

# Overview of NCI CCR Office of Sponsor and Regulatory Oversight (OSRO)

July 12, 2019

# Agenda

- A. Introductions
- B. Overview of OSRO
- C. Sponsor Responsibilities
- D. Oversight Process Changes
  - 1. Serious Adverse Event (SAE) Reporting
  - 2. Protocol and Amendments
  - 3. Agreement Process
  - 4. Pharmacy, Study Agent Management
  - 5. Clinical Site Monitoring
- E. Other OSRO Future Plans

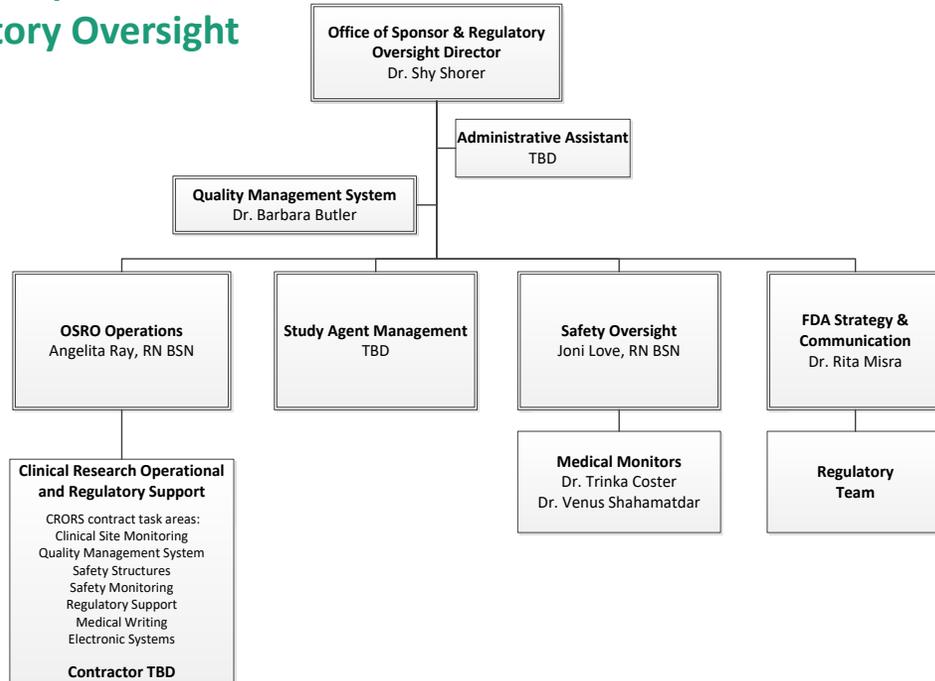
# Overview of OSRO

July 12, 2019

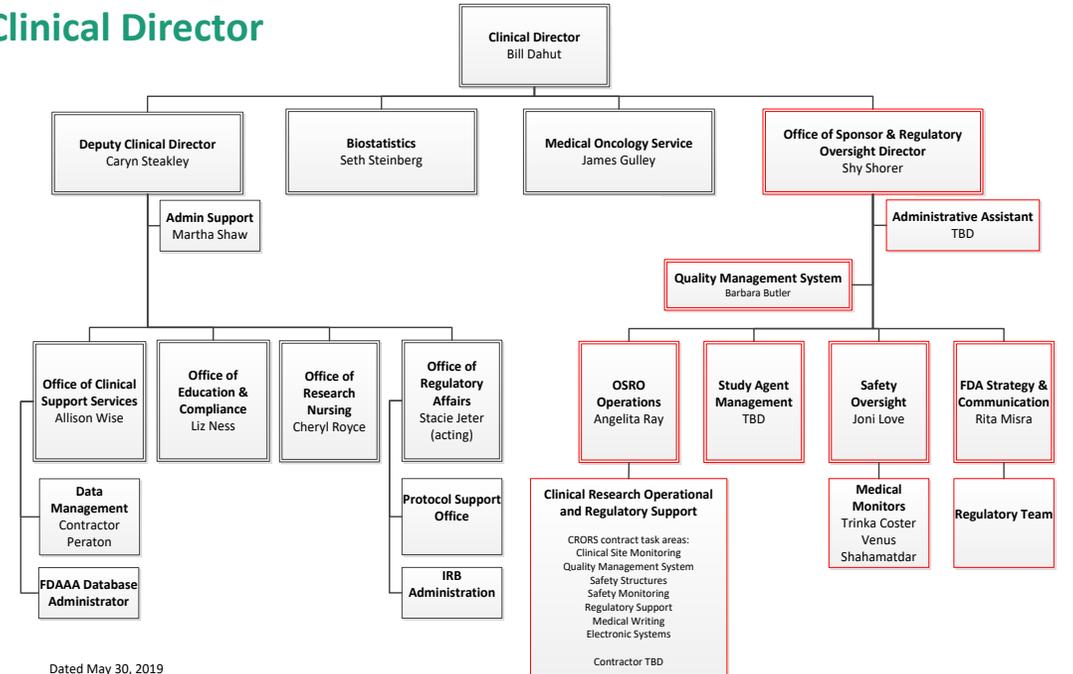
NCI CCR Office of Sponsor & Regulatory Oversight (OSRO)

