RETROVIRUS EPIDEMIOLOGY DONOR STUDY (REDS)

Operations Manual
Version 4

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Sponsored by:

The National Heart, Lung, and Blood Institute (NHLBI)
National Institutes of Health (NIH)

Blood Center Participants:

American Red Cross Blood Services - Greater Chesapeake and Potomac Region
American Red Cross Blood Services - Southeastern Michigan Region
American Red Cross Blood Services - Southern California Region
Irwin Memorial Blood Centers/University of California, San Francisco
Oklahoma Blood Institute

Medical Coordinating Center: Westat, Inc.

Central Laboratory: SRA Technologies

1. STUDY OVERVIEW AND INTRODUCTION

The Retrovirus Epidemiology Donor Study (REDS) is a multi-center collaborative effort sponsored by the National Heart, Lung, and Blood Institute (NHLBI). The REDS protocols have been developed by working committees comprised of representatives from the five participating Blood Centers, the Coordinating Center, and the Central Laboratory. Study protocols are administered by the local blood centers, with central coordination, protocol monitoring, database management, and data analysis responsibilities handled by the Coordinating Center. Westat, Inc. was selected for this role, with SRA Technologies, Inc., serving as the Central Laboratory. The blood centers chosen for REDS include three American Red Cross centers (Southern California, Southeastern Michigan, and the Greater Chesapeake and Potomac Regions), and two independent blood centers (the Oklahoma Blood Institute in Oklahoma City and Irwin Memorial Blood Centers/the University of California at San Francisco (UCSF).

REDS is comprised of the following five major study components.

- **Monitoring** -- A database containing comprehensive demographic data on donors and test result information for each blood donation at the REDS centers (discussed in Chapter 2 of this manual).
- **Population-Based Repositories** -- Repositories of serum (the GSR), leukocyte and plasma aliquots (the GLPR) from a large representative sample of the donor population at the REDS centers (discussed in Chapter 3 of this manual).
- **Repositories of Special Interest** -- Special repositories of serum and cells from selected donor subgroups (discussed in Chapter 4 of this manual).
- **Donor Survey** -- Large-scale anonymous mail surveys to assess and quantify risk behaviors for infectious disease, and obtain information about donor experiences with recent donations (to be included as Chapter 5 of this manual, late 1995).
- **HTLV Cohort Study** -- A case-control study of the risk behaviors associated with HTLV infection with prospective longitudinal follow-up to evaluate health outcomes of infection (discussed in Chapter 6 of this manual).

Activities in support of each of these components have been underway since late 1990. A recent extension of REDS is supporting data collection through 1997 and data analysis through August 1998.

This version of the operations manual (Version 4) provides updated procedures, which should be implemented at all REDS Blood Centers to carry out the study requirements as outlined in the protocols (available as separate documents). Each Blood Center is responsible for establishing any specific procedures which are not addressed in this operations manual. These procedures should be documented and available to the Coordinating Center and NHLBI, upon request. Archival information and reference materials on general procedures, the General Serum Repository, Phases One and Two of the HTLV Cohort Study, and examples of study forms no longer in use, can be found in Version 3 of the REDS Operations Manual with accompanying Field Memos #1 through #55. Where relevant, information from these field memos has been incorporated into this version of the operations manual.

Three computer systems have been developed and recently modified to assist Blood Centers in carrying out tasks associated with Phase Three of the HTLV Cohort Study, and in processing specimens for the general population and special repositories:

(1) The General Leukocyte/Plasma Repository Database System;

(2) The Special Repository Database System; and

(3) The HTLV Tracking System.

User guides have been written and distributed for each of these systems as separate documents.

Requests for additional copies of any study materials should be directed to the appropriate individual(s) at the Coordinating Center. A listing of contact names for the different study components is provided in the front of this operations manual.

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2. MONTHLY DONATION RECORDS

2.1 Introduction

A well-developed database on blood donations, which can provide prevalence and incidence estimates of infectious disease markers (e.g. HIV, hepatitis), is key to helping ensure the safety of the blood supply. From these data, estimates of the risk of disease transmission, impact of changing screening methodology and test performance also can be derived. Coupled with demographic information, a monitoring system that provides quick and accurate data is invaluable. REDS investigators have made the creation of such a database a high priority; therefore, monthly donation records will be collected from all REDS Blood Centers through December 1997.

The REDS donation database is also used for the following purposes:

- To select a representative sample of donors to receive the REDS donor survey;
- To initially identify repeat reactive donors for potential recruitment into the HTLV Cohort Study and HIV-indeterminate special repository;
- To select HTLV-negative controls for the HTLV Cohort Study; and
- To provide demographic information about donors included in the General Serum Repository (GSR) and the General Leukocyte/Plasma Repository (GLPR).

This chapter details the donation data collected for REDS, and the methods the Blood Centers should use to obtain this information and report it to the Coordinating Center.

2.2 Collection of Short Form Data Items

To provide continuous demographic profiles on the donor population, each Blood Center has added certain items (referred to as "short form" data items) to their existing donor registration forms (DRFs). This has been accomplished by either stamping or overlaying the questions onto the DRF, printing new DRFs, or by developing a separate form containing these questions, at the discretion of each center.

Short form data items collected are in response to the following questions:

(1) Have you ever received someone else's blood?

(2) Were you born in the U.S.? (If no, in what country were you born?)

(3) How much school have you completed?

(4) Are you of Hispanic/Spanish origin? (If yes, what type?)

(5) What is your race?

Responses to Questions 3 through 5 are printed on a blue laminated response card supplied to each Blood Center (see Exhibit 2-1). Subjects may be given the response card from which to choose their answers to these questions. Codes which correspond to the donor's responses should be recorded on the DRF.

Since some community and individual issues may arise in response to the collection of racial and educational data, Blood Center staff should be familiar with the purpose and goals of this study, as well as the increased ability these data afford the centers to serve minority patients in need of rare blood types. All nursing and registration staff should be informed about the workscope and goals of this component of REDS. Any donor inquiries related to the collection of short form data should be answered fully and confidently by Blood Center staff. If questioned specifically about the collection of racial and/or educational data, the staff should stress that the responses to these questions are voluntary. If a question or situation arises that cannot be dealt with by the staff, the donor should be referred to a nursing supervisor. The nursing supervisor then has several options available, including referral to the Blood Center's REDS Principal Investigator, if appropriate. Exhibit 2-2 provides detailed information on why collection of the short form data is so important.

After the short form items on the DRF have been completed by the donor, Blood Center staff should review the responses to make sure they are complete. If possible, any missing or unclear responses should be discussed with the donor and corrected on the DRF. Responses should be edited to make sure that the code letters from the blue response card have been entered correctly.

If the donor has provided the name of a country of birth (other than the U.S.), the center staff must assign a code to the country, using the code list developed by the Coordinating Center (see Exhibit 2-3). The assigned code should be marked clearly on the form so that Blood Center data entry

staff will be able to routinely key this code along with all other donor information. Some centers may have alternative plans for entering country codes into the database (e.g., scanning bar code labels for the country codes). These methods are acceptable -- the only requirement is that codes rather than country names appear on the data file sent monthly to the Coordinating Center.

2.3 Preparation of REDS Monthly Data File

Requirements for preparing the REDS monthly data files have been communicated to key data management personnel at each Blood Center by the Coordinating Center, and are detailed in this section for reference purposes. A specific day of each month has been agreed upon by each center for preparation of a magnetic computer tape or diskette containing one record for each donation at the center during the previous month (including short form data). This tape or diskette should be sent to the Coordinating Center, to arrive each month by the agreed-upon date.

On the data file, each donation must be identified by both a Whole Blood Number/Blood Unit Identifier (WBN/BUI) and Donor ID. Both identifiers are important for the Coordinating Center to be able to link all donations from a particular donor. For confidentiality reasons, the files sent to the Coordinating Center should never contain information which could be used to identify an individual. Each Blood Center must maintain the link between the Donor ID and the donor's identifying information to facilitate donor contact, if necessary in the future.

Exhibit 2-4 lists items to be included on each monthly data file sent to the Coordinating Center, and the requirements for field length, codes, and format of each.[1] Exhibit 2-5 provides lists of valid codes for each field variable. All Blood Centers must conform to this format, unless other arrangements have been made directly with the Coordinating Center's data management staff. At the time the file is produced each month, it is possible that not all required data items will be available for all donations through the last day of the previous month. This may be particularly true for some of the laboratory results. If not all data items are available, that donation record should not be included in the file, but rather held for inclusion the following month when a complete record can be provided.

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[1] The tape/diskette format should be as follows: ASCII; density 6250 (for magnetic tape only); record length of 128; and block size of 256. The last 46 characters should be filled with blanks, for use if additional data are collected in the future.

Records for all types of donations must appear on the file; however, only records for persons who actually donated blood should be included (i.e. information on persons who were deferred prior to donating should not be included). Data on donors who confidentially exclude (CUE) after donation should appear on the file since a donation was collected. Records on donors whose blood was not completely tested for any reason should also be included.

EXHIBITS

Exhibit 2-1. Short Form Response Card

Choose the letter next to the answer that applies to you. Write the letter in the space on the donor form. These answers are optional.

How much school have you completed?

A = 8th grade or less
B = 9th, 10th, 11th, or 12th grade (no diploma)
C = High school graduate (high school diploma or equivalent, for example GED)
D = Some college or technical school
E = Bachelor's degree (for example BA, AB, BS)
F = Master's or professional degree (for example MA, MS, MEd, PhD, MD)

If you are of Hispanic/Spanish origin, choose the group that you identify with:

A = Mexican, Mexican-American, or Chicano
B = Puerto Rican
C = Cuban
D = Other Hispanic/Spanish

Thank you for your help!

Choose the race that you identify with:

White
A = White
Black
B = Black, African-American
C = Black, Caribbean
D = Black, Other
American Indian
E = Indian, North American
F = Indian, South American
G = Indian, Central American
Asian or Pacific Islander
H = Asian Indian
I = Chinese
J = Filipino
K = Hawaiian native
L = Korean
M = Vietnamese
N = Japanese
Alaskan Native
O = Eskimo or Aleut
Other
P = Other racial group

Exhibit 2-2. Justification for Collecting Short Form Data

It is important to collect information on race/ethnicity from all donors for the following reasons:

1. **To screening the blood inventory for rare blood group phenotypes**

   For example, the Duffy A and Duffy B blood group antigens are common in Caucasian individuals but frequently absent in black donors. Consequently, when a Duffy antigen-negative black donor is exposed to antigen-positive blood (due to childbirth or transfusion), antibodies to the Duffy antigens are produced. This complicates subsequent transfusion therapy due to the reaction of host antibody against transfused Duffy antigen-positive red blood cells. Since this transfusion reaction can be life threatening, blood banks are frequently called upon to screen existing inventories for red cell products that do not contain the Duffy antigen. Since typically greater than 80% of U.S. blood donors are Caucasian, and 90% of Caucasian donors carry this antigen, it would be preferable for the Blood Center to be able to target its screening programs to find appropriate blood units in the shortest time to provide support to an antibody positive patient in need of transfusion.

2. **To allow targeted screening for rare antigens**

   Examples would include the high prevalence of anti-platelet antibodies in Japanese donors, and the unusual HLA phenotypes important for bone marrow transplantation and apheresis procedures. This issue has received nationwide media coverage based on extensive searches conducted on behalf of local leukemia patients whose life-saving marrow transplants depend on the identification of HLA-matched marrow donors.

3. **To enhance donor recruitment**

   Minority donors are a major untapped resource for homologous whole blood donations. Despite the importance of race/ethnicity data, few Blood Centers have access to an accurate racial composition of their own donor base. For example, many advantages are offered by the ability to target Hispanic donors. The high prevalence of the O-positive blood type in this population makes them a strong target for recruitment efforts. Improvement of minority blood donor recruitment is a major goal of the National Heart, Lung, and Blood Institute (NHLBI).

4. **To provide background and control data**

   These data may be used for comparison with information from studies that collect data primarily from donors of specific interest, such as those who carry a specific blood or infectious disease marker.

5. **To define any problems associated with current donor educational materials**

   This may include considerations of cultural relevance, reading levels, and existing donor knowledge and reading interest. This information will be important in designing improvements at both the local and national level.

Exhibit 2-3. Geographic Locations and Country Codes

Directions: Use the list on the following pages to find the code corresponding to donor's country of birth as it is written on the Donor Registration Form. Before data files are forwarded to the Coordinating Center, country of birth must be assigned one of these three-digit codes. Note the following:

- ***The code for USA is "000" (to be added at the time the tape is created); and***
- ***Any country for which there is no code from the following list should be coded "XXX" (unless other arrangements have been made with the Coordinating Center).***

Exhibit 2-3. Geographic Locations and Country Codes (continued)

U.S. POSSESSIONS

American Samoa 060
Baker Island 064
Guam 066
Howland Island 084

Jarvis Island 086
Johnston Atoll 067
Kingman Reef 089
Micronesia 075
Midway Islands 071

Navassa Island 076
Northern Mariana Island 069
Palmyra Atoll 095
Puerto Rico 072

Trust Terr. Pacific Island 075
Virgin Islands 078
Wake Island 079
U.S. Military Base .....
(any location) 935

FOREIGN COUNTRIES

Afghanistan 110
Africa 115
Albania 120
Algeria 125
Andorra 140

Angola 141
Anguilla 142
Antarctica 143
Antigua & Barbuda 149
Argentina 150

Ashmore & Cartier Island 155
Australia 160
Austria 165

The Bahamas 180
Bahrain 181
Bangladesh 182
Barbados 184

Bassas Da India 187
Belgium 190
Belize 227
Benin 311

Bermuda 195
Bhutan 200
Bolivia 205
Botswana 210
Bouvet Island 212

Brazil 220
Br. Indian Ocean Terr 228
British Virgin Islands 231

Brunei 232
Bulgaria 245
Burma 250
Burundi 252

Caicos Islands 906
Cambodia 255
Cameroon 257
Canada 260

Cape Verde 264
Caribbean
(unspecified country) 266
Cayman Islands 268
Central African Rep. 269
Central America 270
Chad 273

Chile 275
China 280
Clipperton Island 282
Colombia 285

Comoros 286
Congo 290
Cook Islands 293
Coral Sea Islands 294

Costa Rica 295
Cuba 300
Cyprus 305
Czechoslovakia 310

Denmark 315
Djibouti 317
Dominica 318
Dominican Republic 320

Ecuador 325
Egypt 922

Exhibit 2-3. Geographic Locations and Country Codes (continued)

El Salvador....330
England....925

Equatorial Guinea....332
Europa Island....334
Ethiopia....335
Faroe Islands....336

Falkland & Isl. Malvinas....337
Fiji....338
Finland....340
France....350

French Guiana....355
French Polynesia....367
Fr. Southern & Antarctic....369
Gabon....388

Gambia....389
Gaza Strip....393
Germany....394
Germany, Berlin....960

Germany, Federal Rep. of (West)....394
German Democratic Rep. (East)....395
Ghana....396
Gibraltar....397

Glorioso Island....399
Great Britain....925
Greece....400
Greenland....405

Grenada....406
Guadeloupe....407
Guatemala....415
Guernsey....416

Guinea....417
Guinea-Bissau....737
Guyana....418
Haiti....420

Heard Is....424
Holland....630
Honduras....430
Hong Kong....435

Hungary....445
Iceland....450
India....455

Indonesia....458

Iran....460
Iraq....465
Iraq-Saudi Arabia....467
Ireland....470

Isle of Man....588
Israel....475
Italy....480
Ivory Coast....485

Jamaica....487
Jan Mayen....488
Japan....490
Jersey....495

Juan De Nova Island....497
Jordan....500
Kampuchea....255
Cocds (Keeling) Islands....284

Kenya....505
Kiribati....398
Korea, Dem. Peoples Rep. (North)....514
Korea, Republic of (South)....515

Kuwait....520
Laos....530
Lebanon....540
Lesotho....543

Liberia....545
Libya....550
Liechtenstein....553
Luxembourg....570

Macau....573
Madagascar....575
Malawi....577
Malaysia....580

Maldives....583
Mali....585
Malta....590
Manchuria....280
Martinique....591

Mauritania....592
Mauritius....593
Mayotte....594

Exhibit 2-3. Geographic Locations and Country Codes (continued)

McDonald Island 424

Mexico 595
Monaco.....607
Mongolia.....608
Montserrat.....609

Morocco 610
Mozambique 615
Namibia.....821
Nauru.....621

Nepal 625
Netherlands.....630
Netherlands Antilles.....640
New Caledonia 645

New Zealand.....660
Nicaragua.....665
Niger 667
Nigeria 670

Niue.....672
Norfolk Island 683
North America.....684
Norway.....685
Oman 616

Pakistan 700
Palestine 705
Panama.....710
Papua New Guinea.....712

Paracel Islands.....714
Paraguay 715
Peru.....720
Philippines.....725

Pitcairn Islands 727
Poland 730
portugal 735
Portugese Timor.....738

Qatar.....747
Romania.....755
Russia 825
Rwanda.....758

St. Christopher & Nev. 763
St. Helena 765
St. Lucia 770

St. Pierre & Miquelon 773

St. Vincent/The Grenad.....775
Sahara, Western 831
San Marino 782
Sao Tome & Principe 783

Saudi Arabia 785
Senegal 787
Seychelles.....788
Scotland.....925

Sierra Leone 790
Singapore 795
Solomon Islands 229
Somalia.....800

South Africia.....801
South America 802
Soviet Union 825
- Armenia.....825
- Azerbaijan 825
- Byelorussia 825
- Estonia 825
- Georgia.....825
- Kazakh 825
- Kirghiz 825
- Latvia.....825
- Lithuania.....825
- Moldavia.....825
- Russia 825
- Tajik 825
- Turkmenistan 825
- Ukraine.....825
- Uzbekistan.....825

Spain 830
Spratly Islands 833
Sri Lanka 272
Sudan.....835

Suriname.....840
Svalbard.....845
Swaziland.....847
Sweden.....850

Switzerland.....855
Syria 858
Taiwan 281
Tanzania, United Republic of.....865

Exhibit 2-3. Geographic Locations and Country Codes (continued)

Thailand.....875
Togo 883
Tokelau 884
Tonga886

Trinidad and Tobago 887
Tromelin Island.....889
Tunisia 890
Turkey.....905

Turks Island.....906
Tuvalu.....908
Uganda.....910
United Arab Emirates 888

United Kingdom.....925
United States.....926
Upper Volta.....927
Uruguay.....930

Vanuata 651
Vatican City.....934
Venezuela.....940
Vietnam 945

Wales 925
Wallis & Futuna.....950
Western Samoa 963
Yemen (Aden) 819

Yemen (Sanaa).....965
Yemen People's Dem. of.....968
Yugoslavia.....970
Zaire 291

Zambia 990
Zanzibar 865
Zimbabwe 818

Reference: Worldwide Geographic Location Codes. US General Services Administration; Office of Finance, April, 1984.

Exhibit 2-4. Monthly Data File Requirements

Data Item	Field Length[1]	Columns	Codes	
Blood Center ID	1n	1	1-5	*
Donor ID	10n	2-11		*
Date of Birth	6n	12-17	yymmdd	
Sex	1c	18	MF	
Zip Code of Donor	5n	19-23		
Transfusion History (Has ever had a blood transfusion)	1c	24	Short Form	*
Country of Birth	3n	25-27	Short Form	*
Level of Education	1c	28	Short Form	*
Race	1c	29	Short Form	*
Ethnicity (Type of Hispanic/Spanish Origin)	1c	30	Short Form	*
Blood Unit Identifier (Whole Blood Number)	7c	31-37		*
Donation Site	8n	38-45		
Site Category	6c	46-51		
Donation Type (Pheresis,Whole Blood...)	2c	52-53	WB,PH,AU,DD	*
Date of Donation	6n	54-59	yymmdd	
Self Exclusion (Confidential Unit Exclusion)	1c	60	YN	

**See Exhibit 2-5 for code list.*

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[1]Numeric fields should be right-justified and character fields should be left-justified.

Exhibit 2-4. Monthly Data File Requirements (continued)

Data Item	Field Length[1]	Columns	Codes	
Date of Last (Previous) Donation	6n	61-66	yymmdd	**
First Time to Blood Center	1c	67	YN	**
HIV (Elisa)	2c	68-69		*
HTLV I,II (Elisa)	2c	70-71		*
ALT Enzyme Test (Hepatitis Surrogate)	2c	72-73	NR,1,2,NT	*
HEP Hepatitis B surface antigen	2c	74-75		*
HBCAB Hepatitis B core antibody	2c	76-77		*
HCV Hepatitis C	2c	78-79		*
RPR/STS/VDRL/Syphilis	2c	80-81		*
ABO/Rh	1n	82		*
Filler	46c	83-128	Blanks	

* *See Exhibit 2-5 for code list.*

** *Optional depending on availability of data. Leave blanks in file if not available.*

[1]Numeric fields should be right-justified and character fields should be left-justified.

Exhibit 2-5. Code List for Monthly Data Files

Blood Center ID

1 = ARC, Chesapeake
2 = ARC, Detroit
3 = ARC, Los Angeles
4 = Irwin
5 = Oklahoma

Donor ID

To be encrypted by the Blood Center. The Donor ID must be a unique number for each donor for the duration of the study.

Transfusion History (Have you ever received someone else's blood?)

Y = Yes
N = No

7 = Refused
8 = Don't Know
9 = Not Available

Country of Birth

3-digit code from Exhibit 2-3 for countries other than U.S.A.

000 = U.S.A. (This does not need to be keyed. It should be added at the time the tape/diskette is created.)

xxx = Uncoded country
997 = Refused
998 = Don't Know
999 = Not Available

Level of Education (How much school have you completed?)

A = 8th grade or less
B = 9th, 10th, 11th or 12th grade (no diploma)
C = High school graduate (high school diploma or equivalent, for example GED)
D = Some college or technical school
E = Bachelor's degree (for example BA,AB,BS)
F = Master's or Professional degree (for example MA,MS,MEd,PhD,MD)

7 = Refused
8 = Don't Know
9 = Not Available

Race

White:
A = White

Black:
B = Black, African-American
C = Black, Caribbean
D = Black, Other

American Indian:
E = Indian, North American
F = Indian, South American
G = Indian, Central American

Asian or Pacific Islander:
H = Asian Indian
I = Chinese
J = Filipino
K = Hawaiian native
L = Korean
M = Vietnamese
N = Japanese

Alaskan Native:
O = Eskimo or Aleut

Other:
P = Other racial group

Blood Center Observation*:

R = White, not Hispanic
S = White, Hispanic
T = Black, not Hispanic
U = Black, Hispanic
V = Asian or Pacific Islander
W = American Indian or Alaskan Native
X = Other

Additional Race Codes:

7 = Refused
8 = Don't Know
9 = Not Available

Ethnicity (Types of Hispanic/Spanish Origin)

A = Mexican, Mexican-American, or Chicano
B = Puerto Rican
C = Cuban
D = Other Hispanic/Spanish

0 = Not Hispanic (does not need to be keyed; to be added at time tape/diskette is created)
7 = Refused
8 = Don't Know
9 = Not Available

Blood Unit Identifier/Whole Blood Number

If the WBN/BUI is kept in the Blood Center mainframe computer with alpha codes, but wand entry reads only numeric codes, a conversion is required. Each Blood Center should inform the Coordinating Center if such conversion is necessary.

Donation Type

WB = Whole Blood
PH = Pheresis
AU = Autologous
DD = Designated
OT = Other

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* If possible, Blood Center staff should record observed race/ethnicity using codes R through X if donors refuse to provide self-designation.

Exhibit 2-5. Code List for Monthly Data Files (continued)

Test Result for Test Data Items

R = Reactive
NR = Nonreactive
NT = Not Tested

ALT

1 = Low elevated
2 = High elevated
NR = Nonreactive/Negative
NT = Not Tested

ABO/Rh

0 = Untyped
1 = O Positive
2 = A Positive
3 = B Positive
4 = AB Positive
5 = O Negative
6 = A Negative
7 = B Negative
8 = AB Negative
9 = HOLD

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3. THE GENERAL LEUKOCYTE/PLASMA REPOSITORY

3.1 Overview

The General Serum Repository (GSR), established at the inception of REDS and completed in September 1994, consists of two serum aliquots from over 500,000 representative blood donations. Recently, techniques for rapid preparation of leukocyte pellets have been refined which now enable REDS to build a large repository of donor leukocyte specimens. The move to a combined General Leukocyte/Plasma Repository (GLPR) is considered essential for future studies of transfusion-transmitted viruses, given the increasing emphasis on nucleic acid amplification and probe techniques, and the probability that newly discovered retroviral agents will incorporate their genome within host leukocyte nucleic acids. Additionally, the GLPR, with linked demographic information, will constitute an important national resource for studying the prevalence and significance of genetic alleles of medical interest that are identified through the human genome project and other research programs.

GLPR specimen collection will take place over a 15-month period (October 1994 through December 1995), with a target of approximately 150,000 samples. Like the GSR, the GLPR is designed to be a representative sample of donations from the REDS centers. Specimens for the GLPR are processed and stored at the Blood Centers, and periodically shipped to the NHLBI central storage facility, Ogden Bioservices, for long-term frozen storage.

3.2 GLPR Sampling

GLPR specimens should be collected from all donors and types of donations (e.g., apheresis, autologous, directed, homologous whole blood) at selected collection sites on all days specified by the Coordinating Center. So that the Coordinating Center can accurately specify the donation sites from which to collect GLPR specimens, each Blood Center is responsible for providing a schedule of planned collection sites to the Coordinating Center (Attn: Robin McEntire) at two to four month intervals (depending on each center's pre-arranged agreement with the Coordinating Center). The Coordinating Center should receive the schedule approximately 6 weeks before the next collection period begins. This permits time for the sample to be drawn and for it to be returned to the Blood Center at least 3-4 weeks prior to implementation. The Blood Center is then responsible for

monitoring the schedule for cancellations, drive date changes, and additions of any new sites not included on the schedule from which the sample was selected. (Procedures for handling these schedule changes have been developed by the Coordinating Center's statistical staff.)

At the beginning of every month, each Blood Center should send a report on GLPR collections by site and day to the Coordinating Center for the previous month's collections, along with that month's donation record files and other study computer backup diskettes. A report form is generated by the Coordinating Center for this purpose and is included in the sampling plan packet sent to the centers. (Exhibit 3-1 shows one sample page of this report.) The reports, completed and updated by the Blood Center, are later used by the Coordinating Center to resolve any discrepancies between actual monthly donation records and the sampled donation sites. They are also used to monitor and compare the number of specimens intended for the GLPR versus the number which actually are processed for the GLPR every month.

3.3 GLPR Specimen Collection

The procedures for blood collection at sites selected for the GLPR should follow each Blood Center's Blood Service Directives or Local Operating Procedures. Collection of an additional 10 ml of whole blood should occur after the unit of whole blood or apheresis product has been collected, as well as the tubes required for routine testing by the Blood Center. GLPR specimens should be labeled with the Whole Blood Number/Blood Unit ID, (WBN/BUI) and stored separately at the collection site in appropriate racks at room temperature. Each center is responsible for ensuring that procedures are in place to separate the REDS specimen from those for routine testing and to secure their transport and storage at room temperature until the time of processing in the REDS laboratory at the Blood Center.

To ensure the highest possible yield of leukocytes, GLPR specimen processing at the Blood Center should correspond to the timing of the arrival of the samples from the collection sites. All specimens for the GLPR should be processed within 48 hours of collection.

Exhibit 3-1.

REDS General Leukocyte/Plasma Repository Schedule Jan. - Mar. 1995 3
14:40 Thursday, December 1, 1994

---------- Month=January ----------

Date of Drive	Revised Date	VAN	Site Code	Site Name	Pints Drawn	Tubes Frozen
01/01/95	_____		01515000	Downtown	_____	_____
01/01/95	_____		01518000	North Bay	_____	_____
01/02/95	_____		01515000	Downtown	_____	_____
01/02/95	_____		01518000	North Bay	_____	_____
01/02/95	_____	R001	00302001	WEST VALLEY HIGH SCHOOL	_____	_____
01/03/95	_____		01515000	Downtown	_____	_____
01/03/95	_____		01518000	North Bay	_____	_____
01/04/95	_____		01515000	Downtown	_____	_____
01/04/95	_____		01518000	North Bay	_____	_____
01/05/95	_____			_____	_____	_____
01/05/95	_____			_____	_____	_____
01/05/95	_____			_____	_____	_____
01/05/95	_____		01515000	Downtown	_____	_____
01/05/95	_____		01518000	North Bay	_____	_____
01/06/95	_____		01515000	Downtown	_____	_____
01/06/95	_____		01518000	North Bay	_____	_____
01/06/95	_____	R001	00638000	LEWISTON COMMUNITY	_____	_____
01/07/95	_____		01515000	Downtown	_____	_____
01/07/95	_____		01518000	North Bay	_____	_____

3.4 GLPR Database System

The Coordinating Center has provided each blood center with a PC and software (the GLPR Database System) to track the collection, processing, storage and shipment of blood samples for the GLPR. Detailed instructions on operating the system have been provided to the blood centers in a separate manual, The GLPR Database System User's Guide. Discussions on the information to be entered into the system and how it should be used to facilitate daily tasks are covered throughout the remainder of this chapter. On a monthly basis, the blood center should send a separate backup diskette of the system to the Coordinating Center (Attn: Greg Cox), at the same time that backup diskettes and tapes from other REDS activities are shipped.

3.5 GLPR Specimen Storage Setup

Prior to the startup of new processing procedures for the GLPR, each Blood Center should have separate standard Forma Freezer racks[1] in the -40°C freezer, with box space for the storage of GLPR specimens. Six racks will be in use at all times (three identical racks each for NHLBI and for REDS). Two racks will store whole blood samples, two racks will store DMSO-treated whole blood samples, and two racks will each store plasma. Each rack should have a unique rack label as discussed in the following section (3.6).

Each storage rack holds 20 freezer boxes. Each freezer box has space for 81 tubes, but only 80 tubes should be stored per box, in the same configuration used for the GSR (refer to Chapter IV of the REDS Operations Manual, Version 3). Placement of the tubes should be consecutive in each box, with location determined and tracked by the GLPR Database System. If a particular tube is not available from a donation specimen after processing, that tube's space in the box should be skipped. In the event that any tube spaces must be skipped due to lower volumes than recommended after processing, the corresponding Lab ID label for that tube should be accessioned into the GLPR Database System with a volume of 0 ml adjusted manually. (Lab ID labels are discussed in Section 3.6.)

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[1] Additional standard REDS box racks with 2" storage boxes and 81 cell dividers can be ordered from Forma Scientific (Catalog #189198).

Each box used to store tubes should be assigned a unique box label. In the event that a set of box labels are damaged when setting up a box, the next sequential label should be used, with an empty space left in the rack where the box with a damaged label would have been stored. A complete discussion of the GLPR labelling system for racks, tubes and boxes can be found in the next section.

3.6 GLPR Labelling System and Procedures

Rack, tube and box labels for the GLPR are provided to the Blood Centers by the Coordinating Center. The labels are printed with bar codes to match the printed IDs on them, so that racks, tubes and boxes can be easily accessed and tracked using the GLPR Database System.

One rack label for each rack is provided to the Blood Center. It should be placed on the end of the rack facing outward on the freezer shelving. The format for the rack labels is "ABBC", where:

A = Blood Center	1 = ARC - Chesapeake 2 = ARC - Southeastern Michigan 3 = ARC - Southern California 4 = Irwin Memorial Blood Centers 5 = Oklahoma Blood Institute
BB = Rack Number	01 - 99
C = Rack Contents	1 = NHLBI whole blood 2 = REDS whole blood 3 = NHLBI DMSO-treated whole blood 4 = REDS DMSO-treated whole blood 5 = NHLBI plasma 6 = REDS plasma

Examples of Rack Labels

1762 indicates that the rack contains:

- samples from ARC-Chesapeake;
- is the 76th rack in the freezer; and
- contains REDS whole blood tubes.

3045 indicates that the rack contains:

- samples from ARC-Southern California;
- is the fourth rack in the freezer; and
- contains NHLBI plasma tubes.

Each box should have a box label applied to the bottom of it prior to processing samples for storage. It is suggested that the boxes in each set of six racks be labelled at the same time prior to use. This will assist the laboratory staff in identifying the correct boxes to use for each procedure. The label should not be put on the box top, in the event that box lids are switched erroneously.[2] The format for box labels is "ABBCDD", where:

A = Blood Center	1 = ARC - Chesapeake 2 = ARC - Southeastern Michigan 3 = ARC - Southern California 4 = Irwin Memorial Blood Centers 5 = Oklahoma Blood Institute
BB = Rack Number	01 - 99
C = Rack Contents	1 = NHLBI whole blood 2 = REDS whole blood 3 = NHLBI DMSO-treated whole blood 4 = REDS DMSO-treated whole blood 5 = NHLBI plasma 6 = REDS plasma
DD = Box Number	01 - 20

Examples of Box Labels

501301 indicates that the box of samples:

- was collected at the Oklahoma Blood Institute;
- is stored in the first freezer rack;
- is for NHLBI DMSO-treated whole blood; and
- is the first box of the rack.

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[2] However, at the Blood Center's discretion, the second box label of each set may be applied to the side of the box lid, as a double check that lids have not been switched. In either case, the first Lab ID label on the box lid can always be checked to ensure that it corresponds to the first set of tubes in the box.

475515 indicates that the box of samples:

- was collected at Irwin Memorial Blood Centers;
- is stored in the 75th rack;
- is for NHLBI plasma; and
- is box number 15 of the rack.

Box numbers must be assigned in ascending sequence order. However, they do not need to be consecutive, which enables the Blood Center lab to assign the next sequence number in the event that a set of box labels is damaged. The GLPR Database System keeps track of the last box filled and will display an error message if a box number is not used in sequential order.

There are 16 identical tube labels in a set for each GLPR blood sample. The format for tube Lab ID labels is "ABBBBBB", where:

A = Blood Center		1 = ARC - Chesapeake 2 = ARC - Southeastern Michigan 3 = ARC - Southern California 4 = Irwin Memorial Blood Centers 5 = Oklahoma Blood Institute
BBBBBB =	Sequential tube number for donor identification	001001 - 999999*

An example of tube Lab ID label utilization is shown below for GLPR blood sample #007405 at Detroit. (Note that this is a sequential number assigned to GLPR specimens and is <u>not</u> the same as the encrypted REDS donor ID or the WBN/BUI.)

2007405	Label #1 used for donation sample
2007405	Label #2 used for NHLBI whole blood tube
2007405	Label #3 used for REDS whole blood tube
2007405	Label #4 used for NHLBI DMSO-treated whole blood tube
2007405	Label #5 used for REDS DMSO-treated whole blood tube
2007405	Label #6 used for NHLBI plasma tube
2007405	Label #7 used for REDS plasma tube
2007405	Labels #8-13 to be placed on set of six rack boxes (if this specimen is the first tube in the box)
2007405	Labels #14-16 are three extra labels for use as needed

* The first 1,000 labels for each center were reserved for training purposes.

3.7 Daily Processing Setup

The working racks for daily specimen processing require four spaces for the whole blood tubes and two spaces for the plasma tubes, per GLPR blood donation. Nalgene Cryovial Holders (Catalog # CMS 258-271) are suitable working racks for processing the plasma with this setup arrangement. The optimum rack for the whole blood tubes is the Sarstedt 93.1428 or equivalent, which holds 12 rows of 4 tubes each. At the discretion of each Blood Center, a series of these racks could be set up with the idea of completing a "centrifuge worth" of whole blood transfers from the pilot tubes at a time, thus enabling the efficient handling of the two types of operation.

It is recommended that GLPR storage tubes be labelled with the REDS Lab ID labels ahead of time, so that the Blood Centers can use the same working arrangement for the plasma tubes as used in the past for the GSR. For each donation sample, six tubes (two plasma and four whole blood) should be prepared with labels from the same set of REDS Lab ID labels. Recommended tubes for plasma are SARSTEDT #72.609 (same as used for the GSR); tubes for the whole blood are CST332-4 1.5 ml microcentrifuge tubes, self-standing with 'o'ring and attachment loop (Coast Scientific, 10439 Roselle St, San Diego, CA 92121, cost $99.00/1000.)

3.8 Daily Processing Procedures for GLPR Specimens

3.8.1 Sample Processing Randomization

Depending on the total number of specimens expected for the GLPR on a given day, the Blood Center may choose to process all or a random sample of them -- a decision which must be made prior to beginning daily processing procedures. If it is decided to process all specimens (due to a reasonable workload or extra staff, for example), processing can begin as soon as the first specimens are available.

If the Blood Center decides to process only a subset of the tubes expected on a given day (due to short staffing or heavy sampling day, for example), all samples expected for that day must be received prior to beginning processing. Following the randomization procedures detailed in the GLPR Database System User's Guide, the number of tubes the Blood Center wishes to process is manually entered into the GLPR Database System. The purpose of computerized randomization is to ensure that

all collection sites are represented in the GLPR, as intended by the original sampling plan. After entering the number of donation specimens which can be processed, the WBN/BUI from all blood donation tubes should be wanded into the GLPR Database System. The system will then generate a list of IDs representing the subset of specimens to be processed that day.

3.8.2 GLPR Specimen Volume Requirements

The minimum total volume necessary for a specimen to be included in the GLPR is 6 ml. If less than 6 ml of blood are available from a donation sample, it should not be processed for the GLPR. To allow the REDS laboratory staff to easily approximate if the minimum required volume is available, it is suggested that an empty vacutainer tube marked at the 6 ml level be available for visual comparison during daily processing. The minimum final GLPR volume per tube after processing, is as follows:

0.5 ml whole blood (in each of two tubes)
0.5 ml whole blood with DMSO (in each of two tubes)
1.0 ml plasma (in each of two tubes)

If a plasma tube breaks during centrifugation resulting in no plasma for the GLPR, two empty tubes should always be substituted in the appropriate location within the repository box (with 0 ml volume keyed into the GLPR Database System).

In all cases of less than optimal volume as specified in the GLPR protocol, volume adjustment should be manually entered in the GLPR Database System.

3.8.3 Step-By-Step Processing Procedures

Laboratory staff should follow Universal Precautions throughout the following specimen processing procedures.

1. After labeling the donation sample tube with a Lab ID label, it should be vortexed to resuspend the blood cells evenly. The stoppers from the tubes should then be removed using a 2 x 2 gauze square to cover the top of the tube.

2. The WBN/BUI and the REDS Lab ID label from the donation tubes and the corresponding two whole blood and two DMSO-treated whole blood tubes should be wanded into the GLPR Database System.

3. 0.5 ml whole blood should be pipetted from the donation tubes into each of the four tubes.

4. Sarstedt colored inserts should be used to cap two of the undiluted whole blood tubes using the following scheme:

   NHLBI whole blood - Green cap (Catalog #CST345G)
   REDS whole blood - White cap (Catalog #CST345W)

5. Repeat these procedures until the working rack has been completed.

6. 7.50 µl of DMSO should be pipetted into each of the remaining two whole blood tubes for each sample.

   NOTE: DMSO is a powerful solvent that will leach impurities out of rubber and some plastics. Therefore, it should be kept in its original stock bottle and shielded/stored away from light. It is very hygroscopic. Optimally, storage and use should occur in a fume hood. If a fume hood is not available, bottles (both working and inventory) should be stored in a cool dry place. Gloves and safety goggles should be used when handling DMSO. The bottle in current use should be kept closed between usages (i.e., between each rack-size batch of tubes).

   DMSO can be purchased from Sigma:
   D8418 Dimethyl Sulfoxide, 99.9% pure, 50 ml @ $11.05

7. The two tubes for each sample, containing DMSO should be capped with Sarstedt tops using the following scheme, and vortexed briefly to assure mixing with the samples.

   NHLBI DMSO-treated whole blood - Yellow cap (Catalog #CST345Y)
   REDS DMSO-treated whole blood - Lilac cap (Catalog #CST345L)

   The tubes should be frozen within 30 minutes to prevent cell toxicity by the DMSO. As racks are completed, they can be stored in a laboratory freezer until all samples are processed. (Storage in the -40C freezer is not required for this short-term storage.) However, all samples must be boxed and moved to the REDS freezer before the end of the day.

8. Following the box diagrams which should be printed by the GLPR Database System, place the filled whole blood tubes in the four boxes in the designated slots.

9. The donation sample tubes should be re-capped with temporary caps (SP B3035-540 or equivalent), and centrifuged at 2,500 rpm for 20 minutes to permit removal of the plasma layer.

10. The two Sarstedt tubes for the plasma of each donation sample should be identified. The donation tubes should be placed in sequence to match the empty plasma tubes in the working rack, as they are removed from the centrifuge.

11. For one donation sample at a time, the WBN/BUI and the REDS Lab ID label number from the donation tube should be wanded into the GLPR Database System. The Lab ID label on the two tubes to receive the plasma should then be wanded in.

12. 1.5 ml plasma should be pipetted from the donation tubes to each plasma tube. The tubes should be capped with Sarstedt tops using the following scheme:

    NHLBI plasma tube - blue (Catalog #65.716.001)
    REDS plasma tube - orange (Catalog #65.716.006).

    Volume corrections for the plasma tubes should be made as needed in the GLPR Database System.

13. Following the box diagrams generated by the GLPR Database System, place the filled plasma tubes in the two boxes in the designated slots.

14. Repeat Steps #11-13 until all samples have been processed.

15. When finished with daily processing of specimens for a box (whether or not the box is filled), the box should be stored in the -40 C REDS freezer until shipped to Ogden Bioservices, for central storage. (See Section 3.9.)

