

VAMHCS Research Service  
Guidelines for Setting up a Study Binder and Regulatory Documents Binder  
(Audit Preparation Cheat Sheet!)

**HRP 07.02G****GUIDELINES FOR SETTING UP A STUDY BINDER AND REGULATORY DOCUMENTS BINDER**

**Introduction:** A study should be organized and well planned BEFORE the initiation of patient accrual. The Research Service recommends the following system for organizing all the documentation for a study. However, this is only a *guideline*. You may use any system that enables you to present study documents in a well-organized, up-to-date, complete, convenient way that is easily accessible to monitors and auditors. If documents are organized *and maintained* in such a systematic way, you should easily be in compliance with regulations and you should do well on any audit.

- It is common practice to set up a study binder/study file. for each subject, which is separate from the subject's medical chart. This study binder contains all information specifically related to a subject's progress through the study. It should be consistent with notes, reports or information in the subject's CPRS record. It should be freestanding from the medical chart (it should have copies/printouts of pertinent notes and reports). It should contain all the information (source documentation) used to complete the case report forms (CRFs) as well as substantiating documentation for notes and I/E criteria and the quality of the informed consent process.
- The study binder is different from the study Regulatory Binder. The Regulatory Binder contains documents that are required by the FDA, GCPs, the IRB, and the VAMHCS and which apply to the study as a whole. It is not used for data collection. In contrast, the study binder contains data collection forms (DCFs) and other source documents. It is the repository for data collected by your site on a particular subject or group of subjects.
- The study binder should ALWAYS be current, neat and organized. If there are missing or lost DCFs, there MUST be a note explaining the situation or where else they are located.
- CICERO, CPRS and other electronic data systems ensure that complete documentation is available. However, electronic systems are frequently inconvenient for the purposes of audits or monitoring visits. Therefore, paper documents serve as a convenient, more easily accessible method.

**Steps in preparing study and regulatory binders:**

1. Create a research file for each patient with a hanging folder or a binder. A hanging folder is more convenient for photocopying purposes and requires less space while a binder secures the pages in place.
2. Label the file with protocol number and patient study id number.

VAMHCS Research Service  
Guidelines for Setting up a Study Binder and Regulatory Documents Binder  
(Audit Preparation Cheat Sheet!)

3. Create the following (or similar) sub-sections for the file using manila folders or dividers. Make sure patient and/or study id number is written on the folders to allow easy replacement within the file:

- Patient entry: registration, signed consent form, HIPAA Authorization
- Eligibility checklists
- Time-Event Sheet or study flow sheet
- Response measurements / DCFs: organize by visit: “Recruitment”, “Screening”, “Enrollment/Randomization”, “Visit 1”, “Visit 2”, ...; by type: “Informed Consent”, “Notes”, “Vital Signs”, “Blood Draws”, ...; or other logical system)
- Copies of Enrollment and Progress Notes
- Interactions with participants by telephone or in person
- Treatment administration and accountability
- Adverse event reports for this patient
- Other observations or interventions
- Protocol deviations
- Laboratory, Pathology, Radiology reports: be sure to have PI or designate to sign off as “clinically significant” (CS) or “not clinically significant” (NCS).
- Correspondence: email, note-to-file, telephone documentation
- Questionnaires, diaries, etc.

4. There should also be a more global file which should contain the following:

- Master list of subjects and codes/identifiers
- Signature logs of staff, study monitors, etc.
- Screening logs
- Enrollment logs
- Monitoring logs
- Processing, Storage, Shipping logs of collected specimens
- Study drug/device accountability logs (unless kept in Investigational Pharmacy)
- An Accounting of Disclosure must be maintained for each and every disclosure of information from the study to a non-VA entity.
- DSMB reports
- IND Safety Reports/External SAE reports
- Internal audits/reports

VAMHCS Research Service  
Guidelines for Setting up a Study Binder and Regulatory Documents Binder  
(Audit Preparation Cheat Sheet!)

