Longitudinal Study of Ocular Complications of AIDS (LSOCA)

Handbook (Version 8.0)

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LSOCA Handbook Version 8.0

History

Version 1.0 (20 August 1998): distributed to clinical center

Version 2.0 (9 September 1998): Handbook revised and distributed to clinical centers
- 4.17 Specimen collection, processing and storage revised to specify a lesser amount of blood to be collected; and illustrations of specimen tube/labels added
- 4.18 Specimen shipment and tracking procedures added

Version 3.0 (23 March 1999): Numerous minor changes made please refer to LSOCA PPM#9 for details

Version 4.0 (5 January 2000): Adverse event information (forms and collection) deleted

Version 5.0 (14 April 2005): Specimen collection procedures for cell viability testing and diagnostic specimen shipping procedures

Version 6.0 (6 March 2006): New procedures/forms: Five year fundus photographs; blood pressure measurement; Antiretroviral Treatment History; Cardiovascular/Cerebrovascular Risk Profile; Cardiovascular/Cerebrovascular Events; extended time window (data window); ANC calculations, etc

Version 7.0 (2 February 2007): Revised Visual Acuity/Refraction procedures; Humphrey Automated Perimetry procedures, and Specimen Shipment & Tracking Procedures. Digital Color Imaging procedures added.

Version 8.0 (30 June 2009): Increased upper limit of enrollment from 2,300 to 2,800 patients; revised eligibility criteria to include enrollment of patients diagnosed with AIDS on or after 1 Jan 2001 or patients with newly diagnosed ocular opportunistic infections; revised patient visit schedule to every 6 months for all patients, and changed the nomenclature form MOC/NoMOC to OOI/No OOI. Added following procedures: Cataract grading; Digital Fundus photography; Contrast sensitivity, and Visual Function Questionnaire.

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Contents

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1.Design

1.1. Design summary

Type of study

- Prospective, observational study
- Multicenter
- Sample size: approximately 2,800 patients

Inclusion criteria

- Diagnosis of AIDS according to the 1993 CDC diagnostic criteria (with or without clinical symptoms of CMV retinitis or other ocular complications of AIDS)
- Patients diagnosed with AIDS on or after 1 January 2001; or patients with newly diagnosed (within 45 days of enrollment) Ocular Opportunistic Infection (OOI)
- Age 13 years old or older
- Signed consent statement

Exclusion criteria

None

Outcomes

- Primary outcomes
  - Incidence of ocular complications
  - Mortality
- Secondary outcomes
  - Incidence of sequelae of AIDS-related eye disease (eg, retinal detachment)
  - Incidence of complications of therapy for AIDS-related eye disease
  - Long-term outcome of ocular complications (eg, incidence of blindness)
  - Incidence of extra-ocular CMV disease

Data collection schedule

- Baseline
- Every 6 months: at even numbered followup visits (eg., F2, F4, F6 ...)
- Interim visits at diagnosis of an ocular opportunistic infection
- Missed visits
- Telephone contacts: at odd numbered followup visits (eg., F1, F3, F5 ...) with the target date at least 45 days (1.5 months) after previous in-person visit and before next in-person visit

Data collection

- Demographic data
- Medical histories: medications and diagnosis
- Ophthalmologic data: status, diagnosis, and disease followup
- Fundus photographs
- Quality of Life questionnaire; Visual Functioning Questionnaire - 25 (VFQ-25)

- Hematology, lymphocyte subset analysis, and serum chemistry
- Plasma HIV load (collected from patient's medical record)
- Plasma and polymorphonuclear blood leukocytes specimens banked for future analysis

Analysis plan

- Examine secular trends of ocular complications
  - Changes in annual incidence in the longitudinally followed cohort
- Estimate relative risks of development of ocular complications among subgroups of patients:
  - Demographic characteristics
  - HIV treatment
  - HAART response
  - CMV prophylaxis
  - HIV and CMV viral load
  - CD4+ T cell counts (current and nadir levels)
- Explore interrelationship of HIV viral load, CMV viral load, and CD4+ T cell counts over time
- Examine clinical course (disease progression, survival and visual outcomes) of ocular complications by patient characteristics and treatment strategies
  - Long-term effects of discontinuation of secondary prophylaxis among patients with CMV retinitis who respond to HAART
  - Local versus systemic therapies as primary treatments for ocular complications

Sample size calculations*

- Total sample size = 2,800 patients
- Type I error = 0.05 (two-sided)
- Recruitment rate = 100 patients/year
- Recruitment period = 4 year period
- Minimum followup = 12 months
- Estimated power = 0.80
- Method of calculation
  - Logrank test

Data monitoring plan

- Review of data by Policy and Data Monitoring Board (PDMB) at semiannual meetings or more often if necessary

* Refer to LSOCA protocol Section 6.2 for sample size calculation

1.2. Data collection schedules

1.2.1. Data collection schedules for patients with no ocular opportunistic infection

	Visit code/Target month from enrollment								
Month	BL 0	F1 3	F2 6	F3 9	F4 12	F5 15	F6 18	F7 21	F8 ... 24 ...
Eligibility review	X								
Telephone contact*		X		X		X		X	
Ophthalmologic Slit lamp exam Intraocular pressure Dilated indirect ophthalmoscopy	X		X		X		X		X
Visual acuity with refraction	X		X		X		X		X
Contrast sensitivity	X		X		X		X		X
Humphrey visual field▵	X				X				X
Goldmann visual field**	X								
Fundus photographs‡	X								
Health history AIDS history Treatment history for HIV/CMV Other treatments	X		X		X		X		X
Antiretroviral Treatment History (AR)§									
Cardiovascular/Cerebrovascular Events form (CC)§§ Risk profile form (CR)§									
Laboratory studies Hematology/T-cell subsets/HIV load†	X		X		X		X		X
Specimen collection Plasma /Leukocytes	X		X		X		X		X
Quality of Life	X		X		X		X		X
Visual Functioning Questionnaire - 25	X		X		X		X		X

*Patients with no ocular opportunistic infection will be contacted by telephone or mail/email between clinic visits to ascertain vital status and screen for eye conditions developed during the interval.
*At Baseline and at time of diagnosis of OOI and every followup visit thereafter
†Blood collection for HIV viral load analysis is required if HIV viral load data are unavailable in medical records. HIV viral load determinations should be obtained within the extended time window (data window)
‡Fundus photographs to be taken every five years for all patients with no ocular opportunistic infection; and at time of diagnosis of an OOI and at every followup visit thereafter
§One time only for AR and CR forms (see Handbook): at BL for newly enrolled patients, FU visits, or in a timely manner for patients who are deceased or missed last 3 consecutive visits
§§As needed
▵at diagnosis of an ocular opportunistic infection and every annual followup visit thereafter

1.2.2. Data collection schedules for patients *with* an ocular opportunistic infection

	Visit code/Target month from enrollment								
Month	BL 0	F1 3	F2 6	F3 9	F4 12	F5 15	F6 18	F7 21	F8 ... 24 ...
Eligibility review	X								
Telephone Contact		X				X		X	
Ophthalmologic Slit lamp exam Intraocular pressure Dilated indirect ophthalmoscopy	X		X		X		X		X
Visual acuity with refraction	X		X		X		X		X
Contrast sensitivity	X		X		X		X		X
Humphrey visual field	X				X				X
Goldmann visual field	X		X		X		X		X
Fundus photographs	X		X		X		X		X
Health history AIDS history Treatment history for HIV/CMV Other treatments	X		X		X		X		X
Antiretroviral Treatment History (AR)†									
Cardiovascular/Cerebrovascular Events form (CC) ‡ Risk profile form (CR) †									
Laboratory studies Hematology Serum chemistry T-cell subsets HIV viral load *	X		X		X		X		X
Specimen collection Plasma Leukocytes	X		X		X		X		X
Quality of Life	X		X		X		X		X
Visual Functioning Questionnaire -25	X		X		X		X		X

*Blood collection for HIV viral load analysis is required if HIV viral load data are unavailable in medical records.
†One time only for CR and AR forms (see Handbook)
‡As needed

2. Ocular Complications Classification

2.1. Definition of ocular opportunistic infections

Retinitis/Choroidopathy

CMV retinitis: Diagnosed by a characteristic picture of necrotizing retinitis with either edematous white borders or granular white borders with or without hemorrhage. It is progressive, and leads to severe vision loss if not controlled.

Herpetic retinitis: Most commonly due to varicella zoster virus and, less commonly, herpes simplex virus. There are two types: the acute retinal necrosis syndrome and the progressive outer retinal necrosis syndrome. Varicella zoster retinitis syndromes may or may not be associated with herpes zoster ophthalmicus. [CMV retinitis, though caused by a virus of the herpes family, is classified separately because its clinical syndrome differs].

> **Acute retinal necrosis** is characterized by confluent, full-thickness, yellow necrotizing retinitis with little or minimal hemorrhage, with or without an overlying vitritis. It usually begins in the anterior retinal periphery, spreads circumferentially, and progresses rapidly toward the posterior pole.
>
> **Progressive outer retinal necrosis** is characterized by a multifocal rapidly progressive yellow necrotizing retinitis with early posterior pole involvement. Its appearance is of an "outer" retinal necrosis, though histologically all layers of the retina are involved.

Toxoplasmic retinitis: Diagnosed on the basis of a focal yellow-white necrotizing retinitis with fluffy borders and no or few scattered intraretinal hemorrhages, usually associated with an overlying vitritis. Toxoplasmic retinitis may represent a reactivation of prior retinal infection or a new infection. In the former case, the retinitis is usually adjacent to an area of focal atrophic choroid and retina with retinal pigment epithelial clumping (a toxoplasmosis scar).

Choroidopathy: The presence of (acquired) choroidal lesions without associated retinitis. The lesions may be large or small, diffuse or focal, and of varying color. The most commonly described choroidopathy in AIDS patients for which a specific etiology has been established is pneumocystic choroidopathy, characterized by multiple pale 1-3 mm deep yellow choroidal lesions that are rarely elevated. Pneumocystic choroidopathy usually has no impact on vision. Choroidopathy may also be caused by cryptococcosis, tuberculosis, and perhaps other conditions as well.

2.2. Definition of *other* ocular complications

Other ocular complications - anterior segment and ocular adnexal disease

Anterior uveitis, non-infectious: Inflammation of anterior portion of the uveal tract (the iris and/or ciliary body) not thought to be infectious in etiology, according to the judgment of the study ophthalmologist. Slit lamp examination features include the presence of cells and flare in the anterior chamber, often keratic precipitates, and sometimes intraocular scarring.

Cataract, visually significant: Visually significant opacity of the lens.

Conjunctivitis: Inflammation of the conjunctiva, of non-infectious or infectious etiology.

Extrusion of intraocular implant: protrusion of the strut and/or body of an intraocular implant through the scleral wall.

Herpes zoster ophthalmicus: Herpes zoster involving the ophthalmic division of the trigeminal nerve, characterized by a vesicular skin rash on an erythematous base along the nerve's path. Often preceded by pain, and sometimes accompanied by ocular complications such as conjunctivitis, keratitis, scleritis, or iridocyclitis.

Kaposi's Sarcoma, ophthalmic: A vascular tumor with a characteristic red-purple appearance, affecting the eyelid, conjunctiva or orbit. Diagnosis is by classic clinical appearance or by biopsy.

Keratitis: Any infectious or non-infectious inflammatory disorder of the cornea (excludes cases with keratic precipitates and no other corneal inflammation).

Lymphomas: A tumor of lymphocytes diagnosed by histologic examination of a pathologic specimen. For LSOCA, lymphomas that may constitute an ocular complication include orbital, conjunctival/episcleral, and intraocular lymphomas.

Molluscum contagiosum: A viral infection of the skin creating a characteristic umbilicated raised lesion. Diagnosis may be based upon classic appearance or biopsy.

Other ocular complications - posterior segment

Epiretinal membrane: A pre-retinal proliferation of cells causing traction on the retina, usually affecting the macula.

Endophthalmitis, bacterial: Inflammation involving the ocular cavities and their adjacent structures suspected or proven to be caused by a bacterial infection.

Glaucoma: A heterogenous group of disorders that result in acquired, progressive optic atrophy with a characteristic optic nerve head morphology ("cupping"), associated with compatible visual field defects. For purposes of LSOCA, diagnosis may be made without actually observing progression if characteristic features are present. Note that only subjects with definite glaucoma, and not glaucoma suspects, should be recorded as having "glaucoma" for purposes of LSOCA.

HIV retinopathy: An occlusive microangiopathy characterized by "cotton-wool spots" (microinfarctions of the retinal nerve fiber layer). In some cases intraretinal hemorrhages are also present. Extremely common in AIDS patients.

Hypotony: Pathologically low intraocular pressure (less than 8 mm Hg) other than in the early post-operative period.

Macular edema: Swelling of the macula, as evidenced by ophthalmoscopy or angiography.

