WOMEN'S INTERAGENCY HIV STUDY
SECTION 28: PAP SMEAR RE-READ PROTOCOL

A. PURPOSE

Re-reading of selected Pap smear slides in the WIHS will be undertaken to fulfill three goals:

1. Prospectively, to ensure that participants receive the best clinical care based on the most accurate interpretation of Pap results available.
2. To aid in the prevention and treatment of cervical cancer by documenting cervical abnormalities at an early stage.
3. Retrospectively, to ensure the accuracy of outcomes data for use in analyses even though data will not be current enough to influence clinical care of the participants.

By implementation of this protocol, all abnormal WIHS Pap smears (i.e., ASCUS or above) and 10% of all negative WIHS Pap smears will be re-read independently by a second cytopathologist, and adjudicated by a third if a disagreement occurred.

B. PROSPECTIVE PROTOCOL

1. SELECTION AND REVIEW OF SPECIMENS

   All Pap smears with an initial squamous cell diagnosis of ASCUS or above or a glandular cell abnormality, as well as 10% of all negative Pap smears (the same 10% examined by the first cytopathologist), will be re-read independently by a second cytopathologist. If the first and second readers disagree on the diagnosis (even by a single grade of neoplasia, including differences such as moderate versus severe HSIL), an unblinded third pathologist will adjudicate. Slides read by the second cytopathologist will be mixed in with prospective first reads. If needed, the third reader will know the results of the first two reads before viewing the slide for adjudication.

   Prospective re-read of Pap smears was begun July 1, 2002, midway through WIHS visit 16. After visit 16 data is edited at WDMAC (scheduled for completion April 2003), Dianon will send a list of WIHSIDS that have already received re-reading under the prospective portion of the protocol (those read after July 1, 2002) so that they are not included in the retrospective portion of the protocol, as well.

2. DATA REPORTING

   Only after final adjudication will Pap smear results be transmitted to the WIHS sites for data entry. These data will continue to be reported via the C60 form. Thus, the WIHS sites will receive only the final diagnosis for each participant. In addition, Dianon will send to WDMAC an ASCII or an Excel file for archiving at the end of each visit. WDMAC will develop a codebook for these data set so that it will be available for use by investigators; however, the data will not be incorporated into Apollo. This file will contain the following fields: WIHSID, visit, date specimen obtained, date of first read, initial squamous cell diagnosis, initial glandular cell diagnosis, date of second read, second squamous cell diagnosis, second glandular cell diagnosis, and, if necessary, date of third read, third squamous cell diagnosis and third glandular cell diagnosis.

3. DATA EDITING PROCESS

   Dianon will send the final diagnoses, reported on C60 forms, to the WIHS sites for data entry. These data will continue to be included in WDMAC's biannual central edit process. The

ASCII/Excel data set sent to WDMAC from Dianon will not be incorporated into the central edit process.

4. DOCUMENTATION

Dianon will track via computer the results of first, second and, if necessary, third reads, as well as the final results sent to the sites via the C60 form. Since the sites will receive only adjudicated Pap smear results, they will not be required to perform any additional documentation. WDMAC will provide data quality assurance and long-term storage in Apollo for the C60 data. WDMAC will also archive the Dianon data set containing the results of all reads and make this file, along with an associated codebook, available to investigators who have an approved concept sheet.

C. RETROSPECTIVE PROTOCOL

1. SELECTION OF SPECIMENS FOR RE-READ

a. Priority of specimen re-reads:

- *First priority* – Pap smears collected from visit 1 through visit 15 with initial diagnosis of HGSIL or above (approximately 300 records).
- *Second priority* – Pap smears collected from visit 1 through visit 15 with initial diagnosis of ASCUS or above. [NOTE: At the May 2003 EC meeting, the HPV working group determined that funding was not currently available to pursue second or third priority re-reads. If deemed necessary, they will reconsider in the future.]
- *Third priority* – Pap smears collected at visit 16 that did not receive prospective re-read with initial diagnosis of ASCUS or above (i.e., those initially read prior to July 1, 2002). [NOTE: At the May 2003 EC meeting, the HPV working group determined that funding was not currently available to pursue second or third priority re-reads. If deemed necessary, they will reconsider in the future.]
- *Fourth priority* – 10% of all negative Pap smears collected from visits 1 through 15, and those from visit 16 that were not included in the prospective protocol (i.e., those initially read prior to July 1, 2002).

