IMiC, Inc. Research center

List of Standard Operating Procedures

As of 11/3/2016

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3 NOV16

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SOP #1f-03Nov2016, as a modification of 1e- 20/Jun/2016, as a modification of 1d -01/NOV/15 .

FOR INFORMED CONSENT OF RESEARCH SUBJECTS

This document is a continuation of the current office practices in the process of consenting subjects participating in clinical research in this office.

To ensure that correct version of the informed consent is used preparation for the patient visit should be done in anticipation, upon discussion over phone and scheduling the patient for a visit the study coordinator will prepare the most current version and have it ready in front desk for the patient when he/she arrives. The same can even be emailed to patient for review.

Every prospective patient will be informed of the possible benefits and adverse events of participating in a specific clinical trial, will receive a current version of an approved from Central Ethic Committee Informed Consent Form for the specific study, will be given ample and sufficient time to read it, when possible given the consent days in advance, will be given the opportunity to ask questions and then discuss it with a study team member, to include medically qualified personnel. Information will be given regarding the possibility of a potential claim that can occur if patient receives any damages in relations to study procedures. After that will be signed by patient and designated study team member and a copy will be given to the patient, the original will stay in the patient study file.

Specific attention will be given to additional places that the patient needs to initial and followed up accordingly.

If patient is illiterate the informed consent will be read to him/her and the site staff will assure that the subject understand it before signing with an "x". A witness need to sign on the same page indicating his/her name.

If a minor is consenting one parent needs to sign the consent form. If the minor is in-between 12 and 18 a special assent needs to be presented to the child and he/she will need to review it and sign it as well.

In cases of minors If an IRB requests the consent to be signed by 2 parents all possible effort should be done to locate the additional parent – invite to office to discuss or send via email or fax the consent for review and asked to call office to discuss and sign and send back. If only one parent is living with child all efforts should be made to find the other parent – through public records, school documents, legal

documents search provided by present parent, medical records request for review. In case that the other parent can not be located a note by the PI should be placed in patient chart to that effect.

If an adult lacks the capacity to consent, for example, as a result of trauma, developmental disability, or dementia (either temporary, progressive, or permanent) only a legally authorized representative (LAR) for that adult can give consent for participation in research (needs to be IRB approved), unless the requirement to obtain informed consent has been waived by the IRB. Should the subject regain or develop the capacity to consent, and they are still an "active participant" then his/her consent must be obtained for any further research, as the consent of the LAR is no longer valid (i.e. still have study procedures performed, specimens collected, on-going data collected).
In some research, such as longitudinal studies involving progressive disorders or aging populations, enrolled subjects may be competent to consent on their own behalf at the outset, but over the course of the study they may become decisionally impaired. In these cases will be required that the investigator discuss with the prospective subjects the importance of designating someone to serve as a legally authorized representative at the outset of the study, so at the time the subject loses decision-making capacity, the designated LAR is on file with the investigator and is aware of the subject's desire to continue with study participation.

In the absence of a designated healthcare surrogate, below is the LAR precedence order as follows:

- Attorney in Fact – court documentation required
- Judicially appointed guardian – documentation required
- Proxy:
    i. Subject's spouse
    ii. An adult child of the subject
    iii. A parent of the adult subject
    iv. An adult sibling of the subject
    v. An adult relative of the subject
    vi. A close friend of the subject

All the above will be documented clearly in patient study file and a review in a check list will be done by the person signing the consent and by a second study site person before subject leaving the site.

All study related procedures will be **done after signing** the informed consent.

In all subsequent patient visits the study subject will be asked if he/she maintains the informed consent, before any procedures.

In case of a new study specific informed consent the same will be downloaded from the IRB website in a reasonable time after receiving notice and will be given to all active patients in this study for review and signature on the next scheduled visit. In case of a special notice from sponsor or evaluation by study manager that the new ICF contains critical new information patients can be called over phone and explained the new information, said conversation will be documented in source documents. To avoid using an old version study coordinators or regulatory coordinator will obtain the new consent and file it in the regulatory binder by writing "Old version" on the old one to avoid confusion. The new consent will

also be added to informed consent binder in front desk by replacing the older one. The new consent will be placed in the charts of all active subjects to be readily available for their next visit.

