**INVESTIGATOR’S BROCHURE FOR CLINICAL TRIALS**

Sponsor--------------------------

SOP reference------------------001

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Investigational Product--------covidorganics:

Effective date--------------------

Author------------------------------Designated member of research team at the study site.

Approved by----------------------Chairman, EC/IRB.

*Amendment History*

|  |  |  |  |
| --- | --- | --- | --- |
| Version | Date | Authors | Amendment details |
|  |  |  |  |

**CONFIDENTIALITY STATEMENT**

This Investigator’s Brochure (IB) is a confidential document for the sole information and use of the investigator's team and the IRB/IEC as well as the Data Safety and Monitoring Board.

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**2. SUMMARY**

Covidorganics is a standardized herbal medicine, a water decoction, containing 62% of *Artemisia annua* and 38% of other Malagasy medicinal plants (eg Cinnamum camphora). Covidorgnaics is administered orally in a dose of 33 ml three times a day for 7 days. If the patient is responding to treatment, covidorganics can be given till 14 days. But since recruitment is on a continuous basis, the study duration is based on when the sample size is achieved which may be up to six months. The cut-off point is exit due to cure or death.

Covidorganics was developed and produced by the Malagasy Institute of Applied Research (IMRA),

Covidorganics (CVO) (Tambavy) is an improved traditional herbal remedy containing *Artemisia annua* and other Malagasy medicinal plants (e.g.*Cinnamomum camphora*). The product was developed and produced by the Malagasy Institute of Applied Research (IMRA), Madagascar. The major organ toxicity and median lethal dose (LD50) in the mice and rats were evaluated. The caudal vein injection technique in the mouse was used to assess the LD50 and to observe the damage to the main organs of the mouse. The LD50 value in mice was 5500 mg/ kg body weight and 8960 mg / kg in rats. No significant change was observed in the weights of the organs while histopathological findings showed normal profiles. Both liver and kidney function enzymes were normal. Collectively, the results indicate that the Artemisia extract is not toxic. But at high doses, may have a hepatoprotective effect.

One study shows, however, that an extract of Artemisia reduced lipoprotein-cholesterol, at high density at 100 mg/Kg. The atherogenic index, as well as the rates of low-density lipoprotein-cholesterol were increased. The plant extract should be taken with caution in people with atherosclerosis. Studies show a hypoglycemic activity of Artemisia extract at high concentrations. The test was performed on rats. Blood glucose levels were significantly decreased from 24% to 57% depending on the doses administered (500 mg/kg body weight and 750 mg/ Kg body weight, respectively). This function could be beneficial for subjects with high blood sugar levels. However, although the plant extract will not be taken at these high doses, it would be necessary to monitor patients' blood sugar levels.

Based on the preclinical data for safety, the product did not manifest any toxic effect. Furthermore, the pilot clinical study undertaken at IMRA did not report any adverse effect. It should however be noted that the study population for the pilot clinical trial was small (50). It is therefore significant to conduct multicenter studies with higher sample size (1,056) so as to evaluate the safety and efficacy of covidorganics.

**3. INTRODUCTION**

Covidorgnaics (CVO) is registered by the Malagasy national medicines regulatory agency for the treatment of COVID-19 patients. The registration of covidorganics is for both curative and prophylactic purposes against COVID-19. The preliminary studies at Malagasy Institute of Applied Research (IMRA) indicate that covidorganics may modulate the immune system and also prevents the replication of COVID-19. Furthermore, it has antioxidant effects. Some of the constituents identified so far include artemisinin, essential oils, flavonoids, coumarins, polysaccharides, saponins, tannins, and pentacyclic triterpenes. IMRA scientists are currently studying the exact bioactive compounds responsible for the observed beneficial effects in the pilot clinical trial. The rationale for this study is based on the curative responses in COVID-19 patients during an initial observational study. In addition, the preclinical study showed a very good safety profile with no damage to the kidneys, liver, blood parameters, lungs. The initial observational study justified the conduct of randomized placebo-controlled phase II clinical trial using 50 COVID-19 patients. The result indicated that all the 50 patients were cured after 7 days of treatment with oral covidorganics and no adverse effect was reported. The other two arms of the study were given hydroxychloroquine or hydroxychloroquine plus covidorganics. The clinical outcomes of the two arms of the study have not yet been received from Madagascar. The current study is designed to evaluate the potential curative effect of covidorganics in the treatment of COVID-19 patients in a multicenter multicountry randomized placebo controlled phase III clinical trial using 1,056 COVID-19 patients.

