1a. Writing and modification of Clinical Research Standard operational procedures (SOPs) PT comments.doc

1b. SOP - Storage and Retention of Clinical Research Records Essential Documents PT comments.doc

1c. Document Retention Log.doc

1d. Release Form for the Destruction of a Study Documentation.doc

2. SOP - Informed Consent Process PT comments.doc

3. SOP - Management of IP PT comments.doc

3a. Frm02_IP_Accountablity_Log_Subject_Specific_Sample_.doc

3b. Frm01_IP_Accountability_Log_Site_Inventory_Sample_.doc

3c. Frm03_IP_Return_Form_Sample_.doc

4. SOP - AE and SAE Recording and Reporting PT comments.doc

5. SOP-recrutiment procedure.docx

6. SOP - Equipment Calibration & Maintenance.doc

6a. Equipment List Calibration & Maintenance Log.doc

6b. Temperature Log refr 1.docx

6c. Temperature Log refr 2.docx

6d. Temperature Log refr 3.docx

6e. Temperature Log Room.docx

7. SOP - Site Reserach Team Qualifications and Training.doc

7a. Training Record.doc

7b. SOP Training Documentation Log.doc

8. SOP specmen handling and shipping.doc

8a.. Temperature Log Freez.docx

9. SOP-Essential documents archiving.doc

10. SOP Monitoring visits.doc

2nd Department of Internal Medicine, University Hospital of Ioannina, Greece	**STANDARD OPERATING PROCEDURE**	**Number: 002** **Effective Date: 18 JULY 2017** **Supersedes:**

WRITING AND MODIFICATION OF A CLINICAL RESEARCH STANDARD OPERATIONAL PROCEDURE (SOP)

Purpose

The purpose of this Standard Operating Procedure (SOP) is to describe the procedures to be followed for writing and modifying standard operation procedures (SOPs) as outlined in ICH E6 8.0" and in Greek legislation (31. Dec. 2003 Harmonization of Hellenic Legislation to Directive 2001/20/EC Official Governments' Gazette (FEK) 1973, 07. Oct. 2004 National Ethics Committee Composition & Operating procedures Official Governments' Gazette (FEK) 1503, 25.Jan.2007 Greek Law Harmonization Dir_2005/28/EC Official Governments' Gazette (FEK) 64, 21.Feb.2013 FEK 390/B Supplement to B´1973).

Scope

This SOP applies to all site personnel and to the clinical research records produced at 2nd Department of Internal Medicine, University Hospital of Ioannina, Greece.

Definitions

1. Good Clinical Practice (GCP)

A standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected.

2. Essential Documents

Documents which individually and collectively permit evaluation of the conduct of a study and the quality of the data produced. (IC, E6 1.23)

3. Investigator

A person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the Principal Investigator.

WRITING AND MODIFICATION OF A CLINICAL RESEARCH STANDARD OPERATIONAL PROCEDURE (SOP)

4. Principal Investigator (PI)

The person responsible to the sponsor for the conduct of the clinical trial at the clinical trial site, who is entitled to provide health care under the laws of the province where that clinical trial site is located, and who is

(a) in the case of a clinical trial respecting a drug to be used for dental purposes only; a physician or dentist and a member of good standing of a professional medical or dental association; and

(b) in any other case, a physician and a member of good standing of a professional medical association.

5. Standard Operating Procedure (SOP)

A Standard Operating Procedure (SOP) is a set of written instructions that document a routine or repetitive activity followed by a clinical trial site. The development and use of SOPs are an integral part of a successful quality system as it provides all research team members with the information to perform a clinical trial properly, and facilitates consistency in the quality and integrity of an investigational product or end-result.

Responsibility

The Principal Investigator (PI) is responsible for ensuring that the SOPs are written and modified in accordance with ICH E6 8.0 and with Greek legislation.

All research team members in the 2nd Department of Internal Medicine, University Hospital of Ioannina, Greece have responsibilities in this SOP.

Procedure

Writing of SOPs

1. **Writing styles:** SOPs should be written in a concise, step-by-step, easy-to-read format. The information presented should be unambiguous and not overly complicated. The active voice and present verb tense should be used. The term "you" should not be used, but implied. The document should not be wordy, redundant, or overly lengthy. The SOPs

should be simple and short. Information should be conveyed clearly and explicitly to remove any doubt as to what is required. Also, a flow chart may be used to illustrate the process being described.

2. **SOP Preparation:** A clinical trial site should have a procedure in place for determining what procedures or processes need to be documented. Those SOPs should then be written by individuals knowledgeable with the activity and the site's internal structure. These individuals are essentially subject-matter experts who actually perform the work or use the process. A team approach can be followed, especially for multi-tasked processes where the experiences of a number of individuals are critical, which also promotes “buy-in” from potential users of the SOP. SOPs should be written with sufficient detail so that someone with limited experience with or knowledge of the procedure, but with a basic understanding, can successfully reproduce the procedure when unsupervised. The experience requirement for performing an activity should be noted in the section on personnel qualifications. For example, if a basic chemistry or biological course experience or additional training is required that requirement should be indicated.
3. **SOP format:** SOPs should be organized to ensure ease and efficiency in use and to be specific to the site which develops it. A generalized format includes the following:
    a. **Title** - clearly identifying the activity or procedure, an SOP identification (ID) number, date of issue and/or revision, the name of the clinical trial site to which this SOP applies, and the date approval of the SOP.
    b. **Purpose** - identifying the intended use of the process.
    c. **Scope** - identifying when the procedure is to be followed.
    d. **Definitions** - defining any words, phrases, or acronyms having special meaning or application.
    e. **Personnel Qualifications/Responsibilities** - identifying any special qualifications users should have such as certification or training experience and/or any individual or positions having responsibility for the activity being described.
    f. **Procedure** - identifying all pertinent steps, in order, and the materials needed to accomplish the procedure.
    g. **Reference Section** - Documents or procedures that interface with the SOP should be fully referenced (including version), such as related SOPs, published literature, or methods manuals. Citations cannot substitute for the description of the method being followed in the site.
    h. **Associated documents** - being related to each SOP (specifically, e.g., as forms to be used and locations of files).

i. **SOP revision history** - recording the revision number, the date and the description of change.

j. **Signatories' field** – including the name, title, signature and date of the individuals preparing and approving the SOP, respectively.

k. **Three-year review** – (To be completed only if the SOP has reached the three year timeline for revision) including the name, title, signature and date of the individual reviewing the SOP.

SOP Review and Approval

1. SOPs should be reviewed (that is, validated) by one or more individuals with appropriate training and experience with the process. It is especially helpful if draft SOPs are actually tested by individuals other than the original writer before the SOPs are finalized.

2. The finalized SOPs should be approved as described in the site's Quality Management Plan or its own SOP for preparation of SOPs. Generally the immediate supervisor, such as a section or branch chief, review and approve each SOP. Signature approval indicates that an SOP has been both reviewed and approved by management. As per the Government Paperwork Elimination Act of 1998, use of electronic signatures, as well as electronic maintenance and submission, is an acceptable substitution for paper, when practical.

Frequency of Revisions and Reviews

1. SOPs need to remain current to be useful. Therefore, whenever procedures are changed, SOPs should be updated and re-approved. If desired, modify only the pertinent section of an SOP and indicate the change date/revision number for that section in the Table of Contents and the document control notation.
2. SOPs should be also systematically reviewed on a periodic basis, e.g. every 3 years, to ensure that the policies and procedures remain current and appropriate, or to determine whether the SOPs are even needed. The review date should be added to each SOP that has been reviewed. If an SOP describes a process that is no longer followed, it should be withdrawn from the current file and archived.
3. The review process should not be overly cumbersome to encourage timely review. The frequency of review should be indicated by management in the site's Quality Management Plan. That plan should also indicate the individual(s) responsible for ensuring that SOPs are current.

2nd Department of Internal Medicine, University Hospital of Ioannina, Greece	**STANDARD OPERATING PROCEDURE**	**Number: 002** **Effective Date: 18 JULY 2017** **Supersedes:**

WRITING AND MODIFICATION OF A CLINICAL RESEARCH STANDARD OPERATIONAL PROCEDURE (SOP)

References

EU Directive 2001/20/EC

EU Directive 2005/28/EC

Greek legislation:

31. Dec. 2003 Harmonization of Hellenic Legislation to Directive 2001/20/EC Official Governments' Gazette (FEK) 1973

07. Oct. 2004 National Ethics Committee Composition & Operating procedures

Official Governments' Gazette (FEK) 1503

25.Jan.2007 Greek Law Harmonization Dir_2005/28/EC Official Governments' Gazette (FEK) 64

21.Feb.2013 FEK 390/B Supplement to B´1973

Associated Documents

None

2nd Department of Internal Medicine, University Hospital of Ioannina, Greece	**STANDARD OPERATING PROCEDURE**	**Number: 002** **Effective Date: 18 JULY 2017** **Supersedes:**

WRITING AND MODIFICATION OF A CLINICAL RESEARCH STANDARD OPERATIONAL PROCEDURE (SOP)

SOP Revision History

Revision No.	Revision Date	Description of Change
002	18 JULY 2017	Revised SOP

Signatories

Prepared by: Dr Fotios Barkas MD (Print Name) **Date:** 11 JUNE 2014 (DD MMM YYYY)

Signature: **Time:** 09:00 (24 hr clock)

Title: Sub-Investigator

Approved by: Dr Evangelos Liberopoulos (Print Name) **Date:** 12 JUNE 2014 (DD MMM YYYY)

Signature: **Time:** 11:00 (24 hr clock)

Title: Sub-Investigator

2nd Department of Internal Medicine, University Hospital of Ioannina, Greece	**STANDARD OPERATING PROCEDURE**	**Number: 002** **Effective Date: 18 JULY 2017** **Supersedes:**

WRITING AND MODIFICATION OF A CLINICAL RESEARCH STANDARD OPERATIONAL PROCEDURE (SOP)

Three-year Review

Reviewed by: Dr Evangelos Liberopoulos MD (Print Name) Date: 18 JULY 2017 (DD MMM YYYY)

Signature: Time: 09:00 (24 hr clock)

Title: Sub- Investigator

2nd Department of Internal Medicine, University Hospital of Ioannina, Greece	**STANDARD OPERATING PROCEDURE**	**Number: 002** **Effective Date: 18 JULY 2017** **Supersedes:**

STORAGE AND RETENTION OF CLINICAL RESEARCH RECORDS (ESSENTIAL DOCUMENTS)

Purpose

The purpose of this Standard Operating Procedure (SOP) is to describe the procedures to be followed for the storage and retention of clinical research records - "Essential Documents for the Conduct of a Clinical Trial" as outlined in ICH E6 8.0" and in Greek legislation (31. Dec. 2003 Harmonization of Hellenic Legislation to Directive 2001/20/EC Official Governments' Gazette (FEK) 1973, 07. Oct. 2004 National Ethics Committee Composition & Operating procedures Official Governments' Gazette (FEK) 1503, 25.Jan.2007 Greek Law Harmonization Dir_2005/28/EC Official Governments' Gazette (FEK) 64, 21.Feb.2013 FEK 390/B Supplement to B΄1973).