- Other types of documentation that covers the study as a whole as opposed to individual subjects.
5. Take the protocol apart by the above sections and create your own audit review form, i.e. your checklist for all protocol requirements, to ensure all requirements are met, and documented. If there are uncertainties clarify with the investigator. Write internal SOPs to standardize procedures. The Time-Event Sheet fulfills this in detail. As long as the TE Sheet is followed closely, all data should be collected, documented and well-organized.
  6. Keep a copy of all required elements from #5 and insert it in the corresponding section of your research file. For example, make a copy of the source documentation for each eligibility criterion. The auditor should be able to look at this sub-folder only and determine the eligibility of the patient. (Note: the auditor will check the original as well, so have the originals ready.) This should be done on an ongoing basis so when any auditor comes, including the RCO or external auditors such as the FDA and NCI, you may hand out this research file without any extra work or preparation. It will be self-explanatory and the audit will fly. This will only work if updates are done on an ongoing basis.

**Steps in preparing regulatory binders:**

1. Keep an organized and updated regulatory binder with the following elements:
  - IRB Submission (CICERO protocol)
  - All IRB-approved versions of the protocol and amendments
  - R&D Committee Submission
  - All correspondence including, but not limited to, that with the funding source or sponsor, and with applicable oversight entities including, but not limited to, IRB, R&D Committee, ORO, and FDA
    - IRB approval letters
    - R&D Committee letters/Approval
    - All continuing reviews and IRB/R&D approval letters
    - All amendment applications and IRB/R&D approval letters
  - All versions of IRB-approved consent form.
  - A master list of all subjects for whom informed consent has been obtained in the study
  - All 1571s/1572s and curriculum vitae for all investigators participating in the protocol unless exemption approved
  - Laboratory normal values, licenses and certifications

VAMHCS Research Service  
Guidelines for Setting up a Study Binder and Regulatory Documents Binder  
(Audit Preparation Cheat Sheet!)

- 10-9012s for studies using drugs
  - Financial/budget information (can be kept in a separate place)
2. Review the attached guide to major and minor violation assignment during an audit. This is intended as a *guide* and is subject to interpretation of the auditor. (Attachment 1)
  3. Know the institutional policies. If you are unsure, ask the Research Service (Office of Research Compliance) for guidance.

#### Other Research Documents

- Data analyses
- Reports including, but not limited to, abstracts and other publications

VAMHCS Research Service  
Guidelines for Setting up a Study Binder and Regulatory Documents Binder  
(Audit Preparation Cheat Sheet!)

**Attachments:**

“Clinical Trial Standards That <i>May</i> Be Applied During Audit Proceedings”	Attachment 1
“Guidelines for Time-Event Sheets”	Attachment 2
Examples of Time-Event Sheets	Attachment 3

**See Also:**

Research Service Guideline:	“Guidelines for Source Documentation”
Research Service SOP:	“Auditing Regulatory Documents Files”
Research Service SOP:	“Auditing Source Documents Charts”
IRB Self-Assessment Tool:	“Investigator Records Checklist”
IRB Self-Assessment Tool:	“Subject Records Checklist”
IRB Self-Assessment Tool:	“IRB Records Checklist”

VAMHCS Research Service  
 Guidelines for Setting up a Study Binder and Regulatory Documents Binder  
 (Audit Preparation Cheat Sheet!)

**ATTACHMENT 1:**

## Clinical Trial Standards That *May* Be Applied During Audit Proceedings

The guidelines below, were created at another research institution to help define major and minor violations. The VAMHCS or UMB campuses have NOT formally adapted these guidelines at this time, however, these guidelines can serve as a guide for the types of judgments auditors might make.

An exhaustive list of examples is not given, but the examples are intended to guide the reviewers in their assessment and categorization of specific violations. A major violation is generally defined as that violation which significantly alters the clinical effectiveness of the treatment or the evaluation of its toxicity. Minor violations occur when the protocol is not followed exactly, but the data are usable and valid.

**MAJOR VIOLATIONS****A. IRB/Consent**

- Failure to document properly obtained patient consent
- Consent dated after registration/treatment of pt.
- Consent not obtained in a language fully understood by the patient.
- Outdated consent used
- Failure to comply with Institutional Review Board (IRB) approval and reapproval guidelines, including lapsed or expired annual continuing reviews, inappropriate use of less than full-board review and approval and improper review of appropriate amendments or revisions (i.e. patient entered prior to IRB approval.)

