UPDATES

The Revised Common Rule
Informed Consent Process Policy
Age & Identity Verification Policy
Delegation of Duties Policy
Clinical Quality Management Plan Policy

National Institute of Allergy and Infectious Diseases

45 CFR 46 Subpart A – Basic HHS Policy
for Protection of Human Research Subjects

The Revised Common Rule: Key Changes

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Jui Shah, PhD
Chief, ProPEP
OPCRO, DAIDS

Revisions Affect 3 Key Areas

A. Informed Consents

B. IRBs

C. Other Significant Changes

A: Changes to the Informed Consents - 1

1. New Requirements – Key Information

Concise and focused presentation of key information needed by a "reasonable person" to decide on participation.

2. For research involving collection of identifiable biospecimens or identifiable private information (IPI) for future use:

Identifiers may be removed and deidentified specimens or information used for future research.

OR

IPI or biospecimens will not be used for future research, even if identifiers are removed.

A: Changes to the Informed Consents - 2

Additional Elements (include when relevant):

1. Whether biospecimens will be used for commercial profit (and whether the participant will share in any profit);
2. Whether clinically relevant research results will be disclosed to participants; and
3. Whether research involving biospecimens may include whole genome sequencing.

A: Changes to the Informed Consents - 3

<u>New option[$] for a separate "Broad Consent"*:</u>

For storage, maintenance and secondary/future research using collected identifiable private information and identifiable biospecimens.

[$] If you chose not to include information in the General consent

* This is an alternative to language in blue on the previous 2 slides

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B: Changes Affecting IRBs

- Revised definition of “research” removes certain activities such as public service programs;
- Elimination of IRB review of grant applications and other funding proposals; and
- Elimination of continuing annual review for studies that are either minimal risk studies* (initial IRB approval still required) or have reached a minimal risk stage. Minimal risk determination made by the IRB.

*FDA (21 CFR Parts 50 and 56) and OHRP requirements are no longer harmonized, therefore, when both sets of rules apply, the more stringent requirements must be used. For IND studies, continuing annual review is still required. FDA Guidance

*Additionally, ICH E6(R2) 3.1.4 continuing annual review is still required.

* And for international sites, local RA/IRB/EC rules apply.

C: Other Significant Changes

- One IRB-approved version of a consent form used to enroll participants must be posted to a publicly available federal website (e.g., clinicaltrials.gov or regulations.gov) after study enrollment is complete.

- Multi-institutional research studies at US sites will be required to use a single IRB (sIRB) starting on January 20, 2020 (implementation date differs from NIH's and is not related to funding cycle).

- New and revised definitions: Research, Human Subject, Written/in writing…

If a Site chooses to Transition an on-going study…

- Institutional (not Sponsor) Decision: Therefore, for a multi-site study, some institutions may choose to transition to the revised Common Rule while others may not. Caveats: Bullets 2 & 3

- Once an institution has transitioned a study, study cannot revert.

- Transition to revised Common Rule has to be a full transition, meaning:
  - ICF must comply with revised Common Rule;
  - Post an IRB-approved ICF used to enroll participants; and
  - sIRB review requirement will apply in 2020 for US sites for studies that need continuing review.

How compliance with the new regulation is being implemented by DAIDS

- Updating DAIDS ICF templates for compliance
- Reviewing protocol specific ICs for compliance at Scientific Review Committee and full Regulatory reviews
- Notifying external stakeholders:
  - Network meeting presentations
  - Via HANC
  - Share memo with additional information to Network leadership

Revised Common Rule
OHRP QnA on revised Common Rule

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DAIDS Informed Consent Process Policy Update

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Protection of Participants, Evaluation, and Policy Branch (ProPEP)

2019 DAIDS Network Meetings

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Informed Consent Process Policy

- **Purpose:** Describe the requirements for the:
  - Development & implementation of ICFs
  - Documentation of informed consent
  - Informed consent (IC) process

