Studies of Ocular Complications of AIDS

SOCA General Handbook

May 2013

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(Version 5.0)
May 2013

SOCA Coordinating Center
Johns Hopkins University
615 North Wolfe Street, Room W5010
Baltimore, Maryland 21205
(410) 955-8175
(410) 955-0932 (fax)

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SOCA General Handbook

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Introduction

The SOCA General Handbook is a reference for information of relevance to SOCA. It stands apart from study specific handbooks as it covers the organization of the SOCA research group; policies for participation and publication within SOCA; and basic research principles that apply to studies. It also is a guide for applicable standard procedures such as visual function testing, fundus photography and quality of life assessment. It contains guidelines for adverse event reporting, HIV diagnostic codes, and other scales that are routinely used in data collection.

1. SOCA organization

1.1. Clinical centers

1.1.1. SOCA clinical centers (* see appendix)

SOCA ID	Institution
BCM	Baylor College of Medicine Cullen Eye Institute Houston, TX
EU	Emory University Eye Clinic Atlanta, GA
JHU	Johns Hopkins University Wilmer Ophthalmological Institute Baltimore, MD
LSU	Louisiana State University LSU Eye Center New Orleans, LA
MSK	New York Hospital-Cornell Medical Center Memorial Sloan-Kettering Cancer Center New York, NY
NU	Northwestern University Chicago, IL
NYU	New York University Medical Center Department of Ophthalmology New York, NY
PENN	University of Pennsylvania Philadelphia, PA
UCLA	University of California Los Angeles Jules Stein Eye Institute Los Angeles, CA
UCSD	University of California San Diego UCSD Treatment Center - Eye Clinic San Diego, CA

1.1.1. List of certified clinical centers

SOCA ID	Institution
UCSF	University of California San Francisco Beckman Vision Center San Francisco General Hospital San Francisco, CA
UNC	University of North Carolina Chapel Hill, NC
USF	University of South Florida at Tampa Tampa, FL

Clinics closed (as of IRB termination date):

Indiana University (IU) Medical Center
Indianapolis, IN [Sep 2008]

Mount Sinai Medical Center (MSMC)
New York, New York [Jul 1999]

New Jersey Medical Center (NJMS)
Newark, New Jersey [Sep 2009]

RUSH Presbyterian Medical Center (RUSH)
Chicago, IL [Jul 10]

University of California, Irvine (UCI)
Irvine, CA [Mar 2010]

University of Southern California (USC)
Los Angeles, CA [Jan 2009]

University of Miami (UM)
Miami Florida [Aug 1999]

University of Texas Medical Branch
Galveston, Texas [Jan 2011]

1.1.2. Clinical center operations

Responsibilities

- Recruit and certify staff as required to conduct SOCA studies
- Submit protocols, consent statements and other related documentation to local IRB
- Ensure protocols are conducted in compliance with IRB regulations
- Adhere to FDA regulations for protocols carried out under an IND
- Provide CC with documentation as necessary
- Carry out the patient education and consent process for eligible and willing patients
- Treat (if applicable) and follow recruited patients according to approved protocol
- Collect study data on SOCA forms
- Send data to the CC as required
- Respond to edit queries
- Elect SC representatives
- Participate in RG meetings

Staff

- Center director
- Ophthalmologist
- Ophthalmic surgeon, if applicable
- Clinic coordinator
- Infectious disease specialist/internist
- Visual acuity examiner, visual field examiner
- Fundus photographer
- Pharmacist (trials only)

1.2. Resource centers

1.2.1. List of resource centers (as of 7 June 2009)

SOCA ID	Institution
CO	Chairman's Office Mount Sinai School of Medicine New York, NY
CC	Coordinating Center Johns Hopkins University Baltimore, MD
FPRC	Fundus Photograph Reading Center University of Wisconsin Madison, WI
NEI	National Eye Institute Bethesda, MD

1.2.2. Chairman's Office (CO)

Responsibilities

- Provide leadership for the study
- Lead publicity and recruitment efforts
- Serve as study spokesperson
- Serve as ophthalmologic and medical consultant to CC
- Provide representation to SO, SC, PDMB, and RG
- Coordinate meetings of the SO, SC, PDMB, and RG
- Prepare patient education materials
- Prepare manuscripts for publication
- Participate in preparation of secondary manuscripts
- Order and distribute manuscript reprints

Staff

- Chairman
- Coordinator
- Secretary

1.2.3. Coordinating Center (CC)

Responsibilities

- Provide expertise in the design and operation of SOCA trials and prospective observational studies
- Develop and maintain study documents: SOCA General Handbook, study specific protocols, study specific handbooks and data forms
- Develop and maintain communication with clinics regarding PDMB recommendations, changes to protocols, and status of trials, if applicable
- Develop and maintain study data system (data collection, processing, analysis and quality assurance)
- Conduct site visits and conference calls with clinical centers
- Prepare and submit interim and annual data monitoring reports to the PDMB
- Prepare and submit annual reports to the NEI
- Develop and administer contracts with clinical centers for NEI support
- Provide representation to the SO, SC, PDMB, and RG
- Prepare manuscripts for publication
- Administer clinic funding
- Maintain the official SOCA archive
- Evaluate alternatives for future studies
- Identify additional areas of support

Staff

- Director
- Deputy director
- Project coordinator
- Associate coordinators
- Research assistants
- Biostatisticians
- Programmers
- Secretary
- Administrator

1.2.4. NEI Project Office

Responsibilities

- Serve as a member of the SO, SC, PDMB, and RG
- Provide liaison between the sponsor and the RG
- Provide administrative and fiscal advice
- Participate in site visits to clinical centers
- Participate in the design, conduct, and analysis of SOCA trials and prospective observational studies
- Prepare manuscripts for publication
- Advice regarding appropriateness of a clinical alert, if applicable

Staff

- NEI project officer

1.2.5. Fundus Photograph Reading Center (FPRC)

Responsibilities

- Develop protocol for fundus photography
- Provide training, certification and support for fundus photographers
- Receive, inventory, and store fundus photographs
- Perform masked evaluation of fundus photographs
- Monitor photograph quality and provide reports to clinics and SO
- Provide representation to the SO, SC, RG
- Prepare manuscripts for publication

Staff

- Director
- Associate director
- Coordinator
- Secretary
- Graders
- Statistician

1.2.6. Collaborations

1.2.6.1. North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD)

Status

- LSOCA cohort joins NA-ACCORD in August 2009

Background and purpose

- The North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) is part of the International epidemiologic Databases to Evaluate AIDS (IeDEA). NA-ACCORD is designed to be widely representative of HIV care in the United States and Canada, includes investigators who have a high level of scientific expertise and clinical experience, and has an efficient structure for harmonization of data and the conduct of analyses.

Objectives

- To establish a collaboration of North American HIV/AIDS cohorts and a data center for compilation of data to address HIV/AIDS research questions that cannot be accomplished through smaller cohorts
- To address scientific aims that focus on the failure of highly-active antiretroviral therapy (HAART), with a special focus on multi-drug resistant virus and its consequences and management
- To address additional scientific aims related to events that cannot be as well studied in smaller cohorts (e.g., those that require large sample sizes, such as rare events from new HIV therapies, or those that require long-term followup, such as malignancy), and emerging issues in HIV clinical care such as the impact of aging on HIV treatment response
- To develop and apply novel statistical and epidemiological methodology that is applicable to these scientific research initiatives
- To collaborate with other regional cohorts in IeDEA to compare results and address questions of inter-regional importance

Sponsors

- National Institute of Allergy
- Infectious Diseases and National Cancer Institute

Study characteristics

- NA-ACCORD is a collaborative cohort study designed to compile data on clinical, virologic, immunologic, behavioral, metabolic, service utilization, and psychosocial aspects of HIV infection and disease.

Data principles

- Ownership of individual cohort data remains with the contributing cohort
- Data transmitted to and residing at the Data Management Core (DMC) or the Epidemiology/Biostatistics Core (EBC) will be de-identified, per HIPAA criteria
- A cohort may choose to participate or not
- Cohorts will have input and one vote in the Steering Committee (SC) whether or not a cohort's data are contributed to a specific scientific aim
- By agreeing to participate in a scientific project, participants commit to supplying data in a timely manner
- Data will be used only to address the specific scientific aim or question and not used for unrelated questions without express permission of the cohort
- Following analysis and preparation of manuscript, data will be archived without personal health identifiers including origin of cohort site
- Any investigator from a participating cohort can propose an analysis with combined NA-ACCORD data using the NA-ACCORD concept sheet
- Any investigator from a participating cohort can be a member of the Working Group for analysis conducted with NA-ACCORD data

Support

- Funding: NIH
- Currently in 2nd 5-year funding cycle (started July 2011)

Cohorts

- 23 collaborating cohorts (as of August 2011)
- Participating cohorts:
  - ALIVE: AIDS Link to the IntraVenous Experience
  - ALLRT: AACTG Longitudinal Linked Randomized Trials
  - CWRU: Case Western Reserve University Immunology Unit Patient Care and Research Database
  - FCHC: Fenway Community Health Center
  - HIVRN: HIVE Research Network
  - HOMER: HAART Observational Medical Evaluation and Research
  - HOPS: HIV Outpatient Study
  - JHHCC: Johns Hopkins HIV Clincical Cohort
  - KPNC: Kaiser Permanente Northern California
  - LSOCA: Longitudinal Study of Ocular Complications of AIDS
  - MACS: Multicenter AIDS Cohort Study
  - MHCS-II: Second Multicenter Hemophilia Cohort Study
  - MONT: Montreal Chest Institute Immunodeficiency Service Cohort

Cohorts (cont'd)

- OHTN: Ontario HIV Treatment Network Cohort Study
- SAC: Southern Alberta Clinic Cohort
- SCOPE: Study of the Consequences of the Protease Inhibitor Era
- SUN: Study to Understand the Natural History of HIV/AIDS in the Era of Effective Therapy
- UAB: University of Alabama at Birmingham 1017 Clinic Cohort
- UCHCC: University of North Carolina, Chapel Hill HIV Clinic
- UW: University of Washington HIV Cohort
- VACS: Veterans Aging Cohort Study and Virtual Cohort
- VAND: Vanderbilt-Meharry CFAR Cohort
- WIHS: Women's Interagency HIV Study

Publication policies

- Final abstracts, manuscripts and presentations must be reviewed and approved by the Steering Committee before any presentation or submission for publication.

Credits and Authorship

- Manuscripts will acknowledge that data were collected through NA-ACCORD and credit all collaborating cohorts
- The International Epidemiologic Databases to Evaluate AIDS (IeDEA) will be acknowledged in the manuscript credit

1.2.6.2. Frederick National Laboratory for Cancer Research (FNLCR)

Since 2004, SOCA has collaborated with the Frederick National Laboratory for Cancer Research (FNLCR); investigating host genetic factors influencing infectious and non-infectious ocular complications of AIDS. In 2012, SOCA began collaborating with Dr. Cheryl Winkler, head of molecular genetic epidemiology studies, to continue genetic studies with the SOCA cohort to determine the impact of genetic risk factors for age-related eye complications such as Age-related macular degeneration (AMD), cataract, and retinal vasculature.

1.3. Committees and groups

1.3.1. List of committees and groups

SOCA ID	Committee / Group
SO	Study Officers
SC	Steering Committee
PDMB	Policy and Data Monitoring Board
VFQAC	Visual Function Quality Assurance Committee
RG	Research Group

1.3.2. Study Officers (SO)

Membership*

- Study Chairman
- Director of Coordinating Center
- Deputy Director of Coordinating Center
- Director of Fundus Photograph Reading Center
- Project Officer of National Eye Institute

Responsibilities

- Discuss and set priorities for emerging issues
- Resolve problems
- Fiscal management
- Serve as liaison for SOCA interactions with other private and public research groups
- Appoint writing committees (with advice and consent of SC)

Meeting schedule

- Monthly via conference call
- Annually at the Research Group meeting
- Additional meetings as needed

Meeting assignments

- Arrangements (Chairman's Office)
- Materials (Chairman's Office)
- Minutes
  - Preparation (Chairman's Office)
  - Review (Study Officers)
  - Distribution (Chairman's Office)
  - Archive (Coordinating Center)

*Refer to SOCA Directory for list of current members

1.3.3. Steering Committee (SC)

Membership*

Elected members (voting)

- Infectious disease experts (3)
- Ophthalmologists (3)
- Clinic coordinators (2)
- Photographers (2)

Ex-officio members (voting)

- Study Officers
- Associate Director of Fundus Photograph Reading Center

Terms of office

- Four years (members eligible for re-election)
- Half of the elected membership up for election every 2 years

Responsibilities

- Discuss design issues
- Review and approve study procedures and documents
- Address and resolve issues relating to the execution of studies
- Review study progress and act to correct deficiencies in the data collection or analysis procedures
- Make decisions on allocating resources of the study and on priorities for meeting competing demands in the study
- Promote the publication of study findings
- Review and approve ancillary studies

Meeting schedule

- Annually at the Research Group meeting
- Additional meetings as needed

Meeting assignments

- Arrangements (Chairman's Office)
- Materials (Chairman's Office / Coordinating Center)
- Minutes
  - Preparation (Chairman's Office)
  - Review (Steering Committee)
  - Distribution (Chairman's Office)
  - Archive (Coordinating Center)

*Refer to SOCA Directory for list of current members

1.3.4. Policy and Data Monitoring Board (PDMB)

Membership*
- Voting members
- Non-voting members

Discipline represented
- Ophthalmology (2 voting, 2 non-voting)
- Biostatistics (2 voting, 2 non-voting)
- Infectious Disease (2 voting)
- Research Science (2 non-voting)
- Theology (1 voting)

Study positions represented (all non-voting)
- Study Chairman
- Director of Coordinating Center
- Deputy Director of Coordinating Center
- Director of Fundus Photograph Reading Center
- Project Officer of National Eye Institute

Tenure
- Without term

Attendance
- Members who miss 3 or more consecutive meetings may be asked to step down

Responsibilities
- Review and approve study protocols prior to initiation of study
- Review and comment on analytic approach and plans
- Evaluate patient safety, if applicable
- Recommend changes to protocol as deemed appropriate
- Review accumulating data
- Review performance monitoring reports including enrollment, overall study progress, data quality and compliance to study protocol
- Assess data quality and, when indicated or when asked, provide investigators and sponsors with advice on operational procedures affecting research quality
- Provide advice to SOCA, NEI, and other sponsoring agencies regarding conduct of the study
- Review and comment on mainline manuscripts prior to submission. Major papers are those deemed appropriate by the Study Officers and Steering Committee for review by the PDMB

- Review ancillary study proposals likely to impact on enrollment, data collection, adherence to protocol, or deemed potentially sensitive (e.g., genetic studies), and any other study proposals which the Study Officers desire.
- Periodic review of progress of ancillary studies that require SOCA funding, represents added burden on risk to SOCA patients, or use of banked specimens for the purpose of recommending actions to be considered by the SOCA Steering Committee
- Periodic review of publication plan
- Other duties as proposed by the Study Officers, Steering Committees, or National Eye Institute

Meeting schedule

- In-person meeting annually
- Additional meetings as needed

Meeting assignment

- Arrangements (Chairman's Office)
- Meeting notebooks (Coordinating Center)
- Minutes (Chairman's Office)
- Archive (Coordinating Center)

*Refer to SOCA directory for list of current members.

1.3.5. Visual Function Quality Assurance Committee (VFQAC)

Membership

Elected members (appointed based on a joint consensus of committee members)

- Visual Function examiners
  - Chairperson
- Members from clinical centers (3-5)
- SOCA Coordinating Center representative (1)
- Ophthalmologist as faculty advisor (1)

Term of office

- Open-ended

Responsibilities

- Discuss visual function issues pertaining to protocol administration, changes, and procedures
- Address and resolve issues relating to the execution of visual function procedures at the clinical centers
- Complete VFQAC site visit equipment/room certification (VE) form
- Complete VFQAC Contrast Sensitivity (VC) Score Sheet. VFQAC Goldmann Visual Field Evaluation (VM) score sheet; VFQAC Visual Acuity Testing (VV) Score Sheet; VFQAC Refraction (VR) score sheet; VFQAC Humphrey Visual Field Evaluation (VH) score sheet for all clinic Visual Function examiners
- Act as visual function expert resource for the SOCA Coordinating Center

Meeting schedule

- Once per year at the Research Group meeting
- If clinic coordinator meeting takes place, meeting of VFQAC committee will take place
- Conference calls as necessary

Meeting assignments

- Arrangements (Coordinating Center)
- Materials (Coordinating Center/Chairperson)
- Minutes
  - o Preparation (Chairperson)
  - o Review (VFQAC members)
  - o Distribution (Coordinating Center)
  - o Archive (Coordinating Center for main archives)
    (Chairperson VFQAC files)

1.3.6. Research Group (RG)

Composition*

- All Chairman's Office staff members
- All Coordinating Center staff members
- All certified clinical center staff members
- All Fundus Photograph Reading Center staff members
- All Steering Committee members
- Sponsor representatives

Responsibilities

- Conduct of SOCA
- Election of Steering Committee members

Meeting schedule

- Once per year
- In-person meeting annually
- Conference phone call annually
- Additional meetings as needed

Meeting assignments

- Arrangements (Coordinating Center / Chairman's Office)
- Materials (Coordinating Center / Chairman's Office)
- Minutes (Not taken)

*Refer to SOCA Directory for list of current members

2. Participation in SOCA studies

2.1. Clinical Center

Facilities and equipment

Clinical facilities needed to conduct SOCA studies include:

- Room for measuring visual acuity at least 10 feet in length with floor markers from the examination chair to the ETDRS chart at 10, 5, and 2.5 feet (or 4, 2, and 1 meters) and appropriate lighting
- Pharmacy capable of storing and dispensing investigational new drugs and, when necessary, preparation of medications for administration (trials only)
- Clinical facilities for physical examinations, drug infusions, and access to inpatient care when needed
- Ability to ship specimens to central repository
- Specimen laboratory capable of processing whole blood for plasma and leukocytes

Equipment required to conduct SOCA studies include:

- Wide field ophthalmic camera as follows:
  - fundus camera (similar to the TRC-50 and the Nikon NF-505 model) may be substituted
  - Topcon TRC-50 series (50 VT, 50X, 501A, and 501X or similar models); ZEISS FF 450-plus fundus cameras, all used at 50°; Canon UV (or similar models) used at the 60° setting; the Kowa, Nikons and Olympus fundus camera models at the 50° setting are all suitable for the study.
- Goldmann perimeter & Humphrey Field Analyzer for visual fields
- ETDRS visual acuity charts (preferably backlit)
- Pelli-Robson Contrast Sensitivity charts

Certification

Documents provided by the clinical centers to the Coordinating Center (before every new study):

- IRB notification of approval of current study protocols (to be updated annually)
- Copy of the Consent Statement which has been reviewed and approved by local IRB
- Curriculum Vitae (CV) for all ophthalmologic and infectious disease investigators, and clinic coordinators who will be participating in the SOCA study
- Laboratory Certificate for all laboratories performing hematology and serum chemistry assays
- Laboratory Range (LR) for each laboratory. Every laboratory will be given a sequential number by the clinic coordinator. Always identify the laboratory by the assigned number when the information is needed on study forms.

- Master signature list (maintained at a clinic)
- Certification form for all appropriate personnel
- Disclosure Statement (Conflict of Interest) to be completed, signed and submitted to SOCA CC for files (for trials only)

Documents provided by the Coordinating Center to the clinical centers (available online):

- **SOCA General Handbook** - a generic document describing the organization, policies and procedures used in SOCA studies
- **SOCA General PPM Notebook** - a binder to maintain sequentially numbered general policy and procedure memoranda
- **Study Protocol** - a study specific document describing the study design, treatment plan, data collection methods and outcome measures
- **Study Investigator's Brochure** - a brochure prepared and maintained by the sponsor of a new drug which contains information regarding the chemical nature of the drug, its mode of action or presumed mode of action in the summary of available animal as well as a clinical data related to the safety and efficacy of the drug (trials only)
- **Study Specific Handbook** - a study specific handbook of operations, the design, visit schedule, procedures and treatment administration
- **Study Forms Book** - a study specific document containing master copies of all forms needed for the study
- **Study PPM Notebook** - a binder to maintain sequentially numbered study specific policy and procedure memoranda
- **Consent Form** - a form used to obtain consent from a potential subject to participate in the trial
- **Assent Form** - a form required whenever consent is given by someone else on behalf of the person to be enrolled in the trial
- **Copy of Certificate of Confidentiality** - a certificate issued by the Secretary of Health and Human Services for the purpose of protecting study records and forms from subpoena, criminal, civil, administrative or legislative hearing at the federal, state or local level

2.2. Clinic personnel

Personnel

Personnel (primary and backup) need to be certified for the following positions:

- Ophthalmologists
- Infectious disease specialists
- Ophthalmic Surgeons (if applicable)
- Clinic coordinators
- Pharmacists (if applicable)
- Visual acuity examiners
- Data entry technicians
- Visual field examiners
- Photographers
- Research nurse (if applicable)
- **All new** personnel need to be certified
- Any personnel that **add a new function** within the clinic need to be certified for the new function

The following primary and backup personnel **must be recertified** for each study:

- Ophthalmologists
- Infectious disease specialist
- Clinic coordinators
- Pharmacists (if applicable)

The following primary and backup personnel will be recertified every 5 years, or more frequently if necessary, or for each study if they have not performed their functions for more than one year, or if the ophthalmic protocol has changed:

- Visual acuity examiners
- Visual field examiners
- Fundus photographers

Personnel certification procedures

- **All personnel** should read the protocol and appropriate sections of the SOCA Handbooks (General and Study specific) and become knowledgeable about their responsibilities

- **On initial certification, all personnel** who will be completing study data collection forms should complete a practice baseline form set or forms pertaining to their function. For certification, personnel should function as they would during the study and record data on the relevant practice data collection forms. Data should be recorded from a clinical visit of a patient who is seen at the SOCA clinic. The practice set of forms should be sent to the Coordinating Center for review.
- **All personnel** should complete a Personnel Certification (PC) form for the relevant study. The master copy of the PC form is located in the study forms notebook and SOCA website. Each form should be reviewed, signed by the clinic director and a copy mailed to the Coordinating Center.
- **Ophthalmologists, infectious disease specialists and coordinators** are required to be knowledgeable about eligibility and exclusion criteria, treatment procedures (if applicable), adverse event reporting (if applicable), and their data collection responsibilities
- **Visual acuity examiners** are responsible for performing refractions and visual acuity testing according to the ETDRS protocol. The visual field examiners are responsible for performing visual fields according to the Visual Field protocol.
- **Pharmacists** are responsible for knowing about treatment assignment, masking and unmasking procedures, drug ordering, dispensing, and drug disposal procedures (trial only)
- **Photographers** need to submit two sets of fundus photographs (digital, taken according to the SOCA Photography protocol, to the Fundus Photograph Reading Center (FPRC) for review. Photographs should be identified for SOCA certification purposes and sent to:

  Contact person: (please refer to the online Personnel Directory)
  Fundus Photograph Reading Center
  8010 Excelsior Drive
  Suite 100
  Madison, Wisconsin 53717

- For link to portal for uploading digital images, see section 8.5
- Upon completion of the above requirements, certification numbers will be assigned by the Coordinating Center for those personnel who have successfully completed all requirements

2.3. Clinic contract and funding

- Coordinating Center receives and distributes funding from the sponsor
- Contracts are executed between the clinical site and the Coordinating Center
- When applicable, primary mode of funding for pharmaceutical company sponsored trials is on a per patient basis as enrolled and followed in the study with payments dictated by specifics of the individual trial
- NEI funding is allocated for staff and on a per patient basis based on completion of clinic visit to include eye examination.

2.4. SOCA policy and procedures for replacement of a center director

- Current clinic directors, proposed new director, and representative of administrative office must submit a letter to the SOCA Study Officers stating that he or she intends to step down and name the proposed replacement. The CV of the proposed replacement must be included as well as a Letter of Intent and evidence of Human Subjects certification
- Study Officers review the letter and forward it to the NEI Project Officer with their recommendation for approval or disapproval of the proposed replacement
- Upon approval, NEI Project Officer informs the Study Officers and the current clinic director, proposed new director, and representative of administrative office of NEI's decision

3. Patient enrollment and followup

3.1. Eligibility and consent procedures*

- Explain disease, purpose of the study, and treatment options (if applicable) to the patient
- Assess inclusion/exclusion criteria to evaluate patient's eligibility status, including willingness to comply with protocol and ability to participate
- Describe purpose and design of the study, including treatment regimens (if applicable) and data collection schedule
- Answer questions the patient has regarding the study
- Give patient consent statement to read and consider for 24-hours (if desired)
- Review consent statement with patient and answer any questions when the patient is ready to enroll
- Ask the patient to sign and date the consent statement
- Ask a witness to sign and date the consent statement
- If the patient is a minor, the assent statement should be signed by the patient and a clinic staff member. A consent statement should be signed and dated by a parent or guardian and witnessed by a clinic staff member
- If a person is not interested in participation, thank him/her for his/her time and provide usual services
- Assign a SOCA ID # to the patient using consecutive #s assigned to the clinic. If the patient was previously enrolled in a SOCA study, he/she should keep the same Patient Identification Number (ID#) for all SOCA studies
- Assign a patient name code according to guidelines outlined in the data management chapter of this handbook
- Complete all baseline visit procedures required
- Complete and fax Enrollment form (EF) to the Coordinating Center
- Coordinating Center will contact clinic to review EF form and open database for the patient; at which time data entry of baseline forms may begin

* Enrollment activities ended 31 Jul 2011

3.2. Followup

Purpose

- To monitor medical and ophthalmic history including: anti-retroviral treatment, visual function testing, ophthalmic examinations, laboratory studies, quality of life and specimen banking
- Provide essential care to patients
- Provide uniform basis for observing and recording clinical events
- Provide data for evaluating changes over time from enrollment
- Maintain patient contact
- All patients, once enrolled, are followed to death or termination of study, whichever occurs first

Procedures for patients lost to followup

Purpose

- Ascertain vital status of patient
- Ascertain patient's drug treatment status since the date of most recent clinic visit, if applicable
- Document reason(s) patient did not participate in clinic visit(s)
- Ascertain if patient is lost to followup

Search strategies

- Contact all persons identified on Patient Location Information form (PL form), eg. next of kin, partner, other health care professionals
  - telephone different times during the day/evening
  - send letter via regular or certified registered mail to determine if patient is still at listed address
- Check current telephone directory for listings both for the patient and the patient's contacts specified in the PL form
- Check post office for forwarding address; ask patient's contacts for forwarding address
- Search clinic and hospital records for more up-to-date information
- Trace patient via ACTG patient ID number and ACTG institution, if applicable
- Trace patient via social security number **or** driver's license number (PL form)
- Check Social Security Death Index (SSDI) and National Death Index (NDI)
- Check online search options such as www.legacy.com
- Check obituaries
- Check state vital records

3.3. Patient transfer procedures

Enrolling clinic responsibilities:

As soon as the patient notifies the clinic about an upcoming move to a new area and he/she agrees to transfer to another SOCA clinic (adopting clinic) the enrolling clinic coordinator should:

- Contact the clinic coordinator of the adopting clinic to request permission for transfer
- Provide patient with contact information for adopting clinic and advise patient to contact clinic coordinator to schedule next study visit. In order to maintain patient privacy, patient contact with adopting clinic must be initiated by the patient.
- Complete sections A-C of the Transfer Notification (TN) form
- Fax the TN form to the Coordinating Center
- Send the original TN form to the adopting clinic and copies of the formset from the most recent in-person visit, and the baseline visit (keep copies of all original formsets for your file)
- Send the patient-specific labels for photographs and laboratory specimens to the adopting clinic

Adopting clinic responsibilities:

- Once contacted by transfer patient, schedule in-person followup visit
- Verify receipt of formsets and labels sent by enrolling clinic; if specimen labels are not received or not available from enrolling clinic, contact ThermoFisher Bioservices for replacement labels
- At the first followup visit:
  - the Informed Consent Form approved for use at the adopting clinic must be signed by the patient (or legal representative) in order for the patient to continue in SOCA
  - complete Sections D-E of the Permanent Transfer Notification (TN) form
- Record the TN form on the Forms Checklist on the Visit Guide (Section C, item 47, page 2)
- Send completed TN form to Coordinating Center for data entry and activation of patient in adopting clinic database
- Fax copy of TN form to enrolling clinic for their records

Clinic and patient identifiers:

- Clinic ID code will remain the same as the enrolling clinic ID
- Patient ID# will remain the same
- Patient name code will remain the same

DQQs

- The enrolling clinic will receive DQQs only for the visits that took place at the enrolling clinic
- The adopting clinic will receive DQQs for the visits that took place at the adopting clinic

4. Patient closeout procedures

Pending

5. Data management

5.1. Forms completion

General

- Use ink that is dark enough to photocopy legibly
- Enter the patient ID at the top right of every page of form
- Print all written responses
- Enter data in the units and number of digits prescribed on form. Be sure to include a value preceding a decimal point, if applicable. Do not include a fraction or a decimal if not called for on the form.
- Right justify all numbers, enter leading and following zeroes where applicable
- Left justify all letter codes, leave remaining spaces blank
- Perform all computations using a calculator
- Round values according to the SOCA data rounding rules (refer to Section 4.3)
- **Review all responses** for completeness and accuracy before signing off on form
- To correct a response: draw 1 or 2 lines through incorrect response, write correct response next to or above it, put initials and date in the margin by the correction. **Do not obliterate, erase or white-out responses.**

Missing data

- If some data are missing and can not be obtained when the form is reviewed, write the appropriate code in the first left hand space of the empty data field:
  - **N** = not applicable in this situation
  - **M** = data missing
  - **?** = data temporarily missing; to be collected or resolved in the near future
- If "?" is used - edit form with complete data when available

Coding

- Code lists are located in Appendix of this handbook or in a study specific handbook
- Coding systems needed to complete forms:
  - Drug Codes table is used to complete the Followup Treatment History forms
  - HIV-related Diagnosis Codes list is used to complete Baseline and Followup Medical History forms
- AIDS-defining diseases may be needed to complete the Medical History form

Skip pattern instructions

- Form navigation instructions are in **boldface**
- Skip patterns: denoted by arrow from response to a box with the number of the next item to be completed
- **IF BOTH** skips: arrows from the right and left eye response boxes indicate the skip pattern-- skip only if both of these boxes are checked
- **Stops**: denoted by arrow from response to a stop sign: the remainder of the form should not be completed except for the administrative information

Other special instructions

- Special instructions are always italicized
- **Check one only**: only one of the listed responses should be checked
- **Check all that apply**: one or more of the listed responses can be checked
- **Specify:** a response should be printed on the line(s) provided
- **Code list references**: listed when necessary for form completion

Units and abbreviations

- Abbreviations for dose units for use on SOCA forms:

mg	=	milligram
mcg	=	microgram
g	=	gram
mL	=	milliliter
cc	=	cubic centimeter
DS	=	double strength
sub Q,SC	=	subcutaneous infection
IM	=	intramuscular injection
IV	=	intravenous
cap	=	capsule
tab	=	tablet

- Symbols and abbreviations for dosage frequency cannot be used on SOCA forms

Acceptable codes	Unacceptable
1 per **day**	QD
2 per **day**	BID
3 per **day**	TID
one (tablet, etc)	÷
at night	HS

- PRN (as needed) is acceptable for use on SOCA forms, should be recorded as "___ per **prn**" in dosage frequency items
- For double strength (DS); indicate under dosage (amount and units) not after the name of the drug. Use actual units (mg, mL) whenever possible.
  - (eg, Bactrim 1 tab DS)
  - (not Bactrim DS 1 tab)

5.2. Forms handling

Duplication

- Maintain one complete set of trial master forms in the Forms notebook
- Go to SOCA website and access the following links:
  - Documents
  - Forms
- Make copies of data collection forms as needed
- Forms necessary for each visit are outlined in the study specific handbook
- Use a Visit Guide (VG) form with each visit to insure that all appropriate forms are available and completed

Storage

- Create a separate folder or notebook for each patient enrolled
  - Patient folder or notebook contains all forms for a patient except those with identifying information of patient
  - Medical File Contents (MF) form at the front of each Patient Folder, listing visits chronologically by visit ID and date
  - Visit Guide (VG) form for each visit, followed by the forms completed in association with that visit
  - Sets of forms from each visit separated by dividers or other means
  - Forms arranged chronologically by visit, with the most recent visit immediately behind the Visit Time Windows (VT) form
- Patient Folders should be stored in a **locked room or locked filing cabinet**
- All forms with individual patient identifiers (e.g., Patient Location Information (PL) form and actual death certificates) should be filed separately from the Patient Folders in a secure place

Transmittal to the Coordinating Center

- Data entry will be done at the clinic
- Forms which should be faxed to the CC include Adverse Event Report (AE) if applicable, Death Report (DR), and Enrollment Form (EF) forms. AE and DR forms should be faxed to the CC within 24-hours of clinic being notified (if applicable)
- Do not send any forms containing individual patient identifiers (i.e., Patient Location Information Form and Consent Form)
- Forms with two or more pages to be stapled

5.3. Data rounding rules

Examine the digits following the last data position required on the form:

- If the first digit following the last data position required for the response is less than 5, leave the digit in the last data position required for the response unchanged, e.g., 4.73 = 4.7
- If the first digit following the last data position required for the response is greater than 5, round up the digit in the last data position required for the response, e.g., 4.76 = 4.8
- If the first digit following the last data position required for the response equals 5 and the digit in the last data position required for the response is odd then round the digit in the last position up 1 unit, e.g., 4.75 = 4.8. Leave the digit in the last data position required for the response unchanged if the digit is even, e.g., 4.85 = 4.8.
- Note that zero is an even number

5.4. SOCA IDs

IDs

- Alpha and numeric codes used to identify clinics, patients, visits, and staff
- Used to complete data forms

Clinic ID code

- 2 to 4 character alpha code
- Assigned by the Coordinating Center
- Uniquely identifies the Clinical Center

Patient ID

- Four digit numbers
- Distributed by the Coordinating Center in the form of folder labels
- Assigned in sequence by the Clinic Coordinator
- Remains the same for the duration of the study

Patient name code

- 5 field unique alpha code
- Assigned by the Clinic Coordinator
- Assigned at registration to each patient screened, before eligibility is determined
- Remains the same for the duration of the study, regardless of error or change in name

Visit ID

- 1 to 3 character alpha-numeric code
- Assigned by Clinic Coordinator
- Determined by purpose of visit and timing with respect to visit windows
- Visit ID codes:

BL	baseline
F#	scheduled followup visits, numbered sequentially by visit window
N	data not collected at a specific visit

Staff IDs

- Two digit number/alpha numeric
- Uniquely identifies each clinic coordinator, ophthalmologist, study physician, photographer and ophthalmic technician at the Clinical Center
- Assigned by the Coordinating Center after successful staff certification
- Coordinator(s), ophthalmologist(s), and internist(s) need to be re-certified for each new SOCA study. SOCA - certified visual function examiners and fundus photographers do not need to be re-certified for new studies if the protocol remains the same.