The design is that a country will indicate her willingness to participate in the multicountry trial and sponsor the local financial costs of the trial. Subsequently, the national EC/IRB will inspect a potential study site and develop a report which is sent to the WHO-AFRO. Thereafter, the Expert Committee will send a team to the potential study site to evaluate the available infrastructure and trained personnel . The report of the inspection team will inform the WHO-AFRO the suitability or otherwise for the potential site. Upon approval of a study site, appropriate standard operation procedures (SOPS) will be shared with the site research team. Thereafter, a short training at the study site is organized by members of the Expert Committee which activates the initiation of the study. Recruitment for this study is continuous until the sample size is attained. The selection criteria are stipulated in the protocol and should be strictly adhered to. The research team will develop the methods and materials to be used for recruitment of COVID-19 patients with the approval of both the EC/IRB and the national medicine regulatory authority. Such materials and methods should be ethically sound and also take cognizance of cultural sensitivities.

After the approval of the methods and materials for recruitment of study subjects, selection criteria are applied accordingly. Those who qualify to participate in the study are adequately briefed in the language of their preference on the Informed Consent (IC). A template of IC is shown in Annex 1 which can be adapted appropriately. Furthermore, the subject’s Informed Consent Statement and Investigator’s Informing Statement are shown in Annexes 2 and 3 while the schedule of activities is indicated in Annex 4. Those who qualify and willingly sign the IC will then be registered using templates on personal data, prior history and physical examination (Annexes 5, 6 and 7). Subsequently, pre-trial tests are conducted using the templates shown in Annexes 8-10. Any of the case report forms (CRF) can be modified to suit local regulations and practice. Any adverse events should be promptly recorded (Annex 11) and managed according to the national standard care of practice. On Days 3, 5, 7 and possibly 14, the quality of life of study subjects should be assessed using Karnofysky Performance Scale (Annex 12). On the other hand, any signs of toxicity related to covidorganics can be evaluated using the Toxicity Grading Scale (Annex 13). The Essential/Source Documents are shown in Annexes 14, 15 and 16. They must be stored in a locked fire proof cabinet or password protected in an electronic format. Access to the Essential Documents is highly limited to only authorized personnel (eg PI, NMRA, Sponsor, WHO Expert Committee).

Once the clinical trial commences, the responsibility regarding the daily conduct of all the members of the research team rests on the Principal Investigator (PI). The PI should ensure that at all times the health, safety and quality of health of the study subjects are paramount and adhered to ICH-GCP ethical standards. On the other hand, it is the responsibility of the national medicine regulatory authority (NMRA) to provide oversight functions by monitoring the trial frequently. If the NMRA identifies any anomalies in the management of the trial, the PI, sponsor and the WHO Expert Committee should be alerted in writing. Immediate efforts under the leadership of the NMRA should be activated to resolve the observed anomalies. In view of the potential significance of this study both at local and international levels, the WHO Expert Committee will serve as the International Scientific Committee. It is the responsibility of the WHO Expert Committee to articulate an effective monitoring mechanism for this study. Members of the WHO Expert Committee should be given direct access to all essential documents and data to enable them articulate timely reports to the WHO-AFRO and ACDCshall. If the Expert Committee observes any pattern of concern, the PI should be informed. The WHO Expert Committee members visiting the study site should immediately organize a meeting with all members of the research team so as to correct the unacceptable situation. Disposal of remaining unused covicorganics has been described in the protocol.

At the end of the study, the PI prepare a detailed Final Report to the sponsor with a copy to the WHO Expert Committee. All electronic data (password protected) should be sent to the WHO Expert Committee to enable all the results from the participating countries to be pooled and analysed by the biostatistician. The outcome of the statistical analysis will be made available to all participating countries (sponsors). The announcement of the findings of the study will then be made by the President of Madagascar. The statement for announcement by the President must be approved by both the WHO-AFRO and Africa Centre for Disease Control and Prevention.

**4. PHYSICAL, CHEMICAL, AND PHARMACEUTICAL PROPERTIES AND FORMULATION (MORE DETAILS UPON RECEIPT OF THE DATA FOR THE PRECLINICAL STUDIES AND PHASE II CLINICAL TRIALS)**

Covidorganics is a standardized herbal medicine, a water decoction, containing 62% of *Artemisia annua* and 38% of other Malagasy medicinal plants (eg *Cinnamum camphora*). Water is boiled. Then the leaves (1.5 g) of the medicinal plants are added and left for 5 minutes. Thereafter, 33 ml is given to an adult COVID-19 patient three times a day. The decoction should not be boiled again. Fresh decoctions are prepared every day. The leaves of the medicinal plants are Some of the constituents identified so far include artemisinin, essential oils, flavonoids, coumarins, polysaccharides, saponins, tannins, and pentacyclic triterpenes.

**5. NON-CLINICAL STUDIES (to be completed when data from Madagascar is available)**

**5.1 Non-clinical pharmacology**

Water extract of *Artemisia annua* plus other Malagasy medicinal plants manifested immunomodulatory effects through changes in cytokine levels. It also showed antioxidant properties and virostatic effects on New Coronavirus *using in vitro* models.

