA designates this live activity for a maximum of 7.5 AMA PRA Category 1 Credit(s)™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

CME for Physicians: The Society of Clinical Research Associates is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

CNE for Nurses: Society of Clinical Research Associates is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center's Commission on Accreditation. / SOCRA Course Series 500

SOCRA
FOR CLINICAL RESEARCH EXCELLENCE

FDA Conference:

Clinical Trial Requirements, Regulations, Compliance and GCP Conference

Jointly Sponsored FDA U.S. FOOD & DRUG ADMINISTRATION

NOVEMBER 16 TO 18, 2021 I VIRTUAL

Workshop registration fees:
Standard Rate - Member Fee - $100
Standard Rate - Non-Member Fee *- $175
Federal Government Employee Rate - Member Fee - $75
Federal Government Employee Rate - Non-Member Fee*- $150
FDA Employee Rate - FEE WAIVED
** Non-Member Fees include a non-refundable one-year membership in SOCRA* Non-Member Fees include a non-refundable one-year membership in SOCRA*

Goal: SOCRA is pleased to offer this conference that is jointly sponsored with District/Regional offices of the U.S. Food and Drug Administration. This conference on FDA's clinical trial requirements is designed to aid the Clinical Research Professional's understanding of the mission, responsibilities and authority of the FDA and to facilitate interaction with FDA representatives.

Objective: This three-day virtual conference is intended to share information among FDA representatives and the regulated community, to facilitate the understanding of regulations, guidelines and practices, and to suggest methods and opportunities to enhance the research professional's product development experience. The program will focus on the relationships among the FDA and clinical trial staff, investigators and IRBs. The workshop will highlight three areas that present challenges to sponsors and investigational sites: FDA Clinical Research Requirements, Enhancing Success through Communication and Financial Incentives, and Assuring Confidence in Clinical Research.

Learning Objectives - The attendee should be able to:

- Discuss the role of the FDA district offices, how they are structured and their responsibilities
- Describe what FDA expects in a pharmaceutical clinical trial
- Discuss the science, regulation and assessment of adverse events
- Discuss how studies with investigational devices differ from those with drugs and biologics
- Describe the regulations that apply to the informed consent process
- Discuss how the ethical principle of justice underlies responsible participant selection
- Describe the IRB regulations and FDA's mechanisms to assure compliance
- Describe the parameters included in regulations applying to electronic signatures
- Describe how the FDA can assist members of the research community in their efforts to find information and understand FDA regulations.
- Discuss the responsibilities of the clinical investigator
- Describe how Pre-IND meetings and the FDA meeting process assist the research goal
- Describe the sponsor/investigator's legal responsibilities, additional duties and concerns
- Describe how the FDA's Center for Biologics regulates research
- Discuss the array of actions taken when research fails to meet standards enforced by the FDA
- Describe how the FDA's Office of Science and Health Coordination, Good Clinical Practice Program, promotes confidence in clinical research

SOCRA designates this educational activity for a maximum of 11.25 Continuing Education Credits for SOCRA CE, Nurse CNE, and Physician CME.

SOCRA designates this live activity for a maximum of 11.25 AMA PRA Category 1 Credit(s)™.
Physicians should claim only the credit commensurate with the extent of their participation in the activity.

CME for Physicians: The Society of Clinical Research Associates is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.
CNE for Nurses: Society of Clinical Research Associates is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center's Commission on Accreditation.

SOCRA Course Series 700

SOCRA
FOR CLINICAL RESEARCH EXCELLENCE

FDA Conference:

Clinical Trial Requirements, Regulations, Compliance and GCP Conference

Jointly Sponsored FDA U.S. FOOD & DRUG ADMINISTRATION

MARCH 30 AND 31, 2022 I NEWPORT BEACH, CA

Workshop registration fees:
Standard Rate - Member Fee - $575
Standard Rate - Non-Member Fee *- $650
Federal Government Employee Rate - Member Fee - $450
Federal Government Employee Rate - Non-Member Fee*- $525
FDA Employee Rate - FEE WAIVED
** Non-Member Fees include a non-refundable one-year membership in SOCRA*

Goal: SOCRA is pleased to announce this conference that is jointly sponsored with the U.S. Food and Drug Administration regional/district offices. This conference on FDA's clinical trial requirements is designed to aid the Clinical Research Professional's understanding of the mission, responsibilities and authority of the FDA and to facilitate interaction with FDA representatives.

