

SUPPORTING STATEMENT A for

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

OMB No. 0925-0613

Expiration Date: 1/31/2025

This is a Revision of a submission that has been approved. Changes are highlighted in yellow.

September 3, 2024

Check off which applies:

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

Tali Johnson, PharmD, BCOP

Chief, Pharmaceutical Management Branch
Cancer Therapy Evaluation Program
Division of Cancer Diagnosis and Treatment
National Cancer Institute/NIH
9609 Medical Center Drive
Rockville, MD 20860
Phone: (240) 276-6575
Email: tmjohnson@mail.nih.gov

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Attachments

Attachment 1 Investigational Agent Accountability Record Form (a.k.a. Drug Accountability Record Form - DARF)

Attachment 2: Investigational Agent Accountability Record for Oral Agents Form
(a.k.a. Drug Accountability Record Form - Oral Version (DARF-Oral))

Attachment 3: Electronic Agent Accountability Record Form (eDARF)

Attachment 4: Privacy Impact Assessment (PIA)

Attachment 5: Privacy Act Memo

A. Justification

This is a request for the Office of Management and Budget (OMB) to approve a Revision of the “Investigational Agent Accountability Record Forms 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 investigators in its clinical trials program are maintaining systems for accountability. 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.

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 CFR 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 Forms¹ are the instruments 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);
- “...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

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.

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 requires 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**) provide a standardized method of tracking agent disposition across all institutions participating in trials for which the NCI provides agents. 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 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 its record of agent distribution to an investigator and its review of the clinical data on research patients. This paper form will be retired once the electronic accountability record form (Attachment 3) process is fully 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 the 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 is needed. This paper form will be retired once the electronic accountability record form (Attachment 3) process is fully implemented.

The **Electronic Agent Accountability Record Form Report** (a.k.a. electronic Drug Accountability Record - eDARF) (Attachment 3) improves the agent distribution and tracking process. PMB implemented the electronic Drug Accountability Record Form (eDARF) in its inventory management system, AURORA², as of June 2024, and will continue rolling out the form over the next 12 months. AURORA allows for online agent ordering and tracking, thereby improving overall compliance. Electronic tracking will eventually replace paper DARFs.

The Investigational Agent Accountability Record Forms are used by NCI/DCTD/CTEP to manage approximately 280 NCI/DCTD/CTEP-sponsored IND trials with ongoing agent shipment. Pharmacists, nurses, investigators, or their designee at medical institutions use the information entered into 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 can request copies of the DARF or DARF-Oral anytime for audit. AURORA allows NCI/DCTD/CTEP and auditors to access copies of the Investigational Agent Accountability Record (eDARF) Forms as needed.

The information in the Investigational Agent Accountability Record Forms is compared to agent distribution records 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 no diversion of investigational agent supplies to the inappropriate protocol or patients treated outside the clinical trial. The accountability information is also compared to

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

patient flow sheets (protocol reporting forms) during site visits conducted for each institution. All comparisons are completed to ensure 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 during site visit audits, which occur at least once every three years. This requirement is essential to the 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.

A.3 Use of Information Technology and Burden Reduction

Currently, the forms are available on the CTEP website in PDF format. They 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 are reviewed at routine audits (at least once every three years) or on demand.

PMB manages investigational agent inventory and shipments using the PMB-AURORA system. By the end of 2024, the new eDARF module in AURORA will be available online to all sites.

A Privacy Impact Assessment (PIA) was completed and signed by HHS on August 31, 2022 (Attachment 4). 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 the 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 familiar with the data's availability, the collection frequency, and the clarity of instructions and record keeping. At that time, the task force 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 oral medication return. 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 identifying 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.

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 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 use of the electronic version reduces 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 in 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 CFR 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 record retention requirements include retention 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 July 12, 2024, Vol. 89, p. 57157. 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 the 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 an FDA-1572/IIS form and register with CTEP in the RCR, which allows them to use investigational new agents.

The Office of Human Subjects Protection (OHSR) does not need to review this submission since it is an administrative collection of information in which generalization of findings is not conducted. 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 are required to allow comparisons with patient protocol flow sheets (in compliance with HIPPA rules). If linked to other patient information, this information could identify the patient, but agent accountability would be impossible without this reference.

The NIH Privacy Act Officer has reviewed this submission and has determined that the Privacy Act would apply to this data collection (Attachment 5). 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 in the collection. Information is collected in the form of the 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 5000 respondents. It takes an average of 4 minutes per response using paper forms and 1 minute per response using electronic forms, an average of 20 times per year in total (Table A.12-1). It is estimated that 20% of responses will be recorded on the DARF, 50% on the eDARF, and 30% on the DARF-Oral. The respondents are required to make an entry on the record any time an 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.

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	1000	20	4/60	1333
A2: Investigational Agent Accountability Record for Oral Agents Form (DARF-Oral)	Individuals	1500	20	4/60	2000
A3: Electronic Agent Accountability Record Form (eDARF)	Individuals	2500	20	1/60	833
Totals		5,000	100,000		4,166

The annualized cost burden to the respondents is estimated at \$132,562.12 (Table A.12-2). The total cost is \$397,686.36 over the three-year information collection period. 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	1333	\$31.82	\$42,416
A2: Investigational Agent Accountability Record for Oral Agents Form	2000	\$31.82	\$63,640
A3: Electronic Agent Accountability Record Form	833	\$31.82	\$26,506
Totals	4166		\$132,562.12

*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: Pharmacists (Occupation Code 29-1051) making 25% of the entries and Pharmacy Technicians (Occupation Code 29-2052) making 75%. The pharmacist wage rate is \$64.81/hour, and the Pharmacy Technicians wage rate is \$20.83/hour, which amounts to a combined wage of \$31.82.

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 \$28,273.13. Management of the contract is by a GS 14, Step 10 employee and requires 2.5% of a full-time equivalent at a cost of \$4,530.40 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 annual total for government cost is \$23,742.73.

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	\$181,216	2.5%		\$4,530.40
Contractor Cost					\$23,742.73
Travel Cost					\$0
Other Costs					\$0
Total					\$28,272.73

** <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 removes the International Investigator Statement (IIS) form as it was transitioned to the CTEP Branch and Support Contracts Forms and Surveys (OMB#0925-0753) submission, thereby reducing the burden hours by 665 hours annually. The eDARF will be completed online using the AURORA inventory management system, ultimately replacing the DARF and DARF-Oral. Full use of the eDARF will be implemented over the next 12 months, and the burden is based upon a total percentage of the burden for maintaining agent records.

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:

This information collection requires no exceptions to the certification statement.