At the end of the day, a list should be printed from the GLPR Database System which includes the following information on all samples processed and stored that day:

- The Lab IDs;
- The WBN/BUI from the original donation tubes;
- The volumes of each of the stored plasma specimens; and
- The box locations for all tubes stored that day.

This list should be stored at the Blood Center for at least two months, and does not need to be sent to the Coordinating Center. (See the GLPR Database System User's Guide for an example of a printout.)

3.9 Reporting Procedures

On approximately the tenth of each month, the Blood Centers should back up a copy of the GLPR Database System onto a diskette and forward the diskette to the Coordinating Center (Attn: Greg Cox). This diskette should be shipped with the monthly backup diskette from the Special

Repository Database System, and the other monthly backup Blood Center information (discussed in the relevant sections of this Manual). The Coordinating Center will match Lab IDs from the GLPR files to the monthly Blood Center demographic files to prepare a complete record for each specimen in the GLPR.

3.10 Shipping GLPR Specimens to Central Storage

Due to strict new International Air Transport Association (IATA) Dangerous Goods Regulations for air shipments of infectious substances, instituted January 1, 1995, overnight air shipments of frozen repository specimens from the Blood Centers to Ogden has been put on hold until further notice. The IATA regulations require that infectious substances, such as REDS frozen GLPR samples, be shipped in containers specifically designed to withstand a battery of tests. At the time these procedures were written, no containers are known to be available which meet the IATA requirements, and also hold the quantity of tubes and type of tubes/boxes used for the GLPR. As REDS GLPR shipping procedures are developed within the constraints of IATA regulations, additional procedures will be provided.

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4. SPECIAL REPOSITORY COLLECTIONS

4.1 Overview

In addition to the GSR and the GLPR, REDS has established five special repositories consisting of specimens from donors with the selected retrovirus screening assay results described below and illustrated in Table 4-I.

Table 4-I. Summary of Special Repository Collections

Special Repository	Donation/Subject Status	Final Disposition
1	HTLV-I or II EIA repeat reactive	Ogden Storage; and SRA testing if positive
2	HTLV Cohort Study subject specimens	SRA storage; and SRA testing based on protocol
3	HIV-1 indeterminate	Ogden Storage
4	HIV-2 EIA reactive, and HIV-1 Western blot negative or indeterminate	Ogden Storage
5	HIV-1/2 combo EIA repeat reactive	Ogden Storage

Special Repository #1 (SR #1), established when REDS activities began in late 1990, includes peripheral blood mononuclear cells (PBMC) and plasma aliquots from HTLV-I(II) repeat-reactive donation specimens. Beginning in December of 1994, SR #1 leukocyte pellets and plasma aliquots are prepared at the blood centers and then shipped periodically for long-term frozen storage at an NHLBI central storage facility, Ogden Bioservices.

Special Repository #2 (SR #2) represents fresh blood samples collected at the blood centers from subjects enrolled in the HTLV Cohort Study. These specimens are shipped to the Central Laboratory, SRA Technologies, Inc., for processing and storage of PBMC, plasma and serum.

Special Repository #3 (SR #3) consists of followup phlebotomy specimens from recruited donors with HIV-1 indeterminate Western blots by routine blood center testing. After HIV-1 indeterminate donors are notified of their test results by the blood centers, they are presented with the

opportunity to enroll in REDS at the time of routine blood center counseling. In the REDS continuation period, these samples are being processed by the blood centers into leukocyte pellets and plasma aliquots for central storage.

Special Repository #4 (SR #4) consists of followup phlebotomy samples from recruited donors with reactive HIV-2 EIA screening results, and either negative or indeterminate HIV-1 Western blots. Specimens for SR #4 are processed and stored in the same manner as SR #3 specimens.

Special Repository #5 (SR #5) is a new repository initiated in December of 1994. Specimens from donations that test EIA repeat reactive for HIV-1/2 (regardless of confirmatory results) are included in this repository. Samples for SR #5 are obtained by blood centers from the whole blood or packed red blood cell (RBC) component and plasma components of the donation. Leukocyte pellets and plasma aliquots are prepared at the blood centers and shipped periodically to Ogden for central storage.

4.2 Special Repositories #1 and #5 (Samples from Routine Donations)

4.2.1 SR #1 and #5 Eligibility

SR #1 is the designated repository for donation samples found to be repeat reactive for antibodies to HTLV-I(II) by routine EIA screening at the blood center. Generally, if the first screening EIA is reactive, two additional EIA screenings are done. If at least two of the three screening EIA's are reactive, the donation is considered to be repeat reactive for HTLV, and therefore eligible for SR #1.

SR #5 is for samples from donations which are screened routinely by the blood center and found to be repeat reactive for HIV-1/2. A specimen from any donation which tests repeat reactive on the HIV-1/2 Combo EIA should be included in SR #5. Based on confirmatory results of some of these donations, a donor may later be recruited for enrollment in SR #3 or #4 (see Section 4.3).

4.2.2 Confirmatory Test Reporting of Donations Eligible for SR #1 and #5

A REDS HTLV Confirmatory Test Results Form must be completed by the blood center for all donations reported as HTLV-repeat reactive on the monthly donation tape sent to Westat,

regardless of whether or not a sample from the donation is submitted to SR #1 (see Exhibit 4-A). The form should be used to report detailed screening EIA results and confirmatory results, including the Western blot, and/or RIPA.

A REDS HIV-1/2 Confirmatory Test Result Form must be completed for each HIV-1/2 repeat reactive donation reported to Westat on the REDS donation tape, regardless of whether or not a sample from the donation is submitted to SR #5 (see Exhibit 4-B). The form should be used to report detailed HIV-1/2 Combo EIA screening test results, confirmatory HIV-1 Western blot results, and HIV-2 EIA screening test results. In addition, a REDS HIV-2 Confirmatory Test Result Form should be completed for each donation which is reactive by HIV-2 screening EIA testing (see Exhibit 4-C). This form is used to report HIV-2 confirmatory test results, including HIV-2 Western blot and immunoblot testing. The completed form should be attached to the HIV-1/2 Confirmatory Test Result Form for the same donation before sending it to the Coordinating Center.

Completed REDS confirmatory test result forms should be sent to the Coordinating Center at least once a month. A copy of the source document, from which the confirmatory test results were transcribed, must be attached to each REDS confirmatory test result form and sent at the same time to the Coordinating Center.

4.2.3 SR #1 and #5 Collection Activities

As soon as a routinely screened blood donation is found to be repeat reactive for HTLV-I(II) or HIV-1/2, it should be removed from blood center storage to obtain a REDS sample. Whole blood, or plasma and packed red blood cell (RBC) components are the main source of SR #1 and #5 samples. Alternate processing to obtain SR #1 and #5 samples is available if whole blood or RBC components are not available, or if the donation is from a platelet or plasma donor. (See Section 4.4 for details on processing donation specimens for SR #1 and #5.) The donation sample's whole blood number or blood unit identification (WBN/BUI) is a critical link to SR #1 and #5 specimens, and should be the same as that on the monthly donation record sent to the Coordinating Center.

4.2.4 SR #1 Specimen Testing[1]

On January 1, 1992, Coulter peptide testing replaced REDS routine PCR testing of SR #1 donation samples sent to SRA. Coulter testing is now only performed on SR #1 samples from donations which are confirmed positive for HTLV by the blood center. Coulter peptide testing by SRA on an HTLV-positive SR #1 sample is automatically ordered by the Coordinating Center after receiving positive confirmatory test results from the blood center on a REDS HTLV Confirmatory Test Results Form. Depending on the location of the stored SR #1 specimen for which Coulter testing is requested (either in Central Storage or at the blood center), the blood center can expect to routinely receive Coulter results within approximately 6-8 weeks from the time the donor's HTLV Confirmatory Test Results Form is received at the Coordinating Center. Results from SRA testing are reported to the blood centers on a REDS Central Laboratory Result Form (see Exhibit 4-D). These results may be particularly useful if routine blood center HTLV peptide testing is unable to provide an HTLV type for purposes of donor counseling. If a blood center does not receive SRA test results on a subject within 6-8 weeks after sending the subject's completed HTLV Confirmatory Test Results Form to the Coordinating Center, please contact Dawn Hottinger at Westat to inquire about the status of the SRA testing. Based on SRA and blood center typing results, additional testing on selected samples may be ordered by the Coordinating Center, according to REDS Laboratory Committee protocol, and reported to the blood center as results become available.

4.3 Special Repositories #3 and #4 (Samples from Follow-up Phlebotomies)

4.3.1 SR #3 and #4 Eligibility

A donor is eligible for an enrollment SR #3 phlebotomy if his/her HIV-1/2 repeat reactive donation confirms indeterminate for HIV-1 by blood center confirmatory testing, and the HIV-2 EIA screening is nonreactive (also by the blood center). Specifically, for the purpose of REDS, a donation is considered indeterminate for HIV-1 if the confirmatory HIV-1 Western blot (WB) band pattern does not constitute HIV-1 positivity.[2]

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[1] At this time, REDS does not have plans to perform Central Laboratory (SRA) testing on SR #5 samples; only routine blood center confirmatory testing is performed on HIV-1/2 repeat reactive donation specimens (eligible for SR #5).

[2] The REDS definition for HIV-1 positivity requires only band p24 plus either band gp41 or bands gp120/160 (gp120 and gp160 must be present together). REDS does not require the p31 band to be present for positivity.

A donor is eligible for an enrollment SR #4 phlebotomy if the routine testing of his/her donation reveals the following results:

- The HIV-2 screening EIA must be reactive; and
- The HIV-1 Western blot testing is not positive according to REDS criteria for HIV positivity[1].
- Also, HIV-2 confirmatory test results do not affect eligibility for SR #4.

The following table summarizes eligibility criteria for SR #3 and #4.

Table 4-II. Eligibility Criteria for SR #3 and #4

Special Repository	HIV-1/2 EIA	HIV-1 Western blot	HIV-2 EIA	HIV-2 Western blot
3	Repeatedly reactive	Indeterminate	Nonreactive	(not done)
4	Repeatedly reactive	Negative or indeterminate	Reactive	Positive, negative or indeterminate

4.3.2 Tracking HIV-1/2 Repeat Reactive Donors

Each donor who is reported on the REDS donation tape by the blood center as repeat reactive for HIV-1/2 is assigned a REDS Subject ID by the Coordinating Center (e.g., HV3-1000-1). Only one Subject ID is assigned per donor, regardless of the number of HIV-1/2 repeat reactive donations per donor. A subject record in the HTLV Tracking System is created by importing information from a diskette provided monthly by the Coordinating Center to the blood centers, for the purposes of tracking eligibility and study activity. An enrollment form for each HIV-1/2 repeat reactive donor is provided to the blood centers by the Coordinating Center at the same time (see Exhibit 4-E), on which the REDS blood center staff can record test results and enrollment activity.

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[1]The REDS definition for HIV-1 positivity requires only band p24 plus either band gp41 or bands gp120/160 (gp120 and gp160 must be present together). REDS does not require the p31 band to be present for positivity.

One of the following HIV test result codes should be entered into the tracking system as soon as blood center HIV-1 confirmatory testing is completed:

- "P" for HIV-positive;
- "N" for HIV-negative;
- "I" for HIV-indeterminate and eligible for SR #3;
- "4" to signify that a donation is negative or indeterminate for HIV-1, but repeat reactive for HIV-2 (i.e., eligible for SR #4); or
- "0" to specify that a confirmatory result will not be available (for example, when quantity is not sufficient).

If the HIV-1/2 repeat reactive donor is eligible for SR #3 or #4, the enrollment and current status code fields in the tracking system should be left blank until the donor's enrollment outcome is determined. If a donor's HIV results do not meet the eligibility criteria for SR #3 or SR #4, the tracking system enrollment and current status for that donor should be closed out as ineligible. (See Exhibit 4-F for a complete list of REDS subject enrollment and current status codes.) No changes are necessary in the tracking system if later donations by a donor still do not meet SR #3 or #4 criteria. Occasionally however, an HIV-1/2 repeat reactive donor, previously ineligible for SR #3 and #4, may donate again, and the later donation may qualify the donor for enrollment in SR #3 or #4. If the donor is then successfully enrolled in the study, the HTLV Tracking System information should be updated to reflect the most current HIV confirmatory test result status, enrolment status and information from the enrollment phlebotomy, as described in the next section.

4.3.3 SR #3 and #4 REDS Enrollment and Collection Activities

Because of their HIV test results, donors eligible for SR #3 or #4 will be recalled by the blood center as part of the center's standard operating procedures. At that time they should be recruited for REDS enrollment which consists of a phlebotomy draw. No REDS-related interview or physical exam need be administered during the visit. Prior to the REDS phlebotomy draw, the blood center nurse/counselor should review the REDS informed consent form with the donor and obtain his/her informed consent to participate in REDS. (See Exhibit 4-G for a prototype of the form. The actual content may vary by blood center, based on IRB approval.) For either the SR #3 or #4 enrollment phlebotomy draw, two 8.5 ml ACD yellow-top vacutainer tubes should be obtained. Both

tubes should be labeled immediately with a REDS Lab ID label from the duplicate label set. (Labels are discussed in detail in Section 4.4.3.)

For each enrolled SR #3 and #4 subject, the following information should be entered onto a REDS Phlebotomy Form (see Exhibit 4-H):

- The intended repository;
- The number and type of tubes drawn;
- The Lab ID label assigned to the draw (either an actual label may be put on the upper right on the front of the form, or the Lab ID may be written on the form);
- The date of the draw;
- The REDS Subject ID (if known); and
- The outcome code of the phlebotomy (e.g. "PD"-partial draw; "SD"-successful draw; "UD"-unsuccessful draw).

REDS Subject ID's are assigned to all HIV-1/2 repeat reactives by the Coordinating Center after the monthly donation tape is received. It is possible that a donor may be enrolled in SR #3 or #4 prior to receiving the REDS Subject ID. If this is the case, it is very important to include the WBN/BUI of the donation making the donor eligible, on the phlebotomy form. This will facilitate the linking of the enrollment sample to the subject by the Coordinating Center. All completed phlebotomy forms should be faxed to the Coordinating Center on the day of the draw (Fax # 301-738-8379, Attention: Nancy Rippetoe).

The outcome code of each attempted phlebotomy, the Lab ID label number assigned to the sample, and the date of the enrollment draw should be entered in the HTLV Tracking System Phase One visit record for that subject (since SR #3 and #4 subjects do not follow the "Phases" of HTLV Cohort Study subjects). Exhibit 4-F gives a complete list of REDS subject enrollment and current status codes from which to make a selection, to enter in those fields of the tracking system, as well.

SR #3 and #4 samples should be provided to the blood center laboratory as soon as possible after the phlebotomy draw for processing and storage as detailed in the next section.

4.4 Daily Processing Procedures For Special Repositories

4.4.1 Special Repository Database System

The Coordinating Center has provided each blood center with a PC and software (the Special Repository Database System) for an inventory control system to track the collection, processing, storage and shipment of blood samples for the special repositories. Detailed instructions on operating the system have been provided to the blood centers in a separate manual, The Special Repository Database System User's Guide. Discussions on the type of information to be entered into the system and how it should be used to facilitate daily tasks are covered throughout the remainder of this chapter. On a monthly basis, the blood center should send a separate backup diskette of the system to the Coordinating Center (Attention: Greg Cox), at the same time that backup diskettes and tapes from other REDS activities are shipped.

4.4.2 Specimen Storage Setup

Prior to the start up of new processing procedures for Special Repositories #1, #3, #4 and #5, each blood center should have in place separate standard Forma Freezer racks in the -40°C freezer, with box space for the storage of specimens for SR #1, #3 and #5. Each rack can hold 20 boxes. Due to the small number of specimens anticipated in SR #4, a single box should be set up in the same freezer for temporary storage of tubes for this repository.

Each special repository box has space for 81 tubes. Since all eight special repository tubes (4 plasma, 2 whole blood and 2 DMSO-treated whole blood tubes) prepared from a single specimen should be stored in the same box, each box should hold eight tubes each from ten specimens when full, filling 80 of the 81 spaces. Placement of the tubes should be consecutive in each box with location determined and tracked by the Special Repository (SR) Database System. In the event that all eight tubes are not available for a single specimen after processing, the corresponding number of tube spaces in the box should be skipped. In that way, each new specimen will always begin in a set position within a box. In the event that any of the tube spaces must be skipped due to lower volumes than recommended after processing, the corresponding Lab ID label for that tube should be accessioned into the SR Database System with a volume of 0 mls adjusted manually.

Throughout the following sections, use of specific color coded inserts or caps on tubes is recommended when processing is completed on the different pellet preparations and tubes are ready to

be placed in boxes. These inserts may be residual supplies from the REDS General Serum Repository or General Leukocyte/Plasma Repository. Table 4-III at the end of Section 4.4.6 summarizes the recommended color schemes for each type of tube stored.

Each box used to store tubes should be assigned a unique box label. In the event that a set of box labels is damaged when setting up a box, the next sequential label should be used, with an empty space left in the rack where the box with a damaged label would have been stored. A complete discussion of the special repository labelling system for both tubes and boxes can be found in the next section.

4.4.3 Special Repository Labelling System and Procedures

Tube and box labels for SR #1, #3, #4 and #5 are provided to the blood centers by the Coordinating Center. The labels are printed with bar codes to match the printed IDs on them, so that tubes and boxes can be easily accessed and tracked using the SR Database System.

Each box should have a box label applied to the bottom of it prior to processing samples for storage. The label should not be put on the box top, in the event that box lids are switched erroneously.[1] The format for box labels is "AABBBCDD", where:

AA = Blood Center	01 = ARC - Chesapeake 02 = ARC - Southeastern Michigan 03 = ARC - Southern California 04 = Irwin Memorial Blood Centers 05 = Oklahoma Blood Institute
BBB = Rack Number	001 - 999
C = SR Number	1 = SR #1 3 = SR #3 4 = SR #4 5 = SR #5
DD = Box Number	01 - 20

[1]However, at the blood center's discretion, the second box label of each set may be applied to the side of the box lid, as a double check that lids have not been switched. In either case, the first Lab ID label on the box lid can always be checked to ensure that it corresponds to the first set of tubes in the box.

Examples of Box Labels

05001101 indicates that the box of samples:

- was collected at the Oklahoma Blood Institute;
- is stored in the first freezer rack;
- is for Special Repository #1; and
- is the first box of the rack.

04075515 indicates that the box of samples:

- was collected at Irwin Memorial Blood Centers;
- is stored in the 75th rack;
- is for Special Repository #5; and
- is box number 15 of the rack.

Box numbers for each repository must be assigned in ascending sequence order. However, they do not need to be consecutive, which enables the blood center lab to assign the next sequence number in the event that a set of box labels is damaged. The SR Database System keeps track of the last box filled and will display an error message if a box number is not used in sequential order.

There are 16 tube Lab ID labels available for each blood sample, two identical sets of eight each. One complete set must go on the eight repository tubes. Any remaining duplicate eight labels should be used for: (1) the box lid to signify what repository samples are in the box; and (2) for the 15 ml centrifuge tube for SR #1 and #5; or for the REDS Phlebotomy Form and phlebotomy ACD tubes for SR #3 and #4. The remaining duplicates may be used as substitutes for any unusable repository tube labels during the course of processing. The format for tube Lab ID labels is "ABBBBCDD", where:

A = Blood Center	1 = ARC - Chesapeake 2 = ARC - Southeastern Michigan 3 = ARC - Southern California 4 = Irwin Memorial Blood Centers 5 = Oklahoma Blood Institute
BBBB = Sequential tube number in repository	0001 - 9999
C = Tube number for sample type	1 - 4 for plasma 1 - 2 for whole blood and DMSO
DD = Sample type	WB = Whole Blood DM = DMSO PL = Plasma

Examples of Lab ID Labels

2-0004-1-WB indicates that the tube:

- was collected at ARC - Southeastern Michigan;
- is repository tube number 0004; and
- is the first whole blood tube for that repository sample.

1-1190-3-PL indicates that the tube:

- was collected at ARC - Chesapeake;
- is repository tube number 1190; and
- is the third plasma tube for that repository sample.

To apply a label to the tube, hold the tube horizontally and wrap the label on the tube, beginning with the bottom of the label. There will be a slight amount of overlap, but by wrapping from the bottom of the label to the top, neither the bar-code nor the identifying information will be covered.

As a box is filled with tubes, a Lab ID label for each of the ten specimens contained within it should be applied to the box lid in sequential order. Therefore, a filled box should have 11 labels applied to it; one box label on the bottom of the box and 10 (tube) Lab ID labels on the lid.[1] Since all 10 of the Lab ID labels may not fit without some overlap, they should be applied so that all of the bar-code and as much of the identifying information as possible will be visible.

4.4.4 Daily Processing of SR #1 and #5 Specimens

REDS laboratory staff should follow Universal Precautions throughout the following specimen processing procedures. Whole blood or plasma and packed red blood cell (RBC) components should be obtained by the REDS technician from all donations eligible for SR #1 and #5 (see Section 4.2.1 for eligibility criteria). Depending on the type of product obtained for REDS from the donation, Procedure 3A or 3B should be used. If whole blood or RBC components are not available from the donation or, similarly, if a special repository sample will be obtained from a plasma or platelet donation, refer to Section 4.4.5 for alternate processing information.

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[1]The second box label from each set may have been applied to the side of the box lid, making a total of 12 labels applied to a filled box.

1. Four Sarstedt tubes for plasma and four conical tubes (two for whole blood and two for DMSO treated whole blood samples, respectively), should be labeled with the same Lab ID number using a set of eight tube labels. Red or green Sarstedt caps may be used for the plasma samples depending on the source of plasma. Depending on the source of whole blood, green and yellow, or white and lilac caps may be used for the conical tubes.

2. The WBN/BUI from the blood bags should be wanded into the SR Database System, followed by the REDS Lab ID assigned to the specimen. A Lab ID label from the duplicate label set for that ID number should be applied to a 15 ml centrifuge tube.

3A. **For Whole Blood Preparations:**

   a. Using a transfer set, 15 ml whole blood should be transferred to the labelled 15 ml centrifuge tube.

   b. A 1.0 ml aliquot of whole blood should be added to each of the conical tubes with the same Lab ID# and accessioned into the SR Database System.

   c. Two of the aliquots should be capped with green inserts.

   d. 100 μl DMSO should be added to the two remaining aliquots and capped with yellow inserts. The tubes should then be vortexed to thoroughly mix the DMSO and blood. These samples should be stored immediately in the laboratory freezer.

   e. The remaining blood sample should be centrifuged at 2,500 rpm for 10 minutes to separate the plasma from the RBC.

   f. 2.0 ml of plasma should be added to each of the four Sarstedt tubes with the same Lab ID# as the centrifuge tube, and accessioned into the SR Database System. Red caps should be used for these plasma samples.

3B. **For Plasma and RBC Components:**

   a. Frozen plasma bags should be thawed in a 37°C water bath. The plasma bags should be placed in a plastic bag before placing them in the water bath to avoid contamination of the water bath.

   b. Using a transfer set, 8-10 ml plasma should be transferred to a 15 ml tube.

   c. Four 2.0 ml aliquots of plasma should be pipetted into the four Sarstedt tubes with same Lab ID# label, and accessioned into the SR Database System.

   d. Green inserts should be used for these plasma samples.

   e. Using a transfer set, 5-10 ml packed RBC should be transferred to a 15 ml tube.

f. A 1.0 ml aliquot of RBC should be added to each of the conical tubes with the same Lab ID# label, and accessioned into the SR Database System.

g. Two of the aliquots should be capped with white inserts.

h. 100 μl DMSO should be added to the two remaining aliquots and capped with lilac inserts. The tubes should then be vortexed to thoroughly mix the DMSO and blood. These samples should be stored immediately in the laboratory freezer.

4. Storage of All Sample Tubes

a. The four plasma tubes and four whole blood tubes should be placed in the next sequential eight spaces in the SR #1 or #5 box. Placement within the box is determined and tracked by the SR Database System.

b. One of the eight specimen Lab ID labels from the duplicate set of Lab IDs for that specimen should be placed on the box lid.

c. When finished with daily processing of specimens for a box (whether or not the box is filled with 10 specimens), the box should be stored in the -40°C REDS freezer until shipped to Central Storage.

4.4.5 Processing SR #1 and #5 Specimens From Alternate Sources

Occasionally, whole blood or RBC components are unavailable from which to obtain SR #1 or #5 specimens. This situation might arise if packed RBCs from a whole blood donation have been destroyed, or if the REDS special repository specimen is being obtained from an HIV or HTLV repeat reactive platelet or plasma donation. In these cases, cells for SR #1 and #5 may be obtained from one of two other sources depending on availability.

In order of preference, the blood center should first try to obtain cells from a vacutainer tube containing an anti-coagulant such as EDTA, which the blood center may have drawn for non-REDS purposes at the time of donation. If this is not an option, cells may be retrieved from a platelet or plasma donation if available. The following procedures describe how to process specimens for SR #1 and #5 using samples from one of these two sources, respectively. Storage of these sample tubes is the same as for SR #1 and #5 specimens from regular donation sources (see Procedure #4 in Section 4.4.4).

For Specimens from Anti-coagulant Vacutainer Tubes:

1. Four Sarstedt tubes for plasma and four conical tubes (two for whole blood and two for DMSO treated whole blood samples, respectively), should be labeled with the same Lab ID number using a set of eight tube labels. Red Sarstedt caps may be used for the plasma samples, and green and yellow caps for conical tubes.

2. The WBN/BUI from the vacutainer tube should be wanded into the REDS SR Database System, followed by the REDS Lab ID assigned to the specimen. A Lab ID label from the duplicate label set for that ID number should be applied to a 15 ml centrifuge tube.

3. Using a transfer set, 7.5 ml whole blood should be transferred to the labelled 15 ml centrifuge tube.

4. A 0.5 ml aliquot of whole blood should be added to each of the conical tubes with the same Lab ID# and accessioned into the SR Database System.

5. Two of the aliquots should be capped with green inserts.

6. 50 μl DMSO should be added to the two other aliquots and capped with yellow inserts. The tubes should then be vortexed to thoroughly mix the DMSO and blood. These samples should be stored immediately in the laboratory freezer.

7. The remaining blood sample should be centrifuged at 2,500 rpm for 10 minutes to separate the plasma from the RBC.

8. 1.0 ml (minimum) of plasma should be added to each of the four Sarstedt tubes with the same Lab ID# as the centrifuge tube, and accessioned into the SR Database System. Red caps should be used for these plasma samples.

For Specimens from Platelet Donations:

1. Four Sarstedt tubes for plasma and four conical tubes (two for platelets and two for DMSO treated platelet samples, respectively), should be labeled with the same Lab ID number using a set of eight tube labels. Red Sarstedt caps may be used for the plasma samples. Green and yellow caps should be used for the conical tubes.

2. The WBN/BUI from the unit should be wanded into the REDS SR Database System, followed by the REDS Lab ID assigned to the specimen. A Lab ID label from the duplicate label set for that ID number should be applied to a 15 ml centrifuge tube.

3. Using a transfer set, 15 ml platelets should be transferred to the labelled 15 ml centrifuge tube.

4. A 1.0 ml aliquot of platelets should be added to each of the conical tubes with the same Lab ID# and accessioned into the SR Database System.

5. Two of the aliquots should be capped with green inserts.

6. 100 μ DMSO should be added to the two other aliquots and capped with yellow inserts. The tubes should then be vortexed to thoroughly mix the DMSO and platelets. These samples should be stored immediately in the laboratory freezer.

7. The remaining platelet sample should be centrifuged at 2,500 rpm for 10 minutes to separate out the plasma.

8. 2.0 ml (1.0 ml minimum) of plasma should be added to each of the four Sarstedt tubes with the same Lab ID# as the centrifuge tube, and accessioned into the SR Database System. Red caps should be used for these plasma samples.

For Specimens from Plasma Donations:

1. Four Sarstedt tubes with red caps for plasma should be labeled with the same Lab ID number using four labels from a set of eight tube labels.

2. The WBN/BUI from the plasma donation should be wanded into the SR Database System, followed by the REDS Lab ID assigned to the specimen.

3. Four 2.0 ml aliquots of plasma (1.0 ml minimum) should be pipetted into each of the four Sarstedt tubes with the same Lab ID#, and accessioned into the SR Database System. Red caps should be used for these plasma samples.

4. Since only four of the eight possible repository tubes will be available from each plasma donation, four tube spaces should be skipped or filled with empty "spacer" tubes. The corresponding Lab ID labels for those four empty/missing tubes should be accessioned into the SR Database System with a volume of 0 mls adjusted manually.

4.4.6 Daily Processing of SR #3 and #4 Specimens

REDS laboratory staff should follow Universal Precautions throughout the following specimen processing procedures. Two ACD yellow-top vacutainer tubes should be obtained from donors enrolled in SR #3 and #4 (as discussed in Section 4.3.3). The tubes should be stored at room temperature until the REDS laboratory staff is ready to process them, which should be no more than 48 hours after the phlebotomy draw.

1. Four Sarstedt tubes for plasma and four conical tubes (two for whole blood and two for whole blood with DMSO, respectively), should be labeled with the same Lab ID# number using a set of eight tube labels. The same Lab ID# from the duplicate set of labels should also be placed on the two ACD vacutainer tubes.

2. The ACD tubes should be vortexed. Then the stoppers should be removed from the tubes.

3. A 1.0 ml aliquot of whole blood should be added from the ACD tubes to each of the conical tubes with the same Lab ID#, and accessioned into the SR Database System.

4. Two of the aliquots should be capped with green inserts.

5. 100 μl DMSO should be added to the two remaining aliquots and capped with yellow inserts. These aliquots should be stored immediately in the laboratory freezer.

6. The original ACD tubes should be re-capped with temporary caps and centrifuged at 2,500 rpm for 10 minutes.

7. From the centrifuged ACD tubes, 1.5 - 2.0 ml plasma (depending on sample availability) should be pipetted into each of the four Sarstedt tubes. (Optimally, 4.0 ml plasma from each ACD tube should be used.) The plasma tubes should be capped with red inserts and accessioned into the SR Database System.

8. Storage of All Sample Tubes

   a. The four plasma tubes and four whole blood tubes should be placed in the next sequential eight spaces in the SR #3 or #4 box. Placement within the box is determined and tracked by the SR Database System.

   b. One of the eight specimen Lab ID labels from the duplicate set of Lab IDs for that specimen should be placed on the box lid.

   c. When finished with daily processing of specimens for a box (whether or not the box is filled), the box should be stored in the -40°C REDS freezer. For SR #3 the box should be stored until shipped to Central Storage. SR #4 specimens should be stored until the next shipment of boxes from any other special repository are scheduled to be shipped to Central Storage.

Table 4-III. Colored Cap and Insert Guide for Special Repositories

SPECIAL REPOSITORY	SPECIMEN SOURCE	PLASMA	WHOLE BLOOD	DMSO AND WHOLE BLOOD
1 and 5	Whole blood or alternate sources	RED	GREEN	YELLOW
1 and 5	Plasma and packed RBCs	GREEN	WHITE	LILAC
3 and 4	Yellow-top ACD tubes	RED	GREEN	YELLOW

4.5 Shipping Special Repository Specimens To Central Storage

4.5.1 Shipping Instructions for REDS Blood Centers Using Overnight Air Couriers

Implementing frozen pellet specimen preparation for SR #1, #3, #4 and #5 was designed to realize a significant cost savings by eliminating the need to ship fresh blood to the Central Laboratory on a daily basis. Therefore, beginning in December 1994, all specimens for these repositories are being processed at each blood center for eventual long-term central storage at Ogden Bioservices. However, due to strict new International Air Transport Association (IATA) Dangerous Goods Regulations for air shipments of infectious substances, instituted January 1, 1995, overnight air shipments of frozen repository specimens from the blood centers to Ogden has been put on hold until further notice. The IATA regulations require that infectious substances, such as REDS frozen repository samples, be shipped in containers specifically designed to withstand a battery of tests. At the time these procedures were written, no containers are known to be available meeting the IATA requirements, that can hold the quantity of tubes and type of tubes/boxes used for SR #1, #3, #4 and #5. As REDS special repository shipping procedures are developed within the constraints of IATA regulations, additional procedures will be provided.

Fresh REDS blood specimens collected for Special Repository #2, from subjects participating in the HTLV Cohort Study, should continue to be routinely sent to SRA. Procedures for shipping fresh SR #2 blood specimens remain the same in Phase Three as they were in Phases One and Two of the HTLV Cohort Study, except that new IATA air shipping regulations must be followed. (See Chapter 6 "HTLV Cohort Study Procedures") of this manual for details on shipping fresh SR #2 blood specimens to SRA.)

4.5.2 Instructions for Local REDS Blood Center Using Same-Day Land Courier

Frozen pellet specimen preparations from SR #1, #3 and #5 should be couriered to Ogden upon filling the 20th box in a special repository freezer rack at the blood center. Each of the 20 boxes should contain up to eight tubes from each of 10 specimens within a single repository. While it is not likely that the 20th box of two or more repositories will be filled at the same time, it is at the blood center's discretion whether or not they choose to include boxes from different repositories in the same shipment, or to even wait for the completion of the 20th box in a special repository rack before shipping. However, it is recommended that each box shipped contain 10 specimens.

Due to the small number of specimens expected for SR #4 during the remainder of REDS, the single box prepared for the temporary storage of this repository should be couriered to Ogden at the time of every shipment of other repository boxes. When included with other repository shipments to Ogden, the SR #4 box may contain anywhere from one to all ten of the specimens it can hold.

All Special Repository #1, #3, #4 and #5 shipments should be addressed to:

Ogden Bioservices
685 Lofstrand Lane
Rockville, MD 20850
301-340-1620

On the day when Ogden is sent special repository specimens, the blood center laboratory staff should use the Special Repository Database System to inventory the boxes being shipped and to generate a "Boxes Shipped" report, as described in Part C of the Special Repository Database System Users Guide. This report should be faxed on the day of shipping to the Coordinating Center (Attention: Nancy Rippetoe, Fax 301-738-8379) and to Ogden (Attention: Darrin Power, FAX 301-340-9245).

A copy of the "Box Contents" report for each box shipped should be included in each shipment to Ogden. A copy of the "Box Contents" reports should be also sent to the Coordinating Center regular mail on the same day that each shipment is sent to Ogden. The reports should be directed to:

Nancy Rippetoe
Westat, Inc.
Room WB487
1650 Research Blvd.
Rockville, MD 20850

Hard copies of this report should be readily available at the blood center, as it should be routinely printed out using the Special Repository Database System after completely filling each repository box with tubes from ten specimens. If this report is not readily available to send to the Coordinating Center and Ogden when preparing to ship specimens, a hard copy of the report should be generated for each box using the Special Repository Database System. (See Part C of the Special Repository Database System User's Guide for details.)

EXHIBITS

- 4-A HTLV Confirmatory Test Results Form
- 4-B HIV-1/2 Confirmatory Test Results Form
- 4-C HIV-2 Confirmatory Test Result Form
- 4-D Central Laboratory Result Form
- 4-E REDS Enrollment Form
- 4-F List of Subject Enrollment and Current Status Codes
- 4-G HIV Informed Consent Form
- 4-H REDS Phlebotomy Form

EXHIBIT 4-A

Subject ID (if known) _____ Donor ID _____

WBN/BUI _____ Date of Donation _____

REDS HTLV CONFIRMATORY TEST RESULTS FORM

COMPLETE THIS FORM FOR ALL DONORS WITH REPEATEDLY REACTIVE HTLV RESULTS.
FORWARD TO THE COORDINATING CENTER ON THE 1ST OF EACH MONTH.

EIA

Laboratory Performing Test: _____

EIA #1

Absorbance Level: _____ Cut-off Level: _____
Interpretation: ☐ Reactive ☐ Nonreactive

EIA #2

Absorbance Level: _____ Cut-off Level: _____
Interpretation: ☐ Reactive ☐ Nonreactive

EIA #3

Absorbance Level: _____ Cut-off Level: _____
Interpretation: ☐ Reactive ☐ Nonreactive

Western Blot

☐ Not done

_____
(Laboratory Performing Test)

Recording Band Intensities:
0 = Not Present
1 = Slight
2 = Moderate
3 = Strong
x = Intensities not reported but band present

ARC Bands:	p21env	p19	p24	p26	p28	p32	p38tax	p42	gp46	p53	other
	___	___	___	___	___	___	___	___	___	___	___

Non-ARC Bands:	p19	rgp21	gp21	p24	p26	p28	p32	p36	rgp46-I	rgp46-II	gp46	p53	other
	___	___	___	___	___	___	___	___	___	___	___	___	___

Interpretation: ☐ Positive ☐ Negative ☐ Indeterminate ☐ Inconclusive ☐ Dark

---

RIPA

☐ Not done

_____
(Laboratory Performing Test)

Recording Band Intensities:
0 = Not Present
1 = Slight
2 = Moderate
3 = Strong
x = Intensities not reported but band present

Bands:	p15	p19	p24	p33	p40x	gp46	p55	gp61	gp68	other
	___	___	___	___	___	___	___	___	___	___

Interpretation: ☐ Positive ☐ Negative ☐ Indeterminate/Nondiagnostic

---

HTLV FINAL INTERPRETATION: ☐ Positive ☐ Negative ☐ Indeterminate/ Nondiagnostic ☐ Inconclusive ☐ Dark

HTLV POSITIVES ONLY
TYPE INTERPRETATION: ☐ HTLV-I ☐ HTLV-II ☐ Untypeable

(Form revised 4/21/94)

EXHIBIT 4-B

WBN/BUI_____

Donor ID_____

Date of donation_____

REDS HIV-1/2 CONFIRMATORY TEST RESULTS

COMPLETE THIS FORM FOR ALL DONORS WITH REPEATEDLY REACTIVE HIV RESULTS. FORWARD TO THE COORDINATING CENTER ON THE 1ST OF EACH MONTH.

HIV - 1/2 COMBO EIA Laboratory Performing Test_____

EIA #1 Absorbance Level:_____ Cutoff Level:_____
Interpretation: ☐ Reactive ☐ Nonreactive

EIA #2 Absorbance Level:_____ Cutoff Level:_____
Interpretation: ☐ Reactive ☐ Nonreactive

EIA #3 Absorbance Level:_____ Cutoff Level:_____
Interpretation: ☐ Reactive ☐ Nonreactive

HIV-1 WESTERN BLOT Laboratory Performing Test_____

Record band intensities if available:

0 = Not present
1 = Slight
2 = Modest
3 = Strong
✓ = Present but intensity not reported

Bands:	p17	p24	p31	gp41	p51	p55	p66	gp120	gp160	Nonviral
	___	___	___	___	___	___	___	___	___	___

Interpretation: ☐ Positive ☐ Negative ☐ Indeterminate/Nondiagnostic

---

HIV - 2 EIA Test Manufacturer_____

EIA #1 Absorbance Level:_____ Cutoff Level:_____
Interpretation: ☐ Reactive ☐ Nonreactive

EIA #2 Absorbance Level:_____ Cutoff Level:_____
Interpretation: ☐ Reactive ☐ Nonreactive

EIA #3 Absorbance Level:_____ Cutoff Level:_____
Interpretation: ☐ Reactive ☐ Nonreactive

IV-2 WESTERN BLOT OR OTHER SUPPLEMENTAL TEST

☐ Pending

☐ Not required

EXHIBIT 4-C

WBN/BUI_____

Donor ID_____

Date of donation_____

REDS HIV-2 CONFIRMATORY TEST RESULTS

COMPLETE THIS FORM FOR ALL DONORS WITH REPEATEDLY REACTIVE HIV-2 RESULTS. FORWARD TO THE COORDINATING CENTER ON THE 1ST OF EACH MONTH.

HIV-2 WESTERN BLOT
or
Other Supplemental Test

Test Manufacturer_____

Record band intensities if available:

0 = Not present
1 = Slight
2 = Modest
3 = Strong
✓ = Present but intensity not reported

ARC Bands:	p16	p26	p31	gp34	p55	p58	p68	gp105	gp120	gp140	Nonviral
	___	___	___	___	___	___	___	_____	_____	_____	_____

Interpretation: ☐ Positive ☐ Negative ☐ Indeterminate/Nondiagnostic

CDC Bands:	p16	p26	p34	gp36/41	p55	p56	p68	gp70	gp125	Nonviral
	___	___	___	_____	___	___	___	_____	_____	_____

Interpretation: ☐ Positive ☐ Negative ☐ Indeterminate/Nondiagnostic

EXHIBIT 4-D

REDS CENTRAL LABORATORY RESULT FORM
SRA TECHNOLOGIES, INC.
9620 Medical Center Drive, Suite 100
Rockville, Maryland 20850

Specimen: WHOLE BLOOD/RBCS/PLASMA/SERUM	Date Shipped: |_|_| |_|_| |_|_|
Blood Center:	
Specimen Category: 1 2 3 Other____	Date Rec'd: |_|_| |_|_| |_|_|
Specimen ID#: |_|_|_|_|_|_|_|_|_|_|_|	
SRA ID#: |_|_|_|_|_|	Date Results Sent: |_|_| |_|_| |_|_|

COMMENTS:

SRA Laboratory Results

HTLV-I ELISA (gp21e) Cambridge

Kit ID	DATE	O.D.	S/C	Result

"Select-HTLV" ELISA (Coulter)

Assay Type	Kit ID	Date	O.D.	Cut-off	Result
HTLV-I					
HTLV-II					

HTLV-I stern ot Retest

Kit ID	Date	p19	gp21	p24	p26/p28	p32	p38	p42	gp46	p53			RESULT

HTLV-I RIPA Retest

Date	p24	p26	p28	p40	p55	gp61	gp68						RESULT

HTLV DNA ANALYSIS VIA PCR

Primers	POL			TAX/REX			OTHER:	
	Date	HTLV-I	HTLV-II	HTLV-I	HTLV-II	Generic		
Result								
Retest								

NR = Nonreactive RE = Reactive ND = Nondiagnostic

R/Serology Interpretation: [ ] for [ ] infection

Approved | | Verified | |

These results are to be used for clinical investigations only.
These are not licensed or certified procedures.