Retinal detachment: Separation of the neurosensory retina from the underlying pigment epithelium as a result of retinal hole(s) ("rhegmatogenous"), an effusion of fluid ("serous"), or traction on the retina ("tractional"). Diagnosed by ophthalmologic examination and/or ultrasonography.

Syphilitic eye disease: Caused by infection with a spirochete, syphilis may cause several ocular inflammatory syndromes including retinitis or chorioretinitis, and nearly any uveitic syndrome. None of these syndromes have a characteristic presentation — there may be various patterns. Diagnosis requires a positive specific serologic test for syphilis (FTA-ABS, MHA-TP, or HATTS), a compatible clinical picture, and evidence of resolution with specific anti-syphilis therapy.

Uveitis, non-Infectious: Any uveitis syndrome that does not fall into one of the other categories specified above or below based on the available information, including anterior uveitis (which is listed above because it affects the anterior segment). Uveitis not obviously fitting into another category should be presumed non-infectious until workup shows otherwise . Note that if a uveitis syndrome is subsequently discovered to be caused by an infection such as syphilis, a corrected Non-Infectious Uveitis and Syphilitic Eye Disease form is to be submitted when diagnosis of syphilis is made.

Vitreous hemorrhage: a non-trivial number of red blood cells in the vitreous cavity for unoperated subjects. For post-operative patients, red blood cells in the vitreous of a degree exceeding expectation for an average individual at a similar postoperative stage.

Neuro-ophthalmologic lesions

Oculomotor nerve lesions: (CN III) Hypo- or non-function of part or all of the oculomotor nerve, resulting in ipsilateral eye movement, upper eyelid movement and/or non-afferent pupillary abnormalities. Diagnosed by clinical presentation.

Trochlear nerve lesions: (CN IV) Hypo- or non-function of the trochlear nerve, resulting in ipsilateral superior oblique dysfunction, usually with a vertical deviation. Diagnosed by clinical presentation.

Trigeminal nerve lesions: (CN V) Dysfunction of the trigeminal nerve, with ipsilateral reduction of facial sensation and/or strength of the masticatory muscles. Diagnosed by clinical presentation.

Abducens nerve lesions: (CN VI) Hypo- or non-function of the abducens nerve, resulting in ipsilateral lateral rectus dysfunction, and resultant ipsilateral eye movement abnormalities. Diagnosed by clinical presentation.

Facial nerve lesions: (CN VII) Dysfunction of the facial nerve, resulting in ipsilateral reduction of facial strength, tearing, and/or other dysfunctions depending on the location of the lesion within the course of the facial nerve. Diagnosed by clinical presentation.

Strabismus (non-paralytic): A non-alignment of the eyes that is not of specific neurologic etiology, diagnosed by clinical presentation.

Supranuclear ocular motility disorders: Eye movement abnormalities attributable to specific brain lesions/disorders at a level "higher" than the cranial nerve nuclei. Many disorders exist (refer to neuro-ophthalmology texts). Diagnosed by clinical presentation, often supplemented by imaging and/or other studies.

Unexplained visual field defects: A measurable visual field defect that cannot be explained after appropriate workup.

Vision loss due to CNS disorders: Significant loss of visual function (acuity, visual field, color, etc) attributable to lesions of the optic chiasm, optic tracts, lateral geniculate nuclei, optic radiations, and/or visual cortex.

Large vessel vaso-occlusive disease

Central retinal vein occlusion: Obstruction/reduction of blood flow through the central retinal artery, typically resulting in diffuse superficial hemorrhages and retinal swelling in all four quadrants of the retina, often with cotton-wool spots, and thickening/tortuosity of the retinal veins. "Ischemic" and "non-ischemic" subtypes exist.

Branch retinal vein occlusion: Obstruction/reduction of blood flow through a branch retinal artery, typically resulting in an area of retina with superficial hemorrhages and retinal swelling often with cotton-wool spots, and often associated with thickening and tortuosity of the vein in that segment of retina.

Central retinal artery occlusion: Obstruction of blood flow through the central retinal artery, usually with nearly immediate profound vision loss. Within hours, edematous opacification and thickening of the retina occurs, typically with eventual appearance of a "cherry red spot" in the center of the macula.

Branch retinal artery occlusion: Obstruction of blood flow through a branch retinal artery, usually with nearly immediate visual dysfunction. Edematous opacification and thickening of the retina follows in hours.

Optic nerve abnormalities

Papillaedema: Optic nerve swelling associated with increased intracranial pressure, diagnosed by ophthalmoscopy showing a swollen optic disk(s) and objective evidence demonstrating increased intracranial pressure.

Optic neuropathy: Acquired, non-glaucomatous optic nerve dysfunction. Typically characterized by loss of visual acuity, loss of color vision, and/or a visual field defect in association with an ipsilateral afferent pupillary defect. Etiologic mechanisms include vascular insults, genetic disease, compression, trauma, inflammation, infection, and others. The optic disk may appear normal, swollen, or pale.

2.3. Ocular complications requiring a separate form

Diagnosis/complication	Form required
Acute Retinal Necrosis	Herpetic Retinitis (HR)
Choroidopathy	Choroidopathy (CH)
CMV retinitis	CMV Retinitis (CV)
Cranial nerve palsies	Cranial Nerve/Motility Abnormality (CN)
Conjunctivitis	Keratitis/Conjunctivitis (KC)
Keratitis	Keratitis/Conjunctivitis (KC)
Motility disorders not specified elsewhere	Cranial Nerve/Motility Abnormality (CN)
Optic nerve disorders Optic neuropathy Papillaedema Other optic nerve disorders	Optic Nerve Abnormality (ON)
Progressive Outer Retinal Necrosis	Herpetic Retinitis (HR)
Retinal detachment	Retinal Detachment (RD)
Strabismus, non-paralytic	Cranial Nerve/Motility Abnormality (CN)
Syphilitic eye disease	Syphilitic Eye Disease (SD)
Toxoplasmic retinitis	Toxoplasmic Retinitis (TR)
Uveitis syndromes	Non-Infectious Uveitis (UN)

3. Visits

3.1. Study visit window table

Visit ID	Target time from enrollment (months)	Time Window* (months)	Type Visit
BL	0	Day -10 to day 0	
F01	3	†	Telephone
F02	6	3, 9	In-person
F03	9	†	Telephone
F04	12	9, 15	In-person
F05	15	†	Telephone
F06	18	15, 21	In-person
F07	21	†	Telephone
F08	24	21, 27	In-person
F09	27	†	Telephone
F10	30	27, 33	In-person
F11	33	†	Telephone
F12	36	33, 39	In-person
F13	39	†	Telephone
F14	42	39, 45	In-person
F15	45	†	Telephone
F16	48	45, 51	In-person
F17	51	†	Telephone
F18	54	51, 57	In-person
F19	57	†	Telephone
F20	60	57, 63	In-person

*There should be a minimum of 3 months between each in-person visit.
†There should be a minimum of 1.5 months between a telephone contact visit and an in-person visit

3.2. Data forms and procedures for patients with no ocular opportunistic infection

	Visit code													
	BL	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**	**F11[▲]**	**F12**	**F13**
Antiretroviral Treatment History (AR)[†]														
Automated Perimetry (HFA printout)	H.A.	.	.	.	H.A.	.	.	.	H.A.	.	.	.	H.A.	.
Automated Perimetry Form (AP)‡	AP	.	.	.	AP	.	.	.	AP	.	.	.	AP	.
Cardiovascular/Cerebrovascular Events (CC)*	.	.	.	.	.	.	.	.	.	.	.	.	.	.
Cardiovascular/Cerebrovascular Risk Profile (CR)[†]	.	.	.	.	.	.	.	.	.	.	.	.	.	.
Death Documentation (DD)*	.	.	.	.	.	.	.	.	.	.	.	.	.	.
Death Report Form (DR)*	.	.	.	.	.	.	.	.	.	.	.	.	.	.
Enrollment Form (EF)	EF	.	.	.	.	.	.	.	.	.	.	.	.	.
Eye Exam (EE)	EE	.	EE	.	EE	.	EE	.	EE	.	EE	.	EE	.
Eye History (EH)	EH	.	EH	.	EH	.	EH	.	EH	.	EH	.	EH	.
Fundus Photograph (FP)▵	FP	.	.	.	.	.	.	.	.	.	FP	.	.	.
Goldmann Visual Fields (VF)†	VF	.	.	.	.	.	.	.	.	.	.	.	.	.
Hematology and Serum Chem (HS)	HS	.	HS	.	HS	.	HS	.	HS	.	HS	.	HS	.
HIV Viral Load (HL)§	HL	.	HL	.	HL	.	HL	.	HL	.	HL	.	HL	.
Lymphocyte Subset Analysis (LA)	LA	.	LA	.	LA	.	LA	.	LA	.	LA	.	LA	.
Medical History (BH) or (FH)	BH	.	FH	.	FH	.	FH	.	FH	.	FH	.	FH	.
Missed Visit (MV)*	.	.	.	.	.	.	.	.	.	.	.	.	.	.
Missed Photograph Fax (MP)*	.	.	.	.	.	.	.	.	.	.	.	.	.	.
Notification of Ocular Opportunistic Infection Form††	.	.	.	.	.	.	.	.	.	.	.	.	.	.
Telephone Contact Form (CF)	.	CF	.	CF	.	CF	.	CF	.	CF	.	CF	.	CF
Patient Location Information (PL)‖	PL	.	.	.	PL	.	.	.	PL	.	.	.	PL	.
Photograph Transmittal Log (PT)	PT	.	.	.	.	.	.	.	.	.	.	.	.	.
Quality of Life (QL)	QL	.	QL	.	QL	.	QL	.	QL	.	QL	.	QL	.
Specimen Collection/Processing(SC)	SC	.	SC	.	SC	.	SC	.	SC	.	SC	.	SC	.
Transmittal Form (TM)	TM	.	TM	.	TM	.	TM	.	TM	.	TM	.	TM	.
Treatment History (BT) or (FT)	BT	.	FT	.	FT	.	FT	.	FT	.	FT	.	FT	.
Visit Guide (VG)	VG	VG	VG	VG	VG	VG	VG	VG	VG	VG	VG	VG	VG	VG
Visit Time Window (VT)**	VT	.	.	.	.	.	.	.	.	.	.	.	.	.
Visual Acuity/Contrast Sensitivity (VA)	VA	.	VA	.	VA	.	VA	.	VA	.	VA	.	VA	.
Visual Functioning Quesionaire - 25(VQ)	VQ	.	VQ	.	VQ	.	VQ	.	VQ	.	VQ	.	VQ	.

*As needed

**Sent by CC

[†]At baseline for newly enrolled patients; at next followup visit for patients already enrolled, or in a timely manner for deceased patients or patients who have missed 3 consecutive in-person visits

†At baseline; and at time of diagnosis of Ocular Opportunistic Infection and every followup visit thereafter

††Fax to CC upon diagnosis of Ocular Opportunistic Infection

‖Update form as needed; **not sent to CC**

▵At baseline; at time of diagnosis of Ocular Opportunistic Infection; and every 5 years for all patients

‡At baseline, annually and at diagnosis of Ocular Opportunistic Infection

§Blood collection for HIV viral load analysis is required if HIV viral load data are unavailable in medical records. HIV viral load determination should be obtained within the extended time window (data window)

3.3. Data forms and procedures for patients *with* ocular opportunistic infections

	Visit code													
	BL	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**	**F11**	**F12**	**F13**
Antiretroviral Treatment History (AR)†														
Automated Perimetry (H.A. printout) H.A.	.	.	.	H.A.	.	.	.	H.A.	.	.	.	H.A.	.	
Automated Perimetry Form (AP)	AP	.	.	.	AP	.	.	.	AP	.	.	.	AP	.
Cardiovascular/Cerebrovascular Events (CC)*	.	.	.	.	.	.	.	.	.	.	.	.	.	.
Cardiovascular/Cerebrovascular Risk Profile (CR)†	.	.	.	.	.	.	.	.	.	.	.	.	.	.
Death Documentation (DD)*	.	.	.	.	.	.	.	.	.	.	.	.	.	.
Death Report Form (DR)*	.	.	.	.	.	.	.	.	.	.	.	.	.	.
Enrollment Form (EF)	EF	.	.	.	.	.	.	.	.	.	.	.	.	.
Eye Exam (EE)	EE	.	EE	.	EE	.	EE	.	EE	.	EE	.	EE	.
Eye History (EH)	EH	.	EH	.	EH	.	EH	.	EH	.	EH	.	EH	.
Fundus Photograph (FP)▵	FP	.	FP	.	FP	.	FP	.	FP	.	FP	.	FP	.
Goldmann Visual Fields (VF)	VF	.	VF	.	VF	.	VF	.	VF	.	VF	.	VF	.
Hematology and Serum Chem (HS)	HS	.	HS	.	HS	.	HS	.	HS	.	HS	.	HS	.
HIV Viral Load (HL)	HL	.	HL	.	HL	.	HL	.	HL	.	HL	.	HL	.
Lymphocyte Subset Analysis (LA)	LA	.	LA	.	LA	.	LA	.	LA	.	LA	.	LA	.
Medical History (BH) or (FH)	BH	.	FH	.	FH	.	FH	.	FH	.	FH	.	FH	.
Missed Visit (MV)*	.	.	.	.	.	.	.	.	.	.	.	.	.	.
Missed Photograph Fax (MP)*	.	.	.	.	.	.	.	.	.	.	.	.	.	.
Notification of Ocular Opportunistic Infection Form§	.	.	.	.	.	.	.	.	.	.	.	.	.	.
Patient Location Information (PL)§§	PL	.	.	.	.	.	.	.	.	.	.	.	.	.
Photograph Transmittal Log (PT)‖	PT	.	PT	.	PT	.	PT	.	PT	.	PT	.	PT	.
Quality of Life (QL)	QL	.	QL	.	QL	.	QL	.	QL	.	QL	.	QL	.
Specimen Collection/Processing(SC)	SC	.	SC	.	SC	.	SC	.	SC	.	SC	.	SC	
Telephone Contact (CF)	.	CF	.	CF	.	CF	.	CF	.	CF	.	CF	.	CF
Transmittal Form (TM)	TM	.	TM	.	TM	.	TM	.	TM	.	TM	.	TM	.
Treatment History (BT) OR (FT)	BT	.	FT	.	FT	.	FT	.	FT	.	FT	.	FT	.
Visit Guide (EG)	EG	.	EG	.	EG	.	EG	.	EG	.	EG	.	EG	.
Visit Time Window (VT)**	VT	.	.	.	.	.	.	.	.	.	.	.	.	.
Visual Acuity/Contrast Sensitivity (VA)	VA	.	VA	.	VA	.	VA	.	VA	.	VA	.	VA	.
Visual Functioning Questionnaire - 25(VQ)	VQ	.	VQ	.	VQ	.	VQ	.	VQ	.	VQ	.	VQ	.

