

The following guide is intended to facilitate the compliance process for investigators after initial IRB approval, and is based upon events and anecdotes encountered over the years. Please note that some items will be more applicable to industry-funded or NIH clinical trials, especially with regard to regulatory documents and recordkeeping. However, other investigators may find many of these procedures to be helpful. In all cases the recordkeeping process as described in the approved protocol must be followed, and will form the basis of comparison during a Quality Assurance (QA) visit and review of documents and records.

## General Information

### I. Principal Investigator (PI) Responsibilities and Delegation of Authority

The PI is responsible for the safe and ethical conduct of the study. Most research studies necessitate the addition of one or more team members to accomplish the activities described in the protocol. Once Institutional Review Board (IRB) approval has been given, the PI should meet with his or her team to ensure that everyone is aware of their role as outlined in the protocol. The more members on the research team, the more it is recommended that a delegation log, outlining the responsibilities of each person, be created and kept in a central location easily accessible by all team members.

All members should be given a list of the protocol procedures. Any member who obtains consent must be described within the approved protocol, and be listed on the consent form (unless permission is waived by the IRB). Those who obtain consent must be aware of how to conduct the consent process, and the PI is encouraged to demonstrate the consent process to team members and/or allow team members to witness the PI consent a subject.

The PI must ensure that the protocol is updated to reflect any changes in the research team or procedures by submitting an amendment to the IRB. If new members are added to the team, they cannot conduct any study procedures until the IRB has approved the addition. If members are taken off the team, this change must also be submitted to the IRB to update the protocol.

Only members who are approved by the IRB can conduct study procedures, *especially administering the informed consent*.

The PI must ensure that all aspects of the study are conducted exactly as outlined in the approved IRB protocol. If there are any changes to the procedures such as recruitment, advertisements, collection, sample size, etc., they must be submitted as an amendment to the IRB.

Any change to the protocol approved by the IRB changes the “last amended” date on the consent form to the date of amendment approval, whether or not the consent form is actually

changed with the amendment. This new consent with the new date must be used following amendment approval.

## II. Recordkeeping

Once the protocol is approved, a folder/binder should be created. This should include all regulatory documents, which may include:

1. General Protocol (This will include a signature page where all persons involved in study have been trained on the protocol by PI or delegated person) including any amendments, deviations, adverse events, UPIRTSOs
2. IRB Approval Letters and other IRB correspondence
3. Delegation of Authority Log (This also needs to be signed by the PI and personnel involved in the study showing what the PI has allowed them to do) (Update as necessary)
4. Informed Consents (Place the consent process here so PI will be reminded how important this is, and necessary documentation).
5. Subject Identification List (Most studies use coding or subject non-identifiers for data, but an identification list is necessary for safety) - for Sponsored studies
6. Investigator CV's and License (FDA requires this)
7. Training Documents (CITI, Dangerous Goods, etc....)
8. Screening log (including individuals who refuse to participate)
9. Safety (This is where monitoring plan is placed as well as notes of regular meetings) -
10. Maintain Drug Accountability Logs
11. Deviation/Violation Acknowledgement Letters

Please note that industry-funded and NIH clinical trials will likely contain all 11 regulatory items and more (as specified by the sponsor). Other studies may not require all of these items.

Separate folders for the following should be kept in a locked cabinet in a secure office:

1. Signed Consent Forms
2. HIPAA forms
2. Code List
3. Data Collection Forms

### Security /HIPAA

Prior to protocol submission to the IRB and once IRB approval is obtained, the PI must have a clear plan of how research records will be secured , because security is key to maintaining subject confidentiality . Documents to secure include subject/patient listing, consents, and data collection forms.

De-identification of data collection tools follows HIPAA principles. When coding is used as a form of de-identification, the master code listing (or subject listing) must be kept in a separate secure area away from the coded data collection tool (s) so de-identification is maintained. To maintain confidentiality, all team members must be knowledgeable on what a HIPAA identifier is and what to document on the data collection tool. No additional subject information can be used if it was not previously approved by the IRB. .

