WOMEN'S INTERAGENCY HIV STUDY
SECTION 12: OUTCOMES ASCERTAINMENT PROTOCOL

A. GOALS

The goal of the Outcomes Ascertainment Protocol is to collect information from various sources in order to:

1. Confirm or specify the likelihood of diagnoses of self-reported conditions which are *known* to be HIV-related (i.e., categorize diagnoses as definitive, presumptive or indeterminate);
2. Confirm or specify the likelihood of diagnoses of self-reported conditions that are thought *likely or possible* to be HIV-related diagnoses;
3. Verify the timing of HIV-related events and death to assist in accurately determining temporal characteristics of HIV disease progression;
4. Assist in assessing the probable cause(s) of death;
5. Confirm or specify the likelihood of diagnoses of certain chronic disease conditions of particular interest to WIHS investigators; and
6. Obtain additional documentation for certain medical procedures (e.g., biopsies, surgeries) of particular interest to WIHS investigators.

B. REPORTABLE OUTCOMES

The following outcomes will be verified and reported as part of this protocol:

1. Death
2. AIDS-defining events – **NOTE:** *MRA discontinued as of visit 26.*
3. Malignancies (both AIDS- and non-AIDS-related)
4. Tuberculosis (non-AIDS defining among HIV-negative participants)
5. Cardio- and cerebro-vascular disease (CVD) events – **NOTE:** *MRA discontinued as of visit 26.*
6. Liver biopsies
7. Hysterectomies – **NOTE:** *MRA discontinued as of visit 29.*

As of visit 26, the WIHS EC has decided to discontinue MRA for selected diagnoses/conditions, i.e., infectious AIDS-defining events (opportunistic infections) and cardiovascular and stroke events. To date, confirmation rates for these events have been very low, resulting in reluctance by investigators to use these data in analyses. Thus, the majority of outcomes analyses rely instead on self-report data, which will continue to be collected for all of the above listed events.

C. ASCERTAINMENT TRIGGERS

This protocol is activated with the occurrence of any of the following:

1. REPORT THROUGH ACTIVE SURVEILLANCE

   Reports from active surveillance include site-initiated searches of (1) the National Death Index; (2) local death registries; (3) local cancer registries; and (4) local tuberculosis registries.

2. PARTICIPANT SELF-REPORT

   a. AIDS-related Events (including TB, cancer)

   An event for outcome ascertainment is identified when any participant reports diagnosis of an ascertainable event (TB, cancer) since her previous study visit. At each visit, participants are administered the WIHS ***Follow-up Health History Questionnaire*** (F22HX), which contains a series of questions regarding diagnosis of HIV-related conditions.

Data on HIV-related conditions are also collected through systematic contact of participants. Systematic contact will include those events reported via the ***Interim Events Protocol***, an ***Abbreviated Visit***, or the ***Family and Personal Medical History Form***.

NOTE: MRA of infectious AIDS-defining events was discontinued as of visit 26. MRA will continue for TB and all cancer (AIDS and non-AIDS related) events for both HIV-positive and HIV-negative women.

b. Chronic disease events (i.e., CVD)

NOTE: MRA of cardiovascular and stroke events was discontinued as of visit 26.

At each visit, participants are administered the WIHS ***Follow-up Health History Questionnaire*** (F22HX), which contains a series of questions regarding various CVD diagnoses. A CVD event is identified when any participant reports one of the following events:

- Coronary revascularization procedure *to look for* or *to open* blocked vessels in the heart performed on an outpatient or inpatient basis (e.g., cardiac catheterization, angioplasty or coronary artery bypass graft): ***F22HX***, Question C44a.
- Myocardial infarction (heart attack): ***F22HX***, Question C42c.
- Stroke: ***F22HX***, Question C42d.
- Hospitalization for congestive heart failure: ***F22HX***, Question C42bi.
- Hospitalization for angina (chest pain related to heart disease): ***F22HX***, Question C42ai.
- Transient ischemic attack (TIA or mini-stroke): ***F22HX***, Question C42e.

c. Liver biopsies

At each visit, participants are administered the WIHS ***Follow-up Health History Questionnaire*** (F22HX), which includes questions regarding liver biopsies. Outcome ascertainment will be triggered when a participant reports having undergone a liver biopsy since her previous study visit. In addition, data on liver biopsies collected through systematic contact of participants will trigger outcome ascertainment.

NOTE: A comprehensive description of the *Liver Biopsy Ascertainment Protocol* is provided in **Section 34 of the WIHS Manual of Operations**.

d. Hysterectomies

NOTE: MRA of self-reported hysterectomy was discontinued as of visit 29.

At each visit, participants are administered the WIHS ***Obstetric, Gynecological and Contraceptive History Questionnaire*** (F23). Outcome ascertainment will be triggered when a participant reports having undergone a hysterectomy (***F23***, Questions B1b or B5) since her previous study visit.

3. REPORT THROUGH PASSIVE SURVEILLANCE

Reports of ascertainable events (i.e., TB, cancer, liver biopsy) from participants, care providers, friends and families, or other sources that are not part of the standard WIHS visit protocol, or that are obtained through systematic review of participants, are considered passive surveillance reports. This also includes reports of events found upon review of participant medical or hospital records that were not self-reported. For example, if during the abstraction of a self-reported event, the abstractionist discovers an additional abstractable event that the participant did not report, this event should be abstracted in addition to the reported event originally abstracted.