Objective: This three-day virtual conference is intended to share information among FDA representatives and the regulated community, to facilitate the understanding of regulations, guidelines and practices, and to suggest methods and opportunities to enhance the research professional's product development experience. The program will focus on the relationships among the FDA and clinical trial staff, investigators and IRBs. The sessions will highlight three areas that present challenges to sponsors and investigational sites: FDA Clinical Research Requirements, Enhancing Success through Communication and Financial Incentives, and Assuring Confidence in Clinical Research.

Learning Objectives - The attendee should be able to:

- Discuss the Role of the FDA District Offices, how they are Structured and their Responsibilities
- Describe how the FDA's Office of Science and Health Coordination, Good Clinical Practice Program, Promotes Confidence in Clinical Research
- Describe what FDA Expects in a Pharmaceutical Clinical Trial
- Discuss how Studies with Investigational Devices differ from those with Drugs and Biologics
- Discuss the Science, Regulation and Assessment of Adverse Events
- Describe how FDA's Center for Biologics Regulates Research
- Discuss how the Ethical Principle of Justice underlies Responsible Participant Selection
- Discuss the Responsibilities of the Clinical Investigator
- Describe how the FDA Small Business Representatives assist the Research Community
- Describe the Sponsor/Investigator's Legal Responsibilities, Additional Duties and Concerns
- Describe how Pre-IND Meetings and the FDA Meeting Process assist the Research Goal
- Describe the Parameters included in Regulations Applying to Electronic Signatures
- Describe the IRB Regulations and FDA's Mechanisms to Assure Compliance
- Describe the Regulations that Apply to the Informed Consent Process
- Discuss the Array of Actions taken when Research Fails to Meet Standards Enforced by the FDA

SOCRA designates this educational activity for a maximum of 13.3 Continuing Education Credits forSOCRA CE, Nurse CNE, and Physician CME.

SOCRA designates this live activity for a maximum of 13.3 AMA PRA Category 1 Credit(s)™.
Physicians should claim only the credit commensurate with the extent of their participation in the activity.

CME for Physicians: The Society of Clinical Research Associates is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.
CNE for Nurses: Society of Clinical Research Associates is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center's Commission on Accreditation.

SOCRA Course Series 700

NEW! FDA Sponsor-Investigator Conference:

Clinical Trial Requirements, Regulations, Compliance and GCP Conference

FOR CLINICAL RESEARCH EXCELLENCE

Jointly Sponsored U.S. FOOD & DRUG ADMINISTRATION

VIRTUAL

NOVEMBER 30 TO DECEMBER 2, 2021

Workshop registration fees:
Standard Rate - Member Fee - Free
Standard Rate - Non-Member Fee *- $75
FDA Employee Rate - FEE WAIVED
** Non-Member Fees include a non-refundable one-year membership in SOCRA*

Goal: SOCRA is pleased to offer this conference that is jointly sponsored with the U.S. Food and Drug Administration. This conference on Sponsor-Investigator clinical research is designed to aid the Clinical Research Professional's understanding the responsibilities of the research site when conducting Sponsor-Investigator research.

Objective: This three-day virtual conference is intended to share information among FDA representatives and the regulated community, and to facilitate the understanding of regulations, guidelines and practices related to Investigator initiated research. It is designed to aid the Sponsor-Investigator's understanding of their responsibilities and to facilitate interaction with FDA representatives

Learning Objectives - The attendee should be able to:

- Relate the history of the role of the sponsor-investigator
- Contrast past regulatory requirements to present expectations
- Describe the responsibilities of a sponsor-investigator who initiates an FDA regulated clinical trial
- Discuss various methods that can be used to ensure compliance with federal regulations and study protocol requirements
- Understand the role of quality management systems, risk assessment and management, and clinical quality by design in investigational product development programs and clinical trials.
- Understand the similarities and differences in regulations and makeup of medical products in clinical trials.
- Understand when an IND application is needed
- Gain a general understanding of medical device classification and pre-market submission types.
- Gain a greater understanding of IDEs and FDA review considerations related to IDEs.
- Gain a general understanding of the 21CFR 812 regulations, the role of a sponsor investigator, and considerations for Bioresearch Monitoring (BIMO) inspections.
- Understand the regulatory requirements regarding source records and data collection for Clinical Investigators who are also Sponsors
- Describe the general requirements for clinical trials registration and results information submission
- Understand the registration and results sections of the study record and the NLM quality control review process.
- Understand FDA's role and responsibilities related to ClinicalTrials.gov
- Describe the requirements for submitting certifications of compliance to FDA and including specific language in the informed consent documents for applicable clinical trials
- Understand the potential consequences of noncompliance with the requirements to submit clinical trial information to the ClinicalTrials.gov data bank and/or certifications to FDA
- Describe FDA's approach to conducting its compliance and enforcement activities involving FDAAA 801 and 42 CFR Part 11
- Describe the sources of drug safety information available to sponsor-investigators.
- Understand the importance of monitoring and assessing safety data, and requirements for safety reporting to the FDA.
- Discuss the paramount importance identifying errors that involve critical trial data and processes to prevent errors that matter most through Risk-Based Monitoring (RBM).