EXHIBIT 4-E

RETROVIRUS EPIDEMIOLOGY DONOR STUDY (REDS)
ENROLLMENT FORM FOR SR#3 and SR#4 SUBJECTS

STUDY SUBJECT ID:
DONOR ID :
WBN/BUI :

Demographic Data from Donor Data File

Date of Birth:
Sex:
Zipcode:
Ever Received Transfusion?
Country of Birth:
Education Completed:
Race:
Ethnicity:

Donation Site:
Type of Donation Site:
Type of Donation:
Date of Donation:
CUE?
Previous Date of Donation:
First-Time Donor?

Test Results from Donor Data File

ELISA for HTLV:
ELISA for HIV-1:
ALT:
Hep B Surface Antigen:
Hep B Core Antibody:

HCV:
RPR:
ABO/Rh:

To Be Collected at Time of Enrollment

Marital Status:
|__| Married/Living as Married
|__| Widowed
|__| Separated
|__| Divorced
|__| Never Married

City of Birth: _____

State of Birth: _____

Eligibility Confirmation

Indeterminate for HIV-1? |_| Yes |_| No

Reactive for HIV-2? |_| Yes |_| No

Eligible For Enrollment in SR#3? |_| Yes |_| No

Eligible For Enrollment in SR#4? |_| Yes |_| No

Enrollment Information

Enrollment Code |_|_|
Current Status |_|_|
Enrollment Lab ID: _____
Plebotomy Outcome |__|__|

Date of Enrollment Outcome: |__|__| |__|__| |__|__|
Mo Day Yr

Date of Scheduled First Visit: |__|__| |__|__| |__|__|
Mo Day Yr

Time of Scheduled First Visit: |__|__|:|__|__| AM PM

EXHIBIT 4-F

HTLV TRACKING SYSTEM
ENROLLMENT AND CURRENT STATUS CODES

ENROLLMENT CODES	DEFINITION	CURRENT STATUS CODES	DEFINITION
EN	Enrolled in SR #3 or #4	AV	Subject enrolled and remains active for future SR #3 or #4 activities
RF	Refused enrollment in REDS	RF	Refused enrollment and/or to continue in REDS
DE	Deceased prior to enrollment attempts	DE	Deceased prior to, or after enrolling
IL	Too ill to enroll	IL	Too ill to enroll and/or continue in REDS
IN	Incompetent to make enrollment decisions	IN	Incompetent to enroll and/or continue in REDS
LP	Cannot enroll due to language problem	LP	Cannot enroll and/or be active in REDS, due to language problem
NL	Eligible subject cannot be located	NL	Cannot be located and/or is lost to followup
NE	Not eligible for enrollment in SR #3 or #4	NE	Not eligible to enroll and/or to continue in REDS
OT	Other reason not enrolled	OT	Other reason not to enroll and/or to continue in REDS
ER	Erroneous or invalid subject ID	ER	Erroneous or invalid subject ID
DP	Duplicate subject record	DP	Duplicate subject record

EXHIBIT 4-G

CONSENT FORM FOR DONORS WITH HIV REPEAT REACTIVE TEST RESULTS

We are asking you to participate in a research study sponsored by the National Institutes of Health. The purpose of this study is to learn more about the health problems associated with certain viruses which may cause disease in people. <BLOOD CENTER NAME> is a study center and we would like to enroll you as a participant.

You recently gave a sample of blood as a donor. This sample was tested and found to be repeat reactive for HIV-1/2. While all current information indicates that this test result does not mean you are infected with HIV-1/2 or any other virus, we wish to collect an additional blood sample from you. If you decide to enroll in this study, we will draw another sample of your blood, approximately 2 tablespoons. This blood will be sent to the National Institutes of Health and other laboratories where it will be stored and used for studies in later years when new tests for viruses are developed.

Cost of all tests will be paid by <BLOOD CENTER NAME> and the National Institutes of Health. You will not be asked to pay for any of the tests or studies. The study does not offer or pay for treatment or hospitalization for any health problems.

The potential physical problems of participating are only those related to the routine procedure of obtaining blood specimens. The minor complications might be discomfort from the needle, slight bruising, bleeding or soreness at the site where the blood was obtained.

In the event that you suffer physical injury as a direct result of your participation in this research activity, <BLOOD CENTER NAME> will assume responsibility for providing immediate medical treatment. This care will be provided to you without charge so long as you notify the Principal Investigator within fifteen days of the date of injury, and you consent to the care offered. Further information concerning compensation and treatment in the event of an injury may be obtained from the Principal Investigator, <NAME> at <TELEPHONE>.

We are being extremely careful to ensure that all information and test results are kept strictly confidential. The blood sample will be identified only with a study number. The link between name and number will be available only to the study investigator and will be destroyed after the study is completed. No identifying information will be included in the published reports of the study.

My signature confirms that I have read this consent form, have asked all of the questions about my participation, and agree to participate in this study. Any additional questions I may have later may be addressed to <NAME>, at <TELEPHONE>, who is fully acquainted with the details of this study.

NAME (print) _____

SIGNATURE _____

DATE _____

WITNESS _____

EXHIBIT 4-H

Date of Birth _____

Sex _____

WBN _____

REDS Subject ID_____

Special Repository #2 ID_____

Note: Assign new SR ID and complete separate Phlebotomy Form each time blood is drawn for the HTLV Cohort Study.

Affix SR #3 or SR #4 Lab ID label here

REDS PHLEBOTOMY FORM

FAX THIS FORM TO WESTAT. DO NOT FORWARD TO SRA.
(INCLUDE SHIPPING LIST WITH FORM FOR SR #2 SAMPLES)

Date of Blood Draw: |__|__| |__|__| |__|__| Time of Draw: |__|__|:|__|__| am/pm
Mo Day Yr

Reason for Blood Draw:
- ☐ SR #2, Phase Two Visit
- ☐ SR #2, Phase Three Visit, (HTLV-positive subjects and controls)
- ☐ SR #2, Phase Three Negative Sex Partner Visit
- ☐ HTLV Cohort Study, Other (Specify Reason_____)
- ☐ SR #3, (HIV-1 indeterminate donors)
- ☐ SR #4, (HIV-2 reactive donors)
- ☐ Other (Specify Reason_____)

Place of Draw:
- ☐ Blood Center ☐ Subject's Home
- ☐ Other (Specify_____)

Position of Subject:
- ☐ Sitting ☐ Reclining

Tubes Drawn: (Enter number)
- ☐ Lavender top
- ☐ Tiger top
- ☐ Red top
- ☐ Yellow top
- ☐ Corvac
- ☐ Other (Specify_____)

Problems with Draw or Handling:
- ☐ Yes (Specify below) ☐ No

_____

_____

Phlebotomy Result Code: |__|__| Phlebotomist Initials: |__|__|__|

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6. PHASE THREE PROCEDURES FOR THE HTLV COHORT STUDY

6.1 Introduction

This chapter focuses on HTLV Cohort Study Phase Three activities for HTLV-positive blood donors, sex partners of HTLV-positive blood donors, and HTLV-negative controls selected from the blood donor population. Most of the activities are interrelated and similar for all types of enrolled subjects. Procedures which differ by subject type are specifically addressed throughout this chapter.

All Phase Three study forms and reports are shown as Exhibits in Appendix A. Copies of the Phase Three Interview and Level 1 and 2 exam forms are included in Appendices B-D, respectively, along with detailed directions and question-by-question specifications for administering them.

General administrative procedures, such as appointment scheduling, retention activities and maintaining study files for the HTLV Cohort Study will not be addressed in this version of the REDS Operations Manual (Version 4). Version 3 of the REDS Operations Manual previously described general procedures, and contains archival study materials on enrollment, procedures for Phases One and Two, and study forms no longer in use.

6.2 Phase Three Visit Timing and Eligibility

Phase Three begins on April 1, 1995. All Phase Three study activities (e.g., Level 2 and 3 exams, repeat CBCs and ascertainment of medical records), must be completed by August 16, 1997.

All subjects who were eligible for Phase Two are eligible for a Phase Three visit regardless of their current status (e.g., "Refused," "Other"), or whether they completed any Phase Two activities. Eligibility criteria to continue in the study after Phase One include the following:

- The subject's HTLV Tracking System enrollment and current status codes were "EN, AV" respectively, at the end of Phase One;

- HTLV-positive subjects (including positive sex partners) and controls must have at least partially completed two of the three following Phase One activities: Baseline Interview; Level 1 exam; and/or phlebotomy draw; and

- Negative sex partners must have completed either a Phase One phlebotomy draw and/or a Baseline Interview.

Additionally, there are a few subjects who were not eligible for a Phase Two visit (e.g., refused to continue the study after Phase One), but who later returned to complete Phase Two visit activities. These subjects are now eligible for Phase Three visit activities, as well.

The Phase Three followup window is unique for each subject, and is dependent on when he/she was administered Phase One activities. The interval between Phase One and Phase Three activities should average 54 months (4 1/2 years), with a minimum of 51 months and a maximum of 57 months (i.e., the "followup window"). The 51-month trigger date between Phase One and Phase Three is calculated based on the date that the Phase One Baseline Interview, Level 1 exam and/or phlebotomy were administered. Therefore, the date(s) on which a subject was administered Phase Two activities does not impact the Phase Three followup window. Appointments for subjects should be made as close to the 54-month mark as feasible, and all Phase Three activities should be completed no later than the 57-month time point, if possible.

6.3 HTLV Tracking System

The Coordinating Center has provided each Blood Center with a PC and software for maintaining records on HTLV Cohort Study subjects, referred to as the "HTLV Tracking System." Detailed instructions for using the system for Phase Three are provided in an updated version of the User's Guide for the HTLV Tracking System. This version of the system contains modifications designed to distinguish data entry management and report generation among all three study phases. The updated tracking system allows customary entry and maintenance of subjects' Phase Three records and preparation of Phase Three status reports. Discussions of information to be entered into the tracking system and how the system can be used to facilitate study tasks are covered throughout this chapter of the REDS Operation Manual.

The latest version of the HTLV Tracking System automatically determines which subjects are eligible to continue in the study for a Phase Three visit, based upon the criteria discussed in

Section 6.2. Blood Center staff can print tracking system reports, similar to the ones generated during Phase Two, which list eligible subjects and specific dates during which they should complete their Phase Three visit. Blood Centers can also access this information for individual subjects using different menu options.

All data entered into the tracking system are to be sent to the Coordinating Center on a monthly basis (except for identifying information on subjects). This enables the Coordinating Center to prepare monthly summary status reports using data from all five participating Blood Centers. Data retrieved from the tracking system also enable the Coordinating Center to provide reports to the Blood Centers informing them of any missing or inconsistent data.

6.4 Overview of Phase Three Study Activities

6.4.1 Summary of Study Activities

The Phase Three visit is again comprised of several different data collection activities similar to those in Phases One and Two. Table 6-1 summarizes the activities for each type of subject. Specific procedures are described in subsequent sections of this chapter.

Table 6-1. Study Activities for Each Subject Type in Phase Three

Type of subject	Sign new informed consent	Counseling	Interview	Level 1 Exam	Phlebotomy	CBC	Peripheral Blood Slides	Pulmonary function Testing[1]	Skin Testing[2]
HTLV-positive donor	X	X	X	X	X	X	X	X	X
HTLV-negative control	X		X	X	X	X	X	X	X
HTLV-positive sex partner	X	X	X	X	X	X	X	X	X
HTLV-negative sex partner		X			X				

[1]Pulmonary function testing will be performed at some REDS Blood Centers.

[2]Skin testing will be performed at some REDS Blood Centers, subject to NHLBI approval.

Some subjects will not be able to complete all activities during a single visit, and may actually need to return more than once. All Phase Three activities should be completed as close as possible to one another, since the study physician needs to have comprehensive information available when making a decision regarding the need for referral to a Level 2 physical exam.

6.4.2 Activities for HTLV-Positive Donors, Positive Partners and Controls

Tasks which must be performed by the blood center staff for HTLV positive subjects and controls include the following:

Prior to the Subject's Appointment:

- Review the subject's Phases One and Two files; and
- Transcribe items from the summary sheet into the Phase Three Interview booklet as described in Appendix B.

During the Subject's Routine Visit:

- If not done in Phase Two, review the revised Informed Consent Form with the subject and request his/her consent to continue the study, as described in Section 6.6.2;
- Administer the Phase Three Interview as described in Section 6.7 and Appendix B;
- Perform a Phase Three Level 1 exam as described in Section 6.8.1 and Appendix C;
- Complete the phlebotomy draw as described in Section 6.9;
- Make a set of peripheral blood smear slides as described in Section 6.11;
- Have the subject receive a pulmonary function test (at selected Blood Centers as described in a forthcoming field memo);
- Administer a skin test (at select Blood Centers as described in a forthcoming field memo, subject to NHLBI approval);
- Complete a REDS Contact Sheet for every subject as described in Section 6.12.1; and
- Provide and review counseling pamphlets with HTLV-positive subjects as described in Section 6.12.2.

After the subject's visit:

- Review and edit the Phase Three Interview according to Section 6.7.3;
- Order laboratory testing on, and ship specimens as described in Sections 6.10 and 6.13;
- Compile all test results and completed Phase Three booklets for review and a referral decision by the study physician; and
- Copy all forms and test results, and send originals to the Coordinating Center, as described in Section 6.13.

6.4.3 Activities for Sex Partners Found to be HTLV-Negative in Phase One/Two

For Phase Three, sex partners not currently known to be HTLV positive (i.e., HTLV-negative in Phase One/Two) should have only a phlebotomy draw for routine blood center HTLV testing and HTLV PCR testing at SRA. Negative sex partners should not be administered a Phase Three Interview or physical exam, should not have CBC testing or be asked to undergo skin testing or pulmonary function testing, and should not have peripheral blood smear slides made.

Blood Centers should notify sex partners of Phase Three HTLV test results (local and SRA testing) as soon as possible, regardless of HTLV status. If a sex partner is confirmed to still be HTLV negative as a result of Phase Three testing, no additional Phase Three visit activities are required except for test result notification, (and additional counseling at the discretion of the Blood Center). Procedures for reporting local HTLV serology results to the Coordinating Center are described in Section 6.13.2.

6.4.4 Activities for Sex Partners Who Seroconverted Since Their Last Study Visit

Sex partners found to be HTLV positive by Phase Three testing should be recalled for additional counseling, and to undergo the additional Phase Three study procedures of a positive partner (see summary of activities in Section 6.4.2).

6.5 Subject Contact

6.5.1 Recruiting Subjects for Phase Three

It is essential to contact every subject who is eligible for Phase Three and encourage him/her to return for this final visit (eligibility is detailed in Section 6.2), since REDS is designed as a followup study focusing on the long-term health effects of HTLV infection. All study dropouts will impact on the ability to draw conclusions from the data collected in previous phases. The Coordinating Center will closely monitor all study dropouts, and expects the Blood Centers to document the circumstances surrounding each failure to return (see Section 6.5.3 for details).

Contact with REDS subjects should begin prior to each subject's 51-month trigger date (follow-up window discussed in Section 6.2). As in earlier phases, standardized procedures for contacting subjects should be in place at each Blood Center. When contacting eligible subjects for Phase Three, each Blood Center should decide whether to contact the subjects by telephone or letter. It is strongly recommended that the Blood Centers send the Followup Visit Information Update pamphlet (Exhibit A-1) to each subject prior to the visit, as it has been designed and written as a subject retention tool, as well as to provide an update on REDS.

Blood Center staff should re-familiarize themselves with procedures for gaining cooperation and refusal conversion, (as discussed in Version 3 of the REDS Operations Manual, Chapter 5, Section 2.6), before beginning to contact subjects for Phase Three, since some subjects initially may not be willing to continue in the study. Since some Phase Three eligible subjects are known to have already refused to continue in the study, each Blood Center will have to make their own determination about the strength of their previous refusal, and whether refusal conversion is possible.

Tracing activities should be initiated for subjects who returned for Phase Two but cannot be readily located for Phase Three (as described in Version 3 of the REDS Operation Manual, Chapter 5, Section 2.8). For subjects lost to followup during Phase Two, tracing activities recorded in the subjects' folders should be reviewed and re-initiated, if feasible.

6.5.2 Procedures for Subjects Who Have Moved Away From the Blood Center

Through the remainder of the study, a handful of enrolled subjects may move to areas served by other REDS Blood Centers. The procedures below should be followed in this event:

(1) Responsibilities of the Original Blood Center

The originating Blood Center should confirm the following three conditions before initiating procedures for subjects who move to other REDS regions:

- That the subject is willing to continue in the study;
- That to the best of the center's knowledge, a subject has *permanently* moved to another REDS region (i.e., the subject is not planning to move back to the original region in the near future); and
- That the subject has consented to having their confidential information relayed to another REDS center by signing and returning an authorization for the transfer of their file from the original center (see Exhibit A-2).

Once these criteria are established, the original study coordinator should contact the coordinator at the center near to which the subject has moved. The new coordinator should ensure that the location to which the subject has moved is, in fact, within their region of operation, before both coordinators agree to the transfer. Initial information to convey may also include the original REDS Subject ID, the followup window, and limited confidential information (e.g. name, phone number if subject would like to be called). The study coordinator from the originating center should notify Dannie Hansma at the Coordinating Center (phone 301-738-3567) of the Subject ID and the center to which the subject has relocated, as soon as possible after establishing the feasibility of a subject's transfer.

After confirming the transfer with the Coordinating Center, the originating center should enter a current status code of "MV" ("moved") into the HTLV Tracking System for that subject to indicate their permanent transfer to a new center. All visit activities which cannot be performed should be closed out with an "MV" code in the tracking system activity result fields (e.g. Interview Result = "MV").

The original blood center is responsible for forwarding a copy of the subject's signed consent form(s) to the new center. ***The new center is still responsible for determining if the subject's consent is required on their newly revised REDS consent form, as well.*** The Coordinating Center will forward copies of other completed study forms to the new center (see below).

No further action or followup on the subject is necessary by the original center's staff, once they update the tracking system to reflect that a subject has relocated and send a copy of the consent form to the new center.

(2) Responsibilities of the Coordinating Center

The Coordinating Center will send copies of the subject's completed study materials to the new center, including the following:

- REDS enrollment form;
- HTLV test results if subject is HTLV-positive;
- Interview booklet(s);
- CBC/SMA results;
- Current summary sheet;
- Level 1 and 2 exam booklet(s); and
- Level 3 report(s) and medical records.

It is <u>not</u> necessary for the new center to have the Phlebotomy Form(s), Subject Referral and Decision Form(s), shipping lists and Phase One and Two participant checklist(s).

A Subject ID will be created by the Coordinating Center with the new center's identification number and a 7000 series number (e.g. original Chesapeake ID: PD1-0002-3; new Irwin ID: PD4-7001-9). A diskette will be sent to the new center with the following information to import into their HTLV Tracking System:

- New subject ID;
- Information needed to calculate the followup window dates and for creating visit record(s);
- Demographic information; and

- Donation test results.

The new blood center will receive the study materials and import diskette approximately two weeks after the Coordinating Center has been notified that a subject has moved.

(3) Responsibilities of the New Blood Center

Once the new center has received the study materials and import diskette from the Coordinating Center, all routine Phase Three REDS activities can be performed (e.g. administering the interview, assigning an SR#, subject retention activities). The subject should not be brought in for a Phase Three visit before the Blood Center receives study materials from the Coordinating Center. It is not necessary for the new center to report information to or send copies of completed study forms to the Blood Center from which the subject originated.

6.5.3 Procedures for Subjects Who Do Not Return for Phase Three

The Non-Visit Report Form

A Phase Three Non-Visit Report Form (see Exhibit A-3) must be completed by the Blood Center for all eligible subjects who fail to return for a Phase Three visit for any reason (other than moving to another Blood Center region). The purpose of the form is to collect standardized information about each subject who does not complete a Phase Three visit. If the subject cannot be reached directly, Blood Center staff should attempt to contact the subject's next-of-kin either to ascertain the subject's whereabouts or to obtain specific information relevant to the situation. For HTLV-positive subjects, it is important to ensure that an HTLV-related disease is not involved. It is as important to obtain closeout information for controls as it is for HTLV-positive subjects, and to ensure that an equal follow-up effort for all study subjects is made.

The Coordinating Center may request that the Blood Centers obtain copies of medical records for an ill or deceased subject. In these cases, the subject or the next-of-kin should sign a medical records release form (see Exhibit A-4 for an example). This release may need to be

customized, depending on the institution from which records are requested. The Blood Center should always check each institution's requirements prior to requesting medical records.

Closing Out the HTLV Tracking System

For subjects failing to return for any or all of their visit activities, Blood Center staff must close out the HTLV Tracking System for each activity, not completed. In this manner, the Coordinating Center can account for each activity for all eligible subjects. To see a list of valid closeout codes for each activity (e.g., interview, phlebotomy), the <F1> key can be pressed with the cursor on that field in the tracking system. The appropriate current status code for the subject also must be entered at the time of study withdrawal. ***The enrollment code should never be changed in the HTLV Tracking System.***

Activity Updates

A new Phase Three form, the Subject Activity Status form, has been developed for optional use by each Blood Center (see Exhibit A-5). It is designed to provide an easy way to update the Coordinating Center about study activities and/or materials, and will enable the Coordinating Center to better track the status of pending non-routine requests. This form should be faxed to the Coordinating Center as needed (Attn: Maureen McTighe, Fax: 301-738-8379).

6.6 Beginning the Phase Three Visit

6.6.1 Providing Study Information to the Subject

The nurse/counselor should spend time initially rebuilding rapport and answering any questions the subject may have about the study or about HTLV infection when they meet in person for the Phase Three visit. If the subject did not receive the Followup Visit Information Update pamphlet (Exhibit A-1) in the mail prior to his/her visit, it should be given to him/her at this time. (Every REDS subject, including sex partners and controls, should receive the pamphlet by mail or in person.)

Since the pamphlet contains material that may not easily be understood by all subjects, the nurse/counselor should review it with the subject in person, particularly if it was received in the mail.

If a subject requests more information than the nurse/counselor and the information pamphlet can provide, his/her request(s) should be referred to the REDS study physician. Informational requests that cannot be met by Blood Center personnel (e.g., for reprints from medical journals), may be referred through the Coordinating Center to the HTLV Diagnosis Review Panel (Contact Dannie Hansma: 301-738-3567).

6.6.2 Informed Consent Review

Each Blood Center must have appropriate consent forms completed and on file for every subject enrolled in REDS. The American Red Cross Blood Centers must ensure that each returning positive donor, positive partner and control subject has reviewed and signed a revised enrollment consent form as a condition of their continued participation in the study (see Exhibits A-6 through A-8, respectively). It is strongly recommended that the non-ARC Blood Centers (i.e., Irwin and OBI) consider adapting the revised consent forms for study standardization (subject to their IRB approval).

The Coordinating Center recommends that the following points be discussed with the subject when requesting a revised consent form to be signed:

- Since REDS is a long-term study which was extended from two visits over four years, to three visits over seven years, the content of the original consent form has been updated to reflect the study extension.
- More importantly, based on findings during the first phase of REDS, the protocol has been modified to include recommending additional procedures for, and/or requesting medical records on certain subjects. These protocol changes necessitated the addition of the following sentence to the consent form, at the end of the third paragraph: *"Based on findings during the course of your study visit(s), you may be asked to give separate written consent to undergo additional clinical or hospital procedures, or to obtain medical records as part of the study."* (The nurse/counselor should point out this sentence in the new form.)
- Based on the evolving nature of a long-term study such as REDS, the original consent form has "expired", and needs to be replaced with an updated form.

6.7 The Phase Three Interview

6.7.1 Preparing for the Phase Three Interview

The following materials should be available for administering the Phase Three Interview:

- The Phase Two Interview Summary Sheet, or the Revised Phase One Interview Summary Sheet for subjects who did not return for a Phase Two Visit (see Appendix B, Pages B-2 and B-4 for examples);
- A blank Phase Three Interview booklet;
- The three Show Cards for Sections D and E of the interview; and
- Two black pens.

Prior to meeting with the subject, the interviewer should transcribe information onto the Phase Three Interview from the appropriate summary sheet, as directed on the inside cover of the interview booklet (and in Appendix B of this manual). This must be done prior to administering the interview, since the information is needed to conduct the interview accurately.

6.7.2 Administering the Phase Three Interview

Refer to Appendix B for detailed specifications on administering the Phase Three Interview. The question-by-question specifications have been revised for Phase Three to address situations and interpretational issues which arose in Phases One and Two. Special attention should be paid to specifications appearing in bold italics.

6.7.3 Editing the Phase Three Interview

After completing the interview, it is extremely important that the nurse/counselor reviews the booklet while the information is still fresh in his/her mind. The nurse/counselor should record any comments or explanations for unanswered questions or discrepancies, and elaborate on a subject's response where necessary. This information will be useful to the Coordinating Center when coding and keying the data. The basic rules of editing are as follows:

- A blue pencil should be used for editing;
- Recorded responses should never be erased;
- Interviewer comments or explanations for any errors or discrepancies should be enclosed in parentheses; and
- If an error is found, the interviewer should put a line through it, write "M.E." for "my error," record the correct answer, and write any explanation in parentheses.

6.8 Phase Three Physical Examination Administration, Reviews and Referrals

6.8.1 The Level 1 Exam and Level 2 Referral Procedures

The Phase Three Level 1 Exam should be conducted on all HTLV-positive subjects, positive partners and HTLV-negative controls. It is important that controls participate in the exam portion of the study to provide data on a "healthy" population which can be compared to findings on HTLV-positive subjects. The purpose of the Level 1 physical exam is to screen for early signs of neuromuscular, dermatologic, and lymph node disorders associated with HTLV-I/II infections, but is not intended to be diagnostic. Item-by-item specifications for conducting the Level 1 exam are in Appendix C. Special attention should be paid to specifications appearing in bold italics, which include helpful suggestions and strict requirements.

The study physician should review each subject's Phase Three CBC results, Level 1 exam findings and interview, after the Level 1 exam is completed. Study materials from Phases One and Two should be available to the study physician for inclusion in his/her review. Additionally, the subject's Medical Conditions List should be available to the study physician (new in Phase Three). The Medical Conditions List is a summary of symptoms and conditions reported on the Phase One and Two Interviews that has been generated by the Coordinating Center for each subject (see Exhibit A-9). Based on this review, it is the study physician's responsibility to determine if there are abnormalities necessitating a Level 2 exam. The Review and Referral Decision section inside the back cover of the Level 1 exam booklet should be used to facilitate this decision. If the study physician decides that no abnormalities are present which warrant a Phase 2 Level exam, the Blood Center should inform the subject of this. However, the subject may be selected later to have a quality control (QC) Level 2

exam or may be referred for a Level 2 exam after the REDS Diagnosis Review Panel (DRP) reviews the study forms (see below).

For quality control purposes, each nurse/counselor must maintain a list of Subject IDs on the Phase Three Level 1 Exam Verification Sheet (see Exhibit A-10). IDs should be listed in order of completion and any subject whose ID falls on a line designated by an asterisk (*) must be referred for a Level 2 exam, regardless of visit findings.

An extra measure of quality control is provided using a computer screening program at the Coordinating Center. For subjects who meet specific referral criteria, the DRP routinely reviews the study forms and laboratory test results and decides whether a Level 2 exam is warranted. Blood Centers are then informed in writing of such decisions. Additionally, the DRP may request a detailed case report from the study physician, or that the Blood Center obtain medical records to confirm the history of certain reported disorders (e.g., sarcoidosis, Hodgkin's disease). The Blood Center must obtain the subject's authorization to obtain medical records by using a medical records release form such as that shown in Exhibit A-4.

6.8.2 The Level 2 Exam and Level 3 Referral Procedures

The Level 2 exam should be conducted as soon as possible after study physician referral, selection for QC, and/or referral by the DRP. The Level 2 exam repeats the Level 1 exam, includes more extensive tests, and should include time for the study physician to verify selected interview items.

Specifically, the study physician should spend time with the subject reviewing Sections A and B of the Phase Three Interview, confirming the subject's responses, and obtaining detailed explanations of any reported symptoms, conditions and diagnoses. The study physician should record responses to his/her inquiries in the margin of the interview booklet, using a different color pen than that used by the interviewer, so responses can be differentiated. If the booklet has already been sent to the Coordinating Center, responses should be recorded on the Blood Center photocopy.

If, after completing a Level 2 exam, the study physician feels that referral to a Level 3 specialist is indicated, he/she should write a case report in the back of the Level 2 exam booklet, summarizing his/her findings and reasons a Level 3 referral may be indicated. Level 3 referrals may

be made for hematology, dermatology or neurology. Upon receiving the Level 2 booklet, CBC results, and the Level 1 exam and Interview booklets, the Coordinating Center will have the DRP review them for a decision regarding a Level 3 referral, taking the study physician's recommendation under consideration. Regardless of the DRP's decision, the Coordinating Center will report it back to the study physician as expeditiously as possible.

If the study physician notes abnormalities that are not thought to be HTLV-related, he/she should refer the subject to a "usual care" physician or another specialist (at the subject's expense). Followup medical records from such a referral may be requested by the DRP. (See Exhibit A-4 for a template of the suggested medical records release form.)

6.8.3 The Level 3 Exam and Specialist Testing

Level 3 exams are arranged by the Blood Center to be conducted by one of the following local specialists: a hematologist/oncologist, neurologist, or dermatologist. If a subject is referred to a specialist for study-related abnormalities, a report with test results, impressions and recommendations should be submitted to the Blood Center by the consulting specialist. This report should be photocopied at the Blood Center to send to the Coordinating Center, and the original kept at the center in the subject's REDS study folder. ***Before the Blood Center sends the copy to the Coordinating Center, the subject's name and any identifying information should be blackened out. The REDS subject ID should be on the form but NAME and other IDENTIFIERS must be deleted.*** The copy should be sent to the Coordinating Center with the next shipment of forms (as described in Section 6.13) for review by the DRP.

When HTLV-associated myelopathy (HAM) is suspected, the Blood Center should ensure that the neurologist has a copy of the HAM Disability Scale Summary Form to complete at the time of the Level 3 exam (see Exhibit A-11). This form has four disability scales to objectively assess subjects with neurologic symptoms which may be related to HAM. In addition to rating the level of overall neurologic disabilities, these scales assess the following three categories of activities of daily living: 1) walking; 2) dressing; and 3) hygiene. A summary page accompanies the scales to provide space for the neurologist to record the level of disability assessed for each scale and to record his/her remarks. The Blood Center should complete the shaded areas of the front summary page, prior to sending it to

the neurologist. Before the completed form is returned to the Coordinating Center with the Level 3 exam report, the subject's name should be blackened out.

Certain information from the Level 3 exam should be entered in the HTLV Tracking System. When the specialist's report is received by the Blood Center, the study physician should review it for a diagnosis which should be entered into the tracking system (see the diagnostic result code list by pressing the <F1> key while the cursor is on the result field). The Blood Center may need to wait until the DRP has reviewed the specialist's report and until additional testing ordered by the DRP has been completed before entering a result code in the system.

In some cases a Level 3 specialist may suggest additional diagnostic testing for subjects with symptoms suspicious of adult t-cell lymphoma/leukemia (ATL), HAM, or another possible HTLV-related condition. Before the Blood Center arranges additional diagnostic testing for a subject, the DRP must first approve it. As part of any DRP-approved additional testing listed below, the consent form listed must be reviewed and signed by the subject:

(1) Consent Form For Diagnostic Procedures For HAM (Exhibit A-12) for:

- MRI of brain and/or spine;
- Blood tests for B-12 levels, thyroid function and syphilis;
- Cystometry or urodynamic testing; and/or
- Lumbar puncture.

(2) Consent Form For Diagnostic Procedures For ATL (Exhibit A-13) for:

- Diagnostic peripheral blood slides;
- Repeat CBC;
- Specialized blood testing using PCR, flow cytometry and/or performing monoclonal integration studies;
- Lymph node biopsy; and/or
- Bone marrow biopsy.

(3) Consent Form For Diagnostic Procedures For Additional Dermatologic Workup (Exhibit A-14) for:

- Skin biopsy.

The American Red Cross (ARC) Blood Centers must use these consent forms, and it is strongly recommended that the non-ARC Blood Centers adopt their usage as well for study standardization (with IRB approval).

6.9 Phase Three Phlebotomy Procedures

6.9.1 Specimen Collection

This section describes procedures for collecting and processing specimens collected during the Phase Three visit. Version 3 of the REDS Operations Manual gives detailed instructions for conducting the phlebotomy draw, in Chapter 5, Sections 5.3 and 5.4. Table 6-2 on page 6-18 of this manual summarizes specimens to collect from each subject type, and describes how each specimen is used in Phase Three. HTLV status for positive subjects and negative controls is already known; therefore blood drawn from these subjects is designated for long-term storage at SRA. HTLV status for negative sex partners returning in Phase Three is not known initially; therefore, the blood drawn from these subjects should be tested for HTLV at the Blood Center and SRA, and stored at SRA.

6.9.2 Assigning Special Repository #2 IDs

Blood specimens obtained from each new and repeat phlebotomy draw (and/or peripheral blood slides made) should be assigned a new Special Repository (SR) #2 ID. This includes specimens obtained for repeat laboratory tests (e.g., CBC), and finger sticks done for preparing peripheral blood smears. In this way, every sample, test result and set of slides can be uniquely identified.

A new series of SR #2 ID bar code labels will be supplied by the Coordinating Center to use for labeling and identifying Phase Three blood specimens, slides and relevant forms. In order to distinguish between Phase Two and Phase Three, the second digit of the SR #2 ID has been changed

Table 6-2. Phlebotomy Specifications for Phase Three

Subject Type	Draw	Disposition
HTLV-positive donors HTLV-positive partners HTLV-negative controls	1 5 ml lavender-top vacutainer tube AND 1 10ml red-top tube (recover serum to be sent to SRA in smallest container appropriate for volume) AND 3 8ml yellow-top vacutainer tubes	CBC with differential SRA storage SRA storage
Sex partners (serostatus unknown or HTLV-negative in Phase Two)	2 10ml red-top tubes (recover serum for local confirmatory testing, and send to SRA in smallest container appropriate for volume) AND 4 8.5ml yellow-top vacutainer tubes	1 tube for EIA and confirmatory tests, and 1 for SRA storage SRA storage and PCR testing

from a "2" (e.g., 4200001) to a "3" (e.g., 4300001). It is very important that Phase Three specimens and slides be labelled only with SR IDs designated for Phase Three.

The latest version of the HTLV Tracking System still only allows space to enter one SR ID and phlebotomy draw date for each subject, per phase of the study. If more than one phlebotomy is performed on a subject, the tracking system should reflect only the most recent Phase Three SR #2 ID, corresponding phlebotomy draw date and result code. (A valid result code list can be viewed by pressing the <F1> key while the cursor is on the result field.)

6.9.3 Completing the Phlebotomy Form

The Phlebotomy Form has been revised for Phase Three (see Exhibit A-15). ***A separate Phlebotomy Form must be completed and a unique SR #2 ID assigned each time a new blood specimen is drawn or slides are made for REDS.***

The reason for the blood draw must be checked on the Phlebotomy Form. This is important for two reasons. First, since subject type is never identified on any shipping lists sent to SRA, the Coordinating Center is responsible for informing SRA of each specimen's disposition (e.g., storage, testing), based on information from the Phlebotomy Form. Secondly, knowing the reason for the draw helps the Coordinating Center to anticipate whether to expect slides, laboratory results, and/or specimens. Other items on the Phlebotomy Form should be completed as directed in Version 3 of the REDS Operations Manual, Chapter 5, Section 5.5. Refer to Section 6.13 below for directions on shipping specimens and forms. Completed Phlebotomy Forms should never be faxed or sent to SRA.

6.10 Specimen Testing

Results of all tests done locally for REDS must be sent to the Coordinating Center. The Blood Centers should also update the Coordinating Center about any changes in their testing algorithms or interpretations, as well as changes in local laboratories used.

6.10.1 EIA and Confirmatory Testing on Negative Sex Partners

Any enrolled sex partner not known to be HTLV-positive should be tested for HTLV during their Phase Three visit. Red-top vacutainer tubes should be drawn for routine blood center screening EIAs (refer to Table 6-2 for quantity). If the EIA is repeatedly reactive, serum from the red-top tube should be used for local confirmatory testing. Information on reporting Blood Center HTLV results to the Coordinating Center is detailed in Section 6.13.

6.10.2 PCR Testing on Negative Sex Partners

SRA performs routine PCRs on all negative sex partners and sex partners whose serostatus is still unknown (same subjects on whom the Blood Center performs local HTLV testing). PCR results are routinely reported back to the Blood Center, regardless of the subject's HTLV status.

6.10.3 CBC with Differential

A local laboratory, determined by each Blood Center, should perform a complete blood count with an automated differential on all HTLV-positive subjects, controls and positive partners, using blood from the lavender-top vacutainer tube (refer to Table 6-2 for quantity). Testing must be performed within the prescribed time limits set by each laboratory. Information on reporting CBC results to the Coordinating Center is detailed in Section 6.13.4.

If results of the subject's first Phase Three CBC are abnormal, the CBC may be repeated at the Blood Center's discretion and/or may be requested by the DRP. The lab values that may trigger a repeat CBC and/or a Level 2 referral are listed inside the back cover of the Phase Three Level 1 exam booklet. The study physician and/or the DRP should make this determination after reviewing the subject's findings and medical history. When abnormal laboratory findings are not replicated on repeat testing, the study physician may decide that additional followup is not necessary.

6.11 Peripheral Blood Slide Preparation

In Phase Three, two peripheral blood slides should be prepared for each HTLV-positive subject, control and positive partner as outlined below. ***(Slides should not be made for any HTLV-negative sex partners, and, if made, should not be submitted to Cytology Services.)*** The reliability of information from slides depends on the quality of the smears. Therefore, it is critical that the following procedures are incorporated into each center's protocol to ensure properly prepared slides. Additional details on supplies and procedures may be found in Chapter 5, Section 5.6.5 of the REDS Operations Manual, Version 3.

All slides should be labelled with the subject's SR#2 ID, followed by a dash and the number of the slide (e.g., 1 or 2), using blank white 1/2" x 1" self-adhesive labels and a waterproof pen. The labels should be placed across the base of the frosted end of the slide, on the opposite side of the blood smear.

Each Blood Center must use blood from a finger or ear lobe stick (or less preferably, directly from a phlebotomy needle). ***Peripheral slides should never be made using blood obtained from any type of vacutainer tube.*** The following technique should be used for blood from a finger or ear lobe stick.

1. Follow Universal Precautions when making slides.
2. For the puncture site, do not use a finger that is heavily calloused, swollen or shows signs of rash or infection.
3. If possible, select the third or fourth finger, using an area to the side of the pad or the finger for the puncture site.
4. Thoroughly clean the finger with alcohol and dry with a sterile gauze pad. THE FINGER MUST BE DRY.
5. Perform the skin puncture and wipe away the first drop of blood. Blood should flow freely. Do not squeeze the subject's finger.
6. Quickly touch a clean slide to the blood drop near the frosted end, trying not to touch the slide to the skin. Spread the drop of blood with the pusher slide and make the smear with a quick and even motion. (Refer to the figure on the following page for illustration of technique).

The surface of the smear should appear smooth with a thin feather edge. The thickness of the smear can be regulated by the size of the blood drop and by varying the angle and pressure used in spreading the blood.

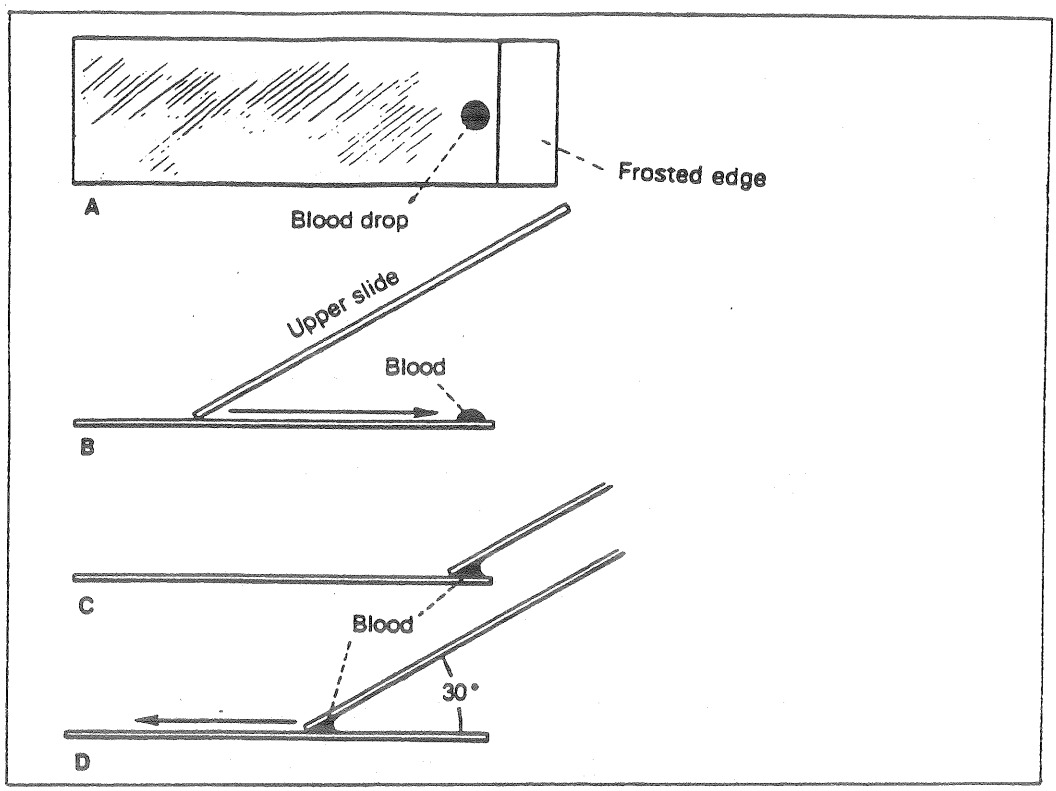
7. Repeat the slide-making process until two good slides are made. The Coordinating Center recommends preparing three or four slides so that the best ones can be selected for use.

