B. Statistical Methods

1. Respondent Universe and Sampling Methods

The Division of Tuberculosis Elimination (DTBE), National Center for HIV, Viral Hepatitis, STD, and TB Prevention, Centers for Disease Control and Prevention requests approval for a 3-year reinstatement with change of the previously approved National Surveillance for Severe Adverse Events Associated with Treatment of Latent Tuberculosis Infection (NSSAE) —(OMB No. 0920–0773, expires April 31, 2011). The changes include a shortened data collection form and an increase in the number of respondents. This project will continue the passive reporting system for severe adverse events (SAEs) associated with therapy for LTBI. The system will rely on medical chart review and/or onsite investigations by TB control staff.

NSSAE will investigate the clinical and other factors that may play a role in the occurrence of SAEs to recommended therapy. Persons who will be included in this study will be already diagnosed with latent tuberculosis infection (LTBI) and started a course of therapy. The majority of the patients will tolerate the anti-TB drug with little or no ill-effect. A small number will have SAEs requiring hospitalization or resulting in death. An SAE may be metabolic acidosis, anaphylaxis, seizure, severe dermatitis, liver injury, or other symptoms leading to hospitalization or death of a person receiving treatment for LTBI. These persons will be the focus of this investigation.

DTBE will continue to solicit reports of SAEs that occurred on or after January 1, 2004 from healthcare providers and health departments (local/state/territorial) from any of the 60 reporting areas for NTSS. During 2004−2008, CDC received 17 reports of SAEs in 15 adults and two children; all patients had received isoniazid (INH) and had

experienced severe liver injury (Morbidity and Mortality Weekly Report 2010; 59:224-9).

2. Procedures for the Collection of Information

Persons who are diagnosed with LTBI are prescribed anti-TB medication as seen appropriate by their physicians. A few develop mild reactions that may be managed in the outpatient clinic. Rarely, the reactions can be life-threatening or lethal. Persons who develop an SAE that resulted in an admission to a healthcare facility (e.g., acute-care hospital, urgent care center, jail infirmary) or death as a result of taking at least one dose of drug therapy for the treatment of LTBI will be evaluated by the patient's physician at the hospital. The physician or health care staff at the hospital will report the case to the local health department, who in turn will report it to their state health department. When the presumptive diagnosis is made, the *Source of Report*, *Basic Patient and Illness Description* sections of the NSSAE form (**Attachment 3**) will be completed by the medical clerk and nurse. The remainder of the NSSAE form will be completed by the respondents as the investigation proceeds. The procedures and case definitions to be used in the investigations of the SAEs are described in the "Guidelines to Investigate Reports of Severe Adverse Events to LTBI Treatment" (**Attachment 4**).

Three different respondents (physicians, nurses, medical clerks) will be involved in collecting the information from each case; a physician, nurse, and a medical clerk. The physician completes Part 3 of NSSAE form with the help of the medical clerk as needed. The information from the physician provides a history of the clinical events and the laboratory findings applicable to the diagnosis of the SAE associated with one or more anti-TB medications. If the patient has been treated or admitted to the hospital

previously, the medical clerk will be able to provide the history from the medical records at this hospital. The medical clerk completes Part 1 of the AELT form and may provide information to the physician to complete Parts 3. The medical clerk assembles the patient's hospital records from the hospital of current admission and hospitals where he/she was admitted previously to complete Part 1.

The nurse completes Part 2 of the NSSAE form. If the patient routinely uses other clinics or hospitals, the nurse will locate all clinical and laboratory information from these sources and supplements the information available at the admitting hospital and accessed by the medical clerk. The nurse completes the collating of all clinical, laboratory, and treatment protocols used in the history of the case. The nurse also collates socio-demographic and risk factor information from the TB surveillance reports that are available at the health department.

State health departments may invite CDC to join their investigation team at their location. When CDC is invited to help with the investigation, CDC team will join the local investigators at the site.

3. Methods to Maximize Response Rates and Deal with Non-response

This section is inapplicable to this surveillance activity because the proposed investigation starts only when a person on TB treatment has been admitted to a hospital or died and has been suspected to be a result of an abnormal reaction to prescribed TB antibiotics. Nevertheless, towards assuaging the patient, we will use a patient consent procedure whereby the patient will be informed of the condition and the need for the interview. The consent form is in Attachment 6.

4. Test of Procedures or Methods to be Undertaken

No tests of procedures or methods are being proposed.

5. Individuals Consulted on Statistical Aspects and Individuals Collecting and/or Analyzing Data

Thomas Navin, MD
Chief, Surveillance, Epidemiology, and Outbreak Investigation Branch
Division of Tuberculosis Elimination, NCHHSTP, CDC
1600 Clifton Road, Atlanta, Georgia 30333
Email: TNavin@cdc.gov

Roque Miramontes, PA-C, MPH
Team Leader, Surveillance Team
Surveillance, Epidemiology, and Outbreak Investigations Branch
Division of Tuberculosis Elimination, NCHHSTP, CDC
1600 Clifton Road, Atlanta, Georgia 30333
Email: Rmiramontes@cdc.gov

Steve Kammerer, MBA
CDC Information Technology Contractor
Surveillance, Epidemiology, and Outbreak Investigations Branch
Division of Tuberculosis Elimination, NCHHSTP, CDC
1600 Clifton Road, Atlanta, Georgia 30333
Email: SKammerer@cdc.gov

Robert Pratt, BS
CDC Information Technology Contractor
Surveillance, Epidemiology, and Outbreak Investigations Branch
Division of Tuberculosis Elimination, NCHHSTP, CDC
1600 Clifton Road, Atlanta, Georgia 30333
Email: RPratt@cdc.gov