

**Retrovirus Epidemiology Donor Study (REDS)**

**REDS Allogeneic Donor and Recipient (RADAR) Repository:  
Repository Use Guidelines**

This manual provides an overview of the RADAR Repository and guidelines for its future use. This manual was developed by the Coordinating Center and by representatives of the REDS Steering Committee, as well as participating blood center study coordinators, at the conclusion of the REDS contract in 2004. The original intent of the repository's establishment was that use of these specimens be limited to studies requiring the use of linked donor-recipient specimens (should be used only when the same hypotheses couldn't be tested using an unlinked repository) and that protocols are reviewed and approved by an oversight committee and appropriate Institutional Review Boards.

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### **I. REDS Background**

The first report of transmission of Acquired Immunodeficiency Syndrome (AIDS) by transfusion appeared in December 1982.<sup>1</sup> By spring 1984, it was known that AIDS was caused by a retrovirus, later named the human immunodeficiency virus (HIV).<sup>2</sup> The virus was in the same family as the human T-lymphotropic virus (HTLV-I) that was described in 1980.<sup>3</sup> In March 1985, an enzyme-linked immunosorbent assay (ELISA) for HIV antibody detection was licensed for use in blood donor screening. The test dramatically reduced, but did not eliminate, the risk of transmission of HIV by transfusion.

In the mid-1980s, evidence also emerged that HTLV was transmitted by transfusion.<sup>4</sup> HTLV consists of two types, HTLV-I and HTLV-II. Adult T-cell leukemia/lymphoma (ATL) and HTLV-I associated myelopathy (HAM) had been definitively linked to HTLV-I, whereas HTLV-II was not at first clearly associated with any medical conditions.

To address these blood safety issues, the National Heart, Lung, and Blood Institute (NHLBI) published a request for proposals to study the epidemiology of human retroviruses in volunteer blood donors in October 1988. In July 1989, NHLBI awarded contracts to five major blood centers and a medical coordinating center (MCC) to develop a major multi-center epidemiologic study of the human retroviruses HIV-1, HIV-2, HTLV-I, and HTLV-II in volunteer U.S. blood donors. The study became known as the Retrovirus Epidemiology Donor Study or REDS.<sup>5</sup> The participating blood centers and medical coordinating center, respectively, included:

- American Red Cross (ARC), Greater Chesapeake and Potomac Region, Baltimore, MD
- ARC Southeastern Michigan Region, Detroit, MI
- ARC Southern California, Los Angeles, CA
- Blood Centers of the Pacific, San Francisco, CA
- Oklahoma Blood Institute, Oklahoma City, OK
- Westat, Rockville, MD

The original mission of REDS was to initiate and facilitate investigations of human retroviruses in volunteer blood donors from areas of the country at varying risk for HIV. During the course of the

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project, NHLBI expanded the original REDS mission to investigate critical questions posed by the transfusion medicine community that are essential to ensuring an adequate blood supply without compromising blood safety. The overall REDS program included epidemiologic, laboratory, and clinical investigations, and provided a comprehensive framework for monitoring blood donations, and in one REDS protocol, transfusion recipients, for infectious disease markers. The operational and database structure of REDS, specifically designed to study blood safety and availability, also provided a framework for rapid analytical response to other research questions of significant importance to the safety of the blood supply: for example, the prevalence and incidence of newly discovered infectious agents could be rapidly estimated; trends in incidence and prevalence of known agents were evaluated; populations at risk for these infections were characterized; and the impact of additional or new blood donor screening methodology could be assessed. REDS was instrumental in evaluating the effectiveness and safety of various strategies that were implemented or considered to increase blood availability. REDS made many unique contributions that have had a significant impact on the knowledge of transfusion safety and on the practice of blood banking.

### References:

1. Prevention of acquired immune deficiency syndrome (AIDS): Report of inter-agency recommendations. *MMWR*. 1983;32:101-103.
2. Marx JL. AIDS virus has a new name--perhaps. *Science*. 1986;232:699-670.
3. Poiesz BJ, Ruscetti FW, Gazdar AF, Bunn PA, Minna JD, Gallo RC. Detection and isolation of type C retrovirus particles from fresh and cultured lymphocytes of a patient with cutaneous T-cell lymphoma. *Proc Natl Acad Sci USA*. 1980;77:7415-7419.
4. Okochi K, Sato H, Hinuma Y. A retrospective study on transmission of adult T-cell leukemia virus by blood transfusion: seroconversion in recipients. *Vox Sang*. 1984;46:245-253.
5. Zuck TF, Thomson RA, Schreiber GB, et al., for the REDS Group. The Retrovirus Epidemiology Donor Study (REDS): rationale and methods. *Transfusion*. 1995;35: 944-951.