5.5. Data Quality Query (DQQ)

Purpose

- The purpose of the Data Quality Query (DQQ) is to resolve problems discovered during the process of editing and keying of the forms

Frequency

- Monthly

Completed by

- Clinic Coordinator

Specific Instructions

- The DQQ is prepared and distributed by the SOCA Coordinating Center
- Outstanding DQQs will be included in the Monthly data report
- Items with edits are flagged with a "?" in the database and won't be used for analyses until the associated query is resolved
- Resolution of the listed queries requires review of the specified forms on a patient by patient basis. The DQQ is to be completed by the clinic coordinator as soon as possible.
- All resulting corrections and/or annotations must be recorded onto the clinic forms and onto the DQQ listing. The corrections to the form sets should be recorded according to SOCA usual standards.
- Problems discovered involving items that do not appear on the DQQ listing ("unsolicited queries") also have to be corrected. For "unsolicited queries", correct and /or annotate the forms following the same procedures as above.
- **Timely turnaround is expected**. DQQs not resolved will roll over each month until corrected and data system updated.

Standards for making changes to data forms:

- Strike through, but do not obliterate, prior values for items that are to be changed. Do not use "white-out."
- Make the corrections or annotations in a different color ink
- Date and initial all corrections or annotations

- Record "BLANK" on the listing if an item is to remain blank
- If a mutually agreeable solution to a problem cannot be reached in a reasonable amount of time, enter "PENDING" on the listing for the items involved, indicating that more time is needed to determine the correct values
- If a telephone editing takes place, date and initials of both, the CC editor and the clinic coordinator have to be written down next to each change on the data form

Instructions for clinics to update data system

- Log into data system; select data entry; then select "change form"
- Click edit button; complete pop-up edit by confirming the SOCA ID, visit ID, form and sequence number separated by commas
- Edit appropriate fields and click "save"

5.6. Followup principles

- Followup data collection schedule is timed from day of enrollment
- Time window construction is contiguous, ie, when window for one visit closes window for next visit opens
- Minimum time separation between data collection visits
- Followup data collection schedule is the same for all patients
- All patients are followed for survival, including patients off study drug (if applicable)

5.7. Data analysis principles

Intention to treat (for clinical trials only)

- The initial underlying comparison of the test treatments will be by treatment assignment, i.e., will be based on comparisons constructed by counting patients in the treatment group to which assigned regardless of course of treatment, degree of compliance, or willingness to adhere to the required data collection schedule

Counting principles

- Once a patient has been randomized that patient is counted in the treatment group to which assigned
- Events and outcomes observed, including deaths, counted regardless of time of occurrence after randomization (a death observed one day after randomization would be counted as a death in the treatment group to which the patient had been assigned)
- Events and outcomes observed counted regardless of degree of treatment compliance achieved
- Events and outcomes will not be counted together until counted and analyzed separately

P-value principle

- Used more as descriptive statistics than indicator of truth
- No adjustment for multiple comparison, looks, or outcomes
- No formal stopping rules

6. Study center monitoring

6.1. Site visits

Purpose

- Conduct an audit of selected patient data
- Review documentation and procedures for the study
- Inspect facilities for visual function testing and fundus photography
- Discuss with resource center personnel any problems that have occurred or that are expected to occur in conducting the study
- Ensure that Good Clinical Practice principles are being followed
- Review of procedures performed by Visual Function Examiner(s) and Fundus Photograher(s) by a VFQAC representative

Clinic preparation

The following should be available:

- Site visit agenda to be prepared by the Coordinating Center and provided to the Clinic Coordinator before the scheduled visit
- IRB communications organized with original approval letters, revision approvals, annual renewals, and any communications regarding concerns or special requests from your review board
- Signed and dated consent statements for all patients including the date and signature of a witness
- PPMs in appropriate binder
- Documents including protocols, study specific handbooks, forms, SOCA General Handbook, and SOCA Directory
- Visual acuity facilities including appropriately marked lanes with adequate lighting, AEMC digital lightmeter, and VA lighting logs maintained as requested
- Medical records for data audit
- Personnel including Coordinator, Principal Investigator, photographer, Visual function/Acuity examiners and specimen laboratory staff

Conducting the site visit

At least two Coordinating Center personnel will attend the site visit. Representatives from resource centers associated with SOCA (VFQAC and FPRC) may also attend. During the site visit a CC site visitor will accompany VFQAC and FPRC representatives during their review of these prospective procedures. During the course of the site visit, the following will be reviewed:

IRB Documentation

- Original approval
- Annual renewals (if applicable)
- IRB submissions (including safety reports for clinical trials)
- Approvals for updated consent statements or protocols

Documents

- Protocol
- Study Specific Handbook
- PPMs
- Forms Notebook
- SOCA General Handbook
- SOCA Directory
- Specimen Processing Checklist

Enrollment (NOTE: LSOCA enrollment activities ended 31 July 2011)

- Status
- Enrollment strategies
- Problems
- Vital status
- Lost to followup

Personnel

- Certification status
- Personnel changes
- Backup

Clinical management

- Coordination between clinical services
- Scheduling
- Clinic concerns or problems

Blood processing

- Phlebotomy
- Location of phlebotomy lab
- Personnel responsible for blood draw
- Processing of cells and plasma, per protocol
- Specimen labeling

Specimen shipment

- Completion and review of information recorded on Specimen Shipment Log (SS) and contents of shipper
- Comparison of specimens expected and received
- Shipping procedures and problems
- Shipping equipment
- Specimen storage

Protocol performance

- Protocol deviations

Forms management

- Monthly Form Status Report
- Data Quality Query
- Source documentation
- Data audit (select patients)
  - Eligibility criteria
  - Drug treatment histories
  - Eye exam histories/visual acuity
  - Death report
- Data audit (all patients)
  - Signed and dated consent

Data Management

- Enrollment
- Timeliness
- Error rate
- Query rate
- Response rate
- Completeness of data

Visual function protocols

- Visual Acuity lane
- Visual Acuity procedure
- Contrast sensitivity procedure
- Goldmann calibration check
- Visual Field procedure
- Lighting check of charts and lanes
- Completion of VFQAC certification forms and score sheets

Photography

- FPRC photographic quality review
- Photograph handling
- Verify copies within clinic
- Clinic concerns or problems

Previous site visit report

- Action items followup
- Data audit followup

Specimen processing

- Review of LSOCA specimen processing protocol
- Review of specimen processing checklist
- Review of specimen shipment log

Site visit followup

A list of action items is compiled at the end of the site visit to identify items which require further action. The procedure for site visit action item followup is:

- Coordinating Center will prepare a draft report to be reviewed by CC site visit participants, as well as clinic coordinator.
- Coordinating Center will send report to the clinic and all site visit participants
- Action Items will be listed at the end of the site visit report
- Clinics to respond to Action Items within 30 days of receipt of the site visit report and send responses, resolution to problems etc. to the Coordinating Center
- If applicable, a followup site visit or conference telephone call will be scheduled to address issues (e.g., performance, data quality) to be resolved

6.2. Site visit conference calls

Purpose

The site visit conference calls take the place of on-site visits and are an abbreviated version of a normal site visit. The purpose of the site visit conference call is:

- Discuss problems or questions the site is having
- Review personnel, recruitment, and performance
- Update IRB documentation and status of specific studies
- Provide information about research group activities

Clinic preparation

To prepare for the conference call the clinic should have the following available:

- Current enrollment and vital status
- IRB approvals/submissions
- Forms status reports

Conducting the conference call

The call is scheduled for one hour. One member of the Coordinating Center and a study officer will be on the call. The following will be reviewed:

Site visit reports
- Review
- Action items

IRB documentation
- IRB approval and submissions

Future or new study (if applicable)
- Recruitment strategies/enrollment
- Personnel and facilities

Currently enrolling study (if applicable)
- Enrollment
- Personnel and facilities
- Protocol performance
- Adverse event reporting

- Forms status
- FPRC report

Closed study (if applicable)

- Closeout
- Vital status
- Drug supply
- Form status

Other issues and announcements

Conference call followup

A list of action items is compiled at the end of the site visit to identify items which require further action. The procedure for site visit action items followup is as follows:

- Actions items will be listed at the end of the conference call report
- Clinics will be required to respond in writing to action items within 30 days of receipt of the site visit report
- The Coordinating Center will be required to respond in writing to action items within 30 days of the site visit report

7. Publication and data access/data sharing policies

7.1. Philosophy regarding publications

- Publication of the results of a study is considered to be a duty that is expected to be carried out in a timely fashion following completion of a study specific study objective and without regard to the direction or the nature of the results obtained or of the source of funding
- SOCA will not enter into any agreement in which the right of primacy in regard to publication is compromised or where SOCA investigators right to publication are fettered by any outside authority or sponsor
- The expected route of publication is via peer-reviewed indexed journals
- The databases supporting results papers will be made available via a public repository shortly after publication and regardless of funding source
- All members of the Research Group are expected to follow established clearance procedures before submitting SOCA related manuscripts
- Decisions regarding timing and content of publications rests with SOCA investigators and their leadership bodies
- Study Officers will approve writing committees and designate chairs of those committees
- All publications utilizing SOCA resources are subject to SOCA review prior to submission
- Chairs of the writing committees will be the corresponding author for their submissions. Chairs of writing committees are responsible for revisions mandated by the journal or internal editorial review. Major revisions of the results and interpretation of the results will require review by the Study Officers
- All publications of SOCA results are to indicate sources of support such as funds, drugs (trials only), and equipment
- All publications are to contain appropriate credit roster including list of participating centers and sponsors as well as list of key personnel associated with those centers and sponsors
- Credit rosters for clinical centers are the responsibility of the clinical directors
- Copies of all abstracts and printed publications are to be sent by the Chairman's Office to the Coordinating Center (CC) for inclusion in the SOCA archives

7.1. Philosophy regarding publications

- All publications utilizing SOCA funding are subject to inclusion in Pub Central. The Coordinating Center or the writing committee chair (e.g., corresponding author) will be responsible for approving manuscripts for release into Pub Central

7.2. Types of publications

- Those resulting from the current SOCA database(s) and generated by a LSOCA investigator
- Papers generated from Ancillary studies
- Papers resulting from outside collaborating and/or data sharing
- Combined SOCA dataset publications

7.3. Publications resulting from current study (LSOCA)

Definition

Any manuscript generated from the LSOCA database and by LSOCA investigators(s). Manuscripts detailing results of a study related to the objectives described in most recent grant application shall be considered "primary objective papers."

Policies

- Primary objective papers should be published under the **modified corporate authorship format**
- Primary papers are group publications, therefore, results from individual clinics may not be published prior to publication of group results, and then only after review by the Study Officers and Steering Committee
- Investigator(s) will submit a written proposal to the SOCA Chairman detailing the objectives, kinds of data and analyses required, proposed writing committee, and the intended audience and/or journal(s) using Publication Proposal (PP) form.
- The proposal, including the appropriateness of the authorship format, will be reviewed and approved by the Study Officers
- Manuscripts must be approved by the SO prior to submission to a journal. Primary objective papers must be reviewed and approved by the SC as well

7.4. Publications resulting from ancillary studies

Definition of an ancillary study

- An ancillary study is any investigation that is not part of the current study protocol. It is a study that is a subsidiary to and not a required part of the main study. It is carried out at one or more centers participating in a SOCA study and utilizes SOCA resources. Resources include specimens provided by patients as part of a SOCA study and/or, any SOCA database of one or more centers.

Submission and approval process

- A written proposal for the ancillary study should be submitted by the ancillary study director to the SOCA Study Chairman's office for distribution, review, and approval
- The proposal should include: description of objectives; methods, and significance; methodology for data collection; proposed statistical analyses; names of collaborators (individuals and centers) who have already agreed to participate; proposed funding sources; discussion of impact on main study and it resources including any manpower issues (i.e., statistical support from CC); and statement as to IRB approval
- Full details should be given regarding any additional procedures involving study participants such as special physical test, psychological testing, or collection of additional blood and the method by which additional procedures shall be funded
- Review and approval by the Study Officers, the Steering Committee, and the PDMB as well as any local IRB (if necessary) will be required prior to implementation of the study
- A study that interferes with the data collection, treatment, or recruitment process of the current study protocol will not be approved

Funding

- Funding for ancillary studies typically will not be supported by the main study
- Contract dollars awarded in relation to the main study contract may not be used to support ancillary studies unless permission is provided by the NEI

Data analysis

- Data analysis, unless otherwise specified and agreed upon, will be the responsibility of the proposing investigator(s)

- Provisions for access to the main study database for the purpose of linking data from an ancillary study must be discussed and agreed upon by the Coordinating Center
- Funding, whenever possible, should be provided via an independent grant or contract

Abstracts, presentations and publications

- Abstracts and presentations arising from ancillary studies are subject to the same policy as presentations arising from the main study (see section 6.7).
- Publications arising from ancillary studies must be reviewed and approved by the SO prior to journal submission
- In general, conventional authorship format will be used for papers arising from ancillary studies (ie, publication under the name of the investigator(s) responsible for the work), acknowledgment of the study may be required depending on the dictates of the SO
- A Publication Proposal form (PP) should be completed and submitted to SOCA Chairman's office for review by the Study Officers

7.5. Publications resulting from outside collaborations/data sharing

Definition

Any publication utilizing any SOCA database as part of a multi-study collaboration OR any publication utilizing a SOCA database and proposed by an investigator not affiliated with SOCA OR Center-specific SOCA data used by a single clinic for a use to produce a clinic based paper

Information access policy

- SOCA General Handbook, protocol, forms and other associated documents are considered to be in the public domain when approved for use in SOCA and may be treated and distributed accordingly
- Any SOCA investigator may reference SOCA documents in the public domain without Study Officers or Steering Committee approval
- Requests for SOCA documentation, beyond that available for general distributing should be made in writing to the SOCA Chairman

Data access and data sharing

- Data sets with documentation supporting all primary publications are available to investigators outside of LSOCA upon request and approval by the SOCA Study Officers
- Data provided are divorced of personal identifiers other than a 4-digit study ID number
- Investigators requesting data are required to sign a Data Use Agreement stating:
  - Data will not be copied or reproduced for use or distribution to any person or organization other than the requesting investigators and his or her organization without the express approval of SOCA Study Officers
  - Individual patients will not be identified in tables or listings
  - Analyses and interpretation of data contained in presentations or publications are those of the requesting investigators and not the SOCA Research Group
  - Corresponding authorship and reprints are the responsibility of the requesting investigators
- The Coordinating Center presently prepares datasets for distribution to participating SOCA sites.

- Notification of availability of datasets used for published papers are also submitted to the National Technical Information System (NTIS)

- Documentation for publications on deposit at NTIS includes information on how to obtain the data, database description, description of directory structure for the data files, data dictionary, and sample data listing for patients

Abstracts, meetings, publications pending

- In general, conventional authorship format will be used for papers and presentations arising from collaborative or shared data study (ie, publication under the name of the investigator(s) responsible for the work), acknowledgment of the study may be required depending on the dictates of the SO

- A Publication Proposal form (PP) should be completed and submitted to SOCA Chairman's office for review by the Study Officers

7.6. Authorship formats

Modified corporate format

- Corporate group is listed in the masthead
- Masthead list of authors: SOCA Research Group
- Credit list: all key personnel and participating centers, including resource centers and funding sponsor; members of the writing committee listed
- Use: e.g., secondary results manuscript

Conventional Format

- Individual authors are listed in the masthead
- Masthead list of authors: Name(s) of author(s)
- Credit list: all key personnel and participating centers, including resource centers and funding sponsor
- Use: e.g., investigator initiated ancillary study manuscript

7.7. Presentation policy

Definitions

- **Presentation** - a manuscript displayed as in a poster session or read at a professional meeting
- **Investigator initiated abstract or presentation** - an abstract or presentation prepared by SOCA investigator(s) on their own initiative
- **Commissioned abstract or presentation** - an abstract or presentation requested by the Study Officers or Steering Committee in relation to a forthcoming national or international meeting or invitation for presentation of SOCA design or results at such meetings
- **Local presentation** refers to the presentation made within an investigator's institution or general locale

Policies

- All abstracts submitted to national and international meetings are to be reviewed and approved by the Study Officers prior to submission; or failing that may be submitted with the understanding that they are to be withdrawn if not so approved
- All decisions regarding the review and approval of abstracts and presentations made by the Study Officers are subject to Steering Committee review
- Any member of SOCA Research Group may prepare and submit an abstract in relation to a proposed presentation at a scientific meeting; subject to SOCA review and approval process
- Investigator initiated abstract or presentation should follow the **modified conventional authorship format**
- Commissioned abstract or presentation may, depending on circumstances, follow the **modified conventional or corporate authorship format**
- Data analysis, unless otherwise specified and agreed upon, will be the responsibility of the proposing investigators
- Provisions for access to the SOCA study database for the purpose of linking data from an ancillary study must be discussed and agreed upon by the Coordinating Center prior to submission

- Requests for additional analyses of those data approved for release, unless indicated in the abstract itself, should specify in writing the kinds of tabulation and analyses desired. Those requests will be submitted to the Coordinating Center, reviewed by the Study Officers and generally will be approved except where the requested analyses violate presentation policies or are onerous.

- Authors must provide a copy of the submitted abstract to the Coordinating Center for the SOCA archives

7.8. Public policy

- Personnel at each center should refer requests from the news media for information about the study to the center director

- Any center director asked to supply information about the study at a local level should emphasize the following points:
  - the study represents a collaborative effort involving multiple centers
  - the local center is only one center in the study
  - the study is funded by the NEI

- Center directors should refer all inquiries concerning SOCA, over and above items or information already in the public domain, to the Study Chairman or to the NEI

7.9. Information access policy

- SOCA General Handbook, protocol, forms and other associated documents are considered to be in the public domain when approved for use in SOCA and may be treated and distributed accordingly
- Any SOCA investigator may reference SOCA documents in the public domain without Study Officers or Steering Committee approval
- Requests for SOCA documentation, beyond that available for general distribution, should be made in writing to the SOCA Chairman

7.10. Policies specific to the collaboration with the North American AIDS Cohort Collaboration on Research and Design

Definition

The North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) is a NIH-funded consortium that began in 2006 and encompasses HIV/AIDS cohorts within North America . Currently the cohorts represent single and multi-site clinical cohorts, and classical epidemiologic HIV cohorts consisting of more than 100 sites in the US and Canada, and more than 100,000 HIV seropositive and 150,000 HIV seronegative participants. NA-ACCORD approved the application for the LSOCA cohort in August 2009. The collaboration consists of investigators with scientific, clinical and biostatistical expertise with responsibility to frame key research questions of current interest, and design analyses to address these questions. The original Specific Aims of the NA-ACCORD focused on the optimal use of currently-available antiretroviral therapy (ART), trends and consequences of multidrug failure, temporal patterns in first presentation for HIV care, and the development and application of state-of-the-art methods to HIV epidemiologic research. In 2009, an American Recovery and Reinvestment Act (ARRA) supplement allowed for the launch of comprehensive identification and validation of severe non-AIDS defining conditions that increasingly affect morbidity and mortality in the HIV-infected population, including cancer, cardiovascular, kidney, metabolic and liver disease, providing a unique scientific platform to define the clinical epidemiology of these diseases and the effects of immunity, ART, aging, and other factors on the development of these illnesses in HIV-infection. North America is a region where HIV-infection has been recognized for almost 30 years, treated with ART for over 20 years, and where HIV has become a chronic long-term infection with a rapidly growing proportion of older individuals.

Specific Aims (as of competitive renewal

Specific Aim 1: To define the current HIV clinical epidemiology in North America as summarized below.

- Determine the incidence, excess risk, and age of death; AIDS-defining illness (ADI) including TB; and clinically significant non-AIDS-defining malignancy, cardiovascular, kidney, liver, and metabolic co-morbidities to evaluate the extent of 'accelerated' aging in HIV-infected individuals as compared to persons without HIV-infection.

7.10. Policies specific to the collaboration with North American AIDS Cohort Collaboration on Research and Design

- Determine the prognostic value of clinical and behavioral factors that contribute to the risk of death and specific co-morbidities including ART (first use, types, duration, patterns); CD4 (nadir, current level, trajectory); HIV-1 RNA burden and clinical laboratory markers; and tobacco, alcohol, and other substance use.
- Evaluate the long-term impact of co-infection (e.g., hepatitis C - a common co-infection in North America) and TB on HIV progression.
- Determine the clinical consequences of co-morbidities, including survival after diagnosis, effectiveness of specific treatments, and impact on HIV clinical progression.

Specific Aim 2: To define comparative effectiveness of ART in North America where effective therapy has been available for over 15 years.

- Determine the utilization patterns of ART in ART-naïve and experienced persons as guidelines for initiation and choice of therapy change, and as new classes of ART become available.
- Determine the optimal use and type of ART for aging HIV infected individuals, including minimizing toxicities with polypharmacy, improving CD4 response and delaying disease progression.
- Determine how timing of ART initiation impacts long-term HIV disease progression. (e.g., does starting ART at higher CD4 levels result in improved clinical outcomes (immunity, non-AIDS-defining co-morbidities, ADIs, survival)
- Determine the patterns of development of accumulated resistance to older and newer ART (integrase inhibitors, 2nd generation PIs, entry inhibitors) in patients with an extensive ART treatment history and those who are less-experienced; and the level of resistance in ART-naïve patients newly presenting for HIV care.

Specific Aim 3: To study important rare events and to support translational research.

- Determine the prognostic importance of uncommon co-morbidities, HIV-infection phenotypes (e.g. long-term nonprogressors, elite and viremic suppressors), and treatment toxicities.
- Provide access to data and specimens for analyses of genetic and serologic biomarkers in defined clinical phenotypes

Structure of NA-ACCORD

The NA-ACCORD has a Chairman's Office, a Core Data Analysis Center, and a Steering Committee (SC). The SC consists of a representative from each cohort and members of the chairman's office and data analysis center. Currently the LSOCA representative to the NA-ACCORD is Jennifer E. Thorne, MD, PhD. Members of NA-ACCORD may submit Concept

7.10. Policies specific to the collaboration with North American AIDS Cohort Collaboration on Research and Design

Sheets that propose a study and analyses that culminate in a manuscript. All Concept Sheets are approved by NA-ACCORD. The members of the SC are responsible for determining the scientific merit of each proposal and whether data from the cohort they represent are available and pertinent to the proposed study. Once a draft manuscript is completed, it is submitted to the NA-ACCORD SC for approval. Abstracts for meetings are submitted to the NA-ACCORD SC for approval as well. LSOCA's internal policies regarding approval of NA-ACCORD concept sheets, procedures for data sharing and dataset preparation for analysis by NA-ACCORD-funded biostatisticians, and procedures for the handling of abstracts and publications are summarized below.

LSOCA Process for reviewing NA-ACCORD Concept Sheets

- Concept Sheets are sent to the LSOCA SC representative (LSOCA rep) for review.
- If the LSOCA rep approves the Concept Sheet and determines that LSOCA has data to contribute to the proposal, it is presented at the LSOCA Coordinating Center (CC) staff meeting to determine if LSOCA data are to be shared.
- If no data AND no specimens are to be shared, the LSOCA rep corresponds with the NA-ACCORD.
- If data or specimens are to be shared, the LSOCA rep presents the concept sheet to the Study Officers (SO) for their approval. If approved by the SO, the LSOCA rep notifies the NA-ACCORD and works with the designated NA-ACCORD and LSOCA CC statisticians to prepare the necessary dataset

Procedure for data sharing/dataset preparation

- LSOCA is part of the NA-ACCORD collaboration and the LSOCA CC has a data sharing agreement as part of their IRB-approved protocol.
- The LSOCA CC and LSOCA rep will ensure appropriate IRB approval prior to any release of LSOCA data.
- The LSOCA CC sends a data dictionary to the NA-ACCORD core analysis center that links LSOCA data variables to variables utilized by the NA-ACCORD.
- The NA-ACCORD requests a specific dataset for the proposed study which may or may not include specimens from the specimen bank.
- The LSOCA CC statistician prepares datasets for NA-ACCORD upon request only after SO approval of the study.
- A spreadsheet documenting each approved concept sheet and the timeline specifying when data and/or specimens are sent is updated by the LSOCA rep. This spreadsheet will be reviewed at the CC staff meetings every 3 weeks.
- Datasets involving identifiable data will be discussed by the CC and the SO and may be subject to additional IRB approval. These instances will be handled on a case-by-case basis.

7.10. Policies specific to the collaboration with North American AIDS Cohort Collaboration on Research and Design

- Correspondence between the NA-ACCORD data Core Data Analysis Center and the LSOCA CC is the responsibility of the LSOCA CC.
- Correspondence regarding datasets will be kept by the LSOCA rep and the CC.

Procedures for NA-ACCORD publications

- Abstracts for annual NA-ACCORD meetings are sent electronically to the LSOCA rep for review and approval on behalf of LSOCA.
- Draft manuscripts are sent electronically to the LSOCA rep for review and approval on behalf of LSOCA.
- Correspondence and tracking of abstracts and manuscripts is the responsibility of the LSOCA rep.
- NA-ACCORD notifies members of the NA-ACCORD SC when a manuscript is accepted for publication. These publications will be added to the LSOCA website and CV as follows:
  - Publications will be listed under the heading of "Collaboration with NA-ACCORD" with the subheadings of "Data Contributed from LSOCA" and "LSOCA Acknowledged/No Data Contributed"
  - Other publications and abstracts/presentations are listed periodically on the NA-ACCORD website. A link to the NA-ACCORD website is provided on the LSOCA website.
- Authorship of NA-ACCORD manuscripts are modified conventional with all cohorts receiving acknowledgment regardless of whether data are shared for the specific study reported.
- NA-ACCORD funding is acknowledged for each manuscript.

Other procedures relevant to NA-ACCORD

- The LSOCA rep is responsible for communication and paperwork regarding the competitive and non-competitive grant renewals specific to the NA-ACCORD grant.
- The LSOCA rep is responsible for participating in NA-ACCORD SC in-person meetings and conference calls.
- Approval of new cohort applications to the NA-ACCORD is the responsibility of the LSOCA rep.
- The LSOCA rep will summarize progress to date at the annual SOCA Research Group meetings and the PDMB meetings.

SOCA General Handbook

8. Cataract Grading Procedures

Certification requirements

- Study ophthalmologist(s) must complete the on-line cataract grading tutorial: AREDS Clinical Lens Grading System, and complete the on-line quiz;
- AREDS Clinical Lens Grading System tutorial and quiz, prepared by the Fundus Photograph Reading Center, is located on the LSOCA website for review and use by LSOCA-certified ophthalmologists and can be accessed at the following link: www.jhucct.com/soca/lsoca/investinfo/investinfo.htm

Purpose

- To access lens opacity using a standardized cataract grading system. The cataract grading procedures were modified from the AGE-related Eye Disease Study (AREDS). Lens grading will be performed by clinical assessment, not via photographs
- AREDS half-step grading procedures will be used to assess 3 types of lens opacities: Nuclear; Cortical, and Posterior subcapsular (PSC)
- Compare severity/extent with opacity standards
- Record grades from1.0 (clear or very mild) to >3.0 (very severe or extensive) in incremented steps of 0.5
- Use the "comments" space on the Eye Exam (EE) form to note any unusual observations or problems

LSOCA Forms/Materials

- Eye Exam (EE) form
- Lens Opacity cards (laminated)

General Instructions

- Review standard image series each time you grade – do not grade from memory
- To reduce bias and improve ability to detect change, avoid looking at prior opacity grades from earlier clinic visits

Instructions for obtaining grading lens opacities from slit-lamp exam

- Dilate pupils to at least 5 mm diameter
- Use brightest slit lamp intensity
- Use ~ 10X magnification
- Compare subjects lenses against a series of standard
- Record type (location) and degree of opacity on the Eye Exam (EE) form, item 21-23
- See on-line tutorial (www.jhucct.com/soca/lsoca/investinfo/investinfo.htm) for instructions for grading Nuclear, Cortical and Posterior subcapsular opacities

Lens Opacity Card

Replacement cards are available upon request.

9. Fundus photography protocol

9.1. Photographer Certification

Photographers taking photographs (or digital images: the terms will be used interchangeably in this procedure) for studies read by the University of Wisconsin-Fundus Photograph Reading Center (UW-FPRC) must be certified for the relevant procedure(s), before submitting actual patient photographs. Only UW-FPRC certified photographers are allowed to take Qualifying Visit (baseline) photographs unless an exception to this rule is granted (on a case-by-case basis) by the study sponsor. The sponsor may suspend patient enrollment if the site does not have a certified photographer available to take the qualifying photographs. Only under extraordinary circumstances may follow-up visit photographs be taken by an uncertified photographer (see section 2.0 below).

Clinical sites are strongly encouraged to have a minimum of two, but no more than three, certified photographers. Photographers are encouraged to contact the UW-FPRC's photographic consultant, Dennis Thayer (608-410-0646) with any photography related questions. Pointers on photographic technique may be found in Section 13.

Photographer certification is study specific and each photographer requesting certification must submit a signed "UW-FPRC Photographer Certification Request Form" found on the UW-FPRC website: http://eyephoto.ophth.wisc.edu, to the UW-FPRC. Certification consists of (1) review of study synopsis or protocol and photography procedures and (2) demonstrating the ability to perform the photographic procedure by submission of photographs of acceptable quality. The second requirement may be waived if the photographer has prior certification at the UW-FPRC using **an identical procedure**, and has been active taking photographs, judged to be of good quality by the UW-FPRC, during the past year. Previously certified photographers who have been inactive for more than one year may be asked to submit sample photographs to become certified for LSOCA. Photographers who are certified for **a similar procedure** may also be asked to submit sample photographs to become certified.

Photographers who are not eligible for certification on the basis of previous UW-FPRC certification should submit color photographs of 4 eyes (preferably 2 right eyes and 2 left eyes) taken using this procedure. The color photographs may be taken of patients in whom photography is being carried out for clinical purposes or in normal volunteers. Photographers previously certified for this procedure on film (9-std-F) electing to perform this procedure digitally (9-std-D) must submit stereo color photographs of two eyes. This allows us to check image quality (stereo effect, color quality and image resolution) and to determine whether we can open the CD and archive the images.

