Title:	Cerebral Spinal Fluid		
Origination Date:	08 April 2013	**Total Pages:**	19
Effective Date:	08 April 2013	**SOP Number**	LTC-SOP-67 v1.0
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	Version Effective Date (dd/mmm/yy)	Comments
Revision History		

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1 Purpose

The purpose of this SOP is to describe procedures for the collection and processing of cerebrospinal fluid (CSF).

2 Scope

This procedure is to be used to standardize the collection and processing of cerebrospinal fluid samples across protocols. Network protocol-specific instructions supersede those in this SOP.

3 Background

HIV enters the brain early after systemic infection and the virus may be recovered from the brain throughout the life of the patient. Neurologic impairment associated with ongoing infection in the brain compartment is common and can be related to the ongoing infection. Most effective treatment of HIV infection and efforts to eradicate HIV must consider the special challenges of the virus in the brain. The brain and its environs are a recognized body compartment pathophysiologically isolated by the blood-brain barrier which is a complicated barrier resulting in differing penetration of drugs to the brain as well as modified access of components of the immune system to the compartment. There is evidence that the virus may evolve independent of the systemic infection within the brain compartment. Sampling the brain is dangerously invasive, but an approximation of the brain compartment is safely available by sampling the cerebrospinal fluid (CSF) via lumbar puncture (LP). CSF collection thus is an important tool utilized to monitor the status of the immune response, drug delivery and viral status close to the brain. CSF can be used to test for concurrent diseases of importance affecting the central nervous system (CNS, e.g. syphilis, CMV, Cryptococcus, TB), to assess the activity of the immune response through analysis of cytokines, chemokines, immunoglobulins, and the cellular reaction, and to ascertain the status of the blood brain barrier (protein, albumin). CSF HIV RNA levels can be assessed using standard assays, ultra-sensitive assays, or single copy assays, and genetic analysis of CSF HIV species can be used to examine compartmentalization and evolution, CNS viral tropism and resistance. Phenotypic assays of CSF can include flow cytometry of CSF for characterization of cells trafficking to the CNS, as well as tropism, replication capacity, and fusogenicity of CSF-derived HIV species, among other parameters.

4 Budgetary Considerations

4.1 See Budgetary Considerations Worksheet, Appendix I.

4.2 Room/facility fees.

4.3 Salary support for physician and other personnel.

4.4 Supplies including LP trays, Sprotte needles.

4.5 Subject reimbursement.

4.6 Sample analyses.

4.7 Laboratory costs vary widely depending on specific assay(s) chosen for protocol.

4.8 Processing, shipping and storage at BRI are additional protocol costs to be considered.

5 Authority and Responsibility

5.1 The Cure Transformative Science Group and Network Laboratory Director (or his/her designees) have the authority to establish, review and update this procedure.

5.2 The ACTG/IMPAACT Laboratory Technologist Committee (LTC) is responsible for the maintenance and control of SOP documentation.

5.3 The Site PI and Laboratory Director are responsible for the implementation of this SOP and for ensuring that all appropriate personnel are trained. Site-specific laboratory SOPs must:

5.3.1 Include, without procedural modification, the portions of the current version of the LTC SOP that are used within the network site-affiliated laboratory.

5.3.2 Reference the current version of the LTC SOP.

5.4 All laboratory technicians are responsible for reading and understanding this SOP prior to performing laboratory-related procedures described for protocol specimens.

5.5 The site PI and designees are responsible for understanding and adhering to the patient preparation and specimen collection components.

6 Requirements

6.1 Lumbar puncture is generally a safe procedure.[(1)] The two major conditions associated with increased risk are:

6.1.1 Patients with an elevated bleeding risk.

Note: Anticoagulated patients (or those with INR >1.5 due to severe liver disease), or those with very low platelet counts (<40K) are at increased risk for bleeding that might form a hematoma following LP resulting in nerve root compression and potential lasting harm. In patients with any history of excessive bleeding or a history of low platelet count or abnormal PT/PTT, elective LP should be done only after confirming that PT/PTT are normal and there are adequate platelets. This complication is very rare, but even the small risk should not be undertaken for elective research procedures.