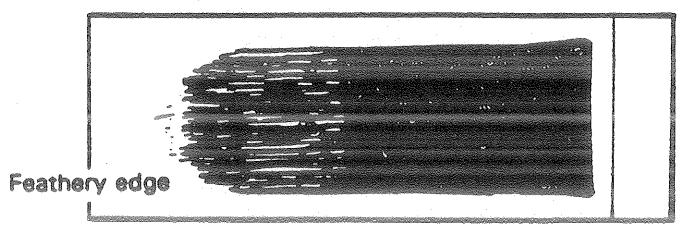
8. If it is necessary to repeat the puncture, always use a new sterile lancet.

9. If the subject's hands are cold, warm compresses may be applied and the hands massaged prior to cleansing.

The same methods described in Steps #6 and #7 above, should be used for smearing the slide with blood from a phlebotomy needle. If using blood from the phlebotomy needle, the needle should be touched to the slide immediately after blood has been drawn from the subject.

TECHNIQUE FOR PREPARATION OF PERIPHERAL BLOOD SMEARS





Two main conditions affect the viscosity of the blood. Polycythemia will increase the viscosity of the blood. Anemia will cause a decrease in the viscosity. When the viscosity is increased, a thinner slide is needed. To accomplish this, the angle between the spreader and the slide should be decreased. When the viscosity is abnormally low, a thicker slide is in order. To make thicker slides, the angle between the spreader and the slides should be increased.

Slides should be allowed to air dry before selecting the two best slides. A well-prepared blood smear has a thick portion beginning at the point of application which is drawn out into a feathery edge. If the Blood Center is unable to determine which slides are the best, all slides from that subject should be sent with the monthly shipment to Cytology Services (see Section 6.13.6 for shipping instructions). Prepared blood smears should not be exposed to moisture, heat or alcohol. Until slides are shipped to Cytology Services, they should be stored in a safe, dry location at room temperature; never in a refrigerator, freezer or incubator.

6.12 Activities to Conclude the Phase Three Visit

6.12.1 The REDS Contact Sheet

The Phase Three visit is the last planned contact with REDS subjects within the contract period. In the event that additional funding becomes available for future visits, it is important that information be available which would enable the Blood Center to locate the subject. The Coordinating Center has developed a REDS Contact Sheet to assist the blood centers in collecting this information (see Exhibit A-16). The nurse/counselor should administer the REDS Contact Sheet to the subject after completion of primary Phase Three visit activities (i.e., interview, Level 1 exam and phlebotomy), by reading the requests to the subject and recording the contacts given by the subject.

Completed contact sheets should be kept in the subject's Blood Center file. Results of attempts to obtain contacts for all subjects should be summarized on the Completion of REDS Contact Sheet Verification form (see Exhibit A-17), and forwarded to the Coordinating Center as each page is filled. This record of attempts is valuable to the Coordinating Center to show funding agencies the possible number of subjects which may be located, in the event that future studies on the cohort are proposed.

6.12.2 The REDS Counseling Message Pamphlet

Before concluding the Phase Three visit, all HTLV-positive subjects and positive partners should be given a copy of the REDS Counseling Message For HTLV-Positive REDS Participants pamphlet (see Exhibit A-18 for an example). The nurse/counselor should review the pamphlet with each subject and ensure that all his/her questions have been answered prior to ending the visit. Questions which the nurse/counselor cannot answer should be referred to the Blood Center study physician, or ultimately to the DRP.

6.13 Reporting Results and Shipping Study Materials

6.13.1 Shipping Forms and Reports

Table 6-3 summarizes the disposition of study forms and reports, and suggested dates for sending materials to the Coordinating Center. Generally, it is recommended that most study materials be shipped at the beginning of each month unless stated otherwise. Outstanding forms requested by the Coordinating Center and special requests should be sent as soon as possible. Additional shipping requirements for study materials are discussed in the next sections.

Before sending any materials, the Blood Center should make copies of all items in the shipment for their files. A completed Shipping List For Forms (see Exhibit A-19), generated by the HTLV Tracking System, must accompany all study materials sent to the Coordinating Center.

6.13.2 Reporting Test Results on Negative Sex Partners

As soon as Blood Center EIA screening and/or confirmatory test results are available for a sex partner, they should be reported to the Coordinating Center on the same HTLV Confirmatory Test Result Form that is routinely used for HTLV-positive donors (see Exhibit A-20), ***regardless of the sex partner's serostatus***.

6.13.3 Faxing the Phlebotomy Form

Completed Phlebotomy Forms should be faxed to Coordinating Center (Attention: Nancy Rippetoe, Fax: 301-738-8379). If specimens are being shipped to SRA as a part of the phlebotomy, the fax should include a special Repository Record of Shipment form generated by the Special Repository Database System (see Exhibit A-21 and Section 6.13.5). Completed Phlebotomy Forms should never be faxed or sent to SRA.

6.13.4 Reporting CBC Results

Blood Centers should send the original, hardcopy CBC laboratory results to the Coordinating Center, along with a completed CBC Results form (see Exhibit A-22). Blood Centers should keep a copy of the original laboratory results in the subject's file. Repeat CBC results should be reported to the Coordinating Center in the same manner.

6.13.5 Shipping SR #2 Specimens to SRA

All subjects returning for Phase Three should have blood drawn for Special Repository (SR) #2. From these draws, SRA should receive one to four yellow-top vacutainer tubes depending on subject type (see Table 6-2), and serum in a plastic centrifuge tube which has been extracted from a red-top tube. These tubes should be labelled with an SR #2 label at the time of collection, as directed in Section 6-9. The plastic centrifuge tube tops should be taped for added security against spills.

Exhibit A-21 shows the SR Record of Shipment form that the Blood Centers should generate and complete for each specimen shipment, using the Special Repository Database System. Since SRA must be notified in advance of all shipments, completed shipping lists should be faxed to SRA (Attn: Jeff Sitzler, Fax: 301-217-0427) and to the Coordinating Center (Attn: Nancy Rippetoe, Fax: 301-738-8379) on the day that the specimens are shipped from the Blood Center. At the same time, only the Coordinating Center should receive the Phlebotomy Forms corresponding to those specimens.

When scheduling appointments for subjects, local overnight carrier pickup schedules should be considered, particularly for weekend appointments. Actual cutoff times for blood collection can then be set by each Blood Center, allowing sufficient time for specimen preparation and packaging. All specimens sent to SRA should be shipped "next day, morning delivery" at room temperature, to arrive within 72 hours of collection.

All Blood Centers must follow regulations for shipping etiologic agents. Effective January 1, 1995, strict new International Air Transport Association (IATA) Dangerous Goods Regulations for air shipments of infectious substances went into effect. ***SR #2 specimen shipments sent by air carriers must meet requirements of the new shipping regulations***. (Copies of 1995 regulations are available from the Coordinating Center upon request.) Specific rules for handling blood specimens may vary by area, and each Blood Center is responsible for following the procedures required by their local overnight air carrier.[1] It is recommended that, in addition to the required packaging, sufficient protective wrapping be included in the boxes to prevent the specimens from being exposed to extreme temperatures. Each shipment should include a copy of the Shipment List for Specimens (already faxed to SRA and the Coordinating Center).

All SR#2 specimen shipments should be sent to the following address:

SRA Technologies
9620 Medical Center Drive
Rockville, MD 20850
Attn: Jeff Sitzlar
Phone: 301-217-0780

6.13.6 Shipping Peripheral Blood Slides to Cytology Services

On the 15th of every month, slides should be shipped to Cytology Services in Laurel, Maryland, via an overnight air carrier (or same day land courier for ARC Chesapeake Region), to arrive in the morning of the next day. If the 15th is a Friday, Saturday, Sunday, or the day prior to a national holiday, slides should be held and shipped so they will arrive on a business day. Slides must be shipped under the same IATA regulations as discussed above in Section 6.13.5.

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[1]The American Red Cross Chesapeake Region is responsible for following any etiologic agents shipping procedures required by their local land courier.

An SR Record of Shipment form (Exhibit A-21) should be generated and completed for each shipment of slides, using the Special Repository Database System. Completed shipping lists should be faxed to Cytology Services (Attn: Fran Shay, Fax: 301-206-2595) and to the Coordinating Center (Attn: Maureen McTighe, Fax: 301-738-8379) the same day the shipment is sent. This alerts Cytology Services and the Coordinating Center that slides are due to arrive the next day. It is essential that all slides made at one time from a subject be sent in the same shipment. Do not send any slides made for negative sex partners, unless specifically requested by the Coordinating Center. Including the original shipping list in the package, the slides should be shipped to:

Cytology Services of MD
Attn: Fran Shay
13900 Laurel Lakes Avenue
Laurel, MD 20707

Table 6-3. Summary and Disposition of Phase Three Forms and Reports

Item	Description	Appendix Exhibit #	Disposition[1]	Shipping Schedule
Authorization for Transfer of REDS Files	Used to obtain consent for subject files to be transferred to another Blood Center.	A-2	Keep at Blood Center	
Phase Three Non-Visit Report Form	Used to gather key information about subjects not returning for Phase Three. Also designed to rule out possibility of HTLV-related complications.	A-3	Send to Coordinating Center	Ship with other forms beginning of each month
Medical Conditions List	Summary list of symptoms and conditions reported by subject in Phase One and Two	A-4	Keep at Blood Center	
Subject Activity Update Form	Optional form for reporting status of activities to Coordinating Center	A-5	Fax or send to Coordinating Center	As needed or with other forms
Medical Conditions List	Summarizes conditions reported by subject in Phases One and Two	A-9	Keep at Blood Center	
Phase Three Level 1 Exam Verification Sheet	Chronological list of all subjects undergoing Level 1 physical exams. Asterisk (*) indicates who automatically got to Level 2.	A-10	Fax or send to Coordinating Center	Fax once a month or ship with other forms beginning of each month
HAM Disability Scale Summary Form	Used by Level 3 neurologist to summarize subject's disability	A-11	Send to Coordinating Center	Ship with Level 3 report as received
Phlebotomy Form	Used to record collection of blood and/or peripheral slides made specifically for REDS.	A-15	Faxed to Coordinating Center on the day of shipment or draw	Accompanying specimens must arrive at SRA within 72 hours of collection
Contact Sheet	Used to record contacts who could locate subject if lost to followup	A-16	Keep at Blood Center	
Contact Sheet Verification	Used to record success of attempts to collect Contact Sheet data	A-17	Send to Coordinating Center	Ship when each page is filled with other forms beginning at each month

[1]Blood Center should keep photocopies of all completed forms that are being sent to the Coordinating Center.

Table 6-3. Summary and Disposition of Phase Three Forms and Reports (continued)

Item	Description	Appendix Exhibit #	Disposition[1]	Shipping Schedule
Shipping List for Forms	Generated from HTLV Tracking System. Used to inventory forms sent.	A-19	Send to Coordinating Center	Accompanies all shipments of study forms
HTLV Confirmatory Test Results Form and source document	Used to summarize local confirmatory test results for negative sex partners. BCs should transcribe information onto form from source documents.	A-20	Send to Coordinating Center with source document	Ship with other forms, beginning of each month
Shipping List for Specimens	SR labels are scanned into repository system from tubes or slides. Inventory of items being sent are checked off manually.	A-21	Send to SRA with specimens; send to Cytology Services with slides; fax to Coordinating Center for specimens and slides	Accompanying specimens must arrive at lab within 72 hours of collection; slides to be shipped 15th of each month
CBC Results Form	CBC results from local lab reports should be transcribed onto this form from source document.	A-22	Send to Coordinating Center with original local laboratory results	Ship with other forms beginning of each month
Interview Summary Sheets	Used to transcribe information from Phase One Baseline Interview or Phase Two Interview to Phase Three Interview.	Appendix B Pages B-2 and B-4	Keep at Blood Center	
Physical Exam Forms Level 1 and 2	Used to collect data during physical exam by nurse (Level 1) and exam by study physician (Level 2).	Appendices C and D, respectively	Send to Coordinating Center	Ship with other forms beginning of each month
Consent Forms	Various forms used to inform subjects about the study and obtain their consent to participate.	A-6 through A-8 and A-12 through A-14	Keep at Blood Center	

[1]Blood Center should keep photocopies of all completed forms that are being sent to the Coordinating Center.

APPENDIX A EXHIBITS

- A-1 Followup Visit Information Update
- A-2 Authorization For Transfer of REDS Files
- A-3 Non-Visit Report Form
- A-4 Medical Records Release Form
- A-5 Subject Activity Status Form
- A-6 Consent Form for Seropositive Donors
- A-7 Consent to Participate in Sex Partner Study
- A-8 Consent Form for Seronegative Controls
- A-9 Medical Conditions List
- A-10 Phase Three Level 1 Exam Verification Sheet
- A-11 HTLV-Associated Myelopathy (HAM) Disability Scale Summary Form
- A-12 Consent Form for Diagnostic Procedures for HTLV-Associated Myelopathy (HAM)
- A-13 Consent Form for Diagnostic Procedures for Adult T-Cell Leukemia/Lymphoma (ATL)
- A-14 Consent Form for Diagnostic Procedures for Additional Dermatologic Workup
- A-15 Phlebotomy Form
- A-16 Contact Sheet
- A-17 Completion of REDS Contact Sheet Verification
- A-18 Counseling Message for HTLV-Positive REDS Participants
- A-19 Shipping List For Forms
- A-20 HTLV Confirmatory Test Result Form
- A-21 Special Repository Record of Shipment
- A-22 CBC Results Form

Retrovirus Epidemiology Donor Study (REDS)

FollowUp Visit Information Update

Sponsored by:
The National Heart, Lung and Blood Institute (NHLBI)
National Institutes of Health (NIH)

Why Am I Being Contacted At This Time?

As you may recall, the purpose of the REDS study is to follow a large group of HTLV-positive individuals and HTLV-negative "controls" over time to obtain information on their health and events affecting their health. Most of the participants enrolled in REDS have returned for their first followup visit. We are contacting you now because the next phase of the study has begun, and all study participants are being invited back for another followup visit.

What Has Been Learned So Far?

Since REDS is the first major study of HTLV infection in U.S. blood donors, your continued participation is very important. Much is being learned about HTLV-I and HTLV-II infection. We have found that, overall, the majority of study participants with HTLV infection are as healthy as the HTLV-negative individuals enrolled in the study. However, four people out of 150 with HTLV-I infections have been diagnosed with an HTLV-associated nerve/muscle condition (HAM). Also, three out of 400 HTLV-II positive individuals have HAM. One case of a type of leukemia called ATL, a cancer associated with HTLV-I infection, was reported when the individual came back for a REDS followup visit. Your REDS nurse/counselor or study physician can provide more details about what has been found so far, and can help to answer any questions you might have.

It is important that as many HTLV-positive study participants as possible return for this next visit so that we can monitor their health for any new conditions. Our HTLV-negative study participants are also important to REDS so that we can compare the health of people not infected with HTLV to the health of people who are infected with HTLV. HTLV-negative individuals serve as a comparison or "control" group for learning about the health of HTLV-positive people.

Who Is Participating?

All five REDS centers (in Southern California, San Francisco, Oklahoma City, Detroit and the Baltimore/Washington DC area) had excellent return rates of study participants. Almost all enrolled HTLV-positive individuals returned for their first followup visit. We are very pleased that an equally large percentage of HTLV-negative study participants returned as well. Many sexual partners of HTLV-positive study participants also returned.

As expected in any long-term study, some study participants moved away from the blood donor where they enrolled. However, we have been a keep in touch with some of them by telephone study participants have moved close enough to another REDS blood donor center to allow co participation in the study (with their permissior transfer study records between REDS centers).

Exhibit A-1

Why Should I Continue To Participate In REDS?

Your continued participation is very important to the success of the study, and you may also benefit from the health screening done as part of it.

- If you are an HTLV-positive study participant, this next visit will give you another chance to be examined by medical staff who are familiar with HTLV and who can help answer any questions you may have about your infection.

- If you are a REDS study participant who is not HTLV positive, your continued cooperation as a control will give researchers important information on your health that can be compared to individuals infected with HTLV. The dedication of our control participants is very important to the success of this major research study.

- If you are the sexual partner of an HTLV-positive study participant, and you have tested negative for HTLV so far, REDS will again give you the chance to have free testing for HTLV. Some partners who have not tested positive so far, could test positive at a later time. Your continued participation will provide REDS researchers with important information about the chance of HTLV infection occurring in partners of HTLV-infected individuals.

What Will My Continued Participation Involve?

During the next REDS visit, both HTLV-positive study participants and HTLV-negative controls will receive an interview, a physical exam and blood work by the REDS nurse/counselor, like the ones you have had before. These activities will help determine whether your health has changed since your last visit. Partners who have tested negative for HTLV so far, will only have their blood tested for HTLV infection during this visit, and will not need to have a physical exam or an interview.

At some blood donor centers, study participants may be asked to participate in one or two additional components of the study, including a simple breathing test to measure how well their lungs work, or a skin test to measure their immune response.

How Will The Results Of This Research Be Used?

Findings on HTLV-I/II from our research are an important part of information available to medical professionals. So far, researchers have made many presentations at medical conferences in the United States and in other countries about what is being discovered from REDS. Results from REDS have also been published in well-known medical journals. More presentations and articles are planned as more information becomes available from the study. Your local REDS center has a list of articles that have been published with REDS results, and can give them to you as they become available. Information from the study will also be used in the future to counsel individuals who are newly diagnosed with HTLV infection. Study participants are never identified in any reports of study findings.

THANK YOU FOR YOUR CONTINUED PARTICIPATION!

What If I Have Other Questions?

If you have additional questions about the study or need to make an appointment, please contact your nurse/counselor at:

American Red Cross Blood Services
Southern California Region
1130 South Vermont Avenue
Los Angeles, CA 90006

Telephone (213) 739-5633

[BLOOD CENTER LETTERHEAD]

AUTHORIZATION FOR TRANSFER OF REDS FILE

I, _____, authorize [ORIGINAL BLOOD CENTER] to transfer the contents of my Retrovirus Epidemiology Donor Study (REDS) file to [NEW BLOOD CENTER]. I have permanently relocated to this area and am willing to continue to participate in this study.

_____
Print Name

_____ _____
Signature Date

SUBJECT ID_____
DATE OF REPORT |__|__|-|__|__|-|__|__|
INTERVIEWER INITIALS |__|__|__|

REDS PHASE THREE NON-VISIT REPORT FORM

1. With whom did you speak during your contact(s)?

REDS Study Subject	1
No one	2
Other (specify relationship to subject)_____	3

2. Why didn't this subject return for a Phase Three visit?

Refusal to participate (RF)	1	(Q.3)
Lost to followup (NL)	2	(Q.8)
Ill (IL)	3	(Q.9)
Deceased(DE)	4	(Q.14)
Other (OT)	5	(Q.17)

3. State and/or explain subject's reason for refusal and circle codes for all reasons that apply:

_____

_____

A.	Confidentiality/too personal	1
B.	Not interested	2
C.	Negative reaction to study	3
D.	Visit too involved/takes too long/too busy	4
E.	No reason given	5
F.	Other (Explain above)	6

4. Strength of refusal. (Circle one)

Mild/no hostility	1
Firm but not hostile	2
Hostile	3

5. Do you think another nurse/counselor might be successful in getting this subject to cooperate?

Yes	1	(Q.6)
No	2	(Q.7)

6. What kind of approach could be used to convert this refusal?

_____

7. Would you recommend that this study subject be recontacted at a later date?

Yes	1
No	2

If no, why not?_____

END

8. What tracing steps were taken to attempt to locate this subject:

	Yes	No
Motor Vehicle Department?	1	2
Directory Assistance?	1	2
Postmaster?	1	2
Certified mail?	1	2
Next-of-kin	1	2
Employer?	1	2
Other_____	1	2

END

9. What is the nature of the subject's illness preventing his/her participation in Phase Three?

_____

10. Did this subject require any hospitalizations since the last time he/she was interviewed?

Yes ..... 1 → How many times? |__|__|
No..... 2 (Q.13)

11. What was the admission date for hospitalization, the name of the hospital, and the main condition for which this subject was treated? (If more than one admission, list information on separate page)

Date of Admission:

|__|__| |__|__| |__|__|
MO DA YR

Hospital Name:_____

_____ City/State:_____

Condition

12. Will this subject be able to participate at a later date?

Yes ..... 1 → When? _____
No..... 2
Maybe ..... 3 → When? _____

END

13. What was subject's date of death?

|__|__| |__|__| |__|__|
MO DA YR

14. In what state did this subject die?

_____

15. What was cause of death? _____

END

16. Briefly describe the circumstances which led to this subject's failure to return for Phase Three.

_____

_____

(BLOOD CENTER LETTERHEAD)

STUDY ID _____

AUTHORIZATION TO OBTAIN INFORMATION FROM MEDICAL RECORDS

To Whom it May Concern:

In connection with the health information given in cooperation with a research study being conducted by <Blood Center Name> for the National Institutes of Health, it will be necessary to obtain medical information on _____, (full name of patient) related to his/her diagnosis/condition specified below.

_____(Specific diagnosis/condition)

I hereby give my permission for <Blood Center Name> to collect medical information from the appropriate physician, clinic, or hospital. I understand that the information to be gathered will be kept confidential, and used for research purposes only.

Would these medical records be listed under any other name due to changes due to marriage or other name changes?

|__| YES |__| NO

IF YES: Please list these other names below.

_____

FIRST MIDDLE LAST

_____

FIRST MIDDLE LAST

Name of Person Authorizing Release (please print): _____

Signature: _____

Date Signed: _____
Month Day Year

(*This authorization expires one year from date of signature*)

Exhibit A-5

Date: _____

Subject ID: _____

REDS SUBJECT ACTIVITY STATUS
REPORT TO THE COORDINATING CENTER

This form may be used to report on the status of information and/or actions requested by the Diagnostic Review Panel, Study Physician, or Westat. It may also be used at the discretion of the blood center as a tool to update the Coordinating Center on any non-routine or outstanding activities. Please send or fax this form to Westat (attention: Maureen McTighe, fax: 301-738-8379).

☐ Laboratory Results: _____

_____

☐ Level 2 Exam: _____

_____

☐ Level 3 Exam: _____

_____

☐ Repeat Slides: _____

_____

☐ Medical Records: _____

_____

☐ Special Studies: _____

_____

☐ Other: _____

_____

<BLOOD CENTER LOGO, NAME, ADDRESS AND TELEPHONE>

CONSENT FORM FOR SEROPOSITIVE DONORS
HTLV COHORT STUDY

We are asking you to participate in a national research study sponsored by the National Institutes of Health. The purpose of the study is to learn more about the health problems associated with certain viruses which may cause diseases in people. Tests have recently become available which allow us to study a transfusion-transmissible virus called Human T-Cell Lymphotropic Virus, or HTLV-I/II. In rare instances, infection with this virus may result in the development of a kind of leukemia called ATL, and a nerve disease called TSP or HAM. The HTLV-I/II virus does not cause AIDS.

You recently gave a sample of blood as a blood donor. This sample was tested and was found to contain antibodies to the HTLV-I/II virus which suggests a prior exposure to the virus. If you decide to enroll in the study, we will examine you for early signs of ATL or TSP/HAM and perform tests for other health problems.

If you enroll, a member of our study team will interview you by asking questions about your medical history, present health, and lifestyle (including sexual practices). You will also be given a brief physical examination by the study nurse. If a health problem related to HTLV-I/II infection is discovered, the study physician will repeat the physical exam and possibly refer you to a specialist. Based on findings during the course of your study visit(s), you may be asked to give separate written consent to undergo additional clinical or hospital procedures or to obtain medical records as part of the study.

At the time of the exam, another blood sample will be collected. The nurse will take about four (4) tablespoons of blood from one of the veins in your arm. This blood will be used for several laboratory tests, some of which are routine and others experimental. The results of routine blood tests will be communicated to you as soon as they are available. In addition, tubes with some of your blood sample (labeled with a code instead of your name to ensure confidentially) will be sent to the National Institutes of Health and other laboratories. This blood will be used for studies in later years when new types of research tests are developed.

You will be asked to make another two visits over the next seven years. During the visits, you will be asked to give a brief history and provide the same amount of blood. You will be given another physical exam.

Costs for the laboratory tests and physician exams will be paid by <Blood Center>. You will not be asked or required to pay for any of them. Additional diagnostic tests due to health problems unrelated to HTLV-I/II that are discovered during the study will be your financial responsibility. The study does not offer or pay for treatment or hospitalization for any health problem.

The benefits to you of participating in the study are the regular laboratory testing and physician exams that may show specific findings or abnormalities important to your health. If so, or if you agree, your physician will be notified as soon as possible about the results. The meaning of the results will be explained to the extent possible. In addition, you recognize that your participation will help medical investigators better understand the immunologic and other changes that may follow exposure to HTLV-I/II.

The potential physical problems due to your participation in the study are only those related to the routine procedure of obtaining blood specimens. The minor complications might be discomfort from the needle, slight bruising, bleeding, or soreness at the site where the blood was obtained.

In the event that you suffer physical injury as a direct result of your participation in this research activity, <Blood Center> will assume responsibility for providing immediate medical treatment. This care will be provided to you without charge so long as you notify the Principal Investigator within fifteen days of the day of the injury, and you consent to the care offered. Further information concerning compensation and treatment in the event of an injury may be obtained from the Principal Investigator, <NAME> at <TELEPHONE>.

We are being extremely careful to assure that all information and test results are kept strictly confidential. All personal identifying information will be separated from the questionnaire, and from the laboratory reports. Only a code number will be used on the forms and blood specimens. All of the reports will be kept in a locked file and will be accessible only to the medical researchers at <Blood Center>. Results of this study will be reported as summaries that will not refer to you personally or permit your identification.

Participation in this study is entirely voluntary. You are free to withdraw from the study at any earlier time, and if you do so, you will not suffer any penalty. If you choose not to participate, you will not be denied any benefits to which you would otherwise be entitled.

My signature confirms that I have read this consent form, have asked all the questions I had about my participation, and agree to participate in the study. Any additional questions I may have later may be addressed to <NAME> at <TELEPHONE> who is fully acquainted with the details of this study.

Name (print) _____

Signature _____

Date _____

Witness _____

Exhibit A-7

<BLOOD CENTER LOGO, NAME, ADDRESS AND TELEPHONE>

CONSENT TO PARTICIPATE IN SEX PARTNER STUDY
HTLV COHORT STUDY

<BLOOD CENTER>

You have been informed that <BLOOD CENTER> in conjunction with the National Institutes of Health is conducting a research study into the sexual transmission of the HTLV-I/II virus. We would like to ask you to participate in the study.

Participation in this study will involve an interview conducted by a member of our study team with you and your spouse/partner separately. The interview will take between 30 and 40 minutes. Many of the questions will be personal, but honest answers will be important to our better understanding of how the HTLV-I/II virus is and is not transmitted by sexual contact. At the time of the interview, approximately 2 tablespoons of blood will be drawn from a vein in your arm. You will be eligible for the follow-up study which will involve reinterviewing and retesting of you and your spouse/partner at a later time during the study.

If you are found to have antibodies to the HTLV-I/II virus, you will also be given a brief physical examination by the study nurse. If a health problem related to the HTLV-I/II virus is discovered, the study physician will repeat the physical exam and possibly refer you to a specialist. Based on findings during the course of your study visit(s), you may be asked to give separate written consent to undergo additional clinical or hospital procedures or to obtain medical records as part of the study.

We are being extremely careful to assure that all information and test results are kept strictly confidential. All identifying information will be kept separated from the questionnaires as soon as the interviews are completed, and the blood samples will be identified only by a study number. The link between name and number will be available only to the <BLOOD CENTER> investigator and will be destroyed after the study is completed. No identifying information will be included in published reports of the study. Costs of all tests will be paid by <BLOOD CENTER>. You will not be asked to pay for any of these studies.

The benefits of participating in this study are your knowledge of the HTLV-I/II seropositivity status of you and your spouse/partner, and the appropriate counseling regarding sexual behavior and the transmissibility of this virus to your spouse/partner. An indirect benefit is that you will be assisting in the conduct of research which will aid in the understanding of HTLV-I/II. The risks of participation are the slight discomfort and possible bruising at the site of the needle stick, and the risk of possible stress from being interviewed with questions that you might find sensitive.

In the event that you suffer physical injury as a direct result of your participation in this research activity, <BLOOD CENTER> will assume responsibility for providing immediate medical treatment. This care will be provided to you without charge so long as you notify the Principal Investigator within fifteen days of the date of the injury, and you consent to the care offered. Further information concerning compensation and treatment in the event of any injury may be obtained from the Principal Investigator, <NAME>, at <TELEPHONE>.

Participation in this study is entirely voluntary. If you decide not to participate, or if you choose to withdraw from this study at any time, you will not be denied any benefits to which you are otherwise entitled.

I have read this consent form and have received a copy of it. I have been given time to ask questions about my participation in this study. I agree to participate in this study.

Name (print) _____

Signature _____

Date _____

Witness _____

<BLOOD CENTER LOGO, NAME, ADDRESS AND TELEPHONE>

CONSENT FORM FOR SERONEGATIVE CONTROLS
HTLV COHORT STUDY

We are asking you to participate in a national research study sponsored by the National Institutes of Health. The purpose of the study is to learn more about the health problems associated with certain viruses which may cause diseases in people. Tests have recently become available which allow us to study a transfusion-transmissible virus called Human T-Cell Lymphotropic Virus, or HTLV-I/II. In rare instances, infection with this virus may result in the development of a kind of leukemia called ATL, and a nerve disease called TSP or HAM. The HTLV-I/II virus does not cause AIDS.

You recently gave a sample of blood as a blood donor. This sample was tested and was found not to contain any antibodies to the HTLV-I/II. We are asking you to participate in this research study because your HTLV-I/II test result is normal.

If you decide to enroll in the study, you will be given the same medical tests as someone who had a positive test for HTLV-I/II. A member of our study team will interview you by asking questions about your medical history, present health, and lifestyle (including sexual practices). You will also be given a brief physical examination by the study nurse. A study physician may repeat the physical exam and possibly refer you to a specialist. Based on findings during the course of your study visit(s), you may be asked to give separate written consent to undergo additional clinical or hospital procedures or to obtain medical records as part of the study.

At the time of the exam, another blood sample will be collected. The nurse will take about four (4) tablespoons of blood from one of the veins in your arm. This blood will be used for several laboratory tests, some of which are routine and others experimental. The results of routine blood tests will be communicated to you as soon as they are available. In addition, tubes with some of your blood sample (labeled with a code instead of your name to ensure confidentially) will be sent to the National Institutes of Health and other laboratories. This blood will be used for studies in later years when new types of research tests are developed.

You will be asked to make another two visits over the next seven years. During the visits, you will be asked to give a brief history and provide the same amount of blood. You will be given another physical exam.

Costs for the laboratory tests and physician exams will be paid by <Blood Center>. You will not be asked or required to pay for any of them. Additional diagnostic tests due to health problems unrelated to HTLV-I/II that are discovered during the study will be your financial responsibility. The study does not offer or pay for treatment or hospitalization for any health problem.

The benefits to you of participating in the study are the regular laboratory testing and physician exams that may show specific findings or abnormalities important to your health. If so, or if you agree, your physician will be notified as soon as possible about the results. The meaning of the results will be explained to the extent possible. In addition, your participation will help medical investigators learn more about how HTLV-I/II infections affect health.

The potential physical problems due to your participation in the study are only those related to the routine procedure of obtaining blood specimens. The minor complications might be discomfort from the needle, slight bruising, bleeding, or soreness at the site where the blood was obtained.

In the event that you suffer physical injury as a direct result of your participation in this research activity, <Blood Center> will assume responsibility for providing immediate medical treatment. This care will be provided to you without charge so long as you notify the Principal Investigator within fifteen days of the day of the injury, and you consent to the care offered. Further information concerning compensation and treatment in the event of an injury may be obtained from the Principal Investigator, <NAME> at <TELEPHONE>.

We are being extremely careful to assure that all information and test results are kept strictly confidential. All personal identifying information will be separated from the questionnaire, and from the laboratory reports. Only a code number will be used on the forms and blood specimens. All of the reports will be kept in a locked file and will be accessible only to the medical researchers at <Blood Center>. Results of this study will be reported as summaries that will not refer to you personally or permit your identification.

Participation in this study is entirely voluntary. You are free to withdraw from the study at any earlier time, and if you do so, you will not suffer any penalty. If you choose not to participate, you will not be denied any benefits to which you would otherwise be entitled.

My signature confirms that I have read this consent form, have asked all the questions I had about my participation, and agree to participate in the study. Any additional questions I may have later may be addressed to <NAME> at <TELEPHONE> who is fully acquainted with the details of this study.

Name (print) _____

Signature _____

Date _____

Witness _____

Exhibit A-9

PHASE ONE AND TWO MEDICAL CONDITIONS LIST

SUBJECT ID C11-0447-0 SUBJECT NAME _____

PHASE ONE INTERVIEW DATE 01/28/92

PHASE TWO INTERVIEW DATE 2 /22 /94

PROBED MEDICAL CONDITIONS	PHASE REPORTED
High blood pressure	TWO
Bronchitis	ONE
Vaginitis	TWO

'OTHER' MEDICAL CONDITION(S) CATEGORIZED *	PHASE REPORTED
Trichomonas	ONE

* Note that 'other' listed conditions are actually categories developed by the Coordinating Center to reflect the general nature of a subject's response, and are not the verbatim responses given by the subject. Any verbatim subject reports of conditions, not categorized by the Coordinating Center, are listed on the next page.

Exhibit A-10

REDS PHASE THREE
LEVEL 1 EXAM VERIFICATION SHEET

Instructions: List IDs of all subjects for whom a Phase Three Level 1 exam has been completed, in the order of completion. IDs on lines with an asterisk (*) are to automatically receive a Phase Three Level 2 exam. Use a separate verification sheet for each examiner. Each month, fax this sheet to Westat (attention Maureen McTighe: fax 301-738-8379), and continue to complete the original at the blood center.

Examiner Initials:_____ **Blood Center:**_____

QC	SUBJECT ID	LEVEL 1 EXAM DATE	QC	SUBJECT ID	LEVEL 1 EXAM DATE
*			*		

Exhibit A-11

Retrovirus Epidemiology Donor Study (REDS)

HTLV-Associated Myelopathy (HAM) Disability Scale Summary Form

TO BE COMPLETED BY NEUROLOGIST	FOR BLOOD CENTER USE
Date of Evaluation _____	Patient Name _____
Neurologist's Signature _____	REDS Study ID _____
	Study Phase _____
	Neurologist's Name _____

INSTRUCTIONS TO NEUROLOGIST FOR COMPLETING FORM

The attached disability scales rate the level of overall neurologic disabilities, and three categories of activities of daily living (walking, hygiene & dressing). When seeing a HAM patient for his/her REDS Level 3 examination, assessment of disabilities by direct observation to the extent possible is preferred to patient self-report. From the descriptions of scale steps, please select and enter a score on this sheet which most closely fits the level of the patient's disability. Ranges of scores may be entered if necessary. Please return this form with your evaluation to:

_____.

[Blood Center Name (Contact) and Telephone Number]

Disability Scale	Score	Comments
Neurologic	_____	
Walking	_____	
Hygiene	_____	
Dressing	_____	
General Comments		

NEUROLOGIC DISABILITY SCALE*

Category	Step (Score)	Description
Normal neurologic examination	0	Pyramidal, cerebellar, brain/stem, sensory, bladder and bowel functions all normal. Exam may include symptoms unsubstantiated by signs.
No dysfunction, minimal sign(s)	1	One demonstrable sign <u>not</u> affecting usual function such as: ■ Babinski; ■ Diminished vibration sense; ■ Minimal finger to nose ataxia; or ■ Mild urinary hesitancy, urgency or retention.
	1.5	Two or more demonstrable signs <u>not</u> affecting usual function (examples in Step 1).
Minimal neurologic dysfunction	2	One monosystemic neurologic sign causing minimal disability such as: ■ Slight weakness or stiffness; ■ Mild gait disturbances; ■ Ataxia; ■ Moderate nystagmus; ■ Moderate bowel or bladder hesitancy, urgency or retention; or ■ Rare urinary incontinence.
	2.5	Two or more neurologic signs causing minimal disability (examples in Step 2).
Moderate neurologic dysfunction	3	Combinations of minor dysfunction (as in Step 2 above), plus one or two moderate dysfunctions such as: ■ Moderate truncal or limb ataxia; ■ Mild to moderate hemiparesis, paraparesis or severe Monoparesis; ■ Frequent urinary incontinence; or ■ Disturbing sensory loss, including touch and revibration.
Relatively severe neurologic dysfunction	4	More than two signs such as listed in Step 3, and/or one severe neurologic dysfunction such as: ■ Severe ataxia, all limbs; ■ Marked dysarthia; ■ Marked paraparesis, homiparesis or monoplegia; or ■ Need for catherization often. * **Patient must still be fully ambulatory, up and about for full 12-hour day, work full time and carry on normal activities of daily living, including hygiene and housework (sexual function not a consideration).**
	4.5	Same level of neurologic dysfunction as in Step 4, with some limitations of full activity (i.e. may not be able to ambulate as long as before); Should be able to work or be up and about most of day.
Severe neurologic dysfunction, with moderate ambulation	5	Patient is unable to be up and about unaided for extended periods (i.e. more than one-half hour at a time). Maximal motor function is walking unaided for a few blocks. One severe dysfunction which precludes working full day, or is severe enough to impair full daily activities such as: ■ Loss of bladder function; ■ Loss of sensation in one or two limbs; ■ Unable to perform coordinated movements due to ataxia; or ■ Loss of proprioception for most of body below head.

(Categories continued on back)

Exhibit A-11 (continued)

NEUROLOGIC DISABILITY SCALE* (continued)

Category	Step (Score)	Description
Assisted walking	6	Need to use unilateral aid (e.g. crutch, brace, cane or person) to walk 100 meters.
	6.5	Ability to only walk about 20 meters without resting, even with constant use of bilateral aids (examples in Step 6).
Essentially wheelchair restricted, but active	7	Inability to walk more than a few steps to 5 meters even with aid or assistance (e.g. canes, walkers, crutches, braces); essentially wheelchair restricted. Patient able to enter/leave wheelchair by self or with mechanical aid, and is able to be up and about in wheelchair most of day. Must be able to wheel self about in non-motorized wheelchair.
Passively wheelchair restricted or bedridden	8	Bed patient who can tolerate being in wheelchair (passively) most of day. Has effective use of arms for feeding self and performing portion of toileting on own.
	8.5	Bed patient who cannot tolerate prolonged periods in wheelchair. Still has some effective use of one or both arms, and can perform some self care.
Complete neurological dysfunction	9	Helpless bedridden patient who can communicate and eat (be fed).
	9.5	Totally helpless, bedridden patient who cannot communicate effectively, eat or swallow.
Death due to HAM	10	Can include death consequent to the chronic bedridden state with terminal pneumonia, sepsis, uremia, or cardiorespiratory failure as well.

* Adapted from Kurtzke, J.F. Rating neurologic impairment in multiple sclerosis: An expanded disability scale (EDSS). Neurology (1983) 33; 1444-52.

WALKING DISABILITY SCALE*

Category Always Walks Alone	Step (Score)	Description
Normal unassisted walking	0	Always walks alone, with normal gait & stride.
Slightly deviant gait	1	■ Gait slightly deviant in quality & speed; ■ Turning is the most difficult task; ■ Posture essentially normal; and ■ No limitations on length of ambulation.
Moderately poor gait	2	■ Quality of gait is poor and rate is slow; ■ Posture moderately affected; ■ There may be a tendency toward mild propulsion; ■ Turning is difficult; and ■ Does not need or use walker, cane or wheelchair.
Severely abnormal gait	3	■ Uses cane (but no walker or wheelchair) & may occasionally walk long distances with assistance; ■ Gait is extremely abnormal; ■ Very slow & posture grossly affected; and ■ There may be propulsion.

Category Sometimes Walks Alone	Step (Score)	Description
Minimally limited walking unaided	4	■ Uses walker and/or cane routinely, but no wheelchair use; ■ Walks short distances with ease; ■ Walking outdoors is difficult but often accomplished with minimal help; and ■ Rarely walks longer distances even with assistance.
Moderately limited walking unaided	5	■ Uses walker and/or can routinely and occasionally uses wheelchair; ■ Walks from room to room with only moderate difficulty; and ■ May occasionally walk outdoors with assistance for short distances.
Severely limited walking unaided	6	■ Uses walker indoors & wheelchair outdoors *but is independent in transferring.* ■ Walks from room to room moving slowly & using external support; and ■ Never walks unaided outdoors.