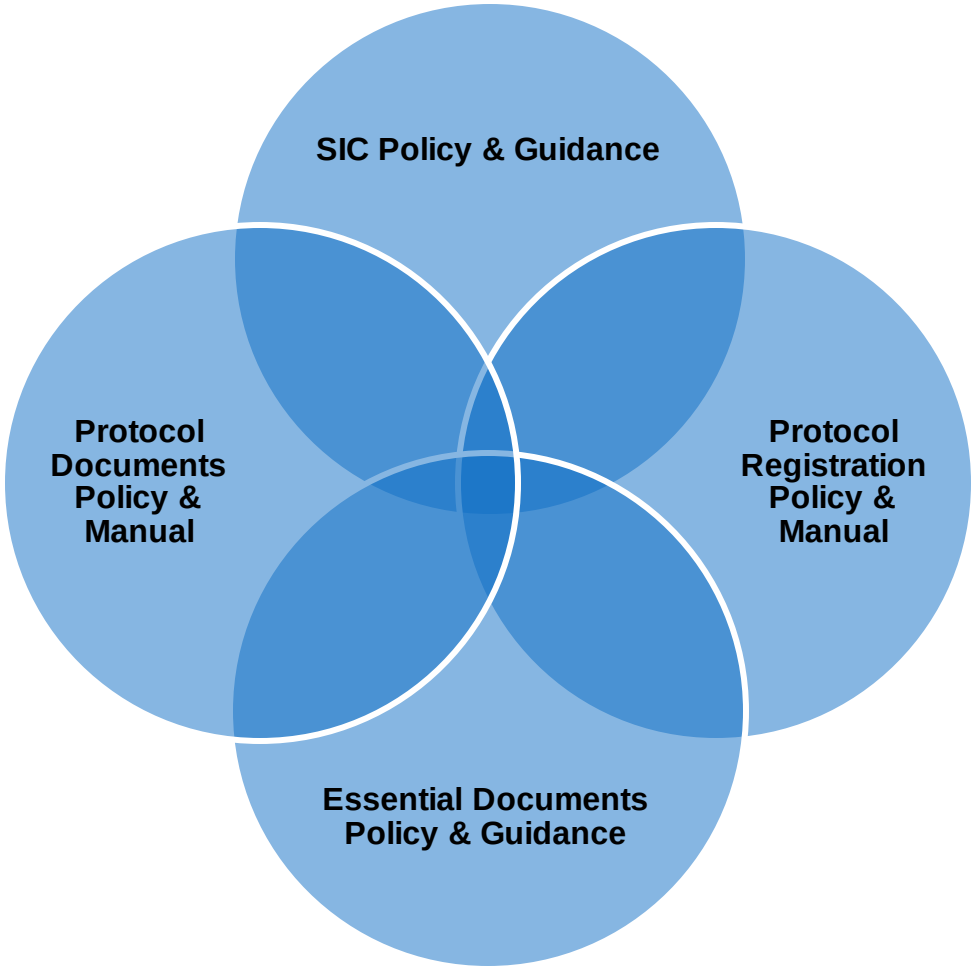
- **Scope:** Applies to all NIAID (DAIDS)-supported and/or-sponsored clinical research involving human subjects/participants

***Note*:** Will replace the 2007 Policy - "Requirements for Informed Consent Development"

Updated the 2007 Policy to:

- Addresses the 2018 Common Rule changes (45 CFR 46) and ICH E6(R2) guidelines
- Focuses more on the IC process & documentation
- Outlines stakeholder roles & responsibilities
- "Codifies" elements in DAIDS Memos (RSC website):
  - 2017 - "New DAIDS Requirements: Informed Consent Process
  - 2018 - "Timing of consent and re-consent with updated IRB/EC/RE-approved informed consent forms"
- Provides a companion guidance document (draft) that addresses:
  - Best practices
  - Other informed consent considerations

Intersection of Related Policies & Manuals/ Guidance Documents



Informed Consent Form Highlights:

- Compliance with:
  - Revised Common Rule (45 CFR 46)
  - ICH E6(R2)
  - NIH/DAIDS policies & other U.S./local regulations/guidance
    - ✓ ClinicalTrials.gov & related NIH Policy
    - ✓ Genomic Data Sharing (GDS)
    - ✓ Certificates of Confidentiality
    - ✓ Genetic Information Nondiscrimination Act (GINA)
    - ✓ Clinical Trials Insurance (CTI) - when an in-country requirement

  Note: The more stringent law, regulation, guidance, and/or policies must be followed

- Focus on information that may impact a participant's willingness to join/continue in the study

- Considerations include:
  - Mandated concepts, not mandated language - ICF info matches protocol
  - IRB/EC/RE/RA approval of protocol/sample/site ICFs prior to use
  - Separate ICF for stored samples – Optional Broad Consent/Tiered ICF

