DF/HCC Practice Differences in Comparison to ICH GCP Guidelines

1. INTRODUCTORY STATEMENT:

Dana-Farber/Harvard Cancer Center (DF/HCC) follows the International Conference on Harmonisation Guidelines for Good Clinical Practice (ICH GCP) to the extent those guidelines reflect the regulations and guidance set forth by the Food and Drug Administration (FDA) regulations. Where the ICH GCP guidelines include recommendations or requirements that go beyond those set forth under the FDA regulations, DF/HCC may or may not choose to institute those additional recommendations or requirements.

2. DF/HCC PRACTICE DIFFERENCES:

2.1. INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE (IRB/IEC) - ICH GCP Section 3

2.1.1. **Responsibilities**

2.1.1.1. The IRB/IEC should obtain the following documents:

2.1.1.1.1. Trial protocol(s)/amendment(s), written informed consent form(s) and consent form updates that the investigator proposes for use in the trial, subject recruitment procedures (e.g. advertisements), written information to be provided to subjects, Investigator's Brochure (IB), available safety information, information about payments and compensation available to subjects, the investigator's current curriculum vitae and/or other documentation evidencing qualifications, and any other documents that the IRB/IEC may need to fulfill its responsibilities. (ICH GCP 3.1.2)

DF/HCC Practice Differences to ICH GCP 3.1.2: *The investigator's current curriculum vitae (CV) is not requested at the time of submission of the protocol. (See below DF/HCC Practice Differences to ICH GCP 3.1.3 for additional information.)*

2.1.1.2. The IRB/IEC should review a proposed clinical trial within a reasonable time and document its views in writing, clearly identifying the trial, the documents reviewed and the dates for the following: approval/favorable opinion; modifications required prior to its approval/favorable opinion; disapproval/negative opinion; and termination/suspension of any prior approval/favorable opinion. (ICH GCP 3.1.2)

DF/HCC Practice Differences to ICH GCP 3.1.2: *All of the above information is maintained in the DFCI IRB files and/or in its data base, however not all of the information is reiterated in the DFCI IRB approval memos.*

2.1.1.3. The IRB/IEC should consider the qualifications of the investigator for the proposed trial, as documented by a current curriculum vitae and/or by any other relevant documentation the IRB/IEC requests. (ICH GCP 3.1.3)

DF/HCC Practice Differences to ICH GCP 3.1.3: *The investigator's current curriculum vitae (CV) is not requested at the time of submission of the protocol. The qualifications of the investigator are confirmed by Disease Program approval of the protocol prior to submission to the DFCI IRB.*

2.1.1.4. The IRB/IEC should conduct continuing review of each ongoing trial at intervals appropriate to the degree of risk to human subjects, but at least once per year. (ICH GCP 3.1.4)

DF/HCC Practice Differences to ICH GCP 3.1.4: *The DFCI IRB conducts bi-annual, rather than annual continuing reviews, for non-federally funded minimal risk research.*

2.1.1.5. The IRB/IEC should ensure that information regarding payment to subjects, including the methods, amounts, and schedule of payment to trial subjects, is set forth in the written informed consent form and any other written information to be provided to subjects. The way payment will be prorated should be specified. (ICH GCP 3.1.9)

DF/HCC Practice Differences to ICH GCP3.1.9: *The DFCI IRB does not require that the written informed consent form include methods and/or amounts of payments to trial subjects.*

2.1.2. **Composition, Functions and Operations**

2.1.2.1. Only those IRB/IEC members who are independent of the investigator and the sponsor of the trial should vote/provide opinion on the trial-related matter. (ICH GCP 3.2.1)

DF/HCC Practice Differences to ICH GCP 3.2.1: *The DFCI IRB allows individuals not listed on the protocol documents to vote on research-related matters. Individuals listed on the protocol documents are required to abstain from the vote.*

2.1.2.2. Only those IRB/IEC members who are independent of the investigator and the sponsor of the trial should vote/provide opinion on the trial-related matter. (ICH GCP 3.2.1)

DF/HCC Practice Differences to ICH GCP 3.2.1: *The DFCI IRB allows individuals not listed on the protocol documents to vote on research-related matters. Individuals listed on the protocol documents are required to abstain from the vote.*

2.1.2.2.1. A list of IRB/IEC members and their qualifications should be maintained. (ICH GCP 3.2.1)

DF/HCC Practice Differences to ICH GCP 3.2.1: *The DFCI IRB maintains but does not provide a list of IRB members to sponsors.*

