Ascension

Ascension Wisconsin

Research Integrity and Protection Newsletter

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Ascension WI IRB Implements Flexibility to Reduce Administrative Burden

IRB "Flexibility" refers to institutional approaches to find simpler ways to review and conduct research, in light of increasingly burdensome federal requirements. The freedom to be compliant yet flexible, is permitted for institutions which have opted to "uncheck the box" on the Federalwide Assurance (FWA) for the Protection of Human Subjects. Unchecking the box limits HHS oversight to projects funded and regulated by OHRP. Ascension Wisconsin unchecks the box on its FWA.
This process will help to reduce unnecessary administrative burdens upon researchers, IRB members, and Research Integrity and Protection staff, while providing research subject protections equivalent to those found in the Common Rule (45 CFR 46).

All other subject protections and ethical standards apply to all research, forms, checklists, documentation and reporting requirements outlined in other policies and procedures that apply to all research, including post approval quality reviews.

The flexibility processes may only be applied to minimal risk research where there is no federal funding, support or regulation.

What are the main changes for Researchers?

- Extended Approval Period for Minimal Risk Human Subject Research: approval to 5-year period (instead of annually)
- Expanding certain exempt research categories to allow additional minimal risk research to qualify as exempt.

Get more information in Mentor:

- SOP: 208- Review Standards for Research Not Covered by Federalwide Assurance- Flexibility Policy and Procedures
- GUIDANCE: Exempt Human Subject Research

What else is the IRB doing to improve the submission process?
The IRB updated the amendment process to allow certain administrative updates to be processed by office staff. This will simplify and speed up the amendment process.

Summary of FDA Warning Letters to Sites

FDA Warning Letters (a.k.a. FDA Form 483) are issued by the FDA following an inspection at the site. FDA inspections are part of the FDA's Bioresearch Monitoring Program and are designed to evaluate the conduct of research and ensure that the rights, safety and welfare of human subjects are protected.

Research Education and Quality Management (REQM) prepared a summary of warning letters to Clinical Investigators posted on the FDA website in 2017. The summary includes finding, site responses and in the FDA's reasoning when they determined the site response was insufficient.

Read the summary here.

CHANGES COMING to the Reportable Event Submission Process!

The IRB will be implementing a new submission process for reportable events (i.e. non-compliance, unanticipated problems and safety update) in an effort to reduce paperwork and speed-up the time to IRB determination.

Main Changes will include:

- Submission forms will be completed in Mentor (no more paper forms)
- PIs will be required to "sign" electronically in Mentor (via email)

More details will be announced soon!

RECENT IRB UPDATES

- **Updated IRB Reliance SOP, guidance & Mentor Page**. Changes included minor updates and clarifications, organization and new tools for PIs serving as the Main PI in multisite studies.
- **Revised Protocol Templates** for studies that are minimal risk and greater than minimal risk. The protocol templates were updated to align with the Ascension National templates.

Summary of the 2017 FDA Warning Letters Issued to Clinical Investigators

Below is a summary the findings and corrective actions noted on the FDA warning letters posted in 2017; seven warning letters to clinical sites were posted. You can view all FDA warning letters on the FDA website.

Findings

Failure to maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation [21 CFR 312.62(b)].

- Investigator failed to maintain adequate, accurate case histories for the Structured interview for Mental Disorders I and II forms which were used to classify subjects into one of two cohorts. Specifically, source records indicate that the forms were not completed for 3 subjects Screening Visit however the electronic case report forms indicate a determination was made.

Failure to maintain adequate records of the disposition of the drug, including dates, quantity, and use by subjects [21 CFR 312.62(a)]**.**

- Drug disposition records including study drug accountability records, records documenting drug return were not maintained.
- Study drug accountability logs failed to document the disposition of 25 units of unused supplies of study drug.
- PI was unable to produce the unused supplies of study drug, and there were no other records indicating the use or disposal of these missing unused supplies of study drug.

Failure to ensure that the investigation was conducted according to the investigational plan [21 CFR 312.60].

- Ineligible subjects were enrolled:
  - Subject was randomized and received study drug, despite meeting the exclusion criteria during the screening visit. Triplicate ECGs performed at baseline visit confirmed the subject's ineligibility.
  - Subject was ineligible but was screened, randomized and dosed with study drug.
  - Three subjects enrolled with a post-bronchodilator FEV1 between 50% and 80% of predicted normal, even though they did not have a documented history of at least 2 moderate or 1 severe exacerbation(s) in the previous 12 months.
  - One subject was randomized to treatment despite experiencing a moderate exacerbation with worsening symptoms requiring oral corticosteroids.
  - One subject enrolled even though this subject had a known history of renal insufficiency and an estimated creatinine clearance, which were exclusion criteria.
  - Three subjects were enrolled who did not meet the smoking criteria specified in the protocol.
  - One subject was enrolled that was taking an exclusionary medication.
  - Enrolled six subjects that did not meet inclusion criteria.
- Study assessments/activities not completed per protocol:
  - Subject withdrew from the study 1 day after being enrolled/receiving study drug; early termination visit was not done.
  - Subject missed ECG.
  - Five subjects did not have required ECGs performed at specific time points used to monitor the QTc interval.
  - Two subjects did not have required an ECG two hours post-dose, and before pharmacokinetic sampling.
  - Two subjects did not receive chest X-rays following moderate exacerbations with worsening symptoms requiring treatment with antibiotics.
  - Two subjects did not have weekly platelet measurements performed and more than 14 days elapsed without platelet testing but study drug was not held.
  - Five subjects did not have clinical laboratory tests at specified intervals.
- Inadequate/Incomplete documentation of study activities:
  - ECG tracings for 7 patients were not retained.
  - Rating scales not retained for one subject.