Category Never Walks Alone	Step (Score)	Description
Minimally assisted ambulation	7	■ Potentially requires help indoors & active help outdoors; and ■ Uses walker indoors and wheelchair outdoors.
Moderately assisted ambulation	8	■ Requires moderate help indoors to transfer to walker or wheelchair; ■ Uses walker indoors & wheelchair outdoors; and ■ May use wheelchair indoors occasionally.
Extensively assisted ambulation	9	■ Needs considerable help even for short distances; and ■ Cannot walk outdoors even with help.
Unable to walk	10	Cannot walk at all, even with maximum assistance.

* Adapted from Tindall, R.S.A., Walker, J.E., Ehle, A.L., et al. Plasmapheresis in multiple sclerosis: Prospective trial of pheresis and immunosuppression versus immunosuppression alone. Neurology (1982) 32; 739-743.

Exhibit A-11 (continued)

HYGIENE DISABILITY SCALE*

Category Complete Self-help	Step (Score)	Description
Normal	0	Hygiene maintained normally by self.
Minimal difficulty unassisted	1	Hygiene maintained normally, with exception of slight slowness.
Moderate difficulty unassisted	2	■ Hygiene activities are moderately time-consuming; ■ No substitute methods (e.g. electric razor); and ■ Few accidents.
Great difficulty unassisted	3	■ Hygiene still maintained independently, but with effort & slowness; ■ Accidents are not infrequent; and ■ May employ substitute methods.

Category Requires Partial Assistance	Step (Score)	Description
Minimal assistance	4	■ Manages most of personal needs alone; and ■ Has substituted methods for accomplishing difficult tasks (e.g. electric razor).
With difficulty and some assistance	5	Requires assistance for some tasks not difficult in terms of coordination.
Moderate assistance	6	Requires assistance for half of toilet needs.
Extensive assistance	7	Performs a few tasks alone with assistant nearby.

Category Requires Complete Assistance	Step (Score)	Description
Complete assistance - able to help	8	■ Hygiene maintained well; and ■ Gives aid to assistant.
Complete assistance - marginally helpful	9	Reasonably good hygiene with assistance, but cannot provide assistant with significant help.
Hygiene unmaintainable	10	Unable to maintain proper hygiene with even maximum help.

* Adapted from Tinadll, R.S.A., Walker, J.E., Ehle, A.L., et al. Plasmapheresis in multiple sclerosis: Prospective trial of pheresis and immunosuppression versus immunosuppression alone. Neurology (1982) 32; 739-743.

DRESSING DISABILITY SCALE*

Category Complete Self-Help	Step (Score)	Description
Self reliant	0	Normal dressing time & capabilities by self.
Minimal difficulty unassisted	1	Dress self completely with only slightly more time and effort than normal.
Moderate difficulty unassisted	2	Dress self completely with slowness and great effort.

Category Requires Partial Assistance	Step (Score)	Description
Minimal assistance	3	Requires partial assistance with fine activities (e.g. tie, buttons).
With difficulty and some assistance	4	Performs more than half of dressing activities alone with considerable effort and slowness.
Moderate assistance	5	Performs about half of dressing activities independently.
Only gross activities by self	6	Can only manage gross activities alone (e.g. hat, coat).

Category Requires Complete Assistance	Step (Score)	Description
Complete assistance - able to help	7	Gives considerable help through bodily movements.
Complete assistance - marginally helpful	8	Can give some help thorugh bodily movements.
Complete assistance - cannot help	9	Movements of patient neither help nor hinder assistant.
Complete assistance - hindrance	10	Patient is a hindrance rather than a help to assistant.

* Adapted from Tindall, R.S.A., Walker, J.E., Ehle, A.L., et al. Plasmapheresis in multiple sclerosis: Prospective trial of pheresis and immunosuppression versus immunosuppression alone. Neurology (1982) 32; 739-743.

Exhibit A-12

< blood center >

Consent Form For Diagnostic Procedures For HTLV-Associated Myelopathy (HAM)

The Retrovirus Epidemiology Donor Study (REDS)

PURPOSE AND BACKGROUND

As a participant in the Retrovirus Epidemiology Donor Study (REDS), I am being asked to undergo some diagnostic tests to confirm the diagnosis of HTLV-associated myelopathy (HAM), a nerve disease caused by the viruses HTLV-I and HTLV-II. I have been asked to participate in these additional studies because I may have a clinical diagnosis of HAM. The medical test(s) are routinely used by neurologists and other doctors, and might be recommended to diagnose my symptoms whether or not I am in a research study. Because the information obtained from these tests will be used by REDS as well as for the management of my condition, my additional consent is requested.

PROCEDURES

If I agree to participate in this part of REDS, the following testing procedures will be offered to me. All of these tests are recommended for most subjects. However, results from each test will be evaluated to rule out any non-HAM related conditions before the next test is arranged. Tests will be conducted in order of complexity and are based on what will provide the most information about the diagnosis of HAM.

I may agree to none, some or all of the following tests in the Consent Section of this form by circling "YES" or "NO" and initialing the appropriate line next to each procedure. My choices are not binding and I can change my decision at any time by informing the physician conducting these tests, the REDS study physician or the REDS nurse/counselor.

MRI scan of my spine.

This test is like an x-ray but uses magnets instead of radiation to view bones and internal structures. The purpose of this test is to make sure that I do not have a tumor of the spinal cord or narrowing of the spinal canal that might be mistaken for HAM. During the MRI I will lie inside a noisy, narrow tube for approximately one hour. The MRI will be done at an Imaging Center in a location convenient to me.

Additional blood tests

These blood tests will require that I have a needle stick to remove approximately 3-4 tablespoons of blood (45-60 mls) from my arm. The blood will be tested for vitamin B12 level, thyroid function and syphilis. My blood will be drawn by the REDS nurse/counselor at a convenient location.

Cystometry or urodynamic testing
This is a test of bladder function requiring a catheter be placed into my bladder which will allow the doctor to measure the pressures inside the bladder when sterile water is introduced. This will allow the doctor to determine whether I have the bladder spasms that often happen with HAM. This procedure takes about one hour and will be done in a urologist's office or clinic.

Lumbar puncture (spinal tap)
A lumbar puncture requires that after numbing the area on my back over the spine, a needle is introduced into my spine and about 1 tablespoon of spinal fluid is removed. This spinal fluid will be analyzed for the level of the HTLV virus as well as for signs that the virus is damaging my spinal cord. Approximately 1-2 tablespoons (15-30 mls) of blood will also be drawn at the same time as the lumbar puncture to test for protein levels and HTLV antibody levels. The lumbar puncture takes up to one hour, and will be done in a neurologist's office or clinic.

All results from these procedures will be treated as confidentially as possible. Although results with my name will be maintained in a medical record by the doctor performing the procedure(s) and by REDS researchers at <blood center>, only a coded study number will be used on result forms and blood specimens. Results of this study will be reported as summaries that will not refer to me personally or permit me to be identified.

RISKS AND DISCOMFORTS

The following risks and discomforts may be associated with each of these procedures:

1) The **MRI scan** will require me to lie in a narrow tube for up to one hour. Persons who dislike being confined in enclosed spaces may find this frightening. The physician may recommend I take a sedative if I am frightened about being confined in enclosed spaces. If taken, the sedative will make me feel drowsy, so I should not drive myself home after the procedure. Because there is a loud banging noise during the procedure, I will be asked to wear ear plugs to avoid hearing damage. I will be able stop the procedure at any time, should I become too uncomfortable. Since the procedure uses a strong magnet, I will not be able to have this procedure done if I have any metal (such as a pacemaker, metal fragment in my eye, or artificial hip) within my body. Because the risks to a fetus from a MRI are unknown, if there is a chance I am pregnant, I must <u>not</u> participate in studies involving MRI procedures.

2) The risks of **taking a blood sample** include the discomfort of the needle stick as well as a very small chance of bruising, bleeding or soreness at the site where the blood was obtained.

3) The **urodynamic study** involves the discomfort of having a catheter placed through my urethra (the tube leading from my bladder to my vulva or penis). In addition, when water is put into this catheter, I may feel a feeling of fullness in my bladder. There is a small risk of a bladder infection or bleeding from the urethra after this procedure.

4) During the **lumbar puncture (spinal tap)**, there is often temporary pain when the needle is introduced, although the doctor will use a local anesthetic. There is a small risk of bleeding, infection, or damage to one of the nerves leading to my legs estimated at less than 1 in 1,000. Another possible side effect that happens in about 1 out of 10 cases is a headache for a day or two after the spinal tap. I should try to lie down as much as possible during the first two hours after the lumbar puncture in order to prevent such a headache. If one occurs, I should take Tylenol and drink fluids. If the headache lasts for longer than two days, I should contact the neurologist who performed the procedure or the REDS nurse/counselor.

TREATMENT AND COMPENSATION FOR INJURY

In the event that I suffer physical injury as a direct result of my participation in this research activity, the <blood center> will assume responsibility for making immediate medical care available to me. This care will be provided to me without charge so long as I notify the <title/position> within 15 days of the date of injury or appearance of symptoms, and I consent to the care offered. Further information concerning treatment and payment of medical expenses in the event of an injury may be obtained from the <title>, <name>, at <telephone number>.

BENEFITS

I understand that I am not guaranteed any benefits from these procedures. However, it is possible that these tests will help to establish a diagnosis of my medical condition, so that my physician(s) will be better able to provide appropriate followup care for my neurological problems. A correct diagnosis will aid in the proper management of my medical condition. I will also benefit, since the costs of these diagnostic tests to confirm or rule out HAM are considerable and would otherwise be my responsibility if I was not participating in this research study.

ALTERNATIVES

Participation in any portion of these tests is entirely voluntary. I may refuse to have any or all of the tests listed above, and may withdraw from having any or all of the tests at any time, without suffering any penalty. Refusal of these tests will in no way influence my participation in the REDS study, and will not deny me any benefits to which I may

otherwise be entitled.

COSTS

The cost of these medical procedures and blood tests will all be covered by the REDS study. I will not be asked or required to pay for any of them. Additional diagnostic tests due to health problems that are discovered through these tests will be my financial responsibility. REDS does not pay for treatment or hospitalization for any health problems. The only cost to me will be my time.

REIMBURSEMENT

I will receive no payment for participating in these studies. *<optional: However, I will be reimbursed for reasonable travel expenses to and from the procedure(s) and the usual REDS visit stipend.>*

QUESTIONS

This study has been explained to me by <name> and my questions were answered. If I have any other questions about this study later, they may be addressed by calling <name> at <telephone number>.

CONSENT

I have been given a copy of this consent form and also a copy of the experimental subjects' bill of rights to keep. **Participation in this research is voluntary.** I may decline to participate or withdraw from this portion of the study at anytime without jeopardy to my continued participation in REDS.

1) YES NO MRI scan of my spine.

_____
initials

2) YES NO Additional blood tests for vitamin B12 level, thyroid function and syphilis.

_____
initials

3) YES NO Cystometry or urodynamic testing

_____
initials

4) YES NO Lumbar puncture (spinal tap)

_____
initials

I wish to participate in the above diagnostic tests, to which I have circled "YES" and initialed.

Signature:_____

Name (print):_____

Date:_____

Person obtaining consent:_____ Date:_____

Exhibit A-13

<blood center>

Consent Form For Diagnostic Procedures For Adult T-Cell Leukemia/Lymphoma (ATL)

The Retrovirus Epidemiology Donor Study (REDS)

PURPOSE AND BACKGROUND

As a participant in the Retrovirus Epidemiology Donor Study (REDS), I am being asked to undergo some diagnostic tests to determine if I have the diagnosis of adult T-cell leukemia/lymphoma (ATL), a blood disease associated with the HTLV virus. Although most of these tests would be recommended by any doctor to diagnose my condition, my additional consent is requested because the tests are part of the REDS study procedures. I have been asked to participate in these additional studies because of abnormal results on a REDS blood test or physical exam.

PROCEDURES

If I agree to participate in this part of REDS, all or some of the following testing procedures will be offered to me. The tests which I am being requested to undergo are marked with an "X" next to the description. I may agree to none, some or all of the following tests in the Consent Section of this form by circling "YES" or "NO" and initialing the appropriate line next to each procedure. My choices are not binding and I can change my decision at any time by informing the physician conducting these tests, the REDS study physician or the REDS nurse/counselor.

____ **Physical Examination**
This exam is identical to one I may have had already during my routine REDS followup visit by the study physician. The study physician will examine my skin, lymph nodes, and nervous system. The exam will be performed at a convenient location.

____ **Blood Smear Slides**
This test is identical to one I may have had already during my routine REDS followup visit. It requires that I have a few drops of my blood from a finger stick put on 4 slides. A doctor will then look at my blood under a microscope. The slides will be made at a convenient location by the REDS nurse/counselor.

____ **Complete Blood Count (CBC)**
This test is identical to one I may have had already during my routine REDS followup visit. It requires that I have a needle stick to remove approximately one half tablespoon of blood (7 mls) from my arm. The CBC test counts the number of different types of cells in my blood. The blood draw will be performed at a convenient location by the REDS nurse/counselor or study physician.

____ **Special Laboratory Tests**

These special tests called "PCR", "monoclonal integration studies" and/or "flow cytometry" are to look at the amount of virus in my blood and the effect of HTLV-I/II on my blood cells. In addition, a portion of the blood specimen will be saved for future laboratory tests. Approximately 2 tablespoons of blood (30 mls) will be removed from my arm by a needle stick. The blood draw will be performed at a convenient location by the REDS nurse/counselor or study physician.

____ **Lymph Node Biopsy**

A qualified surgeon will make a small cut in my skin in the area(s) where I have (an) enlarged lymph node(s), after using local anesthetic (numbing medicine) and maybe a pill or shot to numb the pain or make me sleepy. (S)he will then cut out one or more enlarged lymph nodes so they can be examined under the microscope, and sew the skin up again. A portion of the lymph node will be frozen and stored for future laboratory testing by REDS.

____ **Bone Marrow Biopsy**

A qualified doctor will numb the skin over my hip bone or breast bone with local anesthetic, and maybe give me a pill or shot to numb the pain or make me sleepy. (S)he will than use a big needle to take some bone marrow out of my bone so it can be examined under the microscope. A portion of the bone marrow will be frozen and stored for future laboratory testing by REDS.

RISKS AND DISCOMFORTS

The following risks and discomforts may be associated with each of these procedures that I am being requested to undergo, as indicated by an "X" next to the procedure name.

____ **Additional Blood Draw(s)**

The risks of taking a blood sample include the discomfort of the needle stick as well as a very small chance of bruising, bleeding or soreness at the site where the blood was obtained.

____ **Lymph Node Biopsy**

There is a small risk of infection, bleeding or bruising at the biopsy site. There may also be pain, although medication will be used to minimize this.

____ **Bone Marrow Biopsy**

There is a small risk of infection, bleeding or bruising at the biopsy site. There will also be pain during the biopsy, although medication will be used to minimize this.

TREATMENT AND COMPENSATION FOR INJURY

In the event that I suffer physical injury as a direct result of my participation in this

research activity, the <blood center> will assume responsibility for making immediate medical care available to me. This care will be provided to me without charge so long as I notify the <title/position> within 15 days of the date of injury or appearance of symptoms, and I consent to the care offered. Further information concerning treatment and payment of medical expenses in the event of an injury may be obtained from the <title>, <name>, at <telephone number>.

BENEFITS

I understand that I am not guaranteed any benefits from these procedures. However, it is possible that these tests will help to establish a diagnosis of my medical condition, so that my physician(s) will be better able to provide appropriate followup care for my HTLV-related problems. A correct diagnosis will aid in the proper management of my medical condition.

ALTERNATIVES

I may refuse to have any or all of the tests listed above, and may withdraw from having any or all of the tests at any time, without suffering any penalty. Refusal of these tests will in no way influence my participation in REDS, and will not deny me any benefits to which I may otherwise be entitled.

COSTS

The cost of these medical procedures and blood tests will all be covered by REDS. I will not be asked or required to pay for any of them. Additional diagnostic tests due to health problems that are discovered through these tests will be my financial responsibility. REDS does not pay for treatment or hospitalization for any health problems. The only cost to me will be my time.

REIMBURSEMENT

I will receive no payment for participating in these studies. *<optional: However, I will be reimbursed for reasonable travel expenses to and from the procedure(s) and the usual REDS visit stipend.>*

QUESTIONS

This study has been explained to me by <name> and my questions were answered. If I have any other questions about this study later, they may be addressed by calling <name> at <telephone number>.

CONSENT

I have been given a copy of this consent form and also a copy of the experimental subjects' bill of rights to keep. **Participation in this research is voluntary.** I may decline to participate or withdraw from this portion of the study at anytime without jeopardy to my continued participation in REDS.

1) YES NO Physical examination

_____
initials

2) YES NO Blood smear for slides

_____
initials

3) YES NO Blood test measuring the complete blood count (CBC)

_____
initials

4) YES NO Special laboratory tests

_____
initials

5) YES NO Lymph node biopsy

_____
initials

6) YES NO Bone marrow biopsy

_____
initials

I wish to participate in the above diagnostic tests, to which I have circled "YES" and initialed.

Signature:_____

Name (print):_____

Date:_____

Person obtaining consent:_____ Date:_____

Exhibit A-14

< blood center >

Consent Form For Diagnostic Procedures For Additional Dermatologic Workup

The Retrovirus Epidemiology Donor Study (REDS)

PURPOSE AND BACKGROUND

As a participant in the Retrovirus Epidemiology Donor Study (REDS), I am being asked to undergo some diagnostic tests to determine if I have a skin disease related to HTLV-I/II. Although these tests might be recommended by any doctor to diagnose my condition, my additional consent is requested because the tests are part of the REDS study procedures. I have been asked to participate in these additional studies because a particular skin lesion was found on a REDS physical exam.

PROCEDURES

If I agree to participate in this part of REDS, the following testing procedures will be offered to me. I may agree to one or both of the following tests in the Consent Section of this form by circling "YES" or "NO" and initialing the appropriate line next to each procedure. My choices are not binding and I can change my decision at any time by informing the physician conducting these tests, the REDS study physician or the REDS nurse/counselor.

Additional Blood Draw

This is requested of me so that a sample of my blood can be stored in the event that additional testing may be performed on it in the future. This blood draw requires me to have a needle stick to remove approximately 2 tablespoons of blood (30 mls) from my arm. The blood draw will be performed by the REDS nurse/counselor or by the doctor performing the skin biopsy, if I chose to have one.

Skin Biopsy

A qualified doctor will make a small cut in my skin after using local anesthetic (numbing medicine) to numb the pain. (S)he will then cut out a small circle of skin (less than half an inch in diameter) so it can be examined under the microscope, and sew the skin up again. A portion of the skin will be frozen for future laboratory testing by REDS.

RISKS AND DISCOMFORTS

The following risks and discomforts may be associated with each of these procedures I am requested to undergo:

1) The risks of **taking a blood sample** include the discomfort of the needle stick as well as a very small chance of bruising, bleeding or soreness at the site where the blood was obtained.

2) A **skin biopsy** carries a small risk of infection, bleeding or bruising at the biopsy site. There may also be pain, although medication will be used to minimize this.

TREATMENT AND COMPENSATION FOR INJURY

In the event that I suffer physical injury as a direct result of my participation in this research activity, the <blood center> will assume responsibility for making immediate medical care available to me. This care will be provided to me without charge so long as I notify the <title/position> within 15 days of the date of injury or appearance of symptoms, and I consent to the care offered. Further information concerning treatment and payment of medical expenses in the event of an injury may be obtained from the <title>, <name>, at <telephone number>.

BENEFITS

I understand that I am not guaranteed any benefits from these procedures. However, it is possible that these tests will help to establish a diagnosis of my medical condition, so that my physician(s) will be better able to provide appropriate followup care for my HTLV-related problems. A correct diagnosis will aid in the proper management of my medical condition.

ALTERNATIVES

I may refuse to have any or all of the tests listed above, and may withdraw from having any or all of the tests at any time, without suffering any penalty. Refusal of these tests will in no way influence my participation in the REDS study, and will not deny me any benefits to which I may otherwise be entitled.

COSTS

The cost of these medical procedures and blood tests will all be covered by the REDS study. I will not be asked or required to pay for any of them. Additional diagnostic tests due to health problems that are discovered through these tests will be my financial responsibility. REDS does not pay for treatment or hospitalization for any health problems. The only cost to me will be my time.

REIMBURSEMENT

I will receive no payment for participating in these studies. *<optional: However, I will be reimbursed for reasonable travel expenses to and from the procedure(s) and the usual REDS visit stipend.>*

QUESTIONS

This study has been explained to me by <name> and my questions were answered. If I have any other questions about this study later, they may be addressed by calling <name> at <telephone number>.

CONSENT

I have been given a copy of this consent form and also a copy of the experimental subjects' bill of rights to keep. **Participation in this research is voluntary**. I may decline to participate or withdraw from this portion of the study at anytime without jeopardy to my continued participation in REDS.

1) YES NO Additional blood draw

_____
initials

2) YES NO Skin biopsy

_____
initials

I wish to participate in the above diagnostic tests, to which I have circled "YES" and initialed.

Signature:_____

Name (print):_____

Date:_____

Person obtaining consent:_____ Date:_____

Date of Birth _____

Sex _____

WBN _____

REDS Subject ID_____

Special Repository #2 ID_____

Note: Assign new SR ID and complete separate Phlebotomy Form each time blood is drawn for the HTLV Cohort Study.

Affix SR #3 or SR #4 Lab ID label here

REDS PHLEBOTOMY FORM

FAX THIS FORM TO WESTAT. DO NOT FORWARD TO SRA.
(INCLUDE SHIPPING LIST WITH FORM FOR SR #2 SAMPLES)

Date of Blood Draw: |__|__| |__|__| |__|__| Time of Draw: |__|__|:|__|__| am/pm
Mo Day Yr

Reason for Blood Draw:
- ☐ SR #2, Phase Two Visit
- ☐ SR #2, Phase Three Visit, (HTLV-positive subjects and controls)
- ☐ SR #2, Phase Three Negative Sex Partner Visit
- ☐ HTLV Cohort Study, Other (Specify Reason_____)
- ☐ SR #3, (HIV-1 indeterminate donors)
- ☐ SR #4, (HIV-2 reactive donors)
- ☐ Other (Specify Reason_____)

Place of Draw:
- ☐ Blood Center ☐ Subject's Home
- ☐ Other (Specify_____)

Position of Subject:
- ☐ Sitting ☐ Reclining

Tubes Drawn: (Enter number)
- ☐ Lavender top
- ☐ Tiger top
- ☐ Red top
- ☐ Yellow top
- ☐ Corvac
- ☐ Other (Specify_____)

Problems with Draw or Handling:
- ☐ Yes (Specify below) ☐ No

_____

_____

Phlebotomy Result Code: |__|__| Phlebotomist Initials: |__|__|__|

Exhibit A-16

REDS SUBJECT CONTACT SHEET

SUBJECT NAME: _____ **REDS SUBJECT ID:** _____

INSTRUCTIONS TO NURSE/COUNSELOR: Read the introduction and each request verbatim to the subject, after you have completed their initial Phase Three visit activities (e.g., interview, Level 1 exam).

INTRODUCTION (READ TO SUBJECT)

Due to the limited budget for REDS, at this time we are unable to plan any additional study visits in the coming years. However, we would like to stay in touch with you in the event that more funding becomes available. I am going to ask you for some names and addresses of contacts who would know where you are, if we are not able to locate you directly. **Please be assured that we will not disclose the nature of this study, or any information we have learned about you or your health, if we try to locate you.**

REQUEST FOR INDIVIDUAL NAMES

Please give me the name, address and telephone number of two people, not living in your household, who might know where we could contact you.

PERSON # 1: _____
FIRST MI LAST

ADDRESS: _____
NUMBER STREET APT.

_____
CITY STATE ZIP

HOME TELEPHONE NO.: (____) _____

RELATIONSHIP TO SUBJECT: _____

PERSON # 2: _____
FIRST MI LAST

ADDRESS: _____
NUMBER STREET APT.

_____
CITY STATE ZIP

HOME TELEPHONE NO.: (____) _____

RELATIONSHIP TO SUBJECT: _____

REQUEST FOR ORGANIZATIONS

I would also like to get the names and addresses of one or two organizations through which we may be able to locate you. This could be a place of employment, a club or association of which you are a member, or a church or synagogue. Also, is there a particular person at each of these organizations whom we could contact?

NAME OF ORGANIZATION #1: _____

ADDRESS: _____
NUMBER STREET

_____
CITY STATE ZIP

TELEPHONE NO.: (____) _____

CONTACT PERSON: _____
FIRST MI LAST

NAME OF ORGANIZATION #2: _____

ADDRESS: _____
NUMBER STREET

_____
CITY STATE ZIP

TELEPHONE NO.: (____) _____

CONTACT PERSON: _____
FIRST MI LAST

THANK YOU FOR YOUR HELP!

INSTRUCTIONS TO NURSE/COUNSELOR: If no contacts were provided during visit, check box that applies, and followup with subject if necessary.

Subject refused to provide any information ☐
Subject unable to provide any information ☐
Followup with subject after visit to obtain information: ☐

Exhibit A-17

COMPLETION OF REDS CONTACT SHEET VERIFICATION

Instructions: List IDs of all subjects who were seen for a Phase Three Visit, and check the box reflecting the status of obtaining contact sheet information from each of them. When a page has been completed, send or fax it to Westat (attention Nancy Rippetoe: fax 301-738-8379). Do NOT send the actual contact sheets to Westat.

Examiner Initials:_____ **Blood Center:**_____

REDS SUBJECT ID	COMPLIED WITH REQUEST	COULD NOT COMPLY WITH REQUEST	REFUSED REQUEST	FOLLOWUP NEEDED AFTER VISIT	FOLLOWUP COMPLETED

Retrovirus Epidemiology Donor Study (REDS)

Sponsored by:
The National Heart, Lung and Blood Institute (NHLBI)
National Institutes of Health (NIH)

Counseling Message For HTLV-Positive REDS Participants

Introduction

We would like to take this opportunity to thank you for your participation in REDS. Your cooperation with our research has made it possible to learn important medical information which may help all HTLV-positive individuals. The information in this brochure was prepared for all HTLV-positive REDS participants by the doctors involved with the study. In the future, this information may also greatly benefit persons newly diagnosed with HTLV.

What Are My Chances Of Getting Sick?

We know that once you are infected with the HTLV virus, it is a lifelong infection, which means that it will not go away once you have it. Researchers know more about HTLV-I infection than HTLV-II because of studies done in Japan and Caribbean countries, where it is more common for people to have HTLV-I than in the United States. REDS has contributed much of the information on HTLV-II.

If you are infected with HTLV-I:

Over the lifetime of someone infected with HTLV-I, there is less than a 5% chance of developing either of the two illnesses associated with HTLV-I. This means that out of every 100 HTLV-I positive individuals, less than 5 will probably develop an HTLV-I associated illness. The two known illnesses associated with HTLV-I are:

1) Adult T-cell leukemia (ATL), which is a cancer of the blood and lymph glands; and
2) HTLV-associated myelopathy (HAM), which is a disorder of the nervous system.

Early information from REDS shows that the risk of getting sick from HTLV-I infection is quite low. So far, there has been 1 confirmed case of ATL and 4 cases of HAM out of about 150 HTLV-I positive participants in REDS. Other research studies have shown similar results.

If you are infected with HTLV-II:

Since HTLV-II infection was not studied much in the United States before REDS began, we do not have as much information about illnesses associated with HTLV-II or about the chance of someone developing an HTLV-II related illness. So far, there have been 3 cases of HTLV-associated myelopathy (HAM), out of about 400 HTLV-II positive REDS participants. As we continue to follow the REDS participants, we hope to get a better understanding of any other illnesses that could affect someone infected with HTLV-II. At this point, the chance of becoming sick from having HTLV-II appears to be about 1 out of 100. This means that out of every 100 individuals with HTLV-II, only about 1 of them may get sick from being infected with the HTLV-II virus.

What Are The Signs And Symptoms Of An HTLV-Related Illness?

Throughout the course of REDS, many HTLV-positive study participants have asked about signs or symptoms that may warn them about the beginning of an HTLV-related illness. The following list of signs or symptoms may be associated with HTLV infection, if they are not caused by any other medical condition you have:

1) Unusual difficulty with two of the following:
   - Walking,
   - Getting out of a chair, or
   - Climbing stairs;
2) Two of the following symptoms:
   - A strong urge to urinate, or a feeling that you can't wait to get to the toilet;
   - Urine leaking, or
   - A feeling that your bladder does not empty completely when you urinate;
3) Swollen lymph nodes;
4) Unexplained fevers or night sweats;
5) Weight loss of 10 or more pounds not due to exercise, dieting or eating less than normal; and
6) Loss of bowel control.

In addition, if your doctor diagnoses any of the following conditions, they may be related to HTLV-I or HTLV-II infection:

1) Lymphoma, leukemia or any other cancer;
2) Polymyositis, dermatomyositis or myositis (all forms of muscle inflammation);
3) Muscle spasms, tremors and/or paralysis;
4) Multiple sclerosis; or
5) Uveitis or iritis (eye disease diagnosed by an eye doctor).

Please realize that the symptoms and conditions listed above very often have other causes and do not necessarily mean you are developing or have a illness related to your HTLV infection. If you develop any of these symptoms, you should see a doctor to determine the cause of your problem.

How Does HTLV Spread From Person to Person?

Current information about the transmission of HTLV-I and HTLV-II is the same as when REDS began in 1990. HTLV-I is known to be spread in the following ways:

1) Sexual contact with an HTLV-I positive individual;
2) Receiving a blood transfusion prior to 1988 from an individual infected with the HTLV-I virus;
3) Using a contaminated needle after an HTLV-I positive individual; and
4) Breast feeding of a child by an HTLV-I positive individual.

HTLV-II is spread like HTLV-I, although research is still being done to see if HTLV-II can be transmitted by breast feeding. Our REDS research shows the most common risk for female blood donors becoming infected with HTLV-II has been through sexual contact with an HTLV-II positive individual who has injected drugs.

How Can I Avoid Spreading HTLV To Others?

Information about preventing the spread of HTLV-I and HTLV-II to others comes from what is already known about its transmission. It should be remembered that HTLV is a virus carried in the blood and is not easily spread to other people. However, according to the Centers for Disease Control and Prevention (CDC) and your local blood donor center, it is recommended that you take the following steps to prevent transmitting (or passing along) the HTLV virus to others:

1) Do not donate blood, semen, body organs or other body tissues;
2) Do not inject illegal drugs. If you do inject any drugs, do not share needles or syringes with anyone else;
3) If you have a baby, do not breast feed; and
4) Always use latex condoms during sexual intercourse* (see footnote at end of brochure for additional information). If a lubricant is used in addition to the latex condom, it must be a non-petroleum based lubricant.

If you have any questions about the above guidelines, please discuss them with your REDS nurse/counselor.

Due to the limited budget for REDS, at this time we are unable to plan any additional study visits for our participants. However, we would like to stay in touch with you in the event that more funding becomes available. During your current visit, we will be asking you for information which may help us to locate you in the future.

* Footnote

If your sexual partner is also HTLV-positive, you do not need to use latex condoms to prevent spreading HTLV to each other. However, if either of you has a sexually-transmitted disease, it is recommended that latex condoms be used to prevent spreading the disease.

If your partner is not HTLV-positive, you should use latex condoms to prevent spreading HTLV to your partner.

If the HTLV status of your sexual partner is unknown, it is recommended that your partner be tested as soon as possible.

Using latex condoms is strongly recommended for HTLV-positive people who have more than one sexual partner.

Exhibit A-19

REDS HTLV TRACKING SYSTEM
SHIPPING LIST FOR FORMS

Destination:
Blood Center: CHESAPEAKE
Date of Shipment: 03/17/95

Study Subject ID	Check Items Being Shipped:											
	Conf. Tests	HTLV Quex	Exam Forms/Reports: Lev I	Lev II	Lev III	CBC Rslt	PFT Form	Skin Test	Non-Visit Form	Lvl 1 Verif.	MED Recs	Other (Specify)
PD1-0098-7												
PD1-1329-9												
C21-0465-2												
HV1-3210-1												
HV1-3207-6												

Subject ID (if known) _____ Exhibit A-20 Donor ID _____

WBN/BUI _____ Date of Donation _____

REDS HTLV CONFIRMATORY TEST RESULTS FORM

COMPLETE THIS FORM FOR ALL DONORS WITH REPEATEDLY REACTIVE HTLV RESULTS.
FORWARD TO THE COORDINATING CENTER ON THE 1ST OF EACH MONTH.

EIA

Laboratory Performing Test: _____

EIA #1

Absorbance Level: _____ Cut-off Level: _____

Interpretation: ☐ Reactive ☐ Nonreactive

EIA #2

Absorbance Level: _____ Cut-off Level: _____

Interpretation: ☐ Reactive ☐ Nonreactive

EIA #3

Absorbance Level: _____ Cut-off Level: _____

Interpretation: ☐ Reactive ☐ Nonreactive

Western Blot

☐ Not done

_____
(Laboratory Performing Test)

Recording Band Intensities:
0 = Not Present
1 = Slight
2 = Moderate
3 = Strong
x = Intensities not reported but band present

ARC Bands:	p21env	p19	p24	p26	p28	p32	p38tax	p42	gp46	p53	other
	___	___	___	___	___	___	___	___	___	___	___

Non-ARC Bands:	p19	rgp21	gp21	p24	p26	p28	p32	p36	rgp46-I	rgp46-II	gp46	p53	other
	___	___	___	___	___	___	___	___	___	___	___	___	___

Interpretation: ☐ Positive ☐ Negative ☐ Indeterminate ☐ Inconclusive ☐ Dark

---

RIPA

☐ Not done

_____
(Laboratory Performing Test)

Recording Band Intensities:
0 = Not Present
1 = Slight
2 = Moderate
3 = Strong
x = Intensities not reported but band present

Bands:	p15	p19	p24	p33	p40x	gp46	p55	gp61	gp68	other
	___	___	___	___	___	___	___	___	___	___

Interpretation: ☐ Positive ☐ Negative ☐ Indeterminate/Nondiagnostic

---

HTLV FINAL INTERPRETATION: ☐ Positive ☐ Negative ☐ Indeterminate/ Nondiagnostic ☐ Inconclusive ☐ Dark

HTLV POSITIVES ONLY
TYPE INTERPRETATION: ☐ HTLV-I ☐ HTLV-II ☐ Untypeable

(Form revised 4/21/94)

Exhibit A-21

REDS SPECIAL REPOSITORY RECORD OF SHIPMENT

Destination:CENTRAL LAB
Sender:DETROIT
Date of Shipment:03/15/95
Airbill/Tracking Number: _____

Special Repository ID	Westat Use: SRA NO.	SR#	Enter the Number Of Items Being Shipped For Each ID: Red-Top Tubes	Yellow-Top Tubes	Residual Serum Tube	Peripheral Slides	Other
30000001		2					
30000002		2					
30000003		2					
30000004		2					

Subject ID _____

SR # _____

PHASE THREE CBC RESULTS

COMPLETE FOR ALL CONFIRMED HTLV POSITIVES AND NEGATIVE CONTROLS, AND FORWARD TO THE COORDINATING CENTER WITH OTHER FORMS IN THE BEGINNING OF EACH MONTH.

Laboratory:_____ Date of Testing: |__|__||__|__||__|__|
MO DAY YR

Gender: _____ Age: _____

	RESULTS	REFERENCE VALUES
White count (x1000):	|__||__|.|__|	|__||__|.|__|-|__||__|.|__|
Hemoglobin:	|__||__|.|__|	|__||__|.|__|-|__||__|.|__|
HCT:	|__||__|.|__|	|__||__|.|__|-|__||__|.|__|
MCV:	|__||__||__|.|__|	|__||__||__|.|__|-|__||__||__|.|__|
PLT (x1000):	|__||__||__|.|__|	|__||__||__|-|__||__||__|
<u>Differential</u>		
Poly:	|__||__|	|__||__|-|__||__|
Band:	|__||__|	|__||__|-|__||__|
Lymph:	|__||__|	|__||__|-|__||__|
Mono:	|__||__|	|__||__|-|__||__|
Eos:	|__||__|	|__||__|-|__||__|
Baso:	|__||__|	|__||__|-|__||__|
Myelo/Meta:	|__||__|	
ATYP/Reactive Lymphs		|__||__|
Large Lymphs	|__||__|	
Large Unstained/ Unclassified Cells	|__||__|	

APPENDIX B

PHASE THREE INTERVIEW QUESTION-BY-QUESTION SPECIFICATIONS

The following pages provide detailed specifications for and explanations of questions included in the Phase Three Interview to be administered to HTLV-positive donors, seropositive sex partners, and negative controls. These specifications should serve as a reference for administering the Phase Three Interview throughout Phase Three of REDS.

PHASE TWO INTERVIEW SUMMARY SHEET

FOR ALL SUBJECTS WHO PARTICIPATED IN PHASE TWO

Subject Name _____

Subject ID PD -0009-0

Sex: ☐ Male ☒ Female

Phase Three Followup Window 06/11/95 - 12/08/95

Phase Two Activities:

Interview Date	04/06/93
Level 1 Physical Exam Date	04/06/93

INFORMATION TO TRANSCRIBE FROM PHASE TWO INTERVIEW TO PHASE THREE INTERVIEW:

From Phase Two #	To Phase Three #		YES	NO
B-2a/b	B-1a/b	Unusual difficulty walking because of your legs	☐	☒
B-2c/d	B-1c/d	Unusual difficulty rising from a chair without using your hands	☐	☒
B-2e/f	B-1e/f	Unusual difficulty climbing stairs because of your legs	☒	☐
B-2g/h	B-1g/h	A strong urge to urinate so that you can't wait to get to the toilet	☐	☒
B-2i/j	B-1i/j	A problem with urine leaking	☐	☒
B-2k/l	B-1k/l	A feeling that you still need to go (urinate) after you finish urinating	☐	☒
B-2m/n	B-1m/n	(IF MALE) A problem having or maintaining an erection	☐	☐
B-2o/p	B-1o/p	A burning or tingling sensation in your feet	☐	☒
B-2q/r	B-1q/r	Swollen or painful glands in your neck, groin or under your arms	☐	☒
B-2s/t	B-1s/t	Unexplained fevers	☐	☒
B-2u/v	B-1u/v	Unexplained night sweats	☐	☒
B-2w/x	B-1w/x	Unintentional weight loss of 10 lbs. or more	☐	☒
B-2y/z	B-1y/z	Loss of bowel control	☐	☒

PHASE TWO INTERVIEW SUMMARY SHEET

This summary sheet is generated by the Coordinating Center for every subject who completed a Phase Two Interview. It contains pre-printed information from the HTLV Tracking System and Phase Two Interview that is needed to conduct the Phase Three Interview. ***The information on the summary sheet should be transcribed before the subject is seen for his/her interview.*** Instructions for transcribing the information appear in Box A on the inside cover of the Phase Three Interview booklet.

REVISED PHASE ONE INTERVIEW SUMMARY SHEET

FOR SUBJECTS WHO DID NOT PARTICIPATE IN PHASE TWO

Subject Name _____

Subject ID PD -0091-0

Sex: ☐ Male ☒ Female

Phase Three Followup Window 08/07/95 - 02/03/96

Phase One Activities:

Baseline Interview Date	05/30/91
Level 1 Physical Exam Date	05/30/91

INFORMATION TO TRANSCRIBE FROM PHASE ONE BASELINE INTERVIEW TO PHASE THREE INTERVIEW:

From Phase One #	To Phase Three #		YES	NO
B-1a	B-1a/b	Unusual difficulty walking because of your legs	☒	☐
B-1b	B-1c/d	Unusual difficulty rising from a chair without using your hands	☒	☐
B-1c	B-1e/f	Unusual difficulty climbing stairs because of your legs	☒	☐
B-1d	B-1g/h	A strong urge to urinate so that you can't wait to get to the toilet	☒	☐
B-1e	B-1i/j	A problem with urine leaking	☐	☒
B-1f	B-1k/l	A feeling that you still need to go (urinate) after you finish urinating	☐	☒
B-1h	B-1m/n	(IF MALE) A problem having or maintaining an erection	☐	☐
B-1i	B-1o/p	A burning or tingling sensation in your feet	☐	☒
B-1j	B-1q/r	Swollen or painful glands in your neck, groin or under your arms	☐	☒
B-1k	B-1s/t	Unexplained fevers	☐	☒
B-1l	B-1u/v	Unexplained night sweats	☐	☒
B-1m	B-1w/x	Unintentional weight loss of 10 lbs. or more	☐	☒
B-1n	B-1y/z	Loss of bowel control	☐	☒

REVISED PHASE ONE INTERVIEW SUMMARY SHEET

This summary sheet is generated by the Coordinating Center for all subjects who did not complete a Phase Two interview but are now eligible to return for Phase Three. It has pre-printed information from the HTLV Tracking System and Phase One Baseline Interview that is needed to conduct the Phase Three Interview. ***The information on the summary sheet should be transcribed before the subject is seen for his/her interview.*** Instructions for transcribing the information appear in Box B on the inside cover of the Phase Three Interview booklet.

SUBJECT ID _____

DATE OF INTERVIEW |__|__| |__|__| |__|__|
MO DAY YR

INTERVIEWER INITIALS |__|__|__|

INTERVIEW LOCATION:

BLOOD CENTER 1
SUBJECT'S HOME 2
OTHER 3

_____
(SPECIFY)
TELEPHONE 4

GENDER OF SUBJECT:

MALE 1
FEMALE 2

INTERVIEW RESULT |__|__|

PHASE THREE INTERVIEW
REDS HTLV COHORT STUDY

DATE OF MOST RECENT INTERVIEW: |__|__| |__|__| |__|__|
MO DAY YR

COVER PAGE

PHASE THREE INTERVIEW

On the Phase Three Interview cover page, enter or circle the codes for the following information:

- The REDS Subject ID;
- The date of the interview;
- The interviewer's initials;
- The location code describing where the interview is taking place, or if it is being conducted over the telephone. Specify the location if "Other;"
- The subject's gender; and
- The date when this subject's most recent interview was conducted (either in Phase One or Two), as indicated on that subject's summary sheet.