SOCRA designates this educational activity for a maximum of 13.0 Continuing Education Credits forSOCRA CE, Nurse CNE, and Physician CME.

SOCRA designates this live activity for a maximum of 13.0 AMA PRA Category 1 Credit(s)™.
Physicians should claim only the credit commensurate with the extent of their participation in the activity.

CME for Physicians: The Society of Clinical Research Associates is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.
CNE for Nurses: Society of Clinical Research Associates is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center's Commission on Accreditation.

SOCRA Course Series 320

SOCRA Advanced Concepts for Clinical Investigators and Key Research Staff: GCP & Clinical Trials Management Conference

2022 COURSE DATE COMING SOON

Workshop registration fee - $395 (Non-Member $470- includes one year's membership)

Goal: The purpose of this workshop is to assist Clinical Investigators and key research staff in improving their skills and understanding of the responsibilities of the clinical research site. This program is intended to share information and create opportunity for dialogue among clinical investigators, key research staff and program faculty. The specific goal is to enhance the participants' ability to perform quality clinical research according to existing regulations and guidelines. This program is designed to address all of the functions of the research site related to the Good Clinical Practices as delineated by the U.S. Code of Federal Regulations and the guidelines supported by the International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH Guidelines).

Objective: The goal will be accomplished through lecture and practical application facilitated by clinical research professionals and experts in the field. Information will be presented and discussed regarding administration of clinical trials according to FDA Regulations and International Council on Harmonisation (ICH) guidelines as well as practical procedures and site / sponsor / CRO relationships.

Learning Objectives - The attendee should be able to:

- Describe the drug development Process
- Discuss investigator and investigational site responsibilities related to regulations and ethics
- Describe the protocol development Process
- Describe the research grant proposal development process
- Discuss the informed consent process
- Explain development of informed consent forms: rights, rites, and rewrites
- Describe investigator-initiated research projects
- Discuss safety reporting and adverse events / serious adverse events
- Explain source documentation and research record management
- Discuss the financial management of study funds
- Discuss the elements related to successful clinical study agreements
- Describe the basic requirements of monitoring visits and audits
- Discuss the development and implementation of standard operating procedures

SOCRA designates this educational activity for a maximum of 13.25 Continuing Education Credits for SOCRA CE, Nurse CNE, and Physician CME.
SOCRA designates this live activity for a maximum of 13.25 AMA PRA Category 1 Credit(s)™.
Physicians should claim only the credit commensurate with the extent of their participation in the activity.

CME for Physicians: The Society of Clinical Research Associates is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

CNE for Nurses: Society of Clinical Research Associates is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center's Commission on Accreditation.

SOCRA Course Series 400

SOCRA Clinical Site Coordinator / Manager Workshop

GCP For Site Coordinators, Research Associates, Study Nurses, Site Managers

NOVEMBER 4 AND 5, 2021 I NEW ORLEANS, LA
ADDITIONAL COURSE DATES COMING SOON

Workshop Registration Fee - $615 (Non-member $690 includes one year membership)

Objective: This interactive virtual workshop will be accomplished through lecture and practical application facilitated by clinical research professionals with a combined industry experience of more than 20 years. Information will be presented and discussed regarding administration of clinical trials according to FDA Regulations and International Conference on Harmonisation (ICH) guidelines as well as practical procedures and site / sponsor / CRO relationships.