**B. Eligibility**

- Does not meet eligibility criteria

**C. Pre-therapy**

- Pre-therapy tests of major importance were not done or not done prior to therapy
- Unacceptable frequency of minor violations

**D. Registration/Randomization/Stratification**

- Patient not registered prior to treatment
- Information given at registration is inconsistent with actual data in medical records chart (wrong stage, diagnosis, cell type, etc..)

**E. Forms/Data Submission/Special Requirements**

- Submission of data outside of protocol guidelines
- Incorrect data (substantial amounts of data are incomplete or inaccurate for 1 or more forms)

**MINOR VIOLATIONS****A. IRB/Consent**

- Consents do not have date/witness signature
- Consents do not have unique patient identifiers on each page

**B. Eligibility**

- Small variations of criteria with reasonable explanation/approval (Phase II and III only)

**C. Pre-therapy**

- Missing a small number of minor tests

**D. Regist./Randomization/Strat.**

- Date of birth/date of diagnosis inconsistent

**E. Forms/Data Submission/Special Req.**

- Incorrect data (sporadic pieces of data are incomplete or inaccurate)

VAMHCS Research Service  
 Guidelines for Setting up a Study Binder and Regulatory Documents Binder  
 (Audit Preparation Cheat Sheet!)

**F. Treatment**

- Inappropriate administration of non-protocol anticancer treatment (additional drugs, radiation, etc.)
- Failure to modify doses according to protocol, (especially where doses are expected to have a major impact on outcome)
- Failure to dose reduce in the face of severe toxicity
- Failure to dose escalate on a dose-intensification study
- Inappropriate dose reduction on a dose intensity study
- Repetitive or systemic errors in dosing
- Repetitive or serious errors in dosing, timing or schedule
- Wrong route in administration
- Failure to document drug administration
- Error in Concomitant Medications
  - Failure to administer an important medication or the administration of a prohibited medication or treatment

**G. Toxicity**

- Failure to obtain the required protocol baseline studies required to effectively assess toxicity toxicities
- Failure to get necessary follow-up studies to assess toxicity as required by protocol
- Unreported major toxicity (Grade 4)
- Repetitive failure to report Grade 2 & 3 toxicities
- Serious or repetitive failure to properly characterize toxicity or grade
- Failure to file required NCI Adverse Reaction Reports according to protocol when applicable

**H. Required Evaluation**

- Unacceptable frequency of required evaluation violations

**I. Response/Follow-Up**

- Failure to assess disease status according to the required protocol guidelines either pre-therapy or in response to treatment review
- Failure to obtain baseline CT scan to document pre-therapy tumor size
- Failure to obtain the required follow-up CT scan to document persistent reduction in tumor size to define a response as specified in the protocol
- Inaccurate assessment of tumor response
- Substantial inaccuracy in the detection of cancer (as in a prevention study) or determination of cancer progression

**J. Data Quality**

- Unacceptable level of missing documentation
- Missing charts

**F. Treatment**

- Wrong antiemetic given as per protocol
- Wrong doses (<25% deviation without explanation for one dose; or 25% deviation from dose reduction indicated)
- Wrong timing (<2 week delay with acceptable explanation (i.e. holiday, bad weather, flu sx))

**G. Toxicity**

- Not reporting occasional grade 3 toxicities
- Frequent non-reporting of grade 1 & 2

**H. Required Evaluation**

- Missing a small number of minor required evaluations or tests

**I. Response/Follow-Up**

- Missing minor measurements
- Missing one of several measurements used to assess response and scans unavailable for

**J. Data Quality**

- Acceptable level of missing documentation with explanation
- Minor and sporadic missing tests

VAMHCS Research Service  
Guidelines for Setting up a Study Binder and Regulatory Documents Binder  
(Audit Preparation Cheat Sheet!)

- Repetitive failure to obtain protocol specified laboratory tests or diagnostic studies
- Frequent inaccuracies or errors in submitted data
- Infrequent errors in submitted data

VAMHCS Research Service  
Guidelines for Setting up a Study Binder and Regulatory Documents Binder  
(Audit Preparation Cheat Sheet!)