2.1.2.3. The IRB/IEC should perform its functions according to written operating procedures, should maintain written records of its activities and minutes of its meetings, and should comply with GCP and with the applicable regulatory requirement(s). (ICH GCP 3.2.2)

DF/HCC Practice Differences to ICH GCP 3.2.2: *By virtue of not meeting all ICH GCP requirements, it should be considered that the DFCI IRB is not fully GCP compliant.*

2.1.2.4. Only members who participate in the IRB/IEC review and discussion should vote/provide their opinion and/or advise. (ICH GCP 3.2.4)

DF/HCC Practice Differences to ICH GCP 3.2.4: *The DFCI IRB may solicit opinions from Ad Hoc reviewers when expertise in a particular subject matter is not available through the IRB membership.*

2.1.3. **Procedures**

2.1.3.1. Ensuring that the IRB/IEC promptly notify in writing the investigator/institution concerning: its trial-related decisions/opinions; the reasons for its decisions/opinions; procedures for appeal of its decisions/opinions. (ICH GCP 3.3.9)

DF/HCC Practice Differences to ICH GCP 3.3.9: *The DFCI IRB does not have procedures for the appeal of its decisions.*

2.1.4. **Records**

2.1.4.1. The IRB/IEC may be asked by investigators, sponsors or regulatory authorities to provide its written procedures and membership lists. (ICH GCP 3.1.9)

DF/HCC Practice Differences to ICH GCP 3.1.9: *The DFCI IRB does not provide a list of IRB members to investigators or sponsors, however, a membership list is provided to federal authorities upon their request.*

2.2. INVESTIGATOR- ICH GCP Section 4

2.2.1. **Investigational Product(s)**

2.2.1.1. The investigator/institution and/or a pharmacist or other appropriate individual, who is designated by the investigator/institution, should maintain records of the product's delivery to the trial site, the inventory at the site, the use by each subject, and the return to the sponsor or alternative disposition of unused product(s). These records should include dates, quantities, batch/serial numbers, expiration dates (if applicable), and the unique code numbers assigned to the investigational product(s) and trial subjects. Investigators should maintain records that document adequately that the subjects were provided the doses specified by the protocol and reconcile all investigational product(s) received from the sponsor. (ICH GCP 4.6.3)

DF/HCC Practice Differences to ICH GCP 4.6.3: *Research pharmacy logs do not routinely include investigational product expiration dates, unique code numbers assigned to the investigational product or a list of trial subject names. Documentation pertaining to known expiration dates is housed in the research pharmacy's drug file. Trial subject identifiers on drug accountability logs are limited to initials and medical record number.*

2.2.2. Informed Consent of Trial Subjects

2.2.2.1. In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki. Prior to the beginning of the trial, the investigator should have the IRB/IEC's written approval/favorable opinion of the written informed consent form and any other written information provided to the subjects. (ICH GCP 4.8.1)

DF/HCC Practice Differences to ICH GCP 4.8.1: *DF/HCC requires written informed consent for trials regulated by the FDA. In the case of non-FDA regulated research, the DFCI IRB determines the appropriate means of obtaining informed consent from subjects.*

2.2.2.2. If a subject is unable to read or if a legally acceptable representative is unable to read, an impartial witness should be present during the entire informed consent discussion. After the written informed consent form and any other written information to be provided to subjects, is read and explained to the subject or the subject's legally acceptable representative, and after the subject or the subject's legally acceptable representative has orally consented to the subject's participation in the
trial and, if capable of doing so, has signed and personally dated the informed consent form, the witness should sign and personally date the consent form. By signing the consent form, the witness attests that the information in the consent form and any other written information was accurately explained to, and apparently understood by, the subject or the subject's legally

acceptable representative, and that informed consent was freely given by the subject or the subject's legally acceptable representative. (ICH GCP 4.8.9)

DF/HCC Practice Differences to ICH GCP4.8.9: *DF/HCC does not require that impartial individuals witness the informed consent discussion, however this practice is strongly encouraged. Additionally, DF/HCC does not place the burden of attesting to the accuracy and comprehension of the informed consent discussion on the witness. These burdens are placed on the investigator and research team involved in the consenting process. The signature of a witness merely confirms that the information in the consent form or other written information was explained in the presence of the witness and that informed consent was freely given.*