4. REPORT OF DEATH

   Deaths discovered through registry match or passive surveillance will be reported through the immediate completion of a ***Disenrollment Form*** (DENR). Data entry of the ***DENR*** will trigger ascertainment of the death.

D. CREATION OF ASCERTAINMENT TRACKING CHECKLIST

The first step in the ascertainment of an event is the generation of an ***Ascertainment Tracking Checklist*** (ATC). Each abstractable event reported by a participant is recorded on the ***ATC*** by the interviewer and then becomes a separate record within the "abstract event database" upon data entry of the ***ATC***. The ***Apollo Ascertainment Tracking Checklist (ATC) Report*** originates from the abstract event database, and will be periodically printed by the site's data manager when a participant dies or when self-reported events need to be ascertained.

The purpose of the ***ATC*** is to:

a. Inform the staff of which events have been self-reported, and when and where the diagnosis was made;

b. Inform the staff of the death of a participant and provide a prompt for abstraction of the death;

c. Assign a unique Event Tracking Number (ETN) to self-reported events;

d. Provide a means to track if the medical record was obtained and the level of effort exerted to obtain it;

e. Indicate which events were actually abstracted, regardless of whether the diagnosis was confirmed;

f. Track within Apollo which forms were completed and submitted.

Depending on how ascertainment of an event is triggered, ***ATC*** forms will be generated differently:

1. SELF-REPORTED EVENTS

   Apollo will automatically generate an ***ATC*** with a unique Event Tracking Number (ETN) for each self-reported event (diagnosis or procedure) captured via administration of the ***F22HX, F23, Interim Events Protocol,*** or the ***Abbreviated Visit Protocol***. These ***ATC*** forms can be printed at will from Apollo.

2. DEATHS

   A ***Disenrollment Form*** should be completed immediately following the report of the death of a participant. After local data entry of the ***DENR***, Apollo will automatically generate an ***ATC*** with a unique ETN prompting staff to obtain a death certificate for the participant. The disease code for all deaths is 500. ***ATC*** forms for deaths, like those for self-reported events, can be printed at will from Apollo.

   The actual visit number during which a death occurred should be recorded on the ***DENR***, not the visit during which the death was discovered. The ***DENR*** should be updated with the new visit number if additional information regarding the date of death is found.

3. EVENTS REPORTED AT DEATH

   Ascertainable events (TB, cancer) will sometimes be discovered while abstracting a participant's death certificate. All ascertainable events listed on the death certificate should be reported, regardless of whether they have been reported at an earlier visit. To link events reported at death to the death abstraction, they will be reported under the same ETN as the associated death. Therefore, CORE team members should not generate individual ***ATC*** forms for the events reported at death.

E. OBTAINING MEDICAL RECORDS

In order for the Outcomes Ascertainment Protocol to be standardized and uniform across WIHS sites, all staff should follow the same guidelines for requesting and reviewing medical records to confirm events. Staff should request records since the last visit.

1. CONSENT FOR RELEASE OF MEDICAL RECORDS

   Before a medical record can be released, the participant must sign a medical record release form. Interviewers are instructed to have the participant do so at the time of her core WIHS visit. If a participant has not signed a medical record release form, site staff should follow these guidelines:

   a. For deceased participants: If a medical record release form has not been signed by a participant who is now deceased, the staff should still try to obtain medical record release and review the medical records. Since there may be regional differences in guidelines regarding this issue, it is important that the staff member check with his or her PI and/or PD to find out who would be authorized to provide such release. Sometimes the participant's next of kin may be allowed to give consent for release of medical records; or the participant may have signed an advance directive in which she authorized a specific person to be responsible for making medically-related decisions upon her death; or decision-making authority may have reverted to local convention (e.g., spouse).

   b. For disenrolled or lost to follow-up participants without signed consent: If there is no medical record release form for a participant who is now disenrolled or has been lost to follow-up, the staff should work with the Interviewer and Project Director. Depending on the circumstances, it may still be possible to obtain a medical record release form from the participant.

2. OBTAINING INFORMATION

   When a staff member is requesting a death certificate, s/he should wait at least 30 days after the reported date of death before requesting the death certificate. If the case was referred to the Medical Examiner (ME)/Coroner, the staff member should wait (if possible) until the ME's report is in before obtaining the death certificate and completing the CORE Form. A copy of the death certificate should be requested for all known deaths.

   There are three methods of requesting medical records:

   a. Requests in writing

   In most cases, abstractionists will need to put the request for a medical record in writing. (See below for suggested strategies.) Unobtainable records: A record should be requested at least three times during a six-month period before being considered unobtainable. In addition to three written requests, attempts should also be made to visit the Medical Record Department and abstract the record on site or to contact the participant's clinician by telephone to verify the event.

   b. On-site abstraction

   In some institutions, the Medical Record Department may not have the resources to photocopy and mail out records. Other institutions may require staff to do any abstraction on the premises of their institution. In such cases, it will be necessary to obtain permission to visit the institution to access the record for abstraction.

   c. Medical records at WIHS clinic sites (without a written request)

   Since some WIHS participants receive clinical care at the same institution at which they are enrolled in the WIHS, their medical records may be on-site and easily accessible. If staff are able to obtain medical records in a timely manner by informal requests from members of the

institution's staff, then they are encouraged to do so (assuming, of course, that the participant signed a medical release).

