Supporting Statement A for

Investigational Agent Accountability Record Forms
in the Conduct of Investigational Trials for the Treatment of Cancer
(National Cancer Institute/DCTD/CTEP)

(Previous Title: Investigator Registration and
Financial Disclosure for Investigational Trials in Cancer Treatment)*

OMB No. 0925-0613
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Yellow text identifies changes.

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Check off which applies:

- New
- **X Revision**
- Reinstatement with Change
- Reinstatement without Change
- Extension
- Emergency
- Existing

*Note: A revision to the Title of this ICR has occurred because Investigator Registration is no longer part of this submission. In addition, the title of the forms have changed.

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Attachments

A. Justification

This information collection is a revision for a three-year period. The U.S. Food and Drug Administration (FDA) holds the National Cancer Institute (NCI), Division of Cancer Treatment and Diagnosis/Cancer Therapy Evaluation Program (NCI/DCTD/CTEP) and the Division of Cancer Prevention (DCP) responsible, as a sponsor of investigational drug trials, to assure the FDA that systems for accountability are being maintained by investigators in its clinical trials program. Data obtained from the Investigational Agent Accountability Record Forms are used to track the dispensing of investigational anticancer agents from receipt from the NCI to dispensing or administration to patients. Requirements for the tracking of investigational agents under an Investigational New Drug Application are outlined in Title 21 Code of Federal Regulations (CRF) part 312. NCI and/or its auditors use this information to ensure compliance with federal regulations and NCI policies. Previously, the investigator registration forms and process were part of this submission. These forms were more appropriately submitted and approved under the CTEP Branch and Support Contracts Forms and Surveys in July 2018 (OMB No. 0925-0753; Expiration Date 7/31/2021). Thus, the investigator registration forms are no longer included in this request.

A.1 Circumstances Making the Collection of Information Necessary

The National Cancer Institute, Division of Cancer Treatment and Diagnosis/Cancer Therapy Evaluation Program (NCI/DCTD/CTEP) and the Division of Cancer Prevention (DCP) request OMB approval under the Paperwork Reduction Act (44 U.S.C. 3501 et seq.) for the reporting and record keeping requirements contained in the Food and Drug Administration (FDA) regulation 21 CRF Part 312 specifically as it pertains to NCI/DCTD/CTEP and DCP sponsored clinical trials and the requirements for Investigational New Drug (IND)'s sponsors. The NCI/DCTD/CTEP fosters drug development to benefit cancer patients and as an IND sponsor is required to assure the FDA that accountability is maintained by participating investigators in its clinical trials program.

The FDA requires that investigators and sponsors account for all investigational agents used in these studies. The Investigational Agent Accountability Record Forms[1] are the instrument by which the NCI and NCI registered investigators track the receipt, administration, and disposition of these experimental agents.

The FDA regulations require investigators to:

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

[1] The Investigational Agent Accountability Record forms were formerly titled, Drug Accountability Record Form (DARF) and Drug Accountability Record Form-Oral (DARF-Oral) in prior PRA OMB submissions.

- "…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 collected with these forms is authorized under sections 413(b)(1) of the Public Health Service Act (42 USC 285a-2). NCI/DCTD/CTEP, 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."

A.2 Purpose and Use of the Information Collection

The investigator registration process underwent a technology change from paper to electronic information collection. The use of the electronic investigator registration forms were approved under the CTEP Branch and Support Contracts Forms and Surveys (OMB No. 0925-0753; Expiration Date 7/31/2021) in July 2018 and are not referenced in this submission.

However, the FDA continues to require IND sponsors to maintain adequate records on the shipment and disposition of drugs to investigators. The drug accountability effort for NCI/DCTD/CTEP is managed by the Pharmaceutical Management Branch (PMB) at CTEP. The Investigational Agent Accountability Record (a.k.a. Drug Accountability Report Form-DARF) and DARF-Oral forms are the tools used to provide a standardized method of tracking of agent disposition across all institutions participating in trials for which the PMB provides agent. Institutional auditors verify information on the drug accountability forms for compliance. In addition, PMB staff review Investigational Agent Accountability Record Forms against records maintained in PMB systems to ensure there is no inappropriate use or diversion of investigational agents. A brief description of each form and its purpose follows.

The **Investigational Agent Accountability Record Form** (a.k.a. DARF) (Attachment 1) helps investigators using NCI sponsored agents meet FDA requirements. For the NCI, the DARF serves as the link between NCI's record of drug distribution to an investigator, and NCI's review of the clinical data on research patients.