*As needed

**Sent by CC

†At baseline for newly enrolled patients; at next followup visit for patients already enrolled, or in a timely manner for deceased patients or patients who have missed 3 consecutive in-person visits

▵No form required, send to FPRC at baseline, at time of diagnosis of Ocular Opportunistic Infection, and every 5 years for all patients

§Fax to CC upon diagnosis of Ocular Opportunistic Infection

§§Update form as needed; **not sent to CC**

‖Complete when photos are shipped; **not sent to CC**

3.4. Baseline

Time frame: Within the 10 days prior to and including enrollment

Visit ID

- BL
- Date of visit (see section 4.7 for clarification of 'Date of Visit')

Procedures and interviews

- Eligibility evaluation
- Review LSOCA procedures and visit schedule
- Cataract grading
- Consent statement
- Blood pressure

- Height and weight measurements
- Eye history interview
- Visual acuity assessment with refraction
- Contrast sensitivity

- Visual field assessment (Goldmann)
- Automated perimetry (Humphrey)
- Eye exam
- Fundus photographs

- Medical history interview
- Treatment history interview
- Quality of Life interview
- Patient location information

- Hematology and serum chemistry
- Lymphocyte analysis
- Specimen Collection/Processing
- Visual Functioning Questionnaire - 25(VQ)

Order of procedures

- Quality of Life interview and the Visual Functioning Questionnaire - 25 is recommended to be administered at the beginning of the visit to avoid events at the visit influencing responses to the questionnaire

- During ophthalmologic evaluation, the examinations should be given in the following order:
  - Best corrected visual acuity refraction
  - Cataract grading
  - Contrast sensitivity
  - Humphrey field
  - Goldmann field
  - Ophthalmologic examination
  - Fundus photographs

Specimens collected

- Blood for hematology (one 5 mL ETDA-treated tube)
- Blood for serum chemistry (one 7 mL untreated tube)
- Blood for lymphocyte analysis (one 5 mL in heparinized tube)
- Blood for banking (two 8.5-mL ACD yellow-top tubes)†
  - blood should be processed to obtain aliquots of plasma and cell aliquots (see Section 4.23 of this Handbook)

Forms completed

- Antiretroviral Treatment History (AR)
- Automated Perimetry (HFA Printout)
- Automated Perimetry Form (AP)
- Baseline Medical History (BH)
- Baseline Treatment History (BT)
- Consent Statement (CS)*
- Enrollment Form (EF)
- Eye Exam (EE)
- Eye History (EH)
- Goldmann Visual Field Record (VF)
- Hematology and Serum Chemistry Report (HS)
- HIV Viral Load (HL)
- Lymphocyte Subset Analysis (LA)
- Ocular complication form if applicable (e.g., Form CH, CN, CV, HR, KC, ON, RD, SD, TR, UN)
- Patient Location Information (PL)*
- Photograph Transmittal (PT)
- Quality of Life (QL)
- Specimen Collection/Processing (SC)
- Specimen Shipment Log (SS)
- Visual Acuity/Contrast Sensitivity (VA)
- Visit Guide (VG)
- Visual Functioning Questionnaire - 25(VQ)

*Do not send to Coordinating Center

†Blood collection for HIV viral load analysis required if HIV viral load data are unavailable in patient's medical records.

3.5. Overview of followup schedule

Types of visits

- Clinic visit: when the patient is seen at the clinic (every 6 mos as scheduled): at all even numbered followup visits (F2, F4, F6...)

- Telephone contact: when the patient is contacted by telephone or mail (midway between followup clinic visit): at all odd numbered follow up visits (f1, F3, F5...)

- Interim visit: when a patient has already completed either a followup clinic visit or a followup telephone contact and is subsequently seen again at the clinic during the same visit window for diagnosis of an ocular opportunistic infection. (See Section 3.10 for data collection requirements).

Followup visits

- All patients will be on a 6 month followup schedule
- Patients formerly identified with an MOC who do not have an ocular opportunistic infection will revert to No OOI visit schedule and set of procedures (eg. Followup photographs and Goldman Visual Fields not required)

  Telephone contact visits (i.e., F1, F3, F5, F7 ...) will alternate between clinic Followup Visits (i.e., F2, F4, F6, F8, F10 ...)

3.6. Followup *telephone* contacts for patients*

Visits ID
- F1, F3, F5, F7, F9, F11
- Date of visit

Time windows (Minimum separation between study telephone contacts: 6 weeks)
- F01: Month 3 (± 6 weeks)
- F03: Month 9 (± 6 weeks)
- F05: Month 15 (± 6 weeks)
- F07: Month 18 (± 6 weeks)
- F09: Month 21 (± 6 weeks)
- F11: Month 23 (± 6 weeks)

Procedures and interviews for telephone contacts
- Contact patient, ask if any problems with vision or eyes
- Schedule a clinic visit with study ophthalmologist if patient reports an eye problem
- Ascertain vital status and status of eye for patients with no ocular opportunistic infection

Forms Completed
- Telephone Contact Form (CF)
- Visit Guide

*It is recommended to schedule telephone contact visits greater than 1.5 months from in-person visit.

3.7. Followup clinic visits for patients with no ocular opportunistic infection

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Visit ID

- F02, F04, F06, F08.....
- Date of visit (see section 4.7 for clarification of 'Date of Visit')

Time windows (Minimum separation between study clinic visits: 6 weeks)

- F02: Month 6 (± 6 weeks)
- F04: Month 12 (± 6 weeks)
- F06: Month 18 (± 6 weeks)
- F08: Month 24 (± 6 weeks)
- F10: Month 30 (± 6 weeks)
- F12: Month 36 (± 6 weeks)

Procedures and interviews for clinic visits

- Eye history interview
- Cataract grading
- Visual acuity assessment (with refraction)
- Contrast sensitivity
- Automated perimetry **(every 12 months)** and at time of diagnosis of an ocular opportunistic infection

- Eye exam
- Form associated with ocular complication (if applicable, see Section 2.3 of this Handbook)
- Fundus photographs **(every 5 years)** and at time of diagnosis of an ocular opportunistic infection
- Medical history interview
- Treatment history

- Quality of Life
- Patient location information update **(every 12 months)** ocular opportunistic infection
- Blood pressure
- Hematology and serum chemistry
- Lymphocyte analysis
- HIV viral load (obtain most recent data from patient's medical record)

- Specimen collection/Processing
- Specimen Shipping
- Visual Functioning Questionnaire - 25

3.7. Followup clinic visits for patients no ocular opportunistic infection

Order of procedures

- Quality of Life and Visual Functioning Questionnaire - 25 interview is recommended to be administered at the beginning of the visit to avoid events at the visit influencing responses to the questionnaire

- For the Ophthalmologic evaluation the examination should be given in the following order:
  - Best corrected visual acuity refraction
  - Contrast sensitivity
  - Humphrey field
  - Ophthalmologic examination
  - Fundus photographs

Specimens collected

- Blood for hematology (one 5 mL in EDTA-treated tube)
- Blood for banking (two 8.5 mL ACD yellow-top tubes)
  - blood should be processed to obtain aliquots of plasma and cell aliquots (see Section 4.23 of this Handbook)
- Blood for lymphocyte analysis (one 5 mL in heparinized tube)
- Blood for hematology and lymphocyte subset analysis is collected within 2 weeks of the LSOCA study visit

Forms completed

- Antiretroviral Treatment History (AR)*
- Automated Perimetry Form (AP)
- Cardiovascular/Cerebrovascular Risk Profile (CR)*
- Cardiovascular/Cerebrovascular Events (CC)*
- Clinician versus FPRC Disagreement Form (DS)
- Eye Exam (EE)
- Eye History (EH)
- Followup Medical History (FH)
- Followup Treatment history (FT)
- Hematology and Serum Chemistry Report (HS)
- HIV Viral Load (HL)
- Lymphocyte Analysis (LA)
- Quality of Life (QL)
- Specimen Collection/Processing (SC)
- Specimen Shipment Log (SS)
- Visual Acuity/Contrast Sensitivity (VA)
- Visit Guide (VG)
- Visual Functioning Questionnaire - 25 (VQ)

* If applicable

3.8. Followup clinic visits for patients *with* an ocular opportunistic infection

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Visit ID

- F02, F04, F06, F08 . . .
- Date of visit (see section 4.7 for clarification of 'Date of Visit')

Time Windows: (Minimum separation of 6 weeks between visits

- F02: Month 6 (± 6 weeks)
- F04: Month 9 (± 6 weeks)
- F06: Month 12 (± 6 weeks)
- F08: Month 15 (± 6 weeks)
- F10: Month 30 (± 6 weeks)
- F12: Month 36 (± 6 weeks)

Procedures and interviews

- Eye history interview
- Cataract grading
- Visual acuity assessment/refraction
- Contrast sensitivity
- Goldmann Visual field assessment
- Automated perimetry **(every 12 months)**
- Eye exam
- Form associated with ocular complication (see Section 2.3 of this Handbook)
- Fundus photographs
- Blood pressure

- Medical history interview
- Treatment history interview
- Quality of Life
- Patient location information update **(every 12 months)**
- Hematology and Serum Chemistry
- Lymphocyte analysis
- HIV viral load (obtain most recent data from patient's medical record)
- Specimen collection/Processing
- Specimen Shipment Log
- Visual Functioning Questionnaire - 25

Order of procedures

- Quality of Life interview and Visual Functioning Questionnaire - 25 form interview is recommended to be administered at the beginning of the visit to avoid events during the visit influencing responses to the questionnaire

- For the ophthalmologic evaluation the examination should be given in the following order:

- Best corrected visual acuity refraction
- Contrast sensitivity
- Humphrey field
- Goldmann field
- Ophthalmologic examination
- Fundus photographs

Specimens collected

- Blood for hematology (one 5 mL in EDTA-treated tubes)
- Blood for serum chemistry (one 7 mL in untreated tube)
- Blood for banking (two 8.5 mL ACD yellow-top tubes)
  - blood should be processed to obtain aliquots of plasma and aliquots (see Section 4.23 of this Handbook)
- Blood for lymphocyte analysis (one 5 mL in heparinized tube)
- Blood for hematology and serum chemistry, and lymphocyte subset analysis is collected within 2 weeks of the LSOCA study visit

Forms completed

- Antiretroviral Treatment History (AR)*
- Automated Perimetry Form (AP)
- Cardiovascular/Cerebrovascular Risk Profile (CR)*
- Cardiovascular/Cerebrovascular Events (CC)*
- Clinician versus FPRC Disagreement Form (DS)
- Followup Medical History (FH)
- Followup Treatment History (FT)
- Forms associated with ocular complications (see Section 2.3 of this Handbook)
- Eye Exam (EE)
- Eye History (EH)
- Goldmann Visual Field Record (VF)
- Hematology and Serum Chemistry Report (HS)
- HIV Viral Load (HL)
- Lymphocyte Analysis (LA)
- Photograph Transmittal (PT), as necessary
- Quality of Life (QL)
- Specimen collection/Processing (SC)
- Specimen Shipment Log (SC)
- Visual Acuity/Contrast Sensitivity (VA)
- Visit Guide (VG)
- Visual Functioning Questionaire - 25 (VQ)