3. STRATEGIES FOR WRITTEN REQUESTS OF RECORDS

NOTE: Please remember to keep the nature of all requests confidential.

a. Prior to sending out request letters, contact the appropriate Medical Record Department to determine the following:

- Director/Manager's name, title and direct phone number
- Correspondence clerk's contact information
- Correct address (include building #, floor, etc.)
- The institution's normal turn-around time for sending the records after receipt of your request
- Whether you need to supply additional or special release forms/information for diagnoses related to HIV/AIDS or psychiatric illnesses
- Whether they will accept general parameters (e.g., Fall 1995) or only very specific admission and discharge dates (e.g., Sept. 16, 1995)
- Whether the institution's outpatient records are stored within the same department. If not, query further as to where and how to access these, if needed
- Whether records are available as separate admissions, or are filed by patient including all procedures for an individual

b. Create a letter of request that includes the following:

- Importance of the request
- Need for a timely response
- Director/Manager's name
- Patient's full name (include MAIDEN name), date of birth, Social Security Number (SSN) and signature
- Demonstration of your willingness to facilitate their response; for example, you might consider including:
    i. your site's Federal Express (or other vendor's) authorization number
    ii. a pre-addressed mailing label (multiple copies can usually be procured through the vendor)
    iii. the name and telephone number of a contact person in case there are questions and/or problems (note, however, that a telephone call follow-up may result in disclosure of the nature of the request)

c. Mail the request in a large envelope since it will be more visible and less likely to be misplaced. Mark the envelope "CONFIDENTIAL." Don't forget to include the patient's authorization form (complete with DOB and SSN). The doctor's signature is usually required as additional authorization. The Principal Investigator at your site may opt to sign multiple forms or allow your co-signature. Alternatively, a rubber template of his/her signature can be made and used to stamp forms, as needed.

d. It is a nice gesture to follow up with a thank you phone call or letter once you have received the chart(s). Remember, you will likely be requesting more records from that facility in the future!

4. WHAT RECORDS TO REQUEST

a. TB and Cancer

Appendix A contains a list of what documentation is needed to make a definitive or presumptive diagnosis for each ascertainable event requiring abstraction as part of the Outcomes Ascertainment Protocol. Site staff should base their request for documentation on this list.

b. Liver Biopsies

Request a copy of the pathology report for each reported biopsy. If the pathology report cannot be obtained, record the reason why it was not obtained in Question A11 of the ***Apollo Ascertainment Tracking Checklist (ATC) Report.***

NOTE: Collection of liver biopsy slides for central reading has been discontinued.

c. Hysterectomies

NOTE: MRA of self-reported hysterectomy was discontinued as of visit 29.

Request a copy of the medical records and surgery report for each reported hysterectomy. If the appropriate documentation cannot be found, record the reason why it was not found in Question A11 of the ***Apollo Ascertainment Tracking Checklist (ATC) Report.***

F. REVIEW OF MEDICAL RECORDS

If medical records **were not** reviewed for an event, the reason why they were not reviewed should be entered in Question A11 (ascertainment disposition) on the ***Apollo ATC Report***. This would include records that could not be obtained due to lack of a signed medical record release form, those which could not be found for the date or event being abstracted, those which the hospital would not release, etc.

For records that **are** obtained, the WIHS Outcomes Ascertainment Protocol requires using information from narrative sections of the record, such as the discharge summary, progress notes or consultation reports to determine clinical diagnoses. Any notations recorded by a physician, specialist, physician's assistant or nurse practitioner can be used. Nurse's notes, however, should not be used as a source of documentation for medical record abstraction.

Other aspects of abstraction involve reviewing diagnostic or laboratory results. Staff should always consider the final results (not the preliminary results) in making confirmation decisions. Depending upon the completeness of the record, staff will use either **primary** or **secondary** sources to determine if an event is confirmed and, if so, the level of confidence in the diagnosis.

a. Primary source document

Laboratory results or procedure reports are primary source documents. Use these sources instead of secondary sources whenever possible. Results obtained from an institution's computerized files are also considered to be obtained from a primary source. For example, lab results obtained from a laboratory's main database are collected from a primary source.

b. Secondary source document

Information found in a discharge summary, progress note or consultation report is considered to be obtained from a secondary source when the medical provider has observed the primary source document that specifically references diagnostic test results and has "transcribed it" into his/her notes. As stated above, nurse's notes may not be included as secondary sources of information.

If unable to obtain a copy of the participant's medical records, abstraction staff can attempt to verify a reported diagnosis via a phone call to the participant's clinician. If confirmation of a self-

reported diagnosis is obtained in this manner, the ascertainment disposition should be coded as "obtained via in-person visit or phone call" (Question A11 = 3) on the ***ATC***. While the level of confidence in a diagnosis confirmed in this manner won't be as high, it can be used as a last resort to confirm an event.

Abstraction forms (forms with prefixes of M and CA) can be used as guides for collecting information on ascertainable events. These forms are not be subject to data entry, and therefore can be augmented or modified as needed if they aid in gathering information for fulfilling the *WIHS Criteria for Clinical Outcomes*.

G. REPORTING, DATA MANAGEMENT AND USE OF FORMS

After review of medical records, CORE team members will decide whether the information available on a participant confirms the reported event and fulfills the *WIHS Criteria for Clinical Diagnosis* that warrant reporting using the ***Clinical Outcomes Reporting*** (CORE) ***Form***.