Retrospective re-read of Pap smears will begin in April 2003. After visit 16 data is edited at WDMAC (scheduled for completion April 2003), Dianon will send a list of WIHSIDS to WDMAC. This list will include those IDs that have already been re-read under the prospective portion of the protocol (those read after July 1, 2002) so that they are not included in the retrospective portion of the protocol, as well.

b. Data file from WDMAC

WDMAC will communicate the selection of slides for re-read to Dianon via an Excel file. This file will contain the WIHSID, VISIT, date of specimen collection, source of specimen (cervical or vaginal), age at time of specimen collection, and squamous and glandular diagnoses. To this file, Dianon will append the final squamous and glandular diagnoses as determined by the second and, if necessary, third readers, as well as the date of the final re-read, and send this file back to WDMAC via email after all re-reads are completed.

The data files with specific ID/visit information will be sent in batches to Dianon as indicated in the priority re-read list. The first file will be sent in April 2003.

2. REVIEW OF SPECIMENS

All Pap smears not included in the prospective protocol (visits 1 through 15 and visit 16 prior to July 1, 2002) with an initial diagnosis of ASCUS or above, as well as 10% of all negative Pap

smears from this time period, will be re-read independently by a second cytopathologist. If the first and second readers disagree on the diagnosis, an unblinded third pathologist will adjudicate it. Slides read by the second cytopathologist will be mixed in with prospective first reads. If needed, the third reader will know the results of the first two reads before viewing the slide.

3. DATA REPORTING TO WDMAC

   a. C60a and C60b forms

      Cytopathologists performing second and third reads of Pap smears will be given a copy of either the C60a or C60b form, Retrospective Pap Smear Re-read Reporting Form, to complete after reading the slides. Because the diagnostic categories for squamous and glandular cells listed on the C60 form changed for visit 16 (beginning April 1, 2002), Dianon will need to use both the C60a and C60b forms – C60a for re-reads of visit 1 through visit 15 Pap smears, and C60b for re-reads of visit 16 (through June 30, 2002) Pap smears. The use of both forms is necessary so that the diagnostic categories for re-reads will match those reported for initial reads. (See Appendices A and B for copies of C60a and C60b.)

      C60a forms will contain the following diagnostic categories:

      - **Squamous cells:**
        - Within normal limits
        - ASCUS
        - LGSIL: mild (slight) dysplasia/CIN1/HPV
        - HGSIL: moderate dysplasia/CIN2
        - HGSIL: severe dysplasia/CIN3/carcinoma in situ
        - Squamous cell carcinoma
      - **Glandular cells:**
        - Endocervical cells present and within normal limits
        - Presence of benign endometrial cells consistent with menses
        - Presence of endometrial cells out of phase in pre-menopausal women
        - Presence of endometrial cells in post-menopausal women
        - AGCUS: endometrial
        - AGCUS: endocervical
        - AGCUS: not otherwise specified
        - Adenocarcinoma
        - Other malignant epithelial neoplasm

      C60b forms will contain the following diagnostic categories:

      - **Squamous cells:**
        - Within normal limits
        - ASC-US
        - ASC-HGSIL
        - LGSIL: mild (slight) dysplasia/CIN1/HPV
        - HGSIL: moderate dysplasia/CIN2
        - HGSIL: severe dysplasia/CIN3/carcinoma in situ
        - HGSIL: features of invasion
        - Squamous cell carcinoma
      - **Glandular cells:**
        - Presence of endometrial cells in post-menopausal woman

- Atypical glandular cells (unqualified)
- Atypical glandular cells (favor neoplastic)
- Adenocarcinoma in situ
- Adenocarcinoma
- Other malignant epithelial neoplasm

The C60a and C60b forms will be used solely for Dianon's internal record keeping and will not be sent to either WDMAC or the clinical sites.

b. Excel spreadsheet

As described above in Section C1b, WDMAC will send an Excel file to Dianon containing the WIHSID, VISIT, date of specimen collection, source of specimen (cervical or vaginal), age at time of specimen collection, and squamous and glandular diagnoses. To this file, Dianon will append the final squamous and glandular diagnoses as assigned by the second and, if necessary, third readers, as well as the date of the final re-read, and submit this file back to WDMAC via email after all re-reads are completed.

During WDMAC's biannual edit process, the data contained in this spreadsheet will be compared to the historical data contained in the C60 Apollo data set and used to generate edits in cases where the initial and final diagnoses differ.

4. DATA EDITING PROCESS

WDMAC will compare the data from initial reads reported on C60 forms to the data received in the Excel spreadsheet regarding the final diagnosis. Any discrepancies between initial diagnoses and final reported diagnoses will be transmitted to the sites with the biannual central edits for resolution in the database. Sites will need to change the initial diagnosis reported on the C60 and the specimen reading date to those reported for the final diagnosis.

5. DOCUMENTATION

Dianon will track via computer the results of the initial, second and, if necessary, third reads. Sites will need to document any changes made to Apollo data due to re-reads in the same manner as any other change to Apollo. A note should be added to the initial C60 paper form indicating that the results were amended due to QA re-read, and the date of specimen re-reading should be noted on the form, as well. WDMAC will archive the completed Excel file received from Dianon, along with an associated codebook, for use in QA of the C60 data collected through July 1, 2002.