The **Investigational Agent Accountability Record for Oral Agents Form** (a.k.a. DARF-Oral), (Attachment 2) was developed in 2012 to meet the regulatory requirements for medications dispensed to patients, the DARF-Oral form collects information documenting the disposition of the investigational agent including return of unused oral agents to the treating institution. Development of this form is in response to change in the practice wherein the medication that was developed in the past was produced almost exclusively for intravenous administration, as more investigational agents have been developed for oral administration for the convenience of patients, mechanisms to ensure tracking of patient returned supply are needed.

The Investigational Agent Accountability Record Forms are used by NCI/DCTD/CTEP in the management of approximately 168 NCI/DCTD/CTEP sponsored INDs. Pharmacists, nurses and investigators or their designee at medical institutions use the information entered onto the DARF or DARF-Oral to keep track of the dispensing of investigational anticancer agents to patients. NCI/DCTD/CTEP uses the data from the DARF or DARF-Oral to ensure compliance with our responsibilities as an IND sponsor. The requested information is retained exclusively at the institution and examined on a triennial basis or more frequently if needed. NCI/DCTD/CTEP Management can request copies of the DARF or DARF-Oral at any time for audit.

The information contained in the Investigational Agent Accountability Record Forms is compared to already existing information in the PMB's Drug Authorization Review and Tracking System (PMB-DARTS)[2]. The system contains module histories for each investigator and clinical site to ensure there is no diversion of investigational drug supplies to inappropriate protocol or to

[2] PMB-DARTS is part of the CTEP Enterprise computer database discussed further in Section A.3.

patients treated outside of the clinical trial. 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 three 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/DCTD/CTEP 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.

A.3 Use of Information Technology and Burden Reduction

At this time, the forms are available on the CTEP website in PDF format. The forms are partially fillable using standard PDF write software or can be printed and maintained by hand. The forms are retained at the clinical sites and are not routinely submitted back to PMB, but reviewed at routine audit (at least once every 3 years), or on demand.

As noted in A.2, PMB manages investigational agent inventory and shipments using the PMB-DARTS system. The release of online Investigational Agent Accountability Record Forms is tentatively scheduled for the fall of 2019 with the implementation of AURORA, a system for tracking of investigational agent inventory and disposition of unused investigational agent.

A Privacy Impact Assessment (PIA) has been completed and was signed by HHS on January 23, 2018 (Attachment 3). The name of the PIA is "Cancer Therapy Evaluation System."

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

When NCI/DCTD/CTEP 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. 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. The task force, at that time, was unable to identify any duplication of efforts regarding the Investigational Agent Accountability Record Forms.

In May, 2012, the PMB staff identified the need to further document the return of oral medication. The PMB Staff worked with pharmacists at the institutional level who are responsible for accounting for medication disposition and those who monitor and audit the conduct of trials. This collaboration resulted in the identification of the essential elements for the form DARF-Oral. This form is similar to that developed and implemented by the National Cancer Institute of Canada (NCIC) in collaboration with the NCI/DCTD/CTEP in the United States in 2010.

A.5 Impact on Small Businesses or Other Small Entities

There are no small businesses or other small entities involved.

A.6 Consequences of Collecting the Information Less Frequently

Investigational agent accountability data 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 three 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

To meet federal regulations, institutions and investigators participating on clinical trials are required to maintain ongoing documentation of agent receipt and distribution. This information is maintained at the institution and reviewed upon audit.

Per 21 CRF 312.2, record retention requirements are 2 years following the date of the marketing application, or if no application is filed or approved, 2 years after the investigation is discontinued and the FDA is notified. Additional requirements for record retention include retention of records for 3 years after completion of grant activities, and 6 years under HIPAA regulations for covered entities.

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

The 60-Day Federal Register Notice of the proposed data collection was published on October 25, 2018 (83 FR 53885). One public comment was received requesting information about the changes to the proposed request. The submitter responded to this request with information.

No additional outside agencies were consulted.

A.9 Explanation of Any Payment of Gift to Respondents

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

A.10 Assurance of Confidentiality Provided to Respondents

All information will be kept private to the extent permitted by law. The investigators or their designees are the record keepers of drug accountability information. The information submitted to NCI is made available to the IND sponsor and to FDA upon request to meet regulatory requirements in 21 CFR Part 312.64(d) (for Investigator Registration) and to verify the legal use of investigational drugs (for DARFs). Investigators are made aware of their legal requirements when they complete a FDA-1572 form and register with CTEP in the Registration and Credential Repository (RCR) by which they become eligible to use investigational new drugs.

