National Surveillance for Severe Adverse Events Associated with Treatment of Latent Tuberculosis Infection
OMB No. 0920-0773

Supporting Statement Part A

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NATIONAL SURVEILLANCE FOR SEVERE ADVERSE EVENTS ASSOCIATED WITH TREATMENT OF LATENT TUBERCULOSIS INFECTION

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A. Justification

1. Circumstances Making the Collection of Information Necessary

CDC is requesting a 3-year reinstatement with change (i.e., shortened data collection form and an increase in the number of respondents) to the previously OMB approved standardized form for the National Surveillance for Severe Adverse Events Associated with Treatment for Latent Tuberculosis Infection (NSSAE) collection No. 0920-0773 (expired April 31, 2011). Since OMB approval of the NSSAE collection form 3 years ago, the project officers published an article “Severe Isoniazid-associated Liver Injuries Among persons Being Treated for Latent Tuberculosis Infection--United States, 2004—2008” (Morbidity and Mortality Report 2010;59[08]:224-229). In this article, the project officers described 17 reports of severe adverse events (SAEs) in 15 adults and two children; all patients had received isoniazid (INH) and had experienced severe liver injury. An SAE was defined as any drug-associated reaction resulting in a patient’s hospitalization or death after at least one treatment dose for LTBI. This article emphasized that healthcare providers should prescribe only one month supply of INH with careful monitoring. Providers should report possible INH-associated SAEs to their respective health department staff that will in turn report to CDC.

In addition, the project officers have presented these SAEs to national and international audiences at scientific conferences. After the MMWR article and presentations, there has been an increase in the number of SAE reports. Since 2008, the project officers received an additional 25 SAE reports and investigated 5 of these on site. The project officers gained from conducting onsite investigation of SAEs a better understanding of the data needed to accurately capture important elements describing factors that led to these events. As a result, the NSSAE data collection form has been shortened and broken out into 3 parts to be completed by the medical clerk, the nurse and the physician. Variables such as results of liver biopsy and hepatitis serology were removed because these were usually unreliable as a result of incomplete reporting or misreporting of information. In addition, excessive alcohol use was simplified and interferon gamma release assay was enhanced **(Attachments 4, 5, & 6).**

In order to continue to determine risk factors and to monitor trends of SAEs related to the treatment of LTBI, CDC requests approval to continue collecting SAE reports through NSSAE. These reports are from healthcare providers and health departments (local/state/territorial) from any of the 60 reporting areas for the National TB Surveillance System (NTSS)OMB No.0920-0026, Exp. Date 5/31/2014. CDC currently conducts and maintains NTSS

pursuant to the provisions of Section 301 (a) of the Public Service Act [42 U.S.C. 241] and Section 306 of the Public Service Act [42 U.S.C. 241 (a)] which also authorizes this proposed information collection (**Attachment 1**).

In compliance with the recommendations of the Institute of Medicine (IOM), Ending Neglect: The Elimination of Tuberculosis in the United States towards reaching the Healthy People (HP) 2010 objective, CDC is detecting and treating latent TB infection (LTBI) through targeted testing and administration of LTBI treatment to prevent transmission. Persons with LTBI are at highest risk for progression from latent infection to TB disease. However, with the increased number of persons with LTBI who will be treated with the recommended regimen of antibiotics, we anticipate that SAEs will occur more frequently.

Privacy Impact Assessment

No identifiable information will be collected on individuals and no personal contact information, electronic or otherwise will be asked of individuals. This information will be collected as part of monitoring and evaluating SAEs. This reporting information will be used to guide healthcare professionals in monitoring patients on LTBI treatment. The proposed data collection will have little or no effect on the individual respondent’s privacy.

Overview of the Data Collection System

Data will be collected on each occurrence of SAEs reported by healthcare providers through the local and state health departments. Data collection is initiated when a health department is notified of a person hospitalized with severe adverse reactions to the medications prescribed to treat LTBI. The investigations may be conducted by the reporting health department with or without CDC staff at the local site. All investigators follow the procedures described in "Guidelines to Investigate Reports of Severe Adverse Events to LTBI Treatment" (**Attachment 3**) and use the NSSAE form developed specifically for these investigations (**Attachment 4, 5, & 6**).

CDC conducts site investigations only when invited by local or state health departments. The physician or health care staff at the health care facility will report the case to the local health department, who in turn will report it to their state health department. Three respondents (physician, nurse, medical clerk) will be involved in collecting information from each case.

Part 1 of the NSSAE data collection form will be filled out by the medical clerk **(Attachment 4)**. Part 2 will be filled out by the nurse **(Attachment 5)**, and Part 3 will be filled out by the physician **(Attachment 6)**.