*If applicable

3.9. Missed visits

Visit ID

- Followup visit (F#)
- Date of visit

Interviews

- Quality of Life
- Visual Functioning Questionnaire - 25
- Ascertain vital status

Forms

- Missed Visit (MV)
- Quality of Life (QL)
- Visual Functioning Questionnaire - 25 (VQ)
- Missed Photographs Fax (MP), if applicable
- Hematology and Serum Chemistry (HS), if applicable
- HIV Viral Load (HL), if applicable

Instructions

- Contact patient at various intervals during the visit time window to schedule and complete visit
- If patient missed visit during time window, complete quality of life interview and the Visual Functioning Questionnaire - 25 form over the telephone, ascertain vital status, whether patient has had any eye problems, and to ascertain vital status
- Complete Missed Visit form, Missed Photographs Fax form and Quality of Life form and the Visual Functioning Questionnaire - 25 form
- Complete the Hematology and Serum Chemistry (HS) form and the HIV Viral Load (HL) form, if these data are available
- Schedule patient if any eye problems reported

3.10. Interim visit

Definition

A visit occurring after a scheduled visit has been completed and within the same time window during which an ocular opportunistic infection is diagnosed

Visit ID

- N visit
- Date of visit

Procedures and Interviews

- Eye History
- Visual Acuity/Contrast Sensitivity
- Goldmann Visual Field
- Automated perimetry
- Eye Exam
- Forms associated with ocular complications (see Section 2.3 of this Handbook)
- Fundus photographs

Forms required

- Automated Perimetry Form (AP)
- Forms associated with ocular complications (see Section 2.3 of this Handbook)
- Eye Exam (EE)
- Eye History (EH)
- Goldmann Visual Field Record (VF)
- Notification of Ocular Opportunistic Infection
- Photograph Transmittal (PT), as necessary
- Visit Guide (VG)
- Visual Acuity/Contrast Sensitivity (VA)

Instructions

- Contact patient at various intervals during the visit time window to schedule and complete visit
- If patient missed visit during time window complete Quality of Life interview and the Visual Functioning Questionnaire - 25 form over the telephone, ascertain vital status, and whether patient has had any eye problems
- Complete Missed Visit form, Missed Photographs Fax form (if applicable) and Quality of Life form and the Visual Functioning Questionnaire - 25 form
- Have patient come in (if possible) if any eye problems reported

3.11. LSOCA forms list

Form abbreviation	Form name
Procedure and interview forms	
AP	Automated Perimetry Form
AR	Antiretroviral Treatment History
BH	Baseline Medical History
BT	Baseline Treatment History
CC	Cardiovascular/Cerebrovascular Events
CF	Telephone Contact Form
CH	Choroidopathy
CN	Cranial Nerve Abnormality
CR	Cardiovascular/Cerebrovascular Risk Profile
CS	Consent Statement
CV	CMV Retinitis
DD	Death Documentation
DR	Death Report
DS	Clinician versus FPRC Disagreement Form
EE	Eye Exam
EF	Enrollment Form
EH	Eye History
FH	Followup Medical History
FT	Followup Treatment History
HL	HIV Viral Load
HR	Herpetic Retinitis
HS	Hematology and Serum Chemistry Report
KC	Keratitis/Conjunctivitis
LA	Lymphocyte Subset Analysis Report
MO	Notification of Ocular Opportunistic Infection
ON	Optic Nerve Abnormality
QL	Quality of Life
RD	Retinal Detachment/Repair
SC	Specimen Collection/Processing
SD	Syphilitic Eye Disease
TN	Permanent Transfer Notification
TR	Toxoplasmic Retinitis
UN	Non-Infectious Uveitis
VA	Visual Acuity/Contrast Sensitivity
VF	Goldmann Visual Field Record
VQ	Visual Functioning Questionnaire - 25 (VQ)

Form abbreviation	Form name
Patient and personnel accountability forms	
DC	Data Entry Certification/Decertification
MF	Medical File Contents
MV	Missed Visit
PC	Personnel Certification
PD	Personnel Decertification
PL	Patient Location Information
Transmittal forms and guides	
LR	Laboratory Range Report
MP	Missed Photographs Fax
PT	Photograph Transmittal Log
SF	Specimen Shipment Fax Coversheet
SS	Specimen Shipment Log
ST	Specimen Tracking
TM	Transmittal Form
VC	Cell Viability/Recovery Specimen Shipment Log
VG	Visit Guide
VT	Visit Time Windows
VL	Visual Acuity Lighting Log

4. Procedures

4.1. Antiretroviral Treatment History

Purpose

- To record date patient started HAART therapy

Forms

- AR: Antiretroviral Treatment History

When

- One time only: At Baseline (for newly enrolled patients) or upcoming followup visit for patient, already enrolled or in a timely manner for patients who are deceased or missed 3 consecutive visits

By whom

- Clinic coordinator

Procedures

- Use information from patient confirmed by medical records of medical records only to record patient first started HAART prior to enrollment in LSOCA

4.2. Blood pressure measurement

Purpose

- To ascertain cardiovascular risk associated with blood pressure

Forms

- BH: Baseline Medical History
- FH: Followup Medical History

When

- Baseline visit (BL) and all followup clinic visits (prior to pupil dilation)

By whom

- Clinic coordinator
- Study physician

Equipment

a. A wall/mobile aneroid blood pressure; and a stethoscope; or
   Suggested vendors:
   - Welch Allyn Tycos
     1-800-535-6663
     http://www.welchallyn.com
   - W.A. Baum Co. Inc., manufacturer of the Baumanometer® spygmomanometer
     1-888-281-6061
     http://.vsmmedtech.com

b. A random zero mercury column spygmomanometer and a stethoscope; or

c. A digital (automatic) blood pressure device/monitor
   Suggested vendors/models:
   - VSM MedTech Ltd.
     The BpTRU™ (Model BPM-100)
     1-877-952-9527
     http://www.vsmmedtech.com
   - Omron Health Care, Inc.
     Model HEM-907
     1-877-216-1333
     http://www.vsmmedtech.com

Patient preparations

- Setting for measurement should be quiet and free of interruptions
- Have patient rest in sitting position for 5 minutes
- Use appropriate cuff size for arm to be tested. The rubber bladder should encircle at least two-thirds of the arm. (A cuff that is 12-14 cm wide is satisfactory for the average adult arm.)
- Blood pressure varies in individuals according to the time of day, meals, smoking, anxiety, temperature, the season of the year, and the medications that they are on. So, there may be variability in the pressures at different visits.
- Tight or restrictive clothing should be removed from the arm. A simple measure is to request that patients wear a loose fitting, short sleeved garment when attending blood pressure measurement.

Blood pressure equipment

If using an aneroid blood pressure instrument:

- Calibrate unit with a Digimano every three to six months.
- Place aneroid dial at eye level
- The column of a wall unit must be vertical for correct reading; or

If using a random zero mercury column sphygmomanometer:

- The column of the wall unit must be vertical for correct reading
- The level of mercury in the tube should be observed with no pressure applied to the cuff
- The tube of the mercury manometer should be inspected regularly for dirt or sign of oxidation
- The stethoscope should be a standard variety and in good condition (with a clear sound reproduction). The stethoscope may be equipped with a bell endpiece or a diaphragm; some may have both

Standard procedures

Using an aneroid blood pressure instrument or a random zero mercury column sphygmomanometer with a stethoscope:

- Locate brachial artery by palpation
- Center bladder of the cuff over brachial artery
- Wrap cuff smoothly and snugly around patient's arm, with the lower edge one inch above bend in elbow
- Check cuff tubing for obstruction
- Place first and second finger firmly over patient's radial pulse
- Inflate cuff to approximately 70 mm Hg. Inflate cuff at 10 mm Hg increments until the patient's pulse disappears
- Deflate slowly a 2 mm per second until the pulse is felt again

- Remember that number and immediately release all pressure in the cuff
- Place ear pieces of a stethoscope in ears, they should fit comfortably (but snugly) and block out most external noise
- Place stethoscope head in bell position
- Place bell side of stethoscope over brachial artery
- Inflate cuff quickly to a level 20-30 mm Hg over the value at which the pulse was not felt. (This value is the peak inflation level to which the cuff is to be inflated for all readings).
- Deflate cuff at a steady rate of 2-3 mm Hg per second
- Obtain and record systolic blood pressure (Phase 1 of Korotkoff sounds, the point at which the initial "tapping" sound is heard. To make sure the sound is not extraneous, one should hear two connective beats as the pressure falls)
- Obtain and record diastolic blood pressure (Phase 5 of Korotkoff sounds or Phase 4 of Korotkoff sounds if Phase 5 is absented. "Muffling" occurs when the crisp Korotkoff sounds change, recognized by a sudden diminution or disappearance of sound. This is the fourth phase. The fifth phase, the point at which sounds disappear/become inaudible)
- Write which arm the pressure is being recorded and the position of the subject should be noted, for example: left arm, sitting, etc.

Using a digital blood pressure device:

- Following instructions per product guidelines

4.3. Cardiovascular/cerebrovascular assessments

Purpose

- Record history of cardiovascular/cerebrovascular disease on the Cardiovascular/Cerebrovascular Risk Profile (CR) form

- Record new documented cardiovascular/cerebrovascular events known to occur during course of the study. These data to be recorded onto the Cardiovascular/Cerebrovascular Events (CC) form

Forms

- CR: Cardiovascular/Cerebrovascular Risk Profile
- CC: Cardiovascular/Cerebrovascular Events

When

- Cardiovascular/Cerebrovascular Risk Profile (CR): At baseline for newly enrolled patients; or upcoming followup visit for patients already enrolled, or in a timely manner for patients who are deceased or missed 3 consecutive visits
- Cardiovascular/Cerebrovascular Events (CC): At all clinic visits, baseline or followup, at which a new cardiovascular/cerebrovascular is just identified/reported

4.4. Cataract grading

Purpose

- Collect data on cataract grading
- Grading will be by clinical assessment

Form

- Eye Exam (EE)

When

- Baseline visit
- Scheduled clinic visits every 6 months
- At time of diagnosis of an ocular opportunistic infection

By whom

- Study ophthalmologist

Equipment

- Ophthalmascope
- Slit lamp
- Tonometer
- Dilation Eye Drops
- Lens opacity card (laminated) - replacements available upon request from the coordinating center

Procedures

- Conduct slit lamp exam
- Dilate eyes
- Conduct an indirect ophthalmoscopy exam of fundus

4.5. Consent and enrollment procedures

Purpose

- Describe study design
- Inform patients of their rights and responsibilities with respect to participation in the study
- Discuss data collection schedule with patients and parents or guardians as applicable
- Evaluate patient's eligibility for enrollment into the study; eg, AIDS diagnosis

Forms

- Longitudinal Study of Ocular Complication of AIDS Consent Statement
- Longitudinal Study of Ocular Complication of AIDS Assent Statement
- Enrollment Form (EF)

When

- During Baseline visit (BL) and prior to enrollment

By whom

- Clinic coordinator
- Study ophthalmologist

Consent procedures

- Describe purpose of study, including data collection schedules
- Discuss patient's questions and concerns
- Give interested persons a copy of the consent statement and or assent statement (as applicable)
- If participant is 13-17 years of age, provide participant with a copy of the assent statement and consent statement
- Thank uninterested persons for their time and provide usual services

Enrollment procedures

- Obtain signed and dated consent and or assent statement (patient keeps copy and original is filed with patient folder)
- Obtain signed and dated assent statement (if patient is 13-17 years of age) and signed and dated consent statement (to be signed and dated by parent or guardian)
- Proceed with enrollment procedures
- Evaluate if patient has an ocular opportunistic infection, as listed in Section 2.1 of this Handbook
- Upon completion of Baseline procedures, complete and fax Enrollment Form (EF) to the CC **(do not mail an additional copy of the EF form to CC)**

4.6. Contrast sensitivity

Purpose
- Collect data on contrast sensitivity

Form
- Visual Acuity/Contrast Sensitivity form (VA)

When
- Baseline visit (BL)
- All scheduled clinic visits
  - every 6 months
- At time of diagnosis of an ocular opportunistic infection

By Whom
- SOCA certified contrast sensitivity examiner

Equipment and room requirements
- Pelli-Robson Contrast Sensitivity Charts
- Hang chart at patient's eye level, adjust chart accordingly
- Phoropter
- Trial frames and lenses
- AEMC Digital Lightmeter (Model 810)
- Adequate and consistent room illumination:
  - Illumination range within lane should be 50-100 foot candles; avoid glare
- Charts should be evenly illuminated by external lighting, avoid glare
- Quiet room with chart preferably mounted on white wall so that its center will be approximately at the level of the patient's eyes
- Examination lane marked at 1 meter (about 40 inches) and 0.5 meters

Procedures
- Testing will be performed on the better seeing eye first
- Test patients before dilating their pupils or applying other drugs to their eyes
- Place appropriate lens in trial frames. Patients should wear their best correction and an additional +0.75 diopter for 1 meter distance.
- If patient has very poor acuity (worse than 20/100), test the patient at 0.5 meter with an additional +1.00 diopter (+1.75 total)
- Eye not being tested is occluded
- Contrast sensitivity Chart 2L will be used for the right eye
- Contrast sensitivity Chart 4L will be used for the left eye
- Steps in contrast sensitivity exam include:

4.6. Contrast sensitivity

1. Patient is positioned 1 meter from chart with eye horizontally aligned with the center of chart.
2. Instruct patient that all the figures are letters, not numbers.
3. Ask patient to start at top line, upper left hand corner, read left to right across, and progress down the chart.
4. The examiner will indicate the beginning of each line, but not point to or otherwise indicate the individual letters to be read.
5. The patient should read until he or she misses two out of three letters in a single contrast group line.* The patient should be encouraged to guess if at all possible.
6. Ask if they see a smudge. Ask if it's round or square, or has corners or lines they can see. Encourage them to guess until they guess 2 of 3 letters correctly.