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## Office of Sponsor & Regulatory Oversight



## CCR Office of the Clinical Director



# Organizational Chart

# OSRO Structure



# The OSRO Mission

- *To facilitate cancer research, prevention and patient care through expertise in regulatory and clinical trial oversight*

# The OSRO Charter

- Implementation of an IND/IDE Sponsor Program to ensure compliance with:
  - [21 CFR 312](#), Investigational New Drug
  - [21 CFR 812](#), Investigational Device Exemptions
  - [45 CFR 46](#), Protection of Human Subjects
  - [Compliance Program 7348.810](#), Bioresearch Monitoring FDA
  - [ICH E6\(R2\) Good Clinical Practice: Integrated Addendum to ICH E6\(R1\) Guidance for Industry \(FDA\)](#)

# Sponsor Responsibilities



# ICH E6 Good Clinical Practice (GCP)

- An international ethical and scientific quality standard for all clinical trials that involve the participation of human subjects
- ICH GCP was adopted by FDA in May 1997 and in March 2018 as the accepted standard for conducting clinical trials
- Strict adherence to ICH-GCP guidelines ensures that ethical and quality considerations are met and that the quality of the research can be assured

# The ICH-GCP guidance defines:

## Responsibilities for

- ⋮ the IRB
- ⋮ the Investigator
- ⋮ the Sponsor

## Requirements

- ⋮ of a protocol
- ⋮ for an Investigator's Brochure
- ⋮ for documentation



<https://www.fda.gov/regulatory-information/search-fda-guidance-documents/e6r2-good-clinical-practice-integrated-addendum-ich-e6r1>

# Sponsor Responsibilities

- ⋮ To implement a system to manage quality throughout all stages of the trial process
- ⋮ To focus on trial activities essential to ensuring human subject protection and the reliability of trial results
- ⋮ To use a risk-based approach
- ⋮ To ensure:
  - efficient design of clinical trial protocols, tools, and procedures for data collection and processing, as well as the collection of information that is essential to decision making
  - methods used are proportionate to the risks
  - all aspects of the trial are operationally feasible and should avoid unnecessary complexity, procedures, and data collection
  - operational documents are clear, concise, and consistent



# Sponsor Responsibilities

## ICH E6, Section 5, Table of Contents

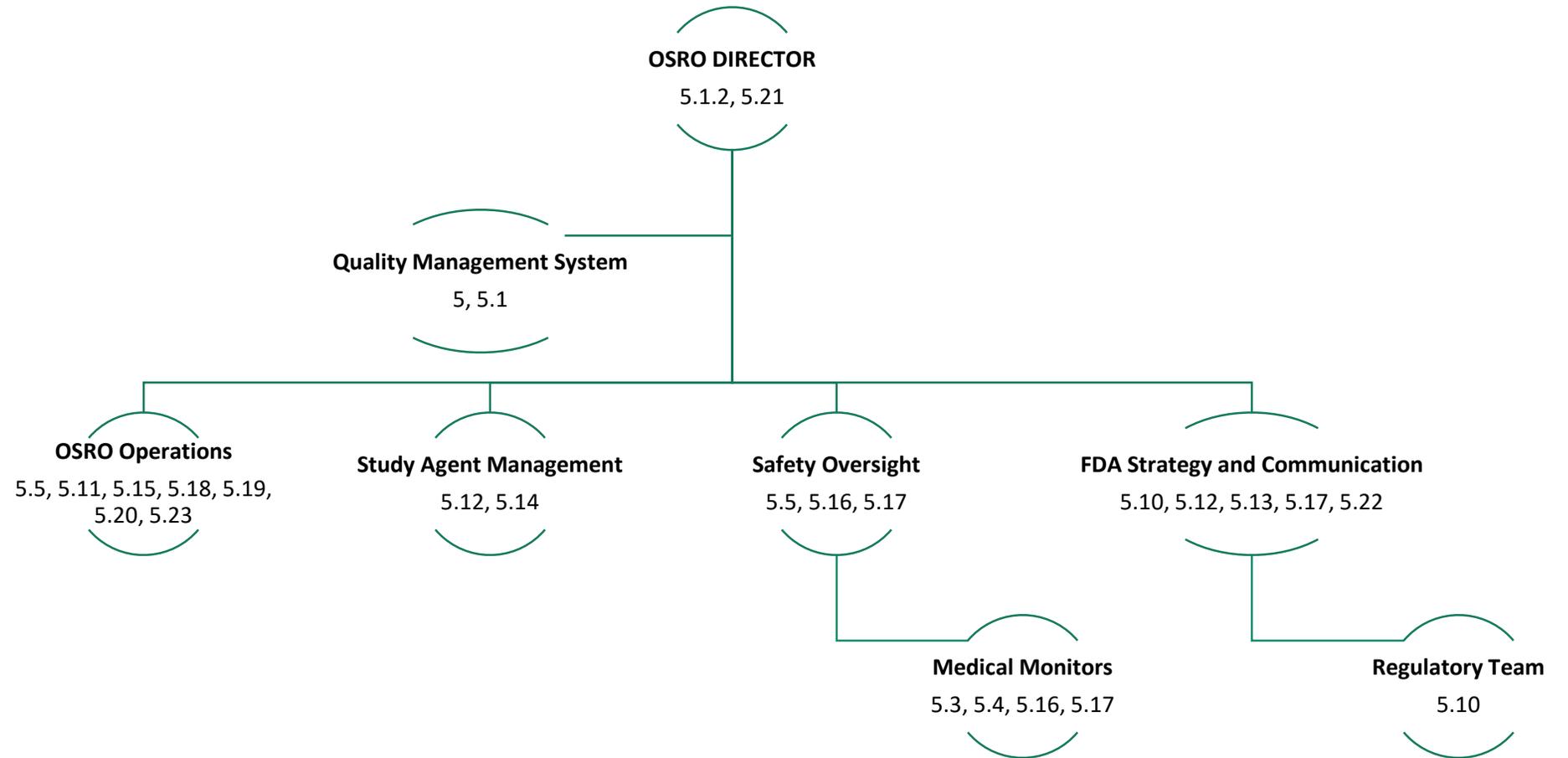
Section #	Title
5.0	Quality Management
5.1	Quality Assurance and Quality Control
5.2	Contract Research Organization (CRO)
5.3	Medical Expertise
5.4	Trial Design
5.5	Trial Management, Data Handling, and Recordkeeping
5.6	Investigator Selection
5.7	Allocation of Responsibilities
5.8	Compensation to Subjects and Investigators
5.9	Financing
5.10	Notification/Submission to Regulatory Authority(ies)
5.11	Confirmation of Review by IRB/IEC
5.12	Information on Investigational Product(s)