Items of Information to be Collected

Each respondent will complete their section of the NSSAE data collection form:

Part 1:

- Source of Report
- Basic Patient and Illness Information

Part 2.

- Language
- Adverse event information
- LTBI diagnosis and treatment

Part 3.

- Monitoring during therapy
- Hepatitis liver injury diagnosis
- Laboratory tests

Identification of Website(s) and Website Content Directed at Children Under 13 Years of Age

There will be no websites or internet content directed at children under the age of 13.

2. Purpose of Use of the Information Collection

SAEs to TB treatment are rare but continue to be a public health problem. We need to know who is affected, how often this occurs

and, whether there are personal risk factors that contribute to severity of adverse reactions. Without this information, we will not be able to recognize which anti-tuberculosis drug(s) are more likely to cause severe adverse reactions and how to change the antibiotic combinations used to treat persons with LTBI. Proper antibiotic regimens are crucial in the elimination of TB in the U.S.

The purpose of this information collection request is to determine the annual number and trends of SAEs associated with treatment of LTBI and identify common characteristics of patients with SAEs during treatment of LTBI. The project officers have gathered this information for the past 3 years when they were invited to conduct onsite investigations for 5 of the 25 reported SAEs. Collection of data on SAEs need to continue to better monitor and characterize these events. The collected data will be used to guide the revision of the TB treatment protocols, if needed, in order to prevent SAEs associated with treatment of LTBI. CDC will use the information from all investigations to monitor trends in LTBI detection and compile the nature of SAEs to treatment regimens associating patient characteristics, clinical events, and the treatment regimens that the patient has been required to take. CDC will use the cumulated data on LTBI treatment and SAEs to convene stakeholders and recommend

revisions of current LTBI treatment regimens, if needed, based on patient's medical history and the perceived risk of SAEs. Concurrent HIV infections will be of particular interest to CDC in evaluating treatment options to reduce or eliminate SAEs to LTBI.

Privacy Impact Assessment Information

The information being collected is important because SAEs are continuing to be reported. The data will help determine reasons or risk factors for the occurrence of SAEs. We need to develop and implement strategies to prevent these from happening.

In the next 3 years, the project officers plan to continue to solicit reports of SAEs associated with treatment for latent tuberculosis infection (LTBI) with the shortened version of the data collection form. This project is increasingly more important with the likely introduction of 12 new weekly doses of INH-rifapentine as an alternative to INH for 6-9 months for LTBI treatment. This project will provide a systematic way of monitoring SAEs to this new LTBI treatment regimen.

The project officers also plan to ascertain missed reporting of SAEs through collaborations with a non OMB approved activity; the Drug Induced Liver Injury Network (DILIN) and liver transplant centers in the United States. DILIN was established by the

National Institutes of Diabetes, Digestive, and Kidney Diseases to create a registry of drug-induced severe liver injury. The United Network for Organ Sharing maintains a database of approximately 44,000 persons who have a received a liver transplant in the United States which provides an opportunity to capture occurrences of severe liver injury associated with LTBI treatment.

No identifiable information will be collected. The proposed data collection will have little or no effect on the individual respondent’s privacy.

3. Use of Improved Information Technology and Burden Reduction

Because we expect to respond to only 10 reported SAEs each year, the use of paper forms is most suited for this small but important information collection. The information collected during each report is from medical records, treatment records, and abstractions from the records at the facility where the case has been admitted during the SAE. Information technology can partially reduce the burden of the physicians and the medical clerk who are contributing clinical information from the medical charts, if the facility where the patient has been admitted uses electronic health record systems. From our 3 years of experience

collecting this data, we estimated that we will receive 10 cases per year instead of only 3 as we previously stated.

At CDC, we maintain all of the information collected in a Microsoft Access database and/or Microsoft Excel. At the local level, paper forms also are used to collect data which are submitted to CDC. Data are obtained by reviewing medical records and interviewing healthcare providers. The Guidelines for investigating adverse events to LTBI treatment (**Attachment 3**) provide instructions to conduct the investigations and the information to be included in the NSSAE form (NSSAE, **Attachments 4, 5, & 6**). If requested by the health departments, or the physician, CDC conducts a site visit to thoroughly investigate each case of severe adverse reaction to LTBI treatment.

4. Efforts to Identify Duplication and Use of Similar Information The MEDWATCH system implemented by the Food and Drug Administration (FDA) Safety Information and Adverse Event Reporting Program, is a passive surveillance of adverse events related to individual drugs and products. However, the data collected by FDA does not include relevant patient medical history nor is it associated with medical conditions of public health priority.

Through literature searches, attendance at national TB meetings/conferences, and ongoing consultations with TB experts nationwide, CDC has determined that the data collected by NSSAE provide the sole source of comprehensive national statistics and are not available from any other source within the federal government or from non-federal sources.

