New DAIDS Requirement: Protocol Signature Page

Request for Feedback

Manizhe Payton, MPH
Director
Office of Clinical Site Oversight
Division of AIDS

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Background

- European Medicines Agency (EMA) inspected 2 clinical research sites in May and July 2017 for P1093
- The inspections supported the December, 2016 GSK/ViiV Marketing Authorization Application (MAA) variation for use of dolutegravir in ≥6 year olds to <12 year olds
- Inspected sites:
  - Chiang Mai University Treatment CRS
  - Shandukani CRS

Major Inspection Finding (MA2)

"*The study specific contract was signed more than 2 years after the start of the trial at the site, so there was no commitment to perform the trial according to a specific protocol and no financial agreement covering the trial until then*."

Reference: ICH GCP 4.5.1, 5.6.3

- ICH/GCP 4.5.1 "*The investigator/institution should conduct the trial in compliance with the protocol agreed to by the sponsor and, if required, by the regulatory authority(ies), and which was given approval/favorable opinion by the IRB/IEC. The investigator/institution and the sponsor should sign the protocol, or an alternative contract, to confirm their agreement*"

Reference: ICH GCP 4.5.1, 5.6.3

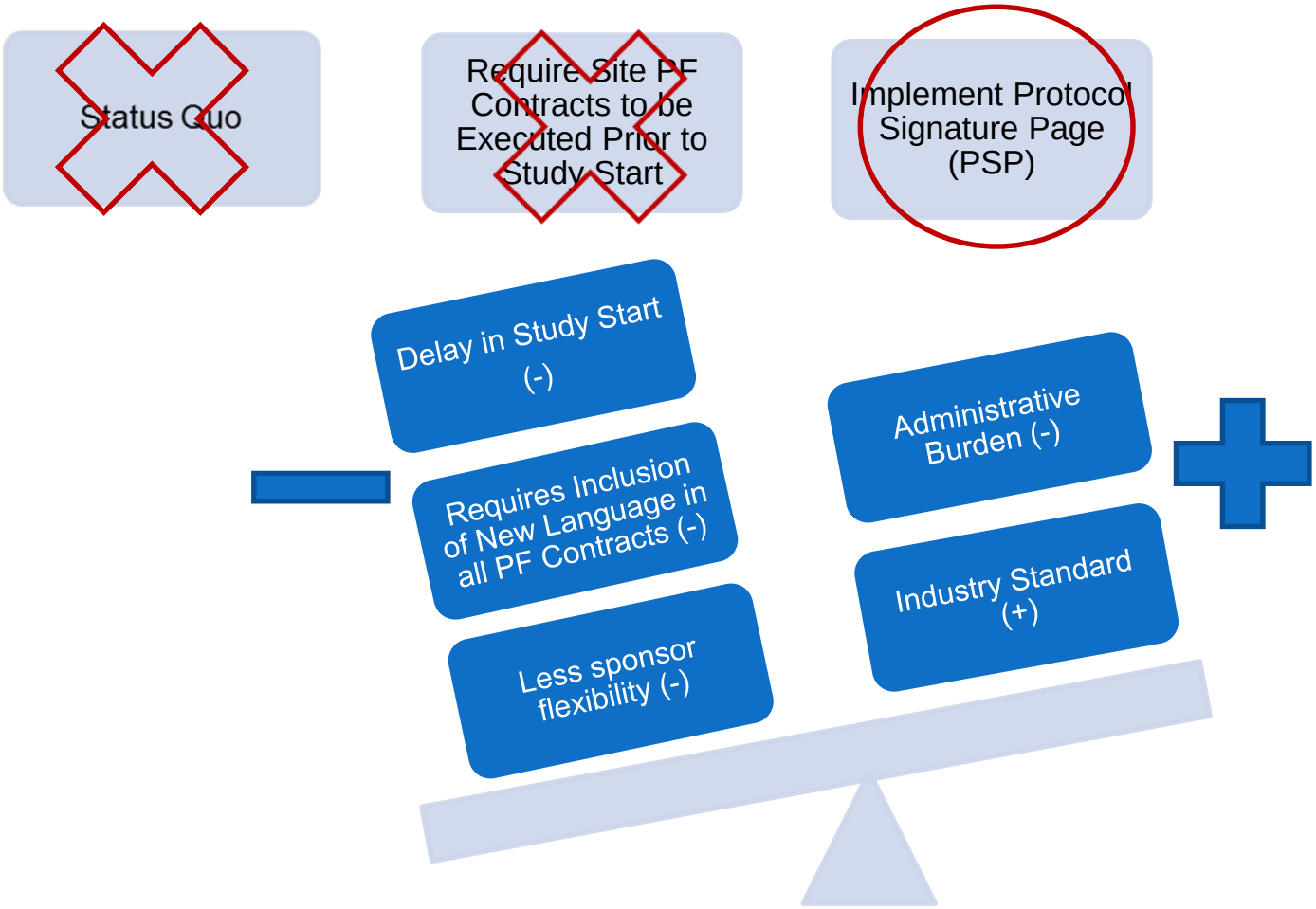
- ICH/GCP 5.6.3 "*The sponsor should obtain the investigator's/institution's agreement:*
  - *To conduct the trial in compliance with GCP, with the applicable regulatory requirement(s), and with the protocol agreed to by the sponsor and given approval/favorable opinion by the IRB/IEC;*
  - *To comply with procedures for data recording/reporting; and*
  - *To permit monitoring, auditing, and inspection (see section 4.1.4)*
  - *To retain the essential documents that should be in the investigator/institution files (see section 8) until the sponsor informs the investigator/institution…*
- *The sponsor and the investigator/institution should sign the protocol, or an alternative document, to confirm this agreement*"

