

**FDA STAFF MANUAL GUIDES, VOLUME IV – AGENCY PROGRAM  
DIRECTIVES**

**COMPLIANCE ACTIVITIES**

**CLINICAL INVESTIGATOR RESTRICTED AGREEMENT COMPLIANCE  
AND CHANGE IN STATUS FROM “RESTRICTED” TO “RESTRICTIONS  
REMOVED”**

Effective Date: 12/27/2012

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**1. PURPOSE**

The purpose of this Staff Manual Guide (SMG) is to provide FDA staff with a process to help evaluate whether a clinical investigator who has entered into a restricted agreement with FDA is complying with the agreed upon restrictions and conditions. This SMG also provides procedures for removal by FDA of a clinical investigator’s restricted status if an investigator has complied with all restrictions and has met all required conditions.

**2. DEFINITIONS**

- A. Commissioner.** Commissioner includes the Commissioner of Food and Drugs and those officials delegated the authority to issue the final decision regarding the disqualification (or, reinstatement) of a clinical investigator as listed in SMG 1410.21.<sup>1</sup>
- B. Consent Agreement.** A negotiated and agreed upon set of terms and conditions (including any exhibits, appendices, addendums, schedules, and amendments) between FDA and a clinical investigator entered into based on FDA inspectional

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<sup>1</sup> See General Delegations of Authority from the Commissioner to Other Officers of the Food and Drug Administration, at <http://www.fda.gov/AboutFDA/ReportsManualsForms/StaffManualGuides/ucm049543.htm>.

observations of deviations sufficiently serious to warrant the initiation of disqualification proceedings.

The Office of Chief Counsel (OCC) has developed template language for consent agreements.<sup>2</sup> This template language should not be modified unless the OCC attorneys counseling the Center concur with the modifications.

See also the definition of Restricted Agreement, which is a type of consent agreement.

- C. Investigator.** An individual who actually conducts a clinical investigation, i.e., under whose immediate direction the investigational test article is administered or dispensed to, or used involving, a subject, or in the event of an investigation conducted by a team of individuals, is the responsible leader of the team (see 21 CFR §§ 312.3, 511.3, and 812.3(i)).
- D. Reinstatement.** An investigator who has been determined to be ineligible to receive FDA-regulated test articles may be reinstated as eligible when the Commissioner of Food and Drugs determines that the investigator has presented adequate assurances that the investigator will employ test articles solely in compliance with the applicable regulatory provisions (see 21 CFR §§ 312.70(f), 511.1(c)(6), and 812.119(f)).
- E. Restricted Agreement.** A negotiated and agreed upon set of terms and conditions (including any exhibits, appendices, addendums, schedules, and amendments) between FDA and a clinical investigator that sets forth certain restrictions or conditions the parties agree to pertaining to the investigator's participation in, or conduct of, clinical investigations of FDA-regulated test articles, offered to the investigator at the discretion of FDA after the initiation of a disqualification proceeding. Restricted agreements generally include performance measures to enable the Center to assess compliance with the agreement and to help ensure clinical investigator compliance with applicable laws and regulations.  
  
A fully executed restricted agreement between FDA and the clinical investigator terminates the disqualification administrative proceeding, provided the investigator adheres to the terms of the restricted agreement.
- F. Restrictions Removed.** Under the terms of a Restricted Agreement, the restrictions in a clinical investigator's agreement no longer apply and are removed, allowing the investigator to again be eligible to conduct an investigation that supports an application for a research or marketing permit for products regulated by FDA in accordance with all applicable statutory and regulatory

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<sup>2</sup> See <http://www.fda.gov/downloads/ICECI/ComplianceManuals/RegulatoryProceduresManual/UCM177273.pdf>.

requirements. When the restrictions are removed, the investigator's status is changed from "Restricted" to "Restrictions Removed" on FDA's web site.<sup>3</sup>

**G. Totally Restricted.** In the past, the phrase "totally restricted" also referred to clinical investigators who had been disqualified. FDA's use of this terminology was discontinued in the 1990's.

### 3. BACKGROUND

FDA regulates scientific studies that are conducted to, among other things, support the safety and effectiveness of investigational drugs (human and animal), biological products, and medical devices. Clinical investigators who conduct these studies are required to comply with applicable statutes and regulations intended to ensure the integrity of clinical data on which product approvals are based and, for research involving human subjects, to help protect the rights, safety, and welfare of those subjects.