Section #	Title
5.13	Manufacturing, Packaging, Labeling, and Coding Investigational Products
5.14	Supplying and Handling Investigational Products
5.15	Record access
5.16	Safety Information
5.17	Adverse Drug Reaction Reporting
5.18	Monitoring
5.19	Audit
5.20	Noncompliance
5.21	Premature Termination or Suspension of a Trial
5.22	Clinical Trial/Study Reports
5.23	Multicenter Trials

# OSRO Regulatory Sponsor Oversight

- Applies to all clinical trials under a CCR-held IND or IDE
- OSRO is responsible regardless of study phase, type of intervention, or whether the investigational study agent is manufactured by NIH or an external Manufacturer/Supplier
- If CCR holds the IND or IDE, OSRO is the Regulatory Sponsor

# OSRO and E6(R2) Sponsor section numbers



# Oversight Process Changes



# Sponsor Data Systems

## **Current:**

- Well organized system utilizing the share drive structure
- Does not comply with good documentation standards or 21 CFR 11
- No Sponsor Quality System in place

## **Plan:**

- Establishment of an electronic Trial Master File (eTMF) utilizing available commercial software
  - Use of eTMF for new protocols
  - Transition of current files into eTMF
- Establishment of an electronic Sponsor Quality Management System (eQMS) utilizing available commercial software

# SAE Reporting

## Current:

- CCR SAE report form sent to [CCRSafety@mail.nih.gov](mailto:CCRSafety@mail.nih.gov)
- CCR Safety (POC- K Gesuwan):
  - Reviews SAE, adds sponsor assessment
  - Sends updated report to PI/study team/and company, if applicable
  - Saves original and updated reports in the regulatory files
- SUSARs-updated SAE report form sent to FDA, then sent to PI/study team/company
- Company queries sent to CCR Safety then to PI/ study team, to CCR Safety and back to company

# SAE Reporting

## Plan (effective 01 August 2019):

### Transition of SAE reporting to OSRO Safety

- OSRO point of contact is J Love (not K Gesuwan)
- *Current protocols* - continue to send SAE reports to [CCRSafety@mail.nih.gov](mailto:CCRSafety@mail.nih.gov)
- *New protocols* - send SAE reports to [OSROSafety@mail.nih.gov](mailto:OSROSafety@mail.nih.gov), OSRO Safety email
- Reporting changes:
  - New SAE report form, includes PI electronic signature (form is secure after signed)
  - Provide baseline H&P/labs, concomitant meds, diagnostic testing report(s) with SAE report form
  - New SAE information sent as follow up SAE report form

# SAE Reporting

Effective  
01 August 2019

## Plan (continued):

- Sponsor assessment/narrative by OSRO Medical Monitors (MMs):
  - MedWatch Form 3500A sent to FDA to report SUSARs
  - CIOMS Form sent to PI/study team/companies for non-SUSARs
- MMs contact PI to request information
- Send follow up SAE report with PI signature to document new information
- SAEs followed to resolution

# SAE Reporting

Effective  
01 August 2019

## Plan (continued):

- Companies will receive safety information from CCR held INDs according to agreements (CTA/CRADA) going forward
- Companies currently receiving SAE reports will receive:
  - Email notification of Initial SAE report with notice of new contact/ CIOMS to follow
  - CIOMS report, no later than 10 business days, with copy to PI/study team
  - Follow up CIOMS report after follow up SAE report sent to OSRO Safety