## II. RADAR Repository Background

The RADAR Repository is a contemporary linked donor-recipient repository that was established to serve as a resource that can be rapidly accessed to determine whether a newly discovered agent is likely to be transmitted by transfusion. The major purpose of this repository (and hence its major design feature)

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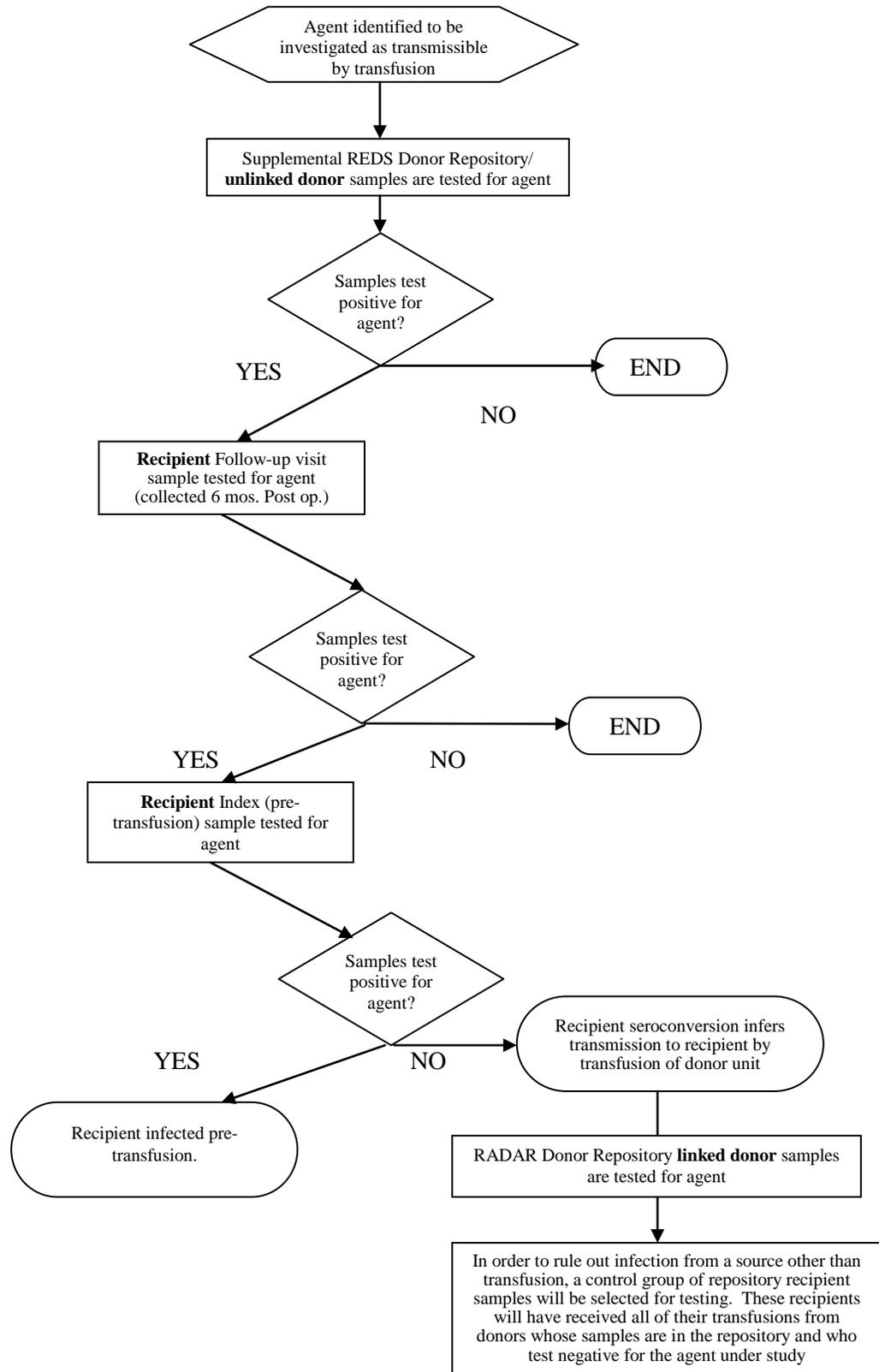
is to show that a given agent is not transmissible by transfusion with a reasonable level (i.e., 95%) of certainty. More precisely, the repository is designed to prove that, with high statistical confidence, the transmission rate of the agent is less than a given low number (i.e., 25%).