FDA may disqualify a clinical investigator if the investigator has repeatedly or deliberately failed to comply with applicable regulatory requirements or the investigator has repeatedly or deliberately submitted to the sponsor or FDA false information in any required report. A disqualified investigator is not eligible to receive investigational drugs, biologics or devices, or to conduct any investigation that supports an application for a research or marketing permit for products regulated by FDA. Until about the early 1990's, the phrase "totally restricted" was also used to refer to clinical investigators who had been disqualified. Presently, however, the term "totally restricted" is no longer used.

When FDA uncovers regulatory violations that are significant, serious or numerous, and the scope, severity, or pattern of violations support a finding that (a) subjects under the care of the investigator would be or have been exposed to an unreasonable and significant risk of illness or injury, or (b) subjects' rights would be or have been seriously compromised, or (c) data integrity or reliability is or has been compromised sufficient to disqualify the investigator from eligibility to receive FDA-regulated test articles,<sup>4</sup> FDA may offer to the investigator the option of entering into a consent agreement. A consent agreement is enclosed with a Notice of Initiation of Disqualification Proceedings and Opportunity to Explain (NIDPOE) letter issued by FDA to an investigator.<sup>5</sup> A fully executed consent agreement between FDA and the clinical investigator terminates the disqualification administrative proceeding.

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<sup>3</sup> See [www.fda.gov/DisqualificationProceedings](http://www.fda.gov/DisqualificationProceedings).

<sup>4</sup> See Compliance Program Guidance 7348.811, Chapter 48 – Bioresearch Monitoring: Clinical Investigators, Part V, Section B., at <http://www.fda.gov/ICECI/EnforcementActions/BioresearchMonitoring/ucm133562.htm>.

<sup>5</sup> A sample of a consent agreement disqualifying a clinical investigator may be found at <http://www.fda.gov/downloads/ICECI/ComplianceManuals/RegulatoryProceduresManual/UCM177273.pdf>.

A restricted agreement is a type of consent agreement. The decision to offer an investigator the option of entering into a restricted agreement is within the discretion of the relevant FDA Center in consultation with OCC. This decision is based on the circumstances of a particular matter (i.e., on a case-by-case basis). The drafting of a restricted agreement is the responsibility of the relevant Center in consultation with the OCC attorneys counseling the Center. The offer of the restricted agreement to an investigator and the subsequent negotiations, if any, are the responsibility of the OCC attorneys counseling the Center. The investigator may be offered a restricted agreement until the issuance of a Commissioner's Decision under 21 CFR § 16.95 or issuance of a notification of disqualification under 21 CFR §§ 312.70, 511.1(c), or 812.119.<sup>6</sup>

FDA maintains on its web site, "Clinical Investigators – Disqualification Proceedings",<sup>7</sup> a list of those clinical investigators who have agreed to certain restrictions with respect to their conduct of clinical investigations. Promptly after a restricted agreement is fully executed, the relevant Center contacts the Office of Regulatory Affairs and requests that the clinical investigator's name and relevant publically-disclosable information be listed on FDA's web site.<sup>8</sup> On this web site, FDA also provides a list of clinical investigators who were previously subject to restrictions which have been removed.

Any restricted agreement executed before the effective date of this SMG is managed in accordance with the relevant Center's policies and procedures in place at the time the restricted agreement was executed. This SMG is not intended to impose any additional obligations on the Centers regarding their assessment of compliance with those previously executed restricted agreements.

#### 4. POLICY

- When FDA finds clinical investigator noncompliance that has adversely impacted or could adversely impact data integrity or study subject safety, FDA is committed to ensuring timely administrative actions<sup>9</sup> to help ensure the integrity and reliability of data generated in investigations of FDA-regulated test articles and the protection of the rights and safety of study subjects.

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<sup>6</sup> See, for example, Staff Manual Guide (SMG) 7711 – Disqualification of a Clinical Investigator: The Hearing Process, section 2, 3<sup>rd</sup> bullet, at

<http://www.fda.gov/AboutFDA/ReportsManualsForms/StaffManualGuides/ucm052928.htm>.

<sup>7</sup> See [www.fda.gov/DisqualificationProceedings](http://www.fda.gov/DisqualificationProceedings). FDA's Office of Regulatory Affairs maintains this web site (see section 7. CONTACTS, below, for contact information regarding posting requests).