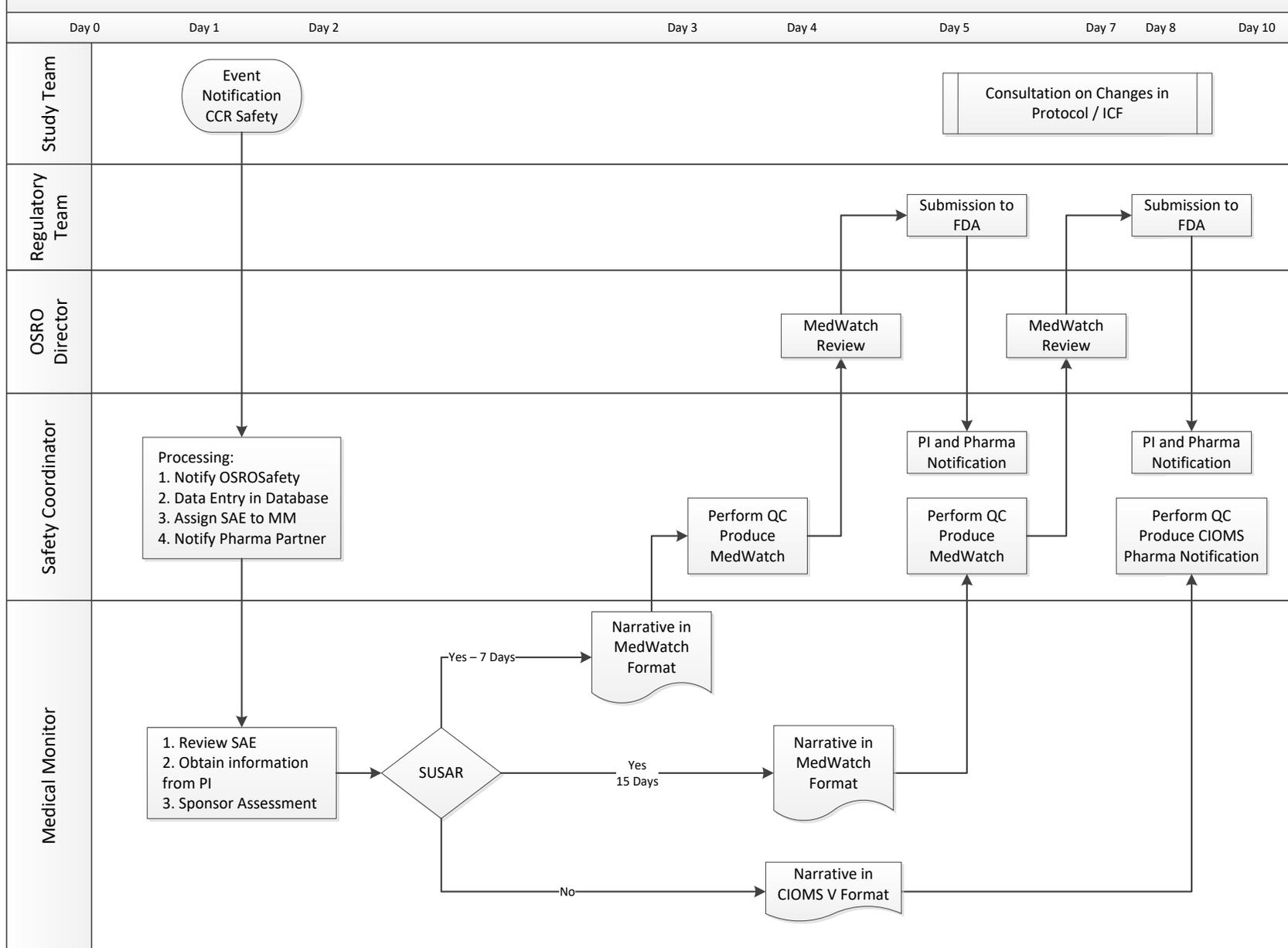
# SAE Reporting

Effective  
01 August 2019

## Plan (continued):

- Company queries will not be automatically passed through to PI/study team
- Companies will receive follow up CIOMS after new information has been evaluated/summarized by OSRO Safety
- OSRO Safety will query the PI/study team as needed
- If contacted directly by company for additional information on SAE report, forward request to OSRO Safety
- SAE reports, CIOMS reports and MedWatch reports will be saved in the regulatory files

# CCR OSRO SAE Reports Processing



# SAE Reports Processing

Dated July 11, 2019

July 12, 2019

NCI CCR Office of Sponsor & Regulatory Oversight (OSRO)

