SUPPORTING STATEMENT A FOR:

THE DRUG ACCOUNTABILITY RECORD

(FORM NIH 2564) (NCI)

Extension of #0925-0240, Expiry 2/28/2011
(changes from previous submission are shown in yellow)

SUBMITTED BY:
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A. JUSTIFICATION

A.1 Circumstances Making the Collection of Information Necessary.

The National Cancer Institute (NCI) fosters drug development to benefit cancer patients and as an Investigational New Drug (IND) sponsor makes investigational drugs available to patients through investigators registered with the sponsor and, in turn, registered with the U.S. Food and Drug Administration (FDA). The FDA has numerous requirements for IND's specified in Title 21 Code of Federal Regulations (Food and Drugs), Part 312. FDA regulations require investigators to:

- "…maintain adequate records of the disposition of the drug, including dates, quantity and use by subjects…" (312.62);

- "……. upon request from any properly authorized officer or employee of FDA, at reasonable times, permit such officer or employee to have access to, and copy and verify any records or reports made by the investigator pursuant to 312.62. The investigator is not required to divulge subject names unless the records of particular individuals require a more detailed study of the cases, or unless there is reason to believe that the records do not represent actual case studies, or do not represent actual results obtained." (312.68)

- "…furnish all reports to the sponsor of the drug who is responsible for collecting and evaluating the results obtained [in the investigation.]" (312.64).

Similarly, 21 Code of Federal Regulations includes requirements for sponsors to:

- "…maintain adequate records showing the receipt, shipment or other disposition of the investigational drug [to investigators]" (312.57);

- "…submit the records or reports (or copies of them) to the FDA [for inspection] (312.58);

- "…discontinue shipments of the investigational new drug to the investigator and end the investigator's participation in the investigation [if this] investigator is not complying with the signed agreement (Form FDA-1572), the general investigational plan, or the requirements of this part or other applicable parts…" (312.56); and

- "…make such reports to FDA regarding information relevant to the safety of the drugs..." (312.56).

The information collection implemented through these forms is authorized under sections 413(b)(1) of the Public Health Service Act (42 USC 285a-2). The NCI, as an IND sponsor, “shall establish or support the large-scale production or distribution of specialized biological materials and other therapeutic substances for cancer research and set standards of safety and care for persons using such materials.” To support this, the NCI has developed the "Drug Accountability Record" form (DARF) **(Attachment 1)** to help investigators using NCI sponsored drugs under NCI protocols to meet FDA requirements. For the NCI, the DARF serves as the missing link between NCI's record of drug distribution to an investigator and NCI's review of the clinical data on research patients; it ensures that investigational drugs are not diverted for inappropriate protocol or patient use. This request is for an extension of OMB #0925-0240 that expires on 2/28/2011.

A.2 Purpose and Use of the Information

In September 1982, each participant received the proposed Drug Accountability Record form and instructions and was asked to apply it to the dispensing of investigational anticancer drugs in their practice setting. In November 1982, each participant submitted his or her records to NCI. A meeting was then arranged at NIH to discuss their experiences. All participants felt that the procedure could be implemented without undue burden. The committee decided that recording of patient's "informed consent" each time a drug was dispensed would be difficult. Since obtaining Informed Consents from patients is a legal requirement for all clinical investigation, it was decided that the recording of the date of each patient's consent was unnecessary and deleted from the original form.

The DARF is used by the NCI in the management of approximately 160 NCI sponsored INDs. Pharmacists, nurses and investigators or their designee at medical institutions use the information entered onto the DARF to keep track of the dispensing of investigational anticancer drugs to patients. NCI uses the data from the DARF to ensure compliance with NCI's responsibilities as an IND sponsor. The requested information is retained exclusively at the institution and

examined on a triennial basis or as needed more frequently if investigational medication can not be accounted for. It is not collected or sent to the NCI or anywhere else. NCI Management request copies of the DARF at any time for audit and review and DARFs are reviewed at least once every 3 years during site audits.