5. Impact on Small Businesses or Other Small Entities

There will be minimal impact on small businesses. Healthcare providers who report SAEs to the local health department are already required by state and national regulation to report TB to NTSS.

6. Consequences of Collecting Information Less Frequently

Information collection is minimal because it is initiated only when CDC receives a report of SAE related to treatment of LTBI.

7. Special Circumstances Relating to the guidelines of 5 CFR 1320.5

Collection of data is conducted in a manner consistent with the guidelines in 5 CFR 1320.5.

8. Comments in Response to the Federal Register Notice and Efforts to Consult Outside the Agency.

A 60 day notice was published in the Federal Register April 21, 2011 Vol. 76, No. 77 pp 22399 – 22400. (**Attachment 2**). CDC received no public comments.

CDC is guided by extramural TB specialists and CDC stakeholders in TB elimination. The NSSAE is supported by the National Tuberculosis Controllers Association (NTCA). The recognition and reporting of SAEs is a voluntary effort by CDC, NTCA, Council of State and Territorial Epidemiologists, state and city TB controllers.

9. Explanation of any Payment or Gift to Respondents

Respondents (physicians, nurses, and medical clerks) do not receive gifts or paid for completing the case report form.

10. Assurance of Confidentiality Provided to Respondents

No sensitive information will be collected on individuals and no personal contact information, electronic or otherwise will be asked of individuals. This information will be collected as part of monitoring and evaluating SAEs. This reporting information will be used to guide healthcare professionals in monitoring patients on LTBI treatment. No identifiable information will be collected. The proposed data collection will have little or no effect on the individual respondent’s privacy.

Data from the local sites are safeguarded as described in the Privacy System of Records Notice 0920-0136, *Epidemiologic Studies and Surveillance of Disease Problems*. Consent from the patients or patient's guardians and the healthcare providers are obtained before the interview to obtain data on the SAEs (**Attachment 8**). Name and address of the patient are retained by the reporting area. The local project officer assigns a unique identification number to each case which excludes personal identifiers (e.g., social security number, date of birth) and is used to facilitate communication between CDC and a reporting area when needed. The patient-masking procedure is the same even if CDC is invited to help the health jurisdiction complete the investigations. All hard copy case reports and associated documents are kept in a locked cabinet by the local and CDC project officers for a period of 3 years. Access to the cabinet is limited to the project officers.

The Access database and/or Microsoft Excel maintained by the CDC project officers are password protected with only authorized DTBE staff having access to the file. Line listed data in hard copy form, when temporarily needed for data management purposes, also are kept in locked cabinet by the CDC project officers for a period of 3 years.

This investigation protocol has been determined by the Associate Director of Science, National Center for HIV, STD, and TB Prevention, CDC as routine surveillance and also post marketing surveillance and as such is not research (**Attachment 7**).

11. Justification for Sensitive Questions

Case investigations of persons with SAEs to LTBI treatment include sensitive issues such as: HIV status: People with HIV-infection are at extremely high risk for developing active TB once infected and have contributed to the resurgence of TB in the late 1980s and early 1990s. We use the information from the investigations of persons with SAEs to LTBI treatment to monitor the impact of the HIV/AIDS epidemic on TB morbidity, increase in drug-resistant TB, and potential interactions of AIDS medications with LTBI treatment regimens. Drug use (injecting, non-injecting) and excess alcohol use: Non-adherence to the prescribed regimen of anti TB medications is one of the major reasons for acquiring drug-resistant TB and persons who use illicit drugs are most note-worthy for non-compliance to prescribed treatments. CDC will also study whether TB patients that abuse alcohol and/or illicit drugs have comparable or different rates of SAEs due to LTBI treatments.

Race/ethnicity – TB incidence rates among minority race groups is very high. By knowing the trends in SAEs by race/ ethnicity, CDC could develop further activities among the stakeholders that serve specific race/ ethnic groups to communicate health information messages as we craft these.

12. Estimates of Annualized Burden Hours and Costs

Since 2008, reporting areas (50 states, the District of Columbia, New York City, Puerto Rico, and 7 jurisdictions in the Pacific and Caribbean) reported 25 SAEs associated with treatment of LTBI to the CDC, an average of 10 cases per year. We anticipate that a single physician, one nurse, and one medical clerk will be involved in collating the information needed by CDC. Each of the three types of respondents (physicians, nurses, and medical clerks) provide uniquely different information in a single NSSAE case form.