Goal: The Society of Clinical Research Associates (SOCRA) recognizes the continuing need for education for Clinical Research Professionals responsible for the activities at the research site or institution. The purpose of this workshop is to assist Site Coordinators, Research Associates, and Study Nurses in improving their skills and their understanding of the responsibilities of the Clinical Research Site. This program is designed to address all of the functions of the research site related to the Good Clinical Practices as delineated by the U.S. Code of Federal Regulations and the guidelines supported by the **International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH Guidelines).**

Learning Objectives - The attendee should be able to:

- Discuss aspects of clinical trials that are governed by regulations and guidelines
- Discuss the basic philosophy and guiding principles of clinical research GCP
- Discuss the elements of the informed consent form, the ethical principles originating in the Declaration of Helsinki, the various aspects of the informed consent process, and those special considerations that may impact the process
- Describe the various aspects of human research protections including the ICH definitions of AEs (adverse events) and SAEs (serious adverse events) and describe the reporting requirements common to all sponsors and IRBs/IECs
- Discuss the role of the Study Coordinator including: submitting a protocol to the IRB; setting up local procedures; source documentation management and control; and working relations with sponsors
- Discuss the rationale and issues surrounding the monitoring visit and the audit process from a site, a sponsor, and a regulatory perspective
- Discuss the parameters, goals, and outcomes of audits and inspections
- Discuss the philosophy and rationale for the development and implementation of standard operating procedures (SOPs)

SOCRA designates this educational activity for a maximum of 11.75 Continuing Education Credits for SOCRA CE, Nurse CNE, and Physician CME.

SOCRA designates this live activity for a maximum of 11.75 AMA PRA Category 1 Credit(s)™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

CME for Physicians: The Society of Clinical Research Associates is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.
CNE for Nurses: Society of Clinical Research Associates is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center's Commission on Accreditation.

SOCRA Course Series 600

SOCRA Clinical Research Project / Program Management Virtual Conference

ADDITIONAL COURSE DATES COMING SOON

Conference registration fee - $430 (Non-member $505 includes one year membership)

Goal: Clinical trial project and program management incorporate a broad range of skill sets in order to plan, administer, track, evaluate and report activities and budgets involved in the health care product development process. The goal of this program is to introduce, affirm or enhance the participant's understanding of the project management endeavor

Objective: Through discussion, presentation, and interaction, this program will broaden the participants' knowledge of the regulatory framework, project management art and science, planning and accounting, and their attitude and aptitude for achieving successful clinical trials

Learning Objectives - The attendee should be able to:

- Describe project management and basic risk management principles following PMI (Project Management Institute) guidelines (initiation, planning, execution, monitoring, controlling, and closing)
- Discuss the processes and procedures that are necessary to develop an infrastructure that will support the various tasks associated with Project Management in Clinical Research
- Discuss how to incorporate IRB interaction activities into a project plan, focusing on issues involved in managing multiple investigational sites. Disaster recovery and contingency planning will be discussed
- Discuss Organizational Dynamics and psychological issues in project management to promote effective team building. Describe conflict resolution strategies; discuss approaches to work effectively with different leadership and personality styles
- Describe general start up issues including; budget development, cash flow issues and solutions, billing to CMS (Centers for Medicare & Medicaid Services), and contract management
- Describe contract development topic issues including: intellectual property (IP) rights, publication, indemnification, payment schedule management, clinical trial sponsor interactions and negotiations
- Describe various international regulatory bodies and their submission processes using the US Code of Federal Regulations (FDA/OHRP) as a baseline
- Describe Project Management of the IND and IDE, review guidance documents, forms and accountability measures designated for use by industry and academic research sponsors and sponsor investigators

SOCRA designates this educational activity for a maximum of 14.5 Continuing Education Credits for SOCRA CE, Nurse CNE, and Physician CME.

SOCRA designates this live activity for a maximum of 14.5 AMA PRA Category 1 Credit(s)™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

CME for Physicians: The Society of Clinical Research Associates is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.
CNE for Nurses: Society of Clinical Research Associates is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center's Commission on Accreditation.

SOCRA Course Series 250

SOCRA Clinical Research Nursing Conference

MAY 19 AND 20, 2022 I NEWPORT BEACH, CA

Conference registration fee - $630 Member

(Non-member $705 includes one year membership)

Goal: To describe and define essential functions of the clinical research nurse with consideration of the recently released ANA Scope and Standards of practice for Clinical Research Nursing. Clinical Research Nurses practice in a variety of clinical research settings, including serving as a bedside clinical research nurse, clinical research manager at a site, clinical research associate for a sponsor, or nurse researcher who is developing protocols and overseeing his/her own research.This program is not only applicable to those currently serving as clinical research nurses but also to those who are considering becoming a clinical research nurse, including nurses practicing in clinical areas and clinical research staff who are not nurses but are thinking of returning to school to obtain a nursing degree. This program contains a wealth of knowledge and can also benefit clinical research staff and managers from all educational backgrounds who are interested in advancing their understanding of this program's content.