**ATTACHMENT 2:****GUIDELINES FOR USE OF TIME-EVENT SHEET (for example\*)**

1. This form is meant to help study staff accomplish all the tasks required for a patient's completion of a study. It assumes that the study coordinator and other study personnel will use it as a checklist on study days. For the sake of space and time I use key words and phrases in order to remind staff what needs to be done. Remember that the study protocol and other materials contain MUCH more detailed information should questions arise.
2. The TE Sheet includes events that are study requirements but also some that are clinical requirements for our unit / PI. The "non-study events" include daily vital signs (even when not required by the protocol), I/O's (which happen to go from 6am to 6am in our unit), q8hr PICC line/heparin lock flushes, discussion of our unit's "Rules and Regulations" with the subject, etc.
3. Whenever there is an empty box with "AM", "PM", "ml", "kg", etc., some piece of data should be inserted. The time-event sheet is meant to be redundant with some Data Collection Forms (DCF's) in order to increase chances that essential information will be obtained. The data are meant to be transcribed to the appropriate form when time allows. For example: weights to the "Weight Summary Sheet", urine volumes to the I/O or "Urine Processing Sheet".
4. Empty boxes for insertion of times are ESPECIALLY important. At times when a scheduled time can be predicted or approximated, that time has already been entered. However, when scheduled times are timed from an unpredictable event (such as patient voids, actual time of dosing, etc.) the event becomes "t<sub>0</sub>" ("time zero") and all subsequent blood draws, urine collections, etc. are timed from this. As soon as the event occurs, someone (preferably the coordinator) must be able to take a few minutes to accurately fill in the blanks for scheduled times for the remainder of the study day. If this is not done, mistakes in timing are sure to occur.
5. Once scheduled times are filled in, as the day proceeds and study events occur, put a simple checkmark in the grey spaces of the "Actual Time" column if the event occurred on time. If the actual time was different from the scheduled time then enter the actual clock time in the grey space. It is important that SOMETHING be entered into each space so that it is easy to see at a glance where you are/what is your next step (this can be crucial on the hectic dosing mornings and is ideally done by a coordinator whose only task is to coordinate the dosing by/with others and not to do it her/himself).
6. The "Comments" column is for quick jots of reminder notes to be documented later in more detail on appropriate DCF's. For example: "HA" to document the start of the patient's complaint of a headache. This would later be documented on an Adverse Event Form but would at least remind you of what and when something happened.
7. "Events Observed" column is for an observer to document that an event occurred. In our unit, the person actually performing an action signs it off on the appropriate DCF (vital signs, blood draw, etc.) that s/he did it. Therefore the coordinator or other observer can sign off on the TE Sheet that s/he knows it was done.

(\*adapted from a BVAMC research unit's use of T-E Sheets)

VAMHCS Research Service  
 Guidelines for Setting up a Study Binder and Regulatory Documents Binder  
 (Audit Preparation Cheat Sheet!)

**ATTACHMENT 3: Example of a Time-Event Sheet**

**A: Pages 1 and 2 of an outpatient study. These T-E sheets were created in Excel; in actual use, they are sized to fit onto one page per visit if possible. Headers contain the name of the protocol; footers contain "P. \_\_ of \_\_"**

Subject ID: \_\_\_\_\_

Emergency /Contact #'s

DATE: \_\_\_\_\_

EVENTS; done by CRU staff unless otherwise indicated	COMMENTS	INITIALS
<b>Date:</b>	<b>DAY 0: BASELINE</b>	
Check for copy of SIGNED informed consent form		
Make sure that subject has been activated in DHCP system		
Review I / E criteria	Dr. XXXXX	
Sbjt has had no antidepressants for at least 2 months		Y / N
Review concomitant meds		CRF p.76
Psych testing	Dr. XXXXX	
Vital Signs	Wt (w/o shoes)	CRF p.
<b>Sitting BP</b>	HR	RR
		T
Notify J.Haywood of subject enrollment		
Obtain WEEK 1 bottles from J.Haywood	#caps am bottle	#caps pm bottle
Study Medication Record		CRF p.75
Instruct sbjt:	1 cap in am from "am" bottle, 1 cap in pm from "pm" bottle same time every day if poss (ex: 8-9am, 5-6pm) do not take any OTC or other med without checking w study staff phone numbers for questions/emergencies next appointment bring med bottle to next appointment	

