I. **PROCEDURE**

A. Inspection Notification

FDA inspection notification may occur in person, via the telephone or mail (email, letter or delivery service).

The inspection may be one of three types:

- For cause
- Routine
- Follow-up (in response to a previous for cause inspection)

The study team member who is notified of the inspection should obtain the following information from the FDA contact:

- Name, phone, email, and title(s) for the FDA Inspector(s)
- Inspection type (for cause, routine or follow-up)
- The name(s) of the trial(s) to be inspected
- Inspection start date, arrival time and anticipated duration (if known)
- Any specific documents the FDA requests to be available for inspection and the reason requested, if known
- The study team members the FDA requests to be available during the inspection, and when they need to be available

B. Study Team Inspection Preparation

1. Immediately after inspection notification, a study team member should obtain and start completing the Children’s National Food and Drug Administration Inspection Preparation Guide and Checklist. This document can be found on the IRBear Home page under General Information/Guidance Documents/Miscellaneous Documents: [https://irbear.org/eResearch/Rooms/DisplayPages/LayoutInitial?Container=com.webridge.entity.Entity%5BOID%5B6EC3123F8FCBA840AA271EFF22C92D8E%5D%5D](https://irbear.org/eResearch/Rooms/DisplayPages/LayoutInitial?Container=com.webridge.entity.Entity%5BOID%5B6EC3123F8FCBA840AA271EFF22C92D8E%5D%5D)

2. The following entities should be immediately notified of the FDA inspection (names and contact information are on the Preparation Guide and Checklist):

- Principal Investigator
- Director of Accreditation and Licensure, Regulatory Affairs
- Executive Director of Research Administration
- Clinical Research Quality Assurance Program Lead
- Director of Research Regulatory Affairs
- Research Counsel Senior Associate
- Investigational Drug Service (IDS) Pharmacy Manager
- Chief Research Officer
- Division Chief or Research Center Director of the PI being inspected
- Study Sponsor
3. The following stakeholders should also be notified in a timely manner of the inspection:
   - Institutional Review Board (IRB) of record (if not Children’s National IRB)
   - Other study team members
   - Medical Records
   - Information Technology (IT) to request inspector electronic medical record access
   - Study database manager for eCRF access
   - All clinical and research laboratories used in the study
   - Engineering for temperature control, area access and equipment calibration documentation
   - Security, so they will know that federal inspectors will be on campus

4. The study team should choose persons to fill the following Children’s National Inspection Team roles:
   - Inspection Lead
     - Usually the PI or an experienced lead study coordinator
     - Leads the inspection process by serving as the direct interface with the inspector(s), subject matter experts and other study team members
   - Inspection Preparation Coordinator
     - Completes inspection checklist
     - Coordinates inspection preparation activities, including study document quality assurance review
   - Scribe
     - Sits in the inspection room during the audit
     - Takes detailed notes of all conversations had with, and materials reviewed and copied by the FDA inspector(s) for the exhibit log
   - Runner
     - Travels between the inspection room (where the inspector[s], inspection preparation coordinator and scribe are) and the staging room (where ancillary study materials are) to retrieve materials requested by the inspector(s)
   - Back Room/Support Staff
     - Maintain and organize research documents
     - Retrieve and copy documents requested by the inspector(s) and runner
     - Starts and places documents in the exhibit log

5. Space should be reserved for inspection preparation and conduct. If the monitoring rooms on Floor 3.5 Main will be needed, contact the Clinical Research Quality Assurance Program Lead to reserve the space. The following details about the inspection room(s) should also be documented for study team reference:
   - Inspection room and phone number
   - Staging room and phone number
   - Office equipment in the inspection and staging rooms
   - Location of nearest photocopier and scanner

6. The following documents should be available and reviewed prior to the inspection, if possible. All documents should be made as complete and accurate as possible before the inspection:
   - Regulatory Binder: consult the International Counsel on Harmonization (ICH) E6, Good Clinical Practice Guideline and the Children’s National FDA Inspection Preparation Guide and Checklist for a detailed document list:
     - IRB submissions, communications and approvals/acknowledgements
     - Ancillary reviews (e.g. Radiation Safety Committee, Institutional Biosafety, IDS)
     - Study protocols/clarification memos
     - Investigational product information
     - Sponsor safety reports
     - Consent and assent documents
Data Safety and Monitoring (DSM/DSMB) reports

Forms FDA:
- 1571 (Investigational New Drug Application)—if a CNMS sponsor-investigator
- FDA Acknowledgement of Submission and May Proceed Letter (if issued)—if a CNMS sponsor-investigator
- 1572 (Statement of Investigator)
- 3454/3455 (Financial Disclosure)
- 3500/3500A (MedWatch)

Sponsor communications
- Study team credentials and training
- Staff Signature/Delegation of Authority Log
- Subject Master/Screening/Enrollment Log
  - Case histories for all consented participants (including screen failures)
  - IDS records for investigational product receipt, dispensing and return/destruction
  - Clinical and research laboratory records, to include clinical lab normals and credentialing; and sample labeling, storage, accountability and analyses
  - Equipment maintenance and calibration records
  - Environmental security and controls
  - Local Standard Operating Procedures (SOPs)

a. If any study documents are stored off site, contact the Children’s Research Institute (CRI) to obtain remotely stored files. A requisition number and any other subject or document identifiers will be needed to facilitate record retrieval. Allow at least 48 hours from the time of document request to the time of document delivery.

b. A list of all identified deficiencies and missing documentation should be created. The study team should immediately work towards correcting/resolving any issues that can be addressed before the inspection. Explanations for any deficiencies, especially those that can not be corrected, should be developed. As deficiencies are discovered, the team should keep in mind possible corrective and preventative action plans.