Scope

This SOP applies to all site personnel and to the clinical research records produced at 2nd Department of Internal Medicine, University Hospital of Ioannina, Greece.

Definitions

1. Good Clinical Practice (GCP)

A standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected.

2. Essential Documents

Documents which individually and collectively permit evaluation of the conduct of a study and the quality of the data produced. (IC, E6 1.23)

3. Investigator

A person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the Principal Investigator.

STORAGE AND RETENTION OF CLINICAL RESEARCH RECORDS (ESSENTIAL DOCUMENTS)

4. Principal Investigator (PI)

The person responsible to the sponsor for the conduct of the clinical trial at the clinical trial site, who is entitled to provide health care under the laws of the province where that clinical trial site is located, and who is

(a) in the case of a clinical trial respecting a drug to be used for dental purposes only; a physician or dentist and a member of good standing of a professional medical or dental association; and

(b) in any other case, a physician and a member of good standing of a professional medical association.

Responsibility

The Principal Investigator (PI) is responsible for ensuring that the clinical research records and documentation is stored in accordance with ICH E6 8.0 and with Greek legislation.

All research team members in the 2nd Department of Internal Medicine, University Hospital of Ioannina, Greece have responsibilities in this SOP.

Procedure

Ongoing Site File Essential Study Documentation

All site research team members

1. Prepare site file Essential documents in accordance with ICH GCP section 8.0 and group into three (3) sections according to stage of the study:
   - Before the clinical phase of the trial commences
   - During the clinical conduct of the trial
   - After completion or termination of the trial

2. Keep Essential documents in a secure location (e.g. locked room or cupboard) to ensure privacy and confidentiality is maintained and accessible only to authorized personnel.

3. Make available all Essential documents in the event of an audit or regulatory inspection.

4. Retain Investigator Site File for a period of the past 15 years or for a specified longer period (according to regulatory requirements or in agreement with the sponsor being responsible to inform our site as to when these documents no longer need to be retained).

Archiving Site File Essential Study Documentation

All site research team members

5. At the completion of the study (start date for record retention) and upon confirmation from the sponsor that the study can be archived, collect the Site File Essential study documentation and prepare it for archiving.
6. Obtain document storage boxes.

7. Label the outside of the archive box with the:
   - Sponsor name
   - Study name
   - Study title reference number
   - Study site number
   - Name of PI/Investigator
   - Archival date
   - Date to be archived until

8. Archive box (on-site or off-site) in such a way that it preserves the integrity and readability of Essential documents:
   - Secure location (professor's locked office at the first basement) – protected from loss, theft or damage
   - Protected from environmental factors (e.g. fire damage or water damage; pests etc)

9. Once the study has completed its scheduled retention time and the PI/Investigator will be responsible for the destruction of the study documents at the secure location after communicating with the Sponsor.

References

EU Directive 2001/20/EC

EU Directive 2005/28/EC

31. Dec. 2003 Harmonization of Hellenic Legislation to Directive 2001/20/EC Official Governments' Gazette (FEK) 1973

07. Oct. 2004 National Ethics Committee Composition & Operating procedures Official Governments' Gazette (FEK) 1503

25. Jan.2007 Greek Law Harmonization Dir_2005/28/EC Official Governments' Gazette (FEK) 64

21.Feb.2013 FEK 390/B Supplement to B´1973

Associated Documents

1 Document retention log

2 Release form for the destruction of study documentation

2nd Department of Internal Medicine, University Hospital of Ioannina, Greece	**STANDARD OPERATING PROCEDURE**	**Number: 002** **Effective Date: 18 JULY 2017** **Supersedes:**

STORAGE AND RETENTION OF CLINICAL RESEARCH RECORDS (ESSENTIAL DOCUMENTS)

SOP Revision History

Revision No.	Revision Date	Description of Change
002	18 JULY 2017	Revised SOP

Signatories

Prepared by: Dr Fotios Barkas MD (Print Name) **Date:** 10 JUNE 2014 (DD MMM YYYY)

Signature: **Time:** 09:00 (24 hr clock)

Title: Sub-Investigator

Approved by: Dr Evangelos Liberopoulos (Print Name) **Date:** 11 JUNE 2014 (DD MMM YYYY)

Signature: **Time:** 11:00 (24 hr clock)

Title: Sub-Investigator

2nd Department of Internal Medicine, University Hospital of Ioannina, Greece	**STANDARD OPERATING PROCEDURE**	**Number: 002** **Effective Date: 18 JULY 2017** **Supersedes:**

STORAGE AND RETENTION OF CLINICAL RESEARCH RECORDS (ESSENTIAL DOCUMENTS)

Three-year Review

Reviewed by: Dr Evangelos Liberopoulos MD (Print Name) Date: 18 JULY 2017 (DD MMM YYYY)

Signature: Time: 11:05

Title: Sub-Investigator (24 hr clock)

Document Retention Log		2nd Department of Internal Medicine, University Hospital of Ioannina, Greece
Sponsor:	Study:	
Date of Study Closure:		
Location of Retention: Professor Elisaf's locked office in the first basement of University Hospital of Ioannina, Greece		

Client / Study	Investigator	Box # &/or Bar Code	Documents Retained	# of years to be retained	Start Date	End Date	Authorized by to be Destroyed	Destruction Date

<table>
<tr><td colspan="2">Document Retention Log</td><td rowspan="2">2nd Department of Internal Medicine, University Hospital of Ioannina, Greece</td></tr>
<tr><td>Sponsor:</td><td>Study:</td></tr>
<tr><td colspan="3">Date of Study Closure:</td></tr>
<tr><td colspan="3">Location of Retention: Professor Elisaf's locked office in the first basement of University Hospital of Ioannina, Greece</td></tr>
</table>

RELEASE FORM FOR THE DESTRUCTION OF STUDY DOCUMENTATION		2nd Department of Internal Medicine, University Hospital of Ioannina, Greece
Sponsor/CRO Name	Protocol Title/Number	
Principal Investigator		

I hereby have been authorized by <<sponsor name>> to destroy all documents pertaining to the above study. Documents have been stored for the past 15 years or for a specified longer period (according to regulatory requirements or in agreement with the sponsor being responsible to inform our site as to when these documents no longer need to be retained).

PI Signature:_____	Date:_____

2nd Department of Internal Medicine, University Hospital of Ioannina, Greece	**STANDARD OPERATING PROCEDURE**	**Number: 002** **Effective Date: 18 JULY 2017** **Supersedes:**

INFORMED CONSENT PROCESS

Purpose

Ensuring that clinical research study participants are fully informed about a study is an essential step in conducting clinical research. The written informed consent Form (ICF) is an important part of this process. The ICF is comprised of the document of information and consent signature form. The information provided in the ICF must meet the International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) guidelines, as well as local requirements and regulatory and sponsor requirements. In addition, the ICF must be approved by the appropriate ethics committee (EC) prior to use.

Scope

This Standard Operating Procedure applies to all staff at this study site who are permitted to obtain informed consent from study participants. These staff will be identified in the Delegation of Responsibilities Log.

The Investigator of Record has ultimate responsibility for ensuring that all applicable study site staff members follow this SOP.

Definitions

1. **Principal Investigator**

   The person responsible to the sponsor for the conduct of the clinical trial at the clinical trial site, who is entitled to provide health care under the laws of the province where that clinical trial site is located, and who is

   a. in the case of a clinical trial respecting a drug to be used for dental purposes only; a physician or dentist and a member of good standing of a professional medical or dental association; and

   b. in any other case, a physician and a member of good standing of a professional medical association.

2. **Subinvestigator**

   Any individual member of the clinical trial team designated and supervised by the investigator at a trial site to perform critical trial-related procedures and/or to make important trial-related decisions (e.g., associates, residents, research fellows).

2nd Department of Internal Medicine, University Hospital of Ioannina, Greece	**STANDARD OPERATING PROCEDURE**	**Number: 002** **Effective Date: 18 JULY 2017** **Supersedes:**

INFORMED CONSENT PROCESS

3. Informed Consent

Consent by a patient to undergo a medical or surgical treatment or to participate in an experiment after the patient understands the risks involved.

Responsibility

Staff who administer the informed consent process to study participants or to their legally authorized representatives, will be trained in Research Ethics, Good Clinical Practices, and study specific procedures so that they may fully explain the study to prospective participants, and do so in a respectful manner. The prospective participant must fully understand that participation in the research study is voluntary, and the staff who administers informed consent must be able to judge that the prospective participant comprehends the study procedures and is able to freely give consent to join the study.

Procedure

Investigator/ Sub-Investigator/ Study Coordinator

1. When a patient is identified by hospital or study staff as a candidate for participation in the study, the staff responsible for administering informed consent will visit the patient prior to research procedures and explain the study to the patient.

2. If the patient is a child or an adult unable to discuss the study, the study staff will discuss the study with a legally qualified representative, which may be the parent or other family member.

3. The study staff will ensure that informed consent is obtained in a setting free of coercion and undue influence.

4. The study staff will provide as much time as needed in the informed consent discussion to address all the patients' questions and concerns.

5. After completing the informed consent discussion, the study staff member will ensure that the patient understands the information provided in the informed consent form and the discussion by asking the patient or guardian a set of comprehension questions about the form. If the answers indicate any misunderstandings of study-related information, the study staff member will review and explain that information again to correct the misunderstandings.

INFORMED CONSENT PROCESS

6. When the study staff believes the patient understands fully about the study, the staff may ask the patient if he or she accepts to be screened or enrolled in the study.

7. If the patient agrees to be in the study:

    - the study staff will obtain the patient's signature on the consent form, and ask the patient to write the day's date and his or her name on the consent form

    - the study staff will sign on the consent form, and write the day's date and his or her name on the consent form

    - if a parent or other legally authorized representative is required to sign, the study staff will obtain that person's signature, and have that person write the day's date and his or her name on the consent form

    - a copy of the consent form will be offered to the patient or to his or her legally authorized representative.