If the 9-standard fields are photographed using 35mm film (9std-F) the slides should be mounted as shown in Section 8.0. Pre-printed labels may be unavailable for labeling certification photographs: if this is the case please hand label the color slides indicating the field and the eye photographed as well as the right side (RS) or left side (LS) of the stereo pairs. The slide pages containing the color photographs should be labeled with a page identification label indicating the

patient initials or patient identifier, photographer's name, date of photography and that the photographs are certification sets.

Clinical sites using digital color systems instead of 35mm film must obtain UW-FPRC certification for both photographer(s) and digital camera system(s) before initiating study photography.

If the 9-standard fields are imaged digitally (9-std-D) the digital images should be saved to CD at full-resolution using no or lossless compression. Lossy compressed (standard .jpg) images may be accepted but will be evaluated by the UW-FPRC on a case-by-case basis. Images of the right eye should be separated from images of the left eye and should be taken so that stereo pairs have the proper stereo orientation when viewed in proof sheets. Image handling procedures will be unique to the digital capture system used and photographers are encouraged to contact the UW-FPRC photographers to answer additional questions. Because pre-printed labels may be unavailable for labeling the CD, please hand-label the certification CD using a permanent felt-tip marker. The CD should be labeled indicating the fundus camera head serial #, the patient initials or patient identifier, photographer's name, date of photography and that the photographs are certification sets.

Whether using the 9-std-F or the 9-std-D procedure a **signed "UW-FPRC Photographer Certification Request Form" is always required (see the FPRC Forms, Labeling, Study Conventions Information document)**. Copies of the photographer and digital system certification forms are available on the UW-FPRC website.

Photographers previously certified for this procedure on film (9std-F) electing to perform this procedure digitally (9std-D) must submit stereo color photographs of two eyes. This allows us to check image quality (stereo effect, color quality and image resolution) and to determine whether we can open the CD and archive the images.

Photographers who meet certification criteria will receive confirmation of certification. Photographers who do not meet these criteria will receive feedback from the UW-FPRC photographic consultants, and will be required to submit additional sets of photographs. The sponsor will be notified after three complete unsuccessful attempts for certification to discuss a plan for additional photographer training.

Uncertified Photographers (Follow-up Visits Only)

On rare occasions during **follow-up** visits, when a certified photographer is not available to take the photographs, an uncertified photographer familiar with the procedures may take the photos. The uncertified photographer should review the photography procedures before performing photography to be certain they understand and follow the procedures. The name of the uncertified photographer should be entered on the photo page labels or CD.

9.2. Fundus Cameras

The Topcon TRC-50 series (50VT, 50X, 50EX, 50IA, and 50IX or similar models) as well as The Zeiss FF450-plus fundus cameras, all used at 50° are suitable cameras. Additionally, the Canon UVi (or similar models) used at the 60° setting, and the Kowa, Nikon and Olympus fundus camera models used at the 50° settings are suitable cameras for the study.

Cameras other than these may be substituted upon approval of the UW-FPRC. Approval may be obtained by submitting sample photographic sets, taken according to procedure, to the Fundus Photograph Reading Center, Attention: Imaging Services, 8010 Exeelsior Drive, Suite 100, Madison, WI 50717. Photographer certification photographs may be used for camera approval. Cameras used to submit satisfactory certification photographs are considered suitable cameras for the study.

9.3. Digital System Certification for Color Capture Capability

System Requirements

Color digital images must be taken using MRP OphthaVisionÒ, OIS WinstationÒ, Escalon Medical Imaging (EMI), Topcon IMAGEnetÒ, Zeiss VISUPACÒ or Digital Healthcare Classic digital systems using a 3 mega-pixel or larger image sensor. Each color digital system must be certified by the UW-FPRC. The color balance of images is also reviewed by UW-FPRC staff. If a system's color balance does not meet the UW-FPRC's requirements the system will not be certified until these issues are resolved.

It is preferred that the digital system contains software and hardware that allows remote access and operation. The UW-FPRC or a manufacturer representative may inspect the digital camera system to assure that all capture settings are correct for accurate image analysis. This inspection may be performed via "dial-in" access or as part of a site visit. Inspection software may be used to verify and record system settings.

Certification Procedure

Each digital system with color capture capability used for the study must be certified by the UW-FPRC before beginning study participant photography. Certification begins with submission of a study specific "UW-FPRC Digital System Certification Request Form" (see the UW-FPRC Forms, Labeling, Study Conventions Information section of the study specific documents). For step-by-step exporting instructions by digital system; please visit our website at: http://eyephoto.ophth.wisc.edu/Photographers.html.

MRP OphthaVision® System

System certification must be handled through MRP. Contact MRP's Matt Carnevale at (978) 687-7979. CD/DVDs sent to the UW-FPRC must include a .dbf and a .tif file.

OIS Winstation® System, Escalon Medical Imaging (EMI) or Digital Healthcare (DHC)

Each system requires a calibration for certification. The calibration uses 10 color images, of 10 different eyes, at the acceptable image angle (determined by camera type). The color images should be centered on the posterior pole so that both the disc and macula are in view. If the center of the macula and the center of the disc are not clearly defined they can not be used for calibration. The UW-FPRC would prefer that OIS Winstation® systems have software version 10.0 or higher. EMI systems must have RCPrep software version 1.4 or higher. DHC Classic systems must have software version 4.19 or higher.

If there are any hardware or software changes made to the system 10 more color images may be required to recalibrate the system. This requirement can be abbreviated if one of the 10 eyes used in the initial calibration is from someone who can be photographed in the future (i.e. the same staff member's eye photographed under 2 different system perimeters). This way if the system changes, the patient can be re-photographed and the old and new photos can be sent to the UW-FPRC for calibration and recertification.

Topcon IMAGEnet® System

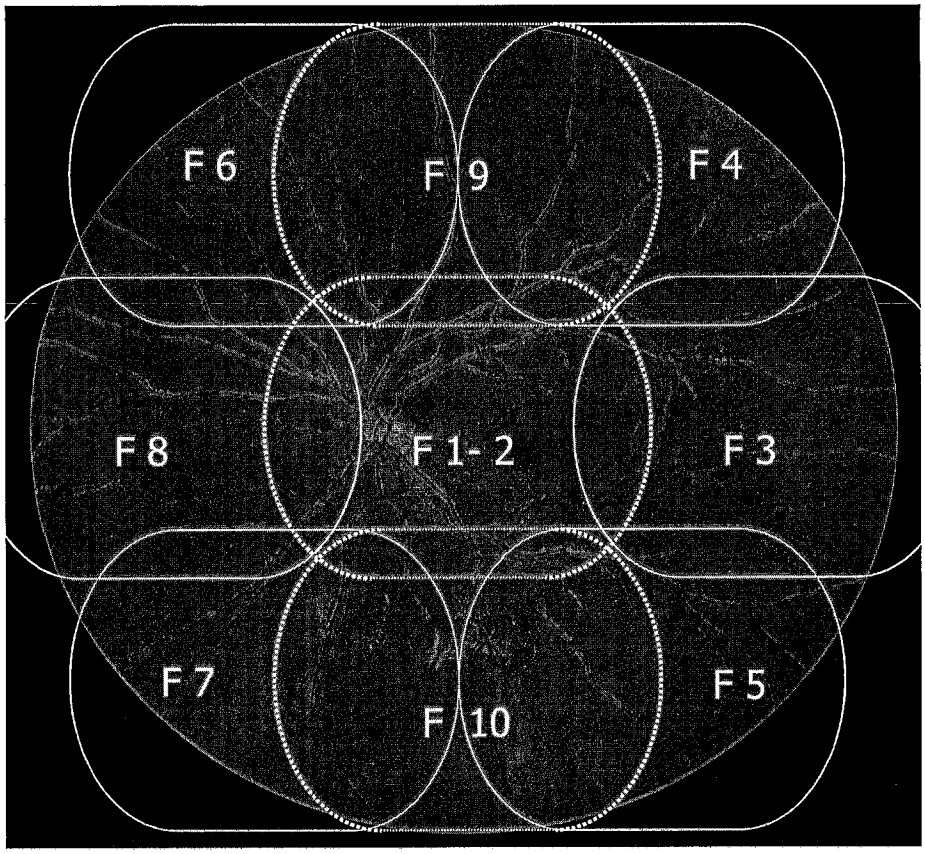
Run the Digital System Evaluation Software (DSES), which can be found on the web at http://eyephoto.ophth.wisc.edu/DSES.html or it can be mailed to you by contacting the UW-FPRC. Follow the directions included with the software and send the results via courier; to Choices for Service in Imaging, Inc., 233 Rock Road #249, Glen Rock, NJ 07452, or to the company's email address, tony@cfsimaging.com. If you have any questions during the process please contact Tony Pugliese at 800-499-2291, tony@cfsimaging.com.

Once Tony Pugliese has verified that the system settings are correct he will issue a document to the UW-FPRC. Upon receipt of this document the UW-FPRC will need to verify the system settings by reviewing recent images (taken after Tony's documentation has been issued).

Zeiss Visupac® System

Receipt of the "UW-FPRC Digital System Certification Request Form" will initiate contact between the UW-FPRC and Carl Zeiss Meditec Inc. Make sure the serial # of the Visupac system and a phone # to access the system are included. A representative from Carl Zeiss Meditec Inc. will in turn contact the site to arrange a time to go through the certification process. CD/DVDs sent to the UW-FPRC must include .dcm files.

9.4. 9-Std Fields and Fundus Reflex Photographs



9 Standard Field Diagram-Left Eye

The nine standard photographic fields of the fundus are defined below for both right and left eyes. These fields are modified from those used in the Diabetic Retinopathy Study (DRS) and are designed for documentation of the observable area which may be involved in CMV retinitis, i.e., most of the post-equatorial fundus. Stereoscopic photography is required for Field 1-2 only.

The following descriptions of the standard fields assume that there are two cross hairs in the camera ocular, one vertical and the other horizontal intersecting in the center of the ocular.

Field 1-2 (F1-2) Disc/Macula - Center the camera on the papillomacular bundle midway between temporal margin of the optic disc and the center of the macula. A stereoscopic photograph is obtained by taking one picture through the left portion of the pupil, moving the joystick laterally, and

then taking a second picture through the right portion of the pupil. This field should include both the disc and macula, and outline the posterior pole.

Field 3 (F-3) Temporal to macula - Move the camera temporal from F1-2 along the same horizontal meridian (i.e., straight temporally). The nasal edge of F3 should be located one disc diameter temporal to the center of the macula; typically just beyond the temporal margin of the hyperpigmented area (thus the center of the macula will not appear in F3). There will be an overlap of about three disc diameters between F3 and F1- 2.

Field 8 (F-8) - Nasal to the optic disc - Move the camera nasal to F1-2 along the same horizontal meridian (i.e., straight nasally). The temporal edge of F8 should be located adjacent to the nasal margin of the disc (thus the disc will not appear in F8). There will be an overlap of about three disc diameters between F8 and F1-2.

Field 9 (F-9) Superior - Move the camera directly superior to F1-2. The inferior edge of F9 should overlap the superior edge of F1-2 by 1 to 1½ disc diameters (be careful to retain at least 1 DD overlap). Selecting a retinal landmark (such as a vessel crossing) located one disc diameter below the center of the superior edge of F1-2 prior to shifting the camera will facilitate placement of F9.

Field 4 (F-4) Superior temporal - From F9, move the camera temporally along the same horizontal meridian. The nasal edge of F4 should be located at the center of F9, resulting in an overlap of about five disc diameters between F4 and F9. (The inferior edge of F4 will overlap the superior margin of F3 by 1 to 1½ disc diameter, although F4 is not as far temporal as F3). Selecting a retinal landmark located at or near the center of F9 prior to shifting the camera will facilitate placement of F4.

Field 6 (F-6) Superior nasal - From F9, move the camera nasally along the same horizontal meridian. The temporal edge of F6 should be located at the center of F9, resulting in an overlap of about five disc diameters between F6 and F9. (The inferior edge of F6 will overlap the superior margin of F8 by 1 to 1½ disc diameter, although F6 is not as far nasal as F8). Selecting a retinal landmark at or near the center of F9 prior to shifting the camera will facilitate placement of F6.

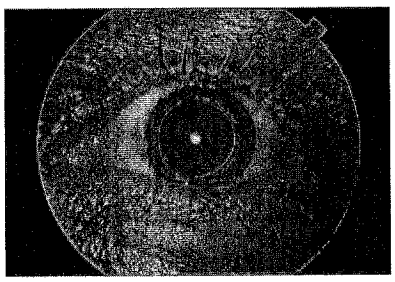
Field 10 (F-10) Inferior - Move the camera directly inferior to F1-2. The superior edge of F10 should overlap the inferior edge of F1-2 by 1 to 1½ disc diameters. (Be careful to retain at least 1 DD overlap). Selecting a retinal landmark located one disc diameter above the center of the inferior edge of F1-2 prior to shifting the camera will facilitate placement of F10.

Field 5 (F-5) Inferior temporal - From F10, move the camera temporally along the same horizontal meridian. The nasal edge of F5 should be located at the center of F10, resulting in an overlap of about five disc diameters between F5 and F10. (The superior edge of F5 will overlap the

inferior margin of F3 by 1 to 1½ disc diameter, although F5 is not as far temporal as F3). Selecting a retinal landmark located at or near the center of F10 prior to shifting the camera will facilitate placement of F5.

Field 7 (F-7) Inferior nasal - From F10, move the camera nasally along the same horizontal meridian. The temporal edge of F7 should be located at the center of F10, resulting in an overlap of about five disc diameters between F7 and F10. (The superior edge of F7 will overlap the inferior margin of F8 by 1 to 1½ disc diameter, although F7 is not as far nasal as F8). Selecting a retinal landmark located at or near the center of F10

Fundus Reflex photograph - At all visits, a single frame fundus reflex photograph should be taken to document media opacities. The photographer is asked to use his/her discretion to achieve a limbal diameter of approximately 9mm on the finished slide. The best stereo effect is obtained by moving the camera laterally about 3mm between exposures. The lateral shift can be obtained by moving the joystick. A fixation target should be positioned to direct the subject's gaze in the primary (straight ahead) position, so that the optic nerve does not appear directly behind the lens and focus should be on the pupillary margin. The ideal magnification is displayed below:



Fundus Reflex Photo
(The ideal limbal diameter is approximately 9 mm on film)

All of the peripheral fields specified above are obtained through a combination of shifting the camera and directing the gaze of the subject in the appropriate direction. For example, the following sequence of actions works well to locate Field 9 (superior). Starting from Field 1-2 (centered midway between the temporal margin of the disc and the center of the macula), first tilt the camera up to the limit of its travel (this maneuver achieves about half of the vertical elevation required for Field 9). Then move the fixation target up carefully, being sure not to drift nasally or temporally, until the location described in the protocol is reached.

Some of the peripheral field definitions specify offsets of one disc diameter (DD). For example, Field 3 (the temporal field) is located so that its nasal edge is one disc diameter temporal from the center of the macula. In most Canon cameras, the cross-hairs in the ocular are spaced 1 DD from the center of the frame, and thus can be used to gauge this offset.

The typical locations of the four ampullae of the vortex veins provide an approximate means for checking the proper placement of some of the peripheral fields. The usual relationship is illustrated in Figures 1 and 2. Note that at its proper elevation Field 9 (the superior field) tends to be centered between the two superior ampullae, so that they appear at the middle of both horizontal ends of the frame. When the camera is shifted nasally to obtain Field 6, the supernasal ampulla tends to be centered in the middle of the frame. When the camera is shifted temporally, the supertemporal ampulla tends to be centered in the middle of the frame. Similar relationships exist between the inferior photographic fields (Fields 10, 5, and 7) and the inferior ampullae. It is expected that if at all possible photographers will use retinal landmarks rather than the ampullae to determine proper locations of the peripheral fields. However, in a patient with typical placement of the ampullae they can be used as an approximate check on the definition of these fields, particularly when difficulties with patient cooperation is interfering with the use of retinal landmarks.

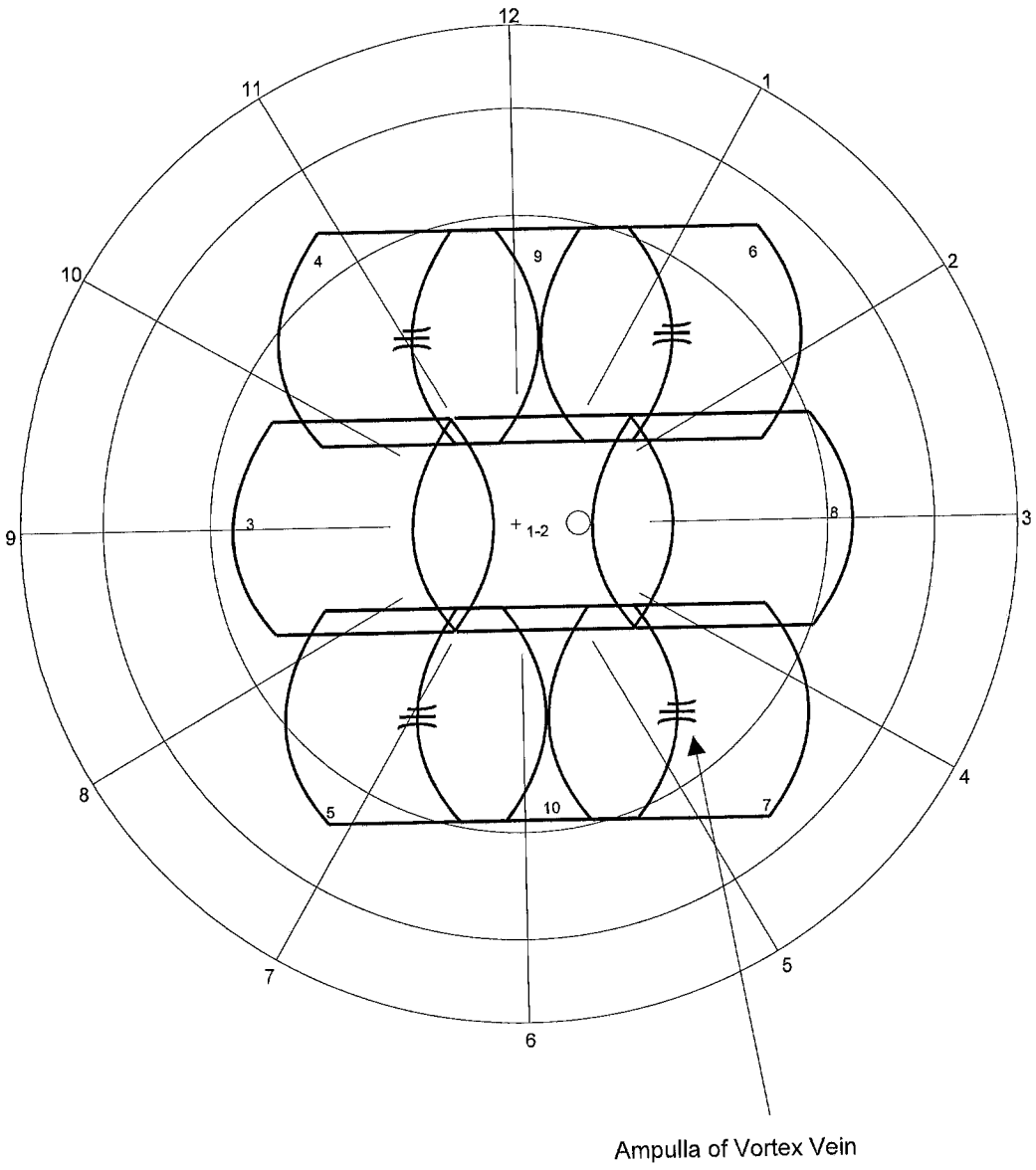
Because of the extent of the periphery photographed, it is not always possible to move the fixation target to the ideal location. It may collide with the nose in some instances, or with the camera lens barrel in others. It may be necessary to instruct the patient to look further to the side than the fixation target for proper alignment of the field. In the case of F4 (superior temporal), the lens barrel may contact the subject's nose, which necessarily restricts the temporal placement of that field.

It will likely be necessary to refocus the camera from field to field, concentrating upon the sharpness of retinal landmarks near the center of each field. Given the curvature of the retina encountered in the peripheral fields, it is not always possible to get all of the retinal features in crisp focus across the entire field. Only if the sole pathology observed in the field is located near the edge should the picture should be focused there rather than on retinal detail near the center.
Since changing the focus has an appreciable effect on the area of retina included in the photographic field (changing the boundary by as much as one disc diameter), it is advisable to focus the camera at least approximately after moving to the desired position of each field and before finalizing its location.

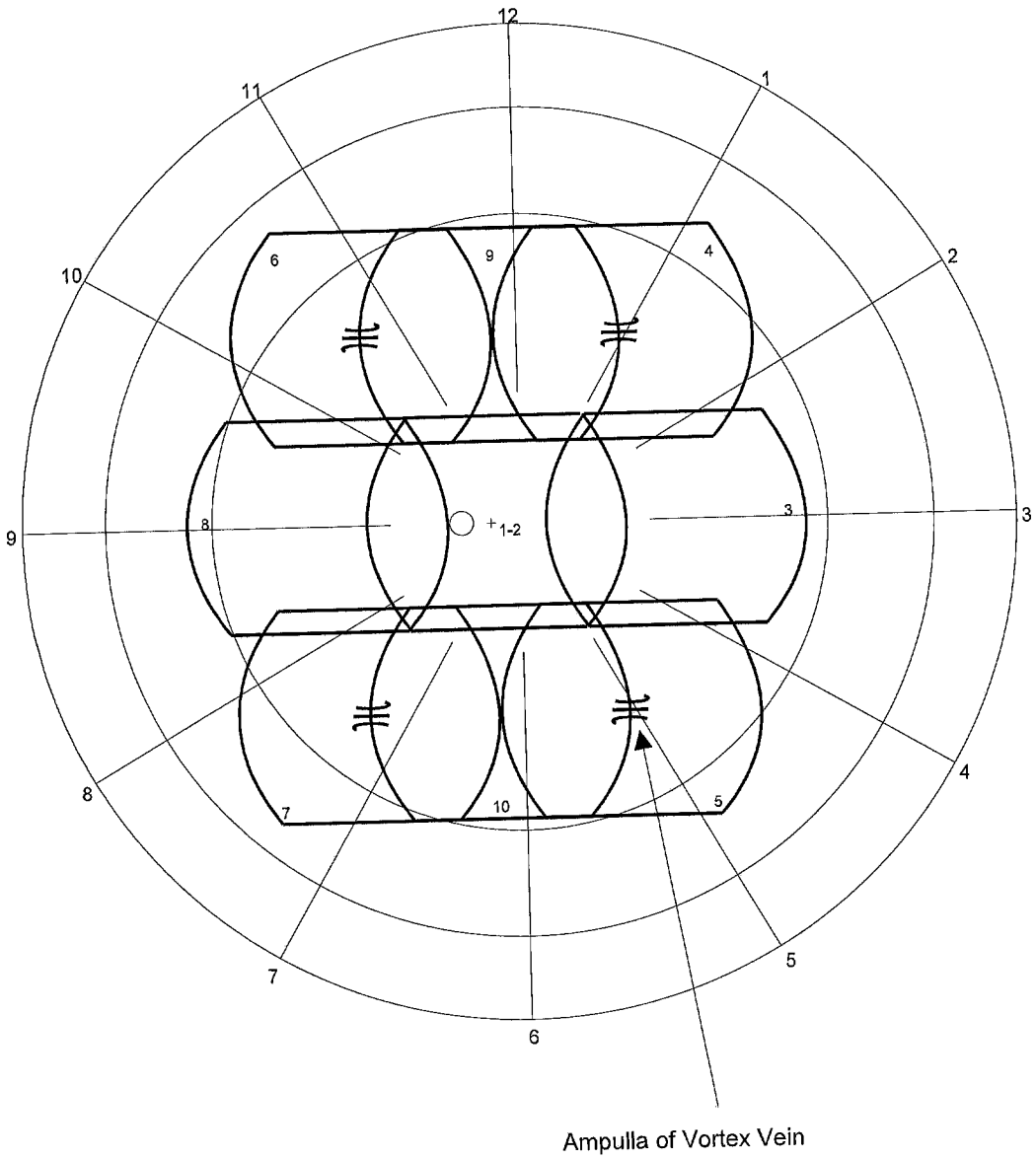
Sometimes it is not possible to obtain even illumination across the entire photographic field, especially in the periphery. This problem is more likely to occur in patients who do not dilate well. If it is not possible to equalize the illumination across the field, it is preferable to restrict the darker area to the more anterior portion of the field.

Diagrams of photographic field positioning in the right and left eye are seen in the two following diagrams

Right Eye Photographic Field Positioning



Left Eye Photographic Field Positioning



9.5. Exporting and Labeling of Digital Images

[1]Digital images should be saved to CD/DVD at full-resolution using no compression or lossless compression. Lossy compressed (standard .jpg) images may be accepted but will be evaluated by the UW-FPRC on a case-by-case basis.

Only the standard methods existing in the software of the imaging system should be used to isolate images for submission. Specific image handling procedures are outlined on the UW-FPRC's website. Digital images should be "burned" to CD/DVD before being archived on the computer system (a process that often compresses the images for storage).

For certification images please comply with HIPPA regulations by masking patient identifiers on the digital files. If pre-printed labels are not available for labeling the CD/DVD, please hand-label using a permanent felt-tip marker. The CD/DVD label must indicate the fundus camera head serial #, patient identifier, photographer's name, date of photography and that the images are for digital system certification.

For submissions of study participants please comply with HIPPA regulations by replacing the subject's ID number, last name, and first name with study specific information, as outlined in **the UW-FPRC Forms, Labeling, Study Conventions Information section of the study specific documents** (for OIS systems editing is only possible with specific versions of Winstation®).

For study submissions the CD/DVD should be labeled using a circular CD/DVD label (as shown below). These labels are provided by the LSOCA Coordinating Center and include the study name, site information, patient ID and visit information (sites may need to manually enter information for initial visits). The CD/DVD label also includes a space for date of photography, the photographer's name(s) and the serial number of the fundus camera used (located on the head of the fundus camera). A full resolution (uncompressed) duplicate of each submission should be retained at the site.

[1] The UW-FPRC recommends Bardes 20-pocket pages, product #62022C available from Bardes Products, Inc., 5245 West Clinton Avenue, Milwaukee, WI 53223-9839, phone 800-223-1357.

9.5. Exporting and Labeling of Digital Images

When shooting the fields digitally, it is preferable to shoot the right eye images first, followed by left eye images and begin photography of each eye by shooting Field 1-2. This procedure will help us separate images from the right eye and left eye when we view the proof sheets. Images of field 1-2 should be taken so that stereo pairs have the proper stereo orientation when viewed in proof sheets. All digital images should be reviewed for quality at the time of photography and the photographer should select the best stereo pairs for each field, deleting extra, unwanted images.

It is very important that photographers optimize flash/gain changes to avoid overexposure or grainy effects in the images. Many digital cameras have a wider range of flash/gain settings available to control image exposure. Some photographers may frequently adjust the flash or gain settings during the photography session to improve image quality. While this is often a useful adjustment, we do not want a wide variety of exposure across fields of the same eye. To safeguard against this, we recommend that photographers determine the best gain and flash combination at the beginning of the photography session, taking one or two test frames to confirm proper exposure/gain settings and then stay with one setting for the photography session. Color balance should be reviewed frequently to insure correct evaluation of pigmentary and vascular changes. Images which have over expressed red channels will not accurately reflect changes of these structures.

Most digital systems have a wide variety of image enhancement tools to adjust image contrast, brightness or sharpness after image capture. Enhancement tools should not be used at the clinical site to adjust image quality. Careful attention must be paid to obtaining optimum exposure, image sharpness and color balance so that enhancements are not necessary.

Transmission of Color Photographs/Images to the UW-FPRC

The original color transparencies or CDs should be prepared and labeled as described above within 10 working days (sooner if possible) after being taken. The sets of photos/images should be sent together with the completed Transmittal Log to the UW-FPRC.

When shooting the fields digitally, it is preferable to shoot the right eye images first, followed by left eye images and begin photography of each eye by shooting Field 1-2. This procedure will help us separate images from the right eye and left eye when we view the proof sheets. Images of field 1-2 should be taken so that stereo pairs have the proper stereo orientation when viewed in proof sheets. All digital images should be reviewed for quality at the time of photography and the photographer should select the best stereo pairs for each field, deleting extra, unwanted images.

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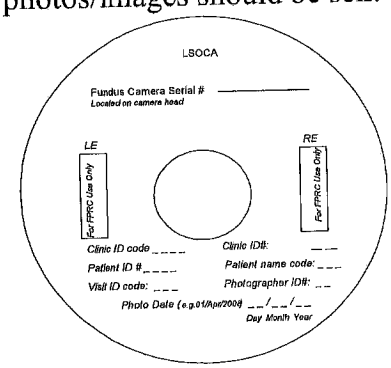


Example of CD Label

9.6. Minimum Protocol When Patients Cannot Adequately Cooperate

Although photographers are strongly encouraged to obtain all of the photographs specified by the protocol at each visit, there may be instances during follow-up in which patients are not able to tolerate the complete procedure. (The full photographic protocol must be carried out at baseline.) In such cases, the following abbreviated procedure (which allows omission of up to four fields if CMV lesions are not present in them) should be substituted:

(1) Take a stereoscopic pair of Field 1-2.
(2) Move nasally to Field 8, and take a photograph.
(3) Move temporally to Field 3, and take a photograph.
(4) Move superiorly to Field 9, and take a photograph.
(5) Move nasally to Field 6 from Field 9, and if any CMV lesions are visible take a photograph (otherwise omit).
(6) Move temporally to Field 4 from Field 9, and if any CMV lesions are visible take a photograph (otherwise omit).
(7) Move inferiorly to Field 10, and take a photograph.
(8) Move nasally to Field 7 from Field 10, and if any CMV lesions are visible take a photograph (otherwise omit).
(9) Move temporally to Field 5 from Field 10, and if any CMV lesions are visible take a photograph (otherwise omit).
(10) Take the red reflex photograph.

If the patient is unable to cooperate sufficiently even to carry out the truncated procedure described above, the photographer should make every effort to obtain the stereoscopic photograph of Field 1-2. If opacities of the ocular media are so great that no red retinal reflex is observed, the photographer should obtain only the "red reflex" photograph to document the opacities.

9.7. Retakes

The color photos should be evaluated for quality by the principal investigator and/or photographer (unless prohibited by Study Protocol) before submission to the UW-FPRC. If quality is not adequate for assessment of key features of the study eye and if no irremediable cause of inadequate quality is present (such as lens opacities or a pupil that will not dilate adequately), the photos should be retaken before submission to the UW-FPRC. When color photos are considered ungradable because of poor quality, the UW-FPRC may issue a Retake Request Form (see SOCA General Handbook &. Fundus photography protocol document).

9.8. Evaluation of Photographic Quality

Color photograph/images of each eye are reviewed and assigned a grade for overall quality. A Confidence Score of 1 indicates that a set can be evaluated with no problem. A Confidence Score of 2 signifies that a set can be assessed, although the image quality compromises the evaluation somewhat. A Confidence Score of 3 indicates that a set cannot be completely evaluated.

Feedback will be provided to the photographers as needed to help with resolution of any problems. Special attention will be given to photographers having difficulty meeting study photo/image quality standards. If a certified photographer consistently fails to meet study standards, certification may be suspended.

9.9. Pointers on Photographic Technique

9.9.1. General

When shooting the fields digitally, please shoot the right eye images first, followed by left eye images and begin photography of each eye by shooting Field 1-2. This procedure will help us separate images from the right eye and left eye when we view the proof sheets. Stereo pairs should be taken shooting the left member of the pair first, followed by the right member of the pair. All digital images should be reviewed for quality at the time of photography and the photographer should select the best stereo pairs for each field, deleting extra, un-needed images.

9.9.2. Patient Cooperation

Photography of the photophobic subject can be very challenging for the photographer and uncomfortable for the subject. Minimizing the number of flashes and the length of time the eye is exposed to a bright viewing lamp are two things that can help make the photography procedure more comfortable. Additionally, keeping the view lamp as low as possible (maybe even dimming the room lights) can help make the photography procedure more tolerable. Patients should be asked to blink to help keep the cornea clear.

If the subject has great difficulty tolerating the screening visit photography procedure and the photographer thinks this will lead to a problem at follow-up visits, the situation should be discussed with the principle investigator and/or coordinator and consideration should be given to not enrolling the subject in the study.

9.9.3. Field Photographic Sequence

When the modified 9-std fields are taken, the following sequence is recommended: disc (Field 1-2), temporal to macula (Field 3), nasal to optic nerve (Field 8), superior to macula (Field 9), temporal (Field 4), superior nasal (Field 6),inferior to macula (Field 10), inferior temporal (Field 5), inferior nasal (Field 7). Fields 1-2, 3 and 8 should be taken on the same horizontal plane. Field 1-2 is taken as a stereo pair.