2.2.2.3. Both the informed consent discussion and the written informed consent form and any other written information to be provided to subjects should include explanations of the following:

2.2.2.3.1. The subject's responsibilities. (ICH GCP 4.8.10e)

DF/HCC Practice Differences to ICH GCP 4.8.10e: *The DFCI IRB does not require that the subject's responsibilities be included in the written informed consent form.*

2.2.2.3.2. The alternative procedure(s) or course(s) of treatment that may be available to the subject, and their important potential benefits and risks. (ICH GCP 4.8.10i)

DF/HCC Practice Differences to ICH GCP 4.8.10i: *The DFCI IRB does require that the alternate procedures or course of treatment are included be included in the written informed consent form but does not require that the description include potential benefits and risks of each alternative. Subjects are encouraged to talk with their physician regarding benefits and risks associated with alternatives.*

2.2.2.3.3. The anticipated expenses, if any, to the subject for participating in the trial. (ICH GCP 4.8.10l)

DF/HCC Practice Differences to ICH GCP 4.8.10l: *The DFCI IRB does require that additional costs to the subject that may result from participation in the research are included in the written informed consent form but does not require that the description include a full breakdown of the anticipated expenses.*

2.2.2.4. When a clinical trial (therapeutic or non-therapeutic) includes subjects who can only be enrolled in the trial with the consent of the subject's legally acceptable representative (e.g. minors, or patients with severe dementia), the subject should be informed about the trial to the

extent compatible with the subject's understanding and, if capable, the subject should sign and personally date the written informed consent. (ICH GCP 4.8.12)

DF/HCC Practice Differences to ICH GCP 4.8.12: *The DFCI IRB requires parental permission and assent from children age 10 years and older for studies involving pediatric populations. One or both parents, as required by the DFCI IRB, must sign and date the written informed consent form. The minor must sign and date the assent form.*

2.2.2.5. Except as described in ICH GCP 4.8.14, a non-therapeutic trial (i.e. a trial in which there is no anticipated direct clinical benefit to the subject), should be conducted in subjects who personally give consent and who sign and date the written informed consent form. (ICH GCP 4.8.13)

DF/HCC Practice Differences to ICH GCP 4.8.13: *The DFCI IRB, rather than ICH GCP guidelines, determines whether a non-therapeutic trial may proceed and the appropriate means of obtaining informed consent from subjects.*

2.2.2.6. Non-therapeutic trials may be conducted in subjects with consent of a legally acceptable representative provided the following conditions are fulfilled: the objectives of the trial cannot be met by means of a trial in subjects who can give informed consent personally; the foreseeable risks to the subjects are low; the negative impact on the subject's well-being is minimized and low; the trial is not prohibited by law; the approval/favorable opinion of the IRB/IEC is expressly sought on the inclusion of such subjects, and the written approval/favorable opinion covers this aspect. Such trials, unless an exception is justified, should be conducted in patients having a disease or condition for which the investigational product is intended. Subjects in these trials should be particularly closely monitored and should be withdrawn if they appear to be unduly distressed. (ICH GCP 4.8.14)

DF/HCC Practice Differences to ICH GCP 4.8.14: *These recommendations are not standard practice and therefore not followed by investigators and the DFCI IRB.*

2.2.2.7. In emergency situations, when prior consent of the subject is not possible, the consent of the subject's legally acceptable representative, if present, should be requested. When prior consent of the subject is not possible, and the subject's legally acceptable representative is not available, enrollment of the subject should require measures described in the protocol and/or elsewhere, with documented approval/favorable opinion by the IRB/IEC, to protect the rights, safety and well-being of the subject and to ensure compliance with applicable regulatory requirements. The subject or the subject's legally acceptable representative should be informed about the trial as soon as possible and consent to continue and other consent as appropriate should be requested. (ICH GCP 4.8.15)

DF/HCC Practice Differences to ICH GCP 4.8.15: *Investigators and the DFCI IRB adhere to the practices outlined in the FDA's emergency use guidelines.*

2.2.3. **Progress Reports**

2.2.3.1. The investigator should submit written summaries of the trial status to the IRB/IEC annually, or more frequently, if requested by the IRB/IEC. (ICH GCP 4.10.1)

DF/HCC Practice Differences to ICH GCP 4.10.1: *The frequency of written summaries of the trial status is determined by the DFCI IRB. Summaries are generally requested at least annually for FDA regulated research and bi-annually for non-federally funded minimal risk research.*