Most data are maintained in a secure, password protected computer. A secure computer can hold PHI. Use of a flash drive as a means for data collection can also be used in two ways. First, the USB flash drive must be encrypted to prevent easy access to subject information. Second, only code numbers can be used on the flash drive, not any identifying information like names or the medical chart number. The IRB recommends that the use of USB and other mobile storage devices be discouraged. Any breach of confidentiality due to loss or theft must be reported to the IRB as an unanticipated problem involving risk to participants or others (UPIRPO). Any individuals who are no longer a member of the research teams must return subject data.

#### Documentation\*

Any study notes need to be documented and maintained. Be sure to document everything that occurs including phone calls, decisions made, consultations, emails, and any other discussions that are relevant to the subject and the study.

To maintain the integrity of the study there may be no changes to any of the data. No strikeouts (initial and date if cross out is required), whiteouts, or changes may be made to approved forms. No information may be written on the forms, including consents. Neither subjects nor research team may write on the forms. Any changes made to approved forms without IRB approval is a protocol violation that could lead to the destruction of collected data.

Clinical research studies should follow Good Clinical Practice (GCP) documentation guidelines. A suggested reference is Bargaje C. Good documentation practice in clinical research. *Perspect Clin Res.* 2011 Apr;2(2):59-63.

### **III Training Personnel**

All research team personnel added after initial study approval must he take the CITI program ethics training.

Online human ethics training (located at <http://www.citiprogram.org>) is required for all studies that go through the IRB. Prior to submission, all WVU-affiliated research team members

(including the PI and primary contact) listed on IRB protocol applications must complete either the Biomedical Research Investigators or Social and Behavioral Research Investigators basic or refresher course. Furthermore, any non-WVU-affiliated research team members (i.e., from another university, the community, etc.) must have either completed their own institution's required training and attached it to the protocol application or complete the Abbreviated Biomedical Research Investigators or Abbreviated Social and Behavioral Research Investigators course from the WVU CITI menu.

Whether the research team members take the Biomedical or Social and Behavioral course is dependent upon what type of research is being conducted. After approval and when conducting the study, the Office of Research Integrity and Compliance and the IRB expects that your entire research team will adhere to the principles, policies, and guidelines communicated through the ethics training. Please direct questions about ethics training to 304-293-7073 or [IRB@mail.wvu.edu](mailto:IRB@mail.wvu.edu).

Please note that CITI training expires after three years, at which time a refresher course must be completed.

In addition to the CITI training, the PI is responsible for ensuring all members of the research team are well versed in procedures of the protocol. The team should be aware of the purpose of the study and how the study should be conducted in order to keep the data untainted and to maintain the integrity of the study.

Subject privacy and confidentiality should always be maintained. Where appropriate, all interactions with subjects should take place in a private setting. After data are collected, the data must be kept in a secure setting. The researcher should be familiar with the study and data collection forms to be able to answer any questions from the subjects or other team members.

The PI is responsible for explaining to the team how to obtain consent. Where appropriate, the setting for consenting should be in a private environment. The individual obtaining consent should be qualified to answer any questions the subject may have without coercing the subject in any manner.

Document in the study files and keep with the consent form (perhaps as an SOP form placed with the consent form) that the consent process took place. Unless waived by the IRB, a copy of consent should be given to subject, a copy placed in the subject's medical record (if applicable), and the original with study files.

#### **IV. Amendments**

As discussed above, changes may occur to the protocol approved by the IRB.

The IRB protocol must reflect the most current research team by submitting an amendment to the protocol. If the research team member is considered key personnel, then that person must be added to the consent forms (unless waived by the IRB).

