Protocol Deviation Guidance Document

It is the responsibility of the PI to determine whether a deviation from the IRB approved protocol is immediately reportable to the IRB.

When making the determination whether or not a protocol deviation is immediately reportable, the PI should consider whether the deviation negatively affected any of the following:

- The rights or welfare of the subject
- Risk benefit assessment
- The integrity of the data, including the ability to draw conclusions from the study data

Deviations that are Immediately Reportable may include, but are not limited to:

- Changes necessary to eliminate apparent immediate hazards to the subject
- Failure to obtain informed consent or obtaining consent after the initiation of study procedures
- Enrollment of an ineligible subject (did not meet all inclusion/exclusion criteria)
- Performing study procedure not approved by the IRB
- Failure to report a serious adverse event (SAE) to the IRB and/or sponsor
- Failure to perform a required lab test that, in the opinion of the PI, may affect subject safety or data integrity
- Dispensing or dosing error of an Investigational Product (IP)
- Study visit conducted outside of required timeframe that, in the opinion of the PI, may affect subject safety
- Failure to follow safety monitoring plan
- Enrollment of subjects after IRB-approval has expired

Deviations that may be reported on the Deviation Log may include, but are not limited to:

- Inappropriate documentation of informed consent, including
  - missing subject signature, printed name or date
  - missing investigator signature, printed name or date
  - missing original signed consent
  - copy not given to the person signing the form
  - someone other than the subject dated the consent form
- Use of outdated/expired consent form that contains all required information and elements of informed consent
- Failure to follow the approved study procedure that, in the opinion of the PI, does not affect subject safety or data integrity
  - Study procedure conducted out of sequence
  - Omitting an approved procedure of the protocol
  - Failure to perform a required lab test
  - Missing lab results
- Failure of subject to return study medication
- Over-enrollment
- Failure to submit continuing review application to the IRB before study expiration

When the IRB reviews protocol deviation submissions, one aspect of its assessment is determining if an unanticipated problem involving risks to subjects or others, serious noncompliance, or continuing noncompliance has occurred. (Definitions attached.) In the event that the IRB determines one or more have occurred, it will reach out to the Principal Investigator to find out further details and then report the incident to the United States Department of Health & Human Services Office of Human Research Protections, as is required by federal regulations, and to the United States Food and Drug Administration, if the research involves an FDA-regulated product. The letter, which comes from WCM's Institutional Official, includes information about the incident and its cause, any corrective actions taken by the study team and the institution, as well as any preventative measures put into place.

For issues concerning privacy, regulations set out by the United States Department of Health & Human Services Office for Civil Rights (OCR) dictate that the institution issue reports to the OCR in two different circumstances. Such assessments are handled by WCM's Privacy Office, and any privacy issue details should be sent to privacy@med.cornell.edu with information including the affected subject(s) so the Privacy Office can assess whether such a report is necessary. Below are the two circumstances that qualify the privacy issue as a "breach" that requires WCM reporting to the OCR. In each paragraph, "a covered entity" refers to Weill Cornell Medical College:

(1) If a breach of unsecured protected health information **affects 500 or more individuals**, a covered entity must notify the Secretary of the breach without unreasonable delay and in no case later than 60 calendar days from the discovery of the breach. The covered entity must submit the notice electronically… and completing all of the required fields of the breach notification form.

(2) If a breach of unsecured protected health information **affects fewer than 500 individuals**, a covered entity must notify the Secretary of the breach within 60 days of the end of the calendar year in which the breach was discovered. (A covered entity is not required to wait until the end of the calendar year to report breaches affecting fewer than 500 individuals; a covered entity may report such breaches at the time they are discovered.) The covered entity may report all of its breaches affecting fewer than 500 individuals on one date, but the covered entity must complete a separate notice for each breach incident. The covered entity must submit the notice electronically by clicking on the link below and completing all of the fields of the breach notification form.

It is rare that a privacy issue qualifies as a breach, but in each case, the Privacy Office will make this determination on the institution's behalf.

What follows are several examples of protocol deviations that should be submitted as per the immediate reporting policy, root causes, possible corrective actions, and possible preventative actions. Examples include over-enrollment, enrolling a subject who doesn't meet inclusion criteria, use of an incorrect informed consent document, a dosing error and a privacy issue.

Before we begin, here are some tips for managing and preventing protocol deviations:

- Have standard operating procedures in place to ensure optimal operation within the research team, and have frequent research team meetings to discuss operations and deviation management.
- When protocol deviations occur, talk to the members of the research team and know the details. Immediate Reports very often leave pieces of the story out, which can result in misunderstandings and increased back and forth between the Principal Investigator and the IRB.
- In your Immediate Report submission, indicate what should have been done according to the protocol and/or IRB policies, and then clearly indicate what was done instead, and by whom, such that the interactions between research team members and any affected parties are clear.
- Make sure the preventative actions stipulated in your Immediate Report address the root cause of the issue. These pieces of information should complement one another.

