"National Surveillance for Severe Adverse Events Among Persons on Treatment of Latent Tuberculosis Infection"

OMB No. 0920-0773
Expiration Date 01/31/2018

Reinstatement without Change

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Supporting Statement Part A

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8. Consent Form

- **Goal of the surveillance system:** To accomplish the goal of monitoring severe adverse events (SAEs) among persons on treatment of latent tuberculosis (TB) infection (LTBI) in the United States, the CDC Division of TB Elimination (DTBE) maintains the National Surveillance for Severe Adverse Events (NSSAE) system. This request is to reinstate without changes the currently approved NSSAE data collection instrument.
- **Intended use of the resulting data:** The collected data will be used to guide the revision of the LTBI treatment protocols, if needed, in order to prevent SAEs among persons on treatment of LTBI. CDC will use the information from all investigations to monitor trends in LTBI-related SAEs 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 accumulated data on LTBI treatment and SAEs to convene stakeholders and recommend revisions of current LTBI treatment regimens, if needed.
- **Methods to be used to collect:** NSSAE is a comprehensive infectious disease surveillance system. The intent is to conduct an actual enumeration of SAEs among persons on treatment of LTBI in the United States so no sampling methodology is necessary. The resulting dataset is analyzed using descriptive statistical methods.
- **The subpopulation to be studied:** NSSAE collects data on the population of persons diagnosed with LTBI in the United States who experience SAEs while on LTBI treatment.
- **How data will be analyzed:** Data are analyzed using descriptive methods (e.g., averages, ranges, measures of dispersion) for general reporting purposes.

A. Justification

1. Circumstances Making the Collection of Information Necessary

CDC is requesting a 3-year reinstatement of the previously OMB-approved standardized form for the National Surveillance for Severe Adverse Events Among Persons on Treatment for Latent Tuberculosis Infection (NSSAE) collection No. 0920-0773 (Expires 1/31/2018). Since OMB approval of the NSSAE collection form, the project officers have received 66 reports of SAEs. DTBE's medical officers have conducted a comprehensive onsite investigation of 47 of these 66 reports. The investigative medical officers have written and presented these reports to DTBE's senior medical officers and the reports were disseminated to the reporting jurisdiction after clearance from CDC. In addition, the project officers have presented these SAEs to national and international audiences at scientific conferences.

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 NTSS (OMB No.0920-0026, Exp. Date 12/31/2019). CDC currently conducts and maintains NTSS pursuant to the provisions of Section 301(a) of the Public Health Service Act [42 U.S.C. 241] and Section 306 of the Public Health 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)

2020 objective, CDC is working with partners to detect and treat 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.

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 (**Attachments 4, 5, & 6**).

CDC conducts on-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, which 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

Severe adverse events to LTBI 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-TB 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 United States.

The purpose of this information collection request is to determine the annual number and trends of SAEs among persons on treatment of LTBI and identify common characteristics of patients with SAEs during treatment of LTBI. Since 2004, the project officers have gathered this information when invited to conduct onsite investigations for 47 of the 66 reported SAEs. Collection of data on SAEs needs 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 among persons on 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.

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 among persons on treatment for LTBI with the previously OMB-approved data collection form. This project is increasingly more important with the increasing use of 12-weekly doses of INH-RPT as an alternative to INH for 6-9 months for LTBI treatment. This project continues to provide a

systematic way of monitoring SAEs to this relatively new LTBI treatment regimen.

The project officers also plan to ascertain missed reporting of SAEs through collaborations with other adverse events reporting systems at CDC and the Food and Drug Administration (FDA). A summary of SAE reports will also be developed and disseminated.

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 6 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 recent 3 years of experience collecting this data, we estimate that we will continue to receive 6 cases per year.

At CDC, we maintain all of the information collected in a Microsoft Excel database. 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 that the MEDWATCH system implemented by the 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.

The CDC's National Electronic Injury Surveillance System–Cooperative Adverse Drug Event Surveillance NEISS-CADES) project is being conducted to estimate and describe the national burden of adverse drug events that lead to emergency department visits. However, data from NEISS-CADES do not have the relevant information to attribute the event to LTBI treatment.

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 (Vol. 82, No. 161, Pages 39787-39788) on Tuesday, August 22, 2017 (**Attachment 2**). CDC received one public comment. The standard CDC response was sent thanking the commenter for their comment (**Attachment 2a**). CDC is guided by extramural TB specialists and CDC stakeholders in TB elimination. The NSSAE is supported by the National TB Controllers Association (NTCA). The recognition and reporting of SAEs is a voluntary effort by CDC, NTCA, Council of State and Territorial Epidemiologists, and state and local TB controllers.