At the end of the interview enter the result code for the interview, either "IC" for a completed interview, or "PC" for a partially completed interview. The "PC" code should only be used if one or more entire sections of the interview are not answered. ***It is not appropriate to use this code if only one or two of the questions are unanswered.***

BOX A

TRANSCRIPTION INSTRUCTIONS
FOR SUBJECTS WHO PARTICIPATED IN PHASE TWO

PRIOR TO PHASE THREE VISIT, TRANSCRIBE INFORMATION FROM PHASE TWO INTERVIEW SUMMARY SHEET TO THE SHADED AREAS OF THIS PHASE THREE INTERVIEW BOOKLET.

FROM PHASE TWO INTERVIEW SUMMARY SHEET	TRANSCRIBE TO:
Date of Phase Two Interview	Front cover; Box B-1 on page 2; Box B-2 on page 9; Box B-3 on page 12; Box B-4 on page 13; Box B-5 on page 14; Box C-1 on page 16; Box C-2 on page 17; and Question D-1 on page 18.
Responses to B-2a through B-2z	B-1a through B-1z on pages 2 through 8

BOX B

TRANSCRIPTION INSTRUCTIONS
FOR SUBJECTS WHO DID NOT PARTICIPATE IN PHASE TWO

PRIOR TO PHASE THREE VISIT, TRANSCRIBE INFORMATION FROM REVISED PHASE ONE INTERVIEW SUMMARY SHEET TO THE SHADED AREAS OF THIS PHASE THREE INTERVIEW BOOKLET.

FROM REVISED PHASE ONE INTERVIEW SUMMARY SHEET	TRANSCRIBE TO:
Date of Phase One Interview	Front cover; Box B-1 on page 2; Box B-2 on page 9; Box B-3 on page 12; Box B-4 on page 13; Box B-5 on page 14; Box C-1 on page 16; Box C-2 on page 17; and Question D-1 on page 18.
Responses to B-1a through B-1f and B-1h through B-1n	B-1a through B-1z on pages 2 through 8

FOR ALL HTLV-POSITIVE AND CONTROL SUBJECTS, BEGIN INTERVIEW WITH SECTION A, AND CONTINUE TO SECTIONS B THROUGH E. NEGATIVE SEX PARTNERS ARE NOT INTERVIEWED IN PHASE THREE.

INSIDE COVER

TRANSCRIPTION INSTRUCTIONS

BOX A. For Subjects Who Participated in Phase Two

Prior to seeing the subject for his/her Phase Three Interview, using the Phase Two Interview Summary Sheet, transcribe the date of the Phase Two Interview to the shaded areas of the Phase Three Interview listed in BOX A. "Yes/No" responses previously given in Section B of the Phase Two Interview must be transcribed into the shaded columns of Section B of the Phase Three Interview, as they appear on the summary sheet. It is important for the administration of the Phase Three Interview that Phase Two data are correctly transcribed into the interview booklet.

BOX B. For Subjects Who Did Not Participate in Phase Two

Prior to seeing the subject for his/her Phase Three Interview, using the Revised Phase One Interview Summary Sheet, transcribe the date of the Phase One Interview to the shaded areas of the Phase Three Interview listed in Box B. "Yes/No" responses given in Section B of the Phase One Interview should be transcribed into the shaded columns of Section B of the Phase Three Interview, as they appear on the summary sheet. It is important for the administration of the Phase Three Interview that Phase One data are correctly transcribed into the interview booklet.

TIME BEGIN: |___|___| : |___|___| AM PM

A. GENERAL HEALTH

BOX A-1

During this interview, I'll be asking questions about your health and lifestyle. Just as before, all information you give will be kept strictly confidential, and will be used for research purposes only. Your name or other identifying information will not be linked to your answers.

A-1. What is the zip code where you live now? |___|___|___|___|___|

A-2. At the present time, would you say that your health, in general, is:

Excellent,	1
Very good,	2
Good,	3
Fair, or	4
Poor?	5

A-3. Thinking about this same time last year, would you say that your health, in general, at that time was:

Excellent,	1
Very good,	2
Good,	3
Fair, or	4
Poor?	5

A-4. At the present time, are you limited in the kind or amount of work or housework you can do because of a health problem?

YES	1
NO	2

A-5. During the past year, how many days did you miss more than half of the day from your job or business because of illness or injury?

NO. OF WORK-LOSS DAYS	|___|___|___|
NONE	000
NOT WORKING	995

SECTION A. GENERAL HEALTH

Before reading the introduction to the subject, record the time the interview begins in the upper right corner, circling "AM" or "PM" as appropriate.

Box A-1. The introduction printed in this box should always be read verbatim to the subject prior to beginning the interview, particularly to reassure him/her about the confidentiality of his/her answers.

A-1. Enter the Zip Code of the subject's current residence.

A-2. Read the question and possible answers, particularly emphasizing the wording "present time" and "in general."

A-3. Do the same as in A-2, emphasizing "same time last year" and "in general."

A-4. This question is to determine if the subject is limited currently in his/her usual work or housework activities due to a health problem. Circle "YES" if the subject indicates any type of limitation, ***even if it is minor or temporary (e.g., due to injury)***.

A-5. The purpose of this question is to get an indication of the subject's general health by determining how many days were missed. Note the following points:

- This question is directed toward subjects who have been employed the entire past year. If the subject has not been employed the entire year, circle code "995."
- A missed day is defined as "more than half of the day" away from work.
- If the subject has not missed any work days, circle code "000."
- ***Do not include days missed during or after pregnancy (e.g., maternity leave or "morning sickness"), or time away from work for doctor's appointments.***

B. HEALTH HISTORY

BOX B-1

Now I'm going to ask you some questions about your health. Please be sure to tell me only about symptoms and medical conditions you've had since your last interview on _____ (DATE).

SYMPTOM:	B-1. REPORTED LAST INTERVIEW? (TRANSCRIBE FROM SUMMARY SHEET)	B-2.	B-3.	B-4.	B-5.
Unusual difficulty walking because of your legs	a. YES ..... 1→	Since your last interview, have you had (SYMPTOM)? YES ..... 1 → NO 2 (B-2c/d)	Since your last interview, would you say this is worse, better or about the same? WORSE .... 1 BETTER .... 2 SAME ..... 3 } →	Has a doctor or other medical person told you anything about this problem since your last interview? YES .... 1 → NO 2 (B-2c/d)	What did he or she say? _____ _____ _____ _____ _____
	b. NO ..... 2→	Since your last interview, have you had (SYMPTOM) for more than one continuous month? YES ..... 1 → NO 2 (B-2c/d)	How long did this last? |__|__| NO. MONTHS .. 1 YEARS ..... 2 } →	Did you see a doctor or other medical person about this? YES .... 1 → NO 2 (B-2c/d)	What was the diagnosis for this? _____ _____ _____ _____ _____
Unusual difficulty rising from a chair without using your hands	c. YES ..... 1→	Since your last interview, have you had (SYMPTOM)? YES ..... 1 → NO 2 (B-2e/f)	Since your last interview, would you say that this is worse, better or about the same? WORSE .... 1 BETTER .... 2 SAME ..... 3 } →	Has a doctor or other medical person told you anything about this problem since your last interview? YES .... 1 → NO 2 (B-2e/f)	What did he or she say? _____ _____ _____ _____ _____
	d. NO ..... 2→	Since your last interview, have you had (SYMPTOM) for more than one continuous month? YES ..... 1 → NO 2 (B-2e/f)	How long did this last? |__|__| NO. MONTHS .. 1 YEARS ..... 2 } →	Did you see a doctor or other medical person about this? YES .... 1 → NO 2 (B-2e/f)	What was the diagnosis for this? _____ _____ _____ _____ _____

GENERAL SPECIFICATIONS FOR INTERVIEW PAGES 2-8

SECTION B. HEALTH HISTORY

Section B is a series of questions that ask about the subject's health since his/her last interview. ***This date and symptoms that the subject reported in Section B of his/her most recent interview should have been transcribed from the summary sheet before beginning the Phase Three Interview, because previous answers determine the wording of questions in this section.***

It is important to read the questions and medical terminology in this section exactly as written. ***Do not define any of the terms listed or try to make a diagnosis based on a description of symptoms given by the subject. If a subject does not recognize a particular term, then assume that the subject has not had the problem.***

Box B-1. This introduction should be read verbatim to the subject, stressing the date of the subject's most recent interview.

Column B-1. For B-1a through B-1z, the appropriate code should be circled ("1" for Yes; "2" for No) based on the answers reported by each subject during his/her last interview. Each subject's summary sheet (provided to the blood center by the Coordinating Center) lists the responses that must be transcribed into this column prior to seeing the subject for his/her interview.

Column B-2 B-2a through B-2z ask about symptoms which could be complications of HTLV-I/II infection.

- If a subject reported the symptom during his/her most recent interview, REDS is interested in determining if he/she has continued to have this problem since that interview.
- If a subject did not report this problem in his/her last interview, REDS wants to determine if he/she has had this problem for more than one continuous month since the last interview.

Read the appropriate question in Column B-2 for each symptom based on what a subject reported during his/her most recent interview. If a symptom was reported during the last interview, the first row of questions should be asked. If a particular symptom was not reported in the last interview, the second row of questions about the symptoms should be asked. ***Because a symptom may have been only sporadic or of short duration, it is important that the phrases "more than one continuous month" and "since your last interview" be emphasized.***

If a subject answers "YES" to any question in B-2 (a-z), continue across the grid row and ask B-3. If a subject answers "NO" to any question in B-2 (a-z), go to the next symptom listed in Column B-1.

(continued on next page)

Column B-3.

B-3a through B-3z are asked of subjects who either reported a symptom during their most recent interview and still have this problem, or who have had this problem for more than one continuous month since the last interview. For subjects who reported this symptom during the last interview, REDS wants to find out if the problem is worse, better or the same. For subjects who did not report this symptom before, REDS wants to know long this symptom has lasted. Please note the following points:

- ***For subjects who did not report a symptom in their last interview, if the symptom has occurred more than once, for more than a continuous month, enter the length of the longest continuous occurrence.***
- Subjects have the option of answering either in months or years.
- If a subject gives a fraction of a month (e.g., 3-1/2 months), round off to the nearest even whole number.
- If a subject responds in years and months, (e.g., 1 year and 8 months), convert the entire time period into months (e.g., 20 months).

Column B-4.

Continue across the grid to B-4 for each reported symptom. If the subject saw a physician or other medical person because of the symptom, continue to B-5; otherwise skip to the next symptom, and ask the appropriate question in Column B-2.

- "Other medical person" includes nurse, nurse practitioner, physician's assistant, etc.
- ***This question also includes the REDS HTLV Cohort Study nurse/counselor, study physician and/or a REDS Level 3 specialist.***

Column B-5.

For subjects who saw a doctor or other medical person, enter the diagnosis or information, verbatim, about this symptom that was provided to the subject by the doctor/medical person.

If no diagnosis was given to the subject, write "NONE" in Column B-5 for that particular symptom.

SYMPTOM:	B-1. REPORTED LAST INTERVIEW? (TRANSCRIBE FROM SUMMARY SHEET)	B-2.	B-3.	B-4.	B-5.
Unusual difficulty climbing stairs because of your legs.	e. YES ..... 1 →	Since your last interview, have you had (SYMPTOM)? YES ..... 1 → NO 2 (B-2g/h)	Since your last interview, would you say this is worse, better or about the same? WORSE .... 1 BETTER .... 2 SAME ..... 3 } →	Has a doctor or other medical person told you anything about this problem since your last interview? YES .... 1 → NO 2 (B-2g/h)	What did he or she say? _____ _____ _____ _____ _____
	f. NO ..... 2 →	Since your last interview, have you had (SYMPTOM) for more than one continuous month? YES ..... 1 → NO 2 (B-2g/h)	How long did this last? |__|__| NO. MONTHS .. 1 YEARS ..... 2 } →	Did you see a doctor or other medical person about this? YES .... 1 → NO 2 (B-2g/h)	What was the diagnosis for this? _____ _____ _____ _____ _____
A strong urge to urinate so that you can't wait to get to the toilet	g. YES ..... 1 →	Since your last interview, have you had (SYMPTOM)? YES ..... 1 → NO 2 (B-2i/j)	Since your last interview, would you say that this is worse, better or about the same? WORSE .... 1 BETTER .... 2 SAME ..... 3 } →	Has a doctor or other medical person told you anything about this problem since your last interview? YES .... 1 → NO 2 (B-2i/j)	What did he or she say? _____ _____ _____ _____ _____
	h. NO ..... 2 →	Since your last interview, have you had (SYMPTOM) for more than one continuous month? YES ..... 1 → NO 2 (B-2i/j)	How long did this last? |__|__| NO. MONTHS .. 1 YEARS ..... 2 } →	Did you see a doctor or other medical person about this? YES .... 1 → NO 2 (B-2i/j)	What was the diagnosis for this? _____ _____ _____ _____ _____

See "General Specifications for Interview Pages 2-8",
on Pages B-13 and B-15 of this appendix.

SYMPTOM:	B-1. REPORTED LAST INTERVIEW? (TRANSCRIBE FROM SUMMARY SHEET)	B-2.	B-3.	B-4.	B-5.
A problem with urine leaking	i. YES ..... 1→	Since your last interview, have you had (SYMPTOM)? YES ..... 1 → NO 2 (B-2k/l)	Since your last interview, would you say this is worse, better or about the same? WORSE .... 1 BETTER .... 2 SAME ..... 3 } →	Has a doctor or other medical person told you anything about this problem since your last interview? YES .... 1 → NO 2 (B-2k/l)	What did he or she say? _____ _____ _____ _____ _____
	j. NO ..... 2→	Since your last interview, have you had (SYMPTOM) for more than one continuous month? YES ..... 1 → NO 2 (B-2k/l)	How long did this last? |__|__| NO. MONTHS .. 1 YEARS ..... 2 } →	Did you see a doctor or other medical person about this? YES .... 1 → NO 2 (B-2k/l)	What was the diagnosis for this? _____ _____ _____ _____ _____
A feeling that you still need to (go/urinate) after you finish urinating	k. YES ..... 1→	Since your last interview, have you had (SYMPTOM)? YES ..... 1 → NO ..... 2 (IF MALE B-2m/n; IF FEMALE B-2o/p)	Since your last interview, would you say that this is worse, better or about the same? WORSE .... 1 BETTER .... 2 SAME ..... 3 } →	Has a doctor or other medical person told you anything about this problem since your last interview? YES .... 1 → NO ..... 2 (IF MALE b-2m/n; IF FEMALE (b-2o/p)	What did he or she say? _____ _____ _____ _____ _____
	l. NO ..... 2→	Since your last interview, have you had (SYMPTOM) for more than one continuous month? YES ..... 1 → NO ..... 2 (IF MALE B-2m/n; IF FEMALE B-2o/p)	How long did this last? |__|__| NO. MONTHS .. 1 YEARS ..... 2 } →	Did you see a doctor or other medical person about this? YES .... 1 → NO ..... 2 (IF MALE B-2m/n; IF FEMALE B-2o/p)	What was the diagnosis for this? _____ _____ _____ _____ _____

(See also, "General Specifications for Interview Pages 2-8"
on Pages B-13 and B-15 of this appendix.)

B-2k/l. Note the alternative wording from which to chose for this symptom (i.e., "go" versus "urinate"). Use whichever wording may be better understood by the subject.

- After asking B-2k/l, male subjects should be asked about the next symptom in B-2m/n. For female subjects, skip to B-2o/p.

SYMPTOM:	B-1. REPORTED LAST INTERVIEW? (TRANSCRIBE FROM SUMMARY SHEET)	B-2.	B-3.	B-4.	B-5.
(IF MALE) A problem having or maintaining an erection	m. YES ..... 1→	Since your last interview, have you had (SYMPTOM)? YES ..... 1 → NO 2 (B-2o/p)	Since your last interview, would you say this is worse, better or about the same? WORSE .... 1 BETTER .... 2 SAME ..... 3 } →	Has a doctor or other medical person told you anything about this problem since your last interview? YES .... 1 → NO 2 (B-2o/p)	What did he or she say? _____ _____ _____ _____ _____
	n. NO ..... 2→	Since your last interview, have you had, for more than one continuous month, (SYMPTOM)? YES ..... 1 → NO 2 (B-2o/p)	How long did this last? |__|__| NO. MONTHS .. 1 YEARS ..... 2 } →	Did you see a doctor or other medical person about this? YES .... 1 → NO 2 (B-2o/p)	What was the diagnosis for this? _____ _____ _____ _____ _____
A burning or tingling sensation in your feet	o. YES ..... 1→	Since your last interview, have you had (SYMPTOM)? YES ..... 1 → NO 2 (B-2q/r)	Since your last interview, would you say that this is worse, better or about the same? WORSE .... 1 BETTER .... 2 SAME ..... 3 } →	Has a doctor or other medical person told you anything about this problem since your last interview? YES .... 1 → NO 2 (B-2q/r)	What did he or she say? _____ _____ _____ _____ _____
	p. NO ..... 2→	Since your last interview, have you had (SYMPTOM) for more than one continuous month? YES ..... 1 → NO 2 (B-2q/r)	How long did this last? |__|__| NO. MONTHS .. 1 YEARS ..... 2 } →	Did you see a doctor or other medical person about this? YES .... 1 → NO 2 (B-2q/r)	What was the diagnosis for this? _____ _____ _____ _____ _____

(See also, "General Specifications for Interview Pages 2-8"
on Pages B-13 and B-15 of this appendix.)

B-2n. Note the wording change for this specific question, where the symptom, "A problem having or maintaining an erection" is inserted <u>at the end</u> of the question.

SYMPTOM:	B-1. REPORTED LAST INTERVIEW? (TRANSCRIBE FROM SUMMARY SHEET)	B-2.	B-3.	B-4.	B-5.
Swollen or painful glands in your neck, groin, or under your arms	q. YES ..... 1→	Since your last interview, have you had (SYMPTOM)? YES ..... 1 → NO 2 (B-2s/t)	Since your last interview, would you say this is worse, better or about the same? WORSE .... 1 BETTER .... 2 }→ SAME 3	Has a doctor or other medical person told you anything about this problem since your last interview? YES .... 1 → NO 2 (B-2s/t)	What did he or she say? _____ _____ _____ _____ _____
	r. NO ..... 2→	Since your last interview, have you had (SYMPTOM) for more than one continuous month? YES ..... 1 → NO 2 (B-2s/t)	How long did this last? |__|__| NO. MONTHS .. 1 YEARS ..... 2 }→	Did you see a doctor or other medical person about this? YES .... 1 → NO 2 (B-2s/t)	What was the diagnosis for this? _____ _____ _____ _____ _____
Unexplained fevers	s. YES ..... 1→	Since your last interview, have you had (SYMPTOM)? YES ..... 1 → NO 2 (B-2u/v)	Since your last interview, would you say that this is worse, better or about the same? WORSE .... 1 BETTER .... 2 }→ SAME 3	Has a doctor or other medical person told you anything about this problem since your last interview? YES .... 1 → NO 2 (B-2u/v)	What did he or she say? _____ _____ _____ _____ _____
	t. NO ..... 2→	Since your last interview, have you had (SYMPTOM) for more than one continuous month? YES ..... 1 → NO 2 (B-2u/v)	How long did this last? |__|__| NO. MONTHS .. 1 YEARS ..... 2 }→	Did you see a doctor or other medical person about this? YES .... 1 → NO 2 (B-2u/v)	What was the diagnosis for this? _____ _____ _____ _____ _____

(See also, "General Specifications for Interview Pages 2-8"
on Pages B-13 and B-15 of this appendix.)

B-2s/t. The word "Unexplained" should be stressed when inserting this symptom into the question.

SYMPTOM:	B-1. REPORTED LAST INTERVIEW? (TRANSCRIBE FROM SUMMARY SHEET)	B-2.	B-3.	B-4.	B-5.
Unexplained night sweats	u. YES ..... 1→	Since your last interview, have you had (SYMPTOM)? YES ..... 1 → NO 2 (B-2w/x)	Since your last interview, would you say this is worse, better or about the same? WORSE .... 1 BETTER .... 2 }→ SAME 3	Has a doctor or other medical person told you anything about this problem since your last interview? YES .... 1 → NO 2 (B-2w/x)	What did he or she say? _____ _____ _____ _____ _____
	v. NO ..... 2→	Since your last interview, have you had (SYMPTOM) for more than one continuous month? YES ..... 1 → NO 2 (B-2w/x)	How long did this last? |__|__| NO. MONTHS .. 1 YEARS ..... 2 }→	Did you see a doctor or other medical person about this? YES .... 1 → NO 2 (B-2w/x)	What was the diagnosis for this? _____ _____ _____ _____ _____
Unintentional weight loss of 10 lbs. or more	w. YES ..... 1→	Since your last interview, have you had (SYMPTOM)? YES ..... 1 → NO 2 (B-2y/z)	Since your last interview, would you say that this is worse, better or about the same? WORSE .... 1 BETTER .... 2 }→ SAME 3	Has a doctor or other medical person told you anything about this problem since your last interview? YES .... 1 → NO 2 (B-2y/z)	What did he or she say? _____ _____ _____ _____ _____
	x. NO ..... 2→	Since your last interview, have you had, for more than one continuous month, (SYMPTOM)? YES ..... 1 → NO 2 (B-2y/z)	How long did this last? |__|__| NO. MONTHS .. 1 YEARS ..... 2 }→	Did you see a doctor or other medical person about this? YES .... 1 → NO 2 (B-2y/z)	What was the diagnosis for this? _____ _____ _____ _____ _____

(See also, "General Specifications for Interview Pages 2-8"
on Pages B-13 and B-15 of this appendix.)

B-2u/v. The word "Unexplained" should be stressed when inserting this symptom into the question.

B-2w/x. through B-5w/x. Note the change in wording for this specific question, where the symptom, "Unintentional weight loss of 10 lbs. or more", is inserted at the end of the question. The word "Unintentional" should be stressed when asking B-2w/x.

- ***Do not include weight loss reported by the subject due to exercise or dieting. If the subject's answer to B-5w/x is either exercise or dieting, go back to B-2w/x and reask the question, stressing "unintentional," after requesting clarification from the subject.***

SYMPTOM:	B-1. REPORTED LAST INTERVIEW? (TRANSCRIBE FROM SUMMARY SHEET)	B-2.	B-3.	B-4.	B-5.
Loss of bowel control	y. YES ..... 1→	Since your last interview, have you had (SYMPTOM)? YES ..... 1 → NO ..... 2 (BOX B-2)	Since your last interview, would you say this is worse, better or about the same? WORSE .... 1 BETTER .... 2 SAME ..... 3 } →	Has a doctor or other medical person told you anything about this problem since your last interview? YES .... 1 → NO ..... 2 (BOX B-2)	What did he or she say? _____ _____ _____ _____ _____
	z. NO ..... 2→	Since your last interview, have you had (SYMPTOM) for more than one continuous month? YES ..... 1 → NO ..... 2 (BOX B-2)	How long did this last? |__|__| NO. MONTHS .. 1 YEARS ..... 2 } →	Did you see a doctor or other medical person about this? YES .... 1 → NO ..... 2 (BOX B-2)	What was the diagnosis for this? _____ _____ _____ _____ _____

PAGE 8

(See also, "General Specifications for Interview Pages 2-8"
on Pages B-13 and B-15 of this appendix.)

BOX B-2

Now I'm going to read a list of medical conditions. Please tell me if you have been diagnosed **for the first time** as having any of these conditions by a doctor or other medical person since your last interview on _____ (DATE).

B-6. Since your last interview, did a doctor or other medical person tell you for the first time that you had:	B-7. What was the month and year when this was first diagnosed?
a. Tuberculosis? YES ..... 1 → NO ..... 2 (b)	|__|__| MO |__|__| YR
b. Lymphoma? YES ..... 1 → NO ..... 2 (c)	|__|__| MO |__|__| YR
c. Leukemia? YES ..... 1 → NO ..... 2 (d)	|__|__| MO |__|__| YR
d. Any other cancer? YES ..... 1 → (SPECIFY _____) NO ..... 2 (e)	|__|__| MO |__|__| YR
e. An enlarged liver or spleen? YES ..... 1 → NO ..... 2 (f)	|__|__| MO |__|__| YR
f. Myositis or inflammation of muscle not due to an injury? YES ..... 1 → NO ..... 2 (g)	|__|__| MO |__|__| YR
g. Arthritis? YES ..... 1 → NO ..... 2 (h)	|__|__| MO |__|__| YR
h. A nerve or muscle problem such as spasms, tremors or paralysis? YES ..... 1 → (SPECIFY _____) NO ..... 2 (i)	|__|__| MO |__|__| YR

GENERAL SPECIFICATIONS FOR INTERVIEW PAGES 9 AND 10

Box B-2. This introduction to the next questions should be read verbatim to the subject, emphasizing "since your last interview."

Column B-6 When asking B-6a through B-6l emphasize "since your last interview" and "for the first time." If the subject answered "YES" to any of these questions in the last interview, the answer should be "NO" here. Record the subject's answer and clarify any discrepancies when asking the month and year in B-7.

For B-6d, B6-h and B6-j and B6-m, ask the subject to specify the exact type or name of condition. If the subject does not know, enter "DK."

- ***For B-6d, probe for the location in the body where the cancer started (primary site), if known.***

- ***The interviewer should make a note to request the subject's consent to obtain medical records, from any subject answering "YES" to B-6d, after completing the interview and prior to the subject's departure.***

Column B-7 Enter the month and year when each condition was first diagnosed to which the subject answered "YES."

- ***If the date is prior to the last interview, probe to clarify when the condition was diagnosed. If the subject is still not sure whether the condition was diagnosed before or after the last interview, record all information about the condition, regardless. It is better to have a condition reported more than once (i.e., in more than one phase of the study) than not to have any information about a condition.***

- Definitions for "Other medical person" can be found in the discussion of Column B-4 on Page B-15 of this appendix.

B-6. Since your last interview, did a doctor or other medical person tell you for the first time that you had:	B-7. What was the month and year when this was first diagnosed?
i. Multiple sclerosis? YES ..... 1 → NO ..... 2 (j)	|__|__| MO |__|__| YR
j. Thyroid disease? YES ..... 1 → (SPECIFY _____) NO ..... 2 (k)	|__|__| MO |__|__| YR
k. High blood pressure? YES ..... 1 → NO ..... 2 (l)	|__|__| MO |__|__| YR
l. Diabetes or sugar in your blood? YES ..... 1 → NO 2 (B-8)	|__|__| MO |__|__| YR

Refer to general specifications on Page B-29 of this appendix for Questions B-6i through B-6l, and B-7i through B-7l.

B-8. Since your last interview, has an eye doctor told you that you had a serious eye disease?

YES 1 (B-9)
NO 2 (B-11)

B-9. Did the eye doctor say the problem was:	B-10. What was the month and year when this was first diagnosed?
a. Iritis? YES ..... 1 → NO ..... 2 (b)	|__|__| MO |__|__| YR
b. Uveitis? YES ..... 1 → NO ..... 2 (c)	|__|__| MO |__|__| YR
c. Glaucoma? YES ..... 1 → NO ..... 2 (d)	|__|__| MO |__|__| YR
d. Conjunctivitis? YES ..... 1 → NO ..... 2 (e)	|__|__| MO |__|__| YR
e. Due to injury? YES ..... 1 → NO ..... 2 (f)	|__|__| MO |__|__| YR
f. Some other serious eye disease? YES ..... 1 (f1) NO ..... 2 (B-11) f1. What did the eye doctor say it was? (SPECIFY, IF DIAGNOSIS IS KNOWN; DESCRIBE PROBLEMS/ SYMPTOMS, IF UNKNOWN.) 1. _____ → 2. _____ →	|__|__| MO |__|__| YR |__|__| MO |__|__| YR

B-8. Ask this question, stressing the phrases "since your last interview" and "an eye doctor." If the subject answers "YES", go to Column B-9. If the subject answers "NO," skip to B-11 on the next page of the interview.

B-9. Ask the subject about each eye disease listed in Column B-9, using the phrase "Did the eye doctor say the problem was _____?"

- ***After a subject gives his/her first "YES" response to one of the diseases and the interviewer ascertains the month and year it was first diagnosed, the interviewer should say "I'm going to read a (few/couple) more names of eye diseases to you, in case the eye doctor said you had any additional problems."***

B-10. Enter the month and year when each condition was first diagnosed to which the subject answered "YES".

- ***If the date is prior to the last interview, probe to clarify when the condition was diagnosed. If the subject is not sure whether the condition was diagnosed before or after the last interview, record all information about the condition, regardless. It is better to have a condition reported more than once (i.e., in more than one phase of the study) than not to have any information about a condition.***

B-11. Since your last interview, did a doctor or other medical person tell you for the first time that you had any other major medical condition?

YES 1 (B-12)
NO ..... 2 (BOX B-3)

B-12. What conditions did he/she tell you that you had?	B-13. What was the month and year when (CONDITION) was first diagnosed?
1. _____ →	|__|__| MO |__|__| YR
2. _____ →	|__|__| MO |__|__| YR
3. _____ →	|__|__| MO |__|__| YR

BOX B-3

Now I'm going to ask you about some illnesses and infections you may have had **for the first time** since your last interview on _____ (DATE).

B-14. Since your last interview, have you had (INFECTION) for the first time?	B-15. What was the month and year when you first had (INFECTION)?
a. Oral herpes, sores or fever blisters? YES ..... 1 → NO ..... 2 (b)	|__|__| MO |__|__| YR
b. Shingles? YES ..... 1 → NO ..... 2 (BOX B-4)	|__|__| MO |__|__| YR

B-11 through B-13. This set of questions asks about any other major medical conditions subjects may wish to report, that were not specifically asked about in the previous sections. If a subject answers "YES" to B-11, continue to B-12 and B-13. If the response is "NO", skip to Box B-3.

- Refer to "General Specifications for Interview Pages 9 and 10" (Page B-29 of this appendix), which are applicable for B-11 through B-13.

Box B-3. This introduction should be read verbatim to the subject, stressing the phrase "for the first time," and specifying the date of the last interview.

Column B-14. These questions ask if the subject has had oral herpes, sores or fever blisters; or shingles, for the first time since his/her last interview.

- ***Note that B-14 does not require the subject to have seen a medical person in order to report about the infections.***

B-14a If the subject answered "YES" to B-14a in the last interview, the answer should be "NO" here. Record the subject's answer and clarify any discrepancy when asking the month and year in B-15a. If the subject answers "YES," ask B-15a. If the subject answers "NO," go to B-14b.

- The subject may know the conditions in B-14a by the term "cold sores."
- ***This question does not ask about or include genital herpes.***

Column B-15. Enter the month and year when the subject had the reported infection for the first time.

- ***If the date is prior to the last interview, probe to clarify when the subject first had the infection. If the subject is not sure whether the condition first appeared before or after the last interview, record all information about the condition, regardless. It is better to have a condition, reported more than once (i.e., in more than one phase of the study), than not to have any information about the condition.***

BOX B-4

Now I'm going to read another list of illnesses and infections. Please tell me if, at any time since your last interview on _____(DATE), a doctor or other medical person treated you for any of these.

B-16. Since your last interview, have you been treated for:	B-17. How many different times have you been treated for (ILLNESS) since your last interview?	B-18. What was the month and year when you were (first) treated for (ILLNESS) since your last interview?
a. Pneumonia? YES ..... 1 → NO ..... 2 (b)	|__|__| NO.	|__|__| |__|__| MO YR
b. Bronchitis? YES ..... 1 → NO ..... 2 (c)	|__|__| NO.	|__|__| |__|__| MO YR
c. A bladder infection? YES ..... 1 → NO ..... 2 (d)	|__|__| NO.	|__|__| |__|__| MO YR
d. A kidney infection? YES ..... 1 → NO ..... 2 (e)	|__|__| NO.	|__|__| |__|__| MO YR
e. Any other major infections that we haven't already discussed such as skin infections, fungal infections, viral infections or parasites? YES (SPECIFY) ..... 1 1. _____ → 2. _____ NO ..... 2 (f)	|__|__| NO. |__|__| NO.	|__|__| |__|__| MO YR |__|__| |__|__| MO YR
f. Asthma? YES ..... 1 → NO 2 (B-19)		|__|__| |__|__| MO YR

Box B-4. This introduction should be read verbatim to the subject. The information requested in the following questions (B-16 through B-18) differs from that requested in B-14 and B-15. Here, REDS is interested in whether a doctor or other medical person treated the subject for specific illnesses and infections.

- Definitions for "Other medical person" can be found in the discussion of Column B-4 on Page B-15 of this appendix.

Column B-16. When reading this question, emphasize "since your last interview." ***In order to answer "YES" to any illness or infection in B-16a through B-16f, the subject must fulfill the two following requirements:***

- ***The subject must have been treated for the infection; and***
- ***This treatment must have been given during the time interval since the last interview.***

If the subject answers "YES" to any condition in B-16, ask B-17 and B-18 before going on to the next illness/infection. If the subject answers "NO," skip to the next illness/infection listed in Column B-16.

- Specify the exact type of infection in B-16e if the subject answers "YES."

Column B-17. When reading this question, insert the name of the illness that the subject reported in B-16 and emphasize "since your last interview." Enter the number of separate times that the subject has been treated for this specific infection since the date of the last interview.

- Because asthma (B-16f) is usually treated prophylactically, REDS is not interested in the number of times it was treated.

Column B-18 Enter the month and year when the subject was first treated for the reported infection since his/her last interview. If the month and date given are prior to the last interview, probe to clarify when the condition was first treated since the subject's last interview.

BOX B-5

Next, I'm going to ask you about some venereal diseases, also known as sexually-transmitted diseases. Please tell me if a doctor or other medical person told you that you've had any of these since your last interview on _____(DATE)

B-19. Since your last interview, has a doctor or other medical person told you that you had:	B-20. How many different times have you had this since your last interview?	B-21. What was the month and year when you were (first) told that you had this since your last interview?
a. Genital herpes or sores? YES ..... 1 → NO ..... 2 (d)	|__|__| NO.	|__|__| |__|__| MO YR
b. Any other sexually-transmitted disease such as syphilis, gonorrhea, chlamydia, trichomonas, or genital warts? YES ..... 1 (b-1) NO ..... 2 (IF MALE, d) (IF FEMALE, c) b1. What did he/she say you had? 1. _____ 2. _____ 3. _____ →	 |__|__| NO. |__|__| NO. |__|__| NO.	 |__|__| |__|__| MO YR |__|__| |__|__| MO YR |__|__| |__|__| MO YR
c. (IF FEMALE) An infection of the vagina, or vaginitis? YES (SPECIFY) ... 1 → _____ NO 2 (B-22)	|__|__| NO.	|__|__| |__|__| MO YR
d. (IF MALE) Urethritis, that is, discharge from the penis not due to gonorrhea? YES ..... 1 → NO ..... 2 (e)	|__|__| NO.	|__|__| |__|__| MO YR
e. (IF MALE) Sores or ulcers on your penis? YES ..... 1 → NO 2 (B-22)	|__|__| NO.	|__|__| |__|__| MO YR

Box B-5. This introduction to the next questions should be read verbatim to the subject.

- ***Because the topic of sexually transmitted diseases can be sensitive, it may be necessary to re-emphasize the confidential nature of the subject's answers.***

Column B-19. Read the question, inserting the specific disease. If the subject answers "YES" to any question in B-19, ask B-20 and B-21 before asking about the next disease.

- If a subject answers "YES" to B-19b, or B-19c (asked of females only), probe for the specific name of the infection or disease the subject was told he/she had.
- Definitions for "Other medical person" can be found in the discussion of Column B-4 on Page B-15 of this appendix.

Column B-20. For any "YES" responses to questions in B-19, ask B-20 stressing the phrase "different times" and "since your last interview."

Column B-21. Enter the month and year when the subject was <u>first</u> told by a doctor or other medical person that he/she had this infection or disease.

- ***If the date is prior to the last interview, probe to clarify when the subject was told about the condition. If the subject is still not sure whether the condition was diagnosed before or after the last interview, record all information about the condition, regardless. It is better to have a condition reported more than once (i.e., in more than one phase of the study), than not to have any information about the condition.***

B-22. Since your last interview, have you had a blood transfusion?

YES	1	(B-23)
NO	2	(B-25)

B-23. Were you given someone else's blood or were you given your own blood?

SOMEONE ELSE'S BLOOD	1
OWN BLOOD	2
BOTH	3

B-24. For what condition were you given the transfusion?

_____

B-25. Since your last interview, have you had any new health problems that we have not already talked about, including any you may have now?

YES	1	(B-26)
NO	2	(BOX C-1)

B-26. Could you give me the names of the problems, or briefly describe them, and tell me the month and year when they first occurred?

a. _____ |__|__| MO |__|__| YR

_____

b. _____ |__|__| MO |__|__| YR

_____

c. _____ |__|__| MO |__|__| YR

_____

d. _____ |__|__| MO |__|__| YR

_____

e. _____ |__|__| MO |__|__| YR

_____

f. _____ |__|__| MO |__|__| YR

_____

g. _____ |__|__| MO |__|__| YR

_____

B-22. This is asked as an indicator of health status, as well as to capture conditions and/or procedures for which a subject would require a blood transfusion. A blood transfusion may include any blood components (e.g., whole blood, packed cells, plasma). If a subject answers "YES," continue to B-23. Otherwise, skip to B-25.

- ***Be sure to stress the phrase "since your last interview" when asking this question, since REDS does not require that the transfusion date be ascertained.***

B-23. This is asked to determine if the subject was given someone else's blood vs. having had an autologous transfusion (i.e., given his/her own blood).

- ***If the subject was given a transfusion of <u>both</u> his/her own blood (autologous) <u>and</u> blood from someone else, either during the same procedure or on different occasions, circle "3" for "Both."***

B-24. Ask the subject for what condition(s) he/she was given the transfusion.

- ***If the subject's response is "surgery," probe to determine for what condition did he/she have the surgery.***
- If a subject had transfusions on different occasions <u>since his/her last interview</u>, note each condition for which he/she had a transfusion, in the space provided.

B-25. This is a "catch all" question asked of all subjects. REDS is trying to capture information on any health problems that subjects have not already discussed. If a subject answers "YES," go to B-26 to inquire about the health problems.

B-26. Obtain a diagnosis and/or <u>very brief</u> description of each specific health problem the subject considers. Record each health problem the subject reports, regardless of how serious or benign the condition may be. Do no try to filter the subject's answers except to limit the time period to "since the last interview." Record as many problems as the subject provides, using one letter (B-26a through B-26g) to describe each separate health problem.

- ***Clarification is necessary if a subject reports a health problem here, which he/she did not report earlier in the interview when asked about specific conditions, (e.g., arthritis, cancer).*** Tell the subject that clarification on a previous question is necessary, based on his/her response to this question (B-26). Probe the subject by referring back to, and re-asking the specific interview question to which the subject answered "NO."

  Note that the subject's denial to having had a condition may be valid, particularly if "a doctor or other medical person" was not consulted, as many of the interview questions require.

C. SMOKING, ALCOHOL AND DRUG USE

BOX C-1

Now I'd like to ask some questions about cigarette smoking and alcohol use since your last interview on _____ (DATE).

C-1. At any time since your last interview, have you smoked cigarettes on a regular basis?

YES 1
NO 2 (C-5)

C-2. Do you smoke cigarettes now?

YES 1 (C-4)
NO 2

C-3. What was the month and year you stopped smoking cigarettes on a regular basis?

|__|__| |__|__|
MO YR

C-4. Thinking about the time that you (have been smoking/smoked) since your last interview, about how many cigarettes (do/did) you usually smoke per day?

|__|__|
NO. PER DAY
LESS THAN ONE CIGARETTE PER DAY 95

C-5. Now I'd like to ask about alcoholic beverages, such as beer, wine, or hard liquor. Since your last interview, have you had at least 12 drinks of any kind of alcoholic beverage?

YES 1
NO ..... 2 (BOX C-2)

C-6. During the past month, have you had at least one alcoholic drink?

YES 1 (C-8)
NO 2

C-7. What was the month and year you last had an alcoholic drink?

|__|__| |__|__|
MO YR

SECTION C. SMOKING, ALCOHOL, AND DRUG USE

In Section C, subjects will be asked about smoking, use of alcohol, and drug use since their last interview.

Box C-1. The introduction to this section should be read verbatim to the subject, stressing the phrase "since your last interview."

C-1. REDS is interested in whether the subject has smoked cigarettes on a regular basis, since his/her last interview. If the subject answers "NO," skip to C-5. ***Do not attempt to define "regular" for the subject. It is whatever he/she considers to be regular.***

C-2. This asks if the subject currently smokes. If the subject answers "YES," skip to C-4. Otherwise, continue with C-3.

C-3. If the subject is not currently a smoker, enter the month and year when the subject says he/she stopped smoking cigarettes. If the month and year given are prior to the subject's last interview, probe the discrepancy. ***The subject may better recall the dates based on events in his/her life at the time.***

C-4. Inquire about the number of cigarettes the subject usually smokes (or smoked) per day since his/her last interview, stressing "usually" and "since your last interview." Note the following points:

- ***Probe for the number of cigarettes the subject would usually have in a day over the entire period of time he/she has smoked.***
- ***Do not single out any one period, (e.g., an attempt to quit or a heavy period), but have the subject think about his/her usual habits over the longest period of time.***
- ***Do not assume that a pack is 20 cigarettes. If a subject answers in packs, probe to find out the number of cigarettes.***

If the number of cigarettes is less than one per day (i.e., less than seven a week), circle code "95" for "LESS THAN ONE A DAY." The subject may give you a range, for example, "between 10 and 15 a day." In that case, write the range in the margin and probe for a more exact answer.