*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.

4.7. Date of visit

Purpose

- To clarify the date to record in item labeled "date of visit" on data collection forms

Definition of 'Date of Visit'

- Record the date when the study physician or other study personnel are face-to-face with the study patient for the purpose of performing a study procedure (or medical history interview);
- The first date on which a procedure is performed if that procedure extends across several days;
- The date of last attempt in terms to telephone contacts;
- For forms that collect laboratory data, record the date the specimen was collected;
- For 'Date of Visit' on forms that record death of a patient, record the date of death, if known. If date of death is unknown, record the estimated (i.e. best guess) date of death. Use "15" for 'Date of Visit' if the day of death is unknown. Use "01-Jul" as the day and month of 'Date of Visit' if the day and month are unknown.
  Do not estimate the date of death if it is unknown. Record "mm" for unknown day of death, and "mm-mmm" for unknown day and month of death.

Forms

- AP: Automated Perimetry
- AR: Antiretroviral Treatment History
- BH: Baseline Medical History
- BT: Baseline Treatment History
- CC: Cardiovascular/Cerebrovascular Events
- CF: Telephone Contact Form
- CN: Cranial Nerve/Motility Abnormality
- CR: Cardiovascular/Cerebrovascular Risk Profile
- CV: CMV Retinitis
- EE: Eye Exam
- EH: Eye History
- FH: Followup Medical History
- FT: Followup Treatment History
- HL: HIV Viral Load
- HS: Hematology and Serum Chemistry Report
- KC: Keratitis/Conjunctivitis
- LA: Lymphocyte Subset Analysis Report

- MO: Notification of an ocular opportunistic infection
- MP: Missed Photographs Fax
- MV: Missed Visit
- ON: Optic Nerve Abnormality
- QL: Quality of Life (QL)
- RD: Retinal Detachment/Repair
- SD: Syphilitic Eye Disease
- UN: Non-infectious Uveitis
- VA: Visual Acuity/Contrast Sensitivity
- VF: Goldmann Visual Field Record
- VG: Visit Guide
- VQ: Visual Functioning Questionnaire - 25

4.8. Death report closeout procedures

Death report requirements

- **FAX** Death Report (DR) form to the Coordinating Center within 24 hours of notification of patient's death. Do not mail an additional copy of DR form to CC
- Key information required on DR form when faxed to the CC includes: patient ID, clinic ID, date of death, source of death notification, and study physician's opinion as to immediate cause of death, if available
- Complete all other items on DR form as soon as possible and fax updated DR to CC; write on bottom of updated DR form "update to DR form"
- **Call** the CC anytime a DR form or an updated DR form is faxed to CC
- Fax Death Documentation (DD) report to the Coordinating Center as soon as a Death Certificate is obtained and data are recorded onto DD form. Attach copy of Death Certificate (if available) with name obliterated to DD. File Death Certificate with Patient Location form in clinic patient folder.

Closeout of patient data upon notification of death

- Review LSOCA Followup Treatment History (FT), the medical files, and Followup Medical History (FH) to confirm that information reflects complete and accurate drug treatment at time of patient's death
- If not yet obtained, complete the Antiretroviral Treatment History (AR) form and the Cardiovascular/Cerebrovascular Risk Profile (CR) form
- Submit completed form set and all other outstanding forms (eg., AR, CR forms) to Coordinating Center within 2 weeks of submitting Death Report form

4.9. Eye exam and eye history

Purpose

- Screen patients for ocular complications at baseline and followup
- Collect data on the ocular status and history of ocular disease

Forms

- Eye History (EH)
- Eye Exam (EE)

When

- Baseline visit (BL)
- All scheduled clinic visits every 6 months (even numbered followup visits: F2, F4, F6 etc)
- At time of diagnosis of an ocular opportunistic infection

By whom

- Clinic coordinator
- Study ophthalmologist

Equipment

- Ophthalmoscope
- Slit lamp
- Tonometer
- Dilating eye drops

Procedures

- Obtain ophthalmic history data by interview
- Assess condition of the external eye
- Conduct slit lamp examination
- Record cataract grades as needed based on clinical assessment. (Refer to Section 7 of SOCA General Handbook or www.jhucct.com/soca/lsoca/investinfo/investinfo.htm and click on AREDS Clinical Lens Grading System tutorial)
- Measure ocular pressure
- Dilate eyes
- Conduct an indirect ophthalmoscopy exam of fundus

4.10. Fundus photography (Film)

Purpose

- Collect data on status of retina at baseline for all patients, and at all followup visits for patients with major ocular complications
- Evaluate changes to the retina compared to fundus photographs taken at Baseline

Forms

- Photograph Transmittal Log (PT)
- Missed Photographs Fax (MP)

When

- Baseline visit (all patients) and every five years for patients with no ocular opportunistic infection
- Followup visits for patients with an ocular opportunistic infection
- At time of diagnosis of a an ocular opportunistic infection

By whom

- SOCA certified photographer

Equipment

- 50° or 60° fundus camera (Canon, Kowa, Topcon or Zeiss) with external fixation device
- Kodachrome 25 or Ektachrome 100 film
- Dilating eye drops
- Plastic folders capable of holding twelve photographs
- SOCA photograph and folder labels

Procedures

- Check to see if pupils are adequately dilated
- Take a fundus reflex photograph of each eye
- Take nine photographs (F1-F2 stereoscopic & F3-F10) of each eye*
- Label each set of photographs with SOCA photograph labels
- Arrange mounted and labeled photographs in plastic sheets as described in SOCA Fundus Photograph protocol (section 8 of the SOCA General Handbook)
- Label sheet with SOCA sheet label
- Ship to Fundus Photograph Reading Center within 2-4 weeks of date of photography
- Keep one set of photographs in clinic files
- For missed visits and when one or both photographs not taken: record on the Missed Photographs (MP) form. Fax (MP) form if fundus photographs, or a fundus photograph for one eye was not taken. (Note: record in the margin of MP form why one photograph was not taken).

* For more detailed information on fundus photography procedures and field definitions see Fundus Photography Section 8 of SOCA General Handbook. If the clinic wants to keep a set of photographs, 2 sets of photographs should be taken or duplicates should be made

4.11. Digital Color Imaging

Purpose

- Collect data on status of retina at baseline for all patients, and at all followup visits for patients with an ocular opportunistic infection
- Evaluate changes to the retina compared to color images taken at Baseline

Forms

- Photograph Transmittal Log (PT)
- Missed Photographs Fax (MP)

When

- Baseline visit (all patients) and every five years
- Followup visits for patients with an ocular opportunistic infection
- At time of diagnosis of a an ocular opportunistic infection

By whom

- LSOCA certified photographer using digital imaging

Equipment

- 50° or 60° fundus camera (Canon, Kowa, Topcon or Zeiss) with external fixation device
- Certified capture software system: OIS, DHC, Escalon, IMAGEnet, MRP, or VISUPAC
- Dilating eye drops
- SOCA CD labels
- CDs (Imation, Sony or TDK)
- "Soft plastic" polypropylene CD holders or cardboard CD mailers

Procedures

- Check to see if pupils are adequately dilated
- Take a fundus reflex photograph of each eye
- Take nine photographs (F1-F2 stereoscopic & F3-F10) of each eye*
- Anonymize patient information on image files with study information
- Download images to CD using the same capture software whenever possible
- Ship CD to FPRC via UPS or Federal Express or any other courier with tracking option
- Make sure original files are archived at site for future review
- For missed visits and when one or both photographs not taken: record in the margin of the Missed Photographs (MP) form why color image(s) was/were not taken. Fax (MP) form to the Reading Center.

* For more detailed information on fundus photography procedures and field definitions see Fundus Photography Section 8 of SOCA General Handbook.

4.12. Height and weight measurements

Purpose

- To calculate and monitor changes in BMI (body mass index)

Forms

- BH: Baseline Medical History
- FH: Followup Medical History

When

- Height: One time only, at Baseline visit (BL); or the next follow-up study visit (if information was not recorded at a previous visit)
- Weight: Baseline visit (BL) and all follow-up study visits

By whom

- Clinic coordinator
- Study physician

Patient preparations

- Explain the measurements to be taken
- Ask the patient to remove his/her shoes
- Ask the patient to remove his/her excess clothing; weight should be recorded with indoor clothing only
- Check to see that the scale balance is set at "zero"
- Ask the patient to step onto the platform of the scale, facing away from the scale
- Instruct the patient to "stand up straight and tall; keep your back straight and hands relaxed at your side, and your eyes looking straight ahead"
- Review the patient's position

Equipment

- A beam balance scale; or
- An electronic balance scale

Procedures on height measurement

Using a beam balance scale:

- Move height lever into place, touching crown of head (check with your hands)
- Carefully read measurement and record on form
- Lift lever from atop patient's head

Using an electronic balance scale:

- Carefully read measurement and record on the form
- Re-set scale for the next user

Procedures on weight measurement

Using a beam balance scale:

- Stand at back of scale
- Slide bottom weight balance (100 lb) first to patient's estimated gross weight; make sure that the weight balance is locked into its slotted position
- Slide the top arm weight balance into position so that the scale indicator is centered
- Carefully read measurement and record on form

Using an electronic balance scale:

- Carefully read measurement and record on form
- Re-set for the next user

4.13. Hematology

Purpose
- Monitor hematologic values

Form
- Hematology and Serum Chemistry Report form (HS)

When
- Baseline visit (BL)
- All scheduled followup clinic visits
- Missed visit, if applicable

By whom
- Phlebotomist
- Clinic coordinator

Equipment
- Blood for hematology: EDTA tube
- Blood for chemistry: SST gel tube (clot activator)

Procedures
- CBC should include an automated differential
- Absolute Neutrophil Count (ANC): Neutrophils are a type of white blood cell. They are also called "segmented cells", "segs", "polys", "PMNs", or "granulocytes". Immature neutrophils are called "bands". ANC is used to assess the ability to respond to bacterial infections. The ANC is usually available on the complete blood count. If not, it could be calculated using the information from the CBC and differential (which delineates the various kinds of white blood cells):

  ANC = $\frac{[(\%\text{neutrophils} + \%\text{bands}) \times \text{WBC}]}{100}$ or
  ANC = (% neutrophils + % bands) x WBC in thousands x 10 or
  ANC = WBC x (segs + bands) or
  ANC = WBC x (% segs + % bands) or
  ANC = WBC x (% neutrophils)
- Report assessments performed at study visits on Hematology and Serum Chemistry Report
- Hematology results should be from labs drawn the visit time within 2 weeks prior to the LSOCA visit, the visit time window?

Units
- ANC μL (translate the real number from a lab sheet that is reported in thousands, $x10^3$, on the HS Form)
- Platelet μL (translate the real number from a lab sheet that is reported in thousands, $x10^3$, on the HS Form)
- WBC μL (translate the real number from a lab sheet that is reported in thousands, $x10^3$, on the HS Form)

4.14. HIV viral load

Purpose

- Record results of HIV viral load analysis from the patient's medical record if within time window
- If HIV viral load data are unavailable, collect 4 mL of blood for local HIV determination

Form

- HIV Viral Load (HL)

When

- Baseline (determined within 90 days of baseline visit)
- All scheduled followup clinic visits
- Missed visits, if applicable

By whom

- Clinic coordinator
- Study nurse

Procedures

- Data for HIV viral load collected for other studies or clinical care may be used for LSOCA if they are collected within the visit time window
- If HIV data are unavailable, 4 mL of blood should be collected for HIV viral load determinations
- Note: Not more than 45 mL of blood collection at a study visit is allowable per protocol.