All study staff will be trained in ICF requirements within 2 days after new employment and every year afterwards.

Created by: 
Aimee Cabo BSN

Approved by: 
Dr Boris Nikolov, Study Manager

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SOP #3B- 04Nov2016, as a revision of 3A-02/07/14, revision of #3- 07/18/12

Regarding Evaluation of Inclusion and Exclusion Criteria

This document is a continuation of the current office practices in the process of evaluating if subjects participating in clinical research in this office meet all the inclusion criteria and do not have any exclusion criteria.

Study team member will evaluate all inclusion criteria and will verify if patients do not have any exclusion criteria by questioning the patient, reviewing pertinent documents and/or perform study related procedures. Specific attention will be given to review of medical records. This will be documented in source documents by listing all medical conditions and medications in appropriate logs.

This information will be presented to the Principal Investigator in the study for final review and approval. The investigator should perform his own review of pertinent medical records using the previously filled out inclusion/exclusion check list as a guide and add comments or corrections, if appropriate.

A check list of inclusion/exclusion criteria should be filled out at screening and updated at Baseline and by checking next to each criteria (yes or no) the person checking it will be documenting the review of each criteria and if the patient meets it or not. Criteria should be supported by data elsewhere in the source or medical records.

After the above steps are done a randomization or final inclusion in the study will take place following the specific protocol requirements, only after final PI aproval.

As needed these criteria will be reviewed in subsequent patient visits as well.

Dr Boris Nikolov, Study Manager

Reviewed and discussed w. staff 2/10/14
Reviewed – no change 1 Feb 15

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SOP #02a-02/25/13

Regarding Adverse events(corrected)

This Document reflects the process of assessing and documenting adverse events in subjects participating in clinical trials.

During each visit before any procedures are performed patients will be asked if they have experienced any new or worsening symptoms and if they have a detailed information will be obtained to describe them as to since when, have they attended hospital or doctors, what medications are being taken for this conditions, have they stopped study medication. The above will be documented and presented to Sub-I or Pi for review and assessment if it is an Adverse Event for the purposes of the study, to determine severity, relationship to study drug, having into consideration the specific study protocol and ICH-GCP. A determination from Sub-I or PI as to whether the study medication needs to be stopped temporarily or permanently or a reduced dose should be applied needs to be done.

Specific consideration should be given to AE that are study specific.

Same determination should be done for abnormal laboratory data which should be marked as clinically significant or insignicant.

Additional determination should be done to see if the AE meets criteria for seriousness, if qualifies as a Serious Adverse Event according to the study protocol and ICH-GCP.

If this event meets criteria for seriousness this has to be documented as well and try to determine the cause of it, notification has to be sent to the Sponsor within 24 hours of receiving knowledge of it, by fax, eCRF or through other established procedures. PI should be notified immediately and he needs to assess the case within 24 hours. If possible patient will be asked to sign release of information form to obtain additional medical records.

In case that the Sponsor determines that a SAE or AE are SUSAR, this needs to be reported to the appropriate IRB within specified time according to their SOP.

2/25/13

Dr Boris Nikolov, Study Manager

Reviewed 5 JAN 14
5 JAN 14

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Reviewed - no change
1 Feb 15

Reviewed - no change
1 Feb 16

SOP #4-07/17/12

Re: Emergency response during clinical trial

This document is a continuation of the current office practice of treating patients and response in case of emergency that involves research subjects while in the office.

In case of emergency the physician on the premises will be notified immediately. Emergency medical care will be initiated immediately by trained personnel onsite using the available equipment. Designated study team members need to have current BLS and ALS certificates.

Upon examination by the doctor and his recommendation a call to 911 needs to be placed immediately.

Patient will be continued to be treated on premises if needed until emergency personnel arrive.