The RADAR Repository was established in 1999 by the REDS blood centers and their collaborating hospitals. The Centers for Disease Control and Prevention (CDC), impressed by the merits of building such a repository, contributed to this effort by supporting two additional recruitment sites, bringing the total number of participating blood centers and hospitals to 7 and 8, respectively. The RADAR Repository consists of samples from 27,958 donations, representing 16,858 donors. These are linked to 4,978 enrolled transfusion recipients who also have samples in the repository. In addition to the recipient enrollment samples, there are approximately 3,575 samples collected from these same recipients who have returned for a follow up questionnaire and blood collection approximately 6 months after their transfusion. Enrollment for this study ran through December 2003 with all 6-month follow-up visits concluding in June 2004.

### **III. Overview of Study Activities**

Participating blood centers designated a portion of their blood collections for distribution to hospitals participating in the study. Blood samples from the consented donors were placed in the RADAR Repository. Hospitals collaborating with the blood center, in turn, targeted their cardiac and/or orthopedic surgical patients to receive the designated RADAR units. Upon patient (recipient) enrollment, a pre-transfusion blood sample was retrieved (and/or a sample collected at enrollment) for the RADAR Repository. Approximately six months subsequent to enrollment, the patient completed a follow-up visit involving the completion of a brief questionnaire and phlebotomy. A portion of blood sample collected at this visit was placed in the repository, while additional aliquots were tested for routine viral markers. The blood sample from the donor at the time of donation and the recipient's pre- and 6-month post-transfusion samples became part of the linked donor-recipient repository. Donor samples which were placed into the repository but were not linked to an enrolled recipient subsequently became part of a Supplemental REDS Donor Repository (discussed in Section 5). These unlinked donor samples enable testing for other purposes, such as determining the prevalence of a new agent. Figure 1 provides an overview of this process.

**Figure 1**  
**RADAR Repository Testing Design**



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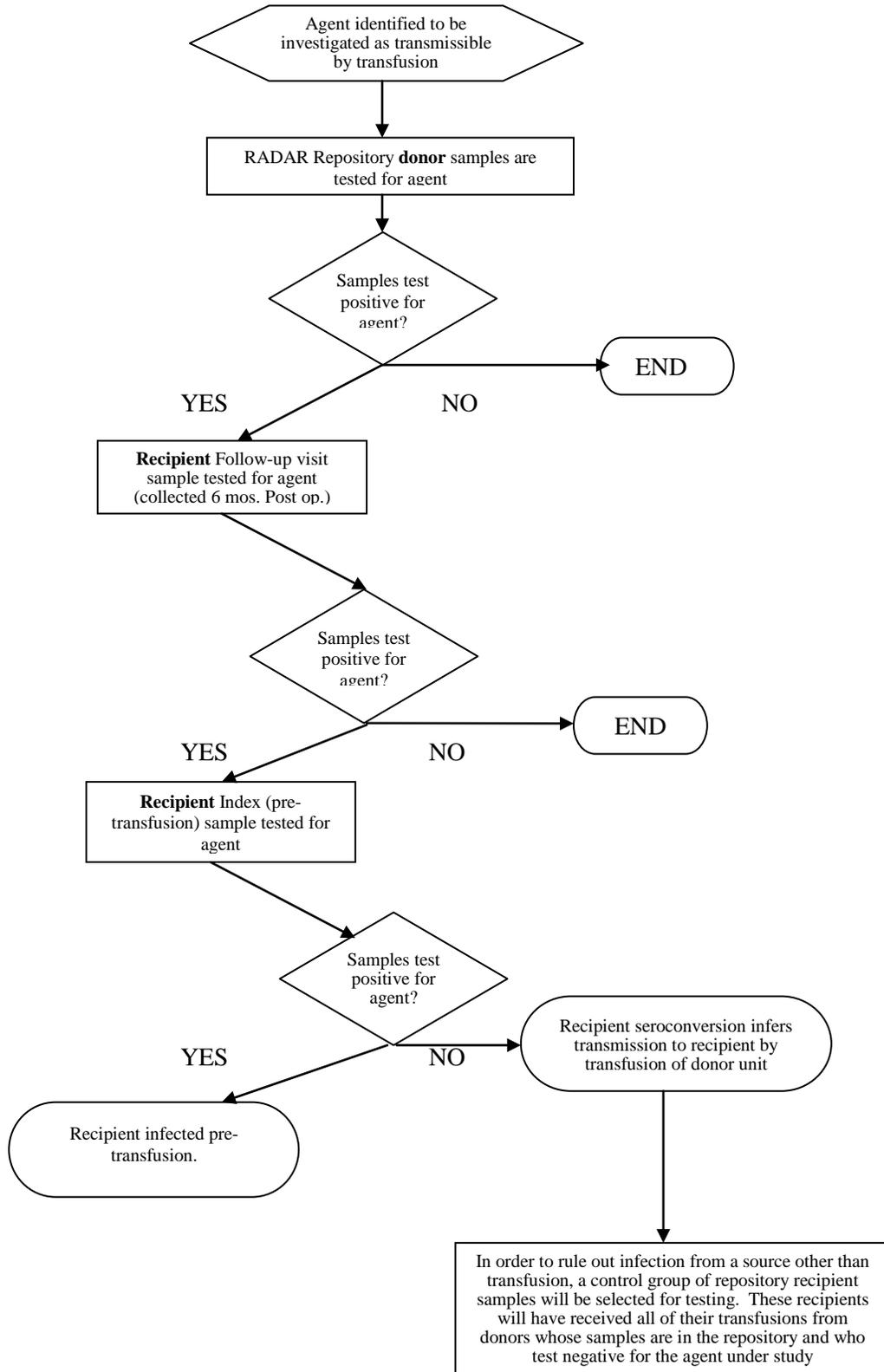
All donors and all recipients signed a consent form for participation in the repository. The protocol required three aliquots stored for each enrolled donor and recipient; (1) 1.5 ml of whole blood, (1) 1.8 ml actual volume of plasma in a 2.0-ml tube, and (1) all the residual plasma. These same volumes were also collected for repository storage during the recipient follow-up phlebotomy. Each blood center prepared the aliquots and stored them in  $-70^{\circ}$  C freezers until such time as they were shipped to the central repository. The medical coordinating center, Westat, developed a Sample Inventory System (SIS) for use at each blood center. The SIS accessioned the study ID on the donor consent forms and the participant's associated aliquots identification and volumes into the SIS, ensuring that each donor aliquot in the SIS was linked to a consent form. A similar step was performed for recipient samples identified by the Recipient ID and linked through the SIS to the repository aliquot IDs. The difference in the recipient consent is that this information was stored in the tracking system described in the next section.