**VAMHCS Research Service**  
**Guidelines for Setting up a Study Binder and Regulatory Documents Binder**  
**(Audit Preparation Cheat Sheet!)**

**remember the time s/he took 1st dose**

- Begin AE monitoring
- Begin NO PSYCHOTROPIC MEDS except: temazepam, lorazepam,  
 zolpidem or oxazepam for sleep
- Continue concomitant med monitoring
- Write progress note
- Notify XXXXXXXX of next appointment
- Submit **Encounter Form** for this visit

**DAY 7: VISIT 1**

- Review AE's CRF p.
- Review concomitant meds / changes CRF p.76
- Sbjt tolerating study med? Y / N
- No psych testing this visit

Vital Signs Wt (w/o shoes) CRF p.

<b>Sitting BP</b>	HR	RR	T
-------------------	----	----	---

Obtain WEEK 1 bottles from sbjt CRF p.

#caps remaining am bottle	#caps remaining pm bottle	Doses missed?
---------------------------	---------------------------	---------------

Obtain WEEK 2 bottles from J.Haywood

#caps am bottle	#caps pm bottle
-----------------	-----------------

Study Medication Record CRF p.75

**If sbjt withdrawn from study, complete Day 56 visit**

Reinforce with sbjt:

1 cap in am from "am" bottle, 1 cap in pm from "pm" bottle  
 same time every day if poss (ex: 8-9am, 5-6pm)

VAMHCS Research Service  
Guidelines for Setting up a Study Binder and Regulatory Documents Binder  
(Audit Preparation Cheat Sheet!)

	do not take any OTC or other med without checking w study staff	
	phone numbers for questions/emergencies	
	next appointment	
	bring med bottle to next appointment	
	Continue AE monitoring	
	Continue NO PSYCHOTROPIC MEDS except: temazepam, lorazepam, zolpidem or oxazepam for sleep	
	Continue concomitant med monitoring	
	Write progress note	
	Notify XXXXXXXX of next appointment	
	Submit <b>Encounter Form</b> for this visit	



**VAMHCS Research Service**  
**Guidelines for Setting up a Study Binder and Regulatory Documents Binder**  
**(Audit Preparation Cheat Sheet!)**

Blood Draw

**Blood Draw Sheet**

Plan to stagger breakfasts and dosing 15 mins apart

**Menu Sheet**

**Randomization:**

**CRF p**

**Sbjt 01**

DOB:

M / F

Must meet criteria:

Meets I/E's:

- Hx previous L-dopa Rx? (N or 2wk washout)
- Hx other dopaminergic Rx? (N or 2wk washout)
- Epworth Sleep Score  $\geq 9$ ? (N)
- Meets other I / E criteria? (Y)

- Pt has signed ICF? (Y)
- All screening labs reviewed & meet criteria? (Y)

Call:

1-877-XXX-XXXX

Enter User ID:

Enter Password:

Choose Menu Option 1

Enter Patient info above

Randomization #

Med Kit #

Reenter Med Kit# to confirm randomization

If error in entering DOB/gender, enter "\*"; see manual

**Sbjt 02**

DOB:

M / F

Must meet criteria:

Meets I/E's:

- Hx previous L-dopa Rx? (N or 2wk washout)
- Hx other dopaminergic Rx? (N or 2wk washout)
- Epworth Sleep Score  $\geq 9$ ? (N)
- Meets other I / E criteria? (Y)

- Pt has signed ICF? (Y)
- All screening labs reviewed & meet criteria? (Y)

Call:

1-877-XXX-XXXX

Enter User ID:

Enter Password:

Choose Menu Option 1

Enter Patient info above

Randomization #

Med Kit #

Reenter Med Kit# to confirm randomization

If error in entering DOB/gender, enter "\*"; see manual

Notify J.Haywood of randomization

Obtain study drug from pharmacy

**T=-30 mins**

Breakfast 15 mins apart

apprx 0830

Sbjt 01

Sbjt 02

Scheduled:	Actual
Scheduled:	Actual

**Day 1 continued on next page**