9. Explanation of any Payment or Gift to Respondents

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

10. Protection of the Privacy and Confidentiality of Information Provided by Respondents

The CDC Privacy Review Officer has assessed this package for applicability of 5 U.S.C. § 552a, and has determined that the Privacy Act does not apply to the information collection. This project will not collect name, social security number, or date of birth, but name and address information is retained by the reporting area, and the local project officer assigns a unique identification number to each case. This identification number is used to facilitate communication between CDC and a reporting area when needed. Sensitive information such as HIV status and drug use is collected. The unique identifier variable will enable serious adverse event (SAE) data to be linked back to LTBI patient identities, therefore PII in a system of records stored by CDC can be retrieved by an identifier assigned to an individual.

Sensitive information will be collected on individuals as questions about HIV status and drug use as described in section 11 are typically considered sensitive information.
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 on individuals and no personal contact information, electronic or otherwise will be asked of individuals. The proposed data collection will have little or no effect on the individual respondent's privacy. The system is undergoing Privacy Impact Assessment, and upon completion the PIA will be uploaded through the Change Request mechanism.

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 according to the CDC Record Control Schedule. Access to the cabinet is limited to the project officers.

The Microsoft Excel database is 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 according to the CDC Record Control Schedule.

This data collection has been determined by the Associate Director for Science, National Center for HIV, STD, and TB Prevention, CDC to be post-marketing surveillance and as such is not human subjects research (**Attachment 7**).

11. Institution Review Board (IRB) and Justification for Sensitive Questions

IRB Approval

IRB approval is not required.

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 TB disease 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 HIV medications with LTBI treatment regimens.
- Drug use (injecting, non-injecting) and excess alcohol use: Nonadherence 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 noteworthy for nonadherence with prescribed treatments. CDC will also evaluate whether TB patients that abuse alcohol or illicit drugs have comparable or different rates of SAEs due to LTBI treatments.
- Race/ethnicity – TB incidence rates among minorities are relatively high. By knowing the trends in SAEs by race/ethnicity, CDC could develop further activities along with stakeholders that serve specific racial/ethnic groups to communicate health information messages.

12. Estimates of Annualized Burden Hours and Costs

Since 2004, reporting areas (50 states, the District of Columbia, New York City, Puerto Rico, and 7 jurisdictions in the Pacific and Caribbean) reported 66 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) provides uniquely different information in a single NSSAE case form.

The burden for the respondents and the total burden hours is the same as the previously approved ICR. 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 1 hour for each case as previously approved. 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 clerk spends 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 health professionals, for 10 cases per year, is estimated to be 60 burden hours.

12.A Estimated Annualized Burden

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

B. Estimate of annualized cost to respondents

CDC's cooperative agreement for TB elimination program to state and local health departments provides salaries of data collection staff at the health departments. We used the median hourly rate for the medical clerk, nurse, and physician from the May 2016 National Occupational Employment and Wage Estimate, U.S. Department of Labor to estimate cost to the responding healthcare providers (http://www.bls.gov/oes/current/oes_nat.htm).

12.B Estimated Annualized Burden Costs

Type of Respondent	Form name	Total Burden Hours	Hourly Wage Rate*	Total Respondent Costs Responses Per Respondent
Physicians	NSSAE	10	$113.18	$1,131.80
Nurses	NSSAE	40	$34.70	$1,388.00
Medical Clerk	NSSAE	10	$18.16	$181.60
Total**				$2,701.40

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 TB disease reports 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. Costs were derived from the 2017 General Schedule (GS) Locality Pay Table: Salary & Wages Table to estimate cost to the respondent https://www.opm.gov/policy-data-oversight//pay-leave/salaries-wages/salary-tables/pdf/2017/ATL.pdf.

14.A 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)	$12,056.50 $ 7,090.90 $ 2,260.60 $ 1,843.63
Travel	Anticipate up to 6 round-trip travels within US or its territories for two staff.	$ 9,600.00
Total		$32,851.63

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

15. Explanation for Program Changes or Adjustments

There are no program changes or adjustments.

16. Plans for Tabulation and Publication and Project Time Schedule

16.A Project Time Schedule: Project is ongoing and will continue from 01/2018 thru 01/2021.

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 Weekly Report and will also be submitted to 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.