1. TB AND CANCER

a. Unconfirmed Events

If, after review of medical records, a diagnosis cannot be confirmed, this should be indicated in Question A12 on the ***Apollo ATC Report***. The purpose of this question is to track whether the event is confirmed, not merely whether or not the medical records were reviewed. The ATC data should be entered into Apollo. No ***CORE Form*** will be completed for unconfirmed diagnoses.

b. Confirmed Events

If an event is confirmed, the site should complete a ***Clinical Outcomes Reporting*** (CORE) ***Form***. Only one source of information (Section A) should be indicated for each ***CORE Form*** completed. If there are multiple sources of information for a particular event, additional ***CORE Forms*** should be completed for each source named. In addition, **only one diagnosis should be reported on each *CORE Form*** completed. If additional diagnoses are found during the abstraction of an event, additional ***CORE Forms*** should be completed. No ***ATC*** will be generated for these events. ***CORE Forms*** completed for ascertained events without an ***ATC*** (those discovered through active or passive surveillance) should have the field "Event Tracking Number" left blank.

When ascertaining self-reported metastatic cancer, if the metastatic cancer is diagnosed and reported sometime after the primary cancer, review your records to ensure that the primary cancer was also confirmed. If both primary and metastatic cancers were reported at the same visit, an ***ATC*** will be generated for each. If both are confirmed, complete a ***CORE Form*** for each respective ***ATC***. If only the primary cancer was reported, only one ***ATC*** will be generated. If you confirm the primary cancer and also find documentation of metastatic cancer, complete two ***CORE Forms*** with the same ETN as the ***ATC*** for the primary cancer.

The level of confidence in the diagnosis (e.g., "presumptive" versus "definitive") is associated with the confirmation of an event. The criteria to be met for determination of the level of confidence are contained in the *WIHS Criteria for Clinical Diagnosis* (**Appendix A**). If the medical record reflects that the criteria outlined in the definitive column were met in making the diagnosis, the diagnosis would be considered "definitive." If the definitive standard was not met, the diagnosis may be made presumptively by meeting a lesser standard. The criteria for making a "presumptive" diagnosis are outlined in the presumptive column. When a diagnosis is confirmed solely through clinician report, registry match or death certificate review, the level of confidence in the diagnosis should be recorded as "indeterminate."

2. LIVER BIOPSIES

When a participant reports having had a liver biopsy since her previous study visit, an ***ATC*** with the appropriate disease code (610) will be generated. If the site cannot obtain a copy of the pathology report, indicate this in Question A11 of the ***Apollo ATC Report***. If the site is successful in obtaining the pathology report, site staff should complete the ***ATC*** to indicate that the event was ascertained (Question A12 = yes), and the pathology report should be sent to the WDMAC Project Director for central reading and completion of the ***Liver Biopsy Abstraction*** (QCLB) ***Form***. **Do not complete a *CORE Form* for self-reported liver biopsies, even if ascertained.**

NOTE: Collection of liver biopsy slides for central reading has been discontinued.

3. HYSTERECTOMIES

NOTE: MRA of self-reported hysterectomy was discontinued as of visit 29.

When a participant reports having had a hysterectomy since her previous study visit, an ***ATC*** with the appropriate disease code (600) will be generated. If the site cannot obtain a copy of the appropriate documentation, indicate this in Question A11 of the ***Apollo ATC Report***. If the site is successful in obtaining the appropriate medical records, site staff should complete the ***ATC*** to indicate that the event was ascertained (Question A12 = yes), and the ***Hysterectomy Abstraction*** (QCHS) ***Form*** should be completed and entered into Apollo. When completing the ***QCHS***, the Event Tracking Number (ETN) from the ***ATC*** should be entered in Question A5. **Do not complete a *CORE Form* for self-reported hysterectomies, even if ascertained.**

4. EVENTS CONFIRMED THROUGH REGISTRY MATCH

When an event is confirmed through TB or cancer registry match, the data obtained from the registry should be recorded on the appropriate registry confirmation form (i.e., ***Tuberculosis – Verified Case Report*** [TB], ***Cancer Registry Case Report*** [CNCR]). These forms should be entered into Apollo, and not sent to WDMAC. If knowledge of an event is obtained through a registry match, no further review of medical records need be done before completion of the ***CORE Form***.

When completing a ***CORE Form*** for an event confirmed through registry match, the method of diagnosis would be coded as "no confirmation/clinician report." The level of confidence in the diagnosis will therefore be "indeterminate" since there was no actual review of medical records by WIHS CORE Team members.

- Disease code 124 (TB elsewhere in body) should be reported when a registry match is made for "extra-pulmonary TB."

5. DEATHS

Upon first report of a participant's death, site staff will immediately complete a ***Disenrollment Form*** (DENR) and enter it into Apollo. After local data entry of the ***DENR***, an ***ATC*** for the death (code 500) can be printed, prompting staff to obtain a death certificate for the participant. An attempt should be made to obtain a death certificate for <u>all</u> known deaths.

In addition, a ***CORE Form*** should be completed upon first report of a death with information about the death from whatever source is available (e.g., report from family/friend, obituary notice, etc.). Reports of death via the ***CORE Form*** should be made <u>prior</u> to obtaining the death certificate, with updated ***CORE Form(s)*** completed when additional data is obtained. This process has been developed to facilitate the continuous ascertainment of deaths in the WIHS cohort for a variety of scientific and administrative reasons.