6.1.2 Patients with asymmetric increased intracranial pressure.

Note: Patients with asymmetric brain masses may have an increased risk of brain herniation and death following LP. If the neurologic exam is non-focal this risk is minimal. Patients with focal deficits require further evaluation prior to undergoing LP. Elective LP should not be performed when there is substantial asymmetric mass effect. Expert opinion may be required to assess risk based on imaging studies, and that risk may be weighed against the proposed value of CSF sampling at that point.

6.2 Inclusion Criteria

6.2.1 Ability to give informed consent.

6.2.2 Demonstration of non-focal neurologic exam. Subjects with focal findings should have expert assessment for mass affect prior to lumbar puncture.

6.2.3 INR ≤ 1.5

6.2.4 Platelets ≥ 400x10^3/uL

6.3 Exclusion Criteria

6.3.1 Inability to give informed consent, or in the case of a pediatric collection, inability to obtain consent from parent or guardian.

6.3.2 Focal findings on neurologic exam.

6.3.3 INR > 1.5

6.3.4 Platelets < 150 x 10^3/uL

7 Reagents and Consumables

7.1 Reagents and Consumables for Specimen Collection

7.1.1 Lumbar puncture tray

Note: Most of items listed below are included in the lumbar puncture tray unit.

7.1.2 Povidone-iodine (10%) (Betadine®) and/or isopropyl alcohol (70%) with applicators or sterile pads

7.1.3 Fenestrated drape

7.1.4 Optional: Local anesthetic (lidocaine 1%, (10mg/mL) 1-2 mL)

7.1.5 Syringe with small needle (1-2 inch, ~23g) for use with local anesthetic

7.1.6 3.5 inch lumbar puncture needle (gauge dependent on purpose of procedure).

Note: Smaller needles incur less risk of post-procedure headache, but may be more difficult to use. In a clinical setting requiring CSF drainage (treatment of increased intracranial pressure during meningitis) a large gauge (16 to 20 g) needle may be used for easier removal of large volumes of fluid and to encourage subsequent leakage. For diagnostic and elective (including research) purposes, smaller needles are preferred (22 g needles recommended). Use of a pencil point (Sprotte) type needle reduces the incidence of post lumbar puncture headaches and is strongly encouraged for research-related lumbar punctures.[(2)] Instructional video for use of pencil point (Sprotte) needle is available at the HANC ACTG/IMPAACT Lab Manual website:

https://www.hanc.info/labs/labresources/procedures/Pages/actgImpaactLabManual.aspx

7.1.7 Sterile tubes with caps for CSF collection. Polypropylene tubes are recommended to decrease possible binding of protocol analytes to the tube surface.

7.1.7.1 Four 10mL disposable centrifuge tubes, sterile, graduated for standard collections.

Note: these collection tubes are often included in the LP tray unit.

7.1.7.2 Additional 15mL disposable centrifuge tubes, sterile, graduated, polypropylene, as needed for larger volumes for research purposes.

Note: These tubes are different from the routine CSF collection tubes included in the LP tray units. Depending on the research analyte, the research samples should be collected in these tubes only.

7.1.8 Sterile gauze pads

7.1.9 Band-Aid

7.1.10 Sterile gloves

7.1.11 Optional Equipment

7.1.11.1 Three-way stopcock attached to sterile manometer for measuring opening and closing CSF pressures.

7.1.11.2 Sterile flexible extension tubing

7.1.11.3 Face Mask.[3]

7.2 Reagents, Equipment and Consumables for Specimen Processing

7.2.1 Class II biosafety cabinet (BSC) uL

7.2.2 Centrifuge, low-speed (capable of 300 to 1000 x g), with swinging bucket rotor, refrigerated preferred, ambient acceptable

7.2.3 Micropipettes, range 200uL, 100uL and disposable tips

7.2.4 Pipet-Aid (cordless preferred)

7.2.5 Disposable 2mL, 5mL serological pipets

7.2.6 2 to 8°C refrigerator

7.2.7 -20°C (or lower) freezer ***without*** automatic defrost (for FBS storage)

7.2.8 -80°C freezer (-65 to -95°C)

7.2.9 -150°C mechanical freezer (if LN2 freezer is not available for long-term storage)

7.2.10 Cryogenic vials (cryovials), 1.8 to 2mL, external threaded, screw cap with o-ring, sterile, polypropylene only, conical, skirted (Sarstedt No. 72.694.006)

7.2.11 Cryopreservation Media (10% DMSO in 90% FBS)

7.3 Cryopreservation

Use one of following options according to manufacturer's instructions. The Stratagene StrataCooler® and BioCision® CoolCell are preferred.