Patient will be asked to sign a release of information and appropriate medical records will be requested from the treating facility afterwards.

17 JUL 12

Dr Boris Nikolov, Study Manager

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SOP #5e – 01sep2016, as a modification of SOP #5d – 20Jun2016, as modification of 5c – 10/21/15, as modification of 5b – 10/01/2013, as modification of 5a-05/09/13

Regarding Investigational Product (IP) management

This document is a modification of the previous SOP in reference to the process of Investigational product management.

IP will be placed and stored under double locked, controlled conditions – Pharmacy room will be locked with 2 security locks. Inside the pharmacy room, study IP will be placed in separate cabinets, assigned per study, which will be kept locked as well. Each cabinet will be labeled with the study protocol number. In the event that IP needs refrigeration it will be placed in a refrigerator inside the Pharmacy. In the event that IP needs to be stored under freezer temperature, the same will be placed in a freezer, inside the pharmacy.

Pharmacy staff will need to pass criminal background check before hiring. Periodic inventory checks will be done by the Study Manager or other site member to verify quantities of IP per study on site. Study manager may also follow up with assigned Monitors to determine their separate accountability records as well. The site will follow the recommendations of the Office of Diversion Control of the DEA, USDJ and the Controlled Substances Act. The pharmacy will be protected by an alarm system and video controlled.

The Pharmacy will have limited access – only Pharmacy technician and back up staff will have access. When medications are dispensed study coordinator or pharmacy technician will access IWRS or assigned system to obtain the appropriate kit(s) for that visit and request the kit(s) to be taken from pharmacy by the authorized staff by providing print out of the study visit dispensing document. Pharmacy staff will disburse the requested IP kit and sign on that document that this is the correct kit. Upon receipt of the kit, study coordinator will verify that the assigned kit(s) are the correct one and sign as well confirming that. Only after that the kit can be given to study participant.

IP accountability will be strictly monitored through IP logs – study level and patient level if needed. Pharmacy technician will record all received kits in each respective logs, when dispensed and when returned with number of tablets, capsules or other units. Periodic reconciliations should be done in between logs to reflect most up to date status of all IP kits.

IP will be received by authorized personnel and reviewed for suitability and damaged kits. The temperature of transport will be reviewed and any excursions will be reported immediately to the Sponsor through the established reporting forms. A printout from the temptale will be done if requested and if possible. If the shipment of IP is a scheduled substance two people will verify receipt. The receipt will be acknowledged by appropriate means – IWRS, IVRS. No product will be used, if excursions of temperature is observed, unless authorized by member of the study team first.

All site staff including personnel not involved in research will be trained to notify research staff upon receipt of marked boxes with labels such as "Refrigerate upon arrival" and attend to them immediately, like placing the products in refrigerator.

The IP will be stored in Research Pharmacy Area according to temperature requirements per protocol – in ambient conditions, refrigerated or frozen. Temperatures in each area – ambient, each refrigerator and each freezer will be maintained through ONSET electronic temperature monitoring system with dataloggers every 5 minutes and registered in the computer system, maintained Monday through Sunday. In case of excursions for more than 15 min alarm would be sent via text to designated staff personnel and an email. In case of temperature excursion below or above indicated storage range notification to Sponsor needs to be done as soon as possible. Research Manager and appropriate study team will be notified immediately. If an alarm sounds during the day from temperature excursion immediate attention should be placed to make sure that the temperature excursion does not stay long and IP should be moved to another location where the temperature requirements are met. In order to maintain clearly identifiable temperature for each day, site staff will maintain handwritten temperature logs which will be the official temperature monitoring documentation. The logs will reflect current temperature, minimal and maximal temperature since last measurement per day and a signature of the person recording it. For Saturday and Sunday only min/max temperatures will be recorded on Monday. Monitoring interval for ambient conditions is 20 to 25 oC; Freezer conditions are maintained below -20oC; Refrigerated conditions are from 2 to 8oC.

In case of power outage IP should be moved to a room with power from emergency back-up generator or a location where they can be in the indicated temperature range.