- If you are unsure of what corrective and/or preventative actions to take, contact the IRB at irb@med.cornell.edu or the Quality Assurance Unit (QAU) at jctoqau@med.cornell.edu.

Enrolling a Subject Who Doesn't Meet Inclusion Criteria	Possibility 1: A subject was enrolled by an investigator based on lab values obtained prior to the screening period rather than during the screening period. Possibility 2: A subject who didn't meet the inclusion criteria was enrolled by an investigator because s/he thought enrollment would be beneficial to the patient.
Root Cause	Possibility 1: The investigator misunderstood the protocol's screening procedure. Possibility 2: Lack of awareness of the IRB Exception Request Policy
Corrective Action	Possibility 1: • A qualified member of the research team should discuss the error and any associated risks with the subject. • Request the IRB's permission for the subject to stay on study using an Exception Request form, and ask if use of the data gathered from this subject is permissible. Possibility 2: • Review the IRB's Exception Request Policy • Request the IRB's permission for the subject to stay on study using an Exception Request form, and ask if use of the data gathered from this subject is permissible.
Preventative Action	Possibility 1: • Contact the sponsor for clarification of any ambiguous language regarding the enrollment of subjects. • Retrain all research staff of the protocol's screening requirements. • Create or update a screening and enrollment checklist and the procedure for its use among the research team. Possibility 2: • Retrain all research staff concerning the IRB's Exception Request Policy. Thoroughly document this training in your research records.

Incorrect Informed Consent Used	A member of the research team enrolled a subject using a previous version of the informed consent document. The current version includes a new risk to participating in the research. **Note**: When you Submit Your Immediate Report to the IRB: • Always include the differences between the informed consent document that was used and the informed consent document that should have been used. This helps determine the significance of the deviation. • Indicate whether any procedure(s) related to the newly identified risk were performed on the subject that day, and whether a discussion took place about those risks prior to the procedure(s), and whether the consent conversation was documented.
Root Cause	Possibility 1: • Different informed consent versions were kept in the same place, or not clearly labeled (e.g., blood draw consent vs. Blood Drawn Consent v.2 10.03.16) which increased the likelihood a member of the research team would retrieve an incorrect version for use. Possibility 2: • The research team was unaware that a new informed consent version had been approved for use.
Corrective Action	• Immediately provide the subject with the correct informed consent document and discuss all newly included information in the updated consent prior to performing any research procedures. • Notify the research team that a new informed consent document has been IRB-approved for use.
Preventative Action	Possibility 1: • Institute a new practice whereby old and new consent documents are kept in separate locations, and labeling of files on the shared drive is standardized. Possibility 2: • Create a standard operating procedure that outlines who will notify the research team when a new informed consent document is IRB-approved for use.

Dosing Error	The protocol indicates that, at Cycle 1 Day 2 subjects older than 60 must receive 20mg of the study drug, while younger subjects must receive 40mg. In error, the 20mg dose was ordered and administered to a 62-year-old subject.
Root Cause	• The individuals on the research team misunderstood the protocol's instruction on dosing subjects.
Corrective Action	• Immediately notify the study subject of the error and any potentially related risks. • Closely monitor the subject for safety and adverse events that may be related to the dosing error. • Provide the IRB with a thorough clinical assessment concerning whether risk posed to the subject was raised as a result of the dosing error – even if no harm ultimately occurred to the subject. This should be done taking into consideration the subject's state of health at the time of the error and the known risk profile of the drug(s).
Preventative Action	• Reeducate the research team on the protocol's instruction on dosing subjects of all ages and at all stages of the protocol. Thoroughly document this training in your research records.

Privacy Issue	A member of the research team mistakenly emailed Protected Health Information (PHI) to a Contract Research Organization (CRO), which the informed consent document does not indicate will be one of the parties viewing subject PHI. The written information was redacted by hand with a black marker, but still visible.
Root Cause	• Lack of familiarity with proper redaction procedures.
Corrective Action	• Notify the Privacy Office at privacy@med.cornell.edu of the privacy issue, providing all details of the privacy issue and noting the affected subject(s). • Contact the CRO for confirmation that any printouts have been destroyed, and any associated emails are deleted from computer hard drives, email inboxes and trash folders. Save this confirmation in your research records. • Notify the affected subject(s) of the privacy issue and all measures taken to manage it by drafting a letter including these measures, Principal Investigator, Privacy Office, and IRB contact information. Then submit this notification for IRB approval in conjunction with your Immediate Report.
Preventative Action	• Retrain the research staff on proper redaction procedures. Thoroughly document this training in your research records. • Utilize the Adobe Acrobat Pro redaction feature, which redacts information using opaque black lines.