Note: If manufacturer's instructions aren't followed, a validation study must be completed.

7.3.1 Stratagene StrataCooler® Cryo

StrataCooler® Cryo must be at 2 to 8°C before starting the cool down of the cryovials. Do not place cryovials in a StrataCooler® Cryo that is below an initial temperature of 2°C.

7.3.2 BioCision® CoolCell

Make sure that all parts of the CoolCell, including the central ring, return to room temperature between uses.

7.3.3 NALGENE® Mr. Frosty, 1°C/minute cryo-freezing container

Mr. Frosty should be stored at ambient temperature (15-30°C) between uses.

The isopropanol level must be correct and the isopropanol must be completely replaced after the fifth freeze-thaw cycle. A log must be used to track freeze/thaw cycles and reagent changes.

7.3.4 Control-rate freezers, such as CryoMed® Freezing Chamber (Gordinier)

8 Environment and Personnel

8.1 Preferred environment: Exam room

8.2 Required personnel

8.2.1 One (1) trained health care provider

9 Procedures

9.1 Pre-sampling procedures

9.1.1 Explain study procedure and consent participant.

9.1.2 If drug levels are to be measured, time the sampling procedure appropriately to dosing and comparative serum blood levels as specified in protocol.

9.1.2.1 List and arrange for collection of concurrent blood labs to be obtained for comparison of values in different compartments (e.g. HIV-RNA in levels in plasma, serum albumin levels).

9.1.2.2 List and arrange for collection of study and/or clinical labs to be obtained (e.g. CSF glucose levels).

9.2 Sampling Procedure

9.2.1 Position patient appropriately for procedure.

Note: Careful positioning of the patient is important. In a massage chair a comfortable resting position with head down and back in a convex arch makes the LP easier. If the lateral decubitus position is used the patient should be positioned with back near edge of table with entire back and both shoulders as exactly perpendicular to the plane of the table as possible. Curling up (in a fetal position) with legs flexed and head and neck curled forward (head supported by pillow) allows easiest access.

9.2.2 Palpate L4-5 or L3-4 found just above iliac crest.

9.2.3 Clean entire lower spine using three applications of betadine, or other sterilizing skin preparation, using a circular motion starting at site of intended puncture and radiating outward.

9.2.4 Drape patient to allow access to sterile skin over lumbar region.

9.2.5 Insert Lidocaine, applying in superficial subcutaneous tissue, then more directly into deeper layer to numb skin down to approximately 1 inch at LP site. Allow several minutes for Lidocaine to take effect.

9.2.6 Insert LP needle at midline position, entering just above the lower spine of the interspace and advancing toward the umbilicus.

Note: Sprotte needle is recommended. If a pencil point (Sprotte) LP needle is used, a shorter 'introducer' cutting needle (which should be part of the Sprotte system) is inserted either prior to or concomitantly with the LP needle. Using midline positioning, enter just above the lower spine of the interspace and advance toward the umbilicus. Generally a 'pop' is felt as the thecal sac is penetrated, but periodic stops and removal of the stylus of the LP needle to be sure that the space has not already been penetrated is good practice.

Note: If a standard cutting LP needle is used, bevel should be oriented sagitally.

9.2.7 Measure the opening pressure, if indicated.

Note: When fluid begins to drip from the LP needle, stopcock and manometer are inserted for measurement of opening pressure if indicated (only performed if the LP is done in the lateral decubitus position). The fluid is allowed to rise in the manometer until it equilibrates. Some fluctuation of the level with deep breathing assures continuity of the space with the manometer, and the level of the fluid in the tube designates the opening pressure. This fluid may then be drained into a collection tube using the stopcock.

9.2.8 Collect CSF by allowing it to drip into tubes held below the needle or attached with flexible tubing. 10-30mL is sufficient for research lumbar punctures.

Note: Larger LP needles allow faster flow and more rapid collection. A syringe may be used to gently withdraw CSF but this may increase discomfort.

9.2.9 Replace stylet in LP needle and withdraw.

9.2.10 Place Band-Aid over puncture wound.

9.2.11 Patient may benefit from a short rest period. Offering fluids may help with hydration and reduce risk of LP headache.