9.9.4. Focus/Clarity

Remember that the best image quality can be acquired if corneas are not disturbed by prior examination with a diagnostic contact lens.

Constant attention must be paid to keeping the cross hairs in the camera ocular in focus; otherwise the images will be out of focus. Proper camera-to-eye distance should be maintained to avoid haziness and artifacts.

If it is not possible to get the entire photographic field in crisp focus, the photographer should concentrate on getting the center of the field in focus, sacrificing a bit on the periphery if necessary. This is especially important in Field 1- 2.

When the photographer moves to Field 3, having just taken Field 1M, **he/she should refocus on retinal vessels near the center of the field.** *Failure to do so results in images that show the foveal area to be slightly out of focus while the periphery is in focus.*

9.9.5. Stereoscopic Effect

Dilation of the pupil to at least 6mm is important to permit good quality stereo photography. If the pupils cannot be dilated to at least 4mm for the screening visit, the subject should not be entered into the study.

The technique described by Allen4 is used for taking non-simultaneous stereo fundus images. The camera should not be rotated or pivoted for stereo images; instead, it should be moved laterally from left to right with the joystick (or by sliding the camera base on its table, if preferred). About 2mm is the minimum separation between members of the stereo pair to be aimed for when moving the joystick or sliding the camera.

Stereo pairs of field 1-2 should be taken shooting the left member of the pair first, followed by the right member of the pair. When obtaining stereo pairs, care should be taken that at least one member of the pair is of good technical quality with crisp focus. In many cases, it will be possible to obtain good quality in both members of the pair, but if this is not the case, the aim should be to obtain good quality in one member and some stereo separation between the members, accepting somewhat poorer quality in the second member of the pair, if necessary.

9.9.6. Exposure, Gain and Flash

It is very important that photographers utilize flash, gain and gamma changes to avoid overexposure or grainy effects in the images. To safeguard against this, we recommend that photographers use the camera controls available to insure good exposure and image quality throughout the angiogram.

Most digital systems have a wide variety of image enhancement tools to adjust image contrast, brightness or sharpness after image capture. Enhancement tools should not be used at the clinical site to adjust image quality. Careful attention must be paid to obtaining optimum exposure and image sharpness so that enhancements are not necessary.

Questions or Comments

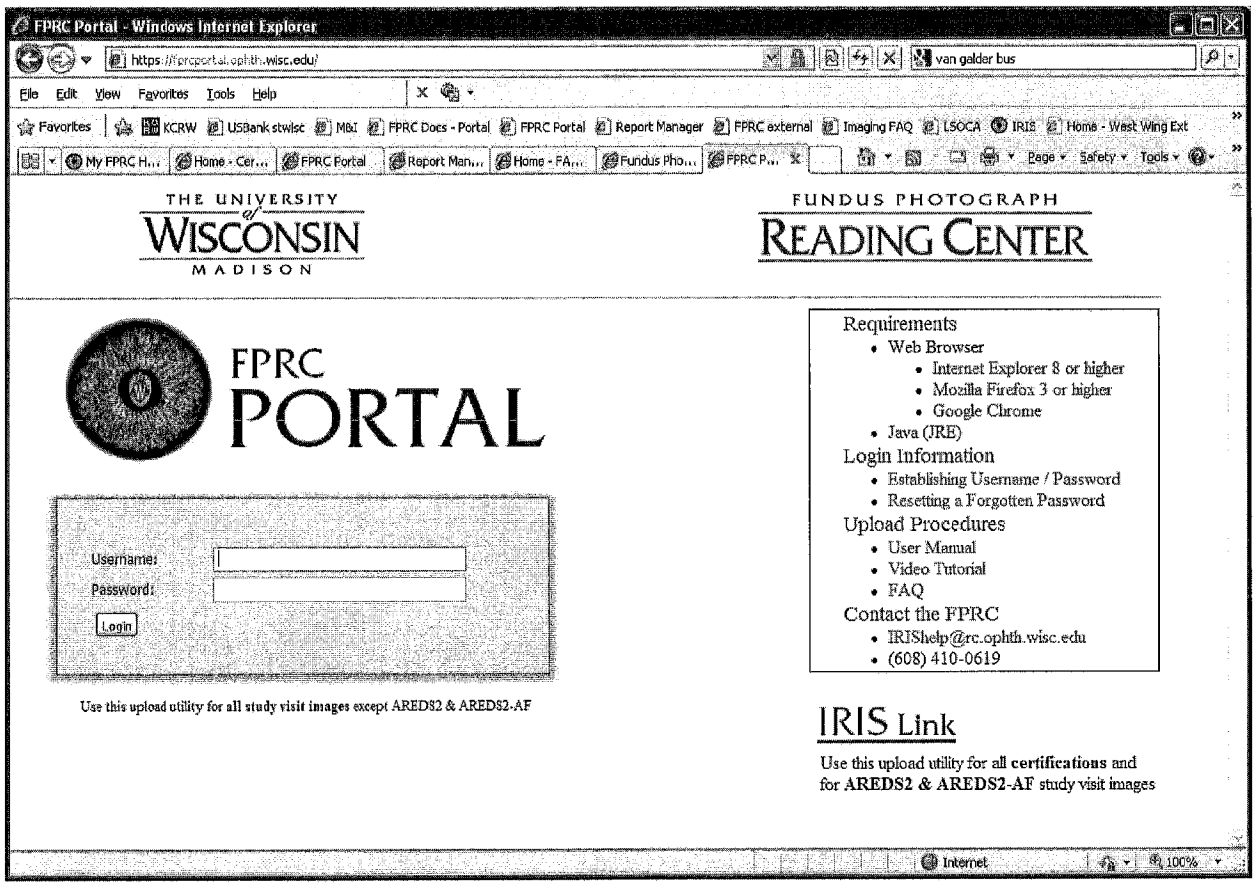
For questions or comments concerning this photography procedure, please contact the UW-FPRC photographic consultants, Dennis Thayer; thayer@rc.ophth.wisc.edu

9.10. FPRC Portal User Manual

FPRC Portal User Manual

1. Accessing the FPRC Portal

- Go to https://fprcportal.ophth.wisc.edu/



- If you have not created a password to log in, click on the link **Establishing Username/Password*.**

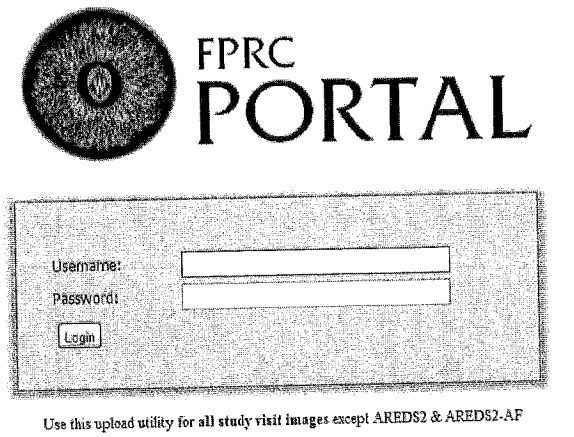
- If you have forgotten a previously created password, click on **Resetting a forgotten password.** (If you have an IRIS username and password, you will use that for the FPRC Portal also.)

  **Per the instructions for setting up a password, you will enter your username. Typically this is the unique email address that was provided to the FPRC. If you are unable to establish a password, it is most likely because the FPRC did not have your email address to enter into our system. If you feel this is the case, please contact the FPRC at FPRC_IRIS@rc.ophth.wisc.edu or contact the FPRC Project Manager for your study.*

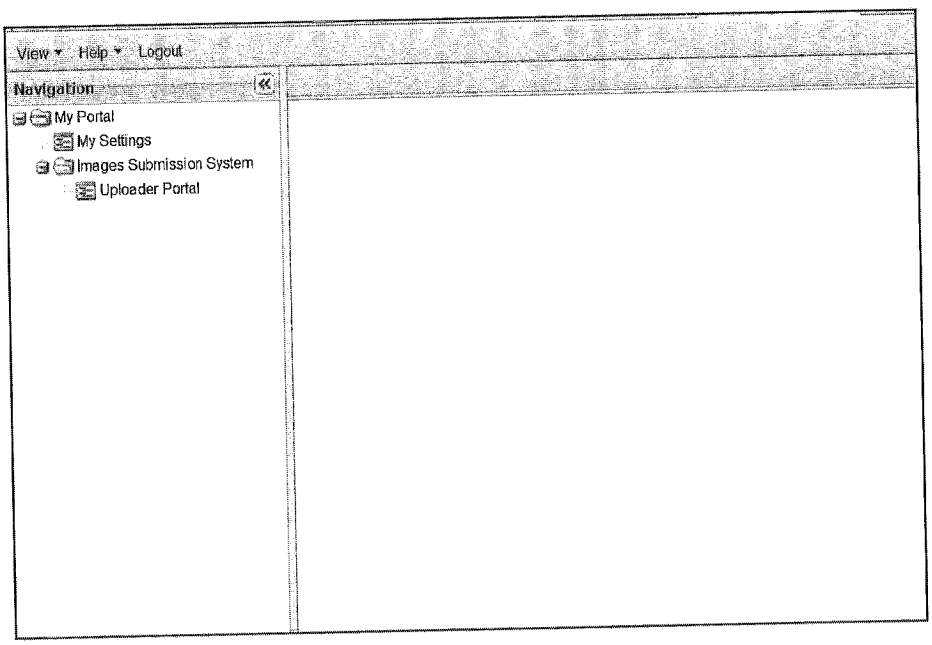
- Java software is required to upload images. If you do not have Java installed on your computer, click **JAVA (JRE)** to download a free copy.

- In addition to the **User Manual** , refer to the links for the **Video Tutorial** and **FAQ** (Frequently Asked Questions).

- On the FPRC Portal home page log in with the FPRC username and password you have established.

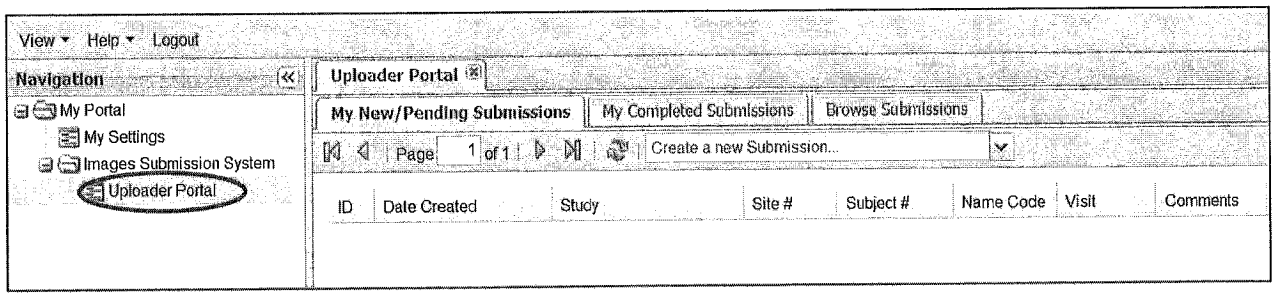


- The FPRC Portal home page will open:

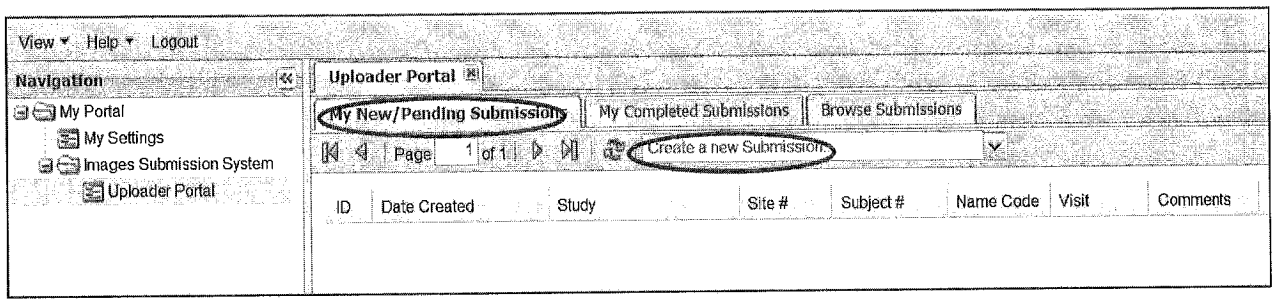


2. Creating a New Submission

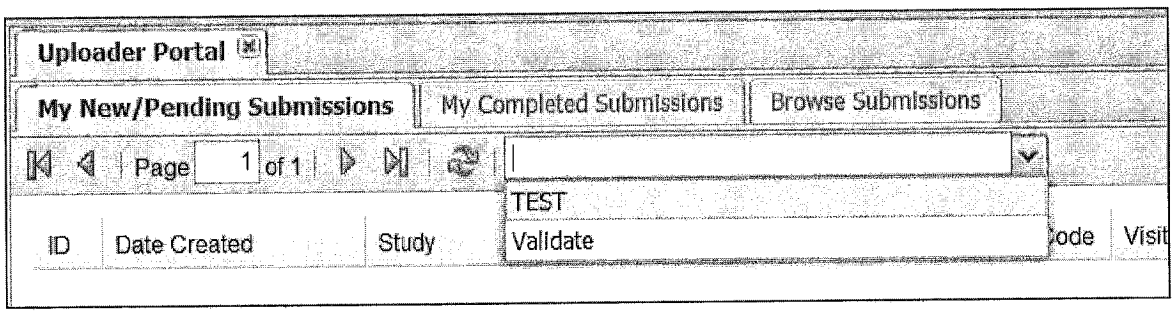
- Click on the **Uploader Portal** in the navigation pane:



- In the **My New/Pending Submissions** tab, select the study from the **Create a new Submission** dropdown menu.

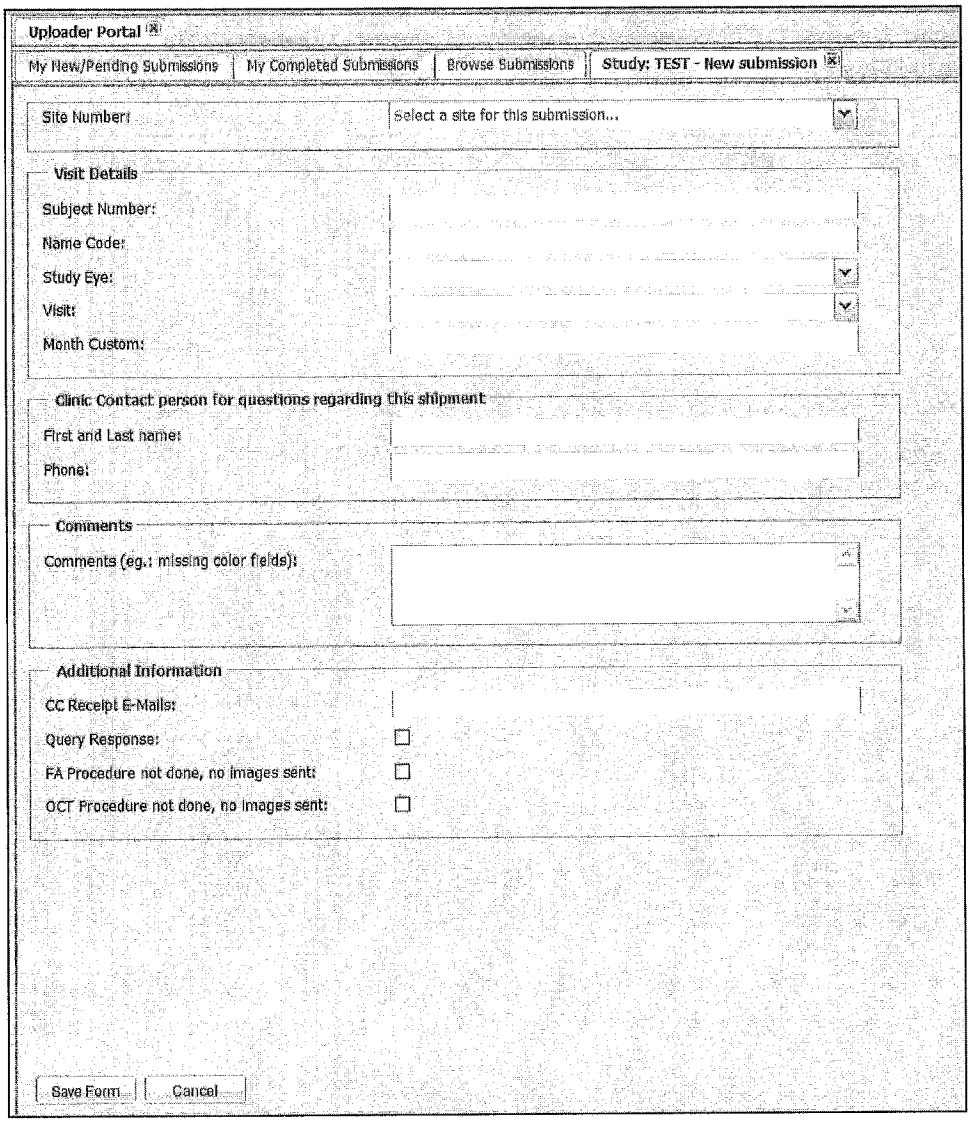


- You will only see the studies for which you have permission.



3. Entering Visit Information

- After choosing a study, the visit information form will open in a new tab. Complete each section (***Information required will vary by study***):



Visit Details

Site Number: Select your site number from drop down menu

Subject Number: Type in subject number

Name Code: Type in name code

Study Eye: Select from dropdown menu - Right Eye (OD) or Left Eye (OS)

Visit: Select from dropdown menu

Clinic contact person for questions regarding this submission

First and Last Name

Phone number

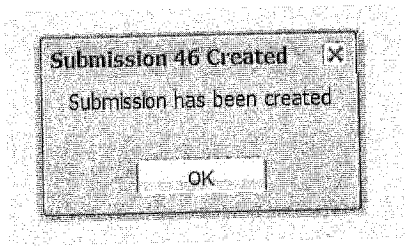
Comments: List any issues about the images that FPRC should know (ex. missing images, scans; uncertified photographers; issues with the procedure, etc.)

Additional Information

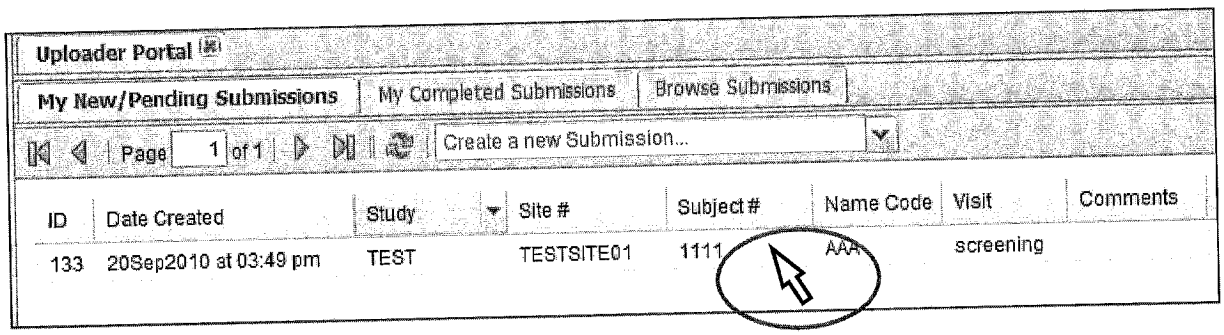
CC Receipt E-mails: An e-mail confirming of the successful submission of uploaded images will be sent automatically to the person who is logged in to the Portal and submitting the images. If you would like others to receive the confirmation e-mail, additional e-mail addresses may be entered in this field. Separate multiple addresses with a comma.

Missed Photographs: Check this box if there are missing images for the visit.

- When form is complete click **Save Form.** A pop-up will indicate that a new submission has been created:

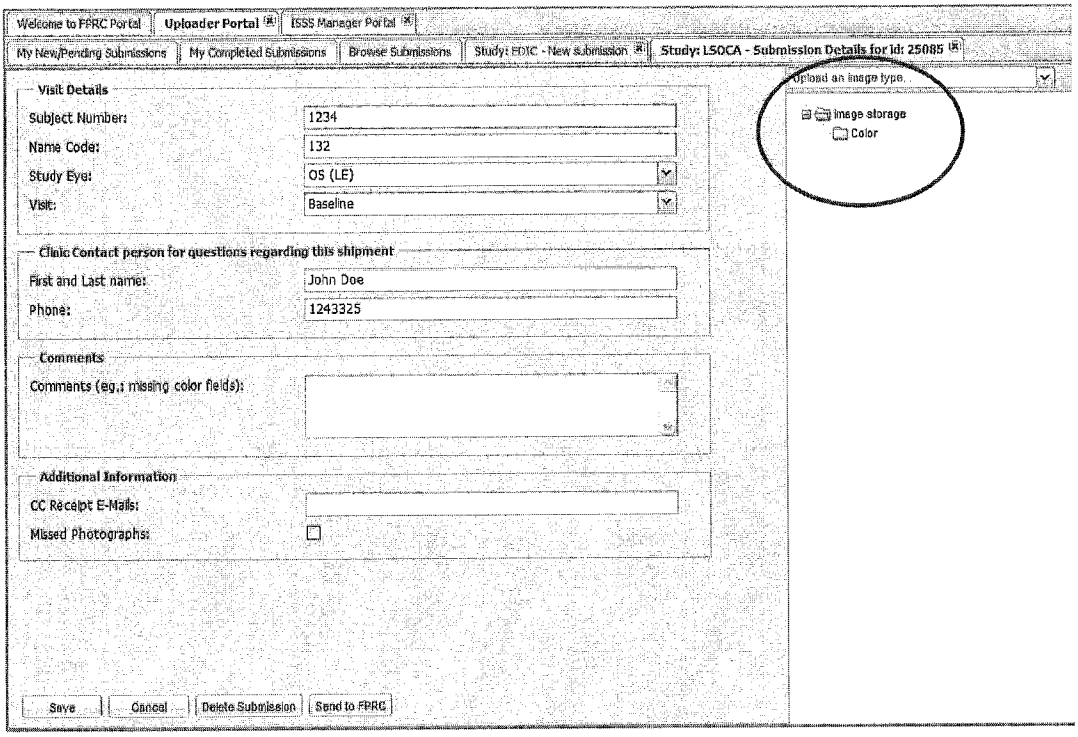


- Visit information will now be displayed in the **My New/Pending Submissions** tab. You may return to edit visit information at any time by double clicking on the row of submission.

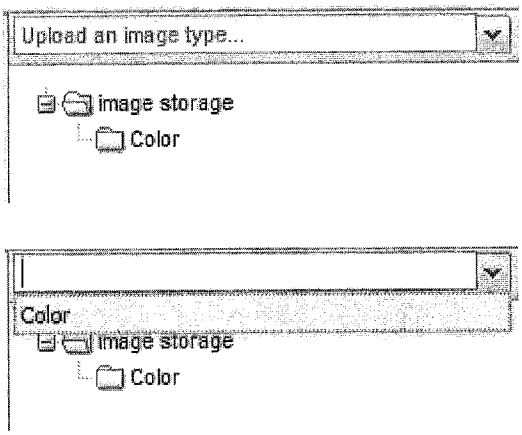


4. Selecting and Uploading Images

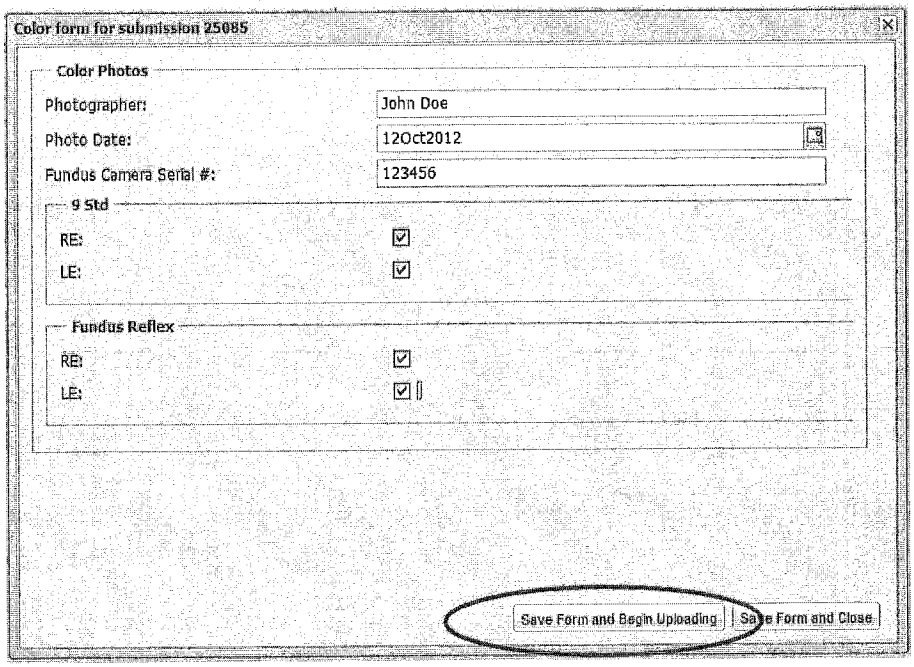
- Double click on the row of the submission in the **My New/Pending Submissions** table. The visit information form opens. On the right hand side of the window, the **image storage** file appears:



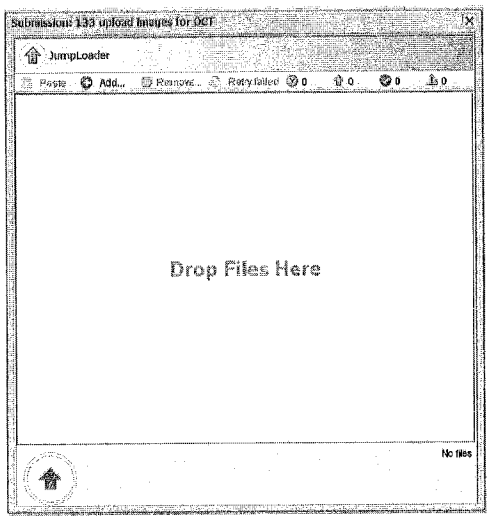
- Use the **Upload an image type** dropdown menu to choose Color.



- The **Color form** window will open:

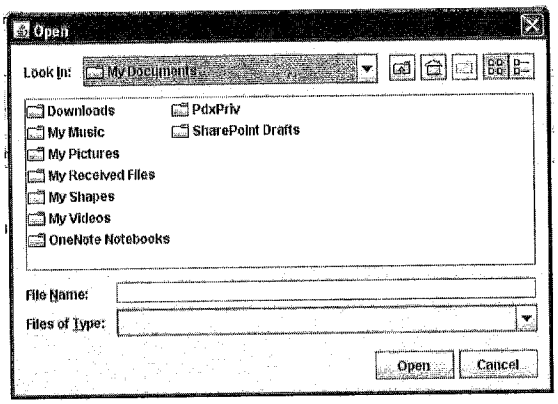


- Enter the information for the color images
    - **Photographer:** Type the name of photographer who took the images
    - **Photo Date:** Enter the date images were taken
    - **Fundus Camera Serial #:** Enter serial # of camera (important information to process images)
    - **9 Std**: Check this box if you have included the required color fields specific to the study.
    - **Fundus Reflex:** Check this box if you have included the FR images. If not, please write a comment in the visit information section.
- Then click **Save Form and Begin Uploading** to add the Color images. The Java applet will appear.
- Click **Save Form and Begin Uploading** to add the image files to the submission.
- The Java Applet window will open:

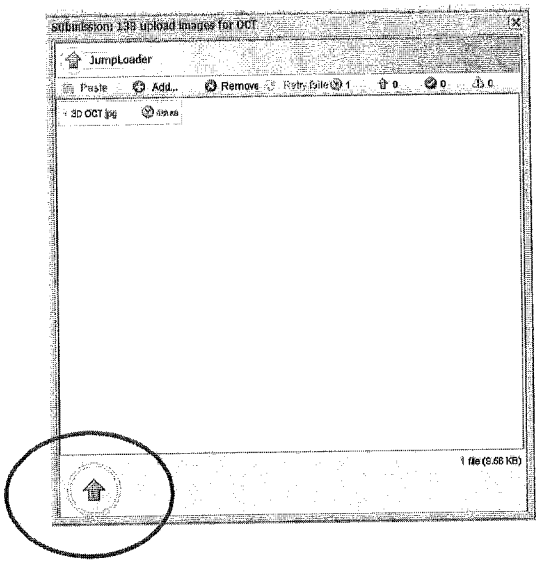


- Choose file images to upload by dragging and dropping files, or by selecting 

to browse for files:



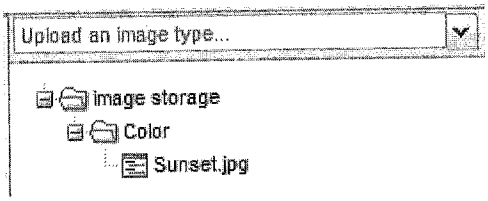
- After images are selected, click on the large green arrow in the lower left corner of the Java window to begin the upload of images.



- A check mark will appear next to the file to indicate it has been uploaded. 

