SUPPORTING STATEMENT A for

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

OMB No. 0925-0613

Expiration Date: 3/31/2022

This is a Revision of a currently approved submission. Changes are highlighted in yellow.

November 17, 2021

Check off which applies:

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

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Attachments

A. Justification

This is a request for Office of Management and Budget (OMB) to approve a revision of the, "Investigational Agent Accountability Record Forms and International Investigator Statement in the Conduct of Investigational Trials for the Treatment of Cancer" for an additional 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 agent 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. Two additional forms have been added to this submission. The Electronic Agent Accountability Record Form Report (aka electronic Drug Accountability Record Form-eDARF) will be phased into use to replace two of the currently existing forms, and will improve tracking and distribution of investigational agents. A second form, the International Investigator Statement (IIS), will ensure compliance of international investigators' participation on CTEP studies.

A.1 Circumstances Making the Collection of Information Necessary

The NCI/DCTD/CTEP and the 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 agent 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 FDA require IND sponsors to maintain adequate records on the shipment and disposition of agents to investigators. The agent accountability effort for NCI/DCTD/CTEP is managed by the Pharmaceutical Management Branch (PMB) at CTEP. The Investigational Agent Accountability Records (a.k.a. Drug Accountability Record) (Attachments 1 to 3) are used to provide a standardized method of tracking of agent disposition across all institutions participating in trials for which the NCI provides agent. Institutional auditors verify information on the agent 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. Additionally, the International Investigator Statement (IIS) (Attachment 4) will be used by non-U.S. investigators, that are unable to sign the FDA 1572 (OMB No. 0925-0753, Expiration 05/31/2024) to attest compliance with applicable country-specific regulations 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 agent distribution to an investigator, and NCI's review of the clinical data on research patients. This paper form will be retired once full implementation of the electronic accountability record form (Attachment 3) process is implemented.

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. This paper form will be retired once full implementation of the electronic accountability record form (Attachment 3) process is implemented.

The **Electronic Agent Accountability Record Form Report** (a.k.a. electronic Drug Accountability Record – eDARF) (Attachment 3) will improve the process for agent distribution and tracking. PMB will implement the electronic Drug Accountability Record Form (eDARF) in its inventory management system, AURORA[2], over the course of the next two years. AURORA will allow for online agent ordering and tracking, thereby improving overall compliance. The electronic tracking will eventually replace the paper DARFs.

The Investigational Agent Accountability Record Forms are used by NCI/DCTD/CTEP in the management of approximately 280 NCI/DCTD/CTEP sponsored INDs with ongoing agent shipment. 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 receipt, dispensing of investigational anticancer agents to patients and final disposition of agent supplies. NCI/DCTD/CTEP uses the data from the Investigational Agent Accountability Record Forms 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. AURORA will

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

allow NCI/DCTD/CTEP Management and auditors to access copies of the Investigational Agent Accountability Record (eDARF) Forms on an as needed basis.

The information contained in the Investigational Agent Accountability Record Forms is compared to agent distribution records existing in the PMB's inventory management system, AURORA, for clinical trial auditing purposes. The inventory management system contains histories for each investigator and clinical site to ensure there is no diversion of investigational agent supplies to inappropriate protocol or to 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 agent accountability information in a standard format is required to allow an investigator to receive, and continue to receive NCI-sponsored agents. This information is reviewed at the time of site visit audits, which currently occur at least once every three years. 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. As noted above, the FDA requires IND sponsors to maintain adequate records on the shipment and disposition of agents to investigators.

The **International Investigator Statement (IIS)** (Attachment 4) will supplement the sponsor investigator qualifications. With an increase in international participation on CTEP studies, a mechanism to ensure investigator compliance under International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) E6 regulations and Good Clinical Practice (GCP), was needed. Collection of ICH/GCP attestation as part of the IIS form for non-U.S. investigators is managed in the Registration and Credential Repository (RCR) dependent on the investigator's selection of a primary site. The signed attestation ensures that non-U.S. investigators agree to conduct research under applicable ICH/GCP guidance and country-specific regulations. The IIS will be used for non-United States (U.S.) investigators who are unable to sign the Form FDA 1572[3] due to applicable country-specific regulations. Many European Union and other non-U.S. participants are not able to sign the Form FDA 1572 per their countries' regulations.

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.

PMB manages investigational agent inventory and shipments using the PMB-AURORA system. With the release and full implementation of the new eDARF module in AURORA, the agent

[3] OMB No. 0925-0753, Expiration 05/31/2024; has been submitted for revision.

accountability information will be available online. The IIS form is also an online form and part of the RCR application. The use of online system helps to reduce the burden of maintaining hard copy forms.

A Privacy Impact Assessment (PIA) has been completed and was signed by HHS on August 8, 2019 (Attachment 5). 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 agents from NCI were asked to form a task force to pilot the proposed agent 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 agents 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.

The electronic version of the DARF (eDARF) consolidates the DARF and DARF-Oral into a single electronic document. The IIS form mirrors the Form FDA 1572 in terms of data collection fields, though instructions and the attestation were revised to meet ICH/GCP guidelines.

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 an agent is received, administered, dispensed, or returned. The IND sponsor reviews the agent accountability data at triennial site visits. Between site visits, the institution should validate the data to maintain the quality of the agent accountability data. If agent 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 agent accountability procedure as an auditing tool. The electronic version will reduced the likelihood of errors in record keeping.