9.3 Post-sampling procedures

9.3.1 The most common complication is orthostatic headache (12-24 hours post-procedure) believed to be due to post-procedure leakage from puncture site.

Note: The primary therapy for this is to lie down. The headache subsides within minutes of lying down and if the patient stays inactive over a day or two the leakage stops. In rare cases where it is prolonged, or the patient must move about, a blood patch can be injected over the site of the puncture, effectively blocking the leakage. An anesthesiologist skilled in epidural injections most often does this procedure. If a pencil point needle is used the risk of LP headache is small (considerably, <10%[1]) and a blood patch is rarely needed.

9.3.2 Patient should stay hydrated and limit strenuous activities, especially exercise and lifting of heavy weights.

9.3.3 Follow-up contact with the patient on the day following procedure is recommended.

9.3.4 Heat and over-the-counter analgesics may be used if low back pain at the site of the puncture develops.

9.3.5 Patient should be seen if any indication of significant increased disability is experienced.

9.4 Timing of CSF Sampling

9.4.1 There is no theoretical minimum time interval between lumbar punctures. CSF that is removed is replaced in <1 hour, so dynamics of CSF production are generally not a factor.

9.4.2 Maximum number of protocol CSF samplings per year should be determined by the protocol team and will require approval by the local IRB or equivalent body.

9.5 Standard Collection Volumes for adults and children

	Total CSF volume (mLs)[4-8]	Safe CSF volume to take at LP (mLs)
Adult	120-170	≤40[6]
Adolescent	120-170	12-17[7]
Young child	60-150	10-15[7]
Infant	40-90	6-9[7]
Term Neonate	20-40	2-4[7]

*Adults replace CSF at a rate of approximately 18-22 mL/hr. By the age of 2, children reach a CSF output equivalent to approximately 64% of that of a 15 year old[4, 5, 7].

9.5.1 Refrigerate until processing is complete and samples are frozen unless otherwise indicated by protocol.

9.5.1.1 Fresh CSF is used for hematological assessments (presence of RBCs reflect blood contamination, WBC are normally 0-5/uL and should not include polymorphonuclear cells).

9.6 Cultures for bacteria and fungi, antigen testing for Cryptococcus, serology for syphilis (VDRL), and PCR testing may be considered in specific circumstances.

9.7 Fractionation of CSF into Cells and Supernatant

9.7.1 Processing CSF samples depends on the intended use. Protocol-specific processing instructions supersede those detailed in this SOP.

9.7.1.1 Refrigerate until processing is complete and samples are frozen unless otherwise indicated by protocol. Use tubes collected later in the procedure to avoid possible RBC contamination. Do not use CSF collected in tube #1. If multiple tubes are collected for fractionation, divide the whole CSF evenly across all the tubes before centrifuging (6-10mL per tube).Centrifuge all tubes at 250xg for 15 min.

9.7.1.2 Transfer supernatant into 0.5 – 1.0mL aliquots and store at -80° C. (defer to protocol instructions), leaving behind approximately 0.05mL of CSF supernatant in each centrifuged tube. Resuspend the cell pellets by gently pipetting the fluid up and down.

9.7.1.3 Add 1mL of cryopreservation media to each tube containing a cell pellet. Aliquot resuspended pellets evenly into appropriately labeled cryovials.

9.7.1.4 Immediately transfer all cryovials to the controlled-rate freezing container. Follow manufacturer's instructions for use and transfer aliquots to final storage.

9.7.1.5 Long-term storage should be in gas-phase LN2 or at -150° C or colder (defer to protocol instructions).

9.7.2 Aliquot numbers and volumes should be sufficient to allow for protocol assay needs without incurring the need to refreeze samples, which may compromise sample integrity.

9.7.3 The total volume of CSF available is generally limited. Typical research taps acquire approximately 20 mL, with up to 50 mL being collected on rare occasions. Larger volumes might increase risk of headache, and will prolong the procedure.

Note: Protocols may need to prioritize assay aliquots to account for samples that do not have sufficient volume for all assays.

9.8 CSF Processing – Pharmacology

9.8.1 For pharmacology collections, the timing of CSF collection relative to the time of prior dose(s) of pharmacological agents is important. Therefore, the precise time of the last dose(s) of drugs of interest taken should be collected on study Case Report Forms (CRF). In addition, the precise time of the CSF collection should also be recorded.