After a copy of the death certificate has been received, all information obtained from the death certificate should be reported on the ***CORE Form***. If a death certificate mentions an ascertainable event (TB, cancer) as contributing to the death, see **Section 5, Events at Death,** for instructions

on completing the ***CORE Form***. If, however, a participant's death certificate makes no mention of an ascertainable event as a contributing factor in the death, there is no need to further abstract the death. Complete Sections A and C of the ***CORE Form***.

The sequence of events (except when first report of a death is through NDI match, which is covered below) is as follows: report of death, complete and enter ***DENR***, complete and enter ***CORE***, generate and print ***ATC***, obtain death certificate, complete and enter additional ***CORE(s),*** end abstraction of the death.

This sequence of events described above differs slightly when the first report of a death is through National Death Index (NDI) match. NDI matches will not be reported through completion of a ***CORE Form***. Instead sites will transmit these data electronically to WDMAC. If the first report of death is obtained via NDI match, a ***DENR*** must still be completed and data entered. This will generate an ***ATC*** and prompt the site to obtain a death certificate for the participant. However, since cause of death data and ICD-10 codes will have already been transmitted to WDMAC with the NDI data, sites will not need to complete a ***CORE Form*** for death certificates received after an NDI match. The sequence of events when first report of a death is through NDI match is as follows: obtain NDI match, complete and enter ***DENR***, generate and print ***ATC***, obtain death certificate, end abstraction of the death.

See **Section 20 of the Manual of Operations** (Registry Match Protocols) for more information regarding NDI data transfer.

6. EVENTS AT DEATH

   If a specific ascertainable event (TB, cancer) is listed on the death certificate as a cause of death, the ***CORE Form*** should be completed for the appropriate disease code. In this case, Sections A, B and C of the ***CORE Form*** should be completed. All TB and cancer causes of death listed on the death certificate should be reported on a ***CORE Form***, regardless of whether or not they have been previously reported. Additionally, a second ***CORE Form*** (Sections A and B) should be completed for each additional ascertainable cause listed. For example, if two ascertainable events (e.g., breast and ovarian cancer) are listed as causes of death, one of the conditions would be reported on the ***CORE Form*** that reports the participant's death, with the second condition reported on a second ***CORE Form*** completed for that event only.

   The same Event Tracking Number (ETN) should be written on each ***CORE Form*** that reports a cause of death from one participant's death certificate. This will allow for easy tracking of those events confirmed through death certificate abstraction.

   For diagnoses that are based on a death certificate alone (i.e., no autopsy confirmation), the method of diagnosis reported on the ***CORE Form*** should be "reported on death certificate." Ascertainable events reported on the death certificate need not be confirmed through further review of medical records.

If additional data is later found to update any original diagnoses or to report additional diagnoses or deaths, additional ***CORE Form(s)*** can be completed. Instructions for completing the ***CORE Form*** are given in the ***CORE Form*** QxQs.

CORE Forms should be entered locally and not sent to WDMAC. In addition, ***Ascertainment Tracking Checklists*** should be entered locally, regardless of outcome. After entry, sites are advised to store these forms with other documentation that was obtained for the clinical diagnosis (not entered into Apollo).

At WDMAC, CORE data will be collected from the sites, as per standard data transfer protocols, and summarized in *OUTCOME.DAT*. This file will be used across all analyses as the primary source of self-reported and confirmed outcomes.

WDMAC will periodically conduct comparisons of self-reported outcomes (***F22HX, F23, Interim Events, Abbreviated Visit***) with data from ***ATC*** and *OUTCOME.DAT* to ascertain the confirmation of events.

APPENDIX A: WIHS CRITERIA FOR CLINICAL DIAGNOSIS

(NOTE: CONDITIONS THAT ARE SHADED GRAY WILL NO LONGER BE ASCERTAINED AS OF VISIT 26.)

CONDITION	DISEASE CODE	DEFINITIVE	PRESUMPTIVE
I. MALIGNANCIES			
BREAST CANCER	106	1. Ductal carcinoma in situ (DCIS). **OR** 2. Lobular carcinoma in situ (LCIS). **OR** 3. Any other histologic type with biopsy proven.	
CERVICAL CANCER, INVASIVE	101	1. Biopsy with evidence of invasive carcinoma. **NOTE: Carcinoma in Situ (CIS) does NOT constitute a case of confirmed invasive cervical cancer.**	
KAPOSI'S SARCOMA	102	1. Biopsy from any site ever + for KS.	1. Clinical diagnosis by dermatologist, oncologist or HIV clinician.
LYMPHOMA (non-Hodgkins) (for Hodgkin's Lymphoma, see "Other Cancers," below)	103	1. Biopsy proven.	
LYMPHOMA, CNS (non-Hodgkins) (for Hodgkin's Lymphoma, see "Other Cancers," below)	104	1. Histologic evidence (tissue biopsy, aspirate, or at autopsy). **OR** 2. Cytologic evidence obtained from CSF.	1. Presence of CNS lesions on imaging scan (CT, SPECT or PET) consistent with lymphoma. **AND EITHER** 2a. Unresponsive to empiric toxoplasmosis treatment or Toxo IgG Ab negative. **OR** 2b. Positive Epstein Barr Virus (EBV) PCR.