# Protocol and Amendments

## Current:

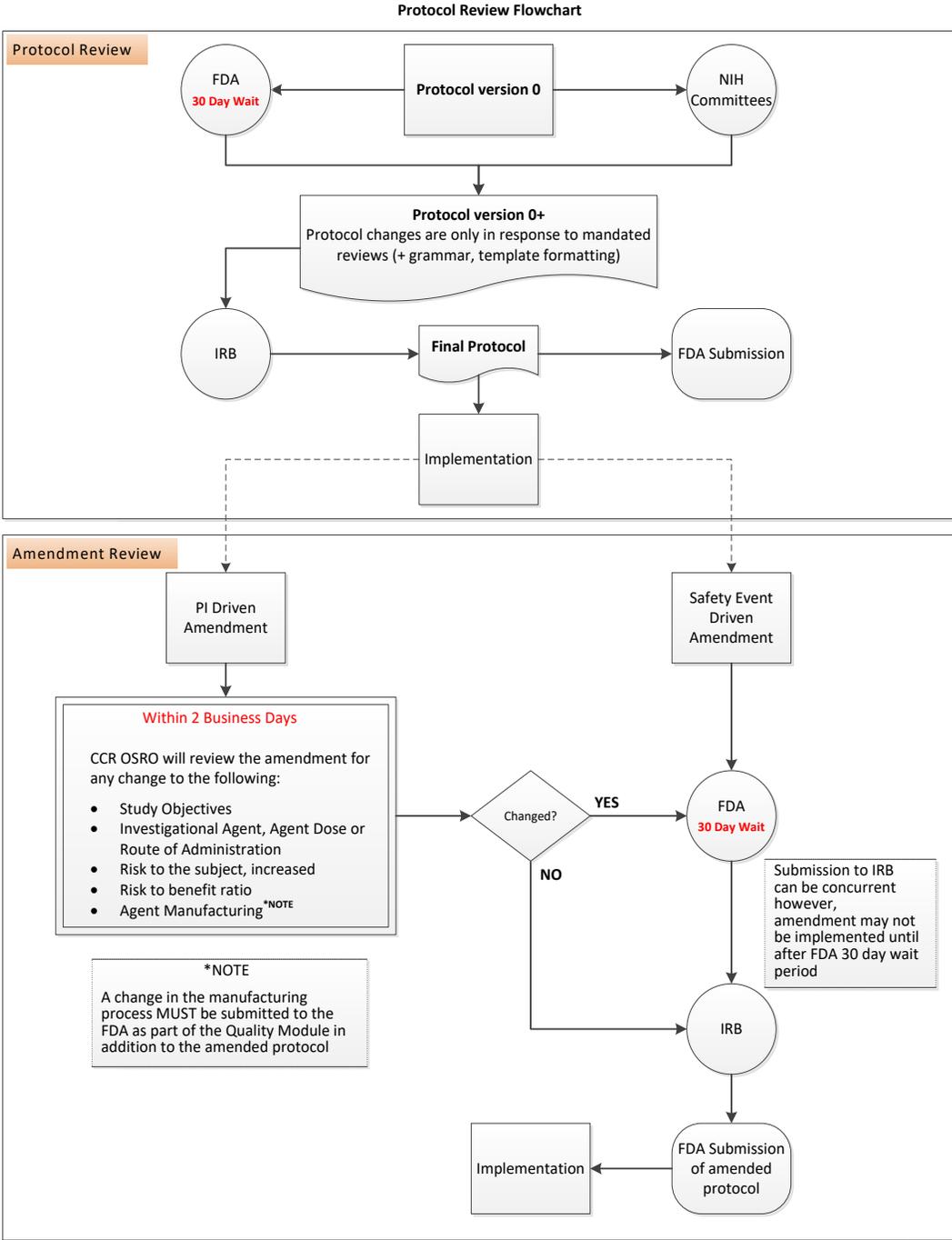
- The protocol development process and protocol approval process is disjointed from FDA communication and approvals
- Protocols are used to introduce manufacturing changes inappropriately
- Variable quality of protocols; version and change control issues

# Protocol and Amendments

## Change:

- New process implemented to tie in protocol and amendments to FDA submission and review
- Sponsor protocol approval process
- **Waiting period** before study subject screening and enrollment may begin:
  - **Initial IND** submission – wait 30 days after submission if the FDA has not put the study on clinical hold
  - **Existing IND** submission – wait 30 days after submission in accordance with CCR OSRO Policy

# Protocol and Amendment Flow



# IND Annual Reports

## **Current:**

- Inconsistent compilation and reporting of events, metrics and general content
- Insufficient standards, process training and instructional materials

## **Plan:**

- Establishment of Annual Report standards, training and review process
- Improve consistency, quality and reliability

# Agreement Process

## **Current:**

- Agreements lack relationship to protocol development timelines
- Deference of important details to outside of the agreement process
- Creates obligations that are not feasible for the support offices

## **Plan:**

- Re-work agreement templates with sections that cannot be changed without upfront agreement of the support offices
- Early involvement in agreement process