The burden for the respondents is less than the previously approved ICR because the data collection form has been shortened. However, because we now estimate 10 cases per year instead of the 3 cases we had previously, the burden hours have increased. The physicians provide medical information from the admission such as treatment, laboratory or pathology findings in the appropriate section of the NSSAE form. Each physician needs one hour for each response/case whereas previously, the physician needed 3

hours for each case. Each nurse spends four hours per case as previously approved, completing the demographic, social, and medical history of the patient in the appropriate sections of the NSSAE form. The medical clerks spend approximately one hour as previously approved to abstract the patient information from the hospital's medical records and complete the NSSAE form.

The total burden for all 3 types of respondents to be 6 hours per response (i.e. per case). The total burden for all 3 health professionals, for 10 cases per year, is estimated to be 60 hours (10 x 6 hours).

12A. Estimated Annualized Burden

Type of Respondent	Form name	No. of Respondents	No. Reponses Per Respondent	Average Burden per Response (in hours)	Total Burden Hours
Physician	NSSAE	10	1	1	10
Nurses	NSSAE	10	1	4	40
Medical Clerk	NSSAE	10	1	1	10
Total					60

[+]NSSAE=National Surveillance for Severe Adverse Events Associated with Treatment for Latent TB Infection

B. Estimate of annualized cost to respondents

The cost per person-hour is based on the mean hourly wage of medical clerk, nurse, and physician from the U.S. Department of Labor at http://www.bls.gov/oes/current/oes_nat.htm#29-0000, accessed on February 24, 2011. Reporting areas receive annual federal funds for TB control and surveillance through CDC cooperative agreements. In hospitals where the local or state health departments have contracts, there is no cost to the respondents for providing the information. Private hospitals may choose to negotiate with the health department for payment which cannot be anticipated at this time.

12B Estimated Annualized Burden Costs

Type of Respondent	Form name	Total Burden Hours	Hourly Wage Rate*	Total Respondent Costs Responses Per Respondent
Physicians	NSSAE[+]	10	$83.59	$835.90
Nurses	NSSAE	40	$31.99	$1279.60
Medical Clerk	NSSAE	10	$16.29	$ 162.90
Total**				$2278.40

[+]NSSAE=National Surveillance for Severe Adverse Events Associated with Treatment for Latent TB Infection

13. Estimates of Other Total Annual Cost Burden to Respondents or Record Keepers

There are no capital or maintenance costs to the respondent resulting from the collection of the information.

14. Annualized Cost to the Government

This project is under the Surveillance Team, DTBE that maintains NTSS which collects notifiable disease reports including TB, from 60 reporting areas in the United States and U.S. jurisdictions. The estimated annualized cost to the federal government for this project is partially derived from the NTSS.

Table A.14: Estimates of Annualized Costs to the Federal Government

Expense Type	Expense Explanation	Annual Costs (dollars)
Direct Costs to the Federal Government	CDC Project Officer (GS-14, .10 FTE) CDC Medical Officer(GS-15, .05 FTE) CDC Supervisory Epidemiologist (GS-14, .025 FTE) CDC Medical Officer (GS-15, .013 FTE)	$ 10,600 $ 5,300 $ 2,300 $ 3,000
	Cooperative agreement for investigations of severe adverse reactions to LTBI treatments	$ 2,278*
Travel	Anticipate 10 round-trip travels within US or its territories for two staff.	$ 16,000
Total		$39, 478

*Cost to the respondents (physicians, nurses, medical clerks) included in A.12B

15. Explanation for Program Changes or Adjustments

The project officers have conducted onsite investigation of SAEs for the past 3 years and now have a better understanding of the data needed to accurately capture important elements describing factors that led to these events. As a result, the NSSAE data collection form has been shortened into four pages instead of the original 6 pages. Variables such as results of liver biopsy and hepatitis serology were removed because these were usually unreliable because of incomplete reporting or misreporting of information. The project officers also have received increased number of SAE reports from 3 to 10 reports per year. The annual reporting burden increased from 24 hours to 60 hours. The reporting time for physicians has decreased from 4 hours as previously approved to one hour per case because the variables needing the physicians' attention has been deleted from the form.

16. Plans for Tabulation and Publication and Project Time Schedule

A.16 – 1 Project Time Schedule

Activity	Time Schedule
Notification of respondents	1-2 months after OMB approval
Collect data on reported SAEs	3-30 months after OMB approval
Analysis	31-32 months after OMB

	approval
Dissemination of results	33-36 months after OMB approval

The NSSAE data are included in DTBE materials for training and education of health care providers, the general public, and the media. Analyses on trends and associations of SAEs to LTBI treatment was published in CDC's Morbidity and Mortality reports and hopefully will be published in peer-reviewed scientific journals.

17. Reason (s) Display of OMB Expiration Date is Inappropriate

Data collection forms will include OMB Expiration date.

18. Exceptions to Certification for Paperwork Reduction Act Submissions

No exceptions to certifications are being made.