9.8.2 To allow measurement of multiple drugs, up to 5mL of CSF should be collected. Consult with the testing laboratory to determine exact volumes needed for planned pharmacological assays.

9.8.3 Centrifuge at 10,000xg for 5 min. Transfer supernatant to cryovials per testing lab instructions for storage at -80° C.

9.8.4 Drug stability will be a factor in determining any time limits which may need to be applied to processing. Consult with the testing laboratory to determine if time limited processing is appropriate.

9.9 CSF Analyses

9.9.1 Potential study clinical evaluations to be considered:

Table 1

	Volume	Evaluations
Tube 1	1mL	Chemistry (i.e. protein, albumin, etc.)

Tube 2	0.5-1mL	Hematology (i.e. RBC, WBC and differential etc.)
Tube 3	1-3mL	Other evaluations (bacterial and fungal smears and/or cultures, serological such as cryptococcal antigen, VDRL or RPR, etc.), as needed
Extra tubes	20-25mL	Research-related assays (i.e. viral PCR assays etc.)

9.9.2 Potential immunological evaluations to be considered:

Table 2

Volume	Evaluation(s)
0.5mL (each)	Neopterin, IP-10, MCP-1
0.5mL	Multiplex cytokine and biomarker assays
0.5mL (each)	Additional chemokine or neural markers if measured by ELISA, or up to 0.5mL for all markers if run on a multiplex assay
1.0mL	Immunoglobulins
15-35mL	Flow cytometry

9.9.3 Potential virological evaluations to be considered:

Table 3

Volume	Evaluation(s)
1-1.5mL	PCR for virus (HIV, CMV,HSV, VZV,JC, EBV, etc.)
1.8mL	HIV-RNA using standard assays (depends on platform used)
3-7mL	HIV-RNA Single Copy Assay – Consult testing lab for optimal volume
1-2mL	Viral sequencing including genotype and single genome amplification, HTA, whole genome sequencing (requires ~500-10,000 copies/mL, depending on assay)

9.9.4 Pharmacological:

9.9.4.1 Drug concentration measurements – consult testing lab for optimal volume.

10 Forms

10.1 Informed consent

10.2 Patient informational materials

10.3 Study-specific case report forms

11 Limitations

11.1 Limitations are assay dependent.

12 Literature References

Clifford video on LP technique using massage chair/Sprotte needle, NEJM video on LP: Ellenby MS et al, NEJM 2006; 355:e12

[ACTG Cerebral Spinal Fluid SOP, ACTG Cerebral Spinal Fluid Working Group, 12 Dec 2011]

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13 Acknowledgments

13.1 ACTG HIV Reservoirs Sampling Focus Group

13.2 ACTG CSF Working Group

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14 Appendices:

Appendix I: Budgetary Considerations Worksheet

Appendix II: Sample Consent Language for Spinal Tap

Appendix I: Budgetary Considerations Worksheet

Direct costs

Component	Cost per patient visit	Comments
Room/Facility Fee		
Salary support for Physician		
Salary support for other personnel		
Subject reimbursement		$75 to $150 (in 2012)
Supplies		See Reagents and Consumables section for list.
Sample analyses		Laboratory costs vary depending on tests required.
Sample processing, storage and shipment		For samples processed by ACTG processing lab and shipped to BRI for storage.

Appendix II: Sample Consent Language for Spinal Tap

INTRODUCTION

You are being asked to participate in this study because [Insert basic description of participant qualification criteria].

The doctor in charge of this study at this site is: (insert name of Principal Investigator). Before you decide if you want to be a part of this study, we want you to know about it.

This is a consent form. It gives you information about this study. The study staff will talk with you about this information. You are free to ask questions about this study at any time. If you agree to take part in this study, you will be asked to sign this consent form. You will get a copy to keep.

WHY IS THIS STUDY BEING DONE?

The purpose of this study is [Insert basic description of the study goals, general information about what will happen to participants in the study and the number of participants expected to enroll in the study].

WHAT DO I HAVE TO DO IF I AM IN THIS STUDY?

If you join this study, you will need to be seen in the clinic [Insert basic description of number, frequency and duration of study visits]. The study staff will tell you about how long each day and visit could be. You may need to have extra visits if you become ill or develop side effects.