Other examples of common changes include:

- Researchers may find the study procedures/research design are incomplete
- Another survey may be needed, or questions are added to the current surveys.
- Revisions to the inclusion/exclusion criteria, timing of therapy, study dose amounts, number of sample population or type of population may be needed
- The researchers may have failed to mention essential elements of the study in the original submission.
- New forms for laboratory studies or a changed methodology for recording outcomes may be initiated.
- To correct omissions, additional procedures or deletion of procedures may be incorporated into the research design.

Researchers often find that they need additional recruiting tools in other sources, such as newspapers, radio, etc. There may be a need to revise the wording of the recruitment tool to add additional information or a contact number.

Consent forms need to be updated when there are personnel updates or location changes. The researcher may want to add a follow-up visit, a test or procedure, add a survey or delete any of these. If a new blood test is added, then the total amount of blood drawn should be changed. . If a questionnaire is added or deleted the total time for completion may change. The consent form must be accurate and explanatory.

Survey changes may be as simple as formatting changes, moving questions around, adding questions, or deleting questions. Any of these changes should be amended to the protocol. The IRB updated version should have the same forms that are being used.

Sometimes the researchers find that they need to add more sites to their study to recruit more subjects or to find a more appropriate setting for the study. Additional sites may include schools, nursing facilities, clinics and public malls to hand out flyers. All sites should provide a letter of support to the PI. This letter of support needs to be attached to the protocol. If sites are added later to the study as a means to increase recruitment, the amendment must include this letter of support and the protocol must be updated to reflect this change.

Recruitment is a very important element of any protocol. If the method of recruitment is found to be insufficient, the PI may wish to alter or add to the approved method (i.e. adding posters, sites, or going on the Internet to recruit subjects). The PI may want to add more schoolroom

classes to the protocol to get a wider sample.

Sponsor changes must necessarily be submitted to the IRB within a limited amount of time. The rule of thumb is within five working days of receipt from the sponsor. Sponsor changes may be minor administrative changes such as telephone numbers or contact persons. They may be major changes such as adding a vulnerable population, changes in dose, update of risks, or changes in administration. The protocol must be updated to reflect the sponsor's update. If there are changes to the consent form then that must also reflect the sponsor's update.

If there is new information which may affect the subject's willingness to continue participation or requires that subjects be informed who have already been enrolled, an amendment must be submitted. If the amendment is a change in risk to the subjects it could require full board review. If it is a minor administrative revision, it should be expedited review. The driving force behind the determination is the level of risk. All changes that increase the risk level to greater than minimal risk, or changes the risk/benefit ration of the current study require full board review. The PI must also consider if subjects need to be informed or re-consented based upon the protocol amendment.

Some sponsors determine that all subjects must be re-consented with a new updated consent form. In other cases, it may be sufficient to develop a letter to the subject informing them of new information. In some minor cases, it may be sufficient to inform the subject in a follow-up visit and make a note to the file which the subject initials. Whichever method is used, the IRB must be informed and must approve the method prior to making this change, and in all cases the IRB approval supersedes the sponsor.

Please remember that during their review, the IRB may request revisions that were not requested with the initial review. Each time an activity is submitted to the IRB, it may require revisions to any part of the protocol, not just the revised amendment wording.

An amendment is not a renewal. The approval period clock does not start over again with the amendment date. If an amendment is approved a month before the renewal date, this does not affect that date. The renewal is still due at the same time as you were informed on the approval letter.

Importantly, every time an amendment is approved, the "last amended" date on the consent form is updated to coincide with the date of the amendment approval regardless of whether or not the actual consent form was changed.

## **V. Adverse Events, Protocol Deviations, and Violations**

- a. Know definitions
- b. Submit reports to IRB if applicable

During the course of the study, unanticipated events may occur. The standard operating procedures (SOPs) located at <http://oric.research.wvu.edu/r/download/104456> define an adverse event, a protocol deviation and a violation. These should be understood by the research team.