C-5. REDS is interested in finding out if the subject has drunk at least 12 alcoholic beverages since his/her last interview. If the subject answers "NO," skip to Box C-2. Otherwise, continue with C-6.

C-6. Circle the code "1" for "YES", if the subject had one or more drinks of alcohol during the past month, and skip to C-8. This establishes the subject as a current drinker.

C-7. This is asked of subjects who answered "NO" to C-6. The date given by the subject should be since his/her last interview. Probe any discrepancy in the same way as suggested in C-3, above.

C-8. Thinking about the time that you (have been drinking/drank) alcohol since your last interview, about how many drinks per day, week, month, or year (do/did) you usually drink? [PROBE IF SUBJECT HAS DIFFICULTY WITH THIS QUESTION: What (is/was) the usual number of drinks you (have/had) during a day, week, month or year?]

|__|__|
NO.

PER DAY	1
PER WEEK	2
PER MONTH	3
PER YEAR	4
LESS THAN ONE PER YEAR	995

BOX C-2

Now I would like to ask about recreational drugs or drugs not prescribed by a doctor that you may have used since your last interview on _____ (DATE). I understand that these could be sensitive questions. Just as before, I want to assure you that all information you give us will be kept strictly confidential. This means that the information will be used for research purposes only. Your responses will not be linked with your name or with anything that could identify you. Your honest answers are very important.

C-9. Since your last interview, have you injected or "shot up" drugs that were not prescribed by a doctor?

YES	1	
NO	2	} (BOX D-1)
REFUSED	7	} (BOX D-1)
DK	8	} (BOX D-1)

C-10. Since your last interview, have you shared a needle or syringe with someone else when you injected drugs?

YES	1
NO	2

C-8. This is asked of all subjects who answered "YES" to C-5. Select alternative wording depending on whether the subject is a current drinker ("YES" to C-6) or a former drinker ("NO" to C-6). Enter the number of alcoholic drinks the subject usually has or had during a day, week, month, or year and circle the code for the appropriate time period. For example, if the subject only drinks on the weekend, then the appropriate unit of time is "per week." REDS is interested in the number of drinks in a unit of time, ***over the entire period*** of time the subject has drunk alcohol.

- ***Do not single out any one time period.(e.g., attempts to cut down, binges), but have the subject think about his/her usual habits over the longest period of time.***
- ***The subject's answers, and the math used to arrive at the final response, should be noted in the margin by the nurse/counselor.***

Box C-2. Read this introductory paragraph verbatim, re-emphasizing the confidential nature of the subject's answers. For the next two questions on substance use, it is very important that nothing in the interviewer's manner or tone of voice imply surprise or disapproval.

C-9. Using a neutral tone of voice, ask this question. If the subject refuses to answer, try to explain how important these answers are to the study. If the subject still refuses to answer, move on to Box D-1 on the next page.

C-10. This is asked of all subjects who answered "YES" to C-9. REDS is trying to determine if the subject shared a needle with anyone since the last interview, ***regardless of who used the needle first.***

D. SEXUAL HISTORY

BOX D-1

Now I would like to ask about your recent sexual activities. I know these are personal questions, but your answers are important and will remain completely confidential.

D-1. Since your last interview on _____ (DATE), have you had sexual relations with anyone?

YES 1
NO ..... 2 (BOX E-1)

D-2. Since your last interview, what is the total number of men you've had sex with?

|__|__|__|
NO. OF MEN
NONE 000

D-3. Since your last interview, what is the total number of women you've had sex with?

|__|__|__|
NO. OF WOMEN
NONE 000

D-4. Please look at this card and tell me how often you used a condom or rubber during sex with (these/this) partner(s)?

SHOW CARD 1

NEVER 1
RARELY 2
SOMETIMES 3
USUALLY 4
ALWAYS 5

SECTION D. SEXUAL HISTORY

Box D-1. The introduction to this section should be read verbatim to the subject, again emphasizing the confidential nature of the subject's answers.

D-1. When asking this question, stress the phrase "since your last interview." ***Sexual relations includes vaginal, oral or anal intercourse with anyone since the date of the last interview.*** If the subject has not had sexual relations with anyone, skip to Box E-1 on the next page.

D-2. This is asked of all subjects (male and female) who had sexual relations with anyone since their last interview. Circle "000" if the subject has not had sex with a man since the last interview. Please note the following points:

- Include all male partners and sexual relations with males whether or not intercourse occurred with the partner's or the subject's consent, or occurred in exchange for money, gifts, or other payments.
- If the subject is having difficulty giving you an exact count, probe by giving ranges. For example, say, "Would you say that you had between 10 and 20 male partners, or between 20 and 30 male partners?" Once the subject has chosen a range, ask him/her to narrow the range until he/she can come up with one number. ***It is important to always offer a range of choices and not lead the subject toward any specific answer.***

D-3. This is also asked of both male and female subjects. The specifications for D-2 also apply here, except this question asks about sexual relations with females.

D-4. Give the subject Show Card #1 prior to asking this question, and ask the subject to use the card to select one of the answers. ***Do not define any of the answers for the subject.*** Note the following points:

- ***The nurse/counselor should probe for one answer if the subject tries to respond to the question differently for each partner. Probing terms such as "overall" or "thinking about all partners with whom you have had sexual relations" may be used in conjunction with re-reading the question to the subject to elicit one response.***
- Responses on the showcard may be read aloud by the nurse/counselor only if the subject has difficulty reading.
- Take the card back from the subject after he/she has responded, so that he/she is not distracted by it during the remainder of the interview.

E. EDUCATION AND INCOME

BOX E-1

Just two more questions and we'll be finished with the interview.

E-1. First, please look at this card and tell me which category includes the highest level of school you have completed.

SHOW CARD 2

A.	8TH GRADE OR LESS	1
B.	9TH, 10TH, 11TH OR 12TH GRADE (NO DIPLOMA)	2
C.	HIGH SCHOOL GRADUATE (HIGH SCHOOL DIPLOMA OR EQUIVALENT, FOR EXAMPLE, GED)	3
D.	SOME COLLEGE OR TECHNICAL SCHOOL	4
E.	BACHELOR'S DEGREE (FOR EXAMPLE, BA, AB, BS)	5
F.	MASTER'S OR PROFESSIONAL DEGREE (FOR EXAMPLE, MA, MS, MEd, PhD, MD)	6

E-2. Finally, what was your total family income last calendar year, that is (1994/1995/1996), from all sources, including wages, tips, Social Security, Aid to Families with Dependent Children, pensions, child support, or any cash income from other sources? Please choose one of the categories on this card.

SHOW CARD 3

A.	< $10,000	1
B.	$10,000 to $19,999	2
C.	$20,000 to $29,999	3
D.	$30,000 to $39,999	4
E.	$40,000 to $49,999	5
F.	$50,000 to $74,999	6
G.	$75,000 or more	7
H.	REFUSED	R

BOX E-2

This ends our interview. Thank you for your cooperation.

TIME END: |__|__| : |__|__| AM PM

SECTION E. EDUCATION AND INCOME

Box E-1. This introduction should be read verbatim to the subject.

E-1. Give the subject Show Card #2 prior to asking this question. In this question, REDS is interested in the highest grade or level of schooling that the subject has completed. For example, if the subject dropped out of school in the 12th grade, 11th grade would be the last completed grade, coded "2." The answer categories should not be read aloud unless the subject has difficulty reading the show card.

- Take the card back from the subject after he/she has responded so that he/she is not distracted by it during the next question.

E-2. Give the subject Showcard #3 after asking the question so he/she is not distracted by the card while asking this lengthy question. Please note the following points:

- Emphasize the words "total family income" and "all sources" when reading the question.
- If the interview is being conducted in 1995, read "1994," etc.
- If the family income includes many different sources, it may be necessary for the nurse/counselor to perform some computations. In this situation, all probes and math computations should be noted in the margins of the questionnaire.
- If the subject is a student, include parent's income, not just income the student earns.
- ***If the subject refuses to provide income information, reassure him/her that the income data will not be reported to anyone, and this information along with other data collected will provide important background information for the study. If the subject still seems reluctant after reassurances, but not adamant, probe to try to find out whether the income was under or over $20,000, or over $75,000. Write the subject's response to this probe in the margin.***

Box E-2 This "Thank you" statement should be read verbatim to the subject.

TIME END Remember to record the time the interview ended after reading Box E-2.

APPENDIX C

ADMINISTERING THE PHASE THREE LEVEL 1 EXAMINATION

This appendix describes procedures for administering the Phase Three Level 1 exam, and provides detailed item-by-item specifications for making and recording observations during it.

SUBJECT ID _____

DATE OF EXAMINATION |__|__| |__|__| |__|__|
MO DAY YR

EXAMINER INITIALS |__|__|__|

LOCATION OF EXAM
BLOOD CENTER 1
SUBJECT'S HOME 2
OTHER 3

_____
(SPECIFY)

SELECTED FOR LEVEL 2 QC?

YES 1
NO 2

EXAM RESULT |__|__|

PHASE THREE
LEVEL 1 EXAMINATION
REDS HTLV COHORT STUDY

INTRODUCTION: I am now going to give you another short physical exam very similar to the one(s) you've had before. I'll be checking your skin, and how your nerves and muscles perform certain tasks. In addition, I'll be checking for any swelling in your lymph nodes. The information from this exam will be reviewed when results of your lab tests are available. We may want to talk with you after that review to discuss any findings.

COVER PAGE

On the Phase Three Level 1 Exam cover page, enter or circle the code for the following information:

- The REDS Subject ID:
- The date of the exam;
- The examiner's initials;
- The location code for where the exam is being conducted, specifying the location if other than the blood center; and
- The appropriate code on the exam cover page to indicate whether this subject will require a quality control (QC) Level 2 Exam.

To determine if the subject should receive a Level 2 for QC, (since neither the nurse/counselor nor the study physician is blinded to subject type), enter the subject's ID number on the Phase Three Level 1 Exam Verification Sheet. If the ID falls on a line with an asterisk (*), then this is a QC subject who will need a Level 2 Exam.

The introduction on the cover should be read to the subject verbatim, prior to beginning the exam.

At the end of the exam, enter the exam result code, either "EC" for a completed exam, or "PE" for a partially completed exam, noting the following rules for their use:

- ***The "PE" code should be used only if one or more entire portions of the exam were not performed. It is not appropriate to use this code if only one or two of the procedures were not performed; and***
- ***If all or a portion of the neuromuscular exam was not performed or was not attempted due to a subject's physical restriction(s), this should be noted within that section of the exam booklet. This does <u>not</u> qualify the exam as partially completed.***

A. GENERAL EXAMINATION

A-1. **Height** (without shoes) |__|__|__|.|__| CM. OR |__|__|__|.|__| INCHES OR |__|.|__|__|.|__| FT. INCHES

A-1a. Measurement method used:

REDS measuring tape 1
Other measuring device 2
Subject's verbal report 3
Other _____ 4
(SPECIFY)

A-2. **Weight** (without shoes or outdoor garments) |__|__|__|.|__| KG. OR |__|__|__|.|__| LBS.

A-2a. Measurement method used:

REDS scale 1
Other scale 2
Subject's verbal report 3
Other _____ 4
(SPECIFY)

A-3. **Blood pressure** (seated, right arm) |__|__|__| / |__|__|__|
SYSTOLIC DIASTOLIC

A-4. **Radial pulse** (seated, right arm) |__|__|
BEATS PER 15 SEC.

If beats per 15 sec. $\leq$ 10 or $\geq$ 25, count for 60 seconds and record.

|__|__|__|
BEATS PER 60 SEC.

A. GENERAL EXAMINATION

In this phase of REDS, additional information about measurement methods is being requested as part of the Height and Weight questions. Although there may be an occasional need to deviate from procedure (and these deviations need to be documented), use of the REDS scale and tape measures provided by the Coordinating Center is a strict requirement.

A-1 and A-1a. Measure the subject's height without shoes, recording height in centimeters.

- ***If height cannot be measured in centimeters, record it in other measurement units, and do not convert to centimeters.***
- In all cases, circle the code for the measurement method used in A-1a.

A-2 and A-2a. Weigh the subject without shoes or outdoor garments, recording weight in kilograms.

- ***If weight cannot be measured in kilograms, record it in pounds and do not convert to kilograms.***
- In all cases, circle the code for the measurement method used in A-2a.

A-3. The subject should be seated for blood pressure measurement. Use the subject's right arm to record systolic and diastolic measurements. One reading is adequate unless noise or another inconvenience interrupts the first reading.

A-4. The subject should remain seated while taking the radial pulse. Count the pulse for 15 seconds and record the number in the space indicated for 15 seconds. One measurement is adequate unless noise or another inconvenience interrupts the first count.

- If the heart beat is slow (i.e., 10 beats or less per 15 seconds), or fast (i.e., 25 beats or more per 15 seconds), count the pulse for 60 seconds and record that number in the box indicated for 60 seconds.

B. DERMATOLOGIC EXAM

EXAMINE HANDS/FOREARMS, FEET, HEAD/NECK FOR LESIONS, NODULES, RASH, PUSTULES, VESICLES, OR ULCERS. IF PRESENT, CODE "YES" AND ANSWER SUBSEQUENT QUESTIONS. EXCLUDE FRECKLES, MOLES, CHERRY HEMANGIOMAS, PIMPLES, LIPOMAS, AND ACNE.

B-1. Are any lesions present?	B-2. Are lesions sufficiently unusual to require a physician's review?	B-3. Do lesions resemble any reference photos?	B-4. (ASK) How long have you had this skin condition?
a. **Hands/Forearms** YES .....1 → NO .....2(b)	YES ..... 1 → NO ..... 2 (b)	YES ..... 1 NO ..... 2 } →	|___|___| NO. DAYS..... 1 WEEKS..... 2 MONTHS ..... 3 YEARS 4
b. **Feet** YES .....1 → NO .....2(c)	YES ..... 1 → NO ..... 2 (c)	YES ..... 1 NO ..... 2 } →	|___|___| NO. DAYS..... 1 WEEKS..... 2 MONTHS ..... 3 YEARS 4
c. **Head/Neck** YES .....1 → NO .....2(B-5)	YES ..... 1 → NO 2 (B-5)	YES ..... 1 NO ..... 2 } →	|___|___| NO. DAYS..... 1 WEEKS..... 2 MONTHS ..... 3 YEARS 4

B. DERMATOLOGIC EXAM

The dermatologic exam is intended primarily to look for early signs of adult t-cell lymphotropic lymphoma/leukemia (ATL). ***While examining the subject's skin, observe if needle track scars indicating IV drug use are present (for B-9 and B-10).***

The skin exam is conducted while the subject is seated on a chair. Be overly inclusive and report all potentially suspicious lesions, nodules, rashes, pustules, vesicles and/or skin ulcers that are observed, since Level 2 exams by the blood center physician will correct for false positive findings. Freckles, moles, cherry angiomas, lipomas, pimples or acne should not be included. Sites a, b, and c in Column B-1, are exposed areas of the skin that could exhibit the skin conditions listed above. Circle the appropriate code to indicate if any of these skin conditions are present.

B-1a. Examine both hands and nailbeds. Examine the anterior and posterior aspects of both forearms up to the elbows.

B-1b. Examine all surfaces of both feet, the skin between the toes and the nailbeds.

B-1c. Examine the subject's face, head and neck, including the eyebrows, nasolabial folds, lips, the scalp (including areas covered by hair); and the area behind both ears. Examine both the anterior and posterior neck area.

Column B-2 For any "YES" answer in B-1a, B-1b, or B-1c, determine if the skin condition should be examined by the study physician. If "YES," answer B-3 and B-4. If "NO," go to the next area of skin or B-5, as appropriate.

Column B-3. Although it is not necessary to link the observed skin condition with a particular reference photo, determine if there is any resemblance to any of the photos and circle the appropriate code. Ask B-4 regardless of the answer to B-3.

Photographs 1 through 6 (provided to each examiner during Phase One) are pictures of patients who developed ATL. The photographs may be used as references for comparing REDS subjects' skin conditions to those found in patients with ATL. Skin conditions in study subjects may be early signs and not as advanced as those in the pictures, so if there are any similarities, code "YES". The photographs show the following dermatopathies:

Photo #1: diffuse erythematous rash or erythroderma(s)
Photo #2: subcutaneous nodules
Photo #3: erythodermas with scales
Photo #4: ulcerated nodule
Photo #5: multiple papules, shiny or flesh-colored
Photo #6: smoldering tumorous lesions of coalesced papules with plaque

If the lesions in a particular site clearly are not unusual enough to warrant physician review, code "NO" and go to the next site. Do not continue across the grid.

Column B-4. Ask the question verbatim to the subject. Enter the number and circle the code for the length and unit of time.

B-5. **(ASK)** Do you have any problems with your skin in areas other than those I've just examined? For example, have you noticed any rashes, lumps, sores, itching, color changes or unusual bruises?

YES..... 1 **(ASK TO EXAMINE)** NO 2 (B-9)	B-6. Are lesions sufficiently unusual to require a physician's review?	B-7. Do lesions resemble any reference photos?	B-8. **(ASK)** How long have you had this skin condition?
1ST AREA a. Chest.....01 b. Back.....02 c. Abdomen.....03 d. Buttocks.....04 e. Thighs.....05 f. Lower legs....06 g. Other.....96 (SPECIFY) _____ _____	YES ..... 1 → NO 2	YES ..... 1 NO ..... 2 →	|___|___| NO. DAYS..... 1 WEEKS..... 2 MONTHS ..... 3 YEARS 4
2ND AREA a. Chest.....01 b. Back.....02 c. Abdomen.....03 d. Buttocks.....04 e. Thighs.....05 f. Lower legs....06 g. Other.....96 (SPECIFY) _____ _____	YES ..... 1 → NO 2	YES ..... 1 NO ..... 2 →	|___|___| NO. DAYS..... 1 WEEKS..... 2 MONTHS ..... 3 YEARS 4
3RD AREA a. Chest.....01 b. Back.....02 c. Abdomen.....03 d. Buttocks.....04 e. Thighs.....05 f. Lower legs....06 g. Other.....96 (SPECIFY) _____ _____	YES ..... 1 → NO 2	YES ..... 1 NO ..... 2 →	|___|___| NO. DAYS..... 1 WEEKS..... 2 MONTHS ..... 3 YEARS 4

B-9. **(DO NOT ASK)** Were needle tracks observed anywhere on the subject's body?

YES 1 (B-10)
NO 2 (C-1)

B-10. **(DO NOT ASK)** Where were the needle tracks located?

_____

[SPECIFY LOCATION(S)]

B-5. Reading verbatim, ask the subject this question. If the answer is "YES," ask to examine the area and circle the code where the condition is located. ***Circle only <u>one</u> code per grid box.*** If the condition is located in an area that is not listed, write that location in the space provided, ***writing only <u>one</u> location per grid box.*** If there is more than one location, complete the section for the 2nd and 3rd areas. Continue across the grid to answer B-6, and if B-6 is "YES", answer B-7 and B-8.

If the subject is hesitant about having the area examined, explain that the reported condition needs to be evaluated for possible referral to the study physician. If the subject refuses to allow examination of the area, get a verbal description from the subject, recording the description in the blank spaces in B-6 and B-7; then ask B-8 about the condition described.

Column B-6. Refer to specifications for Column B-2, on previous page.

Column B-7. Refer to specifications for Column B-3, on previous page.

Column B-8. Refer to specifications for Column B-4, on previous page.

B-9. ***This question should <u>not</u> be asked.*** During the dermatologic exam, look for any scars that resemble needle tracks indicating IV drug use. If present, circle the code for "YES", and specify the location(s) in B-10. If "NO", circle the code "2" and skip to Box C-1.

B-10. ***This question should <u>not</u> be asked.*** If "YES" to B-9, specify all locations where needle tracks were observed.

C. LYMPH NODE EXAM

PALPATE NODES ON RIGHT AND LEFT SIDE (EXCEPT SUBMENTAL NODE ON MIDLINE). IF PALPABLE, CODE SIZE IN CENTIMETERS, AND CATEGORIZE AS SOLITARY OR MULTIPLE.

LOCATION	RIGHT		LEFT	
C-1. **Posterior cervical nodes**	Palpable ..... 1 →	<1.0 cm ..... 1 ≥1.0 cm ..... 2 Solitary ..... 1 Multiple 2	Palpable ..... 1 →	<1.0 cm ..... 1 ≥1.0 cm ..... 2 Solitary ..... 1 Multiple 2
	Nonpalpable ..... 2 Not examined ..... 0 → C-2		Nonpalpable ..... 2 Not examined ..... 0 → C-2	
C-2. **Anterior cervical nodes**	Palpable ..... 1 →	<1.0 cm ..... 1 ≥1.0 cm ..... 2 Solitary ..... 1 Multiple 2	Palpable ..... 1 →	<1.0 cm ..... 1 ≥1.0 cm ..... 2 Solitary ..... 1 Multiple 2
	Nonpalpable ..... 2 Not examined ..... 0 → C-3		Nonpalpable ..... 2 Not examined ..... 0 → C-3	
C-3. **Submandibular nodes**	Palpable ..... 1 →	<1.0 cm ..... 1 ≥1.0 cm ..... 2 Solitary ..... 1 Multiple 2	Palpable ..... 1 →	<1.0 cm ..... 1 ≥1.0 cm ..... 2 Solitary ..... 1 Multiple 2
	Nonpalpable ..... 2 Not examined ..... 0 → C-4		Nonpalpable ..... 2 Not examined ..... 0 → C-4	
C-4. **Submental node** (ALONG THE MIDLINE)	Palpable ..... 1 →	<1.0 cm ..... 1 ≥1.0 cm ..... 2 Solitary ..... 1 Multiple 2		
	Nonpalpable ..... 2 Not examined ..... 0 → C-5			
C-5. **Posterior auricular nodes**	Palpable ..... 1 →	<1.0 cm ..... 1 ≥1.0 cm ..... 2 Solitary ..... 1 Multiple 2	Palpable ..... 1 →	<1.0 cm ..... 1 ≥1.0 cm ..... 2 Solitary ..... 1 Multiple 2
	Nonpalpable ..... 2 Not examined ..... 0 → C-6		Nonpalpable ..... 2 Not examined ..... 0 → C-6	

C. LYMPH NODE EXAM

The lymph nodes to be examined in the head, neck, axillae, and arms on both sides of the subject's body, are usually involved in the lymphadenopathy of leukemias and lymphomas.

The subject should be relaxed and sitting in a chair with armrests. Stand in front of the subject to palpate nodes, beginning with the cervical nodes in the neck. Palpate all listed nodes with the pads of the index and middle fingers, using a rotary motion over the underlying tissues in each area. Do not move fingers over the skin.

- ***To determine if a node is being palpated rather than another structure, remember that a node can be rolled up and down, and side to side. Muscles and blood vessels will not pass this test.***

For most nodes, both sides of the body may be examined simultaneously, or one side at a time. However, the axillary and epitrochlear nodes should be examined on one side of the body at a time. The submental node is along the midline.

C-1 through C-9. If any node is palpable, circle code "1", regardless of its size. Using the small plastic ruler supplied by REDS, determine the node size, circle the appropriate size code, and the code for whether it is solitary or multiple.

If a node is nonpalpable or not examined, circle code "2" or "0", respectively, and go to the next node listed in the "Location" column.

"Right" and "Left" refer to the sides of the subject's body. Therefore, under the column labeled RIGHT, record observations for nodes on the subject's right side, and under the column labeled LEFT, record observations for the subject's left side. Complete the examination for one set of nodes on both sides of the body before going to the next listed node location.

C-1. and C-2. Cervical nodes form a group beginning under the ear lobe. Posterior cervical nodes are along the anterior edge of the trapezius muscle in the neck. Anterior cervical nodes are under the ear lobe in the posterior section of the sternomastoid muscle.

C-3. Submandibular nodes are under the jaw near its angle.

C-4. The submental node is under the chin along the midline.

C-5. Posterior auricular nodes are behind the ear pinna, superficial to the mastoid process.

LOCATION	RIGHT		LEFT	
C-6. **Occipital nodes**	Palpable ..... 1 →	<1.0 cm ..... 1 ≥1.0 cm 2	Palpable ..... 1 →	<1.0 cm ..... 1 ≥1.0 cm 2
		Solitary ..... 1 Multiple 2		Solitary ..... 1 Multiple 2
	Nonpalpable ..... 2 Not examined ..... 0 } C-7		Nonpalpable ..... 2 Not examined ..... 0 } C-7	
C-7. **Supraclavicular nodes**	Palpable ..... 1 →	<1.0 cm ..... 1 ≥1.0 cm 2	Palpable ..... 1 →	<1.0 cm ..... 1 ≥1.0 cm 2
		Solitary ..... 1 Multiple 2		Solitary ..... 1 Multiple 2
	Nonpalpable ..... 2 Not examined ..... 0 } C-8		Nonpalpable ..... 2 Not examined ..... 0 } C-8	
C-8. **Axillary nodes**	Palpable ..... 1 →	<1.0 cm ..... 1 ≥1.0 cm 2	Palpable ..... 1 →	<1.0 cm ..... 1 ≥1.0 cm 2
		Solitary ..... 1 Multiple 2		Solitary ..... 1 Multiple 2
	Nonpalpable ..... 2 Not examined ..... 0 } C-9		Nonpalpable ..... 2 Not examined ..... 0 } C-9	
C-9. **Epitrochlear nodes**	Palpable ..... 1 →	<1.0 cm ..... 1 ≥1.0 cm 2	Palpable ..... 1 →	<1.0 cm ..... 1 ≥1.0 cm 2
		Solitary ..... 1 Multiple 2		Solitary ..... 1 Multiple 2
	Nonpalpable ..... 2 Not examined ..... 0 } D-1		Nonpalpable ..... 2 Not examined ..... 0 } D-1	

C-6. Occipital nodes are at the base of the skull, posteriorly.

C-7. Supraclavicular nodes are in the supraclavicular fossa above the clavicle. ***Press firmly to detect enlargement of these nodes.***

C-8. Axillary nodes form a group that should be palpated on one side of the body at a time.

- The posterior axillary nodes are along the lateral border of the scapula and felt deep in the posterior axillary fold. Have the subject rest his/her forearms on the arms of the chair. ***Slide fingertips up, high into the axilla, pressing firmly to detect enlargement of these nodes.***

- The central axillary nodes are located along the lower border of the pectoralis major muscle inside the anterior axillary fold, near the middle of the thoracic wall of the axilla. ***Feel centrally or medially toward the chest.***

- The lateral axillary nodes are located along the upper humerus along the axillary vein. ***Have the subject elevate his/her arm to palpate these nodes while moving finger pads out toward the subject's arm.***

C-9. Epitrochlear nodes should be palpated on one side of the body at a time. They are located 3 cm proximal to the medial humeral epicondyle. ***Support the subject's forearm while his/her elbow is flexed to about 90 degrees. Reach around behind the subject's arm and feel in the groove between the biceps and triceps muscles, about 3 cm above the medial epicondyle.*** Palpate across the epitrochlear node area in an anterior to posterior direction.

D. NEUROMUSCULAR EXAM

D-1. (**ASK**) Do you have any problems from recent surgery, injury or other health conditions that might prevent you from standing up from a chair or walking?

No restriction, per subject 1
Recent surgery 2
Injury 3
Physical handicap 4
Obesity 5
Other (SPECIFY _____) 6

(DO NOT ASK) Examiner's observations of unreported apparent restrictions (if any):

_____

_____

D-2. (**ASK**) Which hand do you use to write? (USE FOR D-7.)

Right 1
Left 2

DEMONSTRATE EACH MANEUVER. ASK THE SUBJECT TO PERFORM EACH ONE AFTER YOU.

MANEUVER	DEGREE OF IMPAIRMENT
D-3. **Rise from chair without using hands.** Impaired performance ..... 1 → Normal performance ..... 2 Not attempted ..... 0 } (D-4)	Steadies body with hands ..... 1 Uses hands to push up ..... 2 Unable to perform..... 3
D-4. **Walk on heels for 10 feet.** Impaired performance ..... 1 → Normal performance ..... 2 Not attempted ..... 0 } (D-5)	Walks 7 feet without abnormality or 10 feet with some abnormality in gait ..... 1 Walks < 7 feet and/or noticeable abnormality in gait ..... 2 Unable to perform..... 3
D-5. **Walk on toes for 10 feet.** Impaired performance ..... 1 → Normal performance ..... 2 Not attempted ..... 0 } (D-6)	Walks 7 feet without abnormality or 10 feet with some abnormality in gait ..... 1 Walks < 7 feet and/or noticeable abnormality in gait ..... 2 Unable to perform..... 3

D. NEUROMUSCULAR EXAM

The purpose of this portion of the exam is to screen for early signs of HTLV-associated myelopathy (HAM) through certain maneuvers the subject will be performing to test neuromuscular function. Observe the subject's performance to assess balance, strength, coordination, and sensory and neuromotor responses. Observation of any of the following examples of impairments are considered significant during maneuvers involving the lower extremities:

- Legs spread widely apart;
- Subject watching the ground;
- Legs lifted at hip higher than necessary;
- Legs flung forward and outward in abrupt motions;
- Steps varying in length;
- A corrective step to the side;
- Feet making slapping sounds on the floor;
- Knees raised higher to compensate for inability of the feet to dorsiflex at the ankle;
- Trunk held somewhat flexed at hips; or
- Subject waddling, reeling, swaying or losing balance.

D-1. Regardless of the subject's appearance, he/she should be asked this introductory question to determine if there are any physical limitations that could interfere with performance of maneuvers in this section. Circle the appropriate code(s) for all physical limitations the subject reports. If the subject reports a physical limitation other than the ones listed, code "6" and specify the type of limitation on the line provided. Additionally, in the space provided, write observations of any apparent restrictions which the subject did not report.

D-2. Code the subject's answer, which will be needed for D-7.

D-3 through D-7. ***Demonstrate each maneuver for the subject, before having him/her attempt it. Maneuvers should be attempted with the subject's shoes and socks removed.*** If any of the specified degrees of impairment in the subject's performance are observed, circle the one code that most accurately describes the impairment.

Circle the code for "not attempted" if a physical limitation, lack of time, subject refusal or another situation prevents a maneuver from even being attempted. ***It does not mean that the subject tried to, but was unable to perform the maneuver.***

For D-3, impaired performance would include use of the hands to assist with rising from a chair.

For D-4, gait abnormalities would include: (1) how high the subject is able to raise his/her toes; (2) whether one or both feet drop; and (3) whether the subject is able to maintain position and balance.

For D-5, gait abnormalities would include: (1) how high the subject is able to stand; (2) whether one or both heels drop; and (3) whether the subject is able to maintain position.

MANEUVER	DEGREE OF IMPAIRMENT
D-6. **Walk forward heels-to-toes for 10 feet in a straight line.** Impaired performance ..... 1 → Normal performance ..... 2 Not attempted ..... 0 } (D-7)	Walks 7 feet without abnormality or 10 feet with some abnormality in gait ..... 1 Walks < 7 feet and/or noticeable abnormality in gait ..... 2 Unable to perform..... 3
D-7. **Feel tuning fork on great toe of dominant foot (from D-2).** Impaired performance..... 1 → Normal performance (≤ 4 second gap) ..... 2 Not attempted ..... 0 } (D-8)	Subject does not feel vibrations..... 1 Examiner felt vibrations ≥ 5 sec. longer than subject..... 2

D-8. **Plantar reflex** in response to blunt object lightly moved from heel, up lateral aspect, curving medially across ball of foot to great toe.

	RIGHT	LEFT
Absent	0	0
Downward flexion present but diminished or weak	1	1
Normal downward flexion	2	2
Abnormal (dorsiflexion of great toe and/or fanning of other toes)	3	3
Unable to assess due to withdrawal/hypersensitivity	4	4
Reflex response not attempted	5	5

D-9. **Patellar reflex** in response to one brisk tap with pointed end of reflex hammer.

Absent	0	0
Knee extension present but diminished or weak	1	1
Normal contraction of quadriceps and knee extension	2	2
Hyperactive, enhanced contraction and/or extension	3	3
Hyperactive with contractions and maintained stretch	4	4
Reflex response not attempted	5	5

D-10. **Biceps reflex** in response to strike with pointed end aimed through examiner finger or thumb directly toward the biceps tendon.

Absent	0	0
Elbow flexion present but diminished or weak	1	1
Normal contraction of biceps and elbow flexion	2	2
Hyperactive, enhanced contraction and/or extension	3	3
Hyperactive with contractions and maintained stretch	4	4
Reflex response not attempted	5	5

D-3 through D-7. (cont'd)

For D-6, gait abnormalities would include (1) not touching heels to toes, and whether the subject is able to correct that; and (2) whether the subject moves his/her arms to maintain or regain balance.

For D-7, refer to D-2 for the dominant side of the body, and use this foot to test the subject's ability to feel vibrations in the great toe. The examiner should hit the tuning fork against the heel of his/her hand to cause vibrations. Place the vibrating tuning fork on the subject's bony prominence of the interphalangeal (IP) joint of the great toe. At the same time, position the index finger pad on the plantar surface of subject's IP joint to feel the vibrations.

Ask the subject whether he/she feels the vibrations, and if so, to let you know when he/she feels them stop. Let the fork stop on its own. If the subject feels the vibrations, count the seconds between the time the subject says he/she felt vibrations stop and the time you feel them stop. ***A delay of 4 seconds or less is normal. Inability to feel vibrations and delays of 5 seconds or more are not normal.***

D-8.

Test the plantar reflex on both sides of the body, using the sharp end of a key, the handle of the reflex hammer, or the end of a cotton-tipped stick. The subject should sit on the edge of the exam table or lay down. ***Support the subject's leg to aid relaxation and to avoid the sensation of being tickled.*** To elicit the plantar reflex, place the object on the subject's heel of the foot and lightly move it up the lateral aspect of the foot, across the ball of the foot to the metatarsal joint of the great toe.

Observe movement of the toes during the plantar reflex, and circle the code for the description which best describes the subject's response. ***If the subject is hypersensitive, ticklish, and/or withdraws his/her leg during repeated attempts to elicit the plantar reflex, circle code "4."***

D-9 and D-10.

To elicit a reflex response for D-9 and D-10, use the pointed end of the reflex hammer. The strike should be quick and direct. Keep the limb relaxed by supporting it, if necessary, to prevent false positive jerkiness in reflex response. The reflex response depends in part on the force of the stimulus (strike). Use no more force than necessary to elicit a definite positive response. That response is a brief muscle twitch evoked by a rapid stretch of the muscle's tendon. Note the speed, amplitude and force of the muscle contraction.

For D-9 the subject should be seated on the edge of the exam table. Localize the subject's patellar tendon with the thumb, and strike it. Circle the code for the description which best describes the subject's response.

For D-10 the subject should remain seated. Place your thumb on the biceps tendon in the crook of the subject's elbow, hit the thumb fingernail and observe the biceps muscle.

E. POST- EXAM SUMMARY

To be completed by examiner after Level 1 Exam. Code result of examination on front cover (EC = Exam Complete; PE = Partial Exam).

E-1. EXAMINER COMMENTS/RECOMMENDATIONS

Comments/Recommendations _____

_____

_____

_____

_____

Signature _____ Date _____

F. PHYSICIAN'S REVIEW

F-1. Complete the Review and Referral Decision Section on the next page. Summarize below any additional findings, including explanation(s) and additional comments pertaining to your recommendations.

_____

_____

_____

_____

F-2.

Referral Decision at Level 1:

- ☐ Do not refer
- ☐ Refer to usual care or non-REDs specialist
- ☐ Refer to Level 2 (exam only)
- ☐ Repeat CBC and refer to Level 2
- ☐ Repeat CBC, but do not refer to Level 2
- ☐ Repeat CBC. If abnormal, refer to Level 2

Physician Signature_____ Date _____

E. POST-EXAM SUMMARY

Record one of the following result codes on the front cover of the exam booklet:

EC= Exam complete: Use if all (or the majority) of the tests and observations in the Level 1 exam were completed on this subject.

PE= Partial exam: Use if one or more sections of the exam were not performed due to subject refusal or time constraints, for example. ***See page C-3 (COVER PAGE) for more details on the use of the "PE" code.***

E-1. Complete this section by writing relevant comments and recommendations, including those that might not otherwise be communicated to the study physician or the Coordinating Center, due to data collection or recording procedures. ***Sign and date the booklet regardless of whether any comments or recommendations have been written.***

F. PHYSICIAN'S REVIEW

F-1. The study physician should summarize any comments, findings, or explanations, not detailed on the inside back cover in Section G (Review and Referral Decision), which may explain his/her referral decision.

F-2. The study physician should check the appropriate box, reflecting his/her referral recommendation, and sign and date the booklet where indicated.

G. REVIEW AND REFERRAL DECISION SECTION - TO BE COMPLETED BY STUDY PHYSICIAN

CHECK BOX ON LEFT AND COMPLETE RECOMMENDATION SECTION FOR EACH CONDITION REPORTED DURING PHASE THREE VISIT.

PHASE THREE INTERVIEW	RECOMMEND REFERRAL TO LEVEL 2?		
Only If Same, Worse, or New:	Yes	No	If No, Explain
☐ Any two of the following: difficulty walking, climbing or rising	☐	☐	_____
☐ Any two of the following: urinary urgency, incontinence, or post-void urgency	☐	☐	_____
☐ Lymphadenopathy	☐	☐	_____
☐ Unexplained fevers	☐	☐	_____
☐ Night sweats	☐	☐	_____
☐ Unintentional weight loss of ≥ 10 lbs.	☐	☐	_____
☐ Bowel incontinence	☐	☐	_____
If Present At All:			
☐ Lymphoma, leukemia or any other cancer	☐	☐	_____
☐ History of hepatosplenomegaly	☐	☐	_____
☐ History of myositis or muscle inflammation	☐	☐	_____
☐ History of muscle spasms, tremors, paralysis, and/or multiple sclerosis	☐	☐	_____
☐ History of uveitis/iritis	☐	☐	_____
☐ Sarcoidosis or hepatitis reported as major medical condition	☐	☐	_____
☐ Complex medical history and/or poor health reported	☐	☐	_____
☐ Other (SPECIFY)_____	☐	☐	_____
PHASE THREE LEVEL 1 EXAM			
☐ Skin lesion(s) resembling photo or requiring physician review	☐	☐	_____
☐ Palpable supraclavicular, submental and/or epitrochlear node(s)	☐	☐	_____
☐ Other node(s) of ≥ 1 cm	☐	☐	_____
☐ Multiple regional lymphadenopathy of nodes ≤ 1 cm	☐	☐	_____
Without Apparent Restrictions:			
☐ Impairment of heel, toe and/or heel-toe walking	☐	☐	_____
☐ Impaired rising from a chair without using hands	☐	☐	_____
☐ Reduced vibratory sense and either patellar hyperreflexia or impaired rising or walking	☐	☐	_____
☐ Patellar hyperreflexia and either impaired rising or walking	☐	☐	_____
☐ Plantar hyperreflexia of right or left side	☐	☐	_____
☐ Other (SPECIFY)_____	☐	☐	_____
PHASE THREE ABNORMAL CBC VALUES			
☐ Leukocyte count of ≤ 2500 or ≥ 15,000	☐	☐	_____
☐ ≥ 10 bands	☐	☐	_____
☐ ≥ 2 metamyelocytes	☐	☐	_____
☐ HCT: ≤ 38 or ≥ 55 (male); ≤ 32 or ≥ 50 (female)	☐	☐	_____
☐ Lymphs > polys	☐	☐	_____
☐ Platelets ≤ 120,000 or ≥ 500,000	☐	☐	_____
☐ Other (SPECIFY)_____	☐	☐	_____

PAGE 9
(INSIDE BACK COVER)

G. REVIEW AND REFERRAL DECISION

This page should be completed by the study physician while reviewing data from the Phase Three Interview, Level 1 Exam and CBC. Any of the reported findings listed, which cannot be explained by the study physician or nurse/counselor examiner, may serve as a trigger for a Level 2 exam referral. All explanations for Phase Three findings should be noted in the space provided on the inside of the back cover. Since the data also will be reviewed at the Coordinating Center according to REDS Diagnosis Review Panel criteria, the study physician's judgment and explanations are important considerations and are heavily relied upon in the panel's decision process. Additional study physician comments may also be recorded on the previous page in the Physician's Review section.

APPENDIX D

ADMINISTERING THE PHASE THREE LEVEL 2 EXAMINATION

This appendix describes procedures for administering the Phase Three Level 2 exam, and provides detailed item-by-item specifications for making and recording observations during it.

SUBJECT ID _____

DATE OF EXAM |__|__| |__|__| |__|__|
MO DA YR

PHYSICIAN INITIALS |__|__|__|

REASON FOR LEVEL 2 EXAM: (check all that apply)
- ☐ CLINICALLY INDICATED
- ☐ LEVEL 2 QC
- ☐ RECOMMENDED BY DRP

LOCATION OF EXAM
- BLOOD CENTER.....1
- SUBJECT'S HOME 2
- OTHER.....3

_____
(SPECIFY)

EXAM RESULT |__|__|

PHASE THREE
LEVEL 2 EXAMINATION
REDS HTLV COHORT STUDY

COVER PAGE

On the Phase Three Level 2 exam cover page, enter or circle the code for the following information:

- The REDS Subject ID;
- The date of the exam;
- The study physician's initials; and
- The location code for where the exam is being conducted, specifying the location if "Other."