4.15. Lost to followup*

Purpose

- Ascertain vital status of patient
- Ascertain patient's drug treatment status since the date of most recent clinic visit
- Document reason(s) patient did not participate in clinic visit(s)

When

- When clinic personnel cannot locate a patient or is out of contact with a patient for 3 months or longer

Form

- Patient Location Information (PL)
- Missed Visit

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 obituaries
- Use Social Security Death Index or National Death Index
- Check state vital records

Procedure

- Complete Missed Visit form on the last day of the visit time window
- For patients who withdraw from the study and no longer want to participate, complete the Missed Visit (MV) form and record in subitem 7g *Patient has withdrawn consent*

*Defined as: Missed at least 3 consecutive in-person visits (Note: patients may return to study visits at anytime)

4.16. Lymphocyte analysis

Purpose
- Collect data on CD4 and CD8 T-cell counts

Form
- Lymphocyte Subset Analysis (LA)

When
- Baseline (BL)
- All scheduled clinic visits (F#)

By whom
- Phlebotomist
- Clinic Coordinator

Equipment
- 5 mL purple-top tube

Procedures
- Lymphocyte results should be from labs drawn within 2 weeks prior to the visit

4.17. Ocular Opportunistic Infections

Purpose

- Collect information on ocular opportunistic infections

Form

- CMV Retinitis (CV)
- Herpetic Retinitis (HR)
- Toxoplasmic Retinitis (TR)
- Choroidopathy (CH)
- Notification of Ocular Opportunistic Infection (MO)

When

- Baseline visit (BL)
- All scheduled clinic visits for patients with an ocular opportunistic infection
- At time of diagnosis of an ocular opportunistic infection

By whom

- Ophthalmologist
- Clinic coordinator

Procedures

- Report examination and treatment information on appropriate ocular complications form(s) at diagnosis and at followup visits
- Fax MO form to CC

4.18. Medical history

Purpose

- Collect information regarding the patient's personal history and health status
- Collect information about prior and current HIV symptoms and disease
- Contain interim laboratory abnormalities for all patients
- Collect information on cardiovascular/cerebrovascular risk factors, and cardiovascular/cerebrovascular events

Forms

- Baseline Medical History (BH); Followup Medical History (FH)

When

- Baseline visit (BL)
- All scheduled followup clinic visits
- At diagnosis of an ocular opportunistic infection
- Death

By whom

- Clinic coordinator
- Study physician

Procedures

- Collect data by interview, review of medical chart, or contact other medical care providers as necessary
- Use HIV-related diagnosis codes (see SOCA General Handbook; section 14.2) to complete the Baseline and Followup Medical History forms
- Obtain blood pressure, height, and weight
- Interview regarding cardiovascular/cerebrovascular events, risk factors, and recreational drug use

4.19. Quality of Life

Purpose

- Ascertain the effects of CMV Retinitis and other ocular complications and their treatment on the patient's quality of life
- Ascertain information on quality of life in patients without ocular complications (QL)

Form

- Quality of Life questionnaire (QL)

When

- Baseline (BL)
- All scheduled clinic visits (F#)
  - every 6 months for patients
- Missed visits

By whom

- Clinic coordinator

General information

- Length of interview: 10-15 minutes
- Some questions are asked in present tense; others ask about patient's functioning and well-being over the past four weeks
- Not all questions will apply to every patient all of the time; however, it is important for all patients to answer all the questions

Procedures

- Conduct interview in a quiet room with minimum distractions. (Preferably, separate patient from family or companions so that only patient's opinions are measured)
- Introduce quality of life component of trial to patient
  - Purpose: "One of the aims of this study is to figure out how AIDS and your medical treatment (particularly treatment for your eyes) is affecting your quality of life. We would like to ask you some questions about how you have been feeling, the kinds of things you are able to do, and your vision.
  - Use response cards and codes provided
  - Patients should give only one answer
- Conduct interview
  - Read all questions **as written**, slowly enough for patients to consider each statement and respond
  - Maintain a uniform pace but avoid a monotonous style
  - Emphasize important words and concepts
  - Record first response, avoid extended discussions of question or response

- After the interview
  - Review form to make sure all questions have been answered
  - Rate the quality of the interview
    - a good interview is one in which the patient was attentive and appeared to respond appropriately throughout
    - a fair interview is one in which you suspect the patient might not have been answering appropriately
    - a poor interview is one in which the patient did not have adequate mental abilities to answer questions. Fill in reason for poor interview, eg, sedation, extreme malaise or dementia
- Telephone interviews
  - If a patient misses a visit for which a quality of life interview is specified, the interview should be conducted via telephone

- Quality of Life form
  - Read the questions to the patient, asking them to tell you which statement best describes what they are able to do and how they feel
  - Show patients the "thermometer" and read the instructions to the patient
  - Have them draw a line from the box marked "your own health state today" to the area on the scale that corresponds with where they perceive their present state of health is on the scale of 0-100

4.20. Release of medical information

Purpose

- Disclose patients' medical records to be used for confidential research purposes related to the Longitudinal Studies of Ocular Complications of AIDS
- Identify study physician and institutional address where patients' medical findings and information regarding patients' examinations, care, treatment and diagnosis can be forwarded

Format

- Open ended release of medical findings (no expiration date)
- Patient signature and date, and witness signature and date required
- All of the above should be included on a consent form under your institutional letterhead (see sample Release of Medical Information form in section 4.21 of this Handbook)

When

- At enrollment to be kept on file

4.21. Sample: Release of Medical Information Form

Date:_____

To:_____ _____
name of patient

_____ _____ _____
address Hospital/patient history # M/F

_____ _____
birthdate

_____ _____
city, state, zip code father's name

_____
mother's maiden name

Dear_____,

I am now, or was at one time, a patient of (name of study physician), and I authorize you to forward to (name of study physician) any and all findings and information in connection with my examinations, care, treatment, and diagnosis, so that my study here may proceed without delay and so that information needed for research purposes can be obtained in full.

Requestor: Name of Study physician:
Clinical Center address:

The information will be used for confidential research purposes related to the Longitudinal Study of Ocular Complications of AIDS.

I understand that I may revoke my consent to release information from my records at any time, but may not revoke consent of the release of information already made in good faith. I also understand that information obtained will be kept strictly confidential and will be used only for study purposes.

Signature_____ Date_____

Witness_____ Date_____

4.22. Serum chemistry

Purpose
- Monitor serum chemistry for all patients

Form
- Hematology and Serum Chemistry Report (HS)

When
- Baseline visit (BL)
- All scheduled followup clinic visits
- Missed visit, if applicable

By whom
- Phlebotomist
- Clinic coordinator
- Local chemistry laboratory

Equipment
- 7 mL untreated blood collection tube (red top)

Procedures
- Calculate creatinine clearance (CrCl) from serum creatinine:

  For males: CrCl= 140 x wt (kg)/(creatinine x 72)
  For females: CrCl= 0.85 x [140 x wt (kg)/(creatinine x 72)]

- Report assessments performed at study visits on a Hematology and Serum Chemistry Report
- Serum Chemistry results should be from labs drawn within the visit time

4.23. Specimen collection, processing and storage

Purpose

- Collection of plasma and leukocyte aliquots
- Freezing and storage of aliquots for monthly batch shipment to Central Repository

Forms

- Specimen Collection/Processing (SC)
- Specimen Tracking (ST)

When

- Baseline (BL)
- All scheduled followup clinic visits

By whom

- Phlebotomist or research nurse
- Clinic coordinator
- Laboratory technician

Equipment

- 8.5 mL yellow-top ACD (Acid Citrate Dextrose) tubes
- 4 mL (red top) polypropylene specimen tubes for plasma (provided)
- 2 mL (clear top) polypropylene specimen tubes for leukocytes (provided)
- Polypropylene labels for tubes (provided)
- Itoya fine point system marking pen for labels (provided)
- -70°C freezer
- Liquid nitrogen storage tank
- Styrofoam box (Mr. Frosty) for slow freeze procedure for leukocytes
- Accuspin tubes with Ficoll, available from Sigma in 12 mL or 50 mL size tubes (if using Accuspin Method for separation of leukocytes)
- Hemacytometer and microscope or flow cytometer for cell enumeration

Reagents for cell preparation

- Dimethyl Sulfoxide (DMSO) - *Store at room temperature. Use as long as it remains clear (4 to 5 years per Sigma Chemical).*
- Cryoprotective medium (10% sterile DMSO and 90% heat inactivated fetal bovine serum (FBS)). *This medium should be prepared fresh for each freezing procedure and cooled to 2 °-8 °C prior to use.*
- Fetal Bovine Serum (used to make cryoprotective medium) - *Store frozen at -20 °C. Note manufacturer's outdate. When needed, rapidly thaw a bottle in a 37 °C water bath, then heat-inactivate in a 56 °C water bath for 30 minutes with occasional shaking. The level of H_2O in the water bath should be as high as the level of the serum in the bottle. Store at 4 °C after thawing. Heat-inactivated FBS has a one month outdate.*
- PBS (Sterile Phosphate Buffered Saline) or HBSS (Hank's Balanced Salt Solution)
- Sterile Ficoll-Hypaque or Lymphocyte Separation Medium (LSM). *Store at room temperature in the dark. Note manufacturer's outdate, date opened, and storage conditions.*
- Trypan Blue Stain (available from Sigma) - *this stains non-viable cells dark blue, and is used to determine the viable cell count of a culture. To prepare a 0.4% solution of Trypan Blue stain, add 0.4 gm Trypan Blue and 1 mL Glacial Acetic Acid to 99 mL distilled H_2O or saline. After dissolving, filter solution through Whatman filter paper or a 0.45 µ filter.*

Prepare all reagents using deionized water, reagent grade I

Preparation and storage of specimens

- Collect 15 mL of blood in two 8.5 mL yellow-top ACD tubes. Blood must be kept at room temperature until processing. Process within 2-4 hours.
- Centrifuge at room temperature (18°-25°C) for 10 minutes at 400 x g (~1500 rpm)
- Affix preprinted labels (aliquots #3, #4, and #5) to three 4 mL polypropylene tubes for plasma
- Affix preprinted labels (aliquots #1 and #2) to two 2 mL polypropylene tubes for leukocytes

Plasma

- Remove plasma from centrifuged tubes, avoiding the cell layer, and transfer to a clear conical centrifuge tube
- Centrifuge separated plasma at 800 x g (2400 rpm) for an additional 10 minutes to remove any contaminating cells and platelets
- Fill three sterile 4 mL specimen tubes labeled with preprinted labels with 3 mL plasma each (do not exceed the 3.6 mL fill line)

- If amount of plasma is low, you may distribute the plasma so that the aliquot labeled as #5 contains as little as 1 mL, but not less. (This aliquot will be sent to a central repository for CMV PCR assay which requires at least 1 mL of plasma).
- Store at -70°C

Leukocytes (viable PBMC)

- Separate, wash, and count separated leukocytes (PBMC):
  - Separate PBMC, via the Accuspin or the Overlay Method, from the blood as follows:
    - Accuspin Method: Carefully pour blood in Accuspin tubes. Rinse original blood tubes with a volume of PBS or HBSS equal to the volume of plasma previously removed and add to the Accuspin tubes (Use 1-2 small Accuspin tubes for blood volumes less than 15 mL). Centrifuge the tubes at room temperature at 800 x g for 20 minutes (turn centrifuge brake off).
    - Overlay Method: Rinse original blood tubes with a volume of PBS or HBSS equal to the volume of plasma previously removed and add back to cells and remaining plasma. Blood should be carefully overlaid at a ratio of 4 parts diluted blood to 3 to be separated. Centrifuge tubes at room temperature at 800 x g for 30 minutes (turn centrifuge brake off).
  - After centrifugation, remove cloudy interface (leukocyte, or PBMC layer) into appropriately labeled 50 mL centrifuge tubes
  - Wash cells by filling tube with sterile PBS or HBSS and centrifuge at 400 x g for 10 minutes
  - Decant supernatant after centrifugation, resuspend cells and fill tube with sterile PBS or HBSS and wash again
  - Resuspend the pellet in 10 mL of PBS or HBSS
  - Count cells and record the number of viable PBMC/mL
    - Pipette 10 µL of the sample into a 0.5 mL microcentrifuge tube, add 90 µL of Trypan blue stain and mix
    - Load a hemacytometer and count the number of PBMC in the four large cells
    - Calculate the number of PBMC/mL: [(PBMC in all four squares)/4] X 10^5

      Example: (88/4) X 10^5 = 2.2 X 10^6 PBMC/mL = 5 million concentration

    - At a minimum 54,105 cell concentration is
  - Resuspend cells to a concentration of 5 x 10^6 (keep on ice) with cold cryoprotective medium. Cryoprotective medium is added dropwise, with constant mixing, over 1-2 minutes.