Informed Consent Process Highlights:

- Requirement: Site IC process SOP & Vulnerable participants
- Oversight of the IC process
  - Investigator/IoR:
    - ✓ Ensures an adequate IC process
    - ✓ Retains overall responsibility
  - Consent may be delegated
    - ✓ If permitted by local, state, in-county regulation, laws, guidance, and institutional policies
    - ✓ If staff are qualified by education, experience, training, & knowledge of the trial
    - ✓ If staff are listed on the DoD Log – see DAIDS policy
- Documentation of the IC process – in the participant's record
  - Includes info about Investigator's/IoR's availability
  - Describes special procedures – e.g., impartial witness, translator, staff present, etc.

Informed Consent Process Highlights Continued:

New Information/Re-Consent – Information impacting participant's decision to join/remain in the study

- IRB/EC determines how participant's are informed & the need for re-consent
- Revised ICF(s) reviewed and approved by the IRB/EC
  - Used to consent new participants
  - Implemented ASAP
    - ✓ No later than 5 days after receipt from the IRB/EC
    - ✓ Timeline starts the day after receipt

Informed Consent Form & Process Guidance Document (draft)

- Will provide more detailed guidance:
  - Development and implementation of ICFs
  - Documentation of informed consent
  - Informed consent process issues
- Will include information about IC considerations & best practices
  - Other regulations/policies impacting ICFs & the IC process
  - Risks including risks related to study participation
  - DAIDS IC process issues (e.g., re-consent, vulnerable populations)
  - Stored samples & incidental findings/IRRs
- Will include references for protocol & site-specific ICF development
- Will include tools/guidance for ICF development – Updated DAIDS ICF templates
  - General Use
  - Stored Samples with Tiers
  - Broad Consent

So, what are the….

- Addressed stakeholder comments from Fall 2018
- Finalizing policy – under internal review (QMS)

DRAFT AGE & IDENTITY VERIFICATION POLICY

Jess Landis, BS
Lyndi Lahl, RN, MS

Outline

- Background
- Outreach
- Policy Summary
- Timeline and Implementation

Recent Site Findings and DAIDS Response

Findings:

1. Procedure to determine and verify participant age not robust (ICH 5.1.3 and 5.18.4)
2. Insufficient procedure to verify identity (ICH 5.1.3 and 5.18.4)

DAIDS Responses:

1. DAIDS will develop a policy that requires sites to have robust SOP(s) for:
   - Determining and verifying participant age prior to enrollment
   - Verifying a participant's identity prior to enrollment *and* for all subsequent visits
2. All sites must submit their new/revised SOP(s) for DAIDS review and approval

Outreach

- Targeted Site Survey – June 2018
- Public Comment Period – August – Sept 2018
- HIPAA Expert/ FAQ – February 2019
- Targeted Site Calls (10) - February – April 2019
- CAB/Community Calls (3) – April - May 2019

Targeted Site Call Results

- Included 50 sites in 20 countries
- Most participants at most international sites will have ID with name, photo, and DOB
- Many internationals sites already require ID to allow enrollment and use community employees to help disseminate information
- A higher number of concerns reported at US sites, with ID checks being less prevalent
- Difference seen in the experience between hospital/clinic affiliated sites and stand alone research sites

Policy Summary: Age and Identity Verification

- Each CRS will develop one or more robust SOPs that describe how the CRS will verify participant age and identity and will submit to DAIDS for approval

- DAIDS will review and approve the initial CRS SOP(s)

Initial Identity and Age Verification

- Participants show a document to include photo*, name and date of birth. Documents current or expired no greater than 10 years
- Participant name and age/DOB self-report allowed under certain limited circumstances