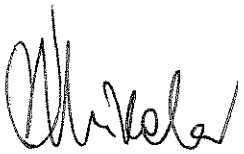
If transporting IP from one office to another all measures should be taken to make sure that IP is kept within temperature ranges, for example if transporting IP that needs to be kept in room temperature the same will be put in portable temperature preservation bags or in case of refrigerated products the same will be placed in portable coolers with cold elements. While transporting the IP, a temperature recording device should be used, If available, or a min/max thermometer with alarm so the person with the package know that IP is kept in temperature range. When transporting IP in the above conditions a personal car of a study team member can be used with working AC. Upon delivery to new location a protocol should be done indicating that the IP was kept within temperature range and all study kits were transported without damage to any of the drug.

In case of transporting controlled substance schedule investigational products 2 people should accompany the transport at all times and sign in beginning and end of transportation that all IP kits are present. In this case the investigational products will be placed in closed and sealed boxes with inventory on them clearly indicating which kits are inside.

In case the pharmacy tech is not available upon return of investigational product by subjects the same kits will be stored by site manager in locked conditions or returned to pharmacy, but upon pharmacy tech return the same will be documented in appropriate logs.

Created by: Aimee Cabo

Aimee Cabo

Reviewed by: 

Dr Boris Nikolov, Research Manager

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SOP #6A – 04NOV2016, as a revision of 6-01/05/13

Regarding IP compliance

This document is a continuation of the current office practices in the process of assessing Investigator product compliance.

When patient returns kits, this will be recorded in the corresponding log and stored in designated place. Special attention will be given to assessing if subjects are compliant taking the IP as prescribed and directed. Staff will record in source documents the number of tablets/capsules dispensed, amount returned, how much subject was supposed to take and how much did he/she take. If subject is very incompliant Sponsor will be notified. In all non-compliance cases, subject will be retrained.

Compliance will be assessed in all visits , if possible.

In case of subject overusing IP, special attention will be given to that situation and Sub-I/PI will address the case, by discussing it with subject.

Created by

Aimee Cabo BSN

Approved by:

Dr Boris Nikolov, Study Manager

(12)

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SOP #7C – 04nov2016, as a revision of 7b -20Jun-2016 as modification of #7 from 01/05/13

Regarding EDC procedures

This document is a continuation of the current office practices in the process of inputting information into eCRF – EDC systems.

Every study team member at each office should be duly trained in the system used for the specific trial. Usually this training will be provided by the Sponsor involved. This training and certification should be documented with a certificate, which will be kept in the study file.

Each user should have each own password and user name for the specific system and study. The same should be kept strictly confidential and unavailable to other team members.

All CRFs for will be keyed by the CRC within 5 days of the study visit utilizing the eData program supplied by Sponsor. Complete operating procedures for the eData program are located in its website or in study binder .

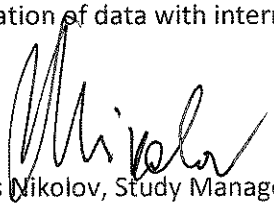
All data entry will be proofed for accuracy by the CTC using the following methods:
(a) Visual proofing of the CRF with the computer screen post data entry.
(b) Cross-referencing with source documents as appropriate.
All information transferred from provided source documentation to CRFs will be proofed for accuracy, completeness, logic, and conformance to CRF completion instructions.

Only information and data clearly available in source will be transcribed to EDC. If source is not complete the same should be returned to author and requested completeness and /or correction which should be done with a note for late entry.

The data manager and study personnel will be trained to resolve queries in accordance with the following requirements.
-Check EDC system every 7 days for posted queries.
-All queries should be resolved within 5 days unless a specific date of resolution is requested.
-If the query is unclear or if more information is required, the appropriate protocol specific Data Manager at the Sponsor/CRO should be contacted.