In addition to the SIS which was used for the tracking of repository samples alone, the Recipient Tracking System (RTS) was developed to enroll and track recipients. This system stored subject contact information, transfusion unit identifiers, admission and discharge dates, surgery type and also allowed for generation of reports, letters and information to schedule follow-up visits.

### **IV. Future Testing**

The approach to testing of the repository for a specific agent is to test donor samples not linked to a study recipient, the Supplemental REDS Donor Repository described in the next section, to first determine the prevalence for the given agent. Following this process will eliminate utilizing the precious samples that are linked to a recipient. It must then be determined "if and what" donor samples that have been transfused into study recipients should then be tested. The recipients linked to the donors of seropositive samples will be identified and the follow-up visit repository samples from these recipients will be tested. If the recipient follow-up sample is positive, the sample collected pre-transfusion will be tested to establish that seroconversion occurred. If seroconversion is documented, it would then be inferred that the seropositive donor blood unit transmitted the infection. This approach to repository testing is similar in concept to the lookback approach (i.e. identify the infected donor and then track the recipient of the unit) with the advantage that the recipient sample is already in the study's possession, avoiding long delays and logistical difficulties. Figure 2 demonstrates the testing schematic.

**Figure 2.**  
**RADAR Repository Testing Design**



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In order to rule out infection from a source other than transfusion, a control group of repository recipient samples will be selected for testing. These recipients will have received all of their transfusions from donors whose samples are in the repository and who test negative for the agent under study.

### **V. The Supplemental REDS Donor Repository**

Previous REDS donor repositories include the General Serum Repository (GSR) and the General Leukocyte/Plasma Repository (GLPR). The Supplemental REDS Donor repository, established as a byproduct of the linked RADAR Repository, consists of samples collected from 84,339 consenting donors (representing 99,906 donations) that are not linked to a recipient. These samples are stored using the same methodology as the GLPR, and can be used for the same purposes as the GLPR, specifically allowing comparisons between the REDS donor populations at approximately 5-year intervals. (i.e. 1995 - 1996 and 2000 - 2001). Additionally, this repository is to be used to establish the prevalence and demographic distribution of specific agents prior to using the linked repository.