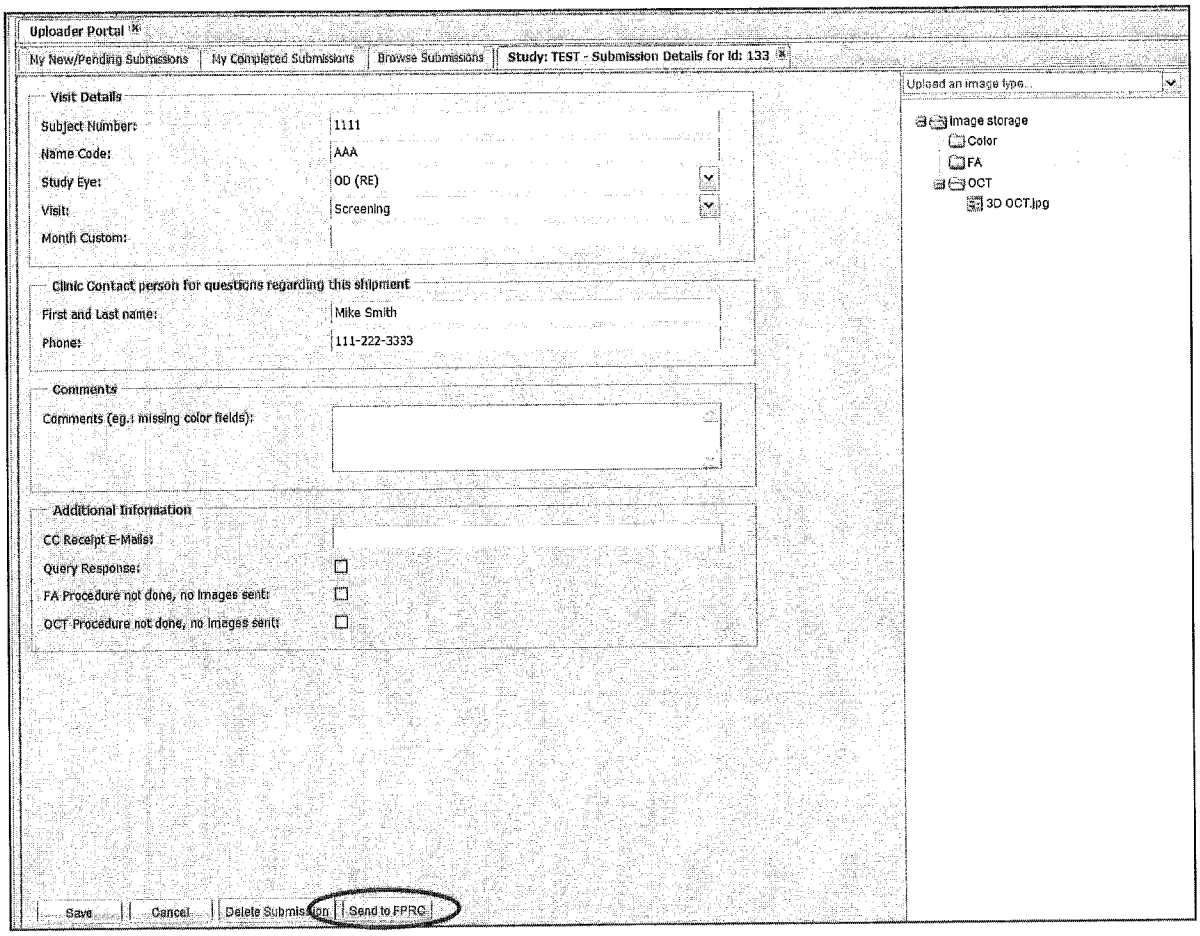
**Note that the images are now uploaded to a temporary folder. They have NOT been submitted to the FPRC. Continue to follow instructions for completing the submission process.*

- The image storage folder will expand to show the files that were uploaded:

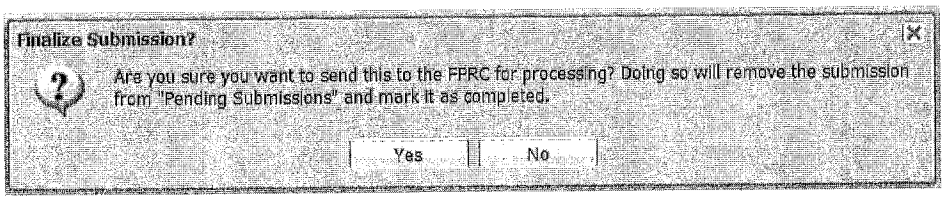


5. Submitting Images

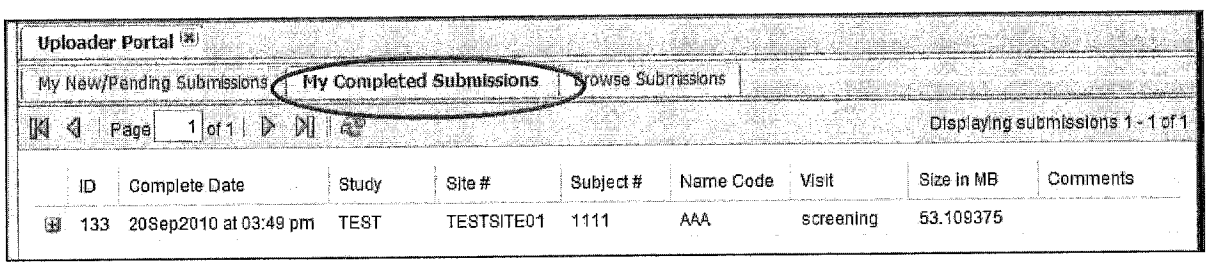
- Double click on the row of the submission to open the **submission details** tab:



- To complete the submission of uploaded images, click on **Send to FPRC** at the bottom of the window.
- A pop-up window will appear prior to submitting. If **Yes** is chosen, the information and uploaded files can no longer be accessed for editing:

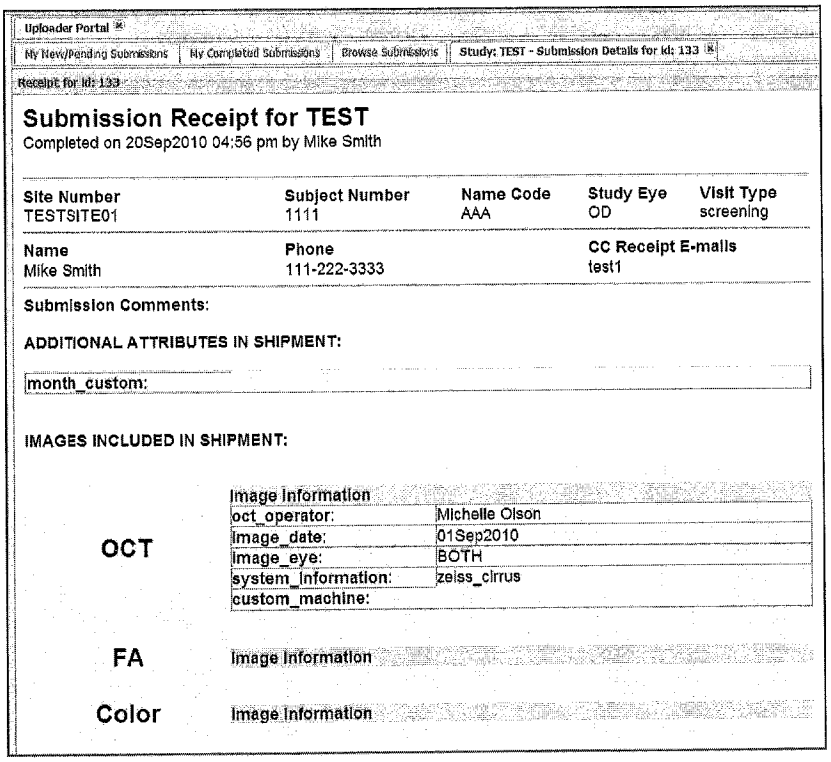


- After choosing **Yes**, the submission will move to the **My Completed Submissions** tab:



6. Confirmation of Submission

- In the **My Completed Submissions** tab, submission details may be viewed by double clicking on the submission:



Uploader Portal

My New/Pending Submissions | My Completed Submissions | Browse Submissions | Study: TEST - Submission Details for Id: 133

Receipt for Id: 133

Submission Receipt for TEST

Completed on 20Sep2010 04:56 pm by Mike Smith

Site Number	Subject Number	Name Code	Study Eye	Visit Type
TESTSITE01	1111	AAA	OD	screening

Name	Phone	CC Receipt E-mails
Mike Smith	111-222-3333	test1

Submission Comments:

ADDITIONAL ATTRIBUTES IN SHIPMENT:

month_custom:

IMAGES INCLUDED IN SHIPMENT:

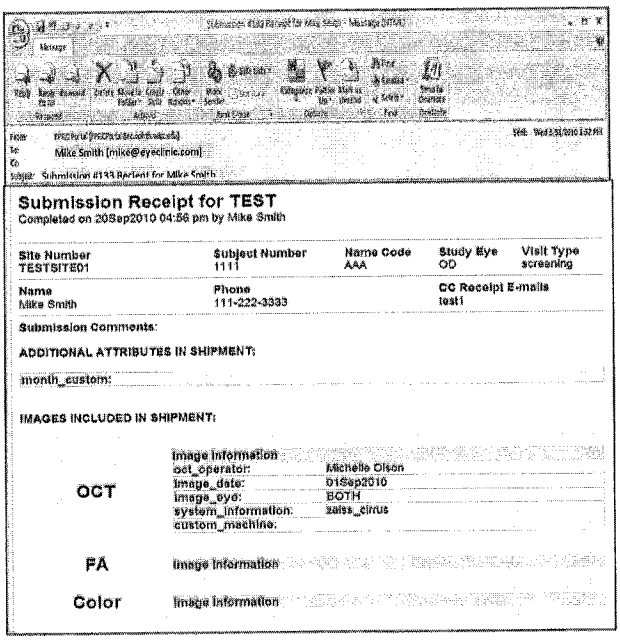
OCT

Image Information	
oct_operator:	Michelle Olson
image_date:	01Sep2010
image_eye:	BOTH
system_information:	zeiss_cirrus
custom_machine:	

FA Image Information

Color Image Information

- An e-mail containing a copy of this Submission Receipt will be sent to the person who logged in and submitted the images, as well as any e-mail address listed in the CC Receipt E-mails (see Section 3). This form serves as confirmation of a successful submission to the FPRC.



To: Mike Smith [mike@eyeclinic.com]

Subject: Submission #133 Received for Mike Smith

Submission Receipt for TEST

Completed on 20Sep2010 04:56 pm by Mike Smith

Site Number	Subject Number	Name Code	Study Eye	Visit Type
TESTSITE01	1111	AAA	OD	screening

Name	Phone	CC Receipt E-mails
Mike Smith	111-222-3333	test1

Submission Comments:

ADDITIONAL ATTRIBUTES IN SHIPMENT:

month_custom:

IMAGES INCLUDED IN SHIPMENT:

OCT

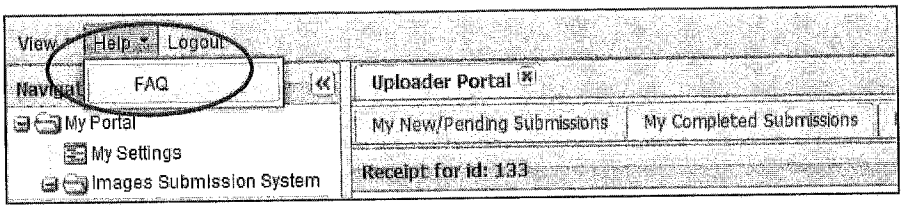
Image Information	
oct_operator:	Michelle Olson
image_date:	01Sep2010
image_eye:	BOTH
system_information:	zeiss_cirrus
custom_machine:	

FA Image Information

Color Image Information

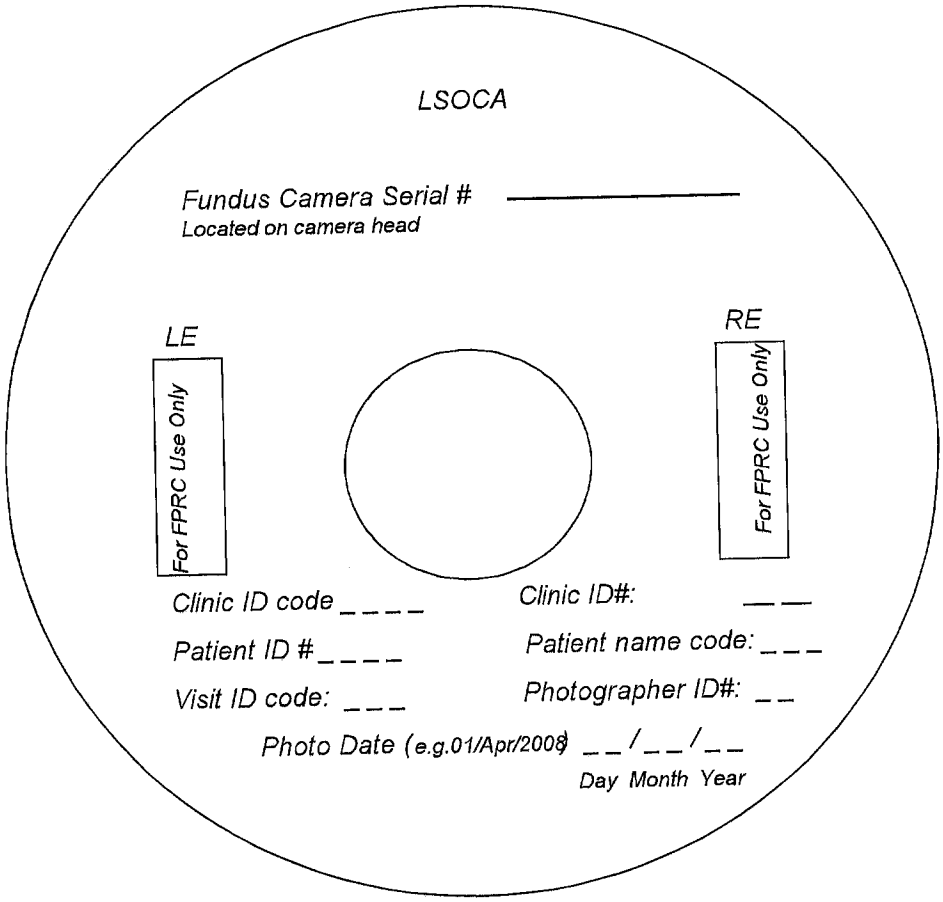
7. Troubleshooting

- Refer to the **Video Tutorial** or **FAQ** (Frequently Asked Questions) link on the FPRC Portal Welcome page for troubleshooting tips. **FAQ** can also be accessed when you are logged in to the Portal by clicking on **Help**:



- If you have any questions or problems submitting images, you may also contact your study Project Manager at the FPRC.

9.11. Diagram: CD Label



10. Visual acuity protocol

10.1. Introduction

Visual acuity will be measured by the methodology described in this chapter at all times. SOCA patients are to be tested with the standard Bailey-Lovie acuity charts in the clinic or the Ferris-Bailey Near Card if the patient is bedridden or hospitalized. The method of measuring visual acuity will be recorded as well as the results of the examination.

Modified Bailey-Lovie Distance Acuity

Visual function test results may provide data used for treatment evaluation. The procedures for measurement of visual function should be followed carefully so that accurate, reproducible, and consistent measurements are obtained. Refraction and all visual function examinations must be performed by study-certified examiners. Standardized lighting, Modified Bailey-Lovie visual acuity charts, Ferris-Bailey Near Cards, and refraction techniques are modified from the Early Treatment for Diabetic Retinopathy Study (ETDRS). All tests of visual function are performed after refraction.

Modified ETDRS Ferris-Bailey Near Card

For patients requiring visual acuity testing with a Ferris-Bailey Near Card, the patient must be bedridden (unable to be tested at a visual acuity lane). Standardized room lighting should be adequate. Refraction is not required when performing acuity using a near card.

When testing with the near card, determine the add required based upon age or accommodation from the chart below:

Patient's age	*Add needed*
<30	no add
30-39	+1.00
40-44	+1.50
45-49	+2.00
50-54	+2.50
>55	+3.00
aphakic, pseudophakic, or dilated (any age) +3.00	

10.2. Instructions for measuring illumination using digital lightmeter

OPERATION OF THE AEMC MODEL 810 DIGITAL LIGHTMETER

- Remove the cover from the light cell.
- Turn the power ON by pressing the green "on/off" button.
- Press the "fc" button, to assure measurement in "foot candles". If the word "LUX" appears in the display, push the "fc" button to convert to "foot candles". The letters "fc" should appear at the top right of the display before any readings are taken.
- Press the "range" button until a "200" appears at the bottom right corner of the display.
- If the letter "H" appears at the top left of the display, push the purple hold button and the "H" will disappear from the display. This button is used to "freeze" the measurement you have taken. It is unnecessary to utilize this function unless desired.
- If the letter "P" appears at the top left of the display, push the peak button and the "P" will disappear from the display. This button is used to record and maintain the highest or "peak" reading taken and hold it. It is unnecessary to utilize this function unless desired.

ROOM ILLUMINATION AND CHART ILLUMINATION MEASUREMENTS

- The first measurement is to be taken at ten feet, or four meters from the light box (essentially, where the patient is sitting). Hold the photo cell at four feet from the ground and point it directly at the ceiling. Take your measurement and record it on the 10ft, or 4 meter, line of the Visual Acuity Lighting Log. The measurement should be between 50-100 ft candles.
- The second measurement is to be taken half-way between the patient and the chart (5ft, or 2 meters). Hold the photo cell at four feet from the ground and point it directly at the ceiling. Take your measurement and record it on the 5ft, or 2 meter, line of the Visual Acuity Lighting Log. The measurement should be between 50-100 ft. candles.

  NOTE: Room illumination should be within the stated limits at all points along a line from the patient to the chart.

- The third reading is the actual measurement of the chart illumination. Place the "R" chart in the chart illuminator and hold the photo cell approx. 2 inches from a non-printed area of the chart. Be sure to point the photo cell at the chart, not at the ceiling. Take your measurement and record it on the "chart reading" portion of the visual acuity lighting log. The measurement should be between 75-125 ft. candles.

  NOTE: The readings are to be taken and recorded on the Visual Acuity Lighting Log on a monthly basis.

10.3. Refraction

10.3.1. Beginning approximate refraction

Note: If utilizing meters as opposed to feet, substitute 4 meters for 10 feet, 2 meters for 5 feet and 1 meter for 2.5 feet in the following sections.

At the initial assessment, the patient's present glasses (if worn) are measured with a lensometer, or retinoscopy is performed, and these measurements are used as the beginning approximate refraction. All study refractions are performed with positive cylinder power. (Note: To convert a beginning refraction with negative cylinder to one with positive cylinder, change the axis by 90°, change the sign of the cylinder power, and subtract the cylinder power from the spherical power). If the patient does not wear glasses for distance vision, the beginning approximate refraction is no lens correction or plano (recorded as 00.00). The best correction determined from subjective refraction at each visit is recorded on the Visual Acuity/Refraction form. At subsequent visits, the refraction recorded at the previous visit is used as the beginning approximate refraction for each eye. Refraction may be performed at distances greater than 10 feet for patients with good vision. However, if this is done, the spherical power refinement step should be repeated after the patient has been positioned at 10 feet or 4 meters to measure visual acuity.

The study charts used for measuring distance visual acuity must not be used for refraction. Each eye is refracted at 10 feet or 4 meters. If the patient cannot read all letters on the top line at 10 feet with the beginning approximate refraction, the vision is checked with a pinhole to see if reduced vision is due, at least in part, to refractive error. If the patient cannot read all letters on the top line at 10 feet, move the patient to 5 feet. If unable to read all letters on the top line at 5 feet, move the patient to 2.5 feet. A phoropter may be used for subjective refraction as long as all the protocol steps are followed. However, the final refraction to be used for the visual acuity testing must be placed in a trial frame and the final spherical correction must be checked. Refraction chart, R (ETDRS), or any visual acuity chart, including mirrors or projection charts, may be used for subjective refraction, as long as it is not the chart used for visual acuity.

If the patient wears contact lenses, but also has spectacle correction, he/she should be asked to remove the contact lenses at home and wear spectacle correction on the day of examination. If the patient arrives with contact lenses, ask the patient to remove his/her contact lenses; perform refractometry with trial frames after the patient has been out of his/her contact lenses for at least 30 minutes or longer if corneal reshaping is suspected due to hard contact lens wear. For corrected aphakic patients, including those with intraocular lenses, please refer to section 9.3.2. For uncorrected aphakic patients, a +10.00 diopter sphere is added to the trial frame as the beginning approximate refraction. The lens correction recorded is the final correction in the trial frame.

10.3.2. Subjective refraction

The goal of subjective refraction is to determine the optimum correction to enable the patient to perform the visual function tests at the specified distance(s). In general, instructions are to "push plus" and to add minus diopter corrections only if the visual acuity is thereby improved demonstrably; that is, the patient is able to read more letters on a line or to read letters on a smaller line.

The steps are as follows:

- Seat the patient 10 feet, 5 feet, or 2.5 feet, (or 4 m, 2 m or 1 m) depending upon the visual acuity determined at 10 feet (or 4 m)
- Use R chart or any standard visual acuity chart other than the #1 and #2 study charts
- Place and adjust the trial frame on the patient's face so that the lens cells are parallel to the anterior plane of the orbit and centered in front of the pupils. Adjust the lens cells for the proper distance from the cornea.
- Begin refracting the right, or better seeing, eye. Occlude the fellow eye.
- Insert the lens correction obtained from the beginning approximate refraction into the trial frame. The lenses should be positioned as follows:
    - Insert the spherical lens correction in the compartment closest to the eye
    - Place the cylindrical lens correction in the compartment in front of the spherical correction and adjust the axis
- Measure and record distance vision on the standard eye chart at 10 feet. Patients should be encouraged to use eccentric fixation if necessary, making certain that the fellow eye remains occluded.
- The refraction steps below are recommended for visual acuities of 20/20 to 20/70 with the beginning approximate refraction. For visual acuities worse than 20/70, refer to the refraction table for the appropriate sphere and cylinder powers and testing distance (refer to "SOCA Refraction Protocol Summary" table at the end of this section) and follow a similar procedure using steps in power that are equal to the power of the lens being presented. (Note: If the visual acuity improved to a higher range, for example, from the 20/80 -20/160 range to the

20/20 - 20/70 range, refinement should be performed with the smaller sphere and cylinder powers given for the improved range).

A. With the patient looking at the visual acuity chart at the smallest line legible, hold a +0.50 spherical lens in front of the right eye. Ask the patient, "Is it better, worse, or no change?"

B. If the patient responds that vision is made worse or is blurred, remove the +0.50 spherical lens from the front of the trial frame, and proceed to Step d. Otherwise, go to Step c.

C. Remove the +0.50 spherical lens from the front of the trial frame and replace the spherical lens in the trial frame with the spherical lens which is a quarter diopter more positive. Continue by returning to Step a.

D. Hold a -0.37 spherical lens in front of the right eye and ask the patient, "Is this better, worse, (or smaller and darker) or no change?" If the patient says worse, or no change proceed to Step f. If better, hold the -0.37 spherical lens in front of the right eye again and ask if it is better or just smaller and darker. Remove the -0.37 spherical lens from the front of the eye. If the patient says smaller and darker proceed to Step f.

E. If the patient responds that the vision is better, ask the patient to read the visual acuity chart. If the visual acuity is improved, even by one letter, replace the spherical correction in the trial frame with a spherical lens which is a quarter diopter less positive and return to Step d. If visual acuity is not improved, proceed to Step f.

F. Remove the -0.37 spherical lens from in front of the trial frame and hold a +0.50 spherical lens in front of the right eye. Ask the patient, "Is this better, worse, or no change?" If the patient responds that the vision is improved or unchanged, go to Step c. Otherwise, go to the next step.

Determine and refine cylinder axis. This is accomplished as follows:

a. Ask the patient to look at a line on the visual acuity chart which is one or two lines larger than the smallest line which the patient can read. Ask the patient to focus on a round letter such as "C", "G", or "O."

b. If a cylinder is present in the beginning approximate refraction proceed to Step c. Otherwise, follow one of the options detailed below to identify a possible need for cylinder correction.

Option 1: Place the +0.50 diopter cross-cylinder with the positive axis (white) first at 90°, then at 180°, then 45° and 135°. If the patient states that the vision is improved at any one of these four

axis positions, place a +0.50 cylindrical lens in the trial frame at the preferred axis and proceed to Step c. If the patient prefers none of the four positions, skip the next step (refining cylinder power) and proceed to the following step, rechecking the power of the sphere.

Option 2: Place the +0.50 diopter cross-cylinder with the positive axis (white) first at 90°, and then compare to no cylinder; then at 180° and then compare to no cylinder; then at 45° and compare to no cylinder; then at 135° and compare to no cylinder. If the patient states that the vision is improved at any of these four axis positions, place a +0.50 cylindrical lens at the preferred axis. If the patient prefers no cylinder over all four cylinder positions, skip the next step (refining cylinder power) and proceed to the following step, rechecking the power of the sphere.

Option 3: Place the +0.50 diopter cross-cylinder with the positive axis (white) first at 90° and then at 180°and ask if either position is preferred over no lens. If neither 180° nor 90° is preferred, place the +0.50 diopter cross-cylinder at 45° and 135° and ask if either position is preferred over no lens. If the patient states that the vision is improved at any one of the positions offered, place a +0.50 cylindrical lens at the preferred axis. If the patients prefers no cylinder over all four cylinder positions, skip the next step (refining cylinder power) and proceed to the following step, rechecking the power of the sphere.

c. Position the +0.50 diopter cross-cylinder first with the positive axis 45° to the right of the cylinder axis (position one), and secondly with the positive axis at 45° to the left of the cylinder axis (position two). Ask the patient which position improves the vision (position one or position two?)

d. If the patient prefers one position to the other, rotate the cylinder toward the preferred positive axis of the cross-cylinder in the step sizes recommended below and return to Step c. (If the patient states that one position of the cross-cylinder is no better than the other position, proceed to the next step).

AXIS STEP SIZES FOR REFINEMENT OF CYLINDER

Cylinder Power	Axis Step Sizes
< 1.00 D	10°
1.00 - < 2.00 D	5°
2.00 - < 3.00 D	3°
3.00 - < 5.00 D	2°
5.00 - < 8.00 D	1°

- Refine cylinder power as follows:

  I. Ask the patient to look at the lowest line on the visual acuity chart which can be read

  ii. Align the 0.25 diopter cross-cylinder first with the positive axis and then with the negative axis coincident with the cylinder axis. Ask the patient which is better.

  iii. If the patient prefers the negative (red) axis coincident with the cylinder axis, decrease the power of the cylinder in the trial frame by 0.25 diopter and return to Step b. Else, go to Step d.

  iv. If the patient prefers the positive (white) axis coincident with the cylinder axis, increase the power of the trial frame by 0.25 diopters and return to Step b. Otherwise, proceed to the next step.

Note: For every half diopter of cylinder power added, you must adjust the spherical power by increasing the minus power by one quarter diopter and the inverse applies. e.g. For every half diopter of cylinder power subtracted, you must adjust the spherical power by decreasing the minus power by one quarter diopter.

- Recheck the power of the sphere in the trial frame alternately by holding a +0.37, then -0.37 sphere in front of the right eye and change the spherical power by 0.25 diopter increments of the appropriate sign until the patient is unable to perceive any improvement in vision

- Record the lens corrections obtained in this subjective refraction on the appropriate examination forms in the section for visual acuity measurements. If the refractive power was changed by more than two diopters from the starting refraction, verify that the patient can read at least as well as with the beginning approximate refraction. If not, begin again at the first step in the procedure.

- Repeat the entire process for fellow eye.

SOCA Refraction Protocol Summary

Vision with best correction (refraction distance)	Sphere		Cylinder			Sphere refinement	
	Power (a)†	Increment	Axis (b)	Power ©	Increment	Power (d)	Increment
20/20-20/70	+.50 -.37	+.50 -.25	.50 JCC*	.25 JCC	+.25 -.25	+.37 -.37	+.25 -.25
20/80-20/160	+1.00 -1.00	+1.00 -1.00	1.00 JCC	1.00 JCC	+1.00 -1.00	+.50 -.50	+.50 -.50
20/200-20/400	+2.00 -2.00	+2.00 -2.00	1.00 JCC	1.00 JCC	+1.00 -1.00	+1.00 -1.00	+1.00 -1.00
worse than 20/400	+2.00 -2.00	+2.00 -2.00	No cylinder test			No refinement	

†Sequence of Refraction: (a) - (d)
*Jackson Cross Cylinder

10.4. Distance visual acuity

Distance visual acuity is measured using two Bailey-Lovie (ETDRS) visual acuity charts, one for each eye. The Coordinating Center provided each clinic with one set of ETDRS visual acuity charts. Additional charts may be obtained from either:

Globe Screen Print
875 Hollins Street
Baltimore, MD 21201
(410) 685-6750

OR

Optelec US, Inc.
3030 Enterprise Court, Suite C
Vista, CA 92081
(800) 826-4200
http://www.optelec.com

10.4.1. Illumination for charts and room

Clinics will be required to illuminate the charts via a direct illumination. Clinics choosing to hang charts and use front illumination, must ensure that the incident illumination on the charts is between 75 to 125 foot candles. The charts should be illuminated in such a way to provide even lighting without shadows or glare. These are met usually only by having bright ambient lighting in the exam room. Clinics choosing back lighted charts should order the charts and the chart illuminator from Lighthouse Low Vision Products. The illuminator may be wall mounted or attached to a floor stand. Room illumination should be at a level of 50-100 foot candles as measured with a photometer held four feet from the floor and directed toward the ceiling. This is equivalent to the room lighting in most office buildings or schools. Illumination should be within the stated limits on all points along a line from the patient to the chart. Chart and lane illumination should be checked each month and recorded on the VA Lighting Log (VL).

The length of the visual acuity lane may be 4.0 meters or 10 feet depending on the size of the room. Visual acuity may be measured at 4.0, 2.0, or 1.0 meters or 10.0, 5.0, or 2.5 feet depending on the maximum length of the lane and the visual acuity level of the eye.

10.4.2. Distance visual acuity measurement

Before testing visual acuity at 10 feet, remove +0.25 diopters from the sphere if patient was refracted at 5 feet, or remove +1.00 diopter if the patient was refracted at 2.5 feet. Remember to add +0.25 diopter to sphere if the patient is unable to read all of the top line at 10 feet and must be moved to 5 feet. Add an additional +0.75 diopters to sphere if patient cannot read all of the top line at 5 feet and must be moved to 2.5 feet.

The patient is positioned 10 feet from the study chart. Chart 1 is used for the right eye and chart 2 for the left. If the subjective refraction was performed at a distance other than 10 feet, the spherical refinement step is repeated with the lens correction obtained by subjective refraction in the trial frame and one eye occluded. The patient is asked to read the smallest line distinguishable on the study chart. If the patient chooses a line and reads it perfectly, he/she is encouraged to read the next smallest line and so on until he/she misses every letter on a line. When the patient says he/she cannot read a line, he/she is asked to read a specific letter in that line (such as the first or last), then the next letter, etc and guesses if necessary. The visual acuity examiner should resist attempts to aid the patient in "guessing." Remarks such as "You are close" are to be suppressed; the patient is not to be told whether a guess is correct or incorrect.

Be certain that the visual acuity charts are not visible to the patient before the eye exam. The patient's right eye must see the right eye chart only and the left eye see only the left eye chart.

The examination proceeds until the patient misses every letter in a line. If the patient misses some of the letters on a particular line, he/she is given another chance by asking that he/she attempt to read the line backwards. In those instances in which the patient has had a difficult struggle, the examiner may elect to ask the patient to reread only the letters missed. If the patient states that a letter is one of two letters, he/she is asked to choose only one letter, and if necessary, to guess.

The patient is encouraged to fixate eccentrically if this strategy improves visual acuity. However, if the patient fixes eccentrically, care must be taken to insure that the fellow eye remains completely occluded.

Visual acuity examiners may direct a patient's attention to a particular line or letter by placing a clipboard or other object under the line. However, after the patient has oriented the eye, the examiner removes any aids and steps away from the chart before asking the patient to read. Under no circumstances is a letter to be isolated by blocking off the surrounding letters. This technique could give inconsistent measurements of visual acuity.

10.4. Distance visual acuity

10.4.2 Distance visual acuity measurement

The two pieces of information recorded for study purposes are (1) the line number corresponding to the line of smallest letters that the patient can read with no mistakes while using the lens corrections determined by subjective refraction, even if some letters on a line of larger letters were missed, and (2) the total number of letters the patient can read on any of the smaller lines of the chart. Investigators using the study chart to determine the visual acuity fraction are cautioned that the fractions shown on the left column of the chart are only appropriate if the actual test distance is used as the numerator. See Table 9.2; The ETDRS chart is designed for use at 4 meters. For example, the largest line on the chart correspondences to a visual acuity of 20/260 at 10 feet (not 20/200).

If the patient cannot read all letters on line 01 at 10 feet, the patient is moved to five feet from the chart. The spherical lens power is increased by +0.25 diopters. If the patient can read one or more lines of the chart perfectly at five feet, the visual acuity is recorded by checking the five-foot distance and recording the number corresponding to the smallest line of print read correctly and the number of extra letters counted as above. In this case, only the five-foot measurement is recorded.

Patients who cannot read all the letters on line 01 at 5 feet should be moved to 2.5 feet. The spherical lens power should be incremented an additional +0.75 diopters. Thus, the total increment in power at 2.5 feet is 1.00 diopter more than the spherical power at 10 feet. The distance should be recorded as "2.5 feet." The refraction recorded is the 10 foot refraction (excluding the +0.25 diopters added at 5 feet or the +0.75 diopters added at 2.5 feet; total of +1.00 diopters. If the patient reads one or more lines of the chart perfectly, the visual acuity should be recorded as the number corresponding to the smallest line of print read correctly and the number of extra letters. If no lines are read perfectly, the line number should be recorded as "00." If no extra letters are read correctly, "00" should be recorded as the number of letters.

The patient is observed carefully to be certain that he/she does not lean forward in the chair. This precaution is especially critical when measuring the visual acuity at five feet or at 2.5 feet. The patient is placed so that the distance from his/her eyes to the chart is exactly 10 feet, 5 feet, or 2.5 feet. Patients unable to read all of the top line at 2.5 feet should be tested, and recorded, as count fingers (CF), hand motion (HM), light perception (LP) or no light perception (NLP).

Table 9.1 Letters on Visual Acuity Charts to be used in SOCA

Line	Chart R	Chart 1	Chart 2
1	H V Z D S	N C K Z O	D S R K N
2	N C V K D	R H S D K	C K Z O H
3	C Z S H N	D O V H R	O N R K D
4	O N V S R	C Z R H S	K Z V D C
5	K D N R O	O N H R C	V S H Z O
6	Z K C S V	D K S N V	H D K C R
7	D V O H C	Z S O K N	C S R H N
8	O H V C K	C K D N R	S V Z D K
9	H Z C K O	S R Z K D	N C V O Z
10	N C K H D	H Z O V C	R H S D V
11	Z H C S R	N V D O K	S N R O H
12	S Z R D N	V H C N O	O D H K R
13	H C D R O	S V H C Z	Z K C S N
14	R D O S N	O Z D V K	C R H D V

Table 9.2 SOCA Visual Acuity Conversion Chart for Snellen Equivalents

Line	(Distance) 10 feet	5 feet	4 meters
1	20/260	20/520	20/200
2	20/210	20/420	20/160
3	20/160	20/320	20/125
4	20/130	20/260	20/100
5	20/100	20/210	20/80
6	20/80	20/160	20/63
7	20/65	20/130	20/50
8	20/50	20/100	20/40
9	20/40	20/80	20/32
10	20/35	20/65	20/25
11	20/25	20/50	20/20
12	20/20	20/40	20/16
13	20/16	20/35	20/13
14	20/13	20/25	20/10

10.4.3. Modified ETDRS Ferris-Bailey Near Cards for bedridden patients

Bedridden patients can have their distance visual acuity measured by using the Ferris-Bailey modified ETDRS Near Card, one side of the card for each eye. The card is used for testing at 40 cm (16 inches).