Failure to retain records required to be maintained under 21 CFR Part 312 for a period of two years following the date a marketing application is approved for the drug for the indication for which the drug is being investigated; or, if no application is filed or if the application is not approved for such indication, until two years after the investigation is discontinued [21 CFR 312.62(c)].

- Investigator stated that all study records had been shredded or destroyed by staff and does not have any paper or electronic records for any study conducted, including but not limited to source documents, case report forms, signed informed consent forms, and investigational drug disposition records.

Investigator Corrective Action Plans (CAP)

Training

- Train all study staff on the protocol and emphasize eligibility criteria.
- Train study staff on a revised Standard Operating Procedure for eligibility and enrollment.
- Site was trained in ECG processing.
- Staff will be retrained on the importance of maintaining accurate and complete records of the investigational drug.
- Study staff has been retrained on the importance of monitoring for adverse events during the early termination assessments and will receive one-on-one retraining in IRB regulations, reporting timelines, and other regulations.

Improved Processes/tools

- Study team will track scheduled dosing dates and all platelet count results for each subject, ensuring that each subject has a platelet level that has been reviewed and is acceptable on the day before each scheduled dosing. If either of these factors is not met, the subject will be informed to hold their scheduled dosing until the investigator has received a platelet count result and confirms that it is acceptable under the guidelines in the protocol.
- Use an eligibility criteria checklist even if the sponsor does not provide one.
- Determine eligibility by source document review and by checking whether that information is verifiable.
- Confirm eligibility by using two qualified individuals (who will initial and date the eligibility checklist).
- Randomize subjects only after the eligibility checklist is complete.
- Rating scales will be signed and filed on the day of the subject's visit.
- Protocol-Specific Training and Source Document Completion Standard Operating Procedures (SOPs) have been updated and all site PIs and staff trained.
- Detailed plan for monitoring accurate, complete drug accountability records in a standard operating procedure was created.
- Study closure visit planned to reconcile drug accountability, ensure destruction of expired supplies of the drug, and ensure completion and retention of all study records.
- Written response to the violations noted above, you indicated that AHN updated its Test Article Accountability SOP to address issues related to investigational drug return. In addition, your response noted that AHN's "Dispensing of Investigational Product" SOP requires that each administration/dispensation of an investigational drug be doubled-checked by another person.
- The Data Management SOP requires that "investigators and study staff take care to ensure that all source data is documented accurately, completely, and consistently."
- Develop adequate oversight of study staff, training of study staff and protocol adherence.
- Protocol Specific Training and Source Document Completion SOPs have been updated and that "all site PIs and staff trained.

Reported to the IRB

- Reported this protocol violation to the IRB in a memo to file.
- Reported protocol violations to the IRB.
- Train clinical research team, to ensure that all subjects have the required tests performed according to the protocol.
- A member of the clinical research team will request laboratory test and will obtain the result of that laboratory test.
- Acquired an independent monitor for clinical research team adherence to the protocol requirements for laboratory testing.

FDA Feedback on Corrective Action Plans (CAP):

- The Investigator's plan to follow document retention guidelines is insufficiently detailed to prevent similar violations in future studies.
- Investigator indicated "do not plan to get involved in clinical research again," but did not provide details about how they personally plans to prevent similar violations if this decision should change and they conduct clinical research in the future.
- CAP appears to represent actions taken by the hospital and do not reflect actions the PI has taken.
- Insufficient details for implementing additional measures and procedures to maintain adequate drug accountability records and follow protocol procedures.
- CAP does not state how site will properly retain records of adequate and accurate case histories for future studies.
- Insufficient details about how investigator will ensure adequate oversight of study procedures and protocol training of self and study team.
- Plan does not include details about the implementation of additional measures and procedures to ensure only eligible subjects are enrolled and to follow protocol procedures.
- Did not include any corrective actions that PI has taken to prevent similar violations in the future.
- Lack of supervision and oversight of the clinical study raises concerns about the adequacy of protection of the study subjects enrolled at site, and raises concerns about the integrity of the data generated at site.
- Did not indicate whether PI and study team underwent retraining activities to prevent future protocol violations.
- Unable to determine if written response provides a CAP that, if properly carried out, would prevent this type of violation in the future.