

DI&A - Quality Manual <i>Global Regulatory Standard Operating Procedure</i>	
SCIENTIFIC MISCONDUCT AND FRAUD	Reference Document ID: GREGU-QAC-PR-01-01 <hr/> Page No: 1 of 7

APPROVAL:		
Lead Optimization	<u>C. Benedict (signature on file)</u> Signature	<u>October 9, 2000</u> Date
Product Realization	<u>S. Rajfer (signature on file)</u> Signature	<u>October 16, 2000</u> Date
Global Regulatory Approvals & Marketing Support	<u>M. Quigley (signature on file)</u> Signature	<u>October 18, 2000</u> Date
Global Medical Affairs	<u>J. Premunereux (signature file)</u> Signature	<u>October 20, 2000</u> Date

1. SCOPE

This SOP outlines the procedure to be followed when the existence of scientific misconduct and/or fraud is suspected and provides a course of action for the investigation and reporting activity to appropriate internal and, in some circumstances, external parties.

2. APPLICABLE TO

This SOP applies to all Aventis staff involved in all Aventis sponsored clinical trials including Drug Innovation and Approval (DI&A), Global Medical Affairs (GMA) and local Medical Departments.

3. RESPONSIBILITIES

3.1 Aventis Staff

All staff members involved in the conduct of clinical studies should be sensitized to the possibility of fraud or scientific misconduct. In addition, such members are responsible for reporting observations of suspected fraud and/or scientific misconduct to Aventis Management according to this procedure.

3.2 Aventis Management

Facilitate and support investigation of suspected fraud or scientific misconduct, provide guidance to Aventis staff members on the handling of the investigation and decide on final actions to be taken.

~~is printed, this is an uncontrolled copy.~~

Printed documents must be checked against Intranet prior to use to ensure version control

Global Regulatory SOP

Approval Date: October 20, 2000

Ref. Doc ID.: GREGU-QAC-PR-01-01

Page 2 of 7

SCIENTIFIC MISCONDUCT AND FRAUD

4. PROCEDURE

Some of the methods that may be utilized in detecting Suspected Fraud/Scientific Misconduct are included in supporting document "Methods for Detection of Fraud or Scientific Misconduct" (GREGU-QAC-SD-01-01).

4.1 Initial Action Upon Suspicion of Fraud/Scientific Misconduct

4.1.1 Initiator

- must document the specific evidence
- if possible, make photocopies of the actual information/data or provide other example(s) of the information/data under question
- must gather any documented evidence that is available
- must report verbally immediately to the following individuals either directly or via line management:
 - his/her line manager,
 - the affiliate Medical Director (if applicable),
 - the affiliate Quality Assurance - Good Clinical Practice (QA GCP) officer (if applicable),
 - the regional or global GCP QA Head,
 - the study manager and/or project leader
- must promptly confirm in writing the notification, initially made verbally,
- must send this strictly confidential report with corresponding documentation, only to the above mentioned individuals.

4.2 Initiate and Conduct the Investigation

4.2.1 *Initiator, his/her line manager, the affiliate Medical Director (if applicable), the affiliate QA GCP officer (if applicable), the regional or global GCP QA Head, the study manager and/or project leader*

Should meet (physically or by telephone/video conference) immediately, and in no more than four (4) working days after notification from the Initiator, in order to :

- conduct a review of the allegation,
- discuss the available documentation
- decide whether an investigation is necessary.

~~If printed, this is an uncontrolled copy.~~

Printed documents must be checked against Intranet prior to use to ensure version control