2.3. SPONSOR - ICH GCP Section 5

2.3.1. **Compensation to Subjects and Investigators**

2.3.1.1. If required by the applicable regulatory requirement(s), the sponsor should provide insurance or should indemnify (legal and financial coverage) the investigator/the institution against claims arising from the trial, except for claims that arise from malpractice and/or negligence. (ICH GCP 5.8.1)

DF/HCC Practice Differences to ICH GCP 5.8.1: *DF/HCC follows the language in the negotiated clinical trial agreement which may limit insurance or indemnification to only injuries or claims from drug and protocol mandated procedures. DF/HCC does not require insurance or indemnification for trials designated as investigator-initiated.*

2.3.2. **Confirmation of Review by IRB/IEC**

2.3.2.1. The sponsor should obtain from the investigator/institution: a statement obtained from the IRB/IEC that it is organized and operates according to GCP and the applicable laws and regulations. (ICH GCP 5.11.1b)

DF/HCC Practice Differences to ICH GCP 5.11.1b: *The DFCI IRB is accredited by the Association for the Accreditation of Human Research Protection Programs (AAHRPP) and functions according to applicable US laws and FDA and DHHS regulations, however it does not meet all ICH GCP requirements.*

2.4. CLINICAL TRIAL PROTOCOL AND PROTOCOL AMENDMENT(S) - ICH GCP Section 6

2.4.1. **Background Information**

2.4.1.1.A statement that the trial will be conducted in compliance with the protocol, GCP and the applicable regulatory requirement(s). (ICH GCP 6.2.5)

DF/HCC Practice Differences to ICH GCP 6.2.5: *DF/HCC compliance is with US regulations and law and implementation of additional recommendations or procedures from ICH GCP guidelines is discretionary.*

2.5. ESSENTIAL DOCUMENTS FO THE CONDUCT OF A CLINICAL TRIAL - ICH GCP Section 8

2.5.1. Before the Clinical Phase of the Trial Commences

2.5.1.1.During this planning stage the following documents should be generated and should be on file before the trial formally starts:

2.5.1.1.1. Signed Protocol and Amendments, if any, and sample Case Report Form (CRF) (ICH GCP 8.2.2)

DF/HCC Practice Differences to ICH GCP 8.2.2: *DF/HCC does not require that the signed protocol and amendment sheets or sample case report forms are included as essential documents in the trial master files. In practice many files do contain this information.*

2.5.1.1.2. Insurance Statement (where required) (ICH GCP 8.2.5)

DF/HCC Practice Differences to ICH GCP 8.2.5: *DF/HCC requires a statement in the clinical trial agreement that the company retains insurance to fulfill its contractual obligations, with minimal acceptable limits stated. DF/HCC does not require an insurance statement for trials designated as investigator-initiated.*

2.5.1.1.3. Dated, documented approval/favorable opinion of Institutional Review Board (IRB)/Independent Ethics Committee (IEC) of the following: CRF (if applicable) (ICH GCP 8.2.7)

DF/HCC Practice Differences to ICH GCP 8.2.7: *CRFs are not requested at the time of submission of the protocol or amendments.*

2.5.1.1.4. Institutional Review Board/Independent Ethics Committee Composition (ICH GCP 8.2.8)

DF/HCC Practice Differences to ICH GCP 8.2.8: *The DFCI IRB does not provide a list of IRB members to investigators or sponsors.*

2.5.1.1.5. Shipping records for investigational product(s) and trial-related materials (ICH GCP 8.2.15)

DF/HCC Practice Differences to ICH GCP 8.2.15: *DF/HCC does not require that the shipping records for investigational product(s) are kept as essential documents in the investigator trial master files. In practice shipping records are maintained in the research pharmacy.*

2.5.1.1.6. Certificate(s) of analysis of investigational product(s) shipped (ICH GCP 8.2.16)

DF/HCC Practice Differences to ICH GCP 8.2.16: *In certain circumstances, a DF/HCC facility may manufacture and ship investigational product(s). A certificate of analysis (release criteria only) is provided to the sponsor for each investigational product shipped to another location. A certificate of analysis is not routinely provided for investigational product under a DF/HCC Sponsor-Investigator IND. However, the documents are part of the product manufacturing record and are available to the DF/HCC Sponsor-Investigator as requested.*