Check all boxes that apply for the reason(s) for the Level 2 exam. There are three possible reasons:

- The subject was referred because of clinically significant findings from the interview, CBC and/or the Level 1 exam;
- The subject is a Level 2 QC subject; and/or
- The subject was recommended for a Level 2 exam after review by the REDS Diagnosis Review Panel.

At the end of the exam, enter the exam result code, either "EC" for a completed exam, or "PE" for a partially completed exam, noting the following rules for their use:

- ***The "PE" code should be used only if one or more entire portions of the exam were not performed. It is not appropriate to use this code if only one or two of the procedures were not performed; and***
- ***If all or a portion of sections of the exam could not be performed or were not attempted due to the subject's physical restriction(s), this should be noted within that section of the exam booklet. This does <u>not</u> qualify the exam as partially completed.***

A. PRELIMINARY QUESTIONS

A-1. **(ASK)** First, I would like to ask if you have any problems from recent surgery, injury or other health conditions that might prevent you from standing up from a chair or walking?

No restrictions per subject	1
Recent surgery	2
Injury	3
Physical handicap	4
Obesity	5
Other (SPECIFY _____)	6

(DO NOT ASK) Physician's observation of unreported apparent restrictions (if any):

_____

_____

A-2. **(ASK)** Which hand do you use to write? (USE FOR D-1 through D-4; E-4; and F-8.)

Right	1
Left	2

START EXAM ON NEXT PAGE (SECTION B) WITH SUBJECT SITTING ON EXAMINATION TABLE, LEGS DANGLING.

A-1. Regardless of the subject's appearance, he/she should be asked this introductory question to determine if there are any physical limitations that could interfere with performance of maneuvers in the Level 2 exam. Circle the appropriate code(s) for all physical limitations the subject reports. If the subject reports a physical limitation other than the ones listed, code "6" and write the limitation on the line provided. Additionally, in the space provided, write observations of any apparent restrictions which the subject did not report.

A-2. Code the subject's answer, which will be needed for D-1 through D-4, E-4 and F-8.

B. DERMATOLOGIC EXAM

EXAMINE HANDS/ARMS, LEGS/FEET, TRUNK/BACK, HEAD/NECK FOR EVIDENCE OF LESIONS, NODULES, RASH, PUSTULES, VESICLES, OR ULCERS. IF PRESENT, CODE "YES" AND ANSWER SUBSEQUENT QUESTIONS ACROSS THE GRID. EXCLUDE FRECKLES, MOLES, CHERRY HEMANGIOMAS, LIPOMAS, PIMPLES AND ACNE.

B-1. Are any lesions present?	B-2. Are any lesions possibly suspicious for ATL?
a. **Hands/Arms** YES ..... 1 → NO ..... 2 (b)	YES ..... 1 → Circle reference photo #1, 2, 3, 4, 5, 6, none → NO ..... 2 → What do lesions resemble? (Describe below) _____ _____ _____ _____ (B-1b)
b. **Trunk/Back** YES ..... 1 → NO ..... 2 (c)	YES ..... 1 → Circle reference photo #1, 2, 3, 4, 5, 6, none → NO ..... 2 → What do lesions resemble? (Describe below) _____ _____ _____ _____ (B-1c)
c. **Legs/Feet** YES ..... 1 → NO ..... 2 (d)	YES ..... 1 → Circle reference photo #1, 2, 3, 4, 5, 6, none → NO ..... 2 → What do lesions resemble? (Describe below) _____ _____ _____ _____ (B-1d)

B. DERMATOLOGIC EXAM

The dermatologic exam is conducted while the subject is seated in a chair. The Level 2 exam involves repeat observations of all sites examined in Level 1, as well as additional observations of the upper arms, trunk, back, and legs. Paper gowns may be available for subjects, in which case, examinations may proceed without any modifications; otherwise, proceed as best able to examine the areas specified. Sites a-d in Column B-1 are areas that could exhibit skin conditions such as lesions, nodules, rash, postules, vesicles or ulcers. Circle the appropriate code to indicate if any of these skin conditions are present.

B-1a Examine the anterior and posterior aspects of <u>both</u> forearms, upper arms including axillae, and hands including nailbeds.

B-1b Examine the trunk, including the chest, shoulders, abdominal area and the back.

B-1c Examine all surfaces of <u>both</u> feet, the skin between the toes and the nailbeds. Additionally, examine surfaces of both legs and thighs.

Column B-2 Photographs 1 through 6 (provided to each study physician during Phase One) are pictures of patients who developed ATL. The photographs should be used as references for comparing REDS subject's skin conditions to those found in patients with ATL. Skin conditions in study subjects may be early signs and not as advanced as the lesions in the pictures, so if there are any conditions suspicious for ATL, code "YES." If the skin condition does not resemble any photos, code "none" and continue across the grid row for that body region. The photographs show the following dermatopathies:

Photo #1 = diffuse erythematous rash or erythroderma(s)
Photo #2 = subcutaneous nodules
Photo #3 = erythodermas with scales
Photo #4 = ulcerated nodule
Photo #5 = multiple papules, shiny or flesh-colored
Photo #6 = smoldering tumorous lesions of coalesced papules with plaque

If the lesions clearly are <u>not</u> suspicious for ATL, code "NO" and write a description. Do not continue across the grid, but go to the next site.

<table>
<tr><th colspan="2">B-3. through B-7.
Describe lesions possibly suspect for ATL:</th><th>B-8.
Has subject seen a physician about this?</th></tr>
<tr><td>B-3. Distribution
Diffuse 01
Localized 02
Other 96
(Specify ____________)

B-4. Border
Regular 1
Irregular 2

B-5. Size |__|__|.|__| cm

B-6. Color______________</td><td>B-7. Texture/Appearance YES NO
Macular 1 2
Papular 1 2
Maculopapular 1 2
Pustular 1 2
Vesicular 1 2
Nodular 1 2
Plaque 1 2
Ulcerated 1 2
Fungating 1 2
Scaly 1 2
Shiny 1 2
Other (DESCRIBE)................. 1 2
____________________</td><td>YES .... 1 → What was the diagnosis?
____

NO .... 2</td></tr>
<tr><td>B-3. Distribution
Diffuse 01
Localized 02
Other 96
(Specify ____________)

B-4. Border
Regular 1
Irregular 2

B-5. Size |__|__|.|__| cm

B-6. Color______________</td><td>B-7. Texture/Appearance YES NO
Macular 1 2
Papular 1 2
Maculopapular 1 2
Pustular 1 2
Vesicular 1 2
Nodular 1 2
Plaque 1 2
Ulcerated 1 2
Fungating 1 2
Scaly 1 2
Shiny 1 2
Other (DESCRIBE)................. 1 2
____________________</td><td>YES .... 1 → What was the diagnosis?
____

NO .... 2</td></tr>
<tr><td>B-3. Distribution
Diffuse 01
Localized 02
Other 96
(Specify ____________)

B-4. Border
Regular 1
Irregular 2

B-5. Size |__|__|.|__| cm

B-6. Color______________</td><td>B-7. Texture/Appearance YES NO
Macular 1 2
Papular 1 2
Maculopapular 1 2
Pustular 1 2
Vesicular 1 2
Nodular 1 2
Plaque 1 2
Ulcerated 1 2
Fungating 1 2
Scaly 1 2
Shiny 1 2
Other (DESCRIBE)................. 1 2
____________________</td><td>YES .... 1 → What was the diagnosis?
____

NO .... 2</td></tr>
</table>

B-3 Select and code one term to describe the distribution of lesions. If the distribution is neither diffuse nor localized, then circle the code for "other" and write the appropriate term in the space provided.

B-4. Select and code one term to describe the border of the lesions.

B-5. Measure the lesion, or spread of the lesions, to the nearest tenth of a centimeter, and record that number.

B-6. Write in the color(s) that most accurately describes the lesion.

B-7. All descriptive terms to describe the texture and appearance should be coded either "YES" (1) or "NO" (2).

B-8. Ask the subject if he/she has seen a physician about this skin problem. If "YES", ascertain the physician's diagnosis. Code "NO" if a physician was not seen.

B-1. Are any lesions present?	B-2. Are any lesions possibly suspicious for ATL?
d. **Head/Neck** YES ..... 1 → NO ..... 2 (e)	YES ..... 1 → Circle reference photo #1, 2, 3, 4, 5, 6, none → NO ..... 2 → What do lesions resemble? (Describe below) _____ _____ _____ _____ (B-1e)
e. **(ASK)** Do you have any problems with your skin in areas other than those I've just examined? YES ..... 1 (Specify locations below) _____ _____ NO 2	YES ..... 1 → Circle reference photo #1, 2, 3, 4, 5, 6, none → NO ..... 2 → What do lesions resemble? (Describe below) _____ _____ _____ _____ (Section C)

B-1d Examine the subject's face, head and neck, including the eyebrows, nasolabial folds, lips, the scalp (including areas covered by hair), and the area behind both ears. Examine both the anterior and posterior neck area.

B-1e. Reading verbatim, ask the subject this question. If the subject has skin problems in another location, write that location in the space provided. Answer B-2 through B-8 as specified for Pages 2 and 3 of the exam.

Column B-2 See specifications detailed for "Page 2" on Page D-7 of this appendix.

B-3. through B-7. Describe lesions possibly suspect for ATL:		B-8. Has subject seen a physician about this?
B-3. **Distribution** Diffuse ..... 01 Localized ..... 02 Other ..... 96 (Specify _____) B-4. **Border** Regular ..... 1 Irregular ..... 2 B-5. **Size** |__|__|.|__| cm B-6. **Color**_____	B-7. **Texture/Appearance** YES NO Macular ..... 1 2 Papular ..... 1 2 Maculopapular ..... 1 2 Pustular ..... 1 2 Vesicular ..... 1 2 Nodular ..... 1 2 Plaque ..... 1 2 Ulcerated ..... 1 2 Fungating ..... 1 2 Scaly ..... 1 2 Shiny ..... 1 2 Other (DESCRIBE) ..... 1 2 _____	YES ..... 1 → What was the diagnosis? _____ NO 2
B-3. **Distribution** Diffuse ..... 01 Localized ..... 02 Other ..... 96 (Specify _____) B-4. **Border** Regular ..... 1 Irregular ..... 2 B-5. **Size** |__|__|.|__| cm B-6. **Color**_____	B-7. **Texture/Appearance** YES NO Macular ..... 1 2 Papular ..... 1 2 Maculopapular ..... 1 2 Pustular ..... 1 2 Vesicular ..... 1 2 Nodular ..... 1 2 Plaque ..... 1 2 Ulcerated ..... 1 2 Fungating ..... 1 2 Scaly ..... 1 2 Shiny ..... 1 2 Other (DESCRIBE) ..... 1 2 _____	YES ..... 1 → What was the diagnosis? _____ NO 2

B-3 through B-8	See specifications detailed for "Page 3" on Page D-9 of this appendix.

C. LYMPH NODE EXAM

PALPATE NODES ON RIGHT AND LEFT SIDE (EXCEPT SUBMENTAL NODE ON MIDLINE). IF PALPABLE, ENTER SIZE IN CENTIMETERS AND CIRCLE ONE DESCRIPTIVE TERM IN EACH BOX. DO NOT ADD OTHER DESCRIPTORS.

LOCATION	RIGHT		LEFT	
C-1. **Posterior cervical nodes**	Palpable .....1 → Nonpalpable.....2 Not examined...0 } C-2	Size __.__ cm Solitary ..... 1 Multiple ..... 2 Hard ..... 1 Soft ..... 2 Fixed ..... 1 Mobile ..... 2 Discrete ..... 1 Matted together .... 2 Tender ..... 1 Non-tender ... 2	Palpable .....1 → Nonpalpable.....2 Not examined...0 } C-2	Size __.__ cm Solitary ..... 1 Multiple ..... 2 Hard ..... 1 Soft ..... 2 Fixed ..... 1 Mobile ..... 2 Discrete ..... 1 Matted together .... 2 Tender ..... 1 Non-tender ... 2
C-2. **Anterior cervical nodes**	Palpable .....1 → Nonpalpable.....2 Not examined...0 } C-3	Size __.__ cm Solitary ..... 1 Multiple ..... 2 Hard ..... 1 Soft ..... 2 Fixed ..... 1 Mobile ..... 2 Discrete ..... 1 Matted together .... 2 Tender ..... 1 Non-tender ... 2	Palpable .....1 → Nonpalpable.....2 Not examined...0 } C-3	Size __.__ cm Solitary ..... 1 Multiple ..... 2 Hard ..... 1 Soft ..... 2 Fixed ..... 1 Mobile ..... 2 Discrete ..... 1 Matted together .... 2 Tender ..... 1 Non-tender ... 2

B. LYMPH NODE EXAM

C-1 through C-10

The Level 2 exam involves palpation of the same lymph nodes as in the Level 1 exam. If any node is palpable, circle code "1," measure it to the nearest tenth of a centimeter, and enter the size in the spaces provided. Describe relevant pathology for each node by circling one term per box in the columns under "RIGHT" and "LEFT". If a node is not palpable or not examined, code "2" or "0", respectively, and examine the next node listed in the "Location" column.

"RIGHT" and "LEFT" refer to the sides of the subject's body. Therefore, under the column labeled "RIGHT", record observations for nodes on the subject's right side, and under the column labeled "LEFT", record observations for the subject's left side.

LOCATION	RIGHT		LEFT	
C-3. **Submandibular nodes**	Palpable .....1 → Nonpalpable.....2 Not examined...0 } C-4	Size |__|__|.|__| cm Solitary ..... 1 Multiple ..... 2 Hard ..... 1 Soft ..... 2 Fixed ..... 1 Mobile ..... 2 Discrete ..... 1 Matted together .... 2 Tender ..... 1 Non-tender ... 2	Palpable .....1 → Nonpalpable.....2 Not examined...0 } C-4	Size |__|__|.|__| cm Solitary ..... 1 Multiple ..... 2 Hard ..... 1 Soft ..... 2 Fixed ..... 1 Mobile ..... 2 Discrete ..... 1 Matted together .... 2 Tender ..... 1 Non-tender ... 2
C-4. **Submental node** (ALONG THE MIDLINE)	Palpable .....1 → Nonpalpable.....2 Not examined...0 } C-5	Size |__|__|.|__| cm Solitary ..... 1 Multiple ..... 2 Hard ..... 1 Soft ..... 2 Fixed ..... 1 Mobile ..... 2 Discrete ..... 1 Matted together .... 2 Tender ..... 1 Non-tender ... 2		
C-5. **Posterior auricular nodes**	Palpable .....1 → Nonpalpable.....2 Not examined...0 } C-6	Size |__|__|.|__| cm Solitary ..... 1 Multiple ..... 2 Hard ..... 1 Soft ..... 2 Fixed ..... 1 Mobile ..... 2 Discrete ..... 1 Matted together .... 2 Tender ..... 1 Non-tender ... 2	Palpable .....1 → Nonpalpable.....2 Not examined...0 } C-6	Size |__|__|.|__| cm Solitary ..... 1 Multiple ..... 2 Hard ..... 1 Soft ..... 2 Fixed ..... 1 Mobile ..... 2 Discrete ..... 1 Matted together .... 2 Tender ..... 1 Non-tender ... 2

PAGE 7

See "General Specifications for Pages 6-9" on Page D-15 of this appendix.

LOCATION	RIGHT		LEFT	
C-6. **Occipital nodes**	Palpable .....1 → Nonpalpable.....2 Not examined...0 } C-7	Size |__|__|.|__| cm Solitary ..... 1 Multiple ..... 2 Hard ..... 1 Soft ..... 2 Fixed ..... 1 Mobile ..... 2 Discrete ..... 1 Matted together .... 2 Tender ..... 1 Non-tender ... 2	Palpable .....1 → Nonpalpable.....2 Not examined...0 } C-7	Size |__|__|.|__| cm Solitary ..... 1 Multiple ..... 2 Hard ..... 1 Soft ..... 2 Fixed ..... 1 Mobile ..... 2 Discrete ..... 1 Matted together .... 2 Tender ..... 1 Non-tender ... 2
C-7. **Supraclavicular nodes**	Palpable .....1 → Nonpalpable.....2 Not examined...0 } C-8	Size |__|__|.|__| cm Solitary ..... 1 Multiple ..... 2 Hard ..... 1 Soft ..... 2 Fixed ..... 1 Mobile ..... 2 Discrete ..... 1 Matted together .... 2 Tender ..... 1 Non-tender ... 2	Palpable .....1 → Nonpalpable.....2 Not examined...0 } C-8	Size |__|__|.|__| cm Solitary ..... 1 Multiple ..... 2 Hard ..... 1 Soft ..... 2 Fixed ..... 1 Mobile ..... 2 Discrete ..... 1 Matted together .... 2 Tender ..... 1 Non-tender ... 2
C-8. **Axillary nodes**	Palpable .....1 → Nonpalpable.....2 Not examined...0 } C-9	Size |__|__|.|__| cm Solitary ..... 1 Multiple ..... 2 Hard ..... 1 Soft ..... 2 Fixed ..... 1 Mobile ..... 2 Discrete ..... 1 Matted together .... 2 Tender ..... 1 Non-tender ... 2	Palpable .....1 → Nonpalpable.....2 Not examined...0 } C-9	Size |__|__|.|__| cm Solitary ..... 1 Multiple ..... 2 Hard ..... 1 Soft ..... 2 Fixed ..... 1 Mobile ..... 2 Discrete ..... 1 Matted together .... 2 Tender ..... 1 Non-tender ... 2

PAGE 8

See "General Specifications for Pages 6-9" on Page D-15 of this appendix.

LOCATION	RIGHT		LEFT	
C-9. **Epitrochlear nodes**	Palpable .....1 → Nonpalpable.....2 Not examined...0 } C-10	Size |__|__|.|__| cm Solitary ..... 1 Multiple ..... 2 Hard ..... 1 Soft ..... 2 Fixed ..... 1 Mobile ..... 2 Discrete ..... 1 Matted together .... 2 Tender ..... 1 Non-tender ... 2	Palpable .....1 → Nonpalpable.....2 Not examined...0 } C-10	Size |__|__|.|__| cm Solitary ..... 1 Multiple ..... 2 Hard ..... 1 Soft ..... 2 Fixed ..... 1 Mobile ..... 2 Discrete ..... 1 Matted together .... 2 Tender ..... 1 Non-tender ... 2
C-10. **Other nodes** (SPECIFY ONE PER LINE) a. _____	Palpable .....1 → Nonpalpable.....2 Not examined...0 } D-1	Size |__|__|.|__| cm Solitary ..... 1 Multiple ..... 2 Hard ..... 1 Soft ..... 2 Fixed ..... 1 Mobile ..... 2 Discrete ..... 1 Matted together .... 2 Tender ..... 1 Non-tender ... 2	Palpable .....1 → Nonpalpable.....2 Not examined...0 } D-1	Size |__|__|.|__| cm Solitary ..... 1 Multiple ..... 2 Hard ..... 1 Soft ..... 2 Fixed ..... 1 Mobile ..... 2 Discrete ..... 1 Matted together .... 2 Tender ..... 1 Non-tender ... 2
b. _____	Palpable .....1 → Nonpalpable.....2 Not examined...0 } D-1	Size |__|__|.|__| cm Solitary ..... 1 Multiple ..... 2 Hard ..... 1 Soft ..... 2 Fixed ..... 1 Mobile ..... 2 Discrete ..... 1 Matted together .... 2 Tender ..... 1 Non-tender ... 2	Palpable .....1 → Nonpalpable.....2 Not examined...0 } D-1	Size |__|__|.|__| cm Solitary ..... 1 Multiple ..... 2 Hard ..... 1 Soft ..... 2 Fixed ..... 1 Mobile ..... 2 Discrete ..... 1 Matted together .... 2 Tender ..... 1 Non-tender ... 2

C-9. See "General Specifications for Pages 6-9" on page D-15 of this appendix.

C-10. If examination of the subject suggests that other nodes, (e.g., submaxillary, inguinal) should be examined, write the location of the node(s), specifying one location per line. Complete the remainder of the grid as described on Page D-15 of this appendix.

GENERAL SPECIFICATIONS FOR PAGES 10-16, (SECTIONS D-F)

During the Level 2 exam, Level 1 exam tests of neuromuscular function will be repeated and supplemented with additional maneuvers and reflex tests. Observe the subject's performance to assess balance, strength, coordination, and sensory and neuromotor responses. Since the purpose of the remainder of the exam is to screen for early signs of HTLV-associated myelophathy (HAM), the following impairments are considered significant during maneuvers involving lower extremities:

- Legs spread widely apart;
- Subject watching the ground;
- Legs lifted at hip higher than necessary;
- Legs flung forward and outward in abrupt motions;
- Steps varying in length;
- A corrective step to the side;
- Feet making slapping sounds on the floor;
- Knees raised higher to compensate for inability of the foot to dorsiflex at the ankle;
- Trunk held somewhat flexed at hips; and
- Subject waddling, reeling, swaying or losing balance.

Demonstrate each maneuver for the subject before having him/her attempt it. Maneuvers should be attempted with the subject's shoes and socks removed. Circle the code for "not attempted" if a physical limitation, lack of time, subject refusal or another situation prevents a maneuver from even being attempted. ***It does <u>not</u> mean that the subject tried to, but was unable to perform a maneuver.*** In all cases, circle the code which best describes the subject's performance of a maneuver or reflex response for each item in Sections D-F.

D. EXAM WITH SUBJECT LYING DOWN

D-1. Toe fanning without resistance (dominant foot from A-2).

	RIGHT	LEFT
Abnormal	1	1
Normal	2	2

DEMONSTRATE EACH MANEUVER. ASK THE SUBJECT TO PERFORM IT AFTER YOU.

MANEUVER (dominant foot from A-2)	DEGREE OF IMPAIRMENT
D-2. **Move heel of dominant foot down shin of opposite leg, from knee to foot.** Impaired performance ..... 1 → Normal performance ..... 2 Not attempted ..... 0 } (D-3)	Slight unsteadiness, wobbling ..... 1 Obvious wobbling, weakness ..... 2 Unable to perform 3
D-3. **Feel tuning fork on interphalangeal joint of great toe of dominant foot.** Impaired sensation ..... 1 → ≤ 4 second gap ..... 2 Not attempted ..... 0 } (D-4)	Examiner felt vibrations 5-7 sec. longer than subject ..... 1 Examiner felt vibrations >7 sec. longer than subject ..... 2 Subject did not feel vibrations 3
D-4. **Sense position of great toe of dominant foot, in response to examiner's manipulations.** Impaired proprioception ..... 1 Normal proprioception ..... 2 Not attempted 0	

D-5. **Plantar reflex** in response to blunt object lightly moved from heel, up lateral aspect, curving medially across ball of foot to great toe.

	RIGHT	LEFT
Absent	0	0
Downward flexion present but diminished or weak	1	1
Normal downward flexion	2	2
Hyperactive (dorsiflexion of great toe and/or fanning of other toes)	3	3
Hyperactive (as above) with reflex flexion at hip and/or knee	4	4
Hyperactive with repetitive rhythmic contractions and sustained stretch	5	5
Unable to assess due to withdrawal/hypersensitivity	6	6

EXAM WITH SUBJECT LYING DOWN

D-1. Toe fanning should be tested on the dominant foot (from subject's answer to A-2). The subject should be lying down while attempting to fan his/her toes out as far as possible. ***This may be difficult, even for normal subjects, so observe the strength of intrinsic foot muscles, rather than focusing only on toes.***

D-2. The subject should lie supine on table with knees flexed so both feet are flat on table. Have the subject lift his/her dominant foot (from A-2) and place the heel on the knee of the opposite leg. Then, have the subject move the heel of the dominant foot down the shin of the opposite leg, starting at the knee and sliding down to the opposite foot. The subject should return the heel to the knee, sliding it down the shin again, and again return it to the knee. ***Impairment is revealed by inability to lift the leg, or the heel slipping off the leg to either side.***

D-3. Use the subject's dominant foot (from A-2) to test his/her ability to feel vibrations in the great toe. Place a vibrating tuning fork on the bony prominence of the interphalangeal (IP) joint of the great toe. At the same time, position the pad of your index finger on the plantar surface of subject's IP joint to feel the vibrations. Ask the subject if he/she feels the vibrations, and if so, to let you know when he/she feels them stop. Let the fork stop on its own. If the subject feels the vibrations, count the seconds between the time the subject says he/she felt them stop and the time you feel them stop. ***A delay of 4 seconds or less is normal. Inability to feel vibrations and delays of 5 seconds or more are not normal.***

D-4. Grasp the subject's great toe of the dominant (from A-2) foot holding it by its sides between the thumb and index finger and pulling it away from the other toes to avoid touching them. Show what is meant by "up" and "down" while moving the subject's toe clearly upward and downward one time. Repeat several times without saying "up" or "down," avoiding simple alteration of movement. Ask the subject whether the toe is "up" or "down." ***If the subject mistakes one direction for the other, or is unable to tell whether the toe is up or down, circle code "1" for impaired proprioception.***

D-5. To test the plantar reflex on both sides of the body, use the sharp end of a key, the handle of the reflex hammer, or the end of a cotton-tipped stick. The subject should be sitting down. ***Support the subject's leg to aid relaxation and to avoid the sensation of being tickled.*** To elicit the plantar reflex, place the object on the subject's heel of the foot, and lightly move it up the lateral aspect of the foot across the ball of the foot to the metatarsal joint of the great toe.

Observe movement of the toes during the plantar reflex. ***If the subject is hypersensitive, ticklish and/or withdraws his/her leg during repeated attempts to elicit the plantar reflex, circle code "6."***

E. EXAM WITH SUBJECT SITTING, LEGS DANGLING

UPPER EXTREMITIES

E-1. **Biceps reflex** in response to strike with pointed end of reflex hammer aimed through your finger or thumb directly toward the biceps tendon.

	RIGHT	LEFT
Absent	0	0
Elbow flexion present but diminished, or weak	1	1
Normal contraction of biceps and elbow flexion	2	2
Hyperactive contraction and/or flexion	3	3
Hyperactive with contractions and maintained stretch	4	4

E-2. **Triceps reflex** in response to direct strike with pointed end of reflex hammer from behind triceps tendon.

	RIGHT	LEFT
Absent	0	0
Elbow extension present but diminished or weak	1	1
Normal	2	2
Hyperactive contraction and/or extension	3	3
Hyperactive with contractions and maintained stretch	4	4

E-3. **Brachioradialis reflex** in response to strike with flat end of reflex hammer, 1-2 inches above wrist.

	RIGHT	LEFT
Absent	0	0
Present but diminished or weak	1	1
Normal	2	2
Hyperactive	3	3
Hyperactive with contractions and maintained stretch	4	4

DEMONSTRATE MANEUVER. ASK SUBJECT TO PERFORM IT AFTER YOU.

MANEUVER (dominant hand from A-2)	DEGREE OF IMPAIRMENT
E-4. **Tapping index finger to thumb at distal joint, dominant hand.** Impaired performance ..... 1 → Normal performance ..... 2 Not attempted ..... 0 } (E-5)	Matches speed of examiner but finger slips to side or to pad of thumb ..... 1 Slower than examiner ..... 2 Unable to perform 3

EXAM WITH SUBJECT SITTING, LEGS DANGLING UPPER EXTREMITIES

E-1. The study physician should place his/her thumb on the biceps tendon in the crook of the subject's elbow, hit the thumb fingernail and observe the biceps muscle. Repeat for the other arm's bicep tendon.

E-2. Flex the subject's arm at the elbow, with his/her palm toward the body and forearm across the chest. Strike the triceps tendon above the elbow, using a direct blow. Watch for contraction of the triceps muscle and extension at the elbow. ***If it is difficult to get a subject to relax in a sitting position for the triceps reflex, support the upper arm with the shoulder abducted, the upper arm parallel to the floor and at a right angle to the body, and the forearm perpendicular to the floor.*** Tell the subject to let the arm go limp, and strike the tendon.

E-3. The subject's forearm should be relaxed and resting on the thigh with the palm down. Strike the brachioradialis tendon, about 1-2 inches above the wrist and watch for flexion and supination of the forearm.

E-4. Have the subject tap on his/her distal joint on the palmar surface of the thumb with the tip of the index finger, instructing the subject to tap as rapidly as possible. ***Impairment is indicated by an inability to maintain rhythm, by the tip of the index finger missing the mark and slipping to either side of the thumb, or persistence in hitting the pad or tip of the thumb.***

E-5. Thenar eminence bulk and shape.

	RIGHT		LEFT
Atrophy/flattening	1	.....	1
Full/convex	2	.....	2

E-6. Hand grip power and strength.

	RIGHT		LEFT
Abnormal	1	.....	1
Normal	2	.....	2

E-7. Tone of arm biceps.

	RIGHT		LEFT
Abnormal	1	.....	1
Describe:_____ (hypotonic, flaccid, rigid, spastic, etc.)			
Normal	2	.....	2

E-8. Biceps power and strength against gravity and resistance.

	RIGHT		LEFT
No movement	0	.....	0
Trace of contraction with no movement	1	.....	1
Movement present but cannot be sustained against gravity	2	.....	2
Movement against gravity but not applied resistance	3	.....	3
Movement against some degree of resistance	4	.....	4
Full power	5	.....	5

LOWER EXTREMITIES

E-9. **Achilles reflex** in response to quick and direct strike with pointed end of reflex hammer.

	RIGHT		LEFT
Absent	0	.....	0
Present but diminished or weak	1	.....	1
Normal	2	.....	2
Hyperactive	3	.....	3
Hyperactive with contractions and maintained stretch	4	.....	4

E-10. **Patellar reflex** in response to one brisk tap with pointed end of reflex hammer.

	RIGHT		LEFT
Absent	0	.....	0
Knee extension present but diminished or weak	1	.....	1
Normal contraction of quadriceps and knee extension	2	.....	2
Hyperactive, contraction and/or extension	3	.....	3
Hyperactive with contractions and maintained stretch	4	.....	4

E-5. To inspect bulk and shape of the right and left thenar eminances, have the subject make a loose fist with each hand. Examine the muscle below the proximal joint of the index finger, where it should be full and convex. ***Note if the muscle appears atrophied, flat, shallow or hollow.***

E-6. Use both your and the subject's hands to test grip strength. Test the subject's grip strength, one hand at a time. Ask the subject to squeeze his/her index and middle fingers as hard as possible but not to let them go (place your own middle fingers on top of your index fingers to avoid being hurt). ***The study physician should not be able to loosen the grip or to pull his/her hands away.***

E-7. Rotate and gently shake each of the subject's arms to reduce tension and aid relaxation. Note if the right and/or left limb seems to "catch" or otherwise displays resistance to movement. ***If abnormal, describe the abnormality present.***

E-8. Testing one arm at a time, rotate the subject's arm at the elbow so that the posterior aspect faces up. Have the subject flex his/her arm (bends up). As the subject flexes, the study physician should apply resistance by pushing his/her hand against the subject's posterior aspect of the forearm. Note if the subject can be overcome and his/her arm moved down. ***If necessary, vary the resistance applied according to the subject's strength to differentiate among the grades (0 through 5).***

LOWER EXTREMITIES

E-9. Hold the foot to be tested and ask the subject to flex his/her foot at the ankle. Then ask the subject to relax. Strike the Achilles tendon. ***Watch for plantar flexion, noting the speed of relaxation after muscular contraction. Repeat for the other foot.***

E-10. Localize the patellar tendon and strike it. Test the reflex on both legs.

E-11. Quadriceps bulk and shape.

	RIGHT	LEFT
Atrophy/flattening	1	1
Full/convex	2	2

E-12. Tone of quadriceps.

	RIGHT	LEFT
Abnormal	1	1
Describe: _____ (hypotonic, flaccid, rigid, spastic, etc.)		
Normal	2	2

E-13. Calf bulk and shape.

	RIGHT	LEFT
Atrophy/flattening	1	1
Full/convex	2	2

E-14. Quadriceps power and strength against gravity and resistance.

	RIGHT	LEFT
No movement	0	0
Trace of contraction with no movement	1	1
Movement present but cannot be sustained against gravity	2	2
Movement against gravity but not applied resistance	3	3
Movement against some degree of resistance	4	4
Full power	5	5

E-15. Hamstrings power and strength against gravity and resistance.

	RIGHT	LEFT
No movement	0	0
Trace of contraction with no movement	1	1
Movement present but cannot be sustained against gravity	2	2
Movement against gravity but not applied resistance	3	3
Movement against some degree of resistance	4	4
Full power	5	5

E-16. Iliopsoas (hip flexors) power and strength against gravity and resistance.

	RIGHT	LEFT
No movement	0	0
Trace of contraction with no movement	1	1
Movement present but cannot be sustained against gravity	2	2
Movement against gravity but not applied resistance	3	3
Movement against some degree of resistance	4	4
Full power	5	5

E-11. Examine the right and left quadriceps for bulk and shape, noting atrophy or flattening of muscle curvature.

E-12. Determine if muscle tone of the right and left quadriceps is normal or abnormal. If the latter, describe the abnormality.

E-13. Examine the right and left calf for bulk and shape, noting atrophy or decreased muscle curvature.

E-14. Testing one leg at a time, the subject should attempt to extend the lower leg by straightening the knee while the study physician applies resistance on the subject's shin by pushing down on the leg. ***Power and strength is normal if the subject is not overcome or moves his/her leg down.***

E-15. Testing one leg at a time, the subject should attempt to lower his/her leg by bending the knee, while the study physician is applying resistance at the subject's calf by pushing up. ***Power and strength is normal if the subject is not overcome or allows his/her leg to move up.***

E-16. Testing one leg at a time, the subject should attempt to lift the thigh by flexing at the hip, while the study physician is applying resistance on the subject's thigh pushing down. ***Power and strength is normal if the subject is not overcome and does not allow his/her thigh to be pushed down.***

E-17. Ankle flexors (dorsiflexion) power and strength against gravity and resistance.

	RIGHT	LEFT
No movement	0	0
Trace of contraction with no movement	1	1
Movement present but cannot be sustained against gravity	2	2
Movement against gravity but not applied resistance	3	3
Movement against some degree of resistance	4	4
Full power	5	5

E-18. Ankle extensors (plantar flexion) power and strength against gravity and resistance.

	RIGHT	LEFT
No movement	0	0
Trace of contraction with no movement	1	1
Movement present but cannot be sustained against gravity	2	2
Movement against gravity but not applied resistance	3	3
Movement against some degree of resistance	4	4
Full power	5	5

E-17. Testing one foot at a time, ask the subject to raise his/her toes and move his/her heel down as the study physician attempts to push the toes down. ***Power and strength is normal if the subject is not overcome and does not allow his/her toes and foot to be pushed down.***

E-18. Testing one foot at a time, ask the subject to push down with his/her foot against the study physician's, while the study physician attempts to push the subject's foot up at the toes. ***Power and strength is normal if the subject is not overcome and does not allow his/her foot to be pushed up.***

F. EXAM WITH SUBJECT STANDING ON FLOOR

MANEUVER	DEGREE OF IMPAIRMENT
F-1. **Walk on heels for 10 feet.** Impaired performance ..... 1 → Normal performance ..... 2 Not attempted ..... 0 } (F-2)	Walks 7 feet without abnormality, or 10 feet with some abnormality in gait ..... 1 Walks < 7 feet and/or noticeable abnormality in gait ..... 2 Unable to perform 3
F-2. **Walk on toes for 10 feet.** Impaired performance ..... 1 → Normal performance ..... 2 Not attempted ..... 0 } (F-3)	Walks 7 feet without abnormality, or 10 feet with some abnormality in gait ..... 1 Walks < 7 feet and/or noticeable abnormality in gait ..... 2 Unable to perform 3
F-3. **Walk forward heels-to-toes for 10 feet in a straight line.** Impaired performance ..... 1 → Normal performance ..... 2 Not attempted ..... 0 } (F-4)	Walks 7 feet without abnormality, or 10 feet with some abnormality in gait ..... 1 Walks < 7 feet and/or noticeable abnormality in gait ..... 2 Unable to perform 3
F-4. **Walk backward toes-to-heels for 10 feet in a straight line.** Impaired performance ..... 1 → Normal performance ..... 2 Not attempted ..... 0 } (F-5)	Walks 7 feet without abnormality, or 10 feet with some abnormality in gait ..... 1 Walks < 7 feet and/or noticeable abnormality in gait ..... 2 Unable to perform 3
F-5. **Rise from chair without using hands.** Impaired performance ..... 1 → Normal performance ..... 2 Not attempted ..... 0 } (F-6)	Steadies body with hands ..... 1 Uses hand to push up ..... 2 Unable to perform 3

EXAM WITH SUBJECT STANDING ON FLOOR

F-1. Abnormalities would include: (1) how high the subject is able to raise his/her toes; (2) whether one or both feet drop; and (3) whether the subject is able to maintain position and balance.

F-2. Abnormalities would include: (1) how high the subject is able to stand; (2) whether one or both heels drop; and (3) whether the subject is unable to maintain position.

F-3. Abnormalities would include: (1) the subject not touching heels to toes, and whether he/she is able to correct that; and (2) whether the subject moves his/her arms to maintain or regain balance.

F-4. Abnormalities would include: (1) the subject not touching toes to heels, and whether he/she is able to correct that; and (2) whether the subject moves his/her arms to maintain or regain balance.

F-5. Abnormalities would include use of the hands to assist with rising from a chair.

MANEUVER	DEGREE OF IMPAIRMENT
F-6. **Stand with feet together, arms extended forward, and eyes closed (20-30 sec.)** Impaired performance ..... 1 → Normal performance ..... 2 Not attempted ..... 0 } (F-7)	Barely noticeable pronator drift ..... 1 Noticeable pronator drift ..... 2 Unable to perform 3
F-7. **Stand with feet together, arms at the side and eyes closed (20-30 sec.)** Impaired performance ..... 1 → Normal performance ..... 2 Not attempted ..... 0 } (F-8)	Unsteady, no corrective step ..... 1 Sways to take corrective step ..... 2 Unable to perform 3
F-8. **Foot tapping, dominant foot. (from A-2)** Impaired performance ..... 1 → Normal performance ..... 2 Not attempted ..... 0 } (G-1)	1-2 taps/sec ..... 1 < 1 tap/sec ..... 2 Unable to perform 3

G. INJECTION DRUG USE

G-1. **(DO NOT ASK)** Were needle tracks observed anywhere on the subject's body?

YES 1 (G-2)
NO 2 (H-1)

G-2 **(DO NOT ASK)** Where were the needle tracks located?

_____

[SPECIFY LOCATION(S)]

F-6. Have the subject stand with his/her arms extended forward, palms up, feet together and eyes closed. ***Stand next to the subject to prevent him/her from falling.*** If the subject maintains his/her position for 20-30 seconds (slight swaying is normal), this is considered normal performance. Impaired performance is revealed by any of the following:

- Loss of balance;
- Movements of arms and hands, for example, pronation of one arm (turning inward), downward, sideward or upward drifting of one arm with fingers or elbow flexed, movement of hands in a piano playing movement;
- Corrective step(s); or
- Movement of toes.

F-7. Have the subject stand with his/her arms at the side, feet together and eyes closed (Romberg test). ***Stand next to the subject to prevent him/her from falling.*** If the subject maintains his/her position for 20-30 seconds (slight swaying is normal), this is considered normal performance. Impaired performance is revealed by a loss of balance.

F-8. Have the subject stand for foot tapping with the dominant foot (from A-2). The study physician should tap his/her dominant foot lightly and rapidly on the floor and ask the subject to match the movement and speed. The subject should be able to match the study physician's tapping rate (if tapping is $\geq$3 taps per second).

G-1. ***This question should not be asked.*** During the Level 2 exam, look for the presence of any scars resembling needle tracks. If present, circle code 1 for "YES", and specify the location(s) in G-2. If "NO," circle code "2" and skip to Section H.

G-2. If "YES' to G-1, specify all locations where needle tracks were observed.

H. PHYSICIAN'S REVIEW & RECOMMENDATION

To be completed by study physician after Level 2 examination. Code result of examination front cover (EC = exam complete; PE = partial exam).

H-1. Record your recommendation.

- ☐ Level 3 not indicated
- ☐ Refer to REDS Neurologist
- ☐ Refer to REDS Oncologist/Hematologist
- ☐ Refer to REDS Dematologist
- ☐ Refer to Usual Care (non-REDS)
- ☐ Other (SPECIFY)_____

H-2. Please summarize your findings, including explanation or additional comments for your recommendation(s). Use additional page at end of booklet if necessary.

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Physician Signature: _____ Date: _____

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H. PHYSICIAN'S REVIEW AND RECOMMENDATION

One of the following result codes should be recorded on the front cover of the exam booklet.

EC= Exam complete: Use if all (or the majority of) the tests and observations in the Level 2 exam were completed.

PE= Partial exam: Use if one or more sections of the exam were not performed due to subject refusal or time constraints, for example. See Page D-3 ("COVER PAGE") for more details on the use of the "PE" code.

H-1. Check the appropriate box, reflecting the referral recommendation for this subject.

H-2. Complete this section by writing relevant comments and recommendations, including those that might not otherwise be communicated to the Diagnosis Review Panel and Coordinating Center, due to data collection or recording procedures. Use Page 18 for more discussion and include additional pages if necessary. Sign and date the booklet regardless of whether written comments or recommendations have been made.

ADDITIONAL PHYSICIAN COMMENTS

PAGE 18

ADDITIONAL PHYSICIAN COMMENTS

Use this page for additional notes, comments and/or explanations from H-2.