Global Regulatory SOP

Approval Date: October 20, 2000

Ref. Doc ID.: GREGU-QAC-PR-01-01

Page 3 of 7

SCIENTIFIC MISCONDUCT AND FRAUD

- 4.2.2** *Initiator, his/her line manager, the affiliate Medical Director (if applicable), the affiliate QA GCP officer (if applicable), the regional or global GCP QA Head, the study manager and/or project leader*
- If an investigation is not deemed necessary, they will document the reasons in a confidential memo to the file. Documentation will be maintained in GCP QA files.
 - If an investigation is deemed necessary, they will:
 - designate a Responsible Person, preferably from GCP QA, to oversee the investigation.
 - decide on a methodology and scope of the investigation.
 - define a time line for the investigation report.
 - discuss whether the regulatory agency(ies) should be notified before the investigation begins. In this case, a Regulatory Affairs representative will be contacted.
 - if suspected fraud involves a clinical investigator the scope of the investigation should include validation of patient participation and data integrity for all ongoing and completed protocols the investigator was involved with.
- 4.2.3** *Responsible person* will ensure that:
- detailed minutes of this first meeting are prepared,
 - an investigation plan is developed,
 - the investigation is conducted according to the established plan,
 - an investigation report is written in a timely fashion.
- 4.2.4** *Responsible person* will inform verbally in addition, according to the affiliation of the suspected author of fraud/scientific misconduct, the following individuals :
- *if the suspected individual is an Aventis employee:* his/her line manager and his/her Human Resources.
 - *if the suspected individual is an investigator:* the corporate and affiliate (if applicable) legal department(s)/advisor and Regulatory Affairs departments.
 - *if the suspected individual is employed by a vendor (such as a contract research organization):* the corporate and affiliate (if applicable) Aventis legal department(s)/advisor and Regulatory Affairs departments

~~It is prohibited, this is an unclassified copy.~~

Printed documents must be checked against intranet prior to use to ensure version control

Global Regulatory SOP

Approval Date: October 20, 2000

Ref. Doc ID.: GREGU-QAC-PR-01-01

Page 4 of 7

SCIENTIFIC MISCONDUCT AND FRAUD

4.3 Action to be Taken Upon Confirmation of Suspected Fraud/Scientific Misconduct

- 4.3.1 Involved parties** Will review the conclusions of the investigation report and prepare a final report.
- 4.3.2 Involved parties**
- If it is determined that there is a reasonable possibility that scientific misconduct or fraud has occurred
 - will agree on recommendations for actions to be taken. Recommendations should consider actions taken to terminate investigator site, re-analysis censoring data for development or marketed projects, agency and ethics committee notifications.
- 4.3.3 Responsible Person** If it is determined that there is a reasonable possibility that scientific misconduct or fraud has occurred
- will send within 2 working days a final confidential report to : Affiliate (if applicable) and corporate Senior Management including the Heads of QA, Regulatory Affairs, Therapeutic Area, Clinical Development (Lead Optimization [LO] & Product Realization [PR]) or GMA, Human Resources (if the suspected author is an Aventis employee) and Legal Department.
This report describes the situation, the investigation plan and results, and includes recommendations agreed by the involved parties.
- 4.3.4 Responsible Person** If the involved parties agree, based upon the investigation report, that suspected Fraud/Scientific Misconduct is not confirmed,
- will issue as soon as possible, a written final report to the file with a copy to all the individuals who have been involved, or informed (as per section 4.3).
This confidential report describes the situation, the investigation plan and results including an explanation of why fraud is not confirmed and further recommended actions (if any).
This report and all documentation pertaining to the investigation will be archived in QA-GCP files.

~~Of interest, this is an unclassified copy.~~

Printed documents must be checked against Intranet prior to use to ensure version control

Global Regulatory SOP

Approval Date: October 20, 2000

Ref. Doc ID.: GREGU-QAC-PR-01-01

Page 5 of 7

SCIENTIFIC MISCONDUCT AND FRAUD

4.4 Responsibility for follow-up action

4.4.1 Senior Management should assume full responsibility for the follow-up action plan.

4.4.2 Responsible Person, in conjunction with the project/line manager should endeavor to keep all the Aventis staff members who have been involved in determining confirmation of the scientific misconduct/fraud informed of the follow-up status until completion of the action plan.

All documentation pertaining to the suspected/confirmed allegations should be archived in Aventis QA-GCP files (corporate and local as appropriate).

5. ARCHIVES

All documentation pertaining to evaluation of suspected and confirmed allegations should be archived in Aventis GCP-QA files (corporate and local as appropriate).

6. HISTORY

This is the first version of this SOP for Aventis Pharma. This procedure was modified from RPR heritage procedure CCD SOP 280.