2.5.1.1.7. Master randomization list (ICH GCP 8.2.18)

DF/HCC Practice Differences to ICH GCP 8.2.18: *The Quality Assurance Office for trials designated as investigator-initiated. The method for randomization of the population is generated by the DF/HCC Biostatistics Core.*

2.5.1.1.8. Pre-trial monitoring report (ICH GCP 8.2.19)

DF/HCC Practice Differences to ICH GCP 8.2.19: *DF/HCC does require a pre-trial monitoring report for multi-center trials designated as investigator-initiated in order to document that the external site is suitable.*

2.5.1.1.9. Trial initiation monitoring report (ICH GCP 8.2.20)

DF/HCC Practice Differences to ICH GCP 8.2.20: *DF/HCC does require that trial initiation monitoring reports are kept as essential for multi-center trial designated as investigator-initiated.*

2.5.2. **During the Clinical Conduct of the Trial**

2.5.2.1.The following should be added to the files during the trial as evidence that all new relevant information is documented as it becomes available:

2.5.2.1.1. Any revision to CRFs (ICH GCP 8.3.2)

DF/HCC Practice Differences to ICH GCP 8.3.2: *The Quality Assurance Office for Clinical Trials (QACT) maintains copies of revised CRFs for trials designated as investigator-initiated.*

2.5.2.1.2. Signed, dated and completed Case Report Forms (CRF) (ICH GCP 8.3.14)

DF/HCC Practice Differences to ICH GCP 8.3.14: *DF/HCC does not require that signed and dated CRFs are kept as essential documents for trials designated as investigator-initiated.*

2.5.2.1.3. Documentation of CRF corrections (ICH GCP 8.3.15)

DF/HCC Practice Differences to ICH GCP 8.3.15: *DF/HCC does require that corrected CRFs be kept as essential documents but does not require documentation of the reasons for the corrections.*

2.5.2.1.4. Subject Screening Log (ICH GCP 8.3.20)

DF/HCC Practice Differences to ICH GCP 8.3.20: *DF/HCC has not consistently required that subject screening logs be kept as essential documents. In practice many files do contain this information.*

2.5.2.1.5. Subject Identification Code List (ICH GCP 8.3.21)

DF/HCC Practice Differences to ICH GCP 8.3.21: *DF/HCC has not consistently required that subject identification code lists be kept as essential documents. In practice many files do contain this information.*

2.5.2.1.6. Subject Enrollment Log (ICH GCP 8.3.22)

DF/HCC Practice Differences to ICH GCP 8.3.22: *The Quality Assurance Office for Clinical Trials (QACT) maintains the subject enrollment log.*

2.5.2.1.7. Investigational products accountability at the site (ICH GCP 8.3.23)

DF/HCC Practice Differences to ICH GCP 8.3.23: *The research pharmacy maintains investigational products accountability records.*

2.5.2.1.8. Signature sheet (ICH GCP 8.3.24)

DF/HCC Practice Differences to ICH GCP 8.3.24: *DF/HCC does require that a signature sheet be kept as essential documents but does not require that it be kept as a stand alone document. In practice the signature sheet is often combined with the Delegation of Authority log.*

2.5.3. **After Completion or Termination of the Trial**

2.5.3.1. After completion or termination of the trial the following documents should be added to the file:

2.5.3.1.1. Investigational product(s) accountability at site (ICH GCP 8.4.1)

DF/HCC Practice Differences to ICH GCP 8.4.1: *The research pharmacy maintains investigational products accountability records.*

2.5.3.1.2. Documentation of investigational product destruction (ICH GCP 8.4.2)

DF/HCC Practice Differences to ICH GCP 8.4.2: *The research pharmacy destroys investigational product returns at the request of the monitor but does not record the destruction action. In practice many monitors record this information as part of their ongoing monitoring visit. The research pharmacy does destroy and record destruction action for investigation product not monitored within the last ninety days.*

2.5.3.1.3. Completed subject identification code list (ICH GCP 8.4.3)

DF/HCC Practice Differences to ICH GCP 8.4.3: *DF/HCC has not consistently required that subject identification code lists be kept as essential documents. In practice many files do contain this information.*

3. FDA REGULATIONS & GUIDELINES RELATING TO GOOD CLINICAL PRACTICE AND CLINICAL TRIALS:

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

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

4. RELATED REFERENCES:

International Conference on Harmonisation – E6