Queries present unique problems that will require the data manager/study personnel to utilize various methods of research. The following list is a sample representation of research methods used by the data manager but is not meant to be comprehensive in nature:

-Verification of data on the CRFs, and/or source documentation.
-Consulting with the appropriate study personnel or clinicians.
-Verification of data with internal and external laboratories.



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SOP #10b – 10/05/2016 as a modification of 10a-04/22/13

Regarding Principal Investigator (PI) oversight

This Document reflects the involvement of the PI in the study. It is imperative that the Principal Investigator has oversight and complete knowledge of all aspects of the study.

The PI should review the patient study charts periodically to ensure compliance with GCP, all applicable regulations and protocol adherence and documents that apply. This can include labs, ECGs, clinical or cognitive assessments, or study procedures. To document that, he/she will sign at the end of the checked visit as "chart reviewed", or "agree with assessments" or other text reflecting that the PI reviewed the chart. PI should have final determination of eligibility of study patients, which should be done after all procedures and/or results are received and should be documented on a separate eligibility check list.

In cases that the Sub-Is, Coordinators and study nurses notice changes, before PI, in patient situation, adverse events, serious adverse events, noncompliance with study drug, missed appointments or any other relevant information that might be needed for the safety of the patient, they will advise the PI about them.

In case that PI is not available for timely review of a lab result or ECG one of the Sub-Is will review them. Sub-I will notify PI of abnormal findings that might be deemed clinically significant so PI can do final determination of that significance.

In the case of an adverse event, one of the Sub-Is will evaluate the complaints/event and file initial report in study chart. PI will review it and will have final determination on causality, severity and other aspects. All adverse event logs should be signed by PI at end of study.

To ensure all the above, periodic study team meetings will be held. Depending on the number of patients and frequency of study visits these meetings will be held weekly, biweekly, monthly or quarterly. These meetings will be documented in meeting minutes.

Dr Boris Nikolov, Site Director

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SOP 11d – 04nov2016, as a modification of #11C- 29Sep2016, as a modification of 11B – 22-jUL-2016, as a modification of 11- 02/05/13

Regarding Training

This Document reflects the periodic training in clinic SOPs, GCP and study protocols.

All personnel will attend yearly trainings in clinic SOPs, documented by training log. These trainings will encompass all changes made during the year and refreshing of current SOPs. Only staff involved in a SOP specific task will be trained in the corresponding SOP. This is responsibility of the Research Manager.

All site personnel will pass GCP training courses every two years and present certificates to Research Manager. In case that there is no availability of training courses a GCP course will be provided at the site, responsibility lies with the Research manager.

All site personnel will pass study specific trainings before beginning participation in a study. The same will be documented by training log or certificates. Responsibility to perform these trainings lies with Sponsor and/or its representatives - the CRAs. In case that Sponsor does not provide training the Principal Investigator should train his/her team before commencing the study and before adding to the delegation log.

Each new study member will begin work in a study after being assigned tasks by PI through study specific delegation logs. Work on a study without delegation in logs can start only with fully authorized, trained and delegated site team member and the trainee will perform tasks under his/her supervision at all times. This time will be used for study specific training of the new member as "on hand training".

Sub-I who is delegated role of ***assisting investigator in the conduct of the investigation*** is to have GCP training, but "Sub-I" who is a contracted ***ancillary service provider*** who are performing routine, standard-of-care procedures or exams for which they have been appropriately trained do not need GCP training. Our SOP clearly delineates this distinction in Sub-I training requirements. We contend that these ancillary providers/physicians do not meet the criteria for being included section 6 of the 1572 under the FDA guidelines regarding who should be listed on the 1572:

> 21 CFR 312.53(c)(1)(viii) requires the investigator to provide "a list of the names of the subinvestigators (e.g., research fellows, residents) who will be assisting the investigator in the conduct of the investigation(s). The purpose of Section #6 is to capture information about individuals who, as part of an investigative team, will assist the investigator and make a direct and significant contribution to the data. The decision to list an individual in Section #6 depends on his/her level of responsibility (i.e., whether he/she is performing significant clinical investigation-related duties).