CONDITION	DISEASE CODE	DEFINITIVE	PRESUMPTIVE
METASTATIC CANCER	111	**EITHER** 1a. Known cancer diagnosis proven by biopsy or cytology. **AND** 1b. Biopsy or cytology of the same type of cancer in another distant site. **OR** 2. In absence of initial known diagnosis of cancer, cytologic or histologic evidence of distant spread from initial source of disease at time of initial diagnosis.	1. Cancer diagnosis proven by biopsy or cytology. **AND** 2. Radiologic lesion suggestive of distant spread from initial source of disease.
OTHER CANCER (e.g., Hodgkin's Lymphoma, lung, liver, colon, etc.) (for non-Hodgkin's Lymphoma, see "Lymphoma" or Lymphoma, CNS," above)	105, 107, 108, 109, 110, 112	1. Biopsy with evidence of cancer.	
PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY (PML) ***(NOTE: MRA DISCONTINUED AS OF VISIT 26.)***	190	**EITHER** 1. Biopsy or autopsy positive for PML. **OR BOTH** 2a. Characteristic lesions on brain imaging. **AND** 2b. CSF positive for JCV PCR.	1. Consistent neurologic changes. **AND EITHER** 2. PCR positive for JCV PCR. **OR BOTH** 3a. Characteristic lesions on initial brain imaging. 3b. Clinical course c/w PML.
II. TUBERCULOSIS			
TUBERCULOSIS	121, 122, 123, 124, 127	1. Isolation of *M. tuberculosis* from fluid or tissue.	
III. OTHER AIDS-DEFINING CONDITIONS *(NOTE: MRA DISCONTINUED AS OF VISIT 26.)*			

CONDITION	DISEASE CODE	DEFINITIVE	PRESUMPTIVE
COCCIDIOIDOMYCOSIS (DISSEMINATED, EXTRAPULMONARY DISEASE)	176	**EITHER** 1. Positive culture for *Coccidiodes immitis* from nonpulmonary site. **OR BOTH** 2a. Positive serology (either complement fixation [CF] or counter immunoelectrophoresis [CIE]). **AND** 2b. Compatible clinical syndrome for disseminated disease (extrapulmonary: skin, bone, CNS, etc.).	
CMV (DISSEMINATED)	165	1. Microscopy (histology or cytology), culture, or detection of antigen in a specimen obtained directly from the tissues affected or a fluid from those tissues.	
CMV ENCEPHALITIS	191	1. Histological evidence of CMV in brain tissue in the setting of a clinical syndrome with altered sensorium with progressive obtundation presenting acutely or subacutely in the absence of CT/MRI showing findings consistent with toxoplasmosis or lymphoma.	1. Clinical syndrome with altered sensorium with progressive obtundation presenting acutely or subacutely in the absence of CT/MRI showing findings consistent with toxoplasmosis or lymphoma. **AND EITHER** 2a. CSF positive for CMV by PCR. **AND** 2b. CSF culture positive for CMV. **OR** 3. Neutrophilic predominance pleocytosis. **AND** 4. No other pathogen to explain syndrome.

CONDITION	DISEASE CODE	DEFINITIVE	PRESUMPTIVE
CMV ESOPHAGITIS, GASTROENTERITIS, COLITIS, PROCTITIS	155, 161	1. At least one symptom: • **Esophagitis:** retrosternal pain or pain on swallowing, dysphagia. • **Gastroenteritis:** abdominal pain. • **Colitis:** abdominal pain and diarrhea (typically small volume associated with mucus and blood). • **Proctitis:** rectal pain, often associated with tenesmus, mucus and blood. **AND** 2. Tissue cytology or histopathology showing typical CMV cytopathology or identification of CMV antigen.	1. Endoscopy, colonoscopy or sigmoidoscopy reveals mucosal erythema, erosion or ulceration (or lesion is directly visualized as an oral or perianal ulcer). **AND** 2. Positive CMV culture from the lesion in the absence of other pathogens or the persistence of symptoms following appropriate treatment for other pathogens.
CMV PNEUMONITIS	131	1. Typical CMV inclusions seen on biopsy or bronchoalveolar lavage specimens, or autopsy. **AND** 2. Compatible clinical syndrome which must include: hypoxemia and abnormal chest X-ray.	
CMV RADICULOMYELOPATHY	163	1. A clinical syndrome such as: decreased lower extremity strength and reflexes. 2. Evidence of CMV in the CSF by polymerase chain reaction. **AND** 3. Absence of other pathogens.	1. Clinical syndrome such as: decreased lower extremity strength and reflexes. 2. Polymorphonuclear pleocytosis. 3. Absence of other pathogens.
CMV RETINITIS	164	1. Positive diagnosis by ophthalmologist with findings of white areas with or without hemorrhages and/or gray-white areas of retinal necrosis with or without hemorrhages.	1. Included as likely or probable in differential by ophthalmologist. **OR BOTH** 2a. Diagnosed by non-ophthalmologist. 2b. Symptoms stabilized with anti-CMV meds.
CRYPTOCOCCUS - DISSEMINATED	175	1. Identification of Cryptococcus in culture or biopsy from a non-pulmonary source (includes blood, urine, CSF; excludes sputa).	1a. Compatible clinical syndrome (extrapulmonary disease such as renal infection). **AND** 1b. Positive serum cryptococcal antigen ($\geq$ 1:8).