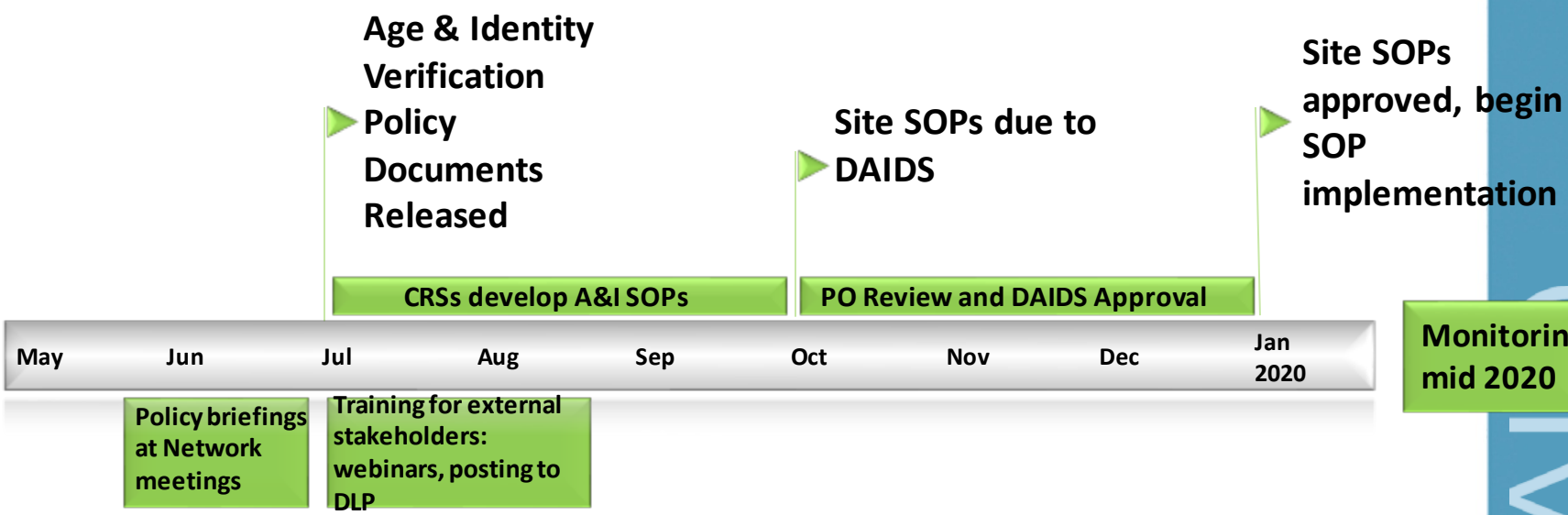
** When an ID with a photo is not available, participant may be enrolled, but the site must take a photo for the site files or create a site ID/biometric for verification at subsequent visits*

Subsequent Visit Identity Verification

At *all* subsequent visits, the site verifies the participants identity by:

- Participant showing document with name and photo *or*
- Using an ID or ID process established at the initial/previous visit, such as
  - Biometric scan
  - Site created ID with photo
  - Photo taken and stored on site

Timeline


Age & Identity Verification Policy Documents Released
Site SOPs due to DAIDS
Site SOPs approved, begin SOP implementation
CRSs develop A&I SOPs
PO Review and DAIDS Approval
May
Jun
Jul
Aug
Sep
Oct
Nov
Dec
Jan 2020
Monitoring: mid 2020
Policy briefings at Network meetings
Training for external stakeholders: webinars, posting to DLP

Other Resources

- FAQs
  - General Age & Identity Policy
  - HIPAA
  - Participant
- Webinars – Review of policy requirements and resources for SOP development (July)
  - Will be recorded and posted to the DAIDS Learning Portal
- POs – Questions can be directed to your DAIDS POs

Implementation

- Policy is flexible and inclusive on what kinds of identification are accepted – work with your PO if you have questions about specific situations
- Messaging will be important during the roll out of new policy and SOP requirements to community
- Participant safety and study integrity are the core reasons for the policy implementation
- After implementation of SOPs, please keep your PO informed about any issues or concerns that arise

Working Group Members

- Lyndi Lahl (ProPEP)
- Jess Landis, Gregg Roby, Eileen Pouliot, Donna Germuga, Odav Jallah (OCSO)
- Mary Allen, Edith Swann (VRP/VCRB)
- Roberta Black (PSP/CMRB)
- Leonard Sowah (TRP/CCRB)
- Renee Browning (PSP/MAPRB)
- Wairimu Chege (PSP/CPRB)

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Division of AIDS Delegation of Duties Log

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Janet O'Brien, MPH
Office for Policy in Clinical Research Operations Division of AIDS

TIMELINE

13 July 2018
First round of public comments

8 August 2018
Second round of public comments

10 September 2018
End of public comment period

4 March 2019
Release of DAIDS DoD Policy, Log, Instructions, and Implementation Memo

IMPLEMENTATION

Studies that have not been opened at the clinical research site:

- Research studies initiated at the clinical research site on or after 14 March 2019, establish a study specific DOD log using the DAIDS DoD Log Template.