Request replacement near cards from the Coordinating Center

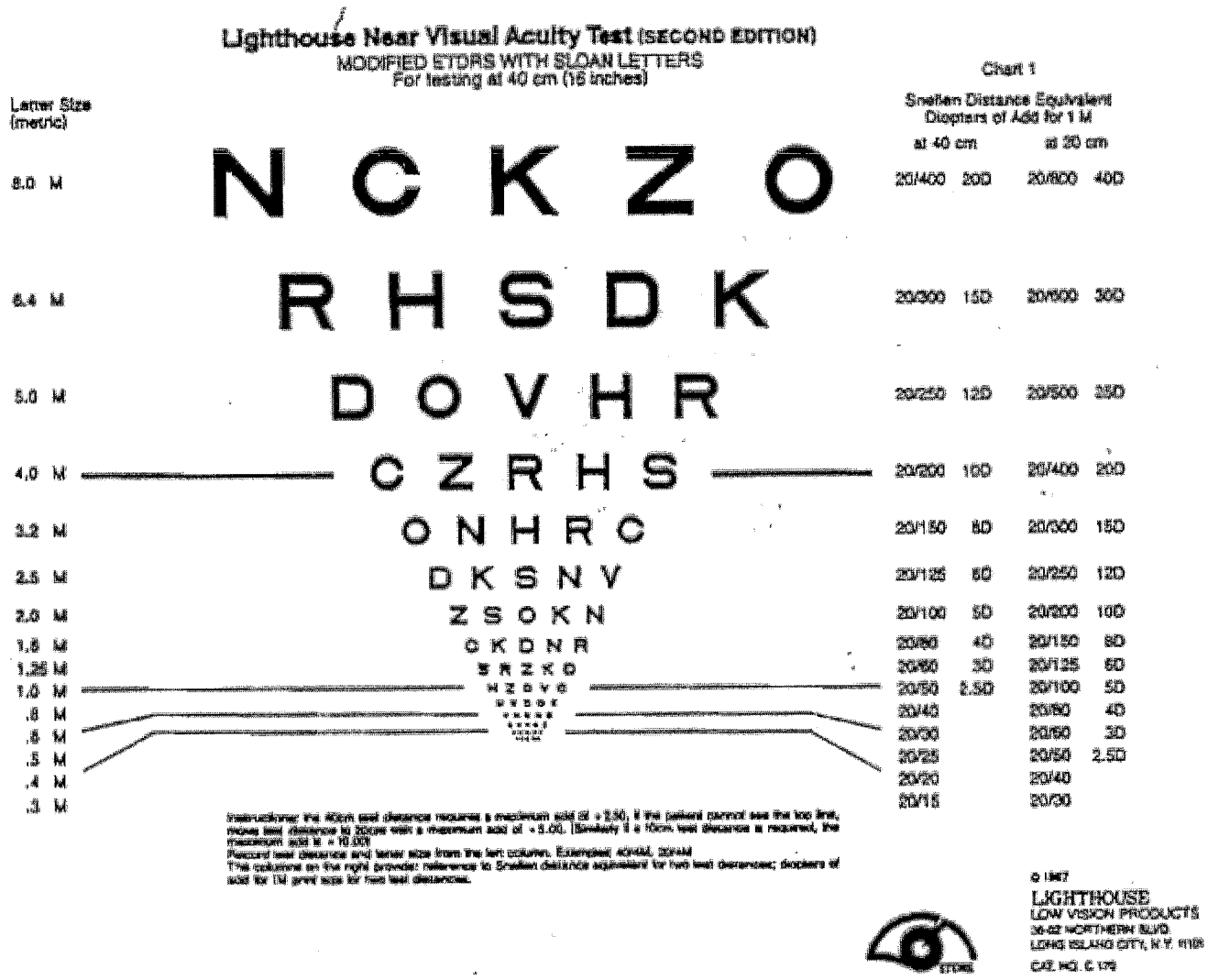
Note: Near cards provided by:
Optelec US, Inc.
3030 Enterprise Court, Suite C
Vista, CA 92081
1-800-453-4923
http://shoplowvision.com

Be certain that the visual acuity near card is not visible to the patient before the eye exam. Average ambient room lighting is used for illumination. Glasses may be worn. The card is held 40 cm or 16 inches from the eye as measured by the string attached to the card. The end of string is held next to the patient's eye, the string is fully extended, and the card is held at eye level. One eye is occluded with the visual acuity measured for the right eye first and then the left eye. For each eye, the patient is asked to read the first line distinguishable on the study chart. If the patient reads it perfectly, ask the patient to read the next smallest line. The examination proceeds until the patient misses every letter in a line.

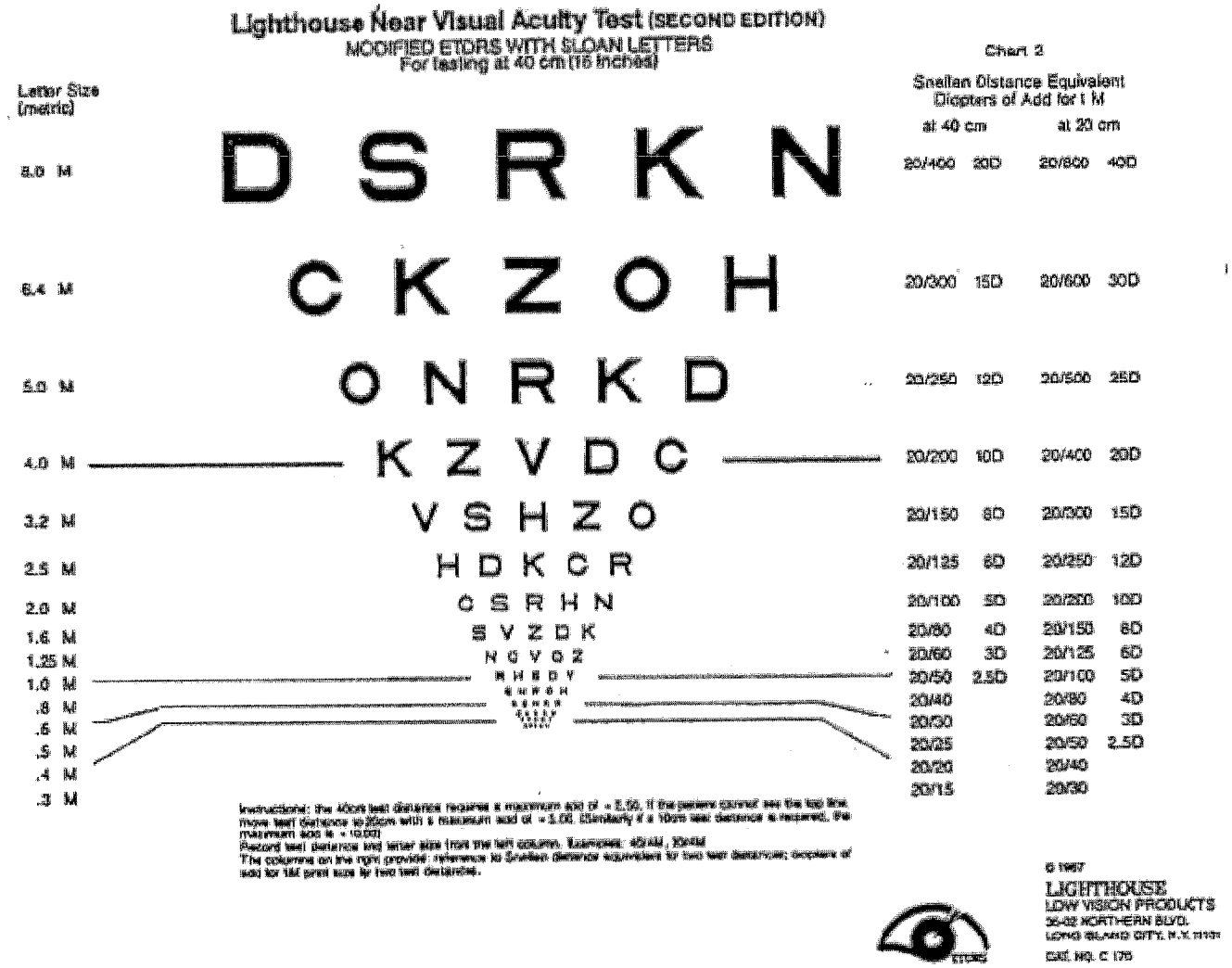
If the patient misses some of the letters on a particular line, he/she is given another chance by asking that he/she attempt to read the line backwards or to read a specific letter in that line (such as the first or last) then the next letter. In those instances in which the patient has had a difficult struggle, the examiner may elect to ask the patient to reread only the letters missed. If the patient states that a letter is one of two letters, he/she is asked to choose only one letter, and if necessary, to guess.

Visual acuity examiners may encourage the patient to fixate eccentrically if this strategy improves visual acuity. However, if the patient fixes eccentrically, care must be taken to insure that the fellow eye remains completely covered.

10.4.4. Ferris-Bailey Near Card - Chart 1



10.4.5. Ferris-Bailey Near Card - Chart 2



11. Visual field assessment protocol

11.1. Introduction

Visual fields assessment procedures developed for the Diabetic Retinopathy Study (DRS) will be used to assess the functional consequences of CMV lesions in zones 2 and 3 of the retina. A Goldmann style perimeter should be used.

The visual field test can be performed with or without pupil dilation. A patient's eyes should not have been exposed to bright light for at least ten minutes prior to the start of the test. Testing should take place in a dark and quiet room. A patient should not wear his or her glasses during the test because spectacle rims tend to obscure the full extent of the peripheral field and the large, bright test object specified for this test can be perceived well even in the presence of a large uncorrected refractive error. If the patient cannot see the test object without correction, do not complete the examination for the eye.

11.2. Calibration of the Goldmann perimeter

The Goldmann perimeter should be calibrated **before each visual field examination**. With the chart paper in place in the holder at the rear of the instrument, the swinging arm is locked in place by placing the tip of the pantograph over the dot located on the chart paper along 180° meridian at the intersection of the circle 70° from fixation. A small locking button along the pantograph arm is then lowered into a hole to fix in place the pantograph arm and swinging arm bearing the test spot.

With the arm fixed in place, the test spot intensity is set at V 4 E and locked in the "ON" position. The light meter supplied with the instrument is placed in its mount which is near the front of the perimeter bowl at the operator's left. The needle gauge on the rear of the light meter can be illuminated by a small lamp on the outside of the perimeter. Next to the light meter at the edge of the perimeter bowl is a small screen which can be raised or lowered by means of a knob. In the raised position, the screen is out of the way and the test spot falls on the light meter. In this position, the needle on the light meter will move. It should come to rest in a position indicating that the test spot intensity at the V 4 E level is 1,430 lux/1,000 apostilbs. If the needle indicates a different intensity, then the test spot intensity is adjusted using the rheostat knob at the left side of the perimeter along its base.

After the test spot intensity has been calibrated, the light meter is removed and the moveable screen lowered into position so that it occludes the opening through which the test spot light falls. The test spot controls are switched to V 1 E. The operator positions himself/herself at the right-hand side of the perimeter bowl and looks through the horizontal slot at this side of the bowl toward the opening through which the test light passes. The light falls upon the screen. The test light should be virtually indistinguishable from the background. If the spot intensity **is** clearly distinguishable from the background, then the background intensity is adjusted by moving the slide which is located at the top of the perimeter bowl just above the patient's head. The slide is adjusted until the test spot and the background cannot be distinguished.

When these operations have been completed, the perimeter background and test spot have been properly calibrated. Great care should be taken not to alter the settings inadvertently during the course of repeated testing of patients. Calibration MUST be performed with the patient sitting in position. Warn the patient NOT to sit back during calibration nor during the test as the projection arm moves in back of their head.

11.3. Evaluation of the Goldmann visual fields

Prior to baseline measurements, the examiner must explain the mechanics of testing to the patient and complete practice field evaluations on at least three meridians. The patient's better eye should be used for the practice field evaluation. Before each visual field examination, calibrate both the intensity of the projected stimulus and the intensity of the background bowl when the patient's chin and forehead are in the proper position.

After explaining the mechanics of testing to a patient, his or her head should be strapped gently into position both to help immobilize it and to prevent its being struck by the target projector arm as it moves. For purposes of teaching and insuring proper fixation, it is best to start the examination by testing a patient's better eye first. The fellow eye should be completely occluded and the eye to be tested centered perfectly on the cross hairs of the examiner's telescope. Fixation must be carefully monitored throughout the test.

Twelve radial meridians are to be tested: 0, 30, 60, 90, 120, 150, 180, 210, 240, 270, 300, and 330 degrees. The order of testing should be random so that the patient cannot anticipate the direction from which the light will next appear. Starting at the extreme extent of the periphery, the examiner should move the IV 4 E test object at a uniform speed radially along one of the test meridians toward the center. The speed of target movement should be varied according to the reaction time and cooperation of the patient, but it should be approximately three to five degrees of arc per second. Always test from non-seeing to seeing areas.

The patient should signal by pressing the signal button or tapping on the Goldmann table with a coin or pencil when he first sees the target peripherally. This spot is then marked on the Goldmann score sheet as the peripheral extent of the field along that particular meridian. Once the target is seen it should be continued along the particular meridian all the way to fixation. The patient should be instructed to signal any time the target disappears from view since this will signify the presence of a scotoma.

The standard method of identifying the boundaries of a scotoma is to move the target from an area of non-seeing into an area of seeing. Therefore, if a scotoma is found, the examiner should reverse the central direction of target motion. Beginning inside the scotomatous area the target should be moved outward until the target reappears. Once the peripheral edge is identified and marked on the Goldmann chart, the direction of the target should be reversed again and the target moved toward the center of fixation. Usually the target will reappear again before the center of fixation is reached. The point of reappearance from the scotomatous area marks the inner or central extent of the scotoma. If multiple scotomata are detected along a given meridian, only record the peripheral edge of the most peripheral scotoma and the central edge of the most central scotoma. However, when calculating the total degrees of scotoma subtract out seeing areas.

Because of the size of the IV 4 E test object, a few patients will not notice the normal

physiologic blind spot. If the normal blind spot is found during testing, its extent along the meridian should be determined and recorded as any other scotoma. It is not required that the boundary of any scotoma, including the normal blind spot, be mapped except the points where the boundary intersects one of the twelve meridians.

The results of the visual field test should be recorded on the Visual Field Record (VF). The VF form has twelve items per eye referring to the meridians to be tested. For each meridian the point of the peripheral field at which the test object is first seen should be recorded in degrees from the center. These results should be recorded in subitem **a.** for the appropriate meridian and eye. If the test object is never seen along a specified meridian, subitems **a.**, **b.**, and **c.** are recorded as "00"; subitem **d.** is recorded as "90." If scotomata are present, the point in degrees from the center at which a scotoma is first encountered in the periphery should be recorded in subitem **b.** for that meridian and eye. The point, in degrees from the center, at which the test object reappears for the last time before the center of fixation should be recorded in subitem **c.** for that meridian. If the test object does not reappear, subitem **c.** should be recorded as "00." The total degrees of the scotoma are recorded in subitem **d.** If there are multiple scotomata present on a particular meridian, the seeing area between scotomata should be subtracted from the difference between subitems **b.** and **c.**; the total degrees of scotomata should then be recorded in subitem **d.** If no scotoma is present on a meridian, subitems **b.**, **c.**, and **d.** should be recorded as "00."

11.4. Humphrey Automated perimetry

Introduction

In February 2007, LSOCA converted from using the Full Threshold 24-2 protocol to the Swedish Interactive Threshold Algorithm (SITA) Standard protocol for Humphrey Visual Field testing. The transition to SITA was a consequence of the technology which enabled the collection of twice as much information per unit time as the original Humphrey Full Threshold standard algorithm. SITA Standard cuts the test time in half without compromising test reproducibility. The SITA Standard must be performed on a 700 Series Humphrey visual field analyzer. Re-certification of automated visual field examiners is not necessary.

Specifications for the 600 and 700 series models

Specifications for the threshold parameter setup for the 600 series:

- Threshold strategy: Full threshold
- Fixation target: Central
- Blind spot check size: III
- Stimulus size: III
- Stimulus color White
- Test speed: Normal
- Foveal threshold: On
- Fluctuations: On
- Fastpac: Off

Specifications for the model 700 series:

- Test Strategy: SITA Standard
- Test Speed: Normal
- Fixation Target: Central
- Fixation monitoring: Gaze/Blind Spot
- Blue Yellow: Off
- Foveal Threshold: On
- Stimulus Size: III
- Stimulus Color: White
- Fluctuation: Off

The parameter specifications on the 600 series Humphrey machine which is summarized in the LSOCA Handbook, section 4.28.2, Humphrey Automated Perimetry, remain the same except for the setting: Fixation Monitoring, which must be set to "Fastpac Off". The 600 Series model Humphrey visual field analyzer requires that the foveal threshold be turned on manually; whereas the 70 series

model does this automatically. *Use of the SITA-Fast protocol is **NOT** acceptable as the data obtained are not comparable to either SITA Standard or the Full Threshold 24-2 Humphrey test.*

Equipment

If your clinic has both the 600 and the 700 model series, use one model for LSOCA testing consistently:

- Humphrey Field Analyzer (HFA) I or II; either the 600 or 700 series; threshold 24-2 SITA program
- Dark, quiet room
- Eye patch/occlusion device
- Diskette to store electronic data locally
- Preprinted diskette label *(provided by Coordinating Center):* printed with study acronym *LSOCA* and *Clinic ID code*

Preparing the patient

Have the patient seated comfortably by adjusting the table if necessary. Place the eye patch over the eye not being tested. Dim the room lights and explain the test procedure to the patient. Position the patient's head against the headrest and align the patient, if necessary. If field analyzer model has a telescope to monitor alignment, center patient's eye with help of mires and the vertical and horizontal alignment wheels. If field analyzer has a video eye monitor, touch Eye Monitor, and use vertical and horizontal alignment wheels to center patient's eye in crosshairs displayed on the screen. Move trial lenses close to patient's eye and make sure patient's lashes do not touch the lens.

Testing, printing and storing results

Touch DEMO to demonstrate test procedure. The field analyzer will beep each time patient presses response button. Position the patient in the Field Analyzer by making sure his/her head is against the headrest and align the patient if necessary. Press START. Check patient alignment via the telescope or video monitor throughout testing. If fixation alarm sounds, remind patient to watch yellow light and re-try to find fixation if necessary. The field analyzer will beep three times at end of test.

For Set-up procedures and testing instructions refer to the LSOCA Handbook, Section 4.28.2, Humphrey Automated Perimetry.

Various printing formats are available depending on type of test used. Save data onto labeled diskette: *labeled with study acronym, clinic, patient and visit ID codes, date of exam and examiner's certification number and initials.* To alter the format, touch CHANGE DISPLAY and review the

other display formats. Test the better seeing eye first. Touch PRINT. Print HFA printout and review for accuracy. Test other eye and print. Review for accuracy. Attach Right/Left Eye label to upper right corner of printout and do not place label over any printed portion of printout.

Reference: Humphrey Instruments, Inc. Owner's Manual: A company of the Carl Zeiss Group.

12. Contrast sensitivity

Introduction

Contrast sensitivity testing gauges the ability to see objects in terms of size and contrast. The ability of a patient to see objects against low contrasting backgrounds is expressed as 'functional vision' and provides data beyond how well a patient can see details on a standard eye chart. Even with 20/20 vision, a patient could have poor contrast sensitivity. Hence, testing is important to enable doctors to assess quality of vision under less than optimum conditions (e.g., driving at night or trying to read a sign on a cloudy overcast day).

Low contrast sensitivity can be a symptom of certain eye conditions or diseases such as cataracts, glaucoma, or diabetic retinopathy. For evaluation of eye disease, contrast sensitivity is tested on each eye individually.

Contrast sensitivity eye charts

In LSOCA the two Pelli-Robson Contrast Sensitivity Charts (Chart 2L and Chart 4L) will be used for the right and left eye, respectively. The figures on the charts are letters, not numbers. The two charts have different letter sequences but are otherwise identical. The letters on the chart are arranged in groups of three (triplets). A single contrast group consists of 3 letters at the same print density (triplet). Two adjacent triplets are printed per line. Within each triplet, all letters have the same contrast. The contrast decreases from one triplet to the next.

The charts should be examined periodically for yellowing, smudges, water or moisture damage etc. Replacement charts can be obtained from the Coordinating Center.

Testing a patient

See Section 4.6 of the LSOCA Handbook (version 8.0, June 2009) for testing instructions. Test patients on the better seeing eye first and prior to dilation of pupils.

13. Quality of life measurement

13.1. Definition and purpose

- Quality of Life measurement describes a person's ability to perform everyday activities, a person's physical, social, and cognitive functioning, and his or her subjective sense of well-being
- Quality of Life Measures are recognized as an important component of comparing the efficacy of AIDS therapies. Patient-reported health status may be especially important when tested therapies have substantial side effects as well as result in physiologic improvement and longer survival.
- In SOCA studies, the Quality of Life measurement helps to assess the impact of treatments for retinitis on patients' daily quality of life. Patients' assessment of their energy level, pain or emotions helps to evaluate effects of AIDS on patients' everyday activities.

13.2. Role of the study coordinator

- Be familiar with the content and format of the questionnaire before it is administered to the patient
- Explain to the patient the purpose and importance of the Quality of Life questionnaire as a component of the study
- Perform interview
- Review completed forms

13.3. General procedures

All General Procedures should be followed for **in-person interview, telephone interview, surrogate interview, and self-administered questionnaire**

The following information should be explained to the patient before the interview

- One aim of the study is to learn how different medicines affect people's quality of life and how the patient has been functioning and feeling. The answers help to understand the effects of the medication.
- All questions refer to the patient's functioning and well-being **over the last 4 weeks**
- Response cards are used to identify the patient's response
- Some questions sound similar to others, but each one is different
- Only **one** answer should be given for each question
- The patient has to give the answer that comes **closest** to the way she/he has been feeling or seeing
- The interview usually takes 10 to 15 minutes

13.4. In-person interview

- If possible, all Quality of Life questionnaires should be conducted by **in-person interview**
- The **baseline** Quality of Life data collection **must be** administered via person-to-person interview
- The setting for an interview should be a quiet, secluded area with minimum distractions (exam room, office, private room)

13.5. Alternative methods (to be used when an in-person interview is not possible)

Telephone interview

- Conducted if a patient is unable to come to the clinic for a scheduled visit
- Calls should be made to the patient's home unless specified otherwise by the patient
- Calls should be made at different times of day and week and a log monitoring telephone attempts should be kept

Surrogate interview

- Can be conducted if a patient is not able (ie, too ill) to answer questions either in person or by telephone
- A **surrogate** is an individual(s) -- a spouse, lover, roommate, caretaker, family member, or friend -- who knows the patient well and sees the patient often enough to be able to report on patient's quality of life. The information on any persons that the patient lists as surrogates should be collected during the first visit. Name, relationship and phone numbers of those individuals are recorded.
- The interview can be conducted in-person, by telephone, or by self-administered method

Self-administered questionnaire

- Is recommended **only in special circumstances**, ie, patient/surrogate strongly prefers to answer the questions by him/herself
- Setting where the patient completes an interview should be a quiet, secluded area with a minimum distractions (exam room, office, private room)
- The completion of the questionnaire should take place prior to the vital signs, history and physical exam
- Response cards should be given to the patient and an explanation of how to complete and code questions should be provided
- To complete the self-administered questionnaire, all general procedures should be followed

- If the questionnaire is not returned within 15 minutes, the coordinator should check with the patient
- When the patient is finished, the questionnaire should be reviewed and any omitted questions should be completed

13.6. Tips for conducting a successful interview

- The interviewer has to be familiar and comfortable with the questionnaire before administering it to the patient. Advanced preparation and practice are necessary.
- Questions and any additional descriptions have to be read slowly, with clear articulation
- The interviewer should sound interested in the questions that he/she reads and not speak in a monotonous tone of voice
- It is important to be sufficiently neutral to avoid biasing the patient's responses
- The interviewer should make sure that the patient fully understands the question, and if necessary should repeat the question as many times as needed
- The interviewer should resist the urge to answer questions for the patient
- People communicate more information when they trust an interviewer. Trust develops when an interviewer communicates personal interest in the participant.

13.7. Guidelines for rating interview quality

- A **good interview** is one in which the patient was attentive and appeared to respond appropriately throughout
- A **fair interview** is one in which an interviewer suspected the patient might not be answering appropriately
- A **poor interview** is one in which the patient did not have adequate mental abilities to answer questions. A reason for poor interview quality has to be given (eg, sedation, extreme malaise, delirium or dementia).

13.8. Questions frequently asked by patients

Q. *"Some of the questions are redundant. Do I have to answer this one?"*
A. Some of the questions are supposed to be redundant. The questionnaire is made up of groups of questions. Each group of questions tries to evaluate an important part of your life, such as how much energy you have. Some of the questions ask about the same thing in a slightly different way to give us a better idea of exactly how you are feeling.

Q. *"I was in the hospital last week but I'm a lot better now"*
A. The questions are about what you have been able to do and how you have been feeling over the last 4 weeks. Try to give an answer that averages your condition over the last 4 weeks.

Q. *"This question does not apply to me, so how should I answer it?"*
A. We ask everyone the same questions so that at the end of the study we can draw some conclusions for everyone in the study. All of the questions do not exactly fit everyone's situation. Just try to give the best answers.

13.9. National Eye Institute Visual Function Questionnaire (VFQ-25)

Definition and purpose

- The VFQ-25 survey measures the influence of visual disability and visual symptoms on generic health domains such as emotional well-being and social functioning, in addition to task-oriented domains related to daily visual functioning.

Role of the study coordinator

- Be familiar with the content and format of the questionnaire before it is administered to the patient
- Explain to the patient the purpose and importance of the NEIVFQ as a component of the study
- Perform interview
- Review completed forms

Confidentiality and informed consent

- Protocol rules regarding confidentiality apply to all information obtained in the Visual Function Questionnaire interview and responses
- For telephone interview, while attempting to reach a patient, confidentiality should be maintained when interacting with the patient's house mates.
- For surrogate interviews, prior consent must be obtained from the patient

General Procedures

In-person interview, telephone interview (eg. Missed visits), or self-administered questionnaire.

- To assess how problems with vision affect people's quality of life
- All questions refer to the patient's vision issues **over the last 4 weeks**
- Only **one** answer should be given for each question; the interview/questionnaire usually takes 15 to 20 minutes.

In-person interview

- If possible, Visual Function questionnaires should be conducted by **in-person interview**
- The baseline Visual Function questionnaire **must be** administered via person-to-person interview
- The setting for an interview should be a quiet, secluded area with minimum distractions (exam room, office, private room)

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* The National Eye Institute (NEI) sponsored the development of the VFQ-25 with the goal of creating a survey that would measure the dimensions of self-reported vision-targeted health status that are most important for persons who have chronic eye diseases.

14. Appendices

14.1. Glossary

AIDS	Acquired Immune Deficiency Syndrome
CC	Coordinating Center
CCG	Clinic Coordinators Group
CMV	Cytomegalovirus
FPRC	Fundus Photography Reading Center
HAART	Highly Active Anti-Retroviral Treatment
HIV	Human Immunodeficiency Virus
IRB	Institutional Review Board
LSOCA	Longitudinal Study of the Ocular Complications of AIDS
NA-ACCORD	North American AIDS Cohort Collaboration on Research and Design
NEI	National Eye Institute
NIH	National Institutes of Health
NTIS	National Technical Information Service
OI	Opportunistic infection
OOI	Ocular opportunistic infection
PDMB	Policy and Data Monitoring Board
RG	Research Group
SC	Steering Committee
SO	Study Officers
SOCA	Studies of Ocular Complications of AIDS
VFQAC	Visual Function Quality Assurance Committee

14.2. Adverse event reporting guidelines

Relationship to Study Drug

None:	Concurrent illness, concurrent medication, or other known cause clearly is responsible for the adverse event
Unlikely:	Based upon available knowledge regarding subject history, disease process, temporal relationship of AE with dosing, and drug pharmacology, a relationship between the drug and the adverse event is unlikely, but cannot be fully excluded.
Possible:	This relationship exists when the adverse event follows a reasonable temporal sequence from the time of drug administration, but could also have been produced by the patient's clinical state or by other drugs administered to the patient.
Probable:	This relationship exists when the adverse event follows a reasonable temporal sequence from the time of drug administration, follows a known response pattern of the drug class, is confirmed by improvement on stopping the drug and the suspect drug is the most likely of all causes.
Definite:	This relationship exists when the adverse event follows a reasonable temporal sequence from the time of drug administration, follows a known response pattern of the drug class, is confirmed by improvement on stopping the drug and no other reasonable cause exits.
Unknown:	There is insufficient data available to make a reasonably informed assessment regarding the etiology of the adverse event, or any possible association with the use of the drug.

Estimating severity grade

For abnormalities NOT found elsewhere on the Tox Table use the scale below to estimate grade of severity:

• Grade 1	Mild	Transient or mild discomfort; no limitation in activity; no medical intervention/therapy required
• Grade 2	Moderate	Mild to moderate limitation in activity - some assistance may be needed; no or minimal medical intervention/therapy required

•	Grade 3	Severe	Marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalizations possible
•	Grade 4	Life-threatening	Extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalization or hospice care probable

Serious or Life-Threatening Adverse Events

ANY clinical event deemed by the clinician to be serious or life-threatening should be considered a grade 4 adverse event. Clinical events considered to be serious or life-threatening include, but are not limited to:

- Seizures, coma, tetany, diabetic ketoacidosis, disseminated intravascular coagulation, diffuse petechiae, paralysis, acute psychosis

Miscellaneous

- When two values are used to define the criteria for each parameter, the lowest values will appear first
- Parameters are generally grouped by body system

Toxicity Tables

- Toxicity tables are study specific and can be found in the study specific handbooks

14.3. HIV diagnosis codes *(Source: ACTG Clinical Events Working Group; 8 August 1996 – N. Jacobson, SOCA representative)*

14.3.1. Viral Infections

Code	Definition
34013P	**PROBABLE CMV RETINITIS** 1. Typical lesions including white areas with or without hemorrhages and/or gray-white areas of retinal necrosis with or without hemorrhages. Lesion(s) has/have irregular, dry-appearing, granular border, with little or no overlying vitreous inflammation. Must be diagnosed by an experienced ophthalmologist using indirect ophthalmoscopy, but is not documented by retinal photographs.
34013C	**CONFIRMED CMV RETINITIS** 1. Typical lesions including white areas with or without hemorrhages and/or gray-white areas of retinal necrosis with or without hemorrhages. Lesion(s) has/have irregular, dry-appearing, granular border, with little or no overlying vitreous inflammation. Must be diagnosed by an experienced ophthalmologist using indirect ophthalmoscopy and documented by retinal photography that can be independently verified.
34012P	**PROBABLE CMV ESOPHAGITIS** 1. Presence of at least one of the following symptoms: retrosternal pain or odynophagia (pain on swallowing). AND 2. Appropriate visualization procedure (endoscopy) that reveals mucosal erythema, erosion or ulceration. AND 3. CMV is isolated from the lesion. AND 4. Anti-CMV therapy initiated or recommended.
34012C	**CONFIRMED CMV ESOPHAGITIS** 1. Presence of at least one of the following symptoms: retrosternal pain or odynophagia (pain on swallowing). AND 2. Tissue biopsy demonstrating CMV by antigen, PCR or characteristic cytopathic changes.

14.3.1 Viral Infections (cont'd)

34015P PROBABLE CMV GASTROENTERITIS

1. Presence of abdominal pain.

AND

2. Appropriate visualization procedure (endoscopy) that reveals mucosal erythema, erosion or ulceration.

AND

3. CMV is isolated from the lesion.

AND

4. Anti-CMV therapy initiated or recommended.

34015C CONFIRMED CMV GASTROENTERITIS

1. Presence of abdominal pain.

AND

2. Tissue biopsy demonstrating CMV by antigen, PCR or characteristic cytopathic changes.

34014P PROBABLE CMV COLITIS

1. Presence of at least one of the following symptoms: abdominal pain or diarrhea (typically in small volume and associated with mucus and blood)

AND

2. Appropriate visualization procedure (colonoscopy, sigmoidoscopy or endoscopy) that reveals mucosal erythema, erosion or ulceration.

AND

3. CMV is isolated from the lesion.

AND

4. Anti-CMV therapy initiated or recommended.

34014C CONFIRMED CMV COLITIS

1. Presence of at least one of the following symptoms: abdominal pain or diarrhea (typically in small volume and associated with mucus and blood).