CONDITION	DISEASE CODE	DEFINITIVE	PRESUMPTIVE
CRYPTOCOCCUS - MENINGITIS	174	1. Positive CSF culture for *C. neoformans.* **OR** 2. Positive CSF cryptoccocal antigen test. **OR** 3. Positive meningeal or brain tissue culture or histology for *C. neoformans.*	1. Compatible clinical syndrome (meningitis – headache, stiff neck, mental status abnormalities, fever, CSF white blood cells, elevated protein or reduced glucose) and positive CSF India ink stain preparation.
CRYPTOSPORIDIOSIS	151	1. Microscopic evidence of cryptosporidium present in either stool, body fluid or tissue specimen. **AND** 2. Diarrhea.	
DEMENTIA/ ENCEPHALOPATHY	193	1a. Acquired abnormalities in cognitive or motor abilities that interfere with work or activities of daily living that are documented in the medical record. **OR** 1b. A neuropsych testing report with findings consistent with dementia. **AND** 2. No etiology determined by laboratory evaluation of CSF (no positive culture or PCR or antigen test from CSF other than HIV). 3. No other etiology such as depression or medication side effect noted. **AND ONE OF THE FOLLOWING** 4a. No etiology detected on CT or MRI imaging of the brain (for example, no masses or stroke). **OR** 4b. No etiology detected at autopsy.	1. Acquired abnormalities in cognitive abilities (which interfere with work or activities of daily living). 2. No other etiology documented (including clinical depression).

CONDITION	DISEASE CODE	DEFINITIVE	PRESUMPTIVE
ESOPHAGEAL CANDIDIASIS	140	1. Endoscopy findings consistent with esophageal candidiasis (+/- culture or histology).	**EITHER** 1a. Documentation of recent onset of retrosternal pain on swallowing or dysphagia. **OR** 1b. Reported result of barium swallow consistent with esophageal candidiasis. **AND EITHER** 2a. Oral candidiasis. **OR** 2b. Response to specific antifungal therapy.
HISTOPLASMOSIS (DISSEMINATED)	173	1. Positive culture from non-pulmonary source (not lung, sputum, cervical or hilar lymph node). **OR** 2. Positive histopathology for histoplasma in tissue (not lungs, hilar or cervical lymph node).	1a. Compatible clinical syndrome of disseminated infection (extrapulmonary). **AND** 1b. Detection of histoplasma antigen in tissue or fluid.
HSV ESOPHAGITIS/ PNEUMONITIS	201	1. Lesion consistent with HSV. **AND** 2. + HSV culture from lesion. **OR** 3. HSV antigen detection by immunoassay or DFA antibody stain.	**EITHER BOTH** 1a. Lesion c/w HSV. 1b. + Tzanck prep from lesion. **OR BOTH** 2a. Persistent dysphagia, non-responsive to anti-fungal meds. 2b. Persistent signs and symptoms, responsive to acyclovir therapy.
ISOSPORIASIS	153	1. Microscopic evidence of Isospora present in either stool, body fluid or tissue specimen. **AND** 2. Diarrhea.	
MAI (other than tuberculosis – Includes MAC, *M. Kansasii* and others)	154, 170, 171	1. Organism isolated (cultured) from extrapulmonary site: blood, bone marrow, liver, cerebrospinal fluid, or other normally sterile site excluding lung, hilar lymph node and cervical lymph note (other lymph nodes meet definition).	

CONDITION	DISEASE CODE	DEFINITIVE	PRESUMPTIVE
MICROSPORIDIOSIS	152	1. Positive microscopy for microsporidium in stool. **AND** 2a. Diarrhea. **OR** 2b. Positive microscopy for microsporidium in body fluid or tissue such as lung, kidney or brain.	
MYCOBACTERIUM KANSASII	171	1. M. kansasii cultured from blood, bone marrow, lymph node, liver, cerebrospinal fluid, or any other normally sterile body fluid, tissue or organ. **OR** 2. M. kansasii cultured from bronchopulmonary, gastrointestinal, urine, skin, or other non-sterile mucosal sites (as the only pathogen coupled with histopathologic confirmation of AFB/M. kansasii in tissue specimens from which the culture was derived.	
PCP	130	1. Sputum, BAL, or biopsy specimen + for pneumocystis. **AND EITHER** 2a. New infiltrate on CXR. **OR** 2b. New symptoms (cough, SOB).	1. No evidence for definitive bacterial pneumonia. 2. Non-productive cough or dyspnea on exertion with documented onset in past 3 months. **AND 1 OF THE FOLLOWING** 3a. CXR showing diffuse bilateral interstitial infiltrates 3b. Gallium scan showing diffuse pulmonary disease. **AND 1 OF THE FOLLOWING** 4a. Response to specific anti-pneumocystis therapy. **OR** 4b. ABGs showing either: arterial pO2 < 70 mm Hg. **OR** 4c. Diffusing capacity < 80% expected. **OR** 4d. Alveolar-arterial O2 tension gradient >30 mm Hg.

CONDITION	DISEASE CODE	DEFINITIVE	PRESUMPTIVE
PNEUMONIA (OTHER THAN PCP OR TB)	132	1. New or progressive infiltrate on CXR. **AND** 2a. + Sputum culture for pneumococcus, H. flu, Klebsiella, Staph. Aureus, Pseudomonas, Enterobacter or Legionella or other bacterial pathogens. **OR** 2b. + Serologic tests for mycoplasma (and no bacterial pathogen found). **OR** 2c. + Blood or pleural fluid culture (and no other identified source). **AND** 3. No other non-bacterial cause identified. **AND EITHER** 4a. Cough or shortness of breath. **OR** 4b. Respiratory rate >20.	1. No evidence for definitive PCP. 2. Acute onset cough, or dyspnea on exertion or shortness of breath or respiratory rate >20. **AND BOTH** 3a. New or progressive infiltrates on CXR 3b. Response to antibacterial medications.
PULMONARY CANDIDIASIS	141	1. Histopathology consistent with invasive candidiasis consistent with trachea, bronchi, or lung.	
SALMONELLOSIS SEPTICEMIA (NON-TYPHOIDAL)	177	1. Non-typhi Salmonella species isolated from blood.	
TOXOPLASMOSIS	172	1. Biopsy + for T. gondii.	1. CT or MRI of brain showing 1 or more mass lesions (enhanced by contrast injection, if given). **AND** 2. Clinical response to anti-toxoplasma medications. **AND** 3. Serology Toxo IgG antibodies.
WASTING	210	1. Documented weight loss >10% of baseline. **AND** 2. No concurrent depression, illness, or other condition associated with weight loss.	