An adverse event that is unexpected, related to the research, and severe, must be reported to the IRB. This should include an assessment of whether the adverse event was preventable. Depending on the severity of the adverse event, enrollment onto the study may be suspended. The PI needs to review his/her institutional policy regarding reporting requirements for severe adverse events (e.g. subject death). The study sponsor may also have specific requirements.

A protocol deviation is an incident involving noncompliance with the approved protocol, but one that typically does not have a significant effect on the subject's rights, safety, welfare, or on the integrity of the collected data. This could relate to a test not being conducted, a missed study visit, or a consent form missing signatures, initials, or dates, among many other things that could occur. Most deviations are unintentional or an oversight. When submitting a protocol deviation or a protocol violation, the PI should submit an action plan to prevent a future recurrence.

A protocol violation is a more serious incident involving noncompliance. Non-compliance generally affects subject's rights, safety, welfare, and integrity of the collected data. This could relate to the sponsor's inability to use the data, such as falsifying data, intentional enrollment of a non-eligible subject, or repeatedly failing to perform a protocol test. If the noncompliance is severe, the IRB will decide how the issue/study will be handled in a meeting of the full board.

When a sponsor monitor visits the sites, they may find a deviation or violation that needs to be reported to the IRB. This should be done as quickly as possible. The sponsor will need to be advised of the Board's review and acknowledgement of the situation.

## VI. Renewal/Continuation Submissions

Per federal regulations, the maximum approval period cannot exceed 12 months. This cannot be extended. Regulations do not accept any justification to allow a protocol's approval to be extended over 12 months, even if it is not the principal investigator's error. This means that if the protocol is approved on March 15, 2012, IRB approval cannot be extended past midnight of March 14, 2013.

If the renewal is submitted early, the annual clock will begin at the time of review and approval. Therefore, the protocol could potentially be approved every nine months. It is the PI's responsibility to be aware of the renewal date and to submit the continuing review in a timely fashion to allow for the renewal.

Please note that although the maximum approval period cannot exceed 12 months, the IRB may require more frequent review of protocols that involve significant risks. Such approval periods can be quarterly or even after the first one or two patients are enrolled.

Normally the electronic system sends out reminders automatically three months, two months, and one month before expiration. It would be expeditious to submit the renewal application as soon as possible. If the protocol was approved by full board review it will require full board review to renew the approval. If by expedited review, then it should receive expedited review for the renewal, unless there are protocol changes that make the risks more than minimal. The renewal process is similar to the initial review and the IRB may require changes or additions during this review. If there have been problems or concerns, the IRB may defer the review to a different level. If there are any questions or problems, this could hold up approval. The potential exists that the protocol will not be renewed before the expiration date.

If the protocol expires before the renewal is submitted, there is no recourse to keep that protocol active. The only action available to the investigator at that point is to copy the study and submit it as a new protocol, referring to the old protocol number and the reason for the renewal. The study will be considered a separate protocol and will receive the same type of review as the original protocol. (

**If the protocol expires during review or in pending awaiting review, then all activities must stop.** No subjects may be enrolled and no research activities may continue until the protocol is renewed. However, if medical treatment is involved and/or patients are at risk from discontinuation of study procedures, the PI should request that subjects continue to receive treatment or procedures for their well-being for review and approval by the Chair. Only those activities involving subjects' welfare may continue until the study is renewed if the Chair gives approval.

A renewal request application requires that certain information be provided. Any problems or withdrawals must be reported. If subjects withdraw their consent or withdrew from the study for any reason, an explanation is required. The reasons for the withdrawal or problem need to be considered.

If there is any new information which may affect the participant's willingness to participate in the study, this needs to be included in the renewal application. In that case the method of revealing the information to the subjects must be addressed. The information may be given to the subjects by 1) sending a letter to the subject (upon approval by the IRB), 2) re-consenting the subjects or 3) putting a note in the file that the subject was informed, which would be initialed by the subject attesting that the information was given.