8. If the patient does not agree to be in the study:

    - The study staff will end the discussion, and thank the patient for his or her time.

    - The patient will not be screened or enrolled in the study

    - The study staff will emphasize that the patient's access to medical care and/or other services provided will not be affected by his or her decision whether or not to screen for or take part in the study.

9. If the patient has signed the consent, the study staff will assign a Participant Number to the participant, and write it on the company provided logs.

10. All original signed and dated consent forms should be filed at the site. During the trial these can be maintained with the appropriate Case Record Forms. After the trial they can be filed with the patient's notes, CRF or in the Investigator Site File as appropriate.

11. It is the responsibility of the sponsor company to inform the investigator when they can destroy these documents.

12. The signed and dated written informed consent forms must be available for review by the sponsor company representatives for data verification purposes or audit. They must also be made available to any regulatory body during regulatory inspection/audit visits.

2nd Department of Internal Medicine, University Hospital of Ioannina, Greece	**STANDARD OPERATING PROCEDURE**	**Number: 002** **Effective Date: 18 JULY 2017** **Supersedes:**

INFORMED CONSENT PROCESS

References

Good Clinical Practice; Consolidated Guidance (ICH-E6), 1997

EU Directive 2001/20/EC

EU Directive 2005/28/EC

Greek legislation:

31. Dec. 2003 Harmonization of Hellenic Legislation to Directive 2001/20/EC Official Governments' Gazette (FEK) 1973

07. Oct. 2004 National Ethics Committee Composition & Operating procedures Official Governments' Gazette (FEK) 1503,

25.Jan.2007 Greek Law Harmonization Dir_2005/28/EC Official Governments' Gazette (FEK) 64

21.Feb.2013 FEK 390/B Supplement to B´1973.

Associated Documents

None

2nd Department of Internal Medicine, University Hospital of Ioannina, Greece	**STANDARD OPERATING PROCEDURE**	**Number: 002** **Effective Date: 18 JULY 2017** **Supersedes:**

INFORMED CONSENT PROCESS

Revision History

Revision No.	Revision Date	Description of Change
002	18 JULY 2017	Revised SOP

Signatories

Prepared by: Dr Fotios Barkas MD (Print Name) **Date:** 12 May 2014 (DD MMM YYYY)

Signature: **Time:** 12:00 (24 hr clock)

Title: Sub-Investigator

Approved by: Dr Evangelos Liberopoulos MD (Print Name) **Date:** 13 May 2014 (DD MMM YYYY)

Signature: **Time:** 11:00 (24 hr clock)

Title: Sub-Investigator

2nd Department of Internal Medicine, University Hospital of Ioannina, Greece	**STANDARD OPERATING PROCEDURE**	**Number: 002** **Effective Date: 18 JULY 2017** **Supersedes:**

INFORMED CONSENT PROCESS

Three-year Review

Reviewed by: Dr Evangelos Liberopoulos MD (Print Name) Date: 18 JULY 2017 (DD MMM YYYY)

Signature: Time: 11:10

Title: Sub-Investigator MD (24 hr clock)

2nd Department of Internal Medicine, University Hospital of Ioannina, Greece	**STANDARD OPERATING PROCEDURE**	**Number: 002** **Effective Date: 18 JULY 2017** **Supersedes:**

MANAGEMENT OF INVESTIGATIONAL PRODUCT

Purpose

This Standard Operating Procedure (SOP) describes the management of Investigational Product (IP) which is used for the conduct of a clinical trial at 2nd Department of Internal Medicine, University Hospital of Ioannina, Greece.

Scope

This SOP is applicable to all drug interventional clinical trials conducted by 2nd Department of Internal Medicine, University Hospital of Ioannina, Greece and describes all handling processes from receipt of IP to destruction of IP.

Definition

1. **Investigator**

   A person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the Principal Investigator.

2. **Investigational Product**

   A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use.

3. **Principal Investigator (PI)**

   The person responsible to the sponsor for the conduct of the clinical trial at the clinical trial site, who is entitled to provide health care under the laws of the province where that clinical trial site is located, and who is

   (a) in the case of a clinical trial respecting a drug to be used for dental purposes only; a physician or dentist and a member of good standing of a professional medical or dental association; and

   (b) in any other case, a physician and a member of good standing of a professional medical association.

4. **Subinvestigator**

Any individual member of the clinical trial team designated and supervised by the investigator at a trial site to perform critical trial-related procedures and/or to make important trial-related decisions (e.g., associates, residents, research fellows).

5. **Study Coordinator**

   A key member of the clinical team who manages the work directly for the investigator**.** Responsibilities usually include maintaining accurate patient documentation, dispensing medication, and general patient correspondence.

Responsibility

The Principal Investigator (PI) is ultimately responsible for IP accountability at 2nd Department of Internal Medicine, University Hospital of Ioannina, Greece. Some of the investigator's duties for IP accountability may be delegated to an appropriate pharmacist or another appropriate individual who is under the supervision of the investigator.

The following clinical research team (as applicable) has responsibilities in this SOP:

- Principal Investigator (PI)
- Subinvestigator (SI)
- Study Coordinator (SC)
- Pharmacist

Procedure

Receipt of Investigational Product

Principal Investigator/ Investigator/ Pharmacist/ Subinvestigator/ Study Coordinator should:

1. Accept IP shipments and inventory against the shipping documentation and inspect for damage.

2. Acknowledge IP receipt and report any damage or discrepancies to the supplier.

3. Record on IP Accountability Log (Site Inventory) the following information:
   - Date of receipt/dispensation

- Subject ID (to whom IP was dispensed
- Kit #
- Lot/Batch #
- # units received/dispensed
- # total units remaining at site
- Staff / Monitor Initials
- Sponsor company IP tracking logs will be used for company sponsored trials

4. File the shipping and inventory documentation and IP Accountability Log (Site Inventory) in the Investigator Site File.

Investigational Product Storage

Principal Investigator/ Investigator/ Pharmacist/ Subinvestigator/ Study Coordinator should:

5. Store IP:
   - According to protocol-specific temperature/humidity/light requirements and maintain a temperature log
   - In an appropriate, secure location with back-up power supply with access to authorized study staff only

Investigational Product Accountability

Principal Investigator/ Investigator/ Pharmacist/ Subinvestigator/ Study Coordinator should:

6. Document IP dispensed to and returned from each subject on the IP Accountability Log (Subject Specific) the following information:
   - Subject identifier
   - Kit #
   - Date IP dispensed/returned
   - Amount dispensed/returned
   - Initials of person dispensing and collecting returned IP from the subject

Sponsor company IP accountability logs will be used for company sponsored trials

7. Ensure IP Accountability Logs include at minimum the following details:
    - Sponsor Name
    - Protocol Title
    - Protocol Code or Identification #
    - Investigator Name
    - Site #
    - IP Name
    - Sponsor company IP accountability logs will be used for company sponsored trials

8. File the IP Accountability Log (Subject Specific) in the Investigator Site File.

Disposition of Investigational Product

Principal Investigator/ Investigator/ Pharmacist/ Subinvestigator/ Study Coordinator should:

In circumstances approved by the sponsor, unused IP may be collected and dispensed for remote destruction considering the following items:

- The remaining unused and returned IP has been checked for quantity and quality by the Clinical Research Associate (CRA) and this review has been documented.
- The destruction is done somewhere else since there is no suitable infrastructure in site. Therefore, the procedure of destruction and the confirmation of destruction, needs to be documented.

9. File the IP Accountability Log (Site Inventory) and/or IP destruction records in the Investigator Site File.

Return of Investigational Product to Sponsor

MANAGEMENT OF INVESTIGATIONAL PRODUCT

Principal Investigator/ Investigator/ Pharmacist/ Subinvestigator/ Study Coordinator should:

10. Return all unused-dispensed and undispensed IP using an appropriate IP return form as directed by the Sponsor. Sponsor company IP return forms will be used for company sponsored trials.

11. Document receipt of returned IP by the Sponsor.

12. File IP return form in the Investigator Site File.

References

EU Directive 2001/20/EC

EU Directive 2005/28/EC

Greek legislation:

31. Dec. 2003 Harmonization of Hellenic Legislation to Directive 2001/20/EC Official Governments' Gazette (FEK) 1973

07. Oct. 2004 National Ethics Committee Composition & Operating procedures Official Governments' Gazette (FEK) 1503,

25.Jan.2007 Greek Law Harmonization Dir_2005/28/EC Official Governments' Gazette (FEK) 64

21.Feb.2013 FEK 390/B Supplement to B´1973.

2nd Department of Internal Medicine, University Hospital of Ioannina, Greece	**STANDARD OPERATING PROCEDURE**	**Number: 002** **Effective Date: 18 JULY 2017** **Supersedes:**

MANAGEMENT OF INVESTIGATIONAL PRODUCT

Associated Documents

1 IP Accountability Log (Site Inventory)

2 IP Accountability Log (Subject Specific)

3 IP Return Form

2nd Department of Internal Medicine, University Hospital of Ioannina, Greece	**STANDARD OPERATING PROCEDURE**	**Number: 002** **Effective Date: 18 JULY 2017** **Supersedes:**

MANAGEMENT OF INVESTIGATIONAL PRODUCT

SOP Revision History

Revision No.	Revision Date	Description of Change
002	18 JULY 2017	Revised SOP

Signatories

Prepared by: Dr Fotios Barkas MD (Print Name) **Date:** 8/JUL/2014 (DD MMM YYYY)

Signature: **Time:** 19:00 (24 hr clock)

Title: Sub-Investigator

Approved by: Dr Evangelos Limperopoulos MD (Print Name) **Date:** 9/JUL/2014 (DD MMM YYYY)

Signature: **Time:** 11:20 (24 hr clock)

Title: Sub-Investigator

2nd Department of Internal Medicine, University Hospital of Ioannina, Greece	**STANDARD OPERATING PROCEDURE**	**Number: 002** **Effective Date: 18 JULY 2017** **Supersedes:**

MANAGEMENT OF INVESTIGATIONAL PRODUCT

Three-year Review

Reviewed by: Dr Evangelos Liberopoulos MD (Print Name) Date: 18 JULY 2017 (DD MMM YYYY)

Signature: Time: 11:15

Title: Sub-Investigator (24 hr clock)

INVESTIGATIONAL PRODUCT ACCOUNTABILITY LOG (SUBJECT SPECIFIC)			2nd Department of Internal Medicine, University Hospital of Ioannina, Greece
Sponsor:	Protocol:	Investigator:	
Investigational Product:	Subject:	Site No.:	

RETURNED BY SUBJECT							COMMENTS	
Date Dispensed (ddMMMyyyy)	Kit #	# units dispensed	Staff Initials	Date Returned (ddMMMyyyy)	# units returned	Staff Initials	Monitor Initials/Date	Inconsistencies, reason if not returned, etc.