- Store two leukocyte (PBMC) aliquots and 1 mL cryoprotective medium (see Reagents above) in two 2 mL specimen
- Once the DMSO is added, ensure specimens are frozen at -70° C within 1 minute
- Place the specimen tubes upright in a small insulated styrofoam container (Mr. Frosty) in the bottom of a -70°C freezer for a minimum of 4 hours, then transfer tubes to vapor-phase liquid nitrogen (-135°) for storage. *(Use of the slow-freeze procedure is important in order to recover viable cells.)*

Notes:

(1) Plasma must be stored in 4 mL, and leukocytes in 2 mL polypropylene tubes provided

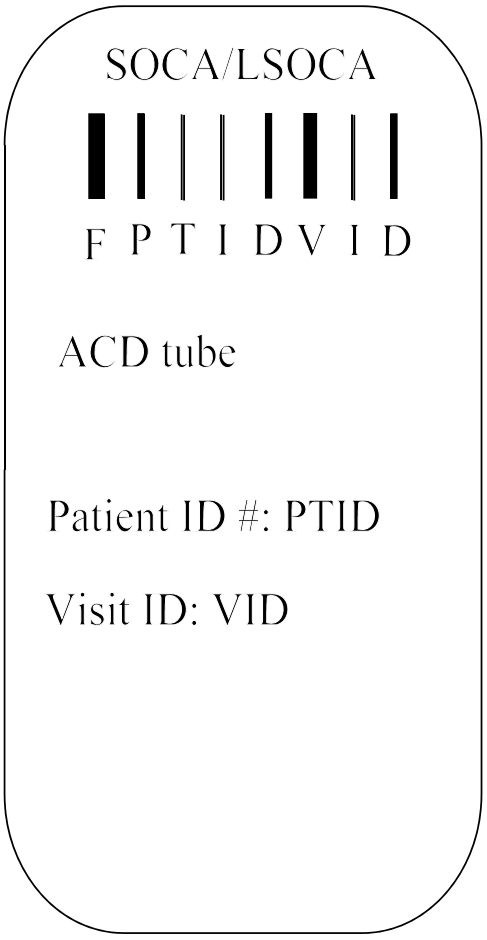
(2) Itoya pen is to be used to create a label whenever a pre-printed label is not available, or to alter a label if necessary

(3) The specimen processing protocol has been adapted from (1) the DAIDS Virology Manual for HIV Laboratories (January 1997), compiled by the Division of AIDS, National Institute of Allergy & Infectious Diseases and Collaborating Investigators, and (2) ACTG Protocol #384

4.23.1. ACD Tube Label Example

ACD TUBE LABEL EXAMPLE

(2 per patient visit)



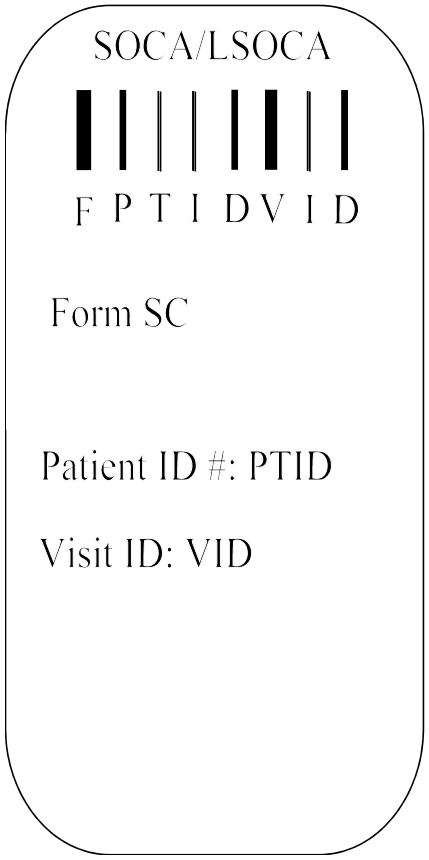
F = Study code (always a "F")
PTID = Patient ID #
VID = Visit ID

(NOTE: 8 Character BarCode)

4.23.2. Form SC Label Example

FORM SC LABEL EXAMPLE

(1 per patient visit)



F = Study code (always a "F")

PTID = Patient ID #

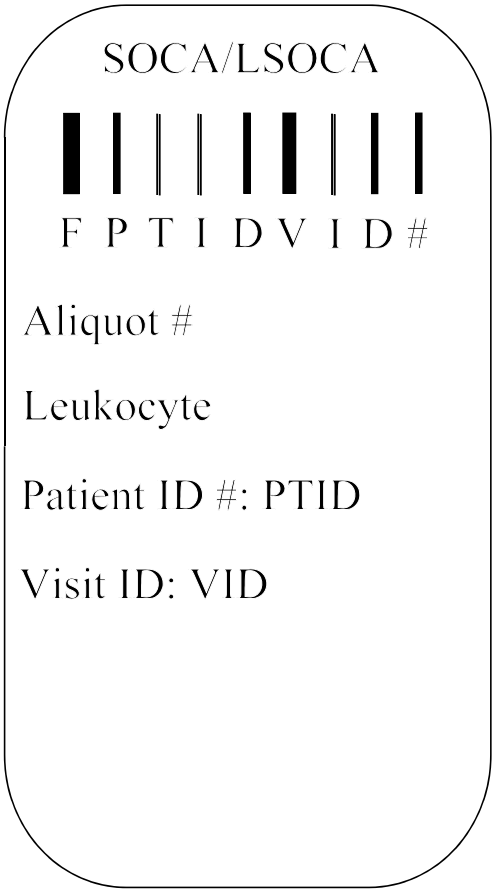
VID = Visit ID

(NOTE: 8 Character BarCode)

4.23.3. Leukocyte Aliquot Label Example

LEUKOCYTE ALIQUOT LABEL EXAMPLE

(2 per patient visit)



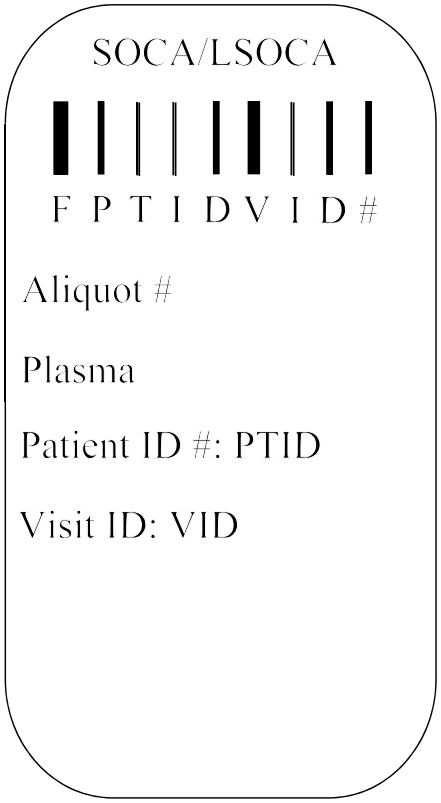
F = Study code (always a "F")
PTID = Patient ID #
VID = Visit ID
# = 1 or 2 for Leukocyte

(NOTE: 9 Character BarCode)

4.23.4. Plasma Aliquot Label Example

PLASMA ALIQUOT LABEL EXAMPLE

(3 per patient visit)



F = Study code (always a "F")
PTID = Patient ID #
VID = Visit ID
# = 3, 4 or 5 for Plasma

(NOTE: 9 Character BarCode)

4.24. Specimen shipment and tracking procedures

Purpose

- Ship aliquots to central repository via diagnostic shipping procedures. Ship to:

  Thermo Fisher Scientific, Inc.
  12401 Washington Avenue
  Rockville, MD 20852
  Telephone: 301-881-2046
  Contact person: (Please refer to the online Personnel Directory)

  Note: Aliquot #7 is for the cell viability testing purposes and will be shipped to the JHU Cell Viability Laboratory (see cell viability page of Handbook).

When

- Batch shipments every three patient visits or once per month, whichever is sooner
- Ship on Monday, Tuesday, or Wednesday

By whom

- Clinic coordinator and person responsible for shipping specimens

Forms

- Specimen Shipment Log (SS)
- Specimen Shipment Fax Coversheet (SF)
- Federal Express Airbill

Equipment

- Shipping container prelabeled with airbill affixed (supplied by Thermo)
  Contents included with shipping container:
  - 1 plastic pressure vessel with orange screw-on lid
  - ISS-I cardboard box
  - White box(es) with dividers
  - 1 absorbent pad
  - 1 foam lid
  - 1 net quantity dry ice label
- Specimen tube labels (supplied by Coordinating Center)
- Specimen tubes
  - 8.5 mL yellow top ACD-treated tubes (supplied by clinics)
  - 4 mL (red top) polypropylene tubes for plasma (supplied by Thermo)
  - 2 mL (clear top) polypropylene tubes for leukocytes (supplied by Thermo)
- Water-proof Itoya marking pen (supplied by Coordinating Center)
- Packing tape
- Specimen Shipment Log (SS) completed and a copy enclosed with specimen shipment

- Specimen Shipment Fax Coversheet (SF) completed and copies faxed to central repository **and** Coordinating Center on day of shipment

Procedures for labeling specimens

- Affix appropriate LSOCA specimen tube labels to tubes:
  - 2 leukocyte aliquot labels
  - 3 plasma aliquot labels
  - 1 label to be affixed to Specimen Collection (SC) form
  - 2 ACD labels to be affixed to 8.5 mL yellow top tubes
- Labels are preprinted. Illustrated examples of the tube labels are on pages 53-56 of this Handbook

Packing plasma and leukocyte specimens

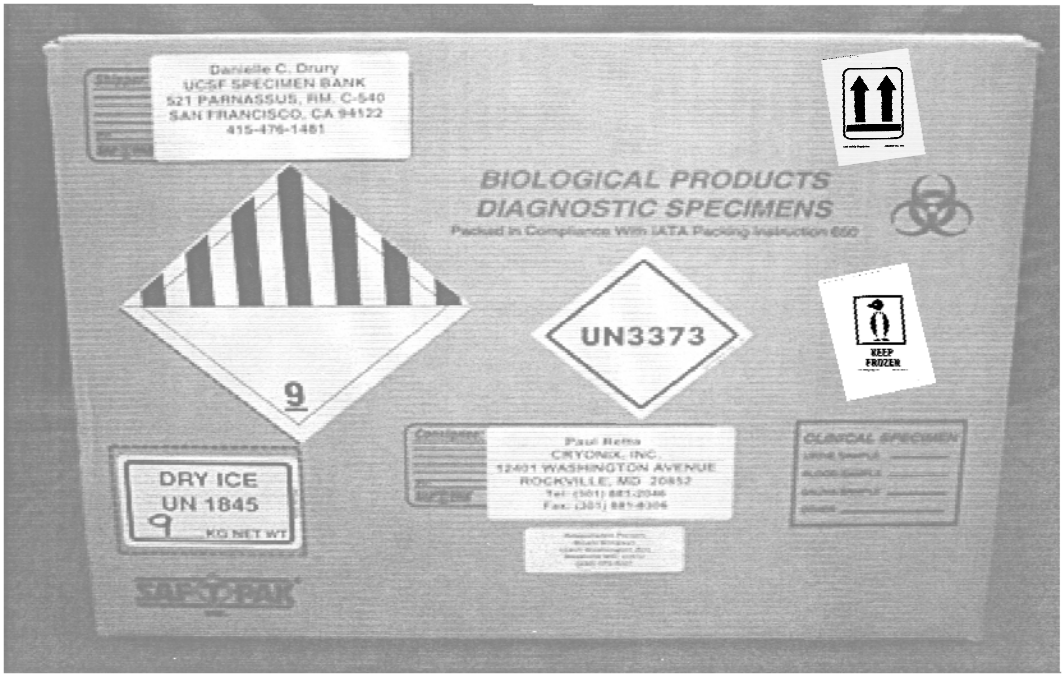
- Place one absorbent pad in bottom of plastic pressure vessel
- Place tube(s) in white cardboard box with divider; one tube per divider
- Place cardboard box(es) **upright** in plastic pressure vessel (with orange screw top cap)
- Lower plastic pressure vessel into center of ISS-I cardboard box
- Surround the ISS-I cardboard box with dry ice all the way to the top
- Total volume of specimens per shipment may not exceed 50 mL (3 patient visits)
- Insert foam lid in top of interior insulated carton, close lid of shipper; secure lid of box with packing tape
- Place a **copy** of Specimen Shipment Log on top of styrofoam lid

Procedure for labeling shipper

- All shipping boxes will be pre-labeled with the following shipper labels (illustration for placement of labels on shipper is on page 60 of this Handbook):
  - Class 9 Dry Ice (diamond shaped) label
  - "Inner packages comply with prescribed specification" label
  - Dry ice label UN1845, 9 kg net wt
  - "Air eligible" sticker
  - UN3373 (diamond shaped) label
  - "Keep frozen" (penguin) label
  - "Double upward arrows" label
- **Do not write on the shipper box**
- Shipper consignee and responsible person address labels are affixed
- Attach Federal Express Airbill to exterior of box
- Arrange for priority shipment next day delivery via Federal Express no later than 4:30 p.m. Eastern time

Specimen Shipment Log and Tracking Form

- Complete a Specimen Shipment Log (SS) to document contents of shipper at time of shipment
- Enclose copy of SS Log in shipping container
- Keep the original SS Log
- Fax copies of the Specimen Shipment Fax Coversheet (SF) to the central repository **and** Coordinating Center on same day as shipment



4.25. Treatment history

Purpose

- At baseline (BL), record information regarding use of antiretroviral and CMV medications ever taken and information regarding other medications taken within the 28 days prior to enrollment into LSOCA
- Record information regarding current and interim (between study visits) use of prescription and experimental medications

