DANA-FARBER / HARVARD CANCER CENTER
POLICIES FOR HUMAN SUBJECT RESEARCH

TITLE: ~~Managing Essential~~ Regulatory ~~Documents~~Documentation		
POLICY #: RCO-203	**Page:** 1 of 13	**Effective Date:** 1/31/19~~1/14/16~~

1. POLICY STATEMENT:

Essential regulatory documents will be on maintained for research sponsored by or conducted at Dana-Farber/Harvard Cancer Center (DF/HCC) to assure compliance with regulatory requirements.

Commented [CC1]: Combining language and policy requirements from RCO-200 (Documenting DOA), RCO-201 (1572) and RCO-202 (CVs and Licenses) with RCO-203: Managing Essential Regulatory Documents

Copied in language from RCO-200, 201 and 202 into the same section as originally present. Changes thereafter are tracked.

2. BACKGROUND:

~~Essential Documents are those~~Regulatory documents ~~that~~ individually and collectively permit evaluation of the conduct of the research and the quality of data produced. These documents serve to demonstrate the compliance of the investigator, sponsor, and monitor with the standards of good clinical practice (GCP) and with all applicable regulatory requirements. ~~These documents should be maintained as required by the applicable regulatory requirement(s). Sponsors and institutions should take measures to prevent accidental or premature destruction of these documents.~~ Upon request of the monitor, auditor, Institutional Review Board (IRB), or regulatory authority, ~~the Sponsor or institution should make~~regulatory documents must be made available for ~~direct access all requested research-specific documents~~review.

3. RESPONSIBLE PERSONNEL:

3.1. Investigator acting as a Sponsor
3.2. Overall Principal Investigator (PI)
3.3. Site Responsible Investigator
3.4. Subinvestigator
3.5. Research Nurse
3.6. Study Coordinator

4. DEFINITIONS:

Commented [FNR2]: This section reordered. Reorganization not tracked, but any text changes are tracked.

~~4.1. **DF/PCC:** Dana-Farber/Partners Cancer Care~~

~~4.2. **Investigator Regulatory Binder:** Files, usually a binder, maintained by the investigator at the investigative site.~~

~~4.3.~~4.1. **Lead Site:** The site at the same physical location as the DF/HCC Overall Principal Investigator.

~~4.4. **Master Regulatory Binder:** The files maintained by the Lead Site.~~

~~4.5. **Network Affiliate:** Select New England area community hospitals that have a contractual agreement with DF/PCC and access to selected Phase II and Phase III trials.~~

~~4.6.~~4.2. **Non-Lead Site:** The site at the same physical location of the DF/HCC Site Responsible Investigator. This does not include Satellite or Network Affiliate sites.

~~4.7.~~4.3. **Satellite Site:** A site licensed and accredited under one of the DF/HCC institutions that functions under the wider umbrella of the parent institution.

4.4. **Network Affiliate:** Select New England area community hospitals that have a contractual agreement with Dana-Farber/Partners Cancer Care.

4.5. **Sponsor Regulatory File:** ~~The essential document files~~ Regulatory documents maintained by the Sponsor~~ that are established~~.

4.6. **Master Regulatory File:** Regulatory documents maintained by the Lead Site.

4.7. **Investigator Regulatory File:** Regulatory documents maintained by the investigator at the ~~beginning~~investigative site.

4.8. **Sponsor**: The entity (i.e., individual, company, institution, or organization) that initiates a research project and bears direct responsibility for the overall conduct of the study.

4.9. **Investigator:** An individual who actually conducts a clinical investigation (i.e., under whose immediate direction the drug is administered or dispensed to a participant). In the event an investigation is conducted by a team of individuals, the investigator is the responsible leader of the team. At DF/HCC, this is the Overall PI.

4.10. **Subinvestigator**: A subinvestigator is any other member (i.e., other than the Overall PI) of the study team who will make clinical decisions during the study or make a direct and significant contribution to the data. The ICH GCP guideline defines sub-investigator as "any individual member of the clinical trial~~, as appropriate. A final closeout of~~ team designated and supervised by the investigator at a trial ~~can only be performed when a monitor has reviewed~~site to perform critical trial-related procedures and/or to make important trial-related decisions".

~~4.8.~~4.11. **Form FDA 1572:** An agreement signed by the investigator ~~files and assured that~~to provide certain information to the sponsor ~~files have all required documents collected and confirmed.~~ and assure that he/she will comply with FDA regulations related to the conduct of a clinical investigation of an investigational drug or biologic.