To be signed once form is complete.

Investigator or Pharmacist (Print): _____ Signature: _____ Date Signed: _____
dd-MMM-yyyy

CRA (Print): _____ CRA Signature: _____ Date Signed: _____
dd-MMM-yyyy

INVESTIGATIONAL PRODUCT ACCOUNTABILITY LOG (SITE INVENTORY)

Sponsor:	Protocol:	Investigator: Site No.:	2nd Department of Internal Medicine, University Hospital of Ioannina, Greece

Investigational Product:

Date of Receipt/ Dispensation ddMMMyyyy	Subject ID (to whom IP was dispensed)	Kit #	Lot/Batch#	# units received	# units dispended	Total number of kits remained in site	Staff Initial	Monitor Initial/Date

To be signed once form is complete.

Investigator or Pharmacist (Print): _____ Signature: _____ Date Signed: _____
dd-MMM-yyyy

CRA (Print): _____ CRA Signature: _____ Date Signed: _____
dd-MMM-yyyy

INVESTIGATIONAL PRODUCT RETURN FORM

2ND DEPARTMENT OF INTERNAL MEDICINE, UNIVERSITY HOSPITAL OF IOANNINA, GREECE

Sponsor:	Protocol:	Investigator Name:	Site #:

Date of Return (dd-MMM-yyyy): Courier: Tracking #:

Sender: (Name and Address)	Ship To: (Name and Address)

Medication Name	**Kit #**	**Quantity**	**Lot/Batch #**	**Expiry Date**	**Comments (e.g. reason for return)**

Prepared by:

Signature: _____ _____

Name, Role (print): **Date (dd-MMM-yyyy)**

Investigator or Pharmacist:

Signature: _____ _____

INVESTIGATIONAL PRODUCT RETURN FORM			2ND DEPARTMENT OF INTERNAL MEDICINE, UNIVERSITY HOSPITAL OF IOANNINA, GREECE
Sponsor:	Protocol:	Investigator Name:	Site #:

Name, Role (print):	**Date (dd-MMM-yyyy)**

2nd Department of Internal Medicine, University Hospital of Ioannina, Greece	**STANDARD OPERATING PROCEDURE**	**Number: 002** **Effective Date: 18 JULY 2017** **Supersedes:**

ADVERSE EVENT & SERIOUS ADVERSE EVENT RECORDING/REPORTING

Purpose

This Standard Operating Procedure (SOP) describes the process of identifying, recording and reporting of Adverse Events (AE) and Serious Adverse Events (SAE) or Serious Adverse Drug Reaction (ADR) for a clinical trial at 2nd Department of Internal Medicine, University Hospital of Ioannina, Greece.

Scope

This SOP is applicable to all clinical research personnel involved in conducting clinical trial activities at 2nd Department of Internal Medicine, University Hospital of Ioannina, Greece.

Definition

(a) Adverse Event

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable or unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

(b) Case Report Form

A printed, optical, or electronic document designed to record all of the protocol required information to be reported to the sponsor on each trial subject.

(c) Serious Adverse Event or Serious Adverse Drug Reaction (SADR)

Any untoward medical occurrence that at any dose:

- Results in death,
- Is life-threatening,
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect

(d) Suspected Unexpected Serious Adverse Reaction (SUSAR)

An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g. Investigator's Brochure for an unapproved investigational product or package insert/summary of product characteristics for an approved product).

Other important medical events that may not be immediately life threatening or result in death or hospitalization, but that may jeopardize the patient or may require intervention to prevent any of the outcomes listed above may also be considered serious.

(e) Principal Investigator (PI)

The person responsible to the sponsor for the conduct of the clinical trial at the clinical trial site, who is entitled to provide health care under the laws of the province/state where that clinical trial site is located, and who is

(f) in the case of a clinical trial respecting a drug to be used for dental purposes only; a physician or dentist and a member of good standing of a professional medical or dental association; and

(g) in any other case, a physician and a member of good standing of a professional medical association.

(h) Subinvestigator

Any individual member of the clinical trial team designated and supervised by the investigator at a trial site to perform critical trial related procedures and/or to make important trial related decisions (e.g., associates, residents, research fellows).

(i) Study Coordinator

A key member of the clinical team who manages the work directly for the investigator**.** Responsibilities usually include maintaining accurate patient documentation, dispensing medication, and general patient correspondence.

Responsibility

The Principal Investigator (PI) is ultimately responsible for the management of AE's and SAE's at 2nd Department of Internal Medicine, University Hospital of Ioannina, Greece. All staff in contact with subjects are responsible for noting AE's and SAE's that are reported by the subject and making it known to the appropriate clinical research team member.

2nd Department of Internal Medicine, University Hospital of Ioannina, Greece	**STANDARD OPERATING PROCEDURE**	**Number: 002** **Effective Date: 18 JULY 2017** **Supersedes:**

ADVERSE EVENT & SERIOUS ADVERSE EVENT RECORDING/REPORTING

The following clinical research team (as applicable) has responsibilities in this SOP:

- All staff in contact with subjects
- Principal Investigator (PI) / Investigator
- Subinvestigator (SI)
- Study Coordinator (SC)

Procedure

Recording and reporting of AE/SAE

Principal Investigator/ Investigator/ Subinvestigator/ Study Coordinator should:

1. Review for adverse events on an ongoing basis (study visit or study assessment) using patient reported history, physical examination, laboratory data, chart review and other available data for each patient enrolled in a clinical trial.

2. Document/record the following information of the AE in the source notes and in the Case Report Form (CRF):

    - Event (e.g., nausea; vomiting; headache)
    - AE classification: serious or not
    - Start and stop dates
    - Start and stop times
    - Severity (as guided by the protocol – mild; moderate; severe)
    - Action taken regarding the study drug or study procedure
    - Treatment/medication given or action taken
    - Outcome

3. **Note: The** Investigator is responsible for documenting the **causality** (e.g., definite; probable; possible; unlikely) between the investigational product and the event as specified in the protocol.

4. Complete and file source documentation and case report form for collection of adverse event information in the subject's file and the Investigator Site File.

Recording and reporting of SAE

Principal Investigator/ Investigator/ Subinvestigator/ Study Coordinator should:

1. Identify the event to be serious.

2. Report the details of the SAE to the Sponsor within 24 hours of the event occurring or within 24 hours after the event has been identified.

3. Complete the Sponsor provided SAE report form.

4. Fax initial SAE report form to the Sponsor or report it through Case Report Form (CRF).

5. Notify the institutional ethics committee (EC) of all incidences of SAE's in accordance with the local requirements of the EC.

6. Provide follow-up information of the SAE to the Sponsor and EC.

References

EU Directive 2001/20/EC

EU Directive 2005/28/EC

Greek legislation:

31. Dec. 2003 Harmonization of Hellenic Legislation to Directive 2001/20/EC Official Governments' Gazette (FEK) 1973

07. Oct. 2004 National Ethics Committee Composition & Operating procedures Official Governments' Gazette (FEK) 1503,

25.Jan.2007 Greek Law Harmonization Dir_2005/28/EC Official Governments' Gazette (FEK) 64

21.Feb.2013 FEK 390/B Supplement to B´1973.

Associated Documents

Not applicable

2nd Department of Internal Medicine, University Hospital of Ioannina, Greece	**STANDARD OPERATING PROCEDURE**	**Number: 002** **Effective Date: 18 JULY 2017** **Supersedes:**

ADVERSE EVENT & SERIOUS ADVERSE EVENT RECORDING/REPORTING

SOP Revision History

Revision No.	Revision Date	Description of Change
002	18 JULY 2017	Revised SOP

Signatories

Prepared by: Dr Fotios Barkas MD (Print Name) **Date:** 8/Jul/2014 (DD MMM YYYY)

Signature: **Time:** 18:00 (24 hr clock)

Title: Sub-Investigator

Approved by: Dr Evangelos Liberopoulos MD (Print Name) **Date:** 9/Jul/2014 (DD MMM YYYY)

Signature: **Time:** 11:16 (24 hr clock)

Title: Sub-Investigator

2nd Department of Internal Medicine, University Hospital of Ioannina, Greece	**STANDARD OPERATING PROCEDURE**	**Number: 002** **Effective Date: 18 JULY 2017** **Supersedes:**

ADVERSE EVENT & SERIOUS ADVERSE EVENT RECORDING/REPORTING

Three-year Review

Reviewed by: Dr Evangelos Liberopoulos MD (Print Name) Date: 18 JULY 2017 (DD MMM YYYY)

Signature: Time: 11:20 (24 hr clock)

Title: Sub-Investigator

2nd Department of Internal Medicine, University Hospital of Ioannina, Greece	**STANDARD OPERATING PROCEDURE**	**Number: 002** **Effective Date: 18 JULY 2017** **Supersedes:**

RECRUITMENT PROCEDURES

Purpose

The purpose of this Standard Operating Procedure (SOP) is to describe the procedures to be followed for patient recruitment in a clinical trial, as outlined in ICH E6 8.0 and in Greek legislation [31. Dec. 2003 Harmonization of Hellenic Legislation to Directive 2001/20/EC Official Governments' Gazette (FEK) 1973, 07. Oct. 2004 National Ethics Committee Composition & Operating procedures Official Governments' Gazette (FEK) 1503, 25.Jan.2007 Greek Law Harmonization Dir_2005/28/EC Official Governments' Gazette (FEK) 64, 21.Feb.2013 FEK 390/B Supplement to B΄1973].

Scope

This Standard Operating Procedure applies to all staff at this study site who are permitted to perform patient recruitment for a clinical study. These staff will be identified in the Delegation of Responsibilities Log.

The Investigator of Record has ultimate responsibility for ensuring that all applicable study site staff members follow this SOP.

Definitions

1. **Principal Investigator (PI)**

   The person responsible to the sponsor for the conduct of the clinical trial at the clinical trial site, who is entitled to provide health care under the laws of the province where that clinical trial site is located, and who is a physician and a member of good standing of a professional medical association.

2. **Subinvestigator**

   Any individual member of the clinical trial team designated and supervised by the investigator at a trial site to perform critical trial-related procedures and/or to make important trial-related decisions (e.g., associates, residents, research fellows).