We would interpret this to mean, those who providers/physicians who simply perform a study procedure (which is not a direct and significant contribution to the data) & are not actually responsible for the conduct of the study, do not need to be listed individually on the 1572. Examples of that can be eye exams or dermatology exams, which are looking for any side effects.

Dr Boris Nikolov, Research Manager

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Reviewed 4/28/15

SOP #12- 02/05/13

Regarding Weather conditions

This Document reflects the necessary steps to be taken in case of extreme weather conditions.

In case of official warning of hurricane or strong storm all precautions will be taken to secure the study documents and investigational products in higher locked cabinets preferably water resistant. All study related visits will be canceled and rescheduled preferably within window. An email or telephone call will be placed to assigned CRAs per protocols to advice of situation.

Upon advisory of normalizing the weather conditions regular day to day activities will resume at clinic.

Staff will undergo specific training for emergency procedures.

Dr Boris Nikolov, Research Manager

Reviewed 3JUN17 -

ADD - ALL FROZEN IP will be PLACED in DRY ICE
- ALL IP requiring REFRIGERATION will be moved to working refrigerator.
- ALL FROZEN SAMPLES will be SHIPPED.
- ALL THE ABOVE will be implemented IF EMG GENERATOR MALFUNCTIONS.

3JUN17

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Reviewed - ok.

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SOP #13- 02/05/13

Regarding Calibration of equipment

This SOP is describing established procedures at investigating site for testing and calibration of all equipment used in clinical trials.

The site will establish a vendor who will check and calibrate all equipment every 12 months per contract. After each calibration/check the vendor will write a protocol to document that and place a sticker on each calibrated/checked equipment indicating next due date.

Equipment that needs to be calibrated/check include – ECG, refrigerators, freezers, centrifuges, weight scale, height scale, spirometer, thermometers used, blood pressure measuring devices, othoscopes, ophthalmoscopes, oxymeters, or any one designated by Study manager.

Dr Boris Nikolov, Research Manager

AKTA MEDIKA/IMIC Inc.

Reviewed - ok.

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SOP #13- 02/05/13

Regarding Calibration of equipment

This SOP is describing established procedures at investigating site for testing and calibration of all equipment used in clinical trials.

The site will establish a vendor who will check and calibrate all equipment every 12 months per contract. After each calibration/check the vendor will write a protocol to document that and place a sticker on each calibrated/checked equipment indicating next due date.

Equipment that needs to be calibrated/check include – ECG, refrigerators, freezers, centrifuges, weight scale, height scale, spirometer, thermometers used, blood pressure measuring devices, othoscopes, ophthalmoscopes, oxymeters, or any one designated by Study manager.

Dr Boris Nikolov, Research Manager

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SOP #14-04/22/13

Regarding review of unexpected serious events (SUSAR)

This Document reflects the review of safety reports – unexpected serious adverse events or Suspected Unexpected Serious Adverse Reaction (SUSARs). The PI or delegated Sub-I will review received safety reports on a timely basis- every two weeks.

Preferably the reports will be reviewed online and documented this review by the system accountability records on which the reports were displayed. If needed, this documentation can be done with a signature on the cover sheets. If not possible, or per sponsor request, the reports will be printed and stored in a separate study specific binder and each report needs to be signed as reviewed.

If a Sub-I reviews the above reports he or she needs to inform the study team about their contents.

Every site user for the safety reports database needs to have a separate login and password.

Dr Boris Nikolov, Study Manager

AKTA MEDIKA/IMIC Inc.

Reviewed - ok.
10/29/15

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SOP #16- 10/05/13

Regarding Mental Health Evaluation

This SOP is describing established procedures at investigating site for evaluating study subjects in need of mental health evaluation.

Following specific study requirements for suicidality assessment or based on PI recommendation the subject will be referred to a psychiatrist for evaluation – Evelyn Lopez-Brignoni MD.

The coordinator in study will contact Dr Lopez at 305-670-1411 to schedule an appointment, based on her schedule the consult can be done in the research clinic or at Dr Lopez's office at 299 Alhambra Circle, Suite 218, Coral Gables FL 33134 as soon as possible.