Ongoing studies listed in memo:

- Clinical research sites have until 14 June 2019 to establish their DAIDS DoD Log.

Ongoing studies not listed in memo:

- Continue to use already-established research study-specific DoD Logs. If a site has studies that do not have a research study-specific DoD Log, establish and maintain a research study-specific DoD Log using the DAIDS DoD Log Template for these studies.

FREQUENTLY ASKED QUESTIONS (FAQs)

Q:Can the DAIDS DoD template be fillable?

- A:Yes, the DAIDS DoD template has been modified and includes “fillable” fields.

Q:What happens if we need extra pages?

- A: Division of AIDS Clinical Research Policies and Standard Procedures Documents for additional pages: DOD Template (Staff Information Additional Lines Fillable) and DOD Template (Research Related Duties Additional Lines Fillable)

FREQUENTLY ASKED QUESTIONS (FAQs)

Q:What study roles should be listed? Should all roles be included, or do certain roles supersede others? Ex. for a nurse that is a study coordinator and sub-investigator, should both or only one be listed?

- A: By definition, delegation of duties is entrusting someone else to do parts of your job. In clinical research, this means investigators can delegate study-related tasks to their staff members to perform on their behalves, but they never relinquish responsibility for those tasks and their outcomes. .Individuals that are delegated by the investigator to perform significant study-specific activities as determined by the protocol must be listed on the DoD log.

FREQUENTLY ASKED QUESTIONS (FAQs)

Q: My site's study specific DoD Log has all the elements included in the DAIDS DoD template. Can I continue to use the site's DoD Log?

- A: Yes, for current ongoing studies including ongoing studies listed in the DAIDS Memo IF they contain all the required elements. New studies need to use the DAIDS DoD Log.

Q: To avoid confusion, can we use the format of DD/MMM/YYYY or is the dating format set as referenced?

- A: As long as the dating format is kept consistent to (day/month/year), the form allows you to type it as (DD/MMM/YYYYY) or (DD/MM/YYYY). The site can use either of the two formats as long as it's clear for monitors.

FREQUENTLY ASKED QUESTIONS (FAQs)

Q:When the site transitions to the DAIDS DoD template, would they indicate an 'end date' on the current site DoD log for each delegated task, and include that same date as the 'start date' on the DAIDS DoD log?

- A: Sites need to close out their current DoD log by entering the current date in the end date column. The DAIDS DoD log should be filled out listing current staff and their delegated duty(ies), and be updated, with applicable with new staff delegations; the start date for the current staff delegated duties should be entered with the same date as entered in the old log's end date.

FREQUENTLY ASKED QUESTIONS (FAQs)

- Q: Item 22 on Delegation Log Template - Study Product Management? What exactly does "management" mean? Does this just apply to the pharmacist? Does this also include the study coordinator receiving returned drug from the subject?

  - A: The term Study Product Management was chosen based on feedback from our external stakeholders. The category is broad to make it easier to include different responsibilities. If the term is confusing or sites prefer different categories, please use the "Other" sections to add more categories.

FREQUENTLY ASKED QUESTIONS (FAQs)

For studies listed on the DAIDS memo:

Q: The study listed in the memo is closed. Do I need to go back and transfer everything to the new DAIDS DoD Log?

- A: No

Q: The study's data will be locked prior to 14 June 2019. Does my site need to transfer to new DAIDS DoD Log?

- A: No

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DAIDS Clinical Research Policies in Development/being Updated

- Age and Identity Verification*
- Co-Enrollment Prevention*
- Emergency Unblinding*
- Requirements for Informed Consent Development
- Essential Documents
- Study Progress, Data Quality, and Safety Monitoring Plans
- Electronic Information System
- Requirements for DAIDS Laboratories
- Requirements for Pharmacy Activities, Personnel and Facilities
- Clinical Quality Management Plans
- Requirements for On-Site Monitoring
- Human Subjects Protection (HSP) and Good Clinical Practice (GCP) Training Requirements
- Enrolling Children (including Adolescents) in Clinical Research: Clinical Research Site Requirements & Protocol Document Requirements and Appendices
- Use of Drug Products Not Marketed in the United States

(*=*new policy)*

QUESTIONS

- Network clinical research sites, contact your OCSO Program Officer.
- Non-network sites, contact your Program Officer.
- For policy related questions contact NIAIDOPCROProPEP@mail.nih.gov.