4.12. **Curriculum Vitae (CV):** A special type of resume traditionally used within the academic and research community. Earned degrees, teaching and research experience, publications, presentations, and related activities are featured to demonstrate training and experience to conduct research trials

5. POLICY:

~~5.1. The contents of the regulatory files, whether maintained at the sponsor location or at the investigative site(s), need not be stored together in one location. Documents that are stored centrally or electronically must be referenced in a *Note to File* stating where the document(s) are kept.~~

5.1. ~~The regulatory documents outlined in the below procedures will be collected and filed for all pending and active research (i.e., **Regulatory Document Requirements**~~

5.1.1. This policy applies to all protocols ~~which have not been completed). For research~~ activated ~~prior to~~on or after September 17, 2012~~, these documents **will not** be retrospectively collected but collected moving forward.~~. National Cancer Institute (NCI) National Clinical Trials Network (NCTN) trials ~~are required to~~ must follow Clinical Trials Monitoring Branch (CTMB) requirements~~, which may differ~~ and are not required to adhere to this policy where it differs from ~~the document~~CTMB requirements~~ outlined below.~~ .

~~5.2. **Sponsor Regulatory File**~~

~~5.2.1.~~ The Sponsor Regulatory File ~~consists of items listed below that are applicable to a given project. These documents are subject to regulatory review.~~

~~5.2.1.1.Certificate of Analysis for all batches of investigational product(s) manufactured and shipped (where applicable)~~

~~5.2.1.2. Clinical Trial Agreements – signed~~

~~5.2.1.3. Correspondence – all~~

~~5.2.1.4. Curricula vitae (CV) - all persons listed on Form FDA 1572 or~~ , Master Regulatory File, and Investigator ~~Agreement~~

~~5.2.1.5. Enrollment Logs – all~~

~~5.2.1.6. FDA Documentation (where applicable)~~

~~5.2.1.7. Form FDA 1572 – cumulative for all sites~~

~~5.2.1.8. Financial Disclosure – all persons listed on Form FDA 1572 or Investigator Agreement (Note: these documents are~~ Regulatory File must contain the required ~~only if~~regulatory documents as per the ~~PI holds the IND or IDE)~~

~~5.2.1.9. Informed Consent Template~~

~~5.2.1.10. Investigator Meeting materials~~

~~5.2.1.11. Investigational Brochure/Device Manual – all versions (where applicable)~~

~~5.2.1.12. IRB Review Documents – all approved IRB submissions and notifications~~

~~5.2.1.13. Laboratory Documentation (central and local where applicable)~~

~~5.2.1.14. Medical Licenses – all persons listed on Form FDA 1572 or Investigator Agreement~~

~~5.2.1.15. Monitoring guidelines, reports, and master list of monitors~~

~~5.2.1.16. Protocol – all versions sent to participating sites~~

~~5.2.1.17. Publications (where applicable)~~

~~5.2.1.18. SAE/Unanticipated Problems – cumulative~~

~~5.2.1.19. Sample of label(s) attached to investigational product container(s) (where applicable)~~

~~5.2.1.20. Screening Log (if screening subjects to determine initial eligibility)~~

~~5.2.1.21. Site Initiation Visit Records (where applicable)~~

~~5.2.1.22. Transfer of Obligations (if using a Clinical Research Organization)~~

~~5.2.2.~~5.1.2. ~~**Investigator**~~DF/HCC Regulatory File ~~**(maintained at investigator site)**~~: Required Document List and are subject to regulatory review.

5.1.3. There is only one ~~master regulatory binder for each~~Master Regulatory File at DF/HCC per protocol ~~conducted at DF/HCC.~~. The Master Regulatory File may be merged with the Sponsor Regulatory File when appropriate.

~~5.2.3.~~5.1.4. Each Non-Lead Site ~~is responsible for maintaining~~, Satellite Site, and Network Affiliate participating in the research maintains a subset of the essential regulatory documents ~~for the protocol. The following items are present in a master regulatory binder depending on the specific protocol. These documents are subject to regulatory review.~~ relevant to their site in an Investigator Regulatory File.