The information contained in the DARF is compared to Pharmaceutical Management Branch-Drug Authorization Review and Tracking System (PMB-DARTS) Module histories for each investigator and clinical site to ensure no diversion of investigational drug supplies to inappropriate protocol or patient use. The accountability information is also compared to patient flow sheets (protocol reporting forms) during site visits conducted for each institution. All comparisons are completed with the intention of ensuring protocol integrity, patient safety, and compliance with FDA regulations. Record keeping of drug accountability information in a standard format is required to allow an investigator to receive, and continue to receive NCI-sponsored drugs. This information is reviewed at the time of site visit audits, which currently occur at least once every 3 years. The IND sponsor may also request copies of the DARF at any time. This requirement is an essential part of investigational agent accountability process and motivates the investigator to maintain accurate, appropriate records. The record keeping retention period is specified by FDA regulation, and the NCI does not deviate from that requirement. As noted above, the FDA requires IND sponsors to maintain adequate records on the shipment and disposition of drugs to investigators.

During the past 20+ years, the Drug Accountability Record form has been in continuous use; there have been no significant problems expressed concerning the use of the form and site visit audit team leaders have not made any suggested changes in the form or procedures.[1] More recently since the last OMB submission was approved in 2008, there are been no changes to the form or the way it is distributed for use.

A.3 Use of Improved Information Technology and Burden Reduction

[1] This section was originally in Supporting Statement A, Section A.8 in the 2008 submission.

At this time, use of improved and additional information technology has not been considered. The system continues to make the electronic version of the form available on the CTEP web site. Sites download and print the form as it is needed.

A.4 Efforts to Identify Duplication and Use of Similar Information

When the NCI proposed development of the DARF in 1982, seven investigators who received investigational anticancer drugs from NCI were asked to form a task force to pilot the proposed drug accountability procedure **(Attachment 2)**. The task force, at that time, was unable to identify any duplication of efforts regarding the Drug Accountability Record.

A.5 Impact on Small Business or Other Small Entities

Data collection for drug accountability mostly involves hospitals, universities and cancer centers, which are not small businesses. In some instances it involves physicians in private practice who receive investigational drugs. Private practice physicians do not receive vast amounts of drugs, and therefore the burden of data collection is minimal.

A.6 Consequences of Collecting the Information Less Frequently

Drug accountability data record keeping is timely; it changes and must be recorded every time a drug is received, administered, dispensed, or returned. The IND sponsor reviews the drug accountability data at triennial site visits. Between site visits, the institution should validate the data to maintain the quality of the drug accountability data. If drug accountability information were reviewed less often than once every 3 years, its accuracy and usefulness during site visits would be questionable. Since accountability data is cumulative by protocol, any error made would be compounded. Compounded errors are more difficult to detect and correct, thus limiting the effectiveness of the drug accountability procedure as an auditing tool.

A.7 Special Circumstances Relating to the Guidelines of 5 CFR 1320.5

It is estimated that the investigator or their designee would make 16 entries on this form annually, based upon the number of patients participating in the investigational study.[1]

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

The 60-Day Federal Register Notice of the proposed data collection was published on August 4, 2010 (75 FR 46945). No public comments were received on the proposed information collection**.**

When the NCI proposed development of the DARF in 1982, seven investigators who received investigational anticancer drugs from NCI were asked to form a task force to pilot the proposed drug accountability procedure **(Attachment 2)**. These investigators were selected from hospitals, universities, adult and pediatric cancer centers, clinical cooperative study groups and private practice settings. They were chosen because they accurately represented the community of investigators receiving investigational drugs from the NCI. These investigators recruited the support of pharmacists and nurses who were familiar with the availability of the data, the frequency of collection and the clarity of instructions and record keeping.

Although the work of this task force was done many years ago, it is still representative of the current drug accountability procedure. No additional consultations have occurred.

A.9 Explanation of Any Payment or Gift to Respondents

Respondents will not receive any payment or gift for answering the questions.

A.10 Assurance of Confidentiality Provided to Respondents

[1] This is not a change from the previous submission, only a correction in this section of the justification. In the 2008 submission, the frequency of response was reported as 16 in the SSA, Section A.12, Table A.12-1.