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Requirements for Clinical Quality Management Plans (CQMP) Policy

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NIAID

Objectives

- To provide the status and highlight the changes of the DAIDS required CQMP policy
  - *Updated Participant Chart Review Tool*
  - *Updated Protocol Regulatory File Review Tool*
  - *Revised CQMP CRS Quality Assurance Summary Report*

CQMP Policy – Purpose

- To describe minimum requirements
- To ensure participant rights and safety
- To ensure accurate and complete data
- To ensure a state of audit readiness
- To ensure compliance with sponsor and applicable regulatory requirements

Background of the DAIDS CQMP Policy

- In additional to monitoring, QM is a component of sponsor oversight responsibility, as emphasized by ICH E6R2.
- As a result, per the DAIDS Policy, sites must have a CQMP in place and submit a QA Summary Report biannually to their OCSO PO.
  - As DAIDS continued to acquire feedback from various stakeholders, sites have not been required to submit the QA Summary Report since 2016.
  - A pilot of a revised template was conducted in 2017
- During the review of the piloted QA Summary Report template in 2017, an OCSO MOB Process Audit occurred.

Results of the OCSO MOB Process Audit

Major Finding: Inadequate QA/QC records

- *"The new QA Summary Report template is not protocol specific, the protocols evaluated are listed on the first page but the data is not presented per protocol."*

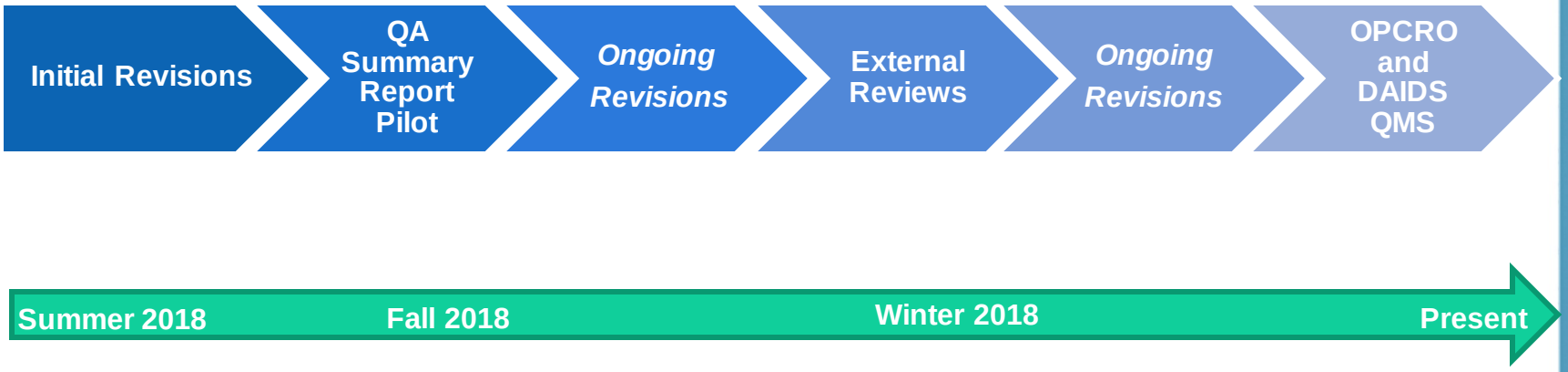
International Council on Harmonization Guidelines (ICH) E6 R2

- *E6(R2)-5.1.1: "The sponsor is responsible for implementing and maintaining quality assurance and quality control systems with written SOPs to ensure that trials are conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirement(s)."*

Recommendation

- *"The new QA Summary Report template should be protocol specific, all regulations are written for individual protocols, therefore it is important that OCSO designs their new tools and systems to go to the granularity of the protocol."*

Addressing Audit Findings: The Review Process



CQMP Policy: Current vs. New

Current CQMP Policy

- PI, CTU, and Non-Network Site stated responsibilities
- 10 Key indicators
- QA Regulatory File and QA Participant Chart Review Tools
- Required template: CRS QA Summary Report
- Compulsory DAIDS review of CRS QA Summary Report

New CQMP Policy

- DAIDS responsibilities clearly outlined
- 11 Key indicators
- Updated regulatory file and participant chart file review tools
- Revised Required CRS QA Summary Report template
- DAIDS periodic review of QM activities