~~5.2.3.1. Confidentiality Agreement (where applicable)~~

~~5.2.3.2. Consent and/or Assent Forms – all IRB approved versions~~

~~5.2.3.3. Correspondence – significant communications with the Sponsor or other DF/HCC sites (where applicable)~~

~~5.2.3.4. Curricula vitae (CV) – all persons listed on Form FDA 1572 or Investigator Agreement~~

~~5.2.3.5. Data and Safety Monitoring – copies of reports or summaries (where applicable)~~

~~5.2.3.6. Delegation of Authority Log – cumulative for all sites~~

~~5.2.3.7. Deviation/Violation Log – cumulative for all sites~~

~~5.2.3.8. Drug & Device Accountability Records (where applicable)~~

~~5.2.3.9. Enrollment Log – all sites (if enrolling and consenting subjects; collect from all DF/HCC and DF/PCC sites at study close out)~~

~~5.2.3.10. Financial Disclosure – all persons listed on Form FDA 1572 or Investigator Agreement and others as required by institutional policy~~

~~5.2.3.11. Form FDA 1572 (where applicable)~~

~~5.2.3.12. IND Safety Reports (where applicable)~~

~~5.2.3.13. Investigational Brochure/Device Manual (where applicable)~~

~~5.2.3.14. IRB Review Documents- all approved IRB submissions and notifications~~

~~5.2.3.15. Laboratory Documentation – (if performing lab procedures/tests)~~

~~5.2.3.15.1. For DF/HCC and DF/PCC facilities: certifications, Lab Director's CV and normal lab/reference values~~

~~5.2.3.15.2. For non-DF/HCC or DF/PCC facilities: certifications and normal lab/reference values~~

~~5.2.3.16. Medical Licenses – all persons listed on Form FDA 1572 or Investigator Agreement~~

~~5.2.3.17. Monitoring Records – logs and reports (where applicable)~~

~~5.2.3.18. OBA Communication and Reporting (where applicable)~~

~~5.2.3.19. Protocol – all versions~~

~~5.2.3.20. Protocol Training records – cumulative for all sites~~

~~5.2.3.21. SAE/Unanticipated Problem report forms (where applicable)~~

~~5.2.3.22. Scientific Review Documentation (where applicable)~~

~~5.2.3.23. Screening Log (if screening subjects to determine initial eligibility)~~

~~5.2.3.24. Site Initiation Visit Records (where applicable)~~

~~5.2.3.25. Tissue Log (if collecting, sharing and/or transferring tissue samples and required by the Sponsor)~~

Financial information (e.g. budget, contracts, billing records, funding notifications, grant applications, etc.) and ~~Audit~~internal audit information are not subject to regulatory review and must be kept in a separate file.

~~5.2.4. Each Non-Lead Site, Satellite Site, and DF/PCC Network Affiliate participating in the research maintains a subset of the essential regulatory documents necessary to demonstrate compliance with regulatory requirements. The following items are present in the other investigative site files depending on the specific protocol. These documents are subject to regulatory review.~~

~~5.2.4.1.Consent and/or Assent Forms – all IRB approved versions~~

~~5.2.4.2.Delegation of Authority Log for that site~~

~~5.2.4.3. Enrollment Log for that site~~

~~5.2.4.4. IRB Activation memo (where applicable)~~

~~5.2.4.5. IRB Approval memo~~

~~5.2.4.6. IRB documentation generated by that site (i.e. SAE reports, deviations, violations, etc.)~~

~~5.2.4.7. Monitoring Log for that site~~

~~5.2.4.8.Pertinent correspondence received or generated by that site~~

~~5.2.4.9. Protocol – all versions~~

~~5.2.4.10. Protocol Training for that site~~

~~5.2.4.11. Only copies of IND Safety reports that have met DFCI IRB reporting requirements will be filed at non-lead sites~~

~~5.2.4.12. Screening Log for that site~~

5.1.5. Regulatory documents need not be stored together in one location. However, the location of files stored separately (including centrally or

electronically) must be documented in a Note to File per DOC-100.

~~5.2.4.13. All versions of the Investigational Drug Brochure/Device manual (as applicable) must be filed at non-lead site~~

~~5.2.5.~~ During the course of the research, ~~the essential~~ regulatory documents will be ~~kept at each investigative site~~stored in a secure location, accessible only to research team members, ~~where the sponsor's confidential information will not be compromised.~~

~~5.2.5.1. The regulatory essential documents will be~~ and updated ~~and maintained on a continuous basis during the course of the research.~~

~~5.2.6. In general, the essential regulatory documents will be kept at each investigative site until the~~ contemporaneously. After site close out ~~visit at which time the essential regulatory documents will be compacted and organized into easily searchable files and placed in boxes for ease of long-term storage.~~

~~5.2.7.~~5.1.6. ~~The documents will be sent off-site to long term storage as soon as conveniently possible following the close out visit and~~ or study completion ~~with the IRB. If there is no close out visit, the essential~~, regulatory documents will be ~~sent off-site to long term storage~~maintained as ~~soon as conveniently possible after the research is terminated with the IRB.~~ per RCL-101.

