National Institute of Allergy and Infectious Diseases / Division of Microbiology and Infectious Diseases	**Policy** Defining Acceptable Laboratory Values for Healthy Volunteer	No.: DMID.PD.001R
	Approval Date: August 7, 2008 Effective Date: August 15, 2008	Version: 2.0

1.0 Purpose

This policy;

1.1 Defines "healthy volunteer" in order to facilitate the determination of eligibility *by evidence of laboratory testing* as described in a clinical research protocol supported by the Division of Microbiology and Infectious Diseases (DMID). This is particularly relevant to the research volunteer screening process to determine eligibility for Phase 1 and Phase 2 clinical trials.

1.2 Establishes the expectations for clinical research personnel as they evaluate protocol-specific laboratory parameters in determining 'healthy volunteer' eligibility.

1.3 Defines acceptable exceptions.

2.0 Scope

This policy applies to:

2.1 Division of Microbiology and Infectious Diseases (DMID) staff responsible for the oversight of DMID-funded clinical research.

2.2 Principal Investigators and their staff conducting clinical research supported by DMID. Investigators are ultimately responsible for adherence to a research protocol, the internal quality management, and protections for human subjects participating in clinical research.

2.3 Staff at all sites conducting clinical research supported by the DMID.

3.0 Background

Much debate has centered on the research volunteer eligibility screening process and the applicability of abnormal values that are not explicitly part of the research protocol. The term "clinically insignificant" refers to the understanding that some laboratory values do not have diagnostic significance.
In research, even clinical research, the limits of acceptable values needs to be defined prospectively to protect subjects and to allow for reproducibility of the study.

Clinical research laboratory tests provide objective evidence of the health status of the research volunteer for the purposes of study eligibility, in the absence of a medical record and reliance upon that volunteer's self report. Only clinical laboratory tests that are specified in the protocol and consistent with the informed consent process can be performed on the study participant.

These practices are intended to ensure the protection of human subjects' safety, and the integrity and reliability of the study design.

4.0 Definition

Healthy volunteer - Human research subject who consents to participate in a clinical trial and whose protocol-specific laboratory assessment is as specified in the protocol and within the normal range for the laboratory performing the assessment.

Transient acute conditions - These include a range of human conditions which present with accompanying interim, short-term symptomology (e.g., local infections, cold and/or flu symptoms, sprains,

strains, and associated swelling and bruising, menstruation) that have commonly accepted laboratory-associated abnormalities (e.g., hematuria, leukocytosis, hyperglycemia, elevated CPK enzymes).

5.0 Implementation

5.1 General Considerations

5.1.1 Perform only laboratory tests that are needed for screening and safety follow-up. However, if the test value is part of a pre-determined panel, all other values included as part of a panel must be recorded on a case report form (CRF) and followed for safety. For example, if a chemistry panel is collected and the protocol only specifies select electrolytes, all values must be recorded on the CRF and a plan in place for following any values which fall out of the normal reference ranges for the local laboratory processing the sample. This plan must be detailed in the protocol.

5.1.2 For multi-centered clinical trials:

5.1.2.1 If clinical laboratory testing is done for screening only, it is permissible to use a local laboratory and its normal reference ranges.

5.1.2.2 If clinical laboratory testing is done as part of end-point assessments, it is highly advisable to designate a core laboratory facility; otherwise, the protocol and/or the statistical analysis plan must address how discrepancies between different laboratory normal reference ranges will be handled.

5.2 Screening

5.2.1 The protocol must specify the essential clinical laboratory tests required for evaluation of subject's general health status and relevant to the study. Those should be general laboratory parameters and product specific safety parameters.

5.2.2 To ensure healthy volunteers participating in clinical research meet eligibility criteria as provided by the approved protocol, Principal Investigators (PI) will rely upon the specified clinical laboratory tests and normal reference ranges of the designated testing laboratory as described in the protocol.

5.2.3 In general, normal reference ranges of the designated testing laboratory should be used; however, the protocol may indicate, with appropriate rationale and approval of DMID Medical Monitor, the laboratory tests that will be allowed to fall outside of the normal range. For example, certain values that are normal for healthy elderly individuals may be outside of the normal reference ranges.

5.2.4 All measured parameters should be in the normal ranges *as defined by the protocol* in order to enroll a subject into the study. There are no exceptions for 'clinically insignificant' laboratory results to determine subject eligibility. The term "clinically insignificant" refers to the understanding that some laboratory values do not have diagnostic significance. In research, even clinical research, the limits of acceptable values needs to be defined prospectively to protect subjects and to allow for reproducibility of the study.

5.2.5 Enrollment clinical laboratory tests will not be repeated as a mechanism to 'screen to inclusion.' However, for subject eligibility if the laboratory results are abnormal due to a processing or handling error, the DMID Medical Monitor will review and may approve a request to repeat the test in question. The approval will be recorded on the appropriate case report form (CRF).

5.2.6 Transient Acute Condition at screening:

5.2.6.1Prior to clinical laboratory screening, volunteers should be evaluated per protocol.

5.2.6.2The PI should confirm, by documentation of the evaluation, any transient acute condition that may affect laboratory results.
5.2.6.3The clinical laboratory assessment can be performed at that visit or delayed; the PI may invite the volunteer to return to the clinic after resolution of the transient acute condition.
5.2.6.4To determine eligibility, clinical laboratory evaluations that fall outside the normal range may be repeated (follow-up screening evaluation) after resolution of the transient acute condition.
5.2.6.5If the timing of the follow-up screening evaluation falls outside the screening window, the volunteer must provide new consent to participate.
5.2.6.6 Clinical laboratory testing for screening will not be performed more than twice (one initial and one repeat test, a total of 2 times). Volunteers who do not meet inclusion criteria by the second clinical laboratory assessment will be ineligible for enrollment.

5.3 Clinical laboratory testing and safety follow-up

5.3.1 A protocol must specify the essential clinical laboratory tests required for evaluation of the subject's general health status and that are relevant to the study. These tests should be general laboratory parameters and product-specific safety parameters.
5.3.2 The protocol must provide toxicity tables (or other grading structures) for all measured parameters.
5.3.3 All abnormal tests must be graded according to the toxicity table in the protocol and reported as an Adverse Event (AE). There are no exceptions for 'clinically insignificant' laboratory results at any follow-up visits.

6.0 References

45 CFR 46.116
http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm#46.116

21 CFR 50.25
http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?fr=50.25

7.0 Inquiries

Questions or comments regarding this policy may be directed to:
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8.0 Availability

This policy is available electronically:
http://www3.niaid.nih.gov/research/resources/DMIDClinRsrch/policies.htm
http://www3.niaid.nih.gov/research/resources/DMIDClinRsrch/protdev.htm
DMID Intranet (DMID staff only)

A signed original document is maintained in the Clinical Trials Management Section (CTMS) within OCRA.

9.0 Change Summary

Version number	Date of Revision: DD/MMM/YYYY	Replaces	Effective Date: DD/MMM/YYYY	Description of Revision/Retirement	Revision Initiated by
1.0 DMID.PD.001	N/A	N/A	07/AUG/2007	N/A	N/A
2.0 DMID.PD.001R	28/APR/2008	1.0	15/AUG/2008	Exception for acute transient condition. Revised implementation.	DMID Policy Development Team