C. Inspection Conduct

1. Upon notification by Security that the inspector(s) have arrived, the Inspection Lead or Quality Assurance Program Lead should greet the inspector(s). Upon introductions, the designated greeter must ask for the FDA Inspector credentials. The inspector should provide identification badge/credentials and present a Form FDA 482, Notice of Inspection. The PI should meet the inspector and sign the Form FDA 482. Make a copy of the Form FDA 482 for the exhibit log. A study team member should document all information on the inspector’s identification badge/credentials, and place this information in the exhibit log.

2. Study Team Conduct During Inspection

   During the inspection it is important to be polite, courteous, honest, and non-confrontational with the FDA inspector(s). Tips for effectively communicating with FDA inspectors are:
   - Answer all questions directly.
   - Keep a log of all questions asked by the inspector(s).
   - Do not make up an answer or dodge a question if the answer is unknown. Let the inspector(s) know that the answer will be found.
   - The subject matter expert should address inspection questions.
   - If it is recognized that incorrect information was given to the inspector(s), provide the correct information as soon as possible.
   - Maintain a professional and business attitude.
   - Clarify questions before providing an answer.
   - Answers should be “short and sweet”—no elaboration.
   - Since inspectors often ask what a typical study visit is like, the study team should review the protocol before the inspection and develop a consistent study team response.
• Review and photocopy all documents before giving them to an inspector.
• Do not fill gaps in conversation. This can lead to confusion and supply the inspector(s) with unnecessary information.

D. Inspection Close Out Meeting, Form FDA 483 Site Response and Possible Inspection Outcomes

1. Inspection Close Out Meeting
   At the conclusion of the inspection the inspector(s) will hold a close out meeting. The Principal Investigator, Inspection Lead (if different from the PI) and Inspection Preparation Coordinator (at a minimum) should attend the close out meeting. A Form FDA 483 (Inspectional Observations) may be issued if the inspection revealed deficiencies.

2. Form FDA 483 Site Responses
   If the inspection results in a Form FDA 483, the Principal Investigator should work with Children’s Research Institute’s Legal Counsel to draft a response to the Form FDA 483. Response to the Form FDA 483 is not mandatory, but it is an industry standard. A response that documents and addresses each concern listed in the Form FDA 483 can go a long way towards preventing a Warning Letter, Clinical Hold, and/or other FDA action.

   Each Form FDA 483 observation AND instance, should assess and address the following:
   1) Is the finding factually accurate? If it is not, state this in the response.
      Example: The protocol requires an ECG at baseline. The Form FDA 483 says a baseline ECG was not done. A baseline ECG was done and is present in the medical record. Unfortunately, the ECG was not placed in the research record. In this instance, the Form FDA 483 finding is not factually accurate. A copy of the “missing” ECG and the study team explanation should be included in the Form FDA 483 response letter.
   2) Is the finding a regulatory violation? If it is not, state this in the response.
      Example: The words “must”, “may”, “shall” and “should” have different meanings per the FDA. If something labeled “should” was not done, it is not a regulatory violation.
   3) What is the significance of the finding on subject safety, rights and welfare? Does the finding impact data integrity? If the finding does not impact these key items, state this in the Form FDA 483 response.

   All Form FDA 483 responses should be reviewed by Children’s National Research Counsel before FDA submission. Please ensure Children’s National Research Counsel receives the Form FDA 483 response early enough to provide a complete review before the 15 day FDA response submission deadline.

3. Possible Inspection Outcomes
   For inspections with findings, the FDA will author an Establishment Inspection Report (EIR). The EIR and the study team’s Form FDA 483 response will be reviewed. One of the following inspection classifications will be assigned:
   • No Action Indicated (NAI) – No objectionable conditions or practices were found during the inspection or the significance of the objectionable conditions does not justify further FDA actions. No Form FDA 483 is issued. This is the best possible inspection outcome.
   • Voluntary Action Indicated (VAI)/Informational or Untitled Letter – Objectionable conditions were found and documented by the FDA, but the FDA is not prepared to take or recommend further regulatory actions because the objectionable conditions are few and did not seriously impact subject safety/welfare and data integrity.
• **Official Actions Indicated (OAI)/Warning Letter** -- Regulatory violations uncovered during the inspection are repeated or deliberate and/or involve submission of false information to FDA or to the sponsor. If an OAI results, the inspection report is sent to the district compliance branch for further review. Warning Letters are issued to achieve voluntary compliance, and include a request for correction and response to the Agency (if not already provided).

• **Notice of Initiation of Disqualification Proceedings and Opportunity to Explain (NIDPOE)** -- FDA may initiate a process to disqualify the clinical investigator from receiving investigational new drugs and/or biologics if the investigator has repeatedly or deliberately failed to comply with applicable regulatory requirements or has deliberately or repeatedly submitted false information to the sponsor or FDA in any required report. The NIDPOE identifies alleged violations and provides the investigator with an opportunity to explain the matter at an informal conference or in writing. If, in response to the NIDPOE, the investigator provides an explanation that is accepted by the agency and the disqualification is not warranted, alternatives such as a detailed corrective action plan may be considered. If the investigator’s explanation is not accepted by the Agency, the Agency may issue a Notice of Opportunity for Hearing (NOOH).

a. When the FDA inspection findings are received, copies of the findings should be provided to the entities and stakeholders that were notified of the inspection.

II. **REVIEW OR REVISION DATE**

Original: 06/21/17

III. **REFERENCES**

Children’s National Food and Drug Administration Inspection Preparation Guide and Checklist

CNMC:A:52 - Children’s National FDA Inspection, Preparation and Study Team Activities Policy