2nd Department of Internal Medicine, University Hospital of Ioannina, Greece	**STANDARD OPERATING PROCEDURE**	**Number: 002** **Effective Date: 18 JULY 2017** **Supersedes:**

RECRUITMENT PROCEDURES

3. **Standard Operating Procedure (SOP)**

   A Standard Operating Procedure (SOP) is a set of written instructions that document a routine or repetitive activity followed by a clinical trial site. The development and use of SOPs are an integral part of a successful quality system as it provides all research team members with the information to perform a clinical trial properly, and facilitates consistency in the quality and integrity of an investigational product or end-result

4. **Patient recruitment**

Patient recruitment includes a variety of services - performed by a Patient Recruitment Service Provider or by our site in the 2nd Department of Internal Medicine, University Hospital of Ioannina, Ioannina, Greece - to increase enrollment into clinical trials.

5. **Eligibility criteria**

In clinical trials, certain requirements must be met for an individual to be included in a study. These requirements help make sure that patients in a trial are similar to each other in terms of specific factors such as age, general health, and previous treatment. When all participants meet the same eligibility criteria, it gives researchers greater confidence that results of the study are caused by the intervention being tested and not by other factors. (NCI) Summary criteria for participant selection; includes Inclusion and Exclusion criteria. (NLM)

Responsibility

Staff who is responsible for recruiting potential study participants will be trained in Research Ethics, Good Clinical Practices, and study specific procedures.

Procedure

1. **Patient recruitment services provided by the sponsor**

   Patient recruitment services may be contracted for by pharmaceutical companies, biotechnology companies, medical device companies or contract research organizations (CROs).

2. **Patient recruitment services provided by our site**

RECRUITMENT PROCEDURES

a. Investigators can search potential participants fulfilling the eligibility criteria of a study through an existing electronic database. This database concerns patients referring to the 2nd Department of Internal Medicine, University Hospital of Ioannina, Ioannina, Greece and is continuously updated.

b. Investigators inform relevant patients referred to our Department about the study being conducted in our site.

c. Investigators make aware physicians of our department or other departments in the University Hospital of Ioannina, Ioannina, Greece of the study being conducted by our site through telephone, e-mail or direct communication.

d. Recruitment materials provided by the sponsor can be given to physicians or potential subjects in order to raise enrollment. These may include brochures, posters, letters, DVDs and flyers.

When relevant patients are referred to our site through the procedures above, the investigators inform them thoroughly about the study being conducted and the SOP regarding the informed consent is followed next.

References

Good Clinical Practice; Consolidated Guidance (ICH-E6), 1997

EU Directive 2001/20/EC

EU Directive 2005/28/EC

Reinventing Patient Recruitment: Revolutionary Ideas for Clinical Trial Success, Joan F. Bachenheimer, Bonnie A. Brescia, Gower Publishing, 2007

Associated Documents

None

2nd Department of Internal Medicine, University Hospital of Ioannina, Greece	**STANDARD OPERATING PROCEDURE**	**Number: 002** **Effective Date: 18 JULY 2017** **Supersedes:**

RECRUITMENT PROCEDURES

Revision No.	Revision Date	Description of Change
002	18 JULY 2017	Revised SOP

Signatories

Prepared by: Dr Fotios Barkas MD (Print Name) **Date:** 1 Sep 2014 (DD MMM YYYY)

Signature: **Time:** 12:00 (24 hr clock)

Title: Sub-Investigator

Approved by: Dr Evangelos Liberopoulos MD (Print Name) **Date:** 1 Sep 2014 (DD MMM YYYY)

Signature: **Time:** 11:00 (24 hr clock)

Title: Subi-Investigator

2nd Department of Internal Medicine, University Hospital of Ioannina, Greece	**STANDARD OPERATING PROCEDURE**	**Number: 002** **Effective Date: 18 JULY 2017** **Supersedes:**

RECRUITMENT PROCEDURES

Three-year Review

Reviewed by: Dr Evangelos Liberopoulos MD (Print Name) Date: 18 JULY 2017 (DD MMM YYYY)

Signature: Time: 11:25

Title: Sub-Investigator (24 hr clock)

2nd Department of Internal Medicine, University Hospital of Ioannina, Greece	**STANDARD OPERATING PROCEDURE**	**Number: 002** **Effective Date: 18 JULY 2017** **Supersedes:**

EQUIPMENT CALIBRATION AND MAINTENANCE

Purpose

The purpose of this Standard Operating Procedure (SOP) is to outline the activities involved in the routine calibration and maintenance of equipment used for clinical research trials to ensure its proper functioning and continued accuracy of the data collected by its use; and that this information is appropriately documented, and available for review and inspection.

Scope

This SOP is applicable to all equipment used in a clinical research trial that involves the participation of human research subjects at 2nd Department of Internal Medicine, University Hospital of Ioannina, Greece.

Definitions

1. **Calibration**

   The act of checking or adjusting the accuracy of a measuring instrument or a piece of equipment.

2. **Maintenance**

   Actions performed to keep equipment or systems in good working order.

Responsibility

The Principal Investigator (PI) is ultimately responsible for maintaining the equipment used in a clinical research trial however, the PI may delegate tasks as set out in this SOP to appropriately qualified research personnel.

The following study personnel have responsibilities in this SOP:

Principal Investigator (PI)
Sub Investigator (SI)
Study Coordinator (SC)

EQUIPMENT CALIBRATION AND MAINTENANCE

Procedure

Assessing Equipment Requirements <u>Before</u> the Clinical Phase of the Trial Commences

Investigator/ Sub-Investigator/Study Coordinator

1. Review the study Protocol to identify each type of equipment that will be required for the foreseen duration of the trial.

2. Prepare a complete equipment list using the Equipment List – Calibration/Maintenance Log (usually provided by the sponsor; otherwise use the corresponding log of our site) detailing the following:

   - Equipment identification (name/description – e.g. 12-Lead ECG machine)
   - Name of manufacturer
   - Model/serial number
   - Location of equipment

3. Review all trial required equipment calibration and maintenance records/documentation (dates/calibration tags) to ensure that the equipment has been properly maintained within an acceptable timeframe (instructed by the manufacturer equipment manual)).

4. Obtain calibration/maintenance service on each piece of equipment that has not been previously calibrated/maintained or if the current calibration date/tag has expired beyond one year of the last recorded date.

5. File the completed Equipment List – Calibration/Maintenance Log within the Investigator Site File so that it can be available for review and inspection.

Maintaining Equipment Requirements <u>During</u> the Clinical Conduct of the Trial

Investigator/ Sub-Investigator/ Study Coordinator

6. Review any Protocol amendments to identify if there have been any changes in the type of equipment that will be required for the duration of the trial. If additional equipment is required, follow steps 2-5.

Maintaining Equipment Requirements for Investigational Product (IP); and biological specimens

Investigator/ Sub-Investigator/ Study Coordinator

7. Ensure that refrigerators and freezers that are used in the storage of Investigational Product (IP) or biological specimens are suitable for the intended purpose and are routinely maintained to ensure that they are in proper working order.

8. Equip each refrigerator/freezer with a calibrated temperature monitoring device such as a digital Min/Max thermometer which includes an alarm/notification climate control system for out-of-range temperatures.

9. Ensure that the refrigerators/freezers are connected to a back-up power source in the event of a power failure.

10. Record refrigerator/freezer temperature readings daily during regular business hours on a Temperature Log provided by the sponsor or the corresponding temperature log of our site if provided; and provide an explanation and action taken if there are any temperature excursions that occur outside of the protocol specific requirements.

11. Maintain and file all completed temperature logs in the location of the refrigerator/freezer or within the Investigator Site File so that it can be available for review and inspection.

References

Good Clinical Practice (GCP) – ICH: International Conference on Harmonisation (E6)

EU Directive 2001/20/EC

EU Directive 2005/28/EC

2nd Department of Internal Medicine, University Hospital of Ioannina, Greece	**STANDARD OPERATING PROCEDURE**	**Number: 002** **Effective Date: 18 JULY 2017** **Supersedes:**

EQUIPMENT CALIBRATION AND MAINTENANCE

Associated Documents

1 Equipment List – Calibration and Maintenance Log

2 Temperature Log refrigerator 1

3 Temperature Log refrigerator 2

4 Temperature Log refrigerator 3

5 Temperature Log Room

2nd Department of Internal Medicine, University Hospital of Ioannina, Greece	**STANDARD OPERATING PROCEDURE**	**Number: 002** **Effective Date: 18 JULY 2017** **Supersedes:**

EQUIPMENT CALIBRATION AND MAINTENANCE

SOP Revision History

Revision No.	Revision Date	Description of Change
002	18 JULY 2017	Revised SOP

Signatories

Prepared by: Dr Fotios Barkas MD (Print Name) **Date:** 17 Nov 2014 (DD MMM YYYY)

Signature: **Time:** 10:00 (24 hr clock)

Title: Sub-Investigator

Approved by: Dr Evangelos Liberopoulos MD (Print Name) **Date:** 17 Nov 2014 (DD MMM YYYY)

Signature: **Time:** 12:00 (24 hr clock)

Title: Sub-Investigator

EQUIPMENT CALIBRATION AND MAINTENANCE

Three-year Review

Reviewed by: Dr Evangelos Liberopoulos MD (Print Name) Date: 18 JULY 2017 (DD MMM YYYY)

Signature: Time: 11:30

Title: Sub-Investigator (24 hr clock)

Example
Equipment List - Calibration and Maintenance Log

Protocol Number : ..... Investigator: .....

Site Number: .....