Objective: The goal will be accomplished through lecture and practical application facilitated by clinical research professionals with extensive experience in nursing, education and clinical research administration and management. Information will be presented and discussed regarding the American Nurses Association (ANA) scopes and standards of practice for clinical research nurses. This program will address the unique challenges clinical research nurses face regarding the administration of clinical research and the care for patients.

Learning Objectives - The attendee should be able to:

- Discuss the key components of the Domains of Clinical Research Nursing Practice
- Identify the necessary skills that embody the core attributes of a clinical research nurse
- Discuss the dimensions of practice for the CRN including; Human Subjects Protection, Care Coordination and Continuity, Contribution to Science in general and Nursing Science/Practice, Clinical Practice, and Study Management
- Apply concepts, regulations, and tools that will promote the safe and ethical conduct of research
- Discuss a variety of communication styles and employ effective navigation of study teams
- Discuss strategies to facilitate an efficient study team
- Discuss various roles and practice environments of nurses in research and clinical research
- Discuss the role of the clinical research nurse as research participant advocates
- Discuss approaches to increasing the quality of the informed consent discussion
- Discuss the role of the CRN in human subjects protection and ethical considerations
- Discuss ways to build infrastructure and operational practices for clinical research units
- Discuss financial considerations and approaches to working with study budgets
- Discuss best practices related to budgeting and financial management of the entire clinical research study lifecycle
- Discuss current trends and issues in Clinical Research Nursing

SOCRA designates this educational activity for a maximum of 12.75 Continuing Education Credits for SOCRA CE, Nurse CNE, and Physician CME.

SOCRA designates this live activity for a maximum of 12.75 AMA PRA Category 1 Credit(s)™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

CME for Physicians: The Society of Clinical Research Associates is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

CNE for Nurses: Society of Clinical Research Associates is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center's Commission on Accreditation. / SOCRA Course Series 550

SOCRA Oncology Clinical Trials Conference

2022 COURSE DATES COMING SOON

Goal: The Society of Clinical Research Associates (SOCRA) recognizes the continuing need for education for Clinical Research Professionals responsible for the activities at the research site or institution. The purpose of this workshop is to assist Research Professionals in improving their skills and their understanding of the responsibilities of conducting oncology clinical research.

Objective: The goal will be accomplished through lecture and practical application facilitated by clinical research professionals. Information will be presented and discussed regarding the administration of oncology clinical trials according to regulation, guidance, policy and procedure.

Learning Objectives - The attendee should be able to:

- Discuss the challenges of conducting oncology clinical research
- Discuss the role and function of a data safety monitoring board in oncology clinical trials
- Discuss the role and function of a central IRB
- Discuss approaches to recruitment in oncology research
- Discuss the challenges of long term follow up
- Discuss compliance issues and methods of study analysis
- Discuss the use of personalized medicine and target therapies in oncology research
- Describe the process of reporting adverse events
- Describe the importance of Pharmacokinetic (PK) evaluations in oncology research
- Describe the role of the research subject advocate
- Discuss the investigators responsibilities regarding investigational agents
- Discuss the process for assessing tumor size in adult oncology trials
- Discuss the process for identifying outcome measures in oncology research studies
- Describe how utilizing project management and basic risk management principles in clinical trials helps to improve site performance
- Describe issues faced in the monitoring of clinical trials
- Discuss how to effectively and efficiently prepare for monitoring and audit visits
- Discuss the importance of self-monitoring
- Describe the process of minimizing risk through good clinical practices

SOCRA designates this educational activity for a maximum of 18.0 Continuing Education Credits for SOCRA CE, Nurse CNE, and Physician CME.

SOCRA designates this live activity for a maximum of 18.0 AMA PRA Category 1 Credit(s)™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Oncology fundamentals Preconference Workshop - maximum 4.0 CE. Main Conference - 14 CE

CME for Physicians: The Society of Clinical Research Associates is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

CNE for Nurses: Society of Clinical Research Associates is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center's Commission on Accreditation.