The drugs that will be provided are [List any applicable drugs, or remove from consent if not applicable. If drugs are listed, give basic description of what condition(s) the drugs treat, if there are differences in drugs based on study groups, how the drugs are taken and the frequency of dosing].

If you agree to be screened for and/or enter this study, the following procedure will occur:

If you agree, you will undergo a procedure called a spinal tap, also known as a lumbar puncture, in order to sample your cerebrospinal fluid. After asking you to lie down on your side, or positioning you comfortably (sometimes done in a seated position) and cleaning off an area of your lower back with sterilizing solutions, a doctor will inject local anesthesia under your skin with a small needle to make your skin numb. You may feel a sharp prick like a bee sting when this small needle enters your skin, then a burning feeling when the local anesthetic is first injected. The doctor will then identify the space between two of your lower backbones, and put a thin needle into this space to withdraw a small amount (approximately __ teaspoons) of spinal fluid. Collection of the fluid takes approximately 10 minutes, and the entire spinal tap requires about 30 minutes. You may be asked to lie flat for approximately 30 minutes after the spinal tap; so the total amount of time the procedure will take is approximately 60 minutes. During your visit, a small amount of blood (approximately __ teaspoons/tablespoons) may be drawn from a vein in your arm. The spinal tap and blood draw may be repeated at multiple study visits.

<u>If you do not enroll into the study:</u>

If you decide not to take part in this study or if you are not eligible to participate, we will still use some of your information. As part of the screening to see if you can participate in the study, some

demographic (for example, age, gender, race), clinical (for example, disease condition, diagnosis), and laboratory information is collected from you. This information will be used so that ACTG researchers may help determine whether there are patterns or common reasons why people do not join a study.

WHAT IF I HAVE TO PERMANENTLY STOP TAKING STUDY-PROVIDED DRUGS AFTER I START TAKING IT/THEM?

During the study:

[Insert basic description of actions that will be expected to occur]

After the study:

[Insert basic description of actions that will be expected to occur]

WHAT ARE THE RISKS/DISCOMFORTS ASSOCIATED WITH THESE PROCEDURES?

For these descriptions "frequent" events will occur in 10 to 50% of subjects, "occasional" events will occur in 1 to 10%, and "rare" events will occur in less than 1% of people.

Spinal tap: Spinal taps are associated with an occasional risk of headache. Based upon their previous experience with similar studies, the investigators expect the risk of any headache to be about 6 percent (6 headaches in 100 spinal taps). Each separate spinal tap carries this same 6 percent risk of headache. Usually, such headaches feel only like light pressure inside the head and go away after one to two days. However, occasionally a more painful headache can persist for a longer time and, in the worst case, can be very uncomfortable (perhaps one in 5 of those who develop headache). These headaches are made worse by standing or sitting and are relieved by lying down. If this should occur, you will be offered medication and advice regarding pain relief, including referral to the Anesthesia Service for administration of a 'blood patch' if needed. Post-lumbar puncture headache is felt to be due to continued leakage of spinal fluid out of the hole made by the spinal needle in the membrane sac that holds the spinal fluid. A blood patch involves injection of some of your own blood in the area of the spinal puncture. The blood forms a clot which then 'plugs' the hole. This is effective in eliminating the headache in about 90 percent of people with post-spinal tap headache. The investigators will cover the costs of this blood patch procedure should it be needed.

Approximately 50% of people experience slight back discomfort at the time of the spinal tap, mainly due to placement of local anesthetic that stings as it is injected into the skin. This sensation is very brief, lasting seconds only. As the needle advances, there may also be some discomfort. After the spinal tap, there is an occasional risk of a mild bruise-like soreness at the needle site which may persist for a day or two before resolving.

Additionally, some participants may feel lightheaded and nauseated during and/or after the spinal tap procedure. This is rare, but if this occurs you will be asked to lie down until the symptoms resolve or improve. Vital signs will be taken before you are discharged.

Spinal taps can cause other very rare but more severe problems. In patients with certain brain conditions a spinal tap can cause the brain to shift within the skull to cause brain 'herniation' which can cause worsening of neurological dysfunction and even lead to death. Your neurological evaluation, and review of your clinical records, prior to the spinal tap will detect these conditions and the spinal tap would not be performed. A second complication is bleeding into the area of the spinal canal where the

needle is placed and compression of the nerves in that area which could lead to paralysis. This is also very rare, particularly in individuals who do not have problems with blood clotting. That is why we ask you about your tendency to bleed and check on certain results of laboratory tests related to blood clotting. An additional risk is bleeding into the spinal fluid space, which can lead to back pain, headache and nausea along with fever lasting for several days.