Investigators or their designees are the record keepers of drug accountability information. The information is made available to the IND sponsor and to FDA upon request to verify the legal use of investigational drugs. Investigators are made aware of their legal requirements when they complete a FDA-1572 form and the Investigator Supplemental Data form by which they become eligible to use investigational new drugs (OMB # 0925-0613, Expiry Date 2/28/2013). The investigators or their designees retain the forms for a period of 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated and closure of the NCI IND. However, if no application is to be filed or if the application is not approved for such indications, the records must be retained until 2 years after the NCI IND closure and FDA is notified.

Individual patient names are not required on accountability forms. Only patient initials and institutional assigned patient specific code numbers are requested to allow comparisons with patient protocol flow sheets (in compliance with HIPPA rules). Without this reference, drug accountability would be impossible.

The Office of Human Subjects Protection (OHSR) does not need to review this submission since this is an administrative collection of information in which generalization of findings is not conducted, and thus it does not meet the definition of "research" under regulations 45 CFR 46.

The NIH Privacy Act Officer has reviewed this submission and has determined that the Privacy Act would apply to this data collection. Although individual patient names are not required on the form, it can be compared with patient protocol flow sheets, which if linked, could identify the patient. Without this reference, drug accountability would be impossible. This data collection is covered by NIH Privacy Act Systems of Record, 09-25-0200, "Clinical, Basic and Population-based Research Studies of the National Institutes of Health (NIH) HHS/NIH/OD," published in the Federal Register on 9/26/2002 (67 FR 60776) **(Attachment 3).**

A. 11 Justification for Sensitive Questions

No sensitive questions are involved. However, personally identifiable information (PII) is collected in the form of patient's initial, patient ID, NCI protocol number and title, NCI investigator number and information pertaining to the drug and its dose form and strength. As mentioned in A.10, alone this information may not be PII, however when linked it could identify a patient.

A. 12 Estimates of Annualized Burden Hours and Costs

The annualized respondent's burden for record keeping is estimated to require 6,714 hours for the DARF or approximately 20,142 hours for the three year approval period. An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

A.12-1 Estimates of Annual Burden Hours

Type of Respondents	Number of Respondents	Frequency of Response	Average Time per Response	Annual Burden Hours
Investigators, or Designees	4,196	16	6/60 (0.1)	6,714

The annualized cost burden to the respondents is estimated at $167,850 or approximately $503,550 for the three year approval period. The record-keeping burden represents an average time required for entries (6 minutes) on the DARF, the average number of forms maintained by each record keeper and the number of record keepers. These estimates are based on the number of investigators supported by PMB. Cost estimates are based upon burden hours at an average cost of $25.00 per hour.

A.12-2 Annualized Cost to Respondents

Type of Respondents	Number of Respondents	Frequency of Response	Hourly Wage Rate	Respondent Cost
Investigators, or Designees	4,196	6,714	$25.00	$167,850.00

A. 13 Estimates of Other Total Annual Cost Burden To Respondents and Record Keepers

There is no additional cost burden to the respondents or record keepers.

A. 14 Annualized Cost to the Federal Government

The total estimated cost to the Federal government is approximately $17,500. The annualized cost to audit the contents of the DARF at the institution is estimated to be approximately $17,500. This is based on one auditor spending 30 minutes (0.5 hours) reviewing the contents of the DARF files. Typically the auditors spend three (3) days auditing patient records of which one auditor spends 30 minutes auditing the DARF records.

There is no additional cost for printing or distribution of the DARF since the form is available exclusively in electronic format and posted on the CTEP web site. Forms are downloaded at the institutional level and printed locally as needed.

A. 15 Explanation for Program Changes or Adjustments

This is a request is for an extension; a program change due to adjustment. The increase in burden from the previous request is a reflection of an increase in actively accruing investigational studies and a greater number of patients participating in those studies.

A. 16 Plans for Tabulation and Publication and Project Time Schedule

There are no plans to publish this data for statistical use.

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

The date will appear on the DARF.

A.18 Exception to Certification of Paperwork Reduction Act Submissions

No exceptions to the certification statement are required by this information collection.