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 two years following the date of the marketing application, or if no application is filed or approved, two years after the investigation is discontinued and the FDA is notified. Additional requirements for record retention include retention of records for three years after completion of grant activities, and six years under HIPAA regulations for covered entities.

A.8.1 Comments in Response to the Federal Register Notice

The 60-Day Federal Register Notice of the proposed data collection was published on September 14, 2021, Vol. 86, p. 51168. No public comments were received.

A.8.2 Efforts to Consult Outside Agency

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 agent accountability and the investigators are the record keepers of their registration 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) to document the selection of qualified investigators and to verify the legal use of investigational agent (for DARFs). Investigators are made aware of their legal requirements when they complete a Form FDA-1572/IIS form and register with CTEP in the RCR by which they become eligible to use investigational new agents.

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, agent accountability would be impossible. Information on the study site(s), ethics board responsible for study review and participating laboratories is collected on the IIS. The investigator will sign the IIS attesting to their responsibilities for conduct of CTEP-supported studies in accordance with ICH E6 Good Clinical Practice.

The NIH Privacy Act Officer has reviewed this submission and has determined that the Privacy Act would apply to this data collection (Attachment 6). 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 agent 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, DARF-Oral, and eDARF is estimated at 3800 respondents. It takes an average of 4 minutes per response using paper forms and 1 minute per response using electronic form, an average of 20 times per year in total (Table A.12-1). It is estimated 20% of responses will be recorded on the DARF, 20% on the eDARF, and 60% on the DARF-Oral. The respondents are required to make an entry on the record any time agent is added or removed from inventory. The number of responses per respondent is derived from experience and discussion with the investigators, nurses and pharmacists. Agent administration varies per agent and protocol (e.g., daily, weekly or monthly). It depends on the patient, the disease state, and the pharmacologic properties of the agent that is being tested per the protocol treatment regimen.

Additionally, there are approximately 2100 non-U.S. investigators registered and active in the RCR. The IIS must be completed annually to continue participation on CTEP-supported studies. It is anticipated that the initial completion of the IIS will take 15 minutes.

Table A.12-1 Estimated Annualized Burden Hours

Form Name	Category of Respondent	Number of Respondents	Number of Responses per Respondent	Average Time per Response (in hours)	Total Annual Burden Hours
A1: Investigational Agent Accountability Record Form (DARF)	Individuals	760	20	4/60	1,013

A2: Investigational Agent Accountability Record for Oral Agents Form (DARF-Oral)	Individuals	2,280	20	4/60	3,040
A3: Electronic Agent Accountability Record Form (eDARF)	Individuals	760	20	1/60	253
A4: International Investigator Statement (IIS)	Individuals	2,100	1	15/60	525
Totals		**5,900**	**78,100**		**4,831**

The annualized cost burden to the respondents is estimated at $171,057.05 (Table A.12-2). The total cost is estimated $513,171.15 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
A1: Investigational Agent Accountability Record Form	1,013	$27.80	$28,161.40
A2: Investigational Agent Accountability Record for Oral Agents Form	3,040	$27.80	$84,512.00
A3: Electronic Agent Accountability Record Form	253	$27.80	$7,033.40
A4: International Investigator Statement (initial response)	525	$97.81	$51,350.25
Totals	**4,831**		**$171,057.05**

*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 the mean hourly wage Pharmacist (Occupation Code 29- 1051) making 25% of the entries and Pharmacy Technicians (Occupation Code 29-2051) making 75% of the entries. Pharmacist wage rate is $60.34/hour and Pharmacy Technicians wage rate is $16.95/hour, which amounts to a combined wage of $27.80. The IIS is completed and signed by investigators with a mean hourly rate of $97.81 (Occupation Code 29-1228 (Physician general).

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 $23,782.15. Management of the contract is by a GS 14, Step 10 employee and requires 2.5% of a full-time

equivlent at a cost of $3,982.15 annually. The contractor cost is based on one auditor spending one hour reviewing the contents of the DARF files. Typically the auditors spend two days auditing patient records of which one auditor spends one hour (1/16) auditing the DARF records. The three-year total for government cost is $71,228.19.

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	$159,286	2.5%		$3,982.15
Contractor Cost					$19,800.00
Travel Cost					$0
Other Costs					$0
Total					**$23,782.15**

**https://www.opm.gov/policy-data-oversight/pay-leave/salaries-wages/salary-tables/pdf/2021/DCB.pdf

A.15 Explanation for Program Changes or Adjustments

This revision involves a request for an additional 778 burden hours from the 2019 submission due to the phasing in of two new forms, the eDARF and the IIS. The eDARF will be completed online using the AURORA inventory management system, and will ultimately replace the DARF and DARF-Oral. Full use of the eDARF will be implemented over the next 24-months and burden is based upon a total percentage of burden for maintaining agent records.

The IIS requirement is for non-U.S. investigators who can no longer sign the Form FDA 1572 as part of their RCR registration. The form is completed annually. The Form FDA 1572 and other forms that are part of the RCR registration process are covered under the CTEP Branch and Support Contracts Forms and Surveys (OMB No. 0925-0753, exp. 5/31/2024).

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.