# Pharmacy, Study Agent Management

## **Current:**

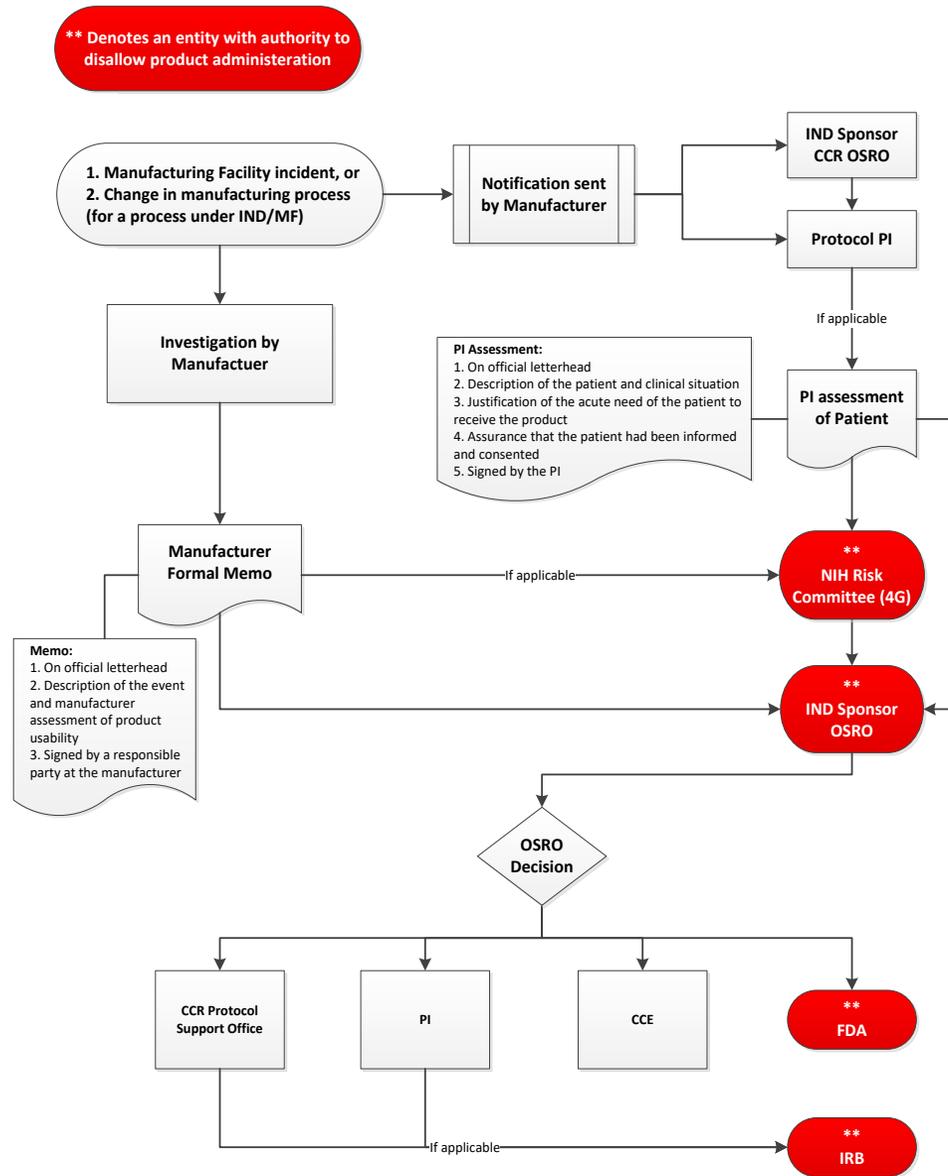
- No clear process for reporting manufacturing deviations
- No clear process for pharmacy involvement in development and initiation of a trial

## **Plan:**

- Establishing clear communication pathway around reporting and evaluations of manufacturing deviations
- Integration with CC Pharmacy (outsourcing and investigational services)

Notification to NCI CCR OSRO for Products Under CCR-held IND

# Notification of Study Agent Manufacturing Deviation Flow



Manufacturer Incident/Change Notification Flowchart, dated 7-8-2019

# Clinical Site Monitoring

## **Current:**

- Maintenance of an NCI CCR monitoring program for IND studies where CCR is the Sponsor.
- Standard procedures for monitoring review of regulatory documents, pharmacy, consent and eligibility.
- Standard approach to study selection, frequency and discontinuation.

# Clinical Site Monitoring Effective 01 October 2019

## Plan:

- **Transition** of responsibility for monitoring services
- **Effective 10/01/19**
  - OSRO will oversee clinical site monitoring of new CCR-held IND/IDE protocols
  - OSRO will implement new procedures for initiation visit requests, protocol-specific monitoring plans, site essential regulatory document review, and monitoring visit reporting
- **Current ongoing protocols** - no change to legacy procedures