5.1.7. All versions of essential regulatory documents must be maintained in the regulatory file. Old versions of essential regulatory documents must not be destroyed or discarded.

5.2. Delegation of Authority Requirements

5.2.1. The Overall PI must maintain a list of the appropriately qualified persons to whom significant trial-related duties have been delegated (delegation of authority log) for all non-exempt human subject research. There must be a separate log for each protocol. Unless otherwise required by an external sponsor (e.g., when NCI requires the use of the CTSU delegation of tasks log), the DF/HCC Delegation of Authority Log Template must be used.

5.2.1.1. Banking, tissue collection, and IRB-determined, minimal risk research are exempted from this requirement.

5.2.2. The delegation of authority log must include all individuals who will be delegated to perform any research activity regulated by the Food and Drug Administration (FDA).

5.2.2.1. Staff members performing routine procedures (i.e. commercial services or standard of care assessments) will not be listed. Therefore, infusion unit or inpatient nurses, radiologists, pathologists, pharmacy technicians, Tumor Imaging Metrics Core (TIMC) staff, residents, fellows and office staff are not included unless it is determined by the Overall PI that they make a direct and significant contribution to the research.

5.2.2.2. Individuals performing only sponsor responsibilities (21 CFR 312 parts 50 through 59) on investigator-sponsored trials do not need to be listed.

5.2.2.3. While authority to perform specified tasks may be delegated, the overall responsibility for those tasks always remains with the Overall PI. Therefore, it is not necessary to list the Overall PI.

5.2.3. Individuals on the delegation of authority log must be qualified to perform their delegated tasks by means of education, training and experience.

5.2.3.1. The DF/HCC Key: Delegation of Tasks for Clinical Research defines which activities an individual may perform based on their research role. Any additional qualifications or restrictions detailed in the protocol document, to the extent that they are more restrictive, take precedence over DF/HCC policy and state law. For example, if state law permits nurse practitioners to perform physical examinations under physician supervision, but the protocol specifies that a physician must do the physical examination, the protocol's requirements take precedence to the extent that they do not contravene state law.

5.2.3.2. All individuals on the delegation of authority log must be trained on DF/HCC Policies as required by EDU-100, and personally sign and initial the Policy Training and Signature record. This training record also serves as a central signature record for the individual to ensure handwritten entries in the research documentation can be attributed to

the person responsible for the information. This is filed at the individual's home institution.

5.2.4. The Overall PI must approve the delegation log prior to initiating research on the protocol. The Overall PI, or designee, will assure that the delegation of authority log is kept up-to-date. The addition of individuals to the delegation log and/or any changes to roles or start dates must be approved by the Overall PI before the additional individual can perform the newly delegated tasks. In the event an individual is identified on the delegation of authority log prior to completing all required training (per EDU-100), that individual may not participate in protocol activities until the required training is completed.

5.3. **Form FDA 1572 Requirements**

5.3.1. All Food and Drug Administration (FDA) regulated research conducted under an Investigational New Drug Application (IND) and managed within DF/HCC requires a protocol specific Form FDA 1572. There is a single Form FDA 1572 for all DF/HCC sites. The designated lead institution will maintain copies of the Form FDA 1572, including the initial form and any subsequent revisions.

5.3.1.1. In very limited situations, exceptions to a single Form FDA 1572 can be made with approval from the Medical Director of Clinical Trials Operations. Even if an exception is made, the oversight responsibilities and structure outlined in the DF/HCC Site Management Plan still apply.

5.3.2. The Overall PI must list in section 6 of the FDA 1572 all Site Responsible Investigators and subinvestigators who will make a direct and significant contribution to the reporting of research data (e.g. recruiting subjects, administering the informed consent document, determining subject eligibility, collecting study data, assessing primary endpoints, evaluating efficacy data, etc.). At DF/HCC, this includes physicians, physician assistants, nurse practitioners, and research nurses for each DF/HCC site.