7. APPENDICES

Appendix 1: Definitions

Appendix 2: Flowchart

8. SUPPORTING DOCUMENTS

No.	Title
GREGU-QAC-SD-01	Methods for Detection of Fraud or Scientific Misconduct

~~It is intended, this is an uncontrolled copy.~~

Printed documents must be checked against intranet prior to use to ensure version control

Global Regulatory SOP

Approval Date: October 20, 2000

Ref. Doc ID.: GREGU-QAC-PR-01-01

Page 6 of 7

SCIENTIFIC MISCONDUCT AND FRAUD

APPENDIX 1: DEFINITIONS

Fraud and scientific misconduct	Intentionally altered information, hidden information, fabricated information, or such information being developed as a result of gross negligence
Initiator	The staff member who observes possible fraud or scientific misconduct

~~If printed, this is an unofficial copy.~~

Printed documents must be checked against Intranet prior to use to ensure version control

Global Regulatory SOP

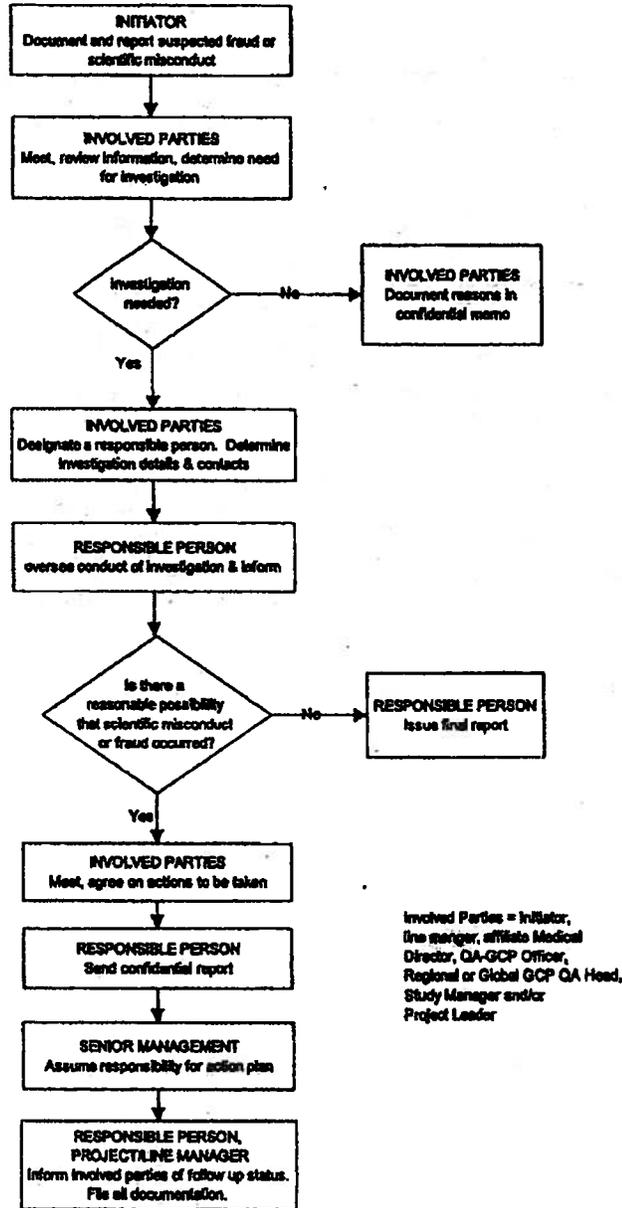
Approval Date: October 20, 2000

Ref. Doc ID.: GREGU-QAC-PR-01-01

Page 7 of 7

SCIENTIFIC MISCONDUCT AND FRAUD

Appendix 2: FLOWCHART



If printed, this is an uncontrolled copy.

Printed documents must be checked against Intranet prior to use to ensure version control



METHODS FOR DETECTION OF FRAUD OR SCIENTIFIC MISCONDUCT

Some methods that may be utilized in detecting these situations include:

- Systematic review of original source records
- Accounting for all records
- Determining if results unexpectedly favor the product under investigation
- Assessing whether the subject inclusion rate matches with the patient population potential of the center
- Identifying if some documents are systematically missing (e.g. lab reports)
- Checking for repeated data patterns
- Checking whether Informed Consent Forms have similar subject signatures
- Checking for problem trends in information capture
- Checking that a person generating and signing for data did not also perform any required cross check verification
- Checking for the sudden appearance of documents which had previously been reported lost
- Identifying record entries and alterations to records which are without plausible explanation
- Assessing whether signatures on source documents are consistent with the signatures log for the site
- Interaction with all study related personnel to confirm their awareness and contribution to the trial

Printed documents must be checked against Intranet prior to use to ensure version control