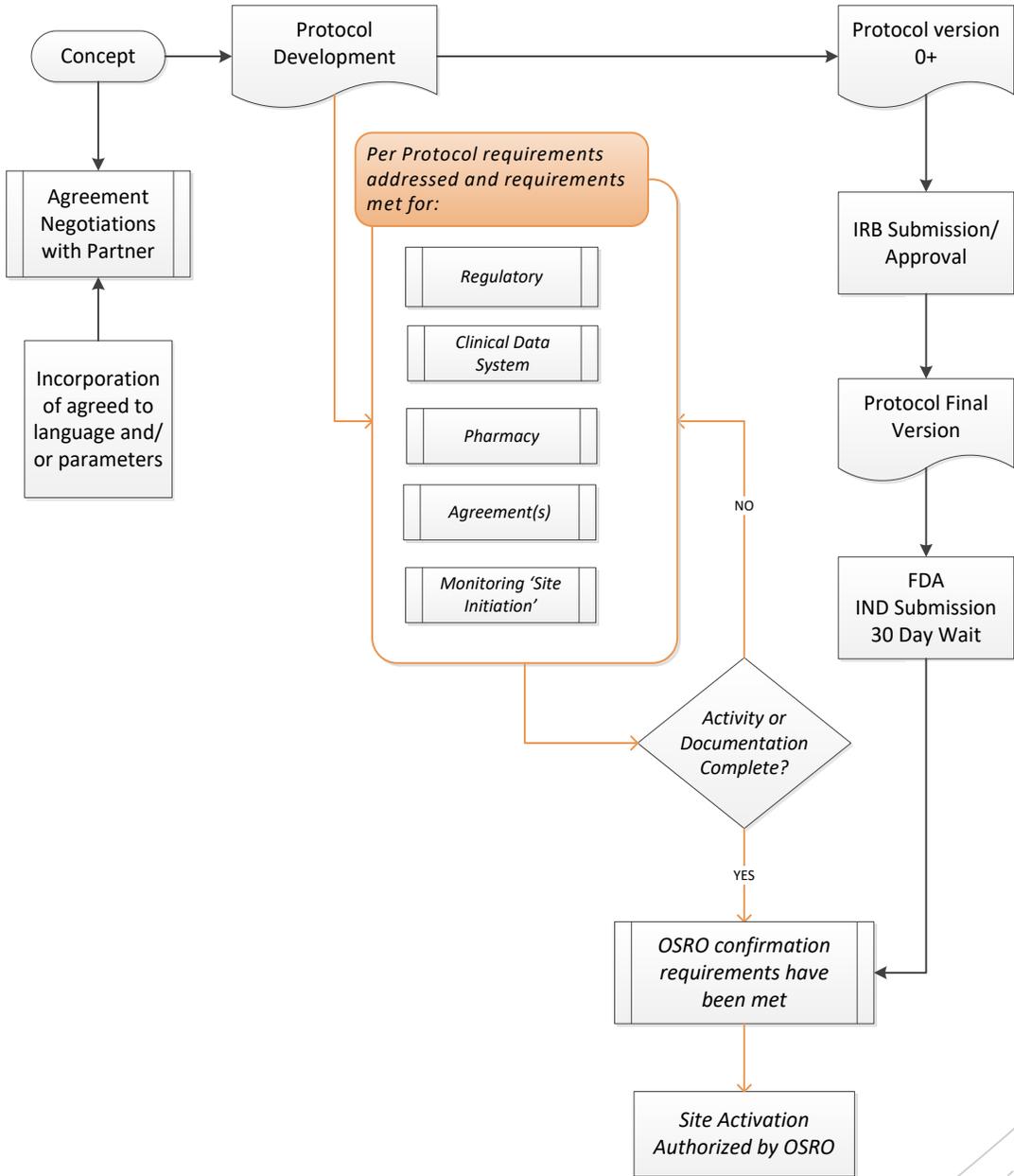
# Clinical Site Monitoring Effective 01 October 2019

## Plan (continued):

- Study Initiation Visit (SIV)
  - ✓ Request for SIV must be submitted at least 4 weeks before the target visit date. Email SIV request to [OSROMonitoring@mail.nih.gov](mailto:OSROMonitoring@mail.nih.gov)
  - ✓ Standard and protocol-specific prerequisites
  - ✓ Visit format may vary, remote webinar or onsite
  - ✓ All issues/action items resolved before OSRO Site Activation authorizing start of screening and enrollment
- Periodic monitoring visits over duration of the research study
- Close-out visits to confirm all study procedures have been completed, and data collected

# Site Activation Flow

## CCR OSRO Sponsor Activation



## Other OSRO Future Plans

- Establish a support contract for OSRO operations to include:
  - Clinical Site Monitoring services
  - Essential Regulatory Documents review
  - Safety reports processing
  - Safety Oversight Committee support
  - Regulatory submission and eTMF support
- Integration with research development
- Study agent support

# Contacts

- Safety – [OSROSafety@mail.nih.gov](mailto:OSROSafety@mail.nih.gov)
- Site Monitoring – [OSROMonitoring@mail.nih.gov](mailto:OSROMonitoring@mail.nih.gov)
- Study Agent – [OSROStudyAgent@mail.nih.gov](mailto:OSROStudyAgent@mail.nih.gov)
- Regulatory – [OSRORegulatory@mail.nih.gov](mailto:OSRORegulatory@mail.nih.gov)



	Office of Sponsor and Regulatory Oversight	Document #: F01-301-S01
	<b>Serious Adverse Event Report Form</b>	Revision #: 0
		Effective Date: TBD

**Instructions**

Send the following to [OSRO Safety](#) immediately:

- Completed SAE report form with PI signature
- List of concomitant medications
- Baseline H&P and baseline lab results (at time of enrollment) for initial report
- Diagnostic test result reports (lab tests and imaging performed as part of SAE evaluation)
- If SAE was “hospitalization” or “prolonged hospitalization”, provide Discharge Summary

**NOTE:** When providing copies of medical records, redact all personal identifiers, label copies with the Protocol # and Protocol Patient ID #

**REPORT TYPE:** (mark one)  INITIAL  
 FOLLOW UP

Report Information		
Date of this Report: <small>(dd-mmm-yy)</small>	Protocol # <small>Text</small>	CTCAE Version: <small>Select</small>

Patient Information			
Protocol Patient ID: <small>(Do not use MRN)</small> <small>Enter Patient ID</small>	Age (years): <small>Numerical Value</small>	Sex: <small>Select Sex</small>	Weight (kg): <small>Numerical Value</small>
Ethnicity: <input type="checkbox"/> Hispanic / Latino <input type="checkbox"/> Not Hispanic / Latino		Race: (check all that apply) <input type="checkbox"/> American Indian or Alaskan Native <input type="checkbox"/> Asian <input type="checkbox"/> Black or African American <input type="checkbox"/> Native Hawaiian or Other Pacific Islander <input type="checkbox"/> White	