Forms

- Baseline Treatment History (BT)
- Followup Treatment History (FT)

When

- Baseline visit (BL)
- All scheduled followup clinic visits (F#)

By whom

- Clinic coordinator
- Study physician

Procedures

- Collect data by interview and review of clinical charts
- Use Drug Code list (in SOCA Drug Code Book) to complete Treatment History form
- For drugs not listed:
  - check the "unknown (category)" section of the drug codes book pg. 164-174) (e.g. unknown antibiotics = 08122810)
  - use the code 99999999 for drugs that don't fix a listed unknown category
- Record dose and frequency for antiretroviral and CMV medications
- Record dose and frequency for other medications taken within the past 28 days

4.26. Visual acuity/refraction

Purpose

- Collect baseline and followup data on visual acuity

Form

- Visual Acuity (VA)

When

- Baseline visit (BL)
- All scheduled followup study clinic visits (F#)
- At time of diagnosis of an ocular opportunistic infection

By whom

- Certified refractionist/visual acuity examiner

Equipment and room requirements

- Lensometer
- Trial frames and lenses
- Phoropter
- ETDRS visual acuity charts (charts 1 and 2)
- ETDRS modified Near Cards for patients who are bedridden
- R chart or other chart for refraction
- Illuminated light box for charts (75 to 125 foot candles)
- Visual Acuity Lane (50 to 100 foot candles)
- Marks on the floor of visual acuity lane at 10 feet, 5 feet, and 2.5 feet (or 4m, 2m, and 1m)
- AEMC Digital Lightmeter (Model 810)

Procedures

Refraction

- Refraction will be performed for the right, or better seeing, eye first; then the left, or other eye
- Eye not being refracted is occluded
- Steps for refracting each eye include:
    1. Determination of beginning approximate refraction
    2. Preparation for subjective refraction
    3. Determination of spherical power
    4. Determination of cylindrical axis
    5. Determination of cylindrical power
    6. Refinement of spherical power
- Any chart except Visual Acuity Charts 1 and 2 may be used for refraction

4.26. Visual acuity/refraction

Standard visual acuity

- Visual acuity will be performed for the right, or better seeing, eye first; then the left, or other eye
- Eye not being tested is occluded
- Visual Acuity Chart 1 will be used for the right eye
- Visual Acuity Chart 2 will be used for left eye
- Steps in visual acuity exam include:
    1. Patient is positioned 10 feet (or 4m) from chart with eye aligned with chart
    2. Patient is asked to start at top line on chart and continue reading
    3. Patient reads chart until he cannot guess a single letter on a line, or he reads the smallest line on the chart
    4. If patient cannot read all 5 letters on top line, move to 5 feet (or 2m) and give instructions 2 and 3 (adjust refraction by adding an additional + 0.25 sph)
- If patient cannot read all 5 letters on top line at 5 feet, move to 2.5 feet (or 1m) and give instructions 2 and 3 above (adjust refraction by adding an additional + 0.75 sph)
- If patient can read nothing at 2.5 feet, (or 1m) assess as follows:
    1. Can the patient count fingers at 2.5 feet (or 1m)
    2. Can the patient see hand motions at 2.5 feet (or 1m)
    3. Does the patient have light perception
    4. If the patient cannot do any of the above, the assessment is no light perception

Visual acuity for patients who are bedridden

- Visual acuity will be performed using modified ETDRS Near Cards for bedridden patients unable to take standard visual acuity exam
- Glasses may be worn if appropriate
- Visual acuity will be performed for right eye first, then the left eye
- Ample overhead lighting

For detailed instructions of each step of refraction and visual acuity, and for instructions for visual acuity testing with near cards, see Section 9 in SOCA General Handbook.

4.27. Visual Functioning Questionnaire - 25

Purpose

- Measure the dimensions of self-reported vision - targeted health status

Form

- Visual Functioning Questionnaire - 25

When

- Baseline (BL)
- All scheduled clinic visits: every 6 months
- Missed visits

By whom

- Clinic coordinator

General information

- Length of interview: 10 minutes

4.28. Visual field assessments

4.28.1. Goldmann visual field assessment

Form

- Visual Field Form (VF)
- Goldmann VF printout for each eye tested
  - use patient ID for name written on the printout
  - attach copy to VF form

When

- Baseline visit (BL)
- All clinic followup visits for patients with an ocular opportunistic infection
- At time of diagnosis of an ocular opportunistic infection

By whom

- Certified visual field examiner

Equipment

- Goldmann perimeter
- Dark, quiet room
- IV-4-E test object

Procedures

- Pupils may be dilated (this is not required)
- Visual fields will be assessed for the better eye first, then the other eye
- Occlude eye not being tested
- Testing at every 30° meridian
- Testing starts at extreme extent of the periphery using IV-4-E test object
- IV-4-E test object is moved at uniform speed radially along one of the test meridians toward the center

For detailed instructions of the visual field measurement, see Visual Field Assessment Section 10 of SOCA General Handbook.

4.28.2. Humphrey automated perimetry

Forms
- Automated Perimetry Form (AP)
- Humphrey Field Analyzer HFA printout for each eye tested
  - affix printed label to upper right hand corner
  - do not cover any information with label
  - if information identifying the patient appears on the printout, black it out.

Purpose
- Collect data on extent and threshold of visual field

Electronic Data Storage Instructions
- Store a diskette containing the electronic version of the visual field data locally
- Affix printed label to diskette

When
- Baseline visit (BL)
- Annual followup visits
- At time of diagnosis of an ocular opportunistic infection

By whom
- Visual field examiner certified in automated perimetry

Equipment
- Humphrey Field Analyzer (HFA) I or II; either the 600 series or the 700 series; threshold test 24-2
- Dark, quiet room
- Eye patch/occlusion device

Set-up procedures
- Attach label provided by Coordinating Center to the electronic data diskette. Label includes: study acronym (LSOCA) and clinic ID code
- If your clinic has both the 600 and 700 series, use one model for LSOCA testing consistently
- Load diskette
- Follow instructions for the Humphrey Field Analyzer at your clinic
- Enter patient data
  - Patient ID: Patient ID number, e.g., 1309
  - Patient name: key clinic ID code and patient name code, e.g., JHU JACAN for Johns Hopkins University, Jim A. Canner
  - Birthday: key date of birth with leading zeros and dashes, e.g., 08-07-63 (MM-DD-YY)
- Enter specific visual acuity and refraction data obtained from the current study visit

- Threshold Parameter Setup for the 600 series
  - Ensure that the following parameter specifications are selected:

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

- Threshold Parameter Setup for the 700 series
  - Ensure that the following parameter specifications are selected:

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 600 series requires that the foveal threshold be turned on manually. Whereas the 700 series does this automatically.

Instructions to patient

- Explain the examination to the patient including an estimate of how long it will take
- Instruct the patient as follows: "Always look straight ahead at the steady yellow light. Other lights will flash one at a time off to the side. Some will be bright, some dim. Press the button whenever you see one of these lights. You are not expected to see all of them. The test is designed so that you may see fewer than half of them. Blink normally so your eyes do not get dry. The best time to blink is just as your press the button. If you want to rest, hold down the button. The test will resume when you release the button".

Test Instructions

- Place appropriate corrective lens in holder. Adjust the trial lens holder close to the patient so that it almost touches the patient's eyelashes.
- Select the 24-2 threshold test
- Instruct the patient to fixate at a point in the center of the four lights that appear on the bowl
- Pause test as necessary to allow the patient to rest. Monitor fixation and re-instruct patient

as necessary

- Test the right, or better seeing, eye first
- At the end of test, save data to diskette (labeled with study, clinic, patient, and visit ID, with today's date and examiners certification number and initials filled in)
- Print Humphrey Field Analyzer (HFA) printout for the right eye
- Review printout for accuracy
- Attach Right/Left Eye label to the upper right hand corner of the printout; the label should not cover any part of the printout
- Setup and run the test for the left/other eye in the same manner
- At the end of test, save data to diskette
- Print Humphrey Field Analyzer (HFA) printout for the left/other eye
- Review printout for accuracy
- Attach Right/Left eye label to the upper right hand corner of the printout; the label should not cover any part of the printout
- If the patient's name, hospital ID code is on the HFA printout, use the printed HFA labels provided at enrollment to cover the identifying information

4.29. Specimen collection for cell viability testing

Purpose

- To obtain blood for preparation of aliquots for cell viability testing
- To compare cell viability results prospectively and at 3 month intervals

Patient selection/collection procedures

- CC to schedule 3 clinics per month on a rotating basis to collect, process and ship aliquots for cell viability testing
- Clinic to select 3 patients (newly enrolled or at followup) during assigned month
- Clinic to obtain 8.5 mL of whole blood from 3 patients seen during assigned month
- Ongoing blood collection in subsequent years for cell viability testing to be scheduled yearly

Blood processing procedures

- Collect 8.5 mL of whole blood in a yellow-top ACD tube - (Note: total amount of blood collected on any one date may not exceed 45mL/patient/visit)
- Collect and process blood for cell viability purposes on Monday, Tuesday, and Wednesday only
- Process leukocytes from whole blood per LSOCA cell separation instructions (see LSOCA Handbook, section titled *Specimen collection, processing and storage)*
- Obtain two 2 mL aliquots of cells and label the aliquot cryogenic tubes with preprinted labels designating aliquot #7 and #8
  - Aliquot #7 to be tested for viability within 2 days of collection and separation
  - Aliquot #8 to be tested for viability every 3 months

Aliquot #7 freezing/shipping instructions

- Freeze aliquot #7 in a Mr. Frosty or comparable slow freeze at 1 ºC per minute in a -70 ºC freezer for a minimum of 4 hours (maximum of 24 hours) and ship on dry ice on the same day specimen was processed to JHU Laboratory. This is the preferable freezing and shipping schedule.
- The following freezing and shipping scenarios are to be followed **only if processing, freezing and shipping of aliquot #7 cannot occur on same day:**
  - *Procedures to store frozen aliquot #7 for shipment next day* - If blood is collected and aliquot #7 cannot be shipped until the next day, than collect, process (including minimum of 4 hours for slow freeze) and transfer aliquot #7 to a -70 ºC freezer overnight and ship next day on dry ice
  - *Procedures to store frozen aliquot #7 if cannot be shipped for more than 2 days (e.g., over a weekend) after specimen is processed* - If blood is collected and processed (including slow freeze for minimum of 4 hours) and aliquot #7 cannot be shipped for several days, perform a slow freeze for a minimum of 4 hours and transfer aliquot #7 to a -70 ºC freezer over the weekend and ship on dry ice on the following Monday

Aliquot #8 freezing/shipping instructions

- Freeze aliquot #8 in a Mr. Frosty or comparable slow freeze at 1 °C per minute in a -70 °C freezer for a minimum of 4 hours (maximum of 24 hours)
- Store aliquot #8 in a -70 °C freezer at the local clinic
- Ship all aliquot #8 samples to Thermo on dry ice **within 5 weeks of freezing locally at -70 °C on dry ice**

Procedures for labeling specimens

- Use a water-proof cryomarker pen, record Patient ID, Visit and Date onto the following preprinted labels (supplied by Thermo):
  - ACD Whole blood tube
  - LSOCA Aliquot #7 LEUKOCYTE
  - LSOCA Aliquot #8 LEUKOCYTE
- Place the preprinted polypropylene label marked ACD Whole Blood Tube onto the 8.5 mL yellow top ACD-treated tube
- Place the pre-printed polypropylene labels marked LSOCA Aliquot #7 Leukocyte and LSOCA Aliquot #8 Leukocyte onto two 2.0 mL cryogenic vials
- Affix appropriate LSOCA cell viability labels to cryogenic vials prior to freezing

Forms

- Complete and fax the Cell Viability/Recovery Specimen Shipment Log (VC) to Stacey Meyerer/Ruth Namuyinga /Samantha Bragan (FAX: 410 614-2640) at JHU Laboratory on same day shipping aliquot #7 and enclose copy of Specimen Log with the shipment. Keep a copy for your files
- Federal Express Airbill

Shipping instructions

- All aliquots should be shipped via Federal Express Next Day Arrival following diagnostic shipping procedures (see Handbook or PPM 70)
- Ship aliquot #7 on same day specimen processed (Monday, Tuesday, Wednesday only) to JHU Laboratory. Ship to:

  Contact person: (Please refer to the online Personnel Directory)
  Johns Hopkins University
  Bloomberg School of Public Health
  615 North Wolfe Street, Room E1205
  Baltimore, MD 21205
  (410) 955-7205

- Batch ship aliquot #8 on Dry Ice via Federal Express Next Day Arrival. Ship to:
  Thermo Fisher Scientific, Inc.
  12401 Washington Avenue
  Rockville, MD 20852
  (301) 881-2046
  Contact person: (Please refer to the online Personnel Directory)

Procedures for packing and labeling specimen shippers

- See LSOCA Handbook for packing and labeling procedures