Once the renewal is approved, a new approval is issued with new approval dates. The consent form will reflect the new approval and expiration dates, and this version of the consent must be used for subjects enrolled after the new approval date. Old consents must be destroyed. The approval dates can be any time up to 12 months. The study may continue.

## VII. Informed Consent

### *Recruitment and Screening:*

Recruitment advertisements, posters, and flyers may be used to recruit subjects and must be placed as specified in the protocol. There is often a phone number for subjects to call and inquire about participation. The contact person should only obtain enough information to verify eligibility. Further personal information or private health information should not be obtained until consent is obtained. If the potential subject does not sign or fails screening, the protocol should state that the screening information from first contact will be destroyed. It can only become part of the research file if the subject signs the consent. ( )

It is the responsibility of the research team to ascertain that the consent form is the newest version approved by the IRB. **Making multiple copies in advance and storing them is not appropriate since consent forms may be updated frequently with amendments or continuing reviews making the previous version invalid.** Subjects must only be given the newest version to sign. A violation occurs if an older version of the consent is signed, and this must be submitted to the IRB.

The team should meet with the investigator and be trained in all aspects of the study. Only a research team member listed on the consent form (unless waived by the IRB) may discuss the consent with the potential subject, and should be listed as key personnel on the study protocol. The team member should be well versed in the study and be able to answer any questions of the subject in a manner that the subject will understand. The procedures, risks, and potential benefits should be made clear.

The subject should be given the opportunity to read the consent closely. When possible, the subject should take the consent form home in order to be given time to read the consent form and discuss it with others (e.g. family and friends). Before signing the consent, the subject should be given another opportunity to ask questions and have them answered by the investigator. Consent forms that are mailed with surveys must include a telephone number that subjects can call to discuss the consent with an investigator. **Under no circumstances may there be any strikeouts or whiteouts on the consent forms. The subject is required to initial and date each page. Upon signing by the subject and the researcher, the subject must be given a copy of the consent for their own files (unless waived by the IRB).**

The researcher should keep the consent form in a separate file, and document the research process steps with dates in the research file where appropriate. The consent form should not have any writing on it except the printed name, signatures, initials, and dates. There should be no notes or medical information written on the consent form.

If re-consent is required, the subject must be given the new information and consent as soon as possible. The new consent should be kept with the original consent. If a re-consent is not

necessary, the subjects must be told any new information by way of letters or obtaining a note with the subject's signature to verify that the subject has been given the information. This information belongs in the research file.

Consenting is much more than just a document and is an ongoing process. The subject should always be informed of any new information, and given the opportunity to withdraw from the study if necessary. The consent form will contain contact numbers so that the subject may contact the researchers with any questions or concerns they may have.

## VII. Study Closure and Document Retention

When the study is closed to enrollment, the IRB needs to be informed with an amendment. At that time the consent forms, assents, ads, and any other correspondence with the subjects needs to be removed from the newest version of the protocol. The IRB will acknowledge and all consents and assents will be watermarked so that they can no longer be used.

Should the PI discover that more data is needed or the subjects need to be re-approached for more information after closure to enrollment, an amendment will be necessary. Subjects may need to be consented with a new consent form.

Some studies may continue for many years. The procedures of the study require that the identification of the subjects be maintained as well as the data links. Articles may be published and, in the case of clinical trials, the data submitted to the FDA while the study is on-going. Subjects may be followed for survival or for long-term follow-up long after study enrollment is completed. When all procedures are completed and data analysis is complete, the study should be closed with the IRB.

In most cases, the data should be de-identified and any lists that link consents to data will need to be destroyed. At that time, the manuscript can be written and submitted for publishing. Once the data is de-identified and the links are destroyed, the protocol may be closed with the IRB. This may occur even if the final analyses are not completed and there are no publications. Sponsors will expect a copy of the closure acceptance letter from the IRB.

The IRB requires that all data be kept for up to three years after study completion. Sponsors and the FDA may require longer periods. The minimum retention is three years.