DAIDS Response to EMA Finding MA2

DAIDS Response: "*1572 captures investigator commitment to perform trial in accordance with protocol, and applicable US Code of Federal Regulations. In addition, CTU Terms of Award commits investigator to comply with protocol, and applicable regulatory requirements.*"

EMA Response: "*When drawing up a contract for the conduct of a clinical trial it should specify the protocol version agreed upon. At the same time it is necessary to specify the deliverable from both sides when conducting the trial. The agreement must be signed before the start of conduct. Non-study specific research grants or signed FDA forms (only applicable to US FDA) cannot replace a study specific contract*."

Recommendation to Address Finding



Proposed Protocol Signature Page (PSP) Language

The signature below constitutes approval of this study in full accordance with the provisions of this protocol and the attachments. I agree to conduct this study in compliance with the protocol, in-country and local regulatory requirements, applicable United States (US) Code of Federal Regulations (CFR) and ICH Good Clinical Practices (E6).

_____ _____

Signature of Investigator **Date**

(Month/Day/Year)

_____

Name of Investigator (PRINT NAME)

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Operational Considerations

- **Scope:**
  - Applies to all full version protocols and LOAs
    - Networks to revise protocol/LOA templates to include a PSP if not already in place
  - Also applies to all ongoing protocols that currently do not include a PSP
    - Ongoing protocols defined as protocols with participant visits still ongoing as of August 1, 2017
- **Ongoing Protocols:**
  - Network memo format will satisfy this requirement instead of revising protocol to include PSP
  - Include PSP in next version of protocol or LOA (if applicable)

Signature Authority

- The IOR must sign the PSP
- This responsibility may not be delegated
- Investigator Turnover
  - New investigators must sign PSP for current version of protocol (or LOA) in effect at time of investigator turnover

Tracking of Protocol Signature Pages (Sponsor)

- PSPs must be uploaded into Protocol Registration Module (PROREG) of N-CRMS
  - For all new and ongoing studies
  - For ongoing studies that already include a PSP:
    - These may be batched and sent to PROREG by Network if PSPs are maintained at Network
    - Otherwise, sites will be required to upload to PROREG
  - Regulatory Support Center (RSC) will be following up with sites to collect missing PSPs
- PSP will be a required document for Protocol Activation

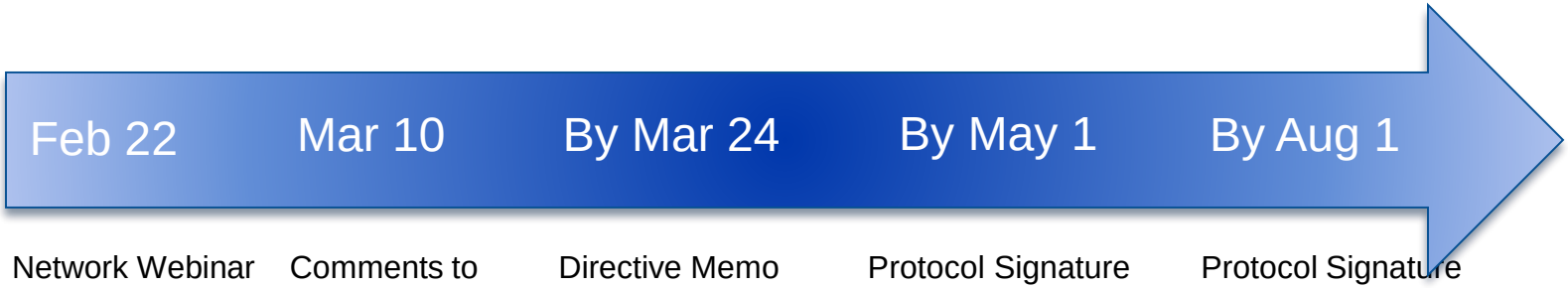
Tracking of Protocol Signature Pages (Site)

- Original PSP(s) maintained in site's regulatory binder

Codifying PSP Requirement

- Revision to Essential Documents and Protocol Documents Policy
- Revision to Protocol Registration Manual
- Revision to Monitoring Templates and PPD work instructions

Proposed Implementation Timeline



Feb 22	Mar 10	By Mar 24	By May 1	By Aug 1
Network Webinar	Comments to DAIDS	Directive Memo to all Networks AND informational memo to all CTU/CRSs	Protocol Signature Pages in Place for all New Studies	Protocol Signature Pages Uploaded to PROREG for all Ongoing Studies

2017

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Your Input is Important

Please send comments by March 10th to:

paytonma@niaid.nih.gov

We are happy to have individual discussions with Networks to clarify requirements

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Coming Attractions…

Investigator Signature on Case Report Forms

Stay tuned!