SOCRA Course Series 750

SOCRA Pediatric Clinical Trials Conference

Conducting Clinical Research in the Pediatric Population

2022 COURSE DATES COMING SOON

Goal: The Society of Clinical Research Associates (SOCRA) recognizes the need for continuing education for Clinical Research Professionals responsible for the activities at pediatric research site. The purpose of this conference is to assist Research Professionals in improving their skill and their understanding of the responsibilities of conducting clinical research and clinical trials in the pediatric population.

Objective: The goal will be accomplished through lecture and practical application facilitated by clinical research experts professionals. Information will be presented and discussed regarding the administration of clinical research/ trials according to FDA Regulations and International Conference on Harmonisation (ICH) Good Clinical Practice guidelines for vulnerable populations.

Learning Objectives

The attendee should be able to:

- Discuss the process of submitting an IND/IDE for a pediatric study/trial
- Discuss the challenges of off label drug use in the pediatric population
- Discuss the consenting/assenting process in pediatric trials
- Discuss the role and function of a data safety monitoring board in pediatric clinical trials
- Discuss approaches to recruitment in pediatric research
- Discuss strategies to retain participants in pediatric trials
- Discuss the process for identifying outcome measures in pediatric research studies
- Discuss the challenges of long term follow up
- Discuss pediatric trial compliance issues and methods of study analysis
- Describe the special considerations when developing budgets for pediatric research studies
- Discuss the differences between master agreements, work orders, CDAs and CTAs
- Discuss best practices for successful contract negotiation
- Discuss the critical pathways in pediatric research program planning
- Describe how to operationalize clinical research through program management
- Discuss how continuous quality improvement is a mechanism for best practices in clinical research
- Discuss how to effectively and efficiently prepare for monitoring and audit visits
- Discuss the importance of self-monitoring
- Describe the process of minimizing risk through good clinical research practices
- Discuss steps to ensure financial compliance
- Discuss the challenges of achieving thorough and compliant record retention
- Discuss the requirements for study closeout

SOCRA designates this educational activity for a maximum of 14.0 Continuing Education Credits for SOCRA CE, Nurse CNE, and Physician CME.

SOCRA designates this live activity for a maximum of 14.0 AMA PRA Category 1 Credit(s)™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

CME for Physicians: The Society of Clinical Research Associates is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

CNE for Nurses: Society of Clinical Research Associates is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center's Commission on Accreditation.

SOCRA Course Series: 850

SOCRA Emergency Clinical Research Symposium

2022 COURSE DATES COMING SOON!

Goal: The Society of Clinical Research Associates (SOCRA) recognizes the continuing need for education for Clinical Research Professionals responsible for the activities at the research site or institution. The purpose of this workshop is to assist Research Professionals in improving their skills and their understanding of the responsibilities of conducting clinical research in the emergency setting. Conducting research in the emergency setting presents unique challenges to clinical research professionals. Information will be presented and discussed regarding the development, approval and administration of emergency clinical trials according to regulation and guidance. The program will address hot topics such as the "challenges of informed consent", "funding potential for emergency research" and "design considerations for emergency clinical research".

Objective: The goal will be accomplished through lecture and practical application facilitated by clinical research professionals. Information will be presented and discussed regarding the administration of clinical trials according to FDA Regulations and International Conference on Harmonisation (ICH) regarding emergency clinical research.

Learning Objectives - The attendee should be able to:

- Understand current regulations related to emergency research
- Understand current challenges facing researchers conducting non therapeutic research in a pediatric emergency department setting.
- Discuss possible solutions to challenges to non therapeutic research in an emergency department setting.
- Describe challenges in Emergency Medicine triage related to psychological and psychiatric behaviors of both researchers and potential research participants.
- Identify behavioral, psychological and psychiatric behavior strategies to address challenges and mitigate risk.
- Discuss the process involved in emergency and expanded access use INDs.
- Discuss site level structures, strategies and best practices for managing and administering a scalable, sustainable research enterprise
- Recognize ethical and regulatory considerations in emergency research with emergency and compassion use drugs.
- Discuss special design considerations for adult emergency research studies including selection of study populations, recruitment and retention of study subjects, outcome measures, assessment effects and efficacy vs. effectiveness.
- Discuss challenges associated with screening and recruitment in urgent and acute care settings.
- Understand IRB requirements for emergency research as well as the process and requirements for exception from informed consent in emergency research under CFR 21.50.24
- Learn the practical aspects, pitfalls and approaches to obtaining pediatric informed consent and trial enrollment in time-sensitive emergency settings and how to apply them.