AND

2. Tissue biopsy demonstrating CMV by antigen, PCR or characteristic cytopathic changes.

34016P PROBABLE CMV PROCTITIS

1. Presence of rectal pain, often associated with tenesmus, mucus and blood.

AND

2. Appropriate visualization procedure (colonoscopy, sigmoidoscopy or endoscopy)

14.3.1 Viral Infections (cont'd)

that reveals mucosal erythema, erosion or ulceration.

AND

3. CMV is isolated from the lesion.

AND

4. Anti-CMV therapy initiated or recommended.

34016C CONFIRMED CMV PROCTITIS

1. Presence of rectal pain, often associated with tenesmus, mucus and blood.

AND

2. Tissue biopsy demonstrating CMV by antigen, PCR or characteristic cytopathic changes.

34028P PROBABLE CMV PNEUMONITIS

1. Hypoxemia and infiltrates on chest X-ray or CT/MRI scan.

AND

2. Positive CMV culture, detection of CMV antigen, or detection of viral nucleic acids of CMV from fluid obtained by BAL.

AND

3. No other pathogens identified by routine testing OR signs/symptoms persist or recur after treatment of copathogens.

AND

4. Anti-CMV therapy initiated or recommended.

34028C CONFIRMED CMV PNEUMONITIS

1. Hypoxemia and infiltrates on chest X-ray or CT/MRI scan.

AND

2. Tissue biopsy or cells obtained by BAL demonstrating CMV by antigen, PCR or characteristic cytopathic changes.

AND

3. No other pathogens identified by routine testing OR signs/symptoms persist or recur after treatment of copathogens.

34017P PROBABLE CMV ENCEPHALITIS

1. Progressive change in mental status, delirium, or rapidly progressive cognitive impairment

AND

2. MRI or contrast CT scan performed which:
   a) Excludes toxoplasmosis, lymphoma, Progressive Multifocal Leukoencephalopathy or other intracranial process, and:

14.3.1 Viral Infections (cont'd)

b) Demonstrates periventricular inflammation or meningeal enhancement

AND

3. Other etiologies ruled out

AND

4. CMV end-organ disease (eg, retinitis, colitis) present

AND

5. Specific therapy initiated, changed or recommended.

34017C CONFIRMED CMV ENCEPHALITIS

1. Progressive change in mental status, delirium, or rapidly progressive cognitive impairment

AND

2. CSF CMV PCR positive or CSF CMV culture positive or brain biopsy demonstrating CMV by antigen, PCR or characteristic cytopathic changes

34019C CONFIRMED Other CMV SYNDROMES

1. Clinical presentation compatible with the following CMV end-organ diseases:
   - Hepatitis or cholangitis
     a) ALT or alkaline phosphatase significantly elevated above the patient's baseline values

     AND

     b) Tissue biopsy demonstrating CMV by antigen, PCR or characteristic cytopathic changes.

   - Radiculomyelopathy (all of the following):
     a) Decreased lower extremity strength and reflexes or syndrome consistent with a cord lesion presenting subacutely (over days to weeks)
     b) myelogram or MRI reveals no mass lesions but lower spinal nerve roots thickened
     c) CMV positive culture in CSF or evidence of CMV in CSF by PCR

34025P PROBABLE CUTANEOUS CMV ULCERS

1. Direct visualization of oral, vulvovaginal or perianal ulcers.

AND

2. CMV is isolated from the lesion.

AND

3. Anti-CMV therapy initiated or recommended.

34025C CONFIRMED CUTANEOUS CMV ULCERS

14.3.1 Viral Infections (cont'd)

1. Direct visualization of oral or perianal ulcers.

AND

2. CMV culture of lesion or histologic demonstration of typical CMV cytopathology on biopsy of lesion.

34026P PROBABLE MUCOCUTANEOUS HERPES SIMPLEX

1. Clinically apparent typical (vesicular or ulcerative) HSV lesion(s)

AND

2. Typical herpes virus inclusions (multinucleated giant cells) evident in cells obtained from the base of an ulcer or vesicular lesion or biopsy

AND

3. Improvement in lesion as a result of specific antiviral therapy

34026C CONFIRMED MUCOCUTANEOUS HERPES SIMPLEX

1. Clinically apparent typical (vesicular or ulcerative) HSV lesion(s)

AND

2. Any one of the following:
   a) HSV isolated from lesion.
   b) HSV antigen detected by immunoassay from vesicular fluid or cells obtained from the base of a vesicle or ulcer
   c) Recurrence of lesion in same general location as prior documented positive HSV culture

34030C CONFIRMED LOCALIZED ZOSTER
HERPES ZOSTER, LOCALIZED

1. Clinically apparent painful or dysesthetic lesions appearing in a dermatomal distribution. May be either typical (macular/papular progressing to vesiculopustular) or atypical (ulcerative, necrotic, and/or nodular)

AND

2. Demonstration of HZV in lesions by Direct Immunofluorescence Assay (DFA), culture or PCR

34031C CONFIRMED DISSEMINATED CUTANEOUS ZOSTER

1. Confirmed localized zoster

AND

2. Greater than 25 vesicles extending beyond the primary and adjacent (flanking) dermatomes

14.3.1 Viral Infections (cont'd)

34038C CONFIRMED ZOSTER WITH VISCERAL DISSEMINATION

1. Clinically apparent painful or dysesthetic lesions appearing in a dermatomal distribution. May be either typical (macular/papular progressing to vesiculopustular) or atypical (ulcerative, necrotic, and/or nodular)

AND

2. Clinical findings, laboratory test abnormalities and/or radiographic (ie, X-ray, ultrasonography, CT and/or MRI findings) consistent with the diagnosis
   a) Pulmonary: I) bilateral interstitial infiltrates on chest x-ray and ii) clinical signs and symptoms of pulmonary disease during the course of infection
   b) Hepatitis: Significant elevations of bilirubin, AST, ALT attributable to VZV
   c) CNS: Encephalopathy and CSF pleocytosis with negative bacterial, acid-fast, fungal and viral cultures (other than HZV)
   d) Myelitis/Paralysis: pain in back or legs, with or without urinary retention, hyperesthesia and motor disturbances or paralysis. Loss or impairment of motor function involve area(s) not within the dermatomal distribution of the patient's localized zoster

AND

3. Demonstration of HZV in cutaneous or visceral lesions by Direct Immunofluorescence Assay (DFA), culture or PCR

34040P PROBABLE PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY (PML)

1. Clinical presentation compatible with PML that includes an abrupt global deterioration in mental and physical condition

AND

2. MRI compatible with PML.

AND

3. Absence of current active intracranial processes such as cryptococcal meningitis, CMV encephalitis, toxoplasmosis, CNS lymphoma, or neurosyphilis

AND

4. Specific therapy for PML considered, recommended or initiated

34040C CONFIRMED PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY (PML)

1. PML diagnosed by characteristic histopathology on brain biopsy or *in situ* hybridization

14.3.2. Parasitic Infections

Code	Definition
31011P	**PROBABLE PNEUMOCYSTIS CARINII PNEUMONIA** 1. A history (within the past three months) of shortness of breath, dyspnea on exertion, cough or fever AND 2. Abnormal chest x-ray (or CT scan) or hypoxemic arterial blood gas, $P_aO_2 < 80$ mm Hg **or** (A-a)DO_2 mm Hg > 15 on room air. AND 3. Specific anti-pneumocystis therapy was recommended or initiated.
31011C	**CONFIRMED PNEUMOCYSTIS CARINII PNEUMONIA** 1. A history (within the past three months) of shortness of breath, dyspnea on exertion, cough or fever AND 2. Histological or cytological evidence of *Pneumocystis carinii* on bronchoalveolar lavage, lung biopsy or sputum specimen
31018P	**PROBABLE EXTRAPULMONARY PNEUMOCYSTOSIS (eye disease only)** 1. Pneumocystis lesions of the retina as indicated by characteristic lesions consistent with Pneumocystis choroiditis according to an experienced ophthalmologist. AND 2. Clinical improvement with systemic therapy.
31018C	**CONFIRMED EXTRAPULMONARY PNEUMOCYSTOSIS** 1. Histological or cytological evidence of extrapulmonary pneumocystosis.
31020P	**PROBABLE TOXOPLASMIC ENCEPHALITIS** 1. Compatible clinical syndrome consisting of headache, seizure, neurologic deficits and/or fever. AND 2. Presence of characteristic mass lesion(s) on brain imaging study (CT or MRI). AND 3. Response after a minimum of two weeks of anti-toxoplasma therapy with documented clinical or radiographic improvement

14.3.2 Parasitic Infections (cont'd)

31020C CONFIRMED TOXOPLASMIC ENCEPHALITIS

1. Histologic evidence of *Toxoplasma gondii* in tissue obtained by brain biopsy or autopsy

OR

2. All of the following:
   a) Compatible clinical syndrome consisting of headache, seizure, neurologic deficits and/or fever.
   b) Presence of characteristic mass lesion(s) on brain imaging study (CT or MRI).
   c) Response after a minimum of two weeks of anti-toxoplasma therapy with documented clinical or radiographic improvement
   d) Positive blood culture for *Toxoplasma gondii*

31028P PROBABLE NON-CNS TOXOPLASMOSIS

No definition at this time

31028C CONFIRMED NON-CNS TOXOPLASMOSIS

1. Histologic evidence of Toxoplasma present in tissue or body fluid obtained by autopsy, biopsy or aspirate.

31035P PROBABLE CRYPTOSPORIDIOSIS

No definition at this time

31035C CONFIRMED CRYPTOSPORIDIOSIS

1. At least **one** of the following:
   a) Diarrhea defined as 2 or more non-formed stools per day for 2 or more days.
   b) Presence of at least one of the following abdominal symptoms: nausea, vomiting, or abdominal pain.
   c) Presence of at least one biliary symptom: biliary colic, jaundice or grade 2 or greater elevation in total bilirubin, alkaline phosphatase or GGTP.

AND

2. Microscopic evidence of Cryptosporidium present in either stool, body fluid or tissue specimen

31045P PROBABLE ISOSPORIASIS

No definition at this time

14.3.2 Parasitic Infections (cont'd)

31045C CONFIRMED ISOSPORIASIS

1. At least **one** of the following:
   a) Diarrhea defined as 2 or more non-formed stools per day for 2 or more days.
   b) Presence of at least one of the following abdominal symptoms: nausea, vomiting, or abdominal pain.
   c) Presence of at least one biliary symptom: biliary colic, jaundice or grade 2 or greater elevation in total bilirubin alkaline phosphatase or GGTP.

AND

2. Microscopic evidence of isospora present in stool, body fluid, or tissue specimen

31055P PROBABLE MICROPORIDIOSIS

No definition at this time

31055C CONFIRMED MICROSPORIDIOSIS

1. At least **one** of the following:
   a) Diarrhea defined as 2 or more non-formed stools per day for 2 or more days.
   b) Presence of at least one of the following abdominal symptoms: nausea, vomiting, or abdominal pain.
   c) Presence of at least one biliary symptom: biliary colic, jaundice or grade 2 or greater elevation in total bilirubin, GGTP, or alkaline phosphatase.

AND

2. Microscopic evidence of microsporidia present in stool, body fluid, or tissue specimen

14.3.3. Fungal Infections

32010P PROBABLE ESOPHAGEAL CANDIDIASIS

1. EITHER:
   a) Compatible clinical syndrome, consisting of two or more of the following symptoms and/or signs: odynophagia, white plaques in esophagus, mucous membrane erythema.

OR

   b) Confirmed or probable oral pharyngeal candidiasis AND odynophagia

AND

2. Response to specific antifungal therapy

14.3.3 Fungal Infections (cont'd)

32010C CONFIRMED ESOPHAGEAL CANDIDIASIS

1. Compatible clinical syndrome, consisting of one or more signs or symptoms: odynophagia, white plaques in esophagus, erythema.

AND

2. Positive culture, KOH or histopathology from esophagus.

32021 PULMONARY CRYPTOCOCCOSIS
32031 PULMONARY HISTOPLASMOSIS
32041 PULMONARY COCCIDIOIDOMYCOSIS

32051 PULMONARY BLASTOMYCOSIS

PULMONARY HISTOPLASMOSIS, BLASTOMYCOSIS, COCCIDIOIDOMYCOSIS OR CRYPTOCOCCOSIS

[Since these diagnoses are not AIDS-defining there is no distinction between confirmed and probable.]

1. Abnormal chest X-ray or CT scan

AND

2. Positive histopathology or culture of lung tissue or BAL of:
   C. neoformans (cryptococcosis)
   H. capsulatum (histoplasmosis)
   C. immitis (coccidioidomycosis)
   B. Dermatitidis (blastomycosis)

OR

Detection of antigen or antibody in serum, urine or BAL, as defined below:
histoplasma antigen (histoplasmosis)
Positive complement fixation titer (coccidioidomycosis)
serum antigen > 1:8 (cryptococcosis)

AND

3. No evidence of extrapulmonary infection.

14.3.3 Fungal Infections (cont'd)

32021P **PROBABLE DISSEMINATED CRYPTOCOCCOSES (PROBABLE DISSEMINATED FUNGAL DISEASE)**

1. Compatible clinical syndrome consisting of one or more signs or symptoms as follows:
   Cryptococcosis: fever $\geq$ 38°C;

AND

2. Detection of positive antigen, as defined below:
   Cryptococcal: serum antigen $\geq$ 1:8

AND

3. Specific antifungal therapy initiated (or recommended).

32021C **CONFIRMED DISSEMINATED CRYPTOCOCCOSES (CONFIRMED DISSEMINATED FUNGAL DISEASE)**

No definition at this time

32023P **PROBABLE CRYPTOCOCCAL MENINGITIS**

1. Compatible clinical syndrome consistent with signs and symptoms of CNS fungal infection.

AND

2. Positive CSF cryptococcal antigen or CSF India Ink preparation.

AND

3. Specific antifungal therapy initiated (or recommended).

32023C **CONFIRMED CRYPTOCOCCAL MENINGITIS**

1. Evidence of species isolates, as below, by positive culture or positive histopathology identifying characteristic appearance of organisms within body tissue or fluids.
   C. neoformans (cryptococcosis)

32031P **PROBABLE DISSEMINATED HISTOPLASMOSIS (PROBABLE DISSEMINATED FUNGAL DISEASE)**

1. Compatible clinical syndrome consisting of one or more signs or symptoms as follows:
   Histoplasmosis: anemia, leukopenia, thrombocytopenia; elevated alkaline phosphatase, SGOT, LDH, or bilirubin; enlarged lymph nodes, spleen and/or liver; skin lesions; or gastrointestinal ulcers.

AND

14.3.3 Fungal Infections (cont'd)

2. Detection of positive antigen, as defined below:
Histoplasma: antigen > 1 unit obtained directly from body fluids (eg, urine, CSF, blood)

32031C **CONFIRMED DISSEMINATED HISTOPLASMOSIS (CONFIRMED DISSEMINATED FUNGAL DISEASE)**

1. Evidence of species isolates, as below, by positive culture or positive histopathology identifying characteristic appearance of organisms within body tissue or fluids.
H. capsulatum (histoplasmosis)

PROBABLE COCCIDIOIDOMYCOSIS

There is no definition for Probable Disseminated Coccidioidomycosis.
See Probable CNS Coccidioidomycosis.

32041C **CONFIRMED COCCIDIOIDOMYCOSIS (CONFIRMED DISSEMINATED FUNGAL DISEASE)**

1. Either:
   a) Positive culture of *C. immitis*

OR

   b) Positive histopathology of invasive disease

32044P **PROBABLE CNS COCCIDIOIDOMYCOSIS**

1. Positive complement fixation serology

AND

2. Compatible clinical syndrome consisting of CSF lymphocytic pleocytosis and signs and symptoms of meningitis (fever and one or more of the following: headache, stiff neck, photophobia, seizures, focal deficits and altered mental status).

AND

3. Specific antifungal therapy initiated (or recommended).

32051P **PROBABLE BLASTOMYCOSIS**

There is no definition for probable Blastomycosis

14.3.3 Fungal Infections (cont'd)

32051C **CONFIRMED BLASTOMYCOSIS**
(CONFIRMED DISSEMINATED FUNGAL DISEASE)

1. Evidence of species isolates, as below, by positive culture or positive histopathology identifying characteristic appearance of organisms within body tissue or fluids.
   B. Dermatitidis (blastomycosis)

32060C **CONFIRMED OROPHARYNGEAL CANDIDIASIS**

1. Compatible clinical syndrome, consisting of one or more signs or symptoms as follows: oral pain, dysphagia; white plaques in oropharynx, mucous membrane erythema.

AND

2. Positive culture, KOH or histopathology

32060P **PROBABLE OROPHARYNGEAL CANDIDIASIS**

1. Compatible clinical syndrome, consisting of two or more of the following symptoms and/or signs as follows white plaques in oropharynx, mucous membrane erythema, oral pain, or dysphagia.

AND

2. Specific antifungal therapy initiated (or recommended)

32070P **PROBABLE VULVOVAGINAL CANDIDIASIS**

1. Compatible clinical syndrome, consisting of two or more of the following symptoms and/or signs; mucous membrane erythema, white plaques/exudate adherent to vaginal mucosa or thick, curdy vaginal discharge, vulvovaginal pruritus, irritation/soreness or dyspareunia.

AND

2. Specific antifungal therapy initiated (or recommended)

32070C **CONFIRMED VULVOVAGINAL CANDIDIASIS**

1. Compatible clinical syndrome, consisting of one or more signs or symptoms as follows: vulvovaginal pruritus, irritation/soreness or dyspareunia; mucous membrane erythema, white plaques/exudate adherent to vaginal mucosa or thick, curdy vaginal discharge.

AND

2. Positive culture, KOH or histopathology

14.3.3 Fungal Infections (cont'd)

OTHER CANDIDIASIS
No specific definition. See definition for "other fungi" which includes disseminated candidemia and invasive candidiasis

32080P **PROBABLE MOLD INFECTIONS (ASPERGILLUS SPECIES, MUCORMYCOSIS AND OTHERS)**

1. Either:
   a) Positive histopathology, cytology or KOH prep from tissue

OR

   b) Positive culture

AND

2. One of the following:
   a) Compatible clinical syndrome consistent with signs and symptoms of pulmonary fungal infection

OR

   b) Localized clinical syndrome in sinus, nose, orbit or ear consisting of any of the following: pain, headache, nasal or ear discharge, changes in vision or hearing, facial tenderness, ulceration or necrotic membrane in nose or face, perforation of tympanic membrane, ocular paralysis, otitis externa or media, or radiographic evidence of sinus opacity or bony erosion

32080C **CONFIRMED MOLD INFECTIONS (ASPERGILLUS SPECIES, MUCORMYCOSIS AND OTHERS)**

1. Evidence of invasive disease on histopathology

AND

2. Positive culture

AND

3. One of the following:
   a) Compatible clinical syndrome consistent with signs and symptoms of pulmonary fungal infection.

OR

   b) Localized clinical syndrome in sinus, nose, orbit or ear consisting of any of the following: pain, headache, nasal or ear discharge, changes in vision or hearing, facial tenderness, ulceration or necrotic membrane in nose or face, perforation of tympanic membrane, ocular paralysis, otitis externa or media, or radiographic evidence of sinus opacity or bony erosion.

OR

14.3.3 Fungal Infections (cont'd)

c) Compatible clinical syndrome consistent with signs and symptoms of skin or soft tissue infection, osteomyelitis, cerebral abscess or meningitis or other organ disease.

32090P PROBABLE OTHER FUNGI

1. Compatible clinical syndrome

AND

2. Positive culture or smear from a non-sterile site

AND

3. Specific antifungal treatment initiated (or recommended).

32090C CONFIRMED OTHER FUNGI
(Including disseminated candidemia, invasive candidiasis)

1. Histologic evidence of invasive disease

AND

2. Positive culture or smear from a sterile tissue site

AND

3. Compatible clinical syndrome

14.3.4. Neoplastic Disease

36011P PROBABLE KAPOSI SARCOMA (KS) MUCOCUTANEOUS
36012P PROBABLE KAPOSI SARCOMA (KS) VISCERAL

1. Characteristic gross appearance of an erythematous or violaceous nodular or plaque like lesion on skin or mucous membranes or seen on endoscopy or bronchoscopy.

(Note: Probable diagnoses should not be made by inexperienced clinicians who have seen few cases. Photographs are strongly recommended in the absence of positive histopathology.
In equivocal cases, it may be important to exclude bacillary angiomatosis by:

- Special stains on biopsy, or
- A therapeutic trial with anti-Rochalimaea antibiotics, or
- Negative serology for *Rochalimaea henselae*)

36011C CONFIRMED KAPOSI SARCOMA (KS) MUCOCUTANEOUS
36012C CONFIRMED KAPOSI SARCOMA (KS) VISCERAL

1. Positive histopathology on tissue biopsy from any site or organ.

14.3.4 Neoplastic Disease (cont'd)

36020P PROBABLE PRIMARY CNS LYMPHOMA (PCL)

1. Neurologic signs with CD4 lymphocyte count < 100/mm^3

AND

2. Contrast enhancing mass lesion(s) on head CT/MRI scan

AND

3. Failure of clinical response to anti-toxoplasmosis therapy or other anti-infective chemotherapy (eg, tuberculosis, cryptococcosis)

AND

4. Lesion(s) become markedly reduced or disappear following high-dose glucocorticoid and/or radiation therapy

36020C CONFIRMED PRIMARY CNS LYMPHOMA (PCL)

1. Positive histopathology/cytology on tissue biopsy of brain or cerebrospinal fluid analysis

39920P PROBABLE CNS MASS LESION OF UNDETERMINED ETIOLOGY

1. Presence of mass lesion(s) on brain imaging study (CT or MRI).

AND

2. Patient does not meet all confirmed or probable criteria for other diagnosis with CNS mass lesion (eg, CNS Toxoplasmosis, CNS Lymphoma)

36025P PROBABLE CERVICAL CANCER

1. Positive Papanicolaou smear with a cervical intraepithelial neoplasia (CIN) grade III or greater

AND

2. Evidence of (malignant) local invasion of vagina, uterus, bladder, rectum, or peripelvic area by CT/MRI scan or bimanual pelvic exam according to the Bethesda grading scheme (1988)

36025C CONFIRMED CERVICAL CANCER

1. Positive histopathology of tissue biopsy and/or a histologic specimen from the cervix or uterus

36031C LYMPHOMA, N-H SMALL NON-CLEAVED
36032C LYMPHOMA, N-H IMMUNOBLASTIC
36033C LYMPHOMA, N-H LARGE CELL
36034C LYMPHOMA, N-H INDETERMINATE

14.3.4 Neoplastic Disease (cont'd)

CONFIRMED SYSTEMIC NON-HODGKIN LYMPHOMA (NHL)

Includes all B cell or indeterminate cell, intermediate to high-grade malignant lymphomas (e.g large cell, immunoblastic, small noncleaved, Burkitt or Burkitt's-like lymphoma)

Pathological/biopsy confirmation of NHL is mandatory in all cases.

1. Positive histopathology/biopsy/fine-needle aspiration on tissue biopsy sampling from any site or organ. (Note: bone marrow sampling can confirm diagnosis despite non-diagnostic biopsies from other sites.)

PROBABLE NON-HODGKIN LYMPHOMA (NHL)

There are no criteria for a probable diagnosis of NHL. Pathological/biopsy confirmation of NHL is mandatory in all cases

14.3.5. Bacterial infections

33011P **PROBABLE PULMONARY TUBERCULOSIS**

1. Clinical and diagnostic evidence of pulmonary TB: fever > 38°C, night sweats, cough, hemoptysis, weight loss, abnormal chest X-ray

AND

2. AFB positive smear from sputum or gastric aspirate

AND

3. Abnormal chest X-ray

AND

4. Specific antituberculin therapy initiated

33011C **CONFIRMED PULMONARY TUBERCULOSIS**

1. Positive culture of Mycobacterium tuberculosis from sputum, BAL or lung tissue.

33012P **PROBABLE EXTRAPULMONARY TUBERCULOSIS**

1. Positive AFB smear from extrapulmonary site(s).

AND

2. One or more of the following signs or symptoms consistent with a clinical syndrome for extrapulmonary TB: fever > 38°C, night sweats, malaise, anorexia

AND

3. Specific antituberculosis therapy initiated (or recommended).

14.3.5 Bacterial Infections (cont'd)

33012C **CONFIRMED EXTRAPULMONARY TUBERCULOSIS**

1. Positive culture for Mycobacterium tuberculosis from extrapulmonary site(s).

33020P **PROBABLE *MYCOBACTERIUM AVIUM* COMPLEX**

1. MAC cultured from bronchopulmonary, gastrointestinal, skin or other non-sterile site (as the only pathogen) coupled with histopathologic confirmation of AFB/MAC in tissue specimens from which the culture was derived.

AND

2. A clinical MAC syndrome consisting of one or more of the following: persistent fever $\geq$ 38°C for more than one week, night sweats, diarrhea, weight loss or wasting, radiographically documented pulmonary infiltrates, hepatomegaly, splenomegaly, anemia (hemoglobin < 8.5 gm/dL), and alkaline phosphatase elevated to greater than twice the upper limit of normal.

33020C **CONFIRMED *MYCOBACTERIUM AVIUM* COMPLEX**

1. MAC cultured from blood, bone marrow, lymph node, liver cerebrospinal fluid or other normally sterile body fluid, tissue or organ.

PROBABLE OTHER NON-TUBERCULOUS, NON-MAC MYCOBACTERIAL INFECTION:

33021P **M. Kansasii**
33022P **M. Genovensii**
33029P **Other non-MAC, non-TB, mycobacteria**

1. Other mycobacterial species cultured from bronchopulmonary, gastrointestinal, urine, skin or other non-sterile site.

AND

2. Clinical symptoms, signs, or radiograph/laboratory abnormalities compatible with mycobacterial infection consisting of one or more of the following: persistent fever $\geq$ 38°C for more than one week, night sweats, diarrhea, weight loss or wasting, radiographically documented pulmonary infiltrates, hepatomegaly, splenomegaly, hemoglobin < 8.5 gm/dL, and alkaline phosphatase elevated to greater than twice the upper limit of normal.

AND

3. No alternative pathogen(s) identified or symptoms/signs persist after treatment for and/or elimination of alternative pathogen(s).

AND

4. Treatment initiated or recommended for other non-tuberculous, non-MAC mycobacteria.

14.3.5 Bacterial Infections (cont'd)

CONFIRMED OTHER NON-TUBERCULOUS, NON-MAC MYCOBACTERIAL INFECTION:

33021C **M. Kansasii**
33022C **M. Genovensii**
33029C **Other non-MAC, non-TB, mycobacteria**

1. Other mycobacterial species cultured from blood, bone marrow, lymph node, liver, cerebrospinal fluid, or any other normally sterile body fluid, tissue or organ.

35209P **PROBABLE SEPSIS**

1. The presence of at least **one** of the following signs or symptoms: fever > 38°C, chills/rigors or hypotension (systolic pressure ≤ 90 mmHg)

AND

2. At least **one** of the following:
   a) Common skin flora (e.g diphtheroids, coagulase-negative staphylococci, *Bacillus* spp., *Propionibacterium* spp., or micrococci) cultured from at least one blood culture **and** appropriate antimicrobial therapy is instituted.
   b) Positive antigen test on blood (eg, *Hemophilus influenzae, Streptococcus pneumoniae, Neisseria meningitides* or Group B *Streptococcus*).

AND

3. Signs and symptoms and positive laboratory results are **not** related to an alternative etiology.

35209C **CONFIRMED SEPSIS**

NOTE: These criteria apply only to bloodstream infections that are **unrelated** to infection at another sites. See criteria for bacterial endocarditis and catheter-related sepsis as necessary.

Laboratory-confirmed bloodstream infection must meet at least **one** of the following criteria:

1. A recognized bacterial pathogen(s) isolated from one or more blood cultures

OR

2. Both:
   a) The presence of at least **one** of the following signs or symptoms: fever > 38°C, chills/rigors or hypotension (systolic pressure ≤ 90 mmHg)

AND

14.3.5 Bacterial Infections (cont'd)

b) Common skin flora (e.g diphtheroids, coagulase-negative staphylococci, *Bacillus* spp., *Propionibacterium* spp., or micrococci) isolated from two or more blood cultures drawn on separate occasions.

35210D PROBABLE CATHETER-RELATED BACTEREMIA/SEPSIS

1. The presence of at least **one** of the following signs or symptoms: fever > 38°C, chills/rigors or hypotension (systolic pressure ≤ 90 mmHg)

AND

2. Common skin flora (e.g diphtheroids, coagulase-negative staphylococci, *Bacillus* spp., *Propionibacterium* spp., or micrococci) isolated from two or more blood culture from a patient with an indwelling catheter

AND

3. Appropriate antimicrobial therapy is instituted.

35210C CONFIRMED CATHETER-RELATED BACTEREMIA/SEPSIS

1. Isolation of a known bacterial pathogens from a blood culture in a patient with an indwelling intravascular catheter **and** no other alternative site of infection

OR

2. Both:
   a) The presence of at least **one** of the following signs or symptoms: fever > 38°C, chills/rigors or hypotension (systolic pressure ≤ 90 mmHg)

AND

   b) Common skin flora (e.g diphtheroids, coagulase-negative staphylococci, *Bacillus* spp., *Propionibacterium* spp., or micrococci) isolated from two or more blood cultures drawn on separate occasions in a patient with an indwelling catheter **AND** no other alternative site of infection.

35211C CONFIRMED CATHETER EXIT SITE AND/OR TUNNEL INFECTION

1. Erythema, tenderness, induration and/or purulent drainage along the subcutaneous tract or at the skin exit site

AND

2. At least **one** of the following:
   a) Isolation of a bacterial pathogen(s) from the exit site, tunnel and/or catheter tip
   b) initiation of antibacterial therapy to treat the catheter exit site and/or tunnel infection

PROBABLE CATHETER EXIT SITE AND/OR TUNNEL INFECTION

There is no definition.

14.3.5 Bacterial Infections (cont'd)

35109P PROBABLE BACTERIAL PNEUMONIA

1. Chest radiographic examination shows new or progressive infiltrate, consolidation or cavitation.

AND

2. At least **one** of the following:

a. Fever and/or cough

b. New onset of purulent sputum or change in character of sputum

c. Appropriately collected (acute and convalescent) serologic tests positive for *Legionella*, *Chlamydia* or *Mycoplasma* and no other pathogen identified.

AND

3. Appropriate antibacterial therapy initiated.

35109C CONFIRMED BACTERIAL PNEUMONIA

1. Chest radiographic examination shows new or progressive infiltrate, consolidation or cavitation

AND

2. At least **one** of the following:

a) Bacterial organism(s) cultured from blood with **no alternative site of infection**

b) Isolation of a bacterial pathogen(s) from a culture specimen obtained by transtracheal aspirate, protected bronchial brushing, or biopsy.

c) Histopathologic evidence of pneumonia with bacterial organism(s) demonstrated by Grams stain or culture of tissue specimen **or** positive Quellung for pneumococcus

d) Demonstration of a predominant bacterial organism through positive culture or gram stain of an adequate sputum specimen (fewer than 10 epithelial cells and greater than 25 PMNs per high power field).

e) Fluorescent antibody or other antigen detection method positive for *Legionella*, *Chlamydia* or *Mycoplasma* spp and no other pathogen identified.

35309P PROBABLE BACTERIAL ENDOCARDITIS

1. Persistently positive blood cultures (at least two blood cultures obtained on separate occasions, with either two of two positive cultures, three of three positive cultures, or at least 70% of cultures positive, if four or more cultures of blood were obtained).

AND

2. At least **one** of the following:

a) New murmur by physical examination

b) Echocardiographic (or other imaging procedure) demonstration of valvular vegetation(s)

c) Vascular stigmata of endocarditis (eg, petechiae, splinter hemorrhages,

14.3.5 Bacterial Infections (cont'd)

conjunctival hemorrhages, Roth spots, Osler's nodes, Janeway lesions, hematuria with active urine sediment consistent with glomerulonephritis, or embolic phenomena)

d) Pulmonary embolic phenomena

OR

1. Negative or intermittently positive blood cultures

AND

2. At least **three** of the following:
   a) Fever > 38°C
   b) New murmur by physical examination
   c) Vascular stigmata of endocarditis (eg, petechiae, splinted hemorrhages, conjunctival hemorrhages, Roth spots, Osler's nodes, Janeway lesions, hematuria with active urine sediment consistent with glomerulonephritis, or embolic phenomena)
   d) Echocardiographic (or other imaging procedure) demonstration of valvular vegetation(s)
   e) Demonstration of a bacterial pathogen(s) by Gram's stain, other histologic stain or culture of peripheral embolus obtained from surgery
   f) Pulmonary embolic phenomena

AND

3. Specific antibacterial therapy initiated or recommended.

35309C CONFIRMED BACTERIAL ENDOCARDITIS

1. Persistently positive blood cultures (at least two blood cultures obtained on separate occasions, with either two of two positive cultures, three of three positive cultures, or at least 70% of cultures positive, if four or more cultures of blood were obtained)

AND

2. Demonstration of a bacterial pathogen(s) by Gram's stain, other histologic stain or culture of valvular vegetation or endocardial tissue

35409P PROBABLE BACTERIAL INFECTION OF DEEP TISSUE, BODY CAVITY OR OTHER NORMALLY STERILE SITE

1. Evidence of a deep tissue, body cavity or normally sterile site focus of infection (eg, abscess, inflammatory fluid collection, enhanced mass lesion, radioisotope uptake, etc) by appropriate diagnostic sampling or imaging procedure (fluid aspiration, biopsy, computerized tomography, ultrasonography, magnetic resonance imaging, radioisotope scanning, plain radiograph).