Equipment Identification & Model	Manufacturer	Serial Number	Equipment Location	Calibration/Maintenance Date of equipment	Next Calibration/Maintenance Due Date (e.g. annually)	Comments

2ND Department of Internal Medicine, University Hospital of Ioannina:
Investigator: M. Elisaf
Year: 2017, Month: April
Refrigerator 1 Location: Professor's Office at -1 Floor of University Hospital of Ioannina

Refrigerator 1/Temperature Log

2ND Department of Internal Medicine, University Hospital of Ioannina:		Investigator:	M. Elisaf
Refrigerator 1 Location:	Year: 2017 Month: APRIL Professor's Office at -1 Floor of University hospital of Ioannina		

IP Storage Acceptable Temperature Range* as per protocol: _2 – 8 °C_____

Specimen Storage Acceptable Temperature Range* as per protocol: _____

*Please notify Sponsor ***as soon as possible*** should any temperature reading be out of the specified range

Month/Day	Time	Actual Temp	Min Temp °C	Max Temp °C	Temperature Excursion Date(s)	Describe Circumstances of temperature excursion & corrective action taken	Signature / initials
APRIL **1**							
2							
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6							
7							
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10							
11							
12							
13							

2ND Department of Internal Medicine, University Hospital of Ioannina:
Investigator: M. Elisaf
Year: 2017, Month: April
Refrigerator 1 Location: Professor's Office at -1 Floor of University Hospital of Ioannina

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31							

2ND Department of Internal Medicine, University Hospital of Ioannina:
Investigator: M. Elisaf
Year: 2017, Month: April
Refrigerator 2 Location: Professor's Office at -1 Floor of University Hospital of Ioannina

Refrigerator 2/Temperature Log

2ND Department of Internal Medicine, University Hospital of Ioannina:		Investigator:	M. Elisaf
Refrigerator 2 Location:	Year: 2017 Month: APRIL Professor's Office at -1 Floor of University hospital of Ioannina		

IP Storage Acceptable Temperature Range* as per protocol: _2 – 8 °C_____

Specimen Storage Acceptable Temperature Range* as per protocol: _____

*Please notify Sponsor ***as soon as possible*** should any temperature reading be out of the specified range

Month/Day	**Time**	**Actual Temp**	**Min Temp °C**	**Max Temp °C**	**Temperature Excursion Date(s)**	**Describe Circumstances of temperature excursion & corrective action taken**	**Signature / initials**
APRIL **1**							
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2ND Department of Internal Medicine, University Hospital of Ioannina:
Investigator: M. Elisaf
Year: 2017, Month: April
Refrigerator 2 Location: Professor's Office at -1 Floor of University Hospital of Ioannina

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31							

2ND Department of Internal Medicine, University Hospital of Ioannina:
Investigator: M. Elisaf
Year: 2017, Month: April
Refrigerator 3 Location: Professor's Office at -1 Floor of University Hospital of Ioannina

Refrigerator 3/Temperature Log

2ND Department of Internal Medicine, University Hospital of Ioannina:	Investigator:	M. Elisaf
Refrigerator 3 Location:	Year: 2017 Month: APRIL Professor's Office at -1 Floor of University hospital of Ioannina	

IP Storage Acceptable Temperature Range* as per protocol: _2 – 8 °C_____

Specimen Storage Acceptable Temperature Range* as per protocol: _____

*Please notify Sponsor ***as soon as possible*** should any temperature reading be out of the specified range

Month/Day	**Time**	**Actual Temp**	**Min Temp °C**	**Max Temp °C**	**Temperature Excursion Date(s)**	**Describe Circumstances of temperature excursion & corrective action taken**	**Signature / initials**
APRIL **1**							
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12							
13							

2ND Department of Internal Medicine, University Hospital of Ioannina:
Investigator: M. Elisaf
Year: 2017, Month: April
Refrigerator 3 Location: Professor's Office at -1 Floor of University Hospital of Ioannina

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2ND Department of Internal Medicine, University Hospital of Ioannina:
Investigator: M. Elisaf
Year: 2017, Month: April
Room Location: Professor's Office at -1 Floor of University Hospital of Ioannina

Room /Temperature Log

2ND Department of Internal Medicine, University Hospital of Ioannina:		Investigator:	M. Elisaf
Room Location:	Year: 2017 Month: APRIL Professor's Office at -1 Floor of University hospital of Ioannina		

IP Storage Acceptable Temperature Range* as per protocol: _15 – 25 °C_____

Specimen Storage Acceptable Temperature Range* as per protocol: _____

*Please notify Sponsor ***as soon as possible*** should any temperature reading be out of the specified range

Month/Day	Time	Actual Temp	Min Temp °C	Max Temp °C	Temperature Excursion Date(s)	Describe Circumstances of temperature excursion & corrective action taken	Signature / initials
APRIL **1**							
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2nd Department of Internal Medicine, University Hospital of Ioannina, Greece	**STANDARD OPERATING PROCEDURE**	**Number: 002** **Effective Date: 18 JULY 2017** **Supersedes:**

SITE RESEARCH TEAM QUALIFICATIONS AND TRAINING

Purpose

The purpose of this Standard Operating Procedure (SOP) is to outline the process in place that ensures that the 2nd Department of Internal Medicine, University Hospital of Ioannina, Greece research team are appropriately qualified by education, training and/or experience to perform their delegated research-related tasks/responsibilities; and that their qualifications and training are fully documented.

Scope

This SOP is applicable to the Principal Investigator (PI) and all other research team members at 2nd Department of Internal Medicine, University Hospital of Ioannina, Greece.

Definitions

1. Curriculum Vitae (CV)

A written description of an individual's qualifications, work experience, skills and educational background.

2. Good Clinical Practice (GCP)

A standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected.

3. Principal Investigator

A person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the Principal Investigator (PI). In addition, PI is responsible to the sponsor for the conduct of the clinical trial at the clinical trial site, who is entitled to provide health care under the laws of the province where that clinical trial site is located, and who is

(a) in the case of a clinical trial respecting a drug to be used for dental purposes only; a physician or dentist and a member of good standing of a professional medical or dental association; and

(b) in any other case, a physician and a member of good standing of a professional medical association.

SITE RESEARCH TEAM QUALIFICATIONS AND TRAINING

4. Training

Training is defined as providing employees with the job or task information needed to develop or enhance the skills, knowledge and experience to performance their delegated responsibilities/tasks.

5. Training Record

A form in which all training is captured such as but not limited to:

- ICH E6: International Conference on Harmonization (ICH) Good Clinical Practice (GCP)
- EU Directive 2001/20/EC
- EU Directive 2005/28/EC
- Study specific training should include: study protocol, investigational medicinal product, study procedures, informed consent taking, Case Report Form completion, IVRS, and other relevant training determined by the Principal Investigator/Investigator
- Tri-Council Policy Statement; Ethical Conduct for Research Involving Humans
- Privacy Legislation - The Personal Information Protection and Electronic Documents Act (PIPEDA)
- Hazardous Materials Shipping certification - IATA
- Other Sponsor-Specific training (e.g. Investigator's Meeting; Site Initiation Visit)

SITE RESEARCH TEAM QUALIFICATIONS AND TRAINING

Responsibility

The Principal Investigator (PI) is to be qualified by education, training, and experience to assume the responsibility for the proper conduct of the trial and should meet all the qualifications specified by the applicable regulatory requirement(s) and should provide evidence of such qualifications through an up-to-date curriculum vitae (CV) and/or other relevant documentation required by the sponsor, the IRB/IEC, and/or the regulatory authorities.

The Principal Investigator (PI) is responsible to ensure that each individual involved in conducting clinical research should be qualified by education, training and experience to perform his or her respective task(s) and the qualifications are documented in CVs and other training records.

All 2nd Department of Internal Medicine, University Hospital of Ioannina, Greece research team members have responsibilities in this SOP.

Procedure

Documentation of Qualifications: Curriculum Vitae (CV) and License(s)

All site research team members

1. Provide a current, personally signed and dated CV and review every two years or each time there is a job change.
2. Provide the identification number of professional license – license is required to be valid throughout the duration of a given clinical trial.
3. File CV in the Investigator Site File.
4. Retain Investigator Site File for a period of 15 years or for a specified longer period (according to regulatory requirements or in agreement with the sponsor being responsible to inform our site as to when these documents no longer need to be retained).

Documentation of Training

All site research team members

1. Document SOP Training on the SOP Training Documentation Log provided by the sponsor.
2. Document all other training on a Training Documentation Record provided by the sponsor along with any certificates obtained.

3. File training records and certificates in the Investigator Site File.
4. Retain Investigator Site File for a period of a period of 15 years or for a specified longer period (according to regulatory requirements or in agreement with the sponsor being responsible to inform our site as to when these documents no longer need to be retained).

References

Health Canada Good Clinical Practice (GCP) – ICH: International Conference on Harmonisation (E6)

EU Directive 2001/20/EC

EU Directive 2005/28/EC

Tri-Council Policy Statement; Ethical Conduct for Research Involving Humans

Privacy Legislation - The Personal Information Protection and Electronic Documents Act (PIPEDA)

Associated Documents

1 Training Record

2 SOP Training Documentation

2nd Department of Internal Medicine, University Hospital of Ioannina, Greece	**STANDARD OPERATING PROCEDURE**	**Number: 002** **Effective Date: 18 JULY 2017** **Supersedes:**

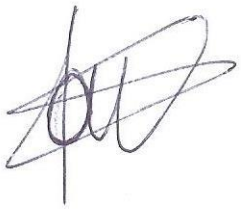
SITE RESEARCH TEAM QUALIFICATIONS AND TRAINING

SOP Revision History

Revision No.	Revision Date	Description of Change
002	18 JULY 2017	Revised SOP

Signatories

Prepared by: Dr Fotios Barkas MD (Print Name) **Date:** 17 Nov 2014 (DD MMM YYYY)



Signature: **Time:** 10:00 (24 hr clock)

Title: Sub-Investigator

Approved by: Dr Evangelos Liberopoulos MD (Print Name) **Date:** 17 Nov 2014 (DD MMM YYYY)

Signature: **Time:** 13:00 (24 hr clock)

Title: Sub-Investigator

2nd Department of Internal Medicine, University Hospital of Ioannina, Greece	**STANDARD OPERATING PROCEDURE**	**Number: 002** **Effective Date: 18 JULY 2017** **Supersedes:**

SITE RESEARCH TEAM QUALIFICATIONS AND TRAINING

Three-year Review

Reviewed by: Dr Evangelos Liberopoulos MD (Print Name) Date: 18 JULY 2017 (DD MMM YYYY)

Signature:  Time: 11:35 (24 hr clock)

Title: Sub-Investigator

TRAINING RECORD

NAME:

DATE	DURATION	COURSE / TRAINING DESCRIPTION	INSTRUCTOR/PROVIDER	CATEGORY / TYPE 1 = SOP 2 = GCP 3 = TRIAL SPECIFIC 4 = INVESTIGATIONAL PRODUCT 5 = THERAPEUTIC AREA 6 = INVESTIGATOR MEETING 7 = OTHER

Signature: _____ Date: _____

SOP TRAINING DOCUMENTATION

The following SOP(s) have been approved and require documentation of training:

SOP/Version Number	SOP Title	Effective Date (dd/MMM/yy)	§Type of Training	Date Training Occurred (ddMMMyyyy)	Initials

§ Self-Study - read
In-house – training via formal classroom setting or one-on-one

I have read and understood the contents of the SOPs listed above and I will comply with their requirements.

Name:	Title:
Signature:	

Please keep a copy of this form for your records.