<sup>8</sup> *Id.*

<sup>9</sup> For other procedures concerning clinical investigator misconduct see:

- Compliance Program 7348.811 – Bioresearch Monitoring: Clinical Investigators, at <http://www.fda.gov/ICECI/EnforcementActions/BioresearchMonitoring/ucm133562.htm>,
- Regulatory Procedures Manual – Chapter 5-9 – Disqualification of Clinical Investigators, at <http://www.fda.gov/ICECI/ComplianceManuals/RegulatoryProceduresManual/ucm176986.htm>, and
- Staff Manual Guide (SMG) 7711 – Disqualification of a Clinical Investigator: The Hearing Process, at <http://www.fda.gov/AboutFDA/ReportsManualsForms/StaffManualGuides/ucm052928.htm>.

- The Commissioner has delegated the authority to perform his or her functions to the officials listed in SMG 1410.21.<sup>10</sup> This includes the authority to determine the eligibility of a clinical investigator to receive FDA-regulated test articles, and the authority to sign a consent agreement between a clinical investigator and FDA.

## 5. RESPONSIBILITIES

- After entering into a restricted agreement with a clinical investigator, the relevant Center is responsible for monitoring the investigator's compliance with the terms and conditions of the restricted agreement and for ensuring that any requirements for investigator reporting are met (e.g., if the agreement states that the investigator must submit to the Center annual progress reports, the Center should monitor for those reports).
- The relevant Center is responsible for notifying other Centers when a restricted investigator may be involved with FDA-regulated articles that are cross-cutting among Centers (e.g., CBER and CDRH for devices). In cross-cutting matters, the relevant Center may need to request support from another Center.
- At its discretion, the relevant Center may request an inspection of the clinical investigator. The relevant Center is responsible for evaluating the results of the inspection to, for example, (a) verify that the investigator is complying with the terms and conditions in the restricted agreement, or (b) to determine whether the investigator has satisfied all terms and conditions in the agreement before changing the investigator's status on FDA's web site<sup>11</sup> from "Restricted" to "Restrictions Removed".
- Before the relevant Center requests a status change from "Restricted" to "Restrictions Removed" on FDA's web site,<sup>12</sup> the Center should be satisfied that the investigator has complied with all restrictions in the executed restricted agreement and has met all conditions. The means of proof the Center may accept as satisfactory generally depends on the terms and conditions of a particular restricted agreement, e.g., certification of course completion for a restricted agreement condition of required training, or submission by the investigator of timely and satisfactory required reporting.
- When the relevant Center determines that a clinical investigator's status may be changed from "Restricted" to "Restrictions Removed", the Center is responsible for notifying the investigator about this determination. The relevant Center is

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<sup>10</sup> See General Redelegations of Authority from the Commissioner to Other Officers of the Food and Drug Administration, at

<http://www.fda.gov/AboutFDA/ReportsManualsForms/StaffManualGuides/ucm049543.htm>.

<sup>11</sup> See [www.fda.gov/DisqualificationProceedings](http://www.fda.gov/DisqualificationProceedings).

<sup>12</sup> *Id.*

responsible for maintaining this notification to the clinical investigator in the administrative record for the matter.

- The relevant Center is responsible for notifying all applicable FDA components about the clinical investigator's change in status to "Restrictions Removed". For a list of applicable FDA components to consider for notification, see section 7. CONTACTS, below.
- Promptly after the clinical investigator is notified, the relevant Center is responsible for contacting the Office of Regulatory Affairs for posting of this information (see section 6.C.4., below).

## **6. PROCEDURES**

### **A. Periodic Review of Active Restricted Agreements**

Each Center will establish, maintain, and follow internal Center procedures to ensure periodic review of all active restricted agreements executed by the Center.

- **Assurance of Clinical Investigator Compliance with Provisions in the Restricted Agreement, as Applicable.**

Among other terms or conditions, a restricted agreement may include one or more of the following for which the relevant Center should provide periodic review:

#### **1. Requirement for a supervising clinical investigator**

- a. The relevant Center should review the credentials, curriculum vitae, or other supporting documentation concerning the supervising clinical investigator to ensure that the supervising investigator is qualified by training and experience to supervise the restricted investigator.
- b. The relevant Center should ensure that the supervising clinical investigator is someone who is independent of the restricted investigator, i.e., not in a former employer-employee, fiduciary, partnership, or other relationship which may present a conflict of interest or the appearance of bias or favoritism.

#### **2. Requirement for a supervising medical monitor**

- a. The relevant Center should ensure that the selected supervising medical monitor is appropriately licensed and qualified to supervise the restricted investigator.
- b. The relevant Center should ensure that the supervising medical monitor is someone who is independent of the restricted investigator, i.e., not in a

former employer-employee, fiduciary, partnership, or other relationship which may present a conflict of interest or the appearance of bias or favoritism.