CRS QA Summary Report Highlights

- **Captures protocols and associated PIDs reviewed from each protocol**
  - No more than 5 protocols reported; must be associated with reported PIDs
    - Protocols reviewed should be rotated with each submission
    - At DAIDS discretion, certain protocols can be requested for inclusion in submission of QA Summary Reports
  - No more than 20 PIDs to be included in the submission of report

CRS Quality Assurance Summary Report

Bethesda, MD USA

Standard Operating Procedure

Appendix III DAIDS Clinical Quality Management Plan (CQMP) Clinical Research Site (CRS) Quality Assurance (QA) Summary Report

Effective Date: Document No.: APP-A28-QCS-003.00

1. Summary of Protocols Reviewed

Complete only for protocols associated with PIDs for which chart review was conducted during this review period. Please report no more than five (5) protocols, even though your QA review may have included more than five (5). Please rotate protocols reviewed with each submission to account for all the protocols at the site.

At DAIDS discretion, certain protocols can be requested for inclusion in submission of QA Summary reports.

Protocol	**Total Number of PIDs Enrolled** *(at the time of completion of this document)*	**Number of PIDs QA Reviewed** *(during this review period)*	**Percent of PIDs QA Reviewed**
Example: Protocol XXXX	*100*	*13*	*(13/100) = 13%*
Example: Protocol YYYY	*150*	*15*	*(15/150) = 10%*

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CRS Quality Assurance Summary Report

3. Summary of Key Indicators (KIs) and Number of Associated Findings

These are the Key Indicators (KI) required in the DAIDS CQMP Policy to be used for QA review. You may add additional site-chosen KIs in the blank cells, if applicable.

Please note that if there was a review of a KI that yielded no findings, a zero (0) should be placed in that cell. However, if a KI was not applicable during this review period, an "N/A" should be placed in that cell. *For example: If there were informed consents conducted during this review period resulting in no findings, then a "0" should be noted. However, if there were no informed consents conducted during this review period, then "N/A" should be noted.*

For determining the number of findings, please note that one KI deficiency may have more than one (1) associated criteria applicable to a PID. Each criterion should then be counted as one (1) finding. *For example: A PID has an ICF with 2 errors (no signature from PI and version used was obsolete), this will count as 2 findings for that protocol in the ICF Key Indicator (KI) row.*

Please list the protocol number in the line provided under "protocol."

Insert rows for additional site-chosen KIs as needed.

Key Indicator(s)	Number of Findings (per protocol)				
	Protocol _____	Protocol _____	Protocol _____	Protocol _____	Protocol _____
Informed Consent Form (ICF) and Process *(initial or subsequent)*					
Assessment of Understanding of ICF as applicable					
Eligibility Criteria and Process *(as stated in the protocol)*					

CRS Quality Assurance Summary Report

DAIDS
Bethesda, MD USA

Standard Operating Procedure
Appendix III DAIDS Clinical Quality Management Plan (CQMP) Clinical Research Site (CRS) Quality Assurance (QA) Summary Report

Effective Date: Document No.: **APP-A28-OCS-003.00**

4. Summary of deficient Key Indicators (KIs) and associated Criteria

Please elaborate on key indicators from the previous section that were deficient in this section. Please report Key Indicator findings in no more than five (5) protocols, and please report no more than 20 PIDs with findings associated with those five protocols. When choosing which PIDs to report, focus on choosing as many different identified deficient KI's as possible.