Upon consultation Dr Lopez will contact the requesting PI via phone for preliminary report and will submit a full report in reasonable time via fax to 786-536-9016. Set report will be filed in subject chart after PI's review.

10/29/15

Dr Boris Nikolov, Research Manager

IMIC Inc.

Reviewed – dc.

DP 01 Feb 15

SOP #17- 11/20/14

Regarding notification of PCP

This SOP is describing established procedures at investigator site for notification of PCP of study participation.

Patients participating in studies should be asked if they want their PCP to be notified of participation in study. Will be explained to them importance of such notification. If they agree contact information of their PCP will be taken and documented in source.

Notification to PCP will be made after randomization, not at screening. This notification can be done over the phone or via a fax and needs to be documented in source. PCP will be provided with contact information of center and will be asked to contact research center if he/she has knowledge of patient being admitted to hospital.

20 Nov 14

Dr Boris Nikolov, Research Manager

IMIC Inc.

SOP #18b- 11/20/14

Regarding Unblinding during clinical trials

This SOP is describing established procedures at investigating site for protecting the blinding during a study.

Every effort should be made to maintain the blind by not allowing study members to know what medication/IP is taking the patient at that time.

In case of laboratory reports and the possibility that the study medication changes certain laboratory values and if a report is received at site with these values from a local lab for example, a designated person will be in charge to obscure that value **before** placing the report in the study chart so the study team members will not see it.

In case that medication is dispensed and is clear which treatment arm is the patient on by access to study medication only a designated unblinded person will dispense the medications. Patients will be advised not to describe the medication and show it only to the unblinded study staff.

20 NOV 14

Dr Boris Nikolov, Research Manager

reviewed - ae!

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SOP# 19- 25Aug2014

Regarding Investigator absence

This SOP is a continuation of established practices at site in case one of the investigators is absent for extended period of time

This Sop is designed to establish procedures in case of absence of Principal or Sub-Investigator.

In case that PI needs to leave the country for more than 5 days, the Sub-Investigator in study should be fully educated and trained in all study procedures and requirements so he can be in charge of study at site. The investigator in charge will be present at site for all study visits. The Investigator in charge will review lab results, spirometry results and other study related tests.

PI will be notified via phone, email or text messages as needed.

All study procedures will be documented by the person performing them at real time following principles of GCP.

If the principal investigator leaves the country for more than 1 week he should inform the Sponsors or corresponding CROs of that absence and who will be taking his responsibilities for that period.

Similar principles should be followed if and Investigator gets ill.

25/8/14

Dr Boris Nikolov, Study Manager

Viewed - ae.
01 Feb 15

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SOP# 21- 25Nov2014

Regarding investigational medicine destruction

This SOP is a continuation of established practices medication destruction during clinical trials

Study medications will be kept on site until is returned to designated facility/vendor after final accountability by site staff and Sponsor representative. This accountability will be documented in study medication logs, clearly showing kit numbers, when dispensed, to which patient, when were returned, and with how many tablets. These logs will be signed by site staff and designated Sponsor representative. When shipping back to Sponsor a copy of airway bill will be kept on site together with copy of the Medication log.

In case of necessity of medication destruction on site, the above procedures will be followed but the medication will be destructed on site, by placing all medication containers in the biohazard containers on site. The same will be collected through routine pick up service, scheduled every 2 weeks and the pick up date will be documented on the logs. Copy of pick up protocol will be attached to the logs aswell.

25 Nov 14

Dr Boris Nikolov, Study Manager

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SOP# 22- 25Nov2014

Regarding Follow up patients who missed appointments

This SOP is a continuation of established practices to proceed with follow up of patients who missed their study appointments

Because of importance of patients/subjects to be attending study appointments in the indicated per protocol time frame **all subjects**:

1. will be reminded at the end of each appointment when is their next one and given a reminder card
2. will be called the day before appointment to remind of tomorrows appointment, if the appointment lies on a Monday these subjects will be called on Friday.