Serious Criteria (check all that apply)		
<input type="checkbox"/> Death	Date of death: <small>(dd-mmm-yy)</small> Date PI informed of death: <small>(dd-mmm-yy)</small>	Autopsy: <input type="checkbox"/> Done (provide report) <input type="checkbox"/> Not Done <input type="checkbox"/> Planned <input type="checkbox"/> Status Unknown
<input type="checkbox"/> Hospitalization	Date of Hospitalization: <small>(dd-mmm-yy)</small>	
<input type="checkbox"/> Prolonged Hospitalization	Date of Prolongation: <small>(dd-mmm-yy)</small>	

	Office of Sponsor and Regulatory Oversight	Document #: F01-301-S01
	<b>Serious Adverse Event Report Form</b>	Revision #: 0
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Serious Criteria (check all that apply)
<input type="checkbox"/> Life-threatening (immediate risk of death)
<input type="checkbox"/> Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
<input type="checkbox"/> Congenital anomaly/birth defect
<input type="checkbox"/> Important Medical Event
Adverse Event of Special Interest (AESI)
<input type="checkbox"/> Reporting required per protocol

- In the section below, list all study interventions that are part of the IND, and commercial products being used to test the research hypothesis:

Study Interventions:		Actual Dose Given Prior to SAE:	Diagnosis for Use:	Route:
Intervention # <span style="background-color: yellow;">#</span> Name: Type the name of the intervention		Enter Dose	Click here to enter text	Select
First dose:	Last dose (prior to SAE):	Frequency:	Action Taken:	
(dd-mmm-yy)	(dd-mmm-yy)	Click here to enter frequency	Select Action	Comment, if "other"

To add more rows: click anywhere inside the table and then on the  sign on the bottom right of the table. Added rows cannot be deleted

- Has dosing for study intervention(s) been Modified or Interrupted previously because of an AE or SAE for this Patient in this clinical trial?

Yes     No

If Yes, describe:

Click here to enter text.

- In the section below, provide adverse event information:

Adverse Event	
Date of Event Onset:	(dd-mmm-yy)
Date PI Notified of Event:	(dd-mmm-yy)

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		Effective Date: TBD

<b>Adverse Event</b>	
Outcome of event: <a href="#">Select Outcome</a>	If resolved, provide date of resolution: (dd-mmm-yy)

- Provide CTCAE Term for Serious Adverse Event/AESI:

Event Term # 1	Grade:	Attribution To:	
<a href="#">Click here to enter text</a>	(Select)	Intervention #1	Select attribution
		Intervention #2	Select attribution
		Intervention #3	Select attribution
		Intervention #4	Select attribution
		Intervention #5	Select attribution
		Other: <a href="#">Click here to enter text.</a>	<a href="#">Click here to enter text</a>

To add more rows: click anywhere inside the table and then on the  sign on the bottom right of the table. Added rows cannot be deleted

- In the section below, provide specified information:

<b>Description of SAE:</b>
<p><b>IMPORTANT - Include the following in the SAE Summary Description:</b></p> <ul style="list-style-type: none"> <li>• Chronological summary of the clinical course of the SAE including any evaluation(s), treatment(s) and events that confound/contribute to the SAE including clinical information during this clinical trial that is relevant for the assessment of this SAE.</li> <li>• Medical history, oncological history and treatment(s), comorbidities, and any medical event that led to dosage reduction and/or hold</li> <li>• Alternate etiologies- must provide if event judged not related to study intervention(s)</li> </ul>
<p><b>From the 'Description of Events' drop-down pick list:</b></p> <ul style="list-style-type: none"> <li>• Select <u>Initial Description of Events</u> for an <u>Initial Report</u>; or</li> <li>• Select <u>Follow up # Description of Events</u> for a <u>Follow up Report</u>.</li> </ul> <p><a href="#">Click here for 'Description of Events' drop-down pick list</a></p>
Provide SAE Summary Description: <a href="#">Click here to enter text.</a>

To add more rows: click anywhere inside the table and then on the  sign on the bottom right of the table. Added rows cannot be deleted

	Office of Sponsor and Regulatory Oversight	Document #: F01-301-S01
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- What diagnostic testing was performed as part of the evaluation of this SAE?

<b>Describe Below. Provide copy of Diagnostic Report(s), Redact all Personal Identifiers, Label Report(s) with Protocol # and Protocol</b>
Click here to enter text.

<b>Reporter Information</b>	
Last name, First name	Text
Credential/Title	Text
CCR Branch	Text
Email address	Text
Phone number	Text

<b>Principal Investigator Name:</b> Click here to enter text.	<b>PI Phone #:</b> Click here to enter text.
<b>Principal Investigator Signature:</b>	
<div style="border: 1px solid black; height: 100px; width: 100%; position: relative;"> <span style="position: absolute; top: 50%; left: 50%; transform: translate(-50%, -50%); font-size: 2em;">X</span> </div>	
<i>Right click in the signature box above and select "Sign" to e-sign. NOTE: the form <b>will not</b> be able to be modified after signature.</i>	