SOCRA designates this educational activity for a maximum of 13 Continuing Education Credits for SOCRA CE, Nurse CNE, and Physician CME.

SOCRA designates this live activity for a maximum of 13 AMA PRA Category 1 Credit(s)™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

CME for Physicians: The Society of Clinical Research Associates is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.
CNE for Nurses: Society of Clinical Research Associates is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center's Commission on Accreditation.

SOCRA Course Series 450

2022 Annual Device Research and GCP Conference

Regulations and Guidelines for Device Clinical Research

APRIL 28 AND 29, 2022 I SAVANNAH, GA
Preconference - April 27, 2022

Program Chairperson, Kathi Goodwin Durdon, MA, CCRP, CNY Biotech Accelerator
Program Co-Chairperson, Donna Headlee, RN, BSN, CCRP

Goal: This DEVICE RESEARCH conference for Clinical Research Professionals will introduce, explain and discuss concepts and current issues relating to compliance, research development and clinical investigation in the current regulatory environment. Those new to device research may also elect to participate in the half-day DEVICE BASICS workshop which will be held the afternoon prior to the main 2-day program.

Objective: This 2-day advanced conference will include experts involved in the research and development of safe and effective medical devices. Day 1 includes an introduction to the FDA's regulatory framework for device research, developing a PMA submission strategy, a 510(k) update, legislative and regulatory developments affecting research, the Physician Payment Sunshine Act, conducting clinical trials in Asia Pacific, as well as a device research case study. Day 2 will include presentations on healthcare trends affecting the medical device industry, issues related to human factors, the benefits of usability testing during the medical device procurement process, and best practices for sourcing outside clinical development support services. Presenters will also discuss strategies for adding software for a medical device and writing protocols for trials involving software as a medical device, issues related to developing a registry, and real-world issues related to medical device research.

Learning Objectives - Pre-Conference Workshop – The participant will be able to:

- Discuss the regulations that govern the administration of device research including risk categorization and device classifications
- Discuss differences between device and pharmaceutical clinical research
- Discuss roles and responsibilities of key device research professionals
- Discuss issues related to CDRH BIMO IRB inspections
- Review the basic concepts related to medical device research

Learning Objectives – Main Conference - The participant will be able to:

- Discuss issues related to the conduct of device clinical research
- Describe approaches to navigate FDA and manage INDs and pre-submissions
- Discuss strategies for PMA submissions
- Describe current issues related to 510(k) guidances
- Describe legislative and regulatory development affecting device clinical research globally
- Discuss how Physician Payment Sunshine Reporting affects medical device research
- Discuss issues related to conducting clinical trials in Asia Pacific
- Describe issues related to IDEs, marketing applications, GCP and compliance strategies as demonstrated through the use of a case study
- Discuss issues faced in conducting medical device research
- Describe important healthcare trends and how they may affect the medical device industry
- Discuss how incorporating human factors and collaboration design can mitigate challenges in the product development process
- Describe the benefits of usability testing during the medical device procurement process
- Discuss best practices in sourcing outside clinical development support services
- Discuss strategies for adding software for a medical device
- Describe strategies for developing successful protocols involving software as a medical device
- Discuss issues related to developing a registry, obtaining regulatory approvals and how to properly use a registry in clinical research
- Discuss real-world issues related to medical device research

SOCRA designates this educational activity for a maximum of 17.25 Continuing Education Credits for SOCRA CE and Nurse CNE.

SOCRA designates this live activity for a maximum of 17.25 AMA PRA Category 1 Credit(s)™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Device Basics - PreConference Workshop - maximum 4.5 CE Device Regulations - 2 day Conference - maximum 12.75 CE

CME for Physicians: The Society of Clinical Research Associates is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

CNE for Nurses: Society of Clinical Research Associates is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center's Commission on Accreditation.

SOCRA Course Series: 900

SOCRA Quality Management Virtual Conference

2022 COURSE DATES COMING SOON

Goal: The Society of Clinical Research Associates (SOCRA) recognizes the continuing need for education for Clinical Research Professionals responsible for the activities at the research site or institution. The purpose of this workshop is to assist research professionals in understanding, developing and implementing quality management systems (QMS) in the conduct of clinical trials. This conference provides attendees with new information, tools, and real life examples to help participants navigate the components of quality management in clinical research - quality planning, quality control, quality assurance, and quality improvement.