### **3. Requirement for continuing education**

- a. If the restricted agreement requires that continuing education materials be submitted in advance, the relevant Center should review the coursework, course description, or syllabus to ensure that the training fulfills the requirements in the restricted agreement for continuing education and to ensure that the coursework is meaningful, relevant, and not redundant.
- b. The requirement for continuing education should be fulfilled by a professional or accredited training program offered by a recognizable and reputable third party with relevant expertise in training health professionals. For example, a consultant must have recognized expertise in the relevant discipline to satisfy this requirement.

In contrast, it would be unacceptable to meet the requirement for continuing education by attending training by a fellow staff member (i.e., a course designed specifically for the restricted investigator).

- c. The relevant Center should request adequate information from the clinical investigator to assure the Center that the investigator has satisfactorily completed the required continuing education.

### **4. Requirement for submission of reports**

- a. The relevant Center should monitor for the timely submission of required reports.
- b. The relevant Center should review promptly within 30 calendar days of receipt the reports for the required content. The receipt of a satisfactory or deficient report should be noted in the administrative record. If the report is deficient, the relevant Center should determine what action is appropriate. For example, the Center may notify the clinical investigator of the reporting deficiencies and request from the investigator (i) the submission of corrections to the report, (ii) a plan of action to correct the deficiencies, or (iii) an explanation about why the investigator thinks the report is not deficient.

## **B. Clinical Investigator Noncompliance with Restricted Agreement**

- **Reinstating a disqualification proceeding or initiating a new disqualification proceeding**

If an investigator who entered into a restricted agreement fails to comply with the terms or conditions of the agreement or if FDA obtains information regarding additional violations, the relevant Center may reinstate the disqualification proceeding or initiate a new disqualification proceeding. The disqualification proceeding may include any matters under complaint in the matter that resulted in the executed restricted agreement, and/or may include new violations and any accompanying evidence. The procedures in FDA's Regulatory Procedures Manual<sup>13</sup> and Staff Manual Guide<sup>14</sup> should be followed when reinstating or initiating a disqualification action.

If the clinical investigator is disqualified, the relevant Center is responsible for requesting posting of the clinical investigator's "Disqualified" status on FDA's web site<sup>15</sup> in accordance with FDA's Staff Manual Guide procedures.<sup>16</sup>

### **C. Restrictions Removed Status for Clinical Investigators**

#### **1. Clinical investigator request for status change to "Restrictions Removed"**

- a. An investigator or an investigator's counsel may initiate the process by a request to the relevant Center or another FDA component. Such a request would be sufficient for consideration regardless of whether the request is made verbally (e.g., by telephone or voicemail) or in writing (e.g., email, letter, or facsimile). An investigator request made to an FDA component other than the relevant Center should promptly be forwarded to the appropriate Office within the relevant Center (i.e., the Center responsible for executing the restricted agreement) for consideration. If made by verbal request, the relevant Center should document for the administrative record the conversation including the date and time of the call and the parties to the conversation.
- b. Within 30 calendar days of the relevant Center's receipt of a clinical investigator's request, the Center should review the request in accordance with internal Center procedures to decide whether the investigator has satisfied all terms and conditions of the restricted agreement and whether the investigator has submitted all required reports.
- c. If the relevant Center determines that the restricted investigator has met the terms and conditions of the restricted agreement, the Center will notify the investigator of this determination. The Center may, at its discretion,

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<sup>13</sup> See Regulatory Procedures Manual, Chapter 5-9, Disqualification of Clinical Investigators, at <http://www.fda.gov/ICECI/ComplianceManuals/RegulatoryProceduresManual/ucm176986.htm>

<sup>14</sup> See Staff Manual Guide 7711, Disqualification of a Clinical Investigator: The Hearing Process, at <http://www.fda.gov/AboutFDA/ReportsManualsForms/StaffManualGuides/ucm052928.htm>.

<sup>15</sup> See [www.fda.gov/DisqualificationProceedings](http://www.fda.gov/DisqualificationProceedings).

<sup>16</sup> *Id.* at footnote 14.



issue this determination in writing. Regardless of the method used to notify the investigator (i.e., verbal, written, or otherwise), the Center will document in the administrative record the determination and investigator notification.