D. BUDGET ISSUES

1. PROSPECTIVE REVIEW

Prospective review has been approved and ongoing since July 1, 2002. Payment for the re-reads has already been incorporated into the WIHS II and WIHS III budgets.

2. RETROSPECTIVE REVIEW

Retrospective review of all HSIL and above slides was incorporated into the WIHS II budgets and thus will begin immediately.

APPENDIX A: FORM C60a – PAP SMEAR RETROSPECTIVE RE-READ REPORTING FORM (VISITS 1 – 15)

APPENDIX B: FORM C60b – PAP SMEAR RETROSPECTIVE RE-READ REPORTING FORM (VISIT 16, INITIAL READ PRIOR TO JULY 1, 2002)

WOMEN'S INTERAGENCY HIV STUDY
PAP SMEAR RETROSPECTIVE RE-READ REPORTING FORM
FORM C60a

NOTE: USE THIS FORM *ONLY* FOR RETROSPECTIVE RE-READS OF SLIDES COLLECTED AT WIHS *VISITS 1 THROUGH 15*.

Participant ID: |__| - |__|__| - |__|__|__|__| - |__| VISIT #: ___ ___ SLIDE NUMBER _____

FORM COMPLETED BY: ___ ___ ___ VERSION DATE **04/01/03**

A1. Date specimen obtained: ___ ___/___ ___/___ ___
M D Y

A2. Date central reading: ___ ___/___ ___/___ ___
M D Y

A3. Specimen site:

Cervical smear 1
Vaginal smear 2
Not given 3

A4. Specimen adequacy:

Satisfactory 1
Unsatisfactory 3

EPITHELIAL CELL:

A11. Squamous cell(s)	Y	N
a. Within normal limits	1	2
b. ASCUS	1	2
c. LGSIL: mild (slight) dysplasia/CIN1/HPV	1	2
d. HGSIL: moderate dysplasia/CIN2	1	2
e. HGSIL: severe dysplasia/CIN3/carcinoma in situ	1	2
f. Squamous cell carcinoma	1	2

A12. Glandular cell(s)	Y	N
a. Endocervical cells present and within normal limits	1	2
b. Presence of benign endometrial cells consistent with menses	1	2
c. Presence of endometrial cells out of phase in premenopausal woman	1	2
d. Presence of endometrial cells in postmenopausal woman	1	2
e. AGCUS: endometrial	1	2
f. AGCUS: endocervical	1	2
g. AGCUS: not otherwise specified	1	2
h. Adenocarcinoma	1	2

SPECIFY PROBABLE ORIGIN SITE: _____

i. Other malignant epithelial neoplasm 1 2

SPECIFY: _____

WOMEN'S INTERAGENCY HIV STUDY
PAP SMEAR RETROSPECTIVE RE-READ REPORTING FORM
FORM C60b

NOTE: USE THIS FORM *ONLY* FOR RETROSPECTIVE RE-READS OF SLIDES COLLECTED AT WIHS *VISIT 16 (INITIALLY READ PRIOR TO JULY 1, 2002)*.

Participant ID: |__| - |__|__| - |__|__|__|__| - |__| VISIT #: _1_ _6_ SLIDE NUMBER _____

FORM COMPLETED BY: ___ ___ ___ VERSION DATE **04/01/03**

A1. Date specimen obtained: ___ ___/___ ___/___ ___
M D Y

A2. Date central reading: ___ ___/___ ___/___ ___
M D Y

A3. Specimen site:

Cervical smear 1
Vaginal smear 2
Not given 3

A4. Specimen adequacy:

Satisfactory 1
Unsatisfactory 3

EPITHELIAL CELL:

A11. Squamous cell(s)	Y	N
a. Within normal limits	1	2
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c. ASC-HGSIL	1	2
d. LGSIL: mild (slight) dysplasia/CIN1/HPV	1	2
e. HGSIL: moderate dysplasia/CIN2	1	2
f. HGSIL: severe dysplasia/CIN3/carcinoma in situ	1	2
g. HGSIL: features of invasion	1	2
h. Squamous cell carcinoma	1	2

A12. Glandular cell(s)	Y	N
e. Presence of endometrial cells in postmenopausal woman	1	2
b. Atypical glandular cells (unqualified)	1	2
c. Atypical glandular cells (favor neoplastic)	1	2
d. Adenocarcinoma in situ	1	2
e. Adenocarcinoma	1	2

SPECIFY PROBABLE ORIGIN SITE: _____

f. Other malignant epithelial neoplasm 1 2

SPECIFY: _____