5.3.2.1. Research nurses may be excluded from the Form FDA 1572 if the Overall PI believes they will not be making a direct and significant contribution to the data for a particular study. The decision to exclude research nurses will reside with the Overall PI and must be documented in the Master Regulatory File.

5.3.2.2. Research pharmacists, pharmacy technicians, study coordinators, infusion or inpatient nurses, radiologists, surgeons, pathologists, radiation oncologists, radiation nurses, residents, fellows and office staff are not generally included when they provide ancillary or intermittent care but do not make a direct and significant contribution to the data. However, they may be included on the Form FDA 1572 if the Overall PI believes they are involved in protocol mandated research or activities which go beyond routine clinical care and which significantly contribute to the research.

5.3.3. The Form FDA 1572 must be double-sided or, if the form has multiple pages and/or attachments, stapled together.

5.3.4. The Overall PI must personally sign and date the Form FDA 1572 (either by hand or using an acceptable electronic method per institutional policy). Stamped signatures and pre-filled dates are not acceptable.

5.3.5. Revisions to the Form FDA 1572 may be batched for periodic updates. New subinvestigators are not required to be listed on the FDA 1572 prior to participating in the research but must be added at the next update.

5.3.6. The Form FDA 1572 does not need to be revised for a laboratory or testing facility that is used infrequently and only to obtain standard of care results. However, any laboratory or testing facility that performs protocol-specific procedures or is responsible for generating significant endpoint, safety, or efficacy data must be added to the 1572.

5.4. Curriculum Vitae (CV) Requirements

5.4.1. The Overall PI, or a designated research team member, must obtain and file a current CV for each physician investigator, nurse practitioner, physician assistant, and research nurse listed on the protocol specific Form FDA 1572. Current CVs are defined as documents that have been updated within the last 2 years. CVs must be signed and dated via ink or electronic means on the first or last page.

5.4.2. An individual's current CV only needs to be filed once at study start up or at the time they join the study team. Upon request, a copy of the CVs on file will be provided to external sponsors. CVs will not be provided for individuals who are not listed on the protocol specific Form FDA 1572. CVs will be provided to sponsors in the format in which they are received from

investigators and will not be altered to accommodate sponsor-specific formats.

5.5. **Licensure Requirements**

5.5.1. The Overall PI, or designee, must verify at the time of study start-up the presence of a valid professional license from the applicable state medical board for physician investigators, nurse practitioners, physician assistants, and research nurses who are listed on the protocol specific Form FDA 1572.

5.5.2. Sponsors seeking to validate licensure will be directed to the relevant state licensing websites, which will allow them to download medical and professional licenses of DF/HCC research personnel. For Massachusetts:
MA state licensing website for physicians:
http://profiles.ehs.state.ma.us/Profiles/Pages/FindAPhysician.aspx
MA state licensing website for Nursing:
https://checkalicense.hhs.state.ma.us/MyLicenseVerification/

5.5.3. All professional licenses will be renewed per state regulations. The Overall PI or designated research team member is responsible for ensuring continued licensure for the duration of each investigator's participation in the clinical trial.

6. APPLICABLE REGULATIONS & GUIDELINES:

21 CFR 50 – Protection of Human Research Subjects
21 CFR 54 – Financial Disclosure by Clinical Investigators
21 CFR 56 – Institutional Review Boards
21 CFR 312 - Investigational New Drugs – Drugs for Human Use
21 CFR 812 – Investigational Device Exemption
45 CFR 46 – Protection of Human Subjects
FDA Industry Guidelines and Information Sheets
FDA Compliance Policy Guidance Programs: 7348.809, 7348.810, and 7348.811
Form FDA 1572 located at CDER forms
U.S.C. Title 18, Sec.1001

7. RELATED REFERENCES:

International Conference on Harmonisation – E6
DF/HCC Site Management Plan

8. RELATED RESOURCES:

RCO-OP-1: Documenting Delegation of Authority
RCO-OP-2: Completion of the Form FDA 1572
~~DF/HCC Master Regulatory File Checklist for Lead Site: Required Document List~~
DF/HCC ~~Regulatory File Checklist~~Centralized Delegation of Tasks for ~~Network Affiliates~~Clinical Research Key
~~DF/HCC Regulatory File Checklist for Non-Lead and Satellite Sites~~
DF/HCC Delegation of Authority Log Template
DF/HCC Policy ~~Sponsor Regulatory File Checklist~~Training and Signature Record
DF/HCC Regulatory File: Required Document List

~~DF/HCC Guidance on Maintaining Regulatory Documents~~