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.

Individual patient names are not required on the agent accountability forms, only patient initials or institutional assigned patient specific code numbers to allow comparisons with patient protocol flow sheets (in compliance with HIPPA rules). It is possible this information could identify the patient if linked to other patient information, but without this reference, drug accountability would be impossible.

The NIH Privacy Act Officer has reviewed this submission and has determined that the Privacy Act would apply to this data collection (Attachment 4). The data collection for the agent accountability forms 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).

A.11 Justification for Sensitive Questions

No sensitive questions are involved for the collection. Information 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 Hour Burden Including Annualized Hourly Costs

Investigational agent accountability facilitated via the use of the DARF and DARF-Oral is estimated to have 2,844 respondents, that take an average of 4 minutes per response, an average of 16 times per year. The respondents make an entry on the record any time a patient receives a treatment. The number of responses per respondent of 16 is derived from experience and discussion with the investigators, nurses and pharmacists. Some agents are administered daily for

a period, or may be administered weekly, or monthly. It depends on the patient, the disease state and the pharmacologic properties of the agent that is being tested. Every time a dose is administered, it must be accounted for and that entry must be made on the record at that time.

This totals an annual burden of 3,033 hours. A three-year burden is estimated to be 9,099 hours.

Table A.12-1 Estimated Annualized Burden Hours

Category of Respondent	Number of Respondents	Number of Responses per Respondent	Average Time per Response (in hours)	Total Annual Burden Hours
Individuals (DARF)	2,133	16	4/60	2,275
Individuals (DARF-Oral)	711	16	4/60	758
Total	2,844	45,504		3,033

The annualized cost burden to the respondents is estimated at $80,556.48 (see Table A.12-2). The total cost is estimated at $241,669.44 over the course of the three-year information collection. These estimates are based on the number of investigators supported by PMB.

Table A.12-2 Annualized Cost to the Respondents

Category of Respondents	Total Annual Burden Hours	Hourly Wage Rate*	Total Annual Costs
Individuals	3,033	$26.56	$80,556.48
Total	3,033		$80,556.48

*Hourly Wage Rates are obtained from the Bureau of Labor Statistics (https://www.bls.gov/oes/current/oes_nat.htm. The Wage Rate was calculated using a combined wage estimate of Pharmacist (Occupation Code 29- 1051) making 25% of the entries and Pharmacy Technicians (Occupation Code 29-2051) making 75% of the entries. Pharmists wage rate is $58.52/hour and Pharmacy Technicians wage rate is $15.90/hour, which amounts to a combined wage of $26.56.

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

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

A.14 Annualized Cost to the Federal Government

The average annualized cost to the Federal Government is estimated to be $23,524. The contract is overseen by a GS 14 Step 10 employee and requires 2.5% of an FTE at a cost of $3,724 annually. The contractor cost is based on one auditor spending one hour reviewing the contents of the DARF files. Typically the auditors spend two (2) days auditing patient records of which one auditor spends one (1) hour (1/16) auditing the DARF records. The three-year total for government cost is $59,400.

Table 14-1 Annualized Federal Staff/Contractor Costs

Staff	Grade/Step	Salary**	% of Effort	Fringe (if applicable)	Total Cost to Gov't
Federal Oversight					
Senior Clinical Research, Pharmacist,	14/10	$148,967	2.5%		$3,724.18
Contractor Cost					$19,800.00
Travel Cost					$0
Other Costs					$0
Total					$23,524.18

**https://www.opm.gov/policy-data-oversight/pay-leave/salaries-wages/salary-tables/18Tables/html/DCB.aspx

A.15 Explanation for Program Changes or Adjustments

The investigator registration process underwent a technology change from paper data collection to electronic data collection. The use of the electronic forms for investigator registration information collection were approved under the CTEP Branch and Support Contracts Forms and Surveys submission (OMB No. 0925-0753) with an expiration date of 7/31/2021. Therefore, removing the investigator registration forms from this submission has decreased the total burden by 11,142 hours.

In addition, this submission requests a reduction of 474 fewer burden hours than the 2016 submission because there is a year to year variation in the number of active studies (and subsequently the number of patients enrolled in those studies).

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

There are no plans to publish this data.

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

The date will appear on all forms and information.

A.18 Exceptions to Certification for Paperwork Reduction Act Submissions:

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