When scheduling appointments can be used pre-calculated excel tables with planned next appointment date with indicated plus or minus days.

If a patient misses his/her appointment a call should be placed on the day of the missed appointment preferably within 1 hour of missed time to remind of appointment and inquire what is the situation. If patient can not attend another appointment will be made within the protocol window. If a patient does not answer the phone call, other phone calls should be placed until contact. If contact not possible a letter should be mailed indicating that patient missed appointment and needs to call office immediately. If there is no response other letters can be mailed periodically to try to contact patients. Copy of those letter should be placed in the patient chart. If not possible to contact patient at any time, the research manager should be contacted and discuss the situation.

Dr Boris Nikolov, Study Manager

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SOP# 23A- 04Nov2016, as a revision of 23- 20Jun2016

Regarding Regulatory documents completion

This SOP is a continuation of established practices to complete regulatory documents at beginning of study and periodically during study

Regulatory documents will be received by site manager and/or assigned regulatory specialist. Upon receipt the same will be prepared for PI and Sub-I review and signature within reasonable time trying to be prepared and sent back to Sponsor ASAP.

All documents will be copied and placed in assigned bins for filing. Originals will be placed in folder for originals awaiting instructions if needs to be mailed.

Upon change of Sub-Investigators or Principal Investigator Sponsor should be notified and requested permission to add to team, upon which preparation of FDF and a new 1572 form will be prepared, a copy of current CV and medical license will be placed in study binders. Copies or originals will be submitted to Sponsor. If needed IRB will be notified. New staff will be trained in all applicable aspects of study and only trained personnel will participate in study procedures.

Upon end of study a new set of FDFs will be collected as required by Sponsor.

Upon release of a new version of a protocol or Investigational brochure the same will be printed and filed, a receipt will be executed by PI and filed. A training of staff will be performed and documented.

Sub-I who is delegated role of ***assisting investigator in the conduct of the investigation*** is following the above guideline, but "Sub-I" who is a contracted ***ancillary service provider*** who are performing routine, standard-of-care procedures or exams for which they have been appropriately trained do not need to be added to 1572. These ancillary providers/physicians do not meet the criteria for being included section 6 of the 1572 under the FDA guidelines regarding who should be listed on the 1572:

> 21 CFR 312.53(c)(1)(viii) requires the investigator to provide "a list of the names of the subinvestigators (e.g., research fellows, residents) who will be assisting the investigator in the conduct of the investigation(s). The purpose of Section #6 is to capture information about individuals who, as part of an investigative team, will assist the investigator and make a direct and significant contribution to the data. The decision to list an individual in Section #6 depends on his/her level of responsibility (i.e., whether he/she is performing significant clinical investigation-related duties).

These providers who simply perform a study procedure (which is not a direct and significant contribution to the data) & are not actually responsible for the conduct of the study, do not need to be listed individually on the 1572. Examples of that can be eye exams or dermatology exams.

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Reviewed – no changes
3 JAN 17

SOP# 21b /11/20/2015 as a continuation of the previous one from 25Nov2014

Regarding investigational medicine destruction

This SOP is a continuation of established practices medication destruction during clinical trials

Study medications will be kept on site until is returned to designated facility/vendor after final accountability by site staff and Sponsor representative. This accountability will be documented in study medication logs, clearly showing kit numbers, when dispensed, to which patient, when were returned, and with how many tablets. These logs will be signed by site staff and designated Sponsor representative. When shipping back to Sponsor a copy of airway bill will be kept on site together with copy of the Medication log.

In case of necessity of medication destruction on site, the above procedures will be followed but the medication will be destructed on site, by placing all medication containers in the biohazard containers on site. The same will be collected through routine pick up service, scheduled every 2 weeks and the pick up date will be documented on the logs. A protocol will be filled out to document that destruction signed by pharmacist and another member of the team. Copy of pick up protocol will be attached to the logs aswell.

Dr Boris Nikolov, Study Manager