2nd Department of Internal Medicine, University Hospital of Ioannina, Greece	**STANDARD OPERATING PROCEDURE**	**Number: 002** **Effective Date: 18 JULY 2017** **Supersedes:**

SPECIMENT HANDLING AND SHIPPING

Purpose

The purpose of this Standard Operating Procedure (SOP) is to outline the activities involved in the proper management of human biological samples for laboratory testing and analysis in order to assure the quality and integrity of data collected in clinical trials, as well as to protect the safety of all those who handle the samples; and that this information is appropriately documented, and available for review and inspection.

Scope

This SOP describes the procedures related to biological sample management, including the collection, processing, storage and handling at the 2nd Department of Internal Medicine, University Hospital of Ioannina, Greece.

Definitions

1. **Biological sample**: A biological laboratory specimen held by a biorepository for research. Such a specimen would be taken by sampling so as to be representative of any other specimen taken from the source of the specimen. When biological specimens are stored, ideally they remain equivalent to freshly-collected specimens for the purposes of research.
2. **Universal Body Substance Precautions (BSP)**: A system that consistently interrupts the transmission of infections thus ensuring increased protection for both patients and health care providers.

Responsibility

The following study personnel have responsibilities in this SOP:

Principal Investigator (PI)
Sub Investigator (SI)
Study Coordinator (SC)

Procedures

A. Biological Sample Management

1. Obtain all of the sample management details from the sponsor or central laboratory if not described in the protocol, including:

a. Laboratory contact information (for central laboratories)

b. Requirements for specimen collection, labelling, processing and storage

c. Supplies

d. Packaging and shipping specifications

2. The sponsor should provide detailed instructions for sample management prior to study activation. All supplies should be available prior to study activation.

3. Equipment such as centrifuges, storage refrigerators/freezers and thermometers should be calibrated and checked on a regular maintenance schedule. Service/maintenance logs should be available and updated as equipment is checked.

B. Collecting biological samples

1. Ensure that proper informed consent has been obtained from the study participants prior to specimen collection.

2. Obtain and prepare the necessary equipment and supplies for sample collection, paying close attention to collection tube color and type.

3. Add the appropriate labels to the collection containers.

4. Prepare any required laboratory requisitions.

5. Using universal body substance precautions (BSP), collect samples according to the protocol instructions. Ensure that the appropriate specimens identified in the study protocol are collected.

6. For time-sensitive samples, ensure that the clocks used to record the drug administration time and sample collection times are synchronized.

7. Record the date and collection time in the participant's source documents and on the laboratory requisition as required. Ensure that a copy of the completed laboratory requisition is maintained with the participants' source documents.

8. Prepare samples for immediate processing as instructed in the protocol.

C. Processing and Storing Biological Samples

1. For those samples not sent immediately to the laboratory for analysis, prepare the necessary equipment and supplies for sample processing.

2. Ensure that the appropriate specimen handling area is used as indicated.

3. Label all storage containers.

4. Process the samples according to the protocol instructions.

5. For centrifuged samples, harvest the required specimen and transfer to the appropriate storage container.

6. Dispose of any unused specimens, or specimen waste, using proper disposal methods according to the protocols of the site.

7. Record any additional information not already pre-printed on the label.

8. Store the sample in a dedicated area under the required storage conditions and temperatures.

9. Refrigerator and freezer temperatures should be monitored using calibrated devices and recorded on a regular basis to ensure the temperatures remain within the ranges allowed in the protocol.

10. It is recommended that uninterrupted power supplies be available for refrigerators and freezers used for storage of biological samples.

D. Preparing Samples for Shipment

1. Confirm the appropriate method of transportation of samples from the site to the laboratory with the sponsor.

2. Determine if any special forms, permits or custom processes are required for shipment of samples.

3. Determine the proper timing for sample shipments and the anticipated turnaround time for results, if applicable.

a. Ensure that the lab will be open to receive samples on the anticipated delivery date to prevent spoilage

4. Review the sample packaging requirements and package the sample(s) as indicated in the protocol or central laboratory manual. The sponsor should supply a checklist with specific packaging and transportation instruction, which should include the following information:

a. How the samples should be packaged for transport

b. How the samples should be contained

c. How the samples should be labelled

d. Instructions for transportation of the samples

e. Instructions for storage conditions of the samples including temperature and stability requirements

f. Shipping documents and how to complete correct information

g. Proper labelling of the samples (e.g. type of class)

h. Proper safety mark for the samples

i. Number of samples that can be shipped at one time

j. Contact numbers and names of personnel to be notified of transport

5. If dry ice is needed, review the proper technique for handling dry ice.

6. Complete the appropriate documentation
7. Maintain the required storage temperature while waiting for pickup.
8. Retain a copy of the shipping receipt (or courier waybill) and commercial invoice and file in the investigator study files with copies to the sponsor as required.

References

Good Clinical Practice (GCP) – ICH: International Conference on Harmonisation (E6)

EU Directive 2001/20/EC

EU Directive 2005/28/EC

Associated Documents

1 Temperature Log Freezer

2nd Department of Internal Medicine, University Hospital of Ioannina, Greece	**STANDARD OPERATING PROCEDURE**	**Number: 002** **Effective Date: 18 JULY 2017** **Supersedes:**

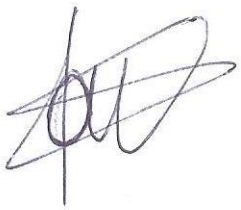
SPECIMENT HANDLING AND SHIPPING

SOP Revision History

Revision No.	Revision Date	Description of Change
002	18 JULY 2017	Revised SOP

Signatories

Prepared by: Dr Fotios Barkas MD (Print Name) **Date:** 17 Nov 2014 (DD MMM YYYY)



Signature: **Time:** 10:00 (24 hr clock)

Title: Sub-Investigator

Approved by: Dr Evangelos Liberopoulos MD (Print Name) **Date:** 17 Nov 2014 (DD MMM YYYY)

Signature: **Time:** 14:00 (24 hr clock)

Title: Sub-Investigator

2nd Department of Internal Medicine, University Hospital of Ioannina, Greece	**STANDARD OPERATING PROCEDURE**	**Number: 002** **Effective Date: 18 JULY 2017** **Supersedes:**

SPECIMENT HANDLING AND SHIPPING

Three-year Review

Reviewed by: Dr Evangelos Liberopoulos MD (Print Name) Date: 18 JULY 2017 (DD MMM YYYY)

Signature: Time: 11:40

Title: Sub-Investigator (24 hr clock)

2ND Department of Internal Medicine, University Hospital of Ioannina:
Investigator: M. Elisaf
Year: 2017, Month: April
Freezer Location: Professor's Office at -1 Floor of University Hospital of Ioannina

Freezer/Temperature Log

2ND Department of Internal Medicine, University Hospital of Ioannina:		Investigator:	M. Elisaf
Freezer Location:	Year: 2017 Month: APRIL Professor's Office at -1 Floor of University hospital of Ioannina		

IP Storage Acceptable Temperature Range* as per protocol: _(-70) – (-15) ºC_____

Specimen Storage Acceptable Temperature Range* as per protocol: _____

*Please notify Sponsor ***as soon as possible*** should any temperature reading be out of the specified range

Month/Day	**Time**	**Actual Temp**	**Min Temp °C**	**Max Temp °C**	**Temperature Excursion Date(s)**	**Describe Circumstances of temperature excursion & corrective action taken**	**Signature / initials**
APRIL **1**							
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2ND Department of Internal Medicine, University Hospital of Ioannina:
Investigator: M. Elisaf
Year: 2017, Month: April
Freezer Location: Professor's Office at -1 Floor of University Hospital of Ioannina

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DOCUMENT ARCHIVING

Purpose

The purpose of this Standard Operating Procedure (SOP) is to describe the standard procedures to be followed when archiving essential documents related to clinical research conducted in the 2nd Department of Internal Medicine, University Hospital of Ioannina, Greece.

Scope

This SOP is applicable to the Principal Investigator (PI) and all other research team members at 2nd Department of Internal Medicine, University Hospital of Ioannina, Greece.

Definitions

1. **Good Clinical Practice (GCP)**

   A standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected.

2. **Essential Documents**

   Essential documents are those documents that individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced. Essential documents include the Trial Master File, source documents and Case Report Forms (CRFs).

3. **Trial Master File**

   The Trial Master File is a file that consists of essential documents, which enable both the conduct of a clinical trial and the quality of the data produced to be evaluated. Those documents shall show whether the investigator and the sponsor have complied with the principles of Good Clinical Practice and with the applicable regulatory requirements.

4. **Source Documents**

   Source documents are original documents, data, and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments,

copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial).

5. **Case Report Forms (CRFs)**

   A printed, optical or electronic document designed to record all of the protocol required information on each trial subject.

6. **Principal Investigator**

   A person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the Principal Investigator (PI). In addition, PI is responsible to the sponsor for the conduct of the clinical trial at the clinical trial site, who is entitled to provide health care under the laws of the province where that clinical trial site is located, and who is

   (a) in the case of a clinical trial respecting a drug to be used for dental purposes only; a physician or dentist and a member of good standing of a professional medical or dental association; and

   (b) in any other case, a physician and a member of good standing of a professional medical association.

Responsibility

The Principal Investigator is responsible for archiving of essential documents at the respective sites in accordance with the requirements of the ICH E6 8.0 and with Greek legislation.

All 2nd Department of Internal Medicine, University Hospital of Ioannina, Greece research team members have responsibilities in this SOP.

Procedure

What to archive?

DOCUMENT ARCHIVING

All essential documents need to be archived i.e. Trial Master File, completed CRFs and source documents.

When to archive?

Essential documents need to be archived once the trial is completed e.g. the trial has undergone a final closeout visit, the closeout report issued and the final report written. The completion of a clinical trial shall be determined by the Principal Investigator and may vary among studies. The date of the completion of a clinical trial should be documented.

How long the essential documents should be archived?

All essential documents must be retained for at least 15 years or for a specified longer period (according to regulatory requirements or in agreement with the sponsor being responsible to inform our site as to when these documents no longer need to be retained).

How to archive?

Documents need to be stored in a way that preserves their integrity and readability and restricts access to appropriate individuals only.

Upon request of the Sponsor, monitor, auditor, Ethics Committee, or regulatory authority, the investigator should make available for direct access all requested trial-related records.

Any transfer of ownership of the data or of the documents shall be documented. The new owner shall assume responsibility for archiving.

Access to archives shall be restricted to all 2nd Department of Internal Medicine, University Hospital of Ioannina, Greece research team members.

The media used to store essential documents shall be such that those documents remain complete and legible throughout the required period of retention and can be made available to the Sponsor, monitor, auditor, Ethics Committee, or regulatory authority upon request.