- d. Promptly after determining the investigator has met the terms and conditions of the restricted agreement and, if applicable, notifying the investigator of this determination, the Center should request a change in status from “Restricted” to “Restrictions Removed” on FDA’s web site.<sup>17</sup>

## **2. Relevant Center’s independent review of a restricted agreement**

The relevant Center may independently determine that the clinical investigator has met all restricted agreement terms and conditions and has satisfied all reporting requirements.<sup>18</sup> Promptly after the relevant Center is satisfied that an investigator has complied with the restricted agreement terms and conditions, the Center should notify the investigator and request a change in status from “Restricted” to “Restrictions Removed” on FDA’s web site.<sup>19</sup>

## **3. Clearances within the Center**

Each Center should establish, maintain, and follow internal procedures for Center review and clearance when making a determination about whether a clinical investigator has satisfied the terms and conditions of the restricted agreement. (For related responsibilities, see section 5. RESPONSIBILITIES, above).

Those procedures should include but not be limited to the following:

- a. identifying responsible parties or positions within the Center to review the matter and determine whether all terms and conditions in the restricted agreement are satisfied;
- b. identifying responsible parties or positions within the Center to review and approve changing an investigator’s status from “Restricted” to “Restrictions Removed”;
- c. identifying final clearance and approval authority within the Center;
- d. setting internal timelines for review and clearance; and

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<sup>17</sup> See [www.fda.gov/DisqualificationProceedings](http://www.fda.gov/DisqualificationProceedings).

<sup>18</sup> Note that the intent of a restricted agreement is for the clinical investigator to demonstrate in a structured way that the investigator is able to conduct investigations of FDA-regulated test articles in compliance with the applicable laws and regulations.

<sup>19</sup> See [www.fda.gov/DisqualificationProceedings](http://www.fda.gov/DisqualificationProceedings).

- e. identifying responsible parties for notifying Center and agency contacts about the disposition of the matter, and for requesting posting of final actions.

#### **4. Restrictions Removed status for clinical investigators**

Promptly after notifying the investigator that the terms and conditions of the restricted agreement are satisfied, the relevant Center should request a change in status on FDA's web site, Clinical Investigators – Disqualification Proceedings<sup>20</sup> from “Restricted” to “Restrictions Removed” along with the date of change in status. This web site is maintained by FDA's Office of Regulatory Affairs (phone: 301-796-5280).<sup>21</sup>

#### **D. Administrative Record and Posting of Documents**

Copies of all documents are sent to the OGCP Project Manager for purposes of recordkeeping (administrative record). The relevant Center is responsible for forwarding the documents to the Center's FOI contact and the Office of Regulatory Affairs so that, as appropriate, all applicable documents may be posted, after redaction, on FDA's web site.<sup>22</sup>

### **7. CONTACTS**

- Center for Biologics Evaluation and Research (CBER); HFM-600; Office of Compliance and Biologics Quality; phone: 301-827-6221.
- Center for Drug Evaluation and Research (CDER); Office of Compliance, WO51; phone: 301-796-3100; CDERCompliance@FDA.HHS.GOV.
- Center for Devices and Radiological Health (CDRH), WO66-3446; phone: 301-796-5490; fax: 301-847-8136; BIMO@CDRH.FDA.GOV.
- Center for Veterinary Medicine (CVM); HFV-234; Office of Surveillance and Compliance, Division of Compliance, Pre-Market Compliance and Administrative Actions Team; phone: 240-276-9238.
- Office of the Commissioner, Office of Good Clinical Practice (OGCP), WO32-5129; phone: 301-796-8340; fax: 301-847-8640.
- Office of the Chief Counsel (OCC); GCF-1; WO31 and WO32; phone: 301-796-8535.

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<sup>20</sup> *Id.*

<sup>21</sup> See, also, Office of Regulatory Affairs contacts, at <http://inside.fda.gov:9003/ORA/OfficeofEnforcement/default.htm>.

<sup>22</sup> [www.fda.gov/DisqualificationProceedings](http://www.fda.gov/DisqualificationProceedings).

- Office of Regulatory Affairs (ORA); phone: 301-796-5280; ORA contacts, at <http://inside.fda.gov:9003/ORA/OfficeofEnforcement/default.htm>.

## 8. EFFECTIVE DATE

The effective date of this guide is 12/27/2012.

STATUS (I, R, C)	DATE APPROVED	LOCATION OF CHANGE HISTORY	CONTACT	APPROVING OFFICIAL
Initial	03/22/2012	N/a	K. Pfaender, Office of Good Clinical Practice (OGCP)	J. Less, Director, OGCP