CONDITION	DISEASE CODE	DEFINITIVE	PRESUMPTIVE
IV. CHRONIC DISEASE CONDITIONS *(NOTE: MRA DISCONTINUED AS OF VISIT 26.)*			
MYOCARDIAL INFARCTION (MI, HEART ATTACK)	331	Final designation of definitive or presumptive diagnosis will be made by a central adjudication committee once all ascertainment materials have been collected and sent to WDMAC.	
HOSPITALIZATION FOR CONGESTIVE HEART FAILURE (CHF)	332		
CEREBRAL VASCULAR ACCIDENT (CVA, STROKE)	333		
HOSPITALIZATION FOR ANGINA OR CHEST PAIN RELATED TO HEART DISEASE	334		
TRANSIENT ISCHEMIC ATTACK (TIA, MINI-STROKE)	335		
SURGERY ON HEART VESSELS	337		
V. OTHER CONDITIONS OR PROCEDURES REQUIRING MRA			
HYSTERECTOMY	600	Complete Hysterectomy Abstraction (QCHS) Form. Do not complete CORE Form.	
LIVER BIOPSY	610	Obtain copy of pathology report and send to WDMAC for central read and completion of Liver Biopsy Abstraction (QCLB) Form. Do not complete CORE Form. **NOTE:** Collection of liver biopsy slides for central reading has been discontinued. **NOTE: See WIHS Manual of Operations, Section 34, for complete Liver Biopsy Ascertainment Protocol.**	

APPENDIX B: DISEASE CODE LIST

Ascertainable Events (as of visit 29)

Code	Description
100*	Cancer
101	Cervical cancer, invasive
102	Kaposi's sarcoma
103	Lymphoma (non-Hodgkin's)
104	Lymphoma in brain/CNS
105	Hodgkin's disease
106	Breast cancer
107	Cancer of the ovary/ovaries
108	Cancer of the uterus/endometrial
109	Skin cancer
110	Other cancer
111	Metastatic cancer
112	Liver cancer
120*	TB (consolidation)
121	TB in lungs
122	TB in blood
123	TB in lymph nodes
124	TB in other part of body
125*	TB – chest X-ray
127	TB meningitis
128*	TB meds taken for 3 or more months
500	Death
610**	Liver Biopsy
611**	Lung Biopsy
612**	Skin Biopsy
613**	Bone Marrow Biopsy
614**	Cervical Biopsy
615**	Breast Biopsy
616**	Other Biopsy
617**	Uterine/endometrial Biopsy

Ascertainment Discontinued as of Visit 29

Code	Description
130	PCP
131	CMV - Pneumonia
132	Bacterial pneumonia
140	Candida/thrush esophagus (esophageal candidiasis)
141	Candida/thrush lungs, trachea, bronchi
151	Diarrhea - Cryptosporidia
152	Diarrhea - Microsporidia
153	Diarrhea - Isospora
154	Diarrhea - MAI
155	Diarrhea – CMV
160*	CMV (consolidation)
161	CMV - GI tract
163	CMV Radiculomyelopathy
164	CMV Retinitis
165	CMV elsewhere in body
170	MAI/MAC
171	Mycobacterium kansasii
172	Toxoplasmosis
173	Histoplasmosis
174	Cryptococcal meningitis
175	Cryptococcal infection in blood or elsewhere
176	Coccidioidomycosis
177	Salmonella
180*	Cryptococcus (consolidation)
190	PML
191	CMV Encephalitis
193	Dementia/Encephalopathy
201	Herpes simplex of lungs
210	Wasting syndrome
220	AIDS, unspecified (surveillance code only)
221	AIDS at death (surveillance code only)
245	CD4 < 200 or CD4% < 14% (surveillance code only)
331	Myocardial infarction (MI, heart attack)
332	Hospitalization for congestive heart failure (CHF)
333	Cerebral vascular accident (CVA, stroke)
334	Hospitalization for angina or chest pain related to heart disease
335	Transient ischemic attack (TIA, mini-stroke)
337	Surgery on heart vessels
600**	Hysterectomy

* **NOTE**: These events, while triggering ascertainment, should not be indicated on the ***CORE Form*** as a confirmed diagnosis in Question B3. Abstraction of one of these events will result in either (1) no confirmation of the event, or (2) confirmation of a more specific event. When a more specific event is confirmed, a ***CORE Form*** should be completed with the more specific disease code, not the general or consolidated disease code.

** **NOTE**: These events, while triggering ascertainment, should not be reported on a ***CORE Form***. Liver Biopsy: send copy of pathology report to WDMAC for central read and completion of the ***Liver Biopsy Abstraction*** (QCLB) ***Form***. All biopsies (610-617): obtain specimen for donation to ACSR.