AND

14.3.5 Bacterial Infections (cont'd)

2. At least **one** of the following:
   a) Isolation of a known bacterial pathogen(s) from a blood culture with **no** culture or negative culture of specimen(s) obtained from involved deep tissue or body cavity site and **no alternative site of infection**
   b) Isolation of common skin flora (e.g diphtheroids, coagulase-negative staphylococci, *Bacillus* spp., *Propionibacterium* spp., or micrococci) from two or more blood cultures with **no** culture or negative culture of specimens(s) obtained from involved deep tissue or body cavity site and **no alternative site of infection**
   c) Clinical signs and symptoms compatible with the site of infection documented by diagnostic sampling or imaging procedures **AND** response to antibacterial therapy demonstrated by improvement in clinical signs and symptoms **and** documented by followup diagnostic sampling or imaging procedure of focus of infection.

35509P PROBABLE BACTERIAL GASTROENTERITIS/DIARRHEA

1. At least **two** of the following:
   a) Two or more non-formed stools per day for two or more days
   b) Nausea, vomiting, abdominal pain or abdominal cramping
   c) Presence of WBC on a methylene blue stain of a stool sample
   d) Ulcerative or other inflammatory lesion of the gastrointestinal mucosa demonstrated by appropriate diagnostic imaging (eg, endoscopy)
   e) Fever > 38°C

AND

2. Isolation of a bacterial pathogen(s) from one or more blood cultures with **no** or negative stool or tissue culture and with **no** other alternative focus of infection.

AND

3. Specific antibacterial therapy initiated.

35509C CONFIRMED BACTERIAL GASTROENTERITIS/DIARRHEA

1. At least **one** of the following symptoms:
   a) Two or more non-formed stools per day for two or more days
   b) Nausea, vomiting, abdominal pain or abdominal cramping
   c) Presence of WBC in stool samples
   d) Ulcerative or other inflammatory lesion of the gastrointestinal mucosa demonstrated by appropriate diagnostic imaging (eg, endoscopy)

AND

14.3.5 Bacterial Infections (cont'd)

2. One of the following:
   a) Isolation of a bacterial pathogen(s) from a stool culture
   b) demonstration of a bacterial antigen/toxin in stool by appropriate microbiologic assay (eg, *Clostridium difficile*)
   c) recovery of a bacterial pathogen(s) in histopathologic tissue obtained from the gastrointestinal tract
   d) Isolation of salmonella from blood

35609P PROBABLE BACTERIAL SINUSITIS

1. At least two of the following symptoms and signs of sinusitis with **NO** other focus of infection:
   a) Fever > 38°C
   b) Postnasal drainage
   c) Facial pain or tenderness

AND

2. No sinus radiograph obtained (or performed).

AND

3. Improvement of presenting signs or symptoms in response to antimicrobial therapy.

OR

1. At least **one** of the following symptoms and signs of sinusitis with **NO** other focus of infection:
   a) Fever > 38°C
   b) Postnasal drainage
   c) Facial pain or tenderness

AND

2. Either:
   a) Radiographic abnormality of one or more sinuses as depicted by plain radiograph, CT or MRI scans

OR

   b) Demonstration of PMNs and bacterial organism(s) on Gram's stain (or other microbial staining technique) from specimens obtained by drainage procedure(s) of involved sinus(es).

AND

3. Improvement of presenting signs or symptoms in response to antimicrobial therapy.

14.3.5 Bacterial Infections (cont'd)

35609C CONFIRMED BACTERIAL SINUSITIS

1. At least one of the following symptoms and signs:
   a) Fever > 38°C
   b) postnasal drainage
   c) facial pain or tenderness

AND

2. Radiographic abnormality of one or more sinuses as depicted by plain radiograph, CT or MRI scan

AND

3. Either:
   a) Isolation of a bacterial pathogen(s) from specimens obtained by drainage procedure(s) of involved sinus(es)

   OR

   b) Isolation of a bacterial pathogen(s) from one or more blood cultures with **no** or negative cultures of specimen(s) obtained by drainage procedure(s) of involved sinus(es) and **no** other focus of infection.

14.3.6. HIV associated disease

37017P PROBABLE HIV-ASSOCIATED MYOPATHY

1. Symptoms of weakness in proximal muscles (thighs, shoulders, or upper arms) with evidence of proximal weakness on physical examination.

AND

2. CPK elevated to greater than twice normal (no EMG, physical trauma, or IM injection within 2 weeks).

AND

3. ZDV muscle toxicity excluded either by no history of ZDV in immediately preceding three months or drug holiday from ZDV for at least one month with no improvement in signs, symptoms or CPK elevation.

37017C CONFIRMED HIV-ASSOCIATED MYOPATHY

1. Symptoms of pain, burning, numbness, or tingling discomfort in **both** feet, or feet and hands, for at least 2 weeks. No history of diabetes mellitus, chemotherapy, or vitamin B_{12} deficiency.

AND

2. Examination show at least 2 of the following abnormalities:
   a) Diminished or absent ankle reflexes,
   b) Diminution of vibration sensation in the toes,
   c) Disturbance in pain or temperature sensation.

AND

14.3.6 HIV Associated Disease (cont'd)

3. Exclusion of nerve toxicity from ddI, ddC, d4T either by history (no ddI, ddC, or d4T in immediately preceding 3 months) or by drug holiday off these medications at least 1 month.

37027P PROBABLE SENSORY NEUROPATHY

1. Symptoms of pain, burning, numbness, or tingling discomfort in **both** feet, or feet and hands, for at least 2 weeks. No history of diabetes mellitus, chemotherapy, or vitamin B_{12} deficiency.

AND

2. Examination show at least 2 of the following abnormalities:
   a) Diminished or absent ankle reflexes,
   b) Diminution of vibration sensation in the toes,
   c) Disturbance in pain or temperature sensation.

AND

3. Exclusion of nerve toxicity from ddI, ddC, d4T either by history (no ddI, ddC, or d4T in immediately preceding 3 months) or by drug holiday off these medications at least 1 month.

37027C CONFIRMED SENSORY NEUROPATHY

1. Symptoms of pain, burning, numbness, or tingling discomfort in **both** feet, or both feet and hands, for at least 2 weeks. No history of diabetes mellitus, chemotherapy, or vitamin B_{12} deficiency.

AND

2. Examination show at least 2 of the following abnormalities:
   a) Diminished or absent ankle reflexes,
   b) Diminution of vibration sensation in the toes,
   c) Disturbance in pain or temperature sensation.

AND

3. Exclusion of nerve toxicity from ddI, ddC, d4T either by history (no ddI, ddC, or d4T for in immediately preceding three months) or by drug holiday off these medications at least 1 month.

AND

4. Electrodiagnostic confirmation by either:
   a) Abnormal nerve conduction tests

OR

   b) Quantitative sensory testing (Vibratron CASE IV or equivalent)

37037P PROBABLE HIV-ASSOCIATED DEMENTIA

1. Acquired cognitive/motor dysfunction for at least 1 month causing impairment of work or activities of daily living (verifiable by report of a key informant), not attributable solely to severe systemic illness.

14.3.6 HIV Associated Disease (cont'd)

AND

2. Examination abnormalities from at least two of the following categories:
   a) Motor abnormality: For example, slowed rapid movements, release signs, abnormal gait, limb incoordination, diffuse hyperreflexia, hypertonia, or weakness.
   b) Behavioral abnormality: For example, change in personality with apathy, inertia, irritability, emotional lability or new onset of impaired judgement characterized by socially inappropriate behavior or disinhibition.
   c) Cognitive abnormalities: For example, abnormality in at least two separate cognitive/motor abilities. Appropriate instruments, ACTG micro, ACTG macro or other neuropsych batteries with interpretation of abnormality or decline by ACTG neuro/neuropsychologist.

BUT

3. Tests to exclude other etiology (active CNS opportunistic infections or malignancy, active psychiatric disorders, active alcohol or substance use or substance withdrawal) not completed or not available.

37037C CONFIRMED HIV-ASSOCIATED DEMENTIA

1. Acquired cognitive/motor dysfunction for at least 1 month causing impairment of work or activities of daily living (verifiable by report of a key informant), not attributable solely to severe systemic illness.

AND

2. Examination abnormalities from at least two of the following categories:
   a) Motor abnormality: For example, slowed rapid movements, release signs, abnormal gait, limb incoordination, diffuse hyperreflexia, hypertonia, or weakness.
   b) Behavioral abnormality: For example, change in personality with apathy, inertia, irritability, emotional lability or new onset of impaired judgement characterized by socially inappropriate behavior or disinhibition.
   c) Cognitive abnormalities: For example, abnormality in at least two separate cognitive/motor abilities. Appropriate instruments, ACTG micro, ACTG macro or other neuropsych batteries with interpretation of abnormality or decline by ACTG neuro/neuropsychologist.

AND

3. No other etiology confirmed by MRI/CT scan, negative serum/CSF cryptococcal antigen: excludes active CNS opportunistic infections or malignancy, active psychiatric disorders, active alcohol or substance use or substance withdrawal.

14.3.6 HIV Associated Disease (cont'd)

37047P **HIV WASTING SYNDROME**

1. Profound involuntary weight loss > 10% baseline body

AND

2. Chronic diarrhea (≥ 2 stools per day ≥ days)

OR

Chronic weakness and documented fever (≥ 30 days intermittent or constant) in the absence of a concurrent illness or condition other than HIV infection that could explain the findings (eg. cancer, tuberculosis, cryptosporidiosis other specific enteritis)

37057C **HIV INFECTION with CD4+ T-lymphocyte counts <200/µl**

CD4+ T-lymphocyte counts of < 200/µl or CD4+ percentage of < 14%

99999 **Other**

Any other diagnosis not specified or described in this list

14.4. Karnofsky performance scale

Able to carry on normal activities: no special care needed	100	Normal; no complaints; no evidence of disease
	90	Able to carry out normal activity; minor signs or symptoms of disease
	80	Normal activity with effort; some signs or symptoms of disease
Unable to work; able to live at home and care for most personal needs; a varying amount of assistance is needed.	70	Cares for self; unable to carry on activity or to do active work
	60	Requires occasional assistance but is able to care for most needs
	50	Requires considerable assistance and frequent medical care
Unable to care for self; requires equivalents of institutional or hospital care; disease may be progressing rapidly	40	Disabled; requires special care and assistance
	30	Severely disabled; hospitalization is indicated although death is not imminent
	20	Very sick; hospitalization necessary; active support treatment is necessary
	10	Moribund; fatal processes progressing rapidly
	0	Dead

14.5. CDC reference list of AIDS-defining diseases

- **candidiasis** of the esophagus, trachea, bronchi or lungs
- **cervical cancer** invasive
- **coccidioidomycosis**, disseminated or extrapulmonary
- **cryptococcosis**, extrapulmonary
- **cryptosporidiosis,** chronic intestinal for longer than 1 month
- **cytomegalovirus** disease of an organ other than liver, spleen, or lymph nodes
- **cytomegalovirus retinitis** (with loss of vision)

- **herpes simplex virus** infection causing a mucocutaneous ulcer persisting more than one month, or bronchitis, pneumonitis, or esophagitis
- **histoplasmosis**, disseminated or extrapulmonary
- **HIV encephalopathy**
- **HIV**, infection with CD4+ count less than 200 cells/mm^3
- **HIV wasting syndrome**
- **isosporiasis** chronic intestinal > 1 month duration

- **Kaposi's sarcoma**
- **lymphoma Burkitt's** (or equivalent term)
- **lymphoma immunoblastic** (or equivalent term)
- **lymphoma of the brain**, primary
- **Mycobacterium tuberculosis**, any site pulmonary or extrapulmonary
- **mycobacterium** other species or unidentified species ? or extrapulmonary

- **Pneumocystis carinii** pneumonia
- **pneumonia**, recurrent
- **progressive multifocal leukoencephalopathy**
- **Salmonella** septicemia, recurrent
- **toxoplasmosis** of the brain
- **tuberculosis**

[1] Centers for Disease Control. Revision of the CDC Surveillance Case Definition for Acquired Immunodeficiency Syndrome. MMWR 36(1S):4S-6S, 1987, updated 1992

14.6. Film Photography

As stated in LSOCA PPM 119 (dated 22, January 2008), LSOCA transitioned from film to digital fundus photography. The following procedures were used for processing film images.

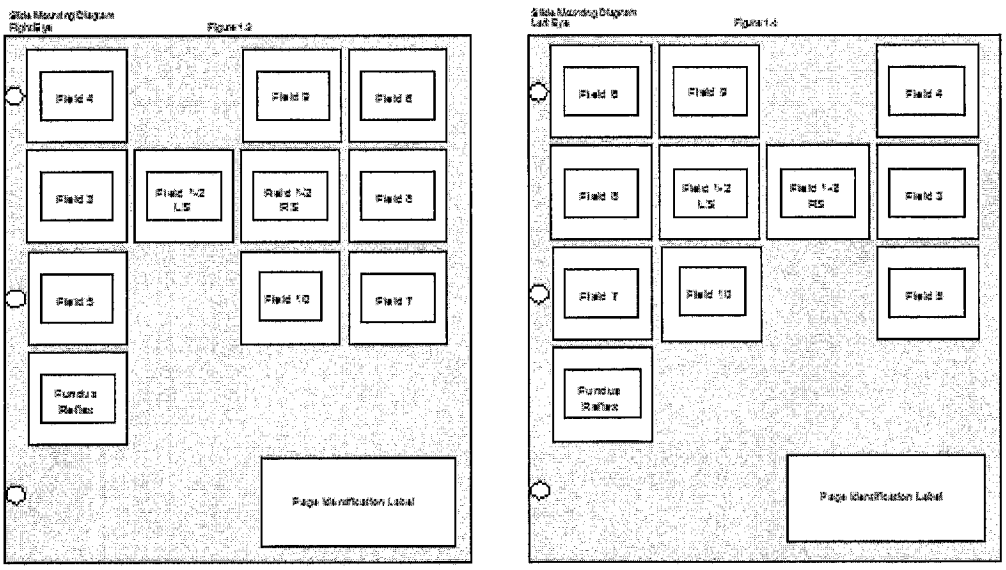
14.6.1. Film and Processing

For color photography, the recommended films are Kodak Professional Ektachrome 100 Daylight films (EPN, EPP or E100G), Fuji (Provia and Velvia) or their equivalent at 100 ISO. If possible the film should be processed by a certified "Q-Lab" or other professional E-6 laboratory to ensure consistent quality. Kodak Kodachrome 64 Daylight film, processed by any authorized Kodalux Laboratory is also acceptable. It is important that the processor correctly number the slide mounts to make slide sorting more accurate and easier. If sites are finding it difficult to process the color film a lab located in Madison Wisconsin processes E-6 on a daily basis. The company is Burne Photo Imaging, Inc., (608) 277-0802, barry@burne.com. They are a "Q-Lab" and have been processing film for clients throughout the country for years.

14.6.2. Mounting and Labeling of Color Film Photographs

The transparencies returned from the processing lab are mounted in standard 2X2 inch mounts. Do not use mounts with glass slides. The mounted transparencies are labeled with individual labels **(see SOCA General Handbook &. Fundus photography protocol document) for slide labeling instructions.**

Photographs of each eye should be mounted in an individual plastic sheet. The plastic sheets should be constructed so that the pockets open at the side rather than at the top; that is, the open side of the left pocket should face the open side of the right pocket. A sheet identification label is completed and attached to the front of each plastic sheet (see Illustration below).



Slide Mounting Diagram

Photographs submitted in frosted plastic pages or thin "archival" plastics may be returned to the site for remounting.

It is suggested, but not required, that duplicates of the photographs be retained at the clinical center for patient management.

14.7. Satellite clinic guidelines

A satellite clinic is one that participates in SOCA studies via an association with a SOCA clinic (sponsor clinic). A satellite clinic must fulfill all certification requirements before enrolling patients into a study. Once certified, satellite clinics must comply with established SOCA procedures for submitting and editing data, conduct the trial according to IRB and FDA regulations, and comply with data monitoring activities. Satellite clinic personnel will have the same rights and responsibilities of any other member of SOCA including acknowledgment in publications.

A satellite clinic will be considered if:

- The sponsor clinic has demonstrated the capability to effectively manage its own clinical trials and has met all minimum performance standards
- The sponsor clinic has the appropriate staff and time to provide liaison and monitoring of the subunits
- The additional resource requirements for managing another subunit will not have a negative impact on the current activities of the sponsor clinic.

Fiscal

All funds for SOCA activities will be forwarded to the sponsor clinic. The sponsor clinic will in turn establish an agreement with the a satellite clinic and funds will flow through the sponsor clinic to the satellite. The same per patient funding will be distributed for patients enrolled at the satellite clinic as at all other sites. There will be no additional travel funds allotted for the satellite clinics.

Sponsor clinic responsibilities

The sponsor clinic must submit in writing a rationale and justification for adding a satellite clinic. The sponsor clinic will be partially responsible for training, certification and monitoring of the satellite clinic, as well as its performance. The Coordinating Center (CC) will work with the sponsor clinic to train and certify the staff at the satellite clinic, and to monitor SOCA activities at that site. The sponsor is responsible for establishing a financial agreement with the clinic and for managing funds for the satellite. The sponsor clinic is responsible for managing administrative and personnel issues that arise between the sponsor and satellite clinics. The satellite clinics performance will reflect upon the overall performance rating of the sponsor.

Coordinating Center responsibilities

The CC will assist the sponsor clinic staff in training and certifying the satellite clinic staff. The CC will take responsibility for monitoring certification requirements and data submission and quality, and will conduct site visits to the satellite clinic. A member of the sponsor clinic staff, usually the center director or coordinator, is expected to participate in site visits to the satellite clinic.

Letter of intent

The sponsor clinic director should submit a letter to the SOCA Study Officers requesting permission to establish a satellite clinic. The letter should be signed by the director and coordinator of the SOCA clinic sponsoring the satellite and personnel at the satellite site who will be conducting the study, namely an ophthalmologist, an internist, a coordinator and a photographer. The letter should include a list of the required equipment at satellite clinic (i.e., type of fundus camera, facilities and equipment for visual acuity evaluations, and perimeter for visual field evaluations).

It should also describe facilities for drug handling and pharmacist responsibilities should the need arise for investigational drug use.

The CC, sponsor and satellite will send a letter of notification of satellite arrangements, once established, to the NEI.

Certification requirements for satellite clinics (same as for sponsor clinic)

Personnel: Primary and backup personnel are required for the following positions: ophthalmologist, infectious disease specialist, clinic coordinator, visual function examiner (for acuity and field assessments), and photographer; in addition many clinics have a study nurse. Clinical trials may require additional personnel including pharmacists, laboratory personnel and surgeons. Personnel at the sponsoring clinic may serve as backup for satellite clinic personnel, and vice versa. Backup personnel must be willing and able to fill in for the primary personnel. The sponsor clinic should ensure that satellite clinic staff include no one presently disbarred from participation in NIH funded activities.

Clinic personnel (i.e., ophthalmologist, coordinator, internist, and visual function examiner) read the study protocol, review assessment and data collection procedures, and must submit to the CC one completed practice form set. Practice forms should record data from a patient with CMV retinitis seen at the clinic.

- **Photographer certification:** Two sets of photographs taken according to the SOCA photography protocol must be submitted to the SOCA Fundus Photograph Reading Center at University of Wisconsin for certification.
- **Surgeon certification (clinical trials only):** Video of surgeon performing an implant procedure according to the SOCA guidelines must be submitted to the SOCA Surgical Quality Assurance Committee (SQAC).
- **Visual function examiners certification:** Visual function examiners must become familiar with the protocols for vision assessment, i.e., visual acuity, refraction, visual field, cataract grading and contrast sensitivity. Examiners must demonstrate to a member of the Visual Function Quality Assurance Committee (VFQAC) the ability to perform the assessment(s) according to the protocol(s).

- **Equipment and facilities**: Facilities needed to conduct the SOCA studies include clinical facilities for ophthalmic, visual function, and medical examinations, facilities for treatment administration (if applicable), laboratory facilities for processing and shipment of biologic specimens, and/or facilities for the storage and handling of investigational drugs (if applicable).

The following equipment is required: a wide angle fundus camera (e.g., Canon 60° or TopCon 50°), ETDRS eye charts 1, 2, and R, Contrast Sensitivity charts, visual acuity exam lanes 10 feet or 4 meters in length with appropriate lighting, a light meter (hand held GE model 217), a Goldmann perimeter, and a Humphrey Field Analyzer. Additional equipment or facilities may be required in the future.

Approvals and documentation: Review by an Institutional Review Board (IRB) that meets Federal Regulations including IRB approval of the current protocol and consent statement. Conflict of interest statements from the director and other personnel must be filed for each trial.

Communication

A satellite clinic will be added to the SOCA clinical center mailing list when the clinic is certified. Before that time, the sponsor clinic is responsible for providing the satellite clinic with copies of correspondence to clinics. A satellite clinic will receive separate data status reports, data quality queries reports, and protocol deviation memoranda. A copy of these reports will be sent to the sponsor clinic. The SOCA CC will provide the satellite clinic with copies of materials needed to complete the certification process, e.g., protocol, forms book, handbooks. Satellite clinic personnel are responsible for addressing queries regarding the conduct of SOCA studies at their clinic to either their sponsor clinic or the CC.

Meetings and site visits

Satellite clinics should send two representatives, usually the clinic director and coordinator, to each meeting of the SOCA Research Group. No additional funds are available for travel other than those provided in the sponsor clinics' budget. Sponsor clinic staff should be available to participate in site visits to the satellite clinic made by CC staff and participate in conference telephone calls.

Timeline

It is the responsibility of the satellite clinic to complete the requirements for certification within the 6 month period. The initial six month period after certification is considered a probationary period.

Termination

If the sponsor clinic staff are unable to provide appropriate monitoring or if the sponsor or satellite site, for any reason, fail to meet minimum performance standards, permission for a satellite to participate may be withdrawn.

14.8. Abbreviated SOCA Chronology

Date	Trial / Trial / SOCA	Clinic / Committee / Group	Notes
04Oct89	FGCRT	IRB	CC approval of FGCRT
13Mar90	FGCRT	NU	1st patient enrolled in trial phase
28Jun90	SOCA	ERC	Central drug distribution opened
27Sep91	FGCRT	FDA	Foscarnet approved
07Oct91	FGCRT	PDMB	Meeting (Baltimore) recommendation to suspend treatment
11Oct91	FGCRT	CC	Notification to patients of suspension of treatment protocol; deadline of 18Oct91
17Oct91	FGCRT	NEI	Clinical alert distributed
21Oct91	FGCRT	NEI	Press release/Press conference (Bethesda)
13Nov91	FGCRT	FDA	Mortality results presented to FDA Antiviral advisory board 19Nov91 mortality results presented to NIH AIDS program advisory board
23Jan92	FGCRT		Publication of mortality paper (NEJM 1992;326:313-20)
18May92	CRRT	IRB	Submission of protocol (version 1.0) to JHU
18Aug92	SOCA		ACTG OI core committee review and approve CRRT, assigned protocol #228
27Aug92	CRRT	IRB	CC approval
16Oct92	FGCRT		Data collection - closed
04Dec92	CRRT	RG	Trial opens (PPM 8)
17Dec92	CRRT	LSU	1st patient enrolled
21Apr94	HPCRT	UM	First patient enrolled
03Aug94	HPCRT	RG	Moratorium on enrollment; clinics notified of carcinogenic effects in rat study
21Oct94	HPCRT	Gilead	Moratorium lifted (per notification from Gilead)
05Jan95	MACRT	IRB	JHU IRB (CC) approve protocol
28Apr95	MACRT	RG	Protocol (dated 26 April 95, version 1) distributed
06Mar96	HPCRT	IRB	Treatment protocol suspended; termination of HPCRT enrollment
16Aug96	MACRT	Gilead	Notified of termination of enrollment
03Sep96	HPCRT		Primary results paper sent to Ann Int Med for review
29Oct96	HPCRT	WC	Main results paper accepted for publication in Ann Int Med

14.8. Abbreviated SOCA Chronology

Date	Trial / Trial / SOCA	Clinic / Committee / Group	Notes
02Sep97	SOCA	CC / CO	Submission of competitive renewal
28Apr00	GCCRT	RG	GCCRT closed; clinics notified by PPM 44
Fall01	LSOCA	WC	Submission of Mortality paper to JAMA
26Feb02	LSOCA	CC	Specimen Banking and Use Statement added to Consent/Assent Form
01Sep02	LSOCA	CC	Competitive Grant application submitted to NEI
Nov-Dec 02	LSOCA	CC	Website configured; files loaded to server and programs tested
01Jun03	LSOCA	RG	Clinics to start web-based data entry
25Aug03	LSOCA	CC	NGA for continued funding (2003-2008)
07Mar07	LSOCA	CO	Relocation of LSOCA Chairman's Office to MSMC
01May07	LSOCA	LSOC	CC LSOCA 5 -year competitive renewal due date
10Aug07	LSOCA	CC	Jennifer Thorne designated LSOCA Deputy Director
28Jul08	LSOCA	CC	NGA for continued funding (2008-2013)
01Jan08	LSOCA	CC	Merger of Fisher Clinical Services with Cryonix
22Jan08	LSOCA	FPRC	Start of transition to digital photogrply
28Jul08	LSOCA	CC/CO	Notice of Grant award from NEI for continued funding 2008-2013
31Jul08	LSOCA		IU, USC discontinuation of LSOCA funding (closeout complete cessation of contract)
14Aug08	LSOCA	CO	Relocation of LSOCA Chair's Office to MSSM
28Sep08	LSOCA	RG	Implementation of lens grading (AREDS)
31Jan09	LSOCA		RUSH, NJMS, UCI discontinuation of LSOCA funding (closeout complete cessation of contract)
23Apr09	LSOCA	PDMB	Resignation of A. Hillis
02Jul09	LSOCA	PDMB	D. Musch to replace A. Hillis
02Jul09	LSOCA		UTMB discontinuation of LSOCA funding (closeout complete cessation of contract)
10Aug09	LSOCA	RG	LSOCA accepted into NA-ACCORD
02Sep09	LSOCA	PDMB	Resignation of H. Smith
17Dec09	LSOCA	UCSD	Igor Kazak replaces W. Freeman AS PI
20Jan10	LSOCA	RG	Transition from film to digital images for fundus photography

14.8. Abbreviated SOCA Chronology

Date	Trial / Trial / SOCA	Clinic / Committee / Group	Notes
20Jan10	LSOCA	RG	Enrollment quota lifted for all patients
27Jan10	LSOCA	PDMB	L. Wolf replaces H. Smith
8-12Feb10	LSOCA	CC	Coordinating Center closed due to blizzard
31Oct11	LSOCA	NEI	Steve Oversby replaces N. Kurinij as LSOCA Project Officer
25Sep12	LSOCA	CC	LSOCA competitive renewal application submitted
31Dec12	LSOCA	NEI	N. Kurinij retires as PO (LSOCA)
31Jan13	LSOCA	NEI	Review of competitive renewal application

14.9. Applications for new SOCA clinical center

A letter should be submitted to the Coordinating Center indicating an interest in joining the SOCA Research Group. All applications will be evaluated by the Study Officers. The letter should include the following information:

- Description of site, location and affiliation
- Summary of facilities and equipment necessary to perform procedures per SOCA protocol
- Description of patient population, number of CMV retinitis cases currently being followed, and number of new CMV retinitis cases seen in the previous year
- Experience in the conduct of multi-center clinical trials or prospective epidemiologic cohort studies
- Listing of prior experience in clinical CMV research
- Listing of ongoing CMV retinitis studies at your institution

14.10. Randomization (applicable to clinical trials only)

Principles

- Randomization scheme is designed and administered by Coordinating Center
- A documented generation scheme that produces a reproducible order of assignment is used
- Assignments are not released until eligibility is determined, consent and assent obtained, and required baseline data collected and recorded
- For trials with masked treatment design, assignments are released in masked fashion and in a manner consistent with masked administration of assigned treatments
- Future assignments are not predictable from past assignments
- Once an assignment is revealed, patient is counted as enrolled
- Time at which assignment is revealed designates end of the baseline data collection phase, and start of the followup and treatment administration data collection phases

Procedures

- Fax a completed Eligibility Review (ER) form to the Coordinating Center (CC)
- The CC will call the clinic to confirm the patient's ID#, patient's name code, eligibility data, and that baseline data and a consent statement have been obtained
- All baseline procedures, with the exception of those requiring data from special laboratory tests, should be completed before randomization. Specimens for laboratory tests should be collected before the treatment assignment is revealed.
- Treatment assignment is faxed (or mailed) from the Coordinating Center to the clinic
- Once the fax is sent from the CC (or the envelope is opened and the treatment assignment is revealed) the patient is counted as enrolled. Data from the patient will be analyzed by assigned treatment group regardless of the subsequent course of treatment or the willingness of the patient to take the assigned treatment
- Original copy of treatment assignment, visit time windows, fundus photography, and specimen labels are mailed from the Coordinating Center to the clinic by Federal Express

14.10. Randomization

Contingency

- If there are any indications that a patient may not agree to participate or that eligibility or baseline data are incomplete, the treatment assignment is not faxed. The treatment assignment is placed in a sealed envelope and mailed to the clinic with instructions to open only when final eligibility is determined.
- If a patient proves to be ineligible, unwilling, or unable to enter the trial, return the unopened treatment assigned envelope to CC with a written explanation
- If the wrong assignment was disclosed, the assignment will stand as issued once it is disclosed to the patient
- If a randomized patient is found to have been ineligible, the Coordinating Center will inform the Principal Investigator; improperly randomized patient should be treated according to Study Officers' recommendation and appropriate medical care guidelines

14.11. National Institute of Allergy and Infection Disease

Responsibilities

- Participate in protocol development
- Serve as a member of the RG, PDMB, JC

Staff

- Medical Officer
- Protocol Specialist
- JC Members

14.12. Surgical Quality Assurance Committee (SQAC)

Composition*

- Chairman
- Ophthalmologists (4)
- Members of CC (2)

Responsibilities

- Create guidelines for implantation and replacement of ganciclovir intraocular device
- Conduct training sessions for surgeons
- Oversee certification of ophthalmic surgeons
- Develop definitions and reporting requirements for ocular disease adverse events

Meeting schedule

- As needed

Meeting assignments

- Arrangements (Chairman's Office)
- Materials (Coordinating Center)
- Minutes (not taken)

*Refer to SOCA Directory for list of current members

14.13. SOCA-ACTG Joint Committee (JC)

Composition*

- ACTG, Chairman of Viral Pathogens Study Group
- ACTG, Chairman of Opportunistic Infections (OI) Committee
- SOCA, Chairman
- SOCA, Coordinating Center Director
- SOCA, Coordinating Center Deputy Director
- SOCA, Fundus Photograph Reading Center Director
- NEI, Representative
- CAB, Representative
- NIAID, Division of AIDS, Treatment Research Operations Program (Associate Director)
- NIAID, Division of AIDS, Medical Branch, Clinical Research Program (Chief)
- ACTG Clinical Events Working Group

Responsibilities

- Discussion of design issues
- Coordinate SOCA and ACTG activities

Meeting schedule

- Two times per year
- Additional meetings as needed

Meeting assignments

- Arrangements (Chairman's Office)
- Materials (Chairman's Office)
- Minutes
  - Preparation (Chairman's Office)
  - Review (SOCA - ACTG Joint Committee)
  - Distribution (Chairman's Office)
  - Archive (Coordinating Center)

14.14. Community Advisory Board (CAB)

Composition

- SOCA Study Officers (4)
- Representatives of AIDS community groups

Responsibilities

- Review study progress
- Review new studies and new directions

Meeting schedule

- Twice a year