Venipuncture: The risks of having a small amount of blood drawn include temporary discomfort from the needle stick, bruising and, very rarely, infection.

ARE THERE BENEFITS TO TAKING PART IN THIS STUDY?

If you take part in this study there may be a direct benefit to you, but no guarantee can be made. [Insert basic description of any possible benefits that may incur from study participation] It is also possible that you may receive no benefit from being in this study. Information from this study may help others who have conditions similar to yours.

WHAT OTHER CHOICES DO I HAVE BESIDES THIS STUDY?

[Insert basic description of other options that may be available] Some study-provided drugs, laboratory tests to monitor how well these drugs are working, and quality medical care may or may not be available to you outside the study. The clinic staff will discuss with you other treatment choices in your area and the risks and benefits of all choices.

[Sites may insert general information about other local study-specific treatment availability]

WHAT ABOUT CONFIDENTIALITY?

The study team will provide you with an identification number. The identification number (not your name or other information that could be used to identify you) will be used for laboratory tests or samples stored for testing in future studies. Your medical records and the list of names, addresses and identification numbers will be kept in a locked room. Only the study staff will have the keys. No publication of this study will use your name or identify you personally.

Efforts will be made to keep your personal information confidential. We cannot guarantee absolute confidentiality. Your personal information may be disclosed if required by law. Your records may be reviewed by the ACTG, Office for Human Research Protections (OHRP), *your country's national/health agency,* the local institutional review board or ethics committee (insert name of site IRB/EC), National Institutes of Health (NIH), other government agencies, study staff, study monitors, and drug companies supporting this study and their designees. An IRB/EC protects the rights and well-being of people in research.

WHAT ARE THE COSTS TO ME?

There will be no cost to you for study drugs, study-related visits, physical examinations, laboratory tests, or other procedures. You, your insurance company, or your health care system may need to assume the cost of drugs not provided by the study *(delete references to insurance company or health care system if*

not applicable at site). In some cases, it is possible that your insurance company or health care system will not pay for these costs because you are taking part in a research study.

WILL I RECEIVE ANY PAYMENT?

[Insert site-specific information on compensation to study participants]

WHAT HAPPENS IF I AM INJURED OR, IF I BECOME PREGNANT, MY BABY IS INJURED?

If your baby or you are injured as a result of being in this study, you or your baby will be given immediate treatment for injuries and be referred for further treatment, if necessary. However, you may/may not *(per site/country policy)* have to pay for this care. There is no program for compensation either through *(this institution)* or the NIH. You will not be giving up any of your legal rights by signing this consent form.

WHAT ARE MY RIGHTS AS A RESEARCH PARTICIPANT?

Taking part in this study is completely voluntary. You may choose not to take part in this study or leave this study at any time. The care that you would normally receive will not be affected if you choose not to take part. Your decision will not have any impact on your participation in other studies conducted by the NIH and will not result in any penalty or loss of benefits to which you are otherwise entitled. If you choose not to take part in this study or leave the study at any time, the study staff will tell you the name of a clinic or clinics where you can get care.

We will tell you about information from this or other studies that may affect your health, welfare or willingness to stay in this study. If you want the results of the study, let the study staff know.

WHAT DO I DO IF I HAVE QUESTIONS OR PROBLEMS?

For questions about this study or research-related injury, contact:

- *Name of the investigator or other study staff*
- *Telephone number of above*

For questions about your rights as a research participant, contact:

- *Name or title of person on the Institutional Review Board or Ethics Committee (IRB or EC) or other organization appropriate for site*
- *Telephone number of above*

SIGNATURE PAGE FOR ACTG Study AXXXX

If you have read this consent form (or had it explained to you), all your questions have been answered, and you agree to take part in this study, please sign your name below.

_____	_____
Participant's Name (print)	Participant's Signature and Date
_____	_____
Participant's Legal Guardian (print) (As appropriate)	Legal Guardian's Signature and Date
_____	_____
Study Staff Conducting Consent Discussion (print)	Study Staff's Signature and Date
_____	_____
Witness's Name (print) (As appropriate)	Witness's Signature and Date