Any alteration of records should be traceable.

All essential documents should be legible and accurate.

There are no regulations on the requirements for labelling archived essential documents. As guidance, all essential documents should be boxed and labelled with the study title

reference number and trial site number (if applicable), the name of the PI (if applicable), the date they were archived, and date to be destroyed (if available).

Where to archive?

The documents should be archived in an appropriate room or locked cupboard (professor's locked office at the first basement). Consider fire protection without water sprinkler systems, water protection, for humid conditions, pests etc. The room or cupboard must be secure with access only by authorised personnel.

References

Health Canada Good Clinical Practice (GCP) – ICH: International Conference on Harmonisation (E6)

EU Directive 2001/20/EC

EU Directive 2005/28/EC

31. Dec. 2003 Harmonization of Hellenic Legislation to Directive 2001/20/EC Official Governments' Gazette (FEK) 1973

07. Oct. 2004 National Ethics Committee Composition & Operating procedures Official Governments' Gazette (FEK) 1503

25. Jan.2007 Greek Law Harmonization Dir_2005/28/EC Official Governments' Gazette (FEK) 64

21.Feb.2013 FEK 390/B Supplement to B΄1973

Associated Documents

None

2nd Department of Internal Medicine, University Hospital of Ioannina, Greece	**STANDARD OPERATING PROCEDURE**	**Number:002** **Effective Date: 18 JULY 2017** **Supersedes:**

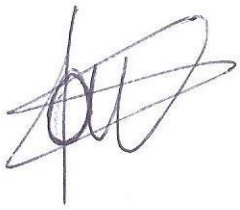
DOCUMENT ARCHIVING

SOP Revision History

Revision No.	Revision Date	Description of Change
002	18 JULY 2017	Revised SOP

Signatories

Prepared by: Dr Fotios Barkas MD (Print Name) **Date:** 25 JAN 2015 (DD MMM YYYY)



Signature: **Time:** 10:00 (24 hr clock)

Title: Sub-Investigator

Approved by: Dr Evangelos Liberopoulos MD (Print Name) **Date:** 25 JAN 2015 (DD MMM YYYY)

Signature: **Time:** 13:00 (24 hr clock)

Title: Sub-Investigator

2nd Department of Internal Medicine, University Hospital of Ioannina, Greece	**STANDARD OPERATING PROCEDURE**	**Number:002** **Effective Date: 18 JULY 2017** **Supersedes:**

DOCUMENT ARCHIVING

Three-year Review

Reviewed by:	Dr Evangelos Liberopoulos MD Print Name	Date:	18 JULY 2017 DD MMM YYYY
Signature:		Time:	11:45
Title:	Sub-Investigator MD		24 hr clock

MONITORING PLAN

Purpose

Monitoring is necessary to assure adequate protection of the rights of human subjects and the safety of all subjects involved in clinical investigations and the quality and integrity of the resulting data submitted.
The objectives the monitoring procedures are:

- To ensure that the study is being carried out in accordance with the approved protocol.
- To identify any problems and suggest / seek solutions.

Overall the monitor should be seen (and behave) as a supportive extension of the study team. They have a professional duty to be impartial and their role is to 'monitor', and NOT audit. Therefore, the monitor should not be perceived as an outside threat but part of the team and there to identify any problems affecting the conduct and quality of data collected.

The purpose of this Standard Operating Procedure (SOP) is to describe the standard procedures to be followed in a monitoring plan related to clinical research conducted in the 2nd Department of Internal Medicine, University Hospital of Ioannina, Greece.

Scope

This SOP is applicable to the Principal Investigator (PI), study management group, the monitors and all other research team members at 2nd Department of Internal Medicine, University Hospital of Ioannina, Greece.

Definitions

1. **Good Clinical Practice (GCP)**

   A standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected.

2. **Essential Documents**

   Essential documents are those documents that individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced. Essential

documents include the Trial Master File, source documents and Case Report Forms (CRFs).

3. Monitoring

The act of overseeing the progress of a clinical study, and of ensuring that it is conducted, recorded, and reported in accordance with the protocol, SOPs, Good Clinical Practice (GCP), and the applicable regulatory requirement(s).

4. Investigator Site file (ISF)

The repository for the essential documents for the conduct of a clinical trial. These documents individually and collectively permit evaluation of the conduct of the study and the quality of the data produced. These documents demonstrate the compliance of the sponsor-investigator and of the monitor with standards of GCP and with all applicable regulatory requirements.

5. Principal Investigator (PI)

The person responsible to the sponsor for the conduct of the clinical trial at the clinical trial site, who is entitled to provide health care under the laws of the province where that clinical trial site is located, and who is

a. in the case of a clinical trial respecting a drug to be used for dental purposes only; a physician or dentist and a member of good standing of a professional medical or dental association; and

b. in any other case, a physician and a member of good standing of a professional medical association.

6. Sub-investigator

Any individual member of the clinical trial team designated and supervised by the investigator at a trial site to perform critical trial-related procedures and/or to make important trial-related decisions (e.g., associates, residents, research fellows).

7. Clinical Research Associates (CRAs)

Part of the sponsor team who ensure compliance with the Regulations, GCP, SOPs and the protocol of the clinical trial, by monitoring clinical trials.

8. Case Report Forms (CRFs)

A printed, optical or electronic document designed to record all of the protocol required information on each trial subject.

MONITORING PLAN

Responsibility

Description of study monitoring arrangement…… e.g. The CRA will be responsible for conducting trial monitoring. The CRA will appoint an appropriately qualified person(s) to monitor the trial (a sub-investigator or the PI). The monitor(s) will be trained on the study protocol and will be familiar with all study procedures.

Site monitoring schedule

Ordinarily, a pre study, initiation, routine and close out monitoring are planned and conducted in the life span of a study. The site initiation visit will be conducted as soon as:

- All the necessary approvals have been obtained
- Staff recruited
- Investigational product has been delivered to site (is about to be delivered to site)
- CRF and source documents are ready
- Laboratory is ready to start storing study samples

The first routine monitoring visit will occur as soon as the first participant is recruited or within 2 weeks of the first participant being recruited. The table below provides an estimate of what will be needed in terms of time on site for the monitor. This needs to be continually assessed by the study management team and the monitors. The monitoring frequency may need to increase if recruitment is faster than predicted, at times of data entry deadlines (such as interim analysis or if the DSMB request a safety report) then two or more people can attend the visit.

MONITORING PLAN

Procedure

Monitoring will focus on the following key processes of the study so as to ensure protection of rights and well-being of study participants and integrity of data:

1. Informed consent process.
2. Study eligibility criteria met for all participants.
3. Timely completion of Study CRFs.
4. Accurate abstraction of data from clinical and laboratory forms.
5. Sample collection and handling in accordance to Protocol and SOP(s).
6. Review of data management procedure i.e. data entry, handling of data discrepancies and data backup.
7. Reporting of adverse events and protocols violations according to SOP(s).
8. Drug accountability.
9. Follow up assessments and procedures.
10. Measures to ensure complete participant follow up.

For each site visit the monitor will work according to an agreed schedule of tasks, including the following that will be given as specifics in the monitoring form and guidelines:

MONITORING PLAN

- Schedule a date with the study investigator for the monitoring procedure and provide them with a list or shell of the study sections that will be monitored in this particular visit.
- Review last monitoring procedure report.
- Review the Site study File: ensuring that it is updated appropriately.
- Verify written informed consents were given for every subject entered into the study and obtained according to the consent SOP.
- Review current status of the study's participant enrolment vs. anticipated enrolment, losses to follow up, outstanding data issues, reported serious adverse events, outstanding laboratory issues.
- Review the study forms and database ensuring that the participants were eligible and note any safety issues and protocol violations or deviations.
- Review laboratory issues: Handling, storage and shipment of samples.
- Source data verification - abstraction of data from clinical and laboratory forms.

During the initial visits the monitors will review 100% of the fields of all the study forms. Subsequently the monitors will review 100% data contributing to the primary endpoint and 100% of fields for a randomly selected sample of study forms. All forms monitored during a visit will be detailed in the monitoring visit report.
A data base check for accuracy of data entry will be performed at regular intervals. The data points to be checked will be end point data and safety data.

After each monitoring visit the monitor will debrief the study team i.e. praise them where they are getting it right and highlight areas which need improvement. The monitor will then write up a

monitoring report citing all findings and status of such findings (resolved or not) and forward a signed copy to the sponsor and/or sponsor appointed project manager. The monitoring report may be shared with the Principal investigator.

At close out visit(s) the monitor will ensure all queries are resolved; the study product is accounted for and returned or destroyed according to sponsor SOP; and study documents are properly archived. The comprehensive list of activities during this visit(s) will be detailed in a study close out SOP.

References

Health Canada Good Clinical Practice (GCP) – ICH: International Conference on Harmonisation (E6)

EU Directive 2001/20/EC

EU Directive 2005/28/EC

31. Dec. 2003 Harmonization of Hellenic Legislation to Directive 2001/20/EC Official Governments' Gazette (FEK) 1973

07. Oct. 2004 National Ethics Committee Composition & Operating procedures Official Governments' Gazette (FEK) 1503

25. Jan.2007 Greek Law Harmonization Dir_2005/28/EC Official Governments' Gazette (FEK) 64

21. Feb.2013 FEK 390/B Supplement to B΄1973

Associated Documents

None

2nd Department of Internal Medicine, University Hospital of Ioannina, Greece	**STANDARD OPERATING PROCEDURE**	**Number: 002** **Effective Date: 18 JULY 2017** **Supersedes:**
MONITORING PLAN		

SOP Revision History

Revision No.	Revision Date	Description of Change
002	18 JULY 2017	Revised SOP

Signatories

Prepared by: Dr Fotios Barkas MD (Print Name) **Date:** 25 JAN 2015 (DD MMM YYYY)

Signature: **Time:** 10:00 (24 hr clock)

Title: Subinvestigator

Approved by: Dr Evangelos Liberopoulos MD (Print Name) **Date:** 25 JAN 2015 (DD MMM YYYY)

Signature: **Time:** 13:00 (24 hr clock)

Title: Subinvestigator

2nd Department of Internal Medicine, University Hospital of Ioannina, Greece	**STANDARD OPERATING PROCEDURE**	**Number: 002** **Effective Date: 18 JULY 2017** **Supersedes:**
MONITORING PLAN		

Three-year Review

Reviewed by:	Dr Evangelos Liberopoulos MD Print Name	Date:	18 JULY 2017 DD MMM YYYY
Signature:		Time:	11:50
Title:	Sub-Investigator		24 hr clock