Objective: The goal will be accomplished through lecture and practical application facilitated by clinical research professionals. Information will be presented and discussed regarding the development and implementation of quality management systems in the conduct of clinical trials according to FDA Regulations and International Council on Harmonisation (ICH) guidance.

Learning Objectives: Upon completion of this (full) course the attendee should be able to:

- Discuss the importance of quality management systems (QMS) in clinical research
- Review the key steps and elements in Risk Management and Quality Systems
- Discuss best practices in assessing and mitigating risk in clinical trial project management
- Discuss risk assessments, monitoring plan creation, and monitor training
- Discuss how to develop and implement a Quality Assurance (QA) Program for Investigator-Initiated Trials (IITs)
- Review the planning and implementation of real life examples of quality initiatives
- Review the essentials of conducting an audit/inspection ready study
- Review best strategies on audit/inspection close out processes including CAPA development and implementation
- Discuss the management of serious breaches and non-compliance
- Outline the impact of system non-compliance, sanctions, and fraud
- Outline the top QA and QC trends to elucidate ideal training and educational needs

SOCRA designates this educational activity for a maximum of 12.0 Continuing Education Credits for SOCRA CE and Nurse CNE.

SOCRA designates this live activity for a maximum of 12.0 AMA PRA Category 1 Credit(s)™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

CME for Physicians: The Society of Clinical Research Associates is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.
CNE for Nurses: Society of Clinical Research Associates is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center's Commission on Accreditation.
SOCRA Course Series: 120

SOCRA EDUCATIONAL OPPORTUNITIES

SOCRA offers education to clinical research professionals on Good Clinical Practice and so much more. Our hope is that by participating in our programming, our members will be leaders in the clinical research profession. SOCRA promises to provide continued educational programming that will offer the most up-to-date information available to the clinical researcher.

LIVE EDUCATIONAL PROGRAMS

We offer a diverse portfolio of live educational courses which are now offered virtually and in-person! Check out our website for the full course calendar.

CONTINUING EDUCATION CREDIT

SOCRA is accredited by ACCME and ANCC to provide CME to physicians and CNE to nurses. All SOCRA courses offer CE toward your CCRP Certification.

ONLINE TRAINING

SOCRA offers online learning offered as self-paced, on-demand presentations. The online education programs can be accessed through our website.

Attention RNs and MDs -
ALL SOCRA conferences offer CME and CNE continuing education credits*!

Consider attending one of SOCRA's 30+ educational programs on Clinical Research Finance and Budgeting, Site Management, Monitoring, Human Research Protections, Legal Issues, FDA Requirements, Device Research, Project Management, AND MORE!

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*CONTINUING EDUCATION CREDITS:

SOCRA's educational programming offers SOCRA CE, Nurse CNE, and AMA PRA Category 1 Credit(s)™. Physicians should claim credit commensurate only with the extent of their participation in the activity.

Accreditation Statements:

- CME for Physicians: The Society of Clinical Research Associates is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.
- CNE for Nurses: Society of Clinical Research Associates is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center's Commission on Accreditation.

You can visit
www.socra.org -
click on Conferences & Education
for current information, program agendas, and conference schedules.

SOCRA ADVERTISING OPPORTUNITIES

Advertise your products and services in SOCRA print materials including the SOCRA Source Journal or Annual Conference Program Book. SOCRA also offers online ads for career services and job opportunities on the SOCRA website.

SOCRA SOURCE JOURNAL

Published: Quarterly
Distribution: Electronic
Cost:
Full Page: $1000
Half Page: $500

ANNUAL CONFERENCE PROGRAM

Published: Annually
Deadline: August 20th
Distribution:
Annual Conference Attendees
Cost:
Full Page Color: $1000
Half Page: $500

JOB OPPORTUNITIES

Published: Updated Daily
(ad cycle is 31 days)
Distribution:
SOCRA Website
Cost:
Standard (up to 50 words): $125
Extended Length:
First 50 words: $125
Additional words: $2/word

CLINICAL RESEARCH SERVICES

Published: Updated Daily (ad cycle is 6 months or 1 year)
Distribution: SOCRA website
Cost: $500 for 6 months / $1,000 for 1 year

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