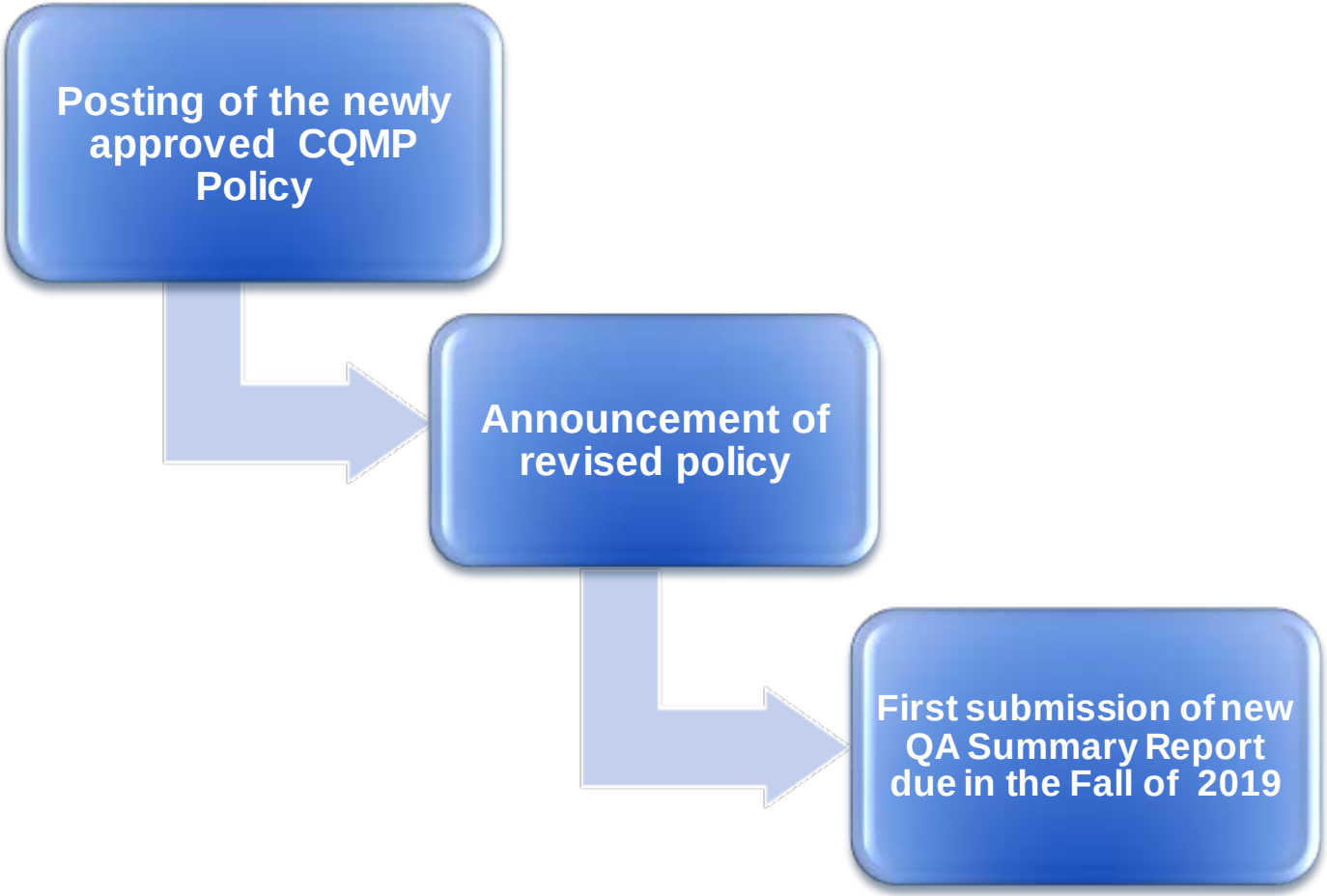
List one Key Indicator Finding per line for each PID. Capture the criteria associated with the deficient KI. ***Use short and concise statements.***

- If there are more than 1 criteria per key indicator, capture all associated criteria in one cell. For examples of some criteria, refer to the chart review tool.
- If a PID has more than one deficient KI, please list each KI on separate rows. Please note that if there are more than one KI per PID, this will still count as one PID towards the 20 PID requirement.

List all corrective and preventative actions (CAPA's) associated with each different criterion. If a CAPA was not performed for a KI finding, list "N/A" under the Corrective Actions column and provide a comment if necessary. ***Use short and concise statements.*** (See example in first row)

PID # (list only 1 PID per line)	**Protocol #**	**Deficient Key Indicator(s)**	**Criteria Associated with Deficient KIs**	**Describe Corrective Actions Implemented**	**Describe Preventative Actions Implemented**
123456	*A1000*	*Informed Consent*	*1. Informed consent process not documented in source* *2. Participant was not offered copy of signed ICF*	*1. Note to File documented by appropriate site staff added in chart* *2. Participant was called, asked to return to clinic, and offered a copy.*	*Revise informed consent (IC) checklist to include review of IC requirements including proper documentation prior to participant departure from clinic.* **This preventative action plan applies to both criteria associated with the deficient KI.*

What's Next?


Posting of the newly approved CQMP Policy
Announcement of revised policy
First submission of new QA Summary Report due in the Fall of 2019

Questions

Please contact your OCSO Program Officer