**5.2 Pharmacokinetics and Product Metabolism in Animals (to be done when data from Madagascar is received)**

**5.3. Toxicology**

Madagascar. The major organ toxicity and median lethal dose (LD50) in the mice and rats were evaluated. The caudal vein injection technique in the mouse was used to assess the LD50 and to observe the damage to the main organs of the mouse. The LD50 value in mice was 5500 mg/ kg body weight and 8960 mg / kg in rats. No significant change was observed in the weights of the organs while histopathological findings showed normal profiles. Collectively, the results indicate that the Artemisia extract is not toxic, has a low potential for acute toxicity. But at high doses, may have a hepatoprotective effect.

**6. EFFECTS IN HUMANS**

**6.1 Pharmacokinetics and Product Metabolism in Humans (no information yet)**

**6.2 Safety and Efficacy**

Pilot clinical studies undertaken by IMRA, Madagascar indicated that all the 50 COVID-19 patients who were treated with covidorgnaics responded well and showed no adverse effects.

**6.3 Marketing Experience (no data yet).**

**7. SUMMARY OF DATA AND GUIDANCE FOR THE INVESTIGATOR**

The limited available preclinical data indicated that covidorganics is safe. However, the data received only showed the safety profile of *Artemisia annua.* Yet, covidorganics contains other Malagasy medicinal plants (about 32%). Similarly, the limited information on safety of covidorganics in humans suggested its safety.

**ANNEXES**

**Annex 1: Informed Consent Form (ICF)**

Multi-centre, randomized, double-blind, placebo-controlled clinical trial to evaluate the efficacy and safety of covidorganics compared to the standard-of care for the treatment of hospitalized patients with novel coronavirus disease (COVID-19).

**Background**

Indeed, COVID-19 is a serious infection. Globally, as at 26th August 2020, 23,752,965 confirmed cases and 815,038 deaths while in Africa 1.019,362 confirmed cases and 20,828 deaths have been reported (WHO Situation Report., 28 August 2020). Confirmed cases of coronavirus have been reported in 216 countries, areas and territories (WHO, 28th August 2020). A novel coronavirus (SARS-CoV-2) that causes the disease Coronavirus Disease 2019 (COVID-19) emerged in a seafood and poultry market in the Chinese city of Wuhan in December 2019. In view of its spread across the world through human to human transmission through close contact, the WHO declared it a pandemic on March 11, 2020. Confirmed cases of COVID-19 have been reported in 188 countries globally).[[1]](#footnote-1)[[2]](#footnote-2)

COVID-19 exists in nature, with potential, intermediate and final hosts. It is highly transmissible and infectious compared to SARS-CoV (Severe Acute Respiratory Syndrome Corona Virus) and MERS-CoV (Middle East Respiratory Syndrome Corona Virus), but with a lower mortality rate. COVID-19 causes upper respiratory tract disease and sometimes severe and fatal lung disease similar to SARS-CoV and MERS-CoV.

**Who will be selected to participate in the study?**

* Subject (or legally authorized representative) provides written informed consent prior to initiation of any study procedures.
* Understands and agrees to comply with planned study procedures.
* Agrees to the collection of OP swabs and venous blood per protocol.
* Male or non-pregnant female adult ≥18 years of age at time of enrolment.
* Laboratory-confirmed SARS-CoV-2 infection as determined by PCR at a Government approved lab. from throat/nasopharyngeal swab.
* Illness of any duration, and at least one of the following:
* Radiographic infiltrates by imaging (chest x-ray, CT scan, etc.), or
* Clinical assessment (evidence of rales/crackles on exam) or
* Requiring mechanical ventilation and/or supplemental oxygen.
* Creatinine ≤ 110 umol/L, creatinine clearance rate (EGFR) ≥ 60 ml / min / 1.73m2, AST and ALT ≤ 5 × ULN, TBIL ≤ 2 × ULN;
* No severe acute respiratory syndrome (SARS), that is, not using mechanical ventilation or supplemental oxygen, with peripheral oxygen saturation >94% in room air, and having a respiratory rate below 24 incursions per minute.
* A Normal ECG Baseline result, which is maintained throughout the study.

**Who should not participate in the study:**

**Subjects with the following conditions will be excluded from the study:**

* ALT/AST > 5 times the upper limit of normal.
* Stage 4 severe chronic kidney disease or requiring dialysis (i.e. eGFR < 30)
* Pregnancy or breast feeding.
* Anticipated transfer to another hospital which is not a study site within 72 hours.
* Allergy to any study medication
* Shortness of breath in resting position
* Known prolonged QT syndrome
* Use of concomitant medications that prolong the QT/QTc interval
* Subjects who have severe underlying diseases that affect survival including uncontrolled malignant tumor with multiple metastases that cannot be resected, blood diseases, dyscrasia, active bleeding and severe malnutrition
* Subjects with allergies to artemisinine containing products
* History of allergic reactions to any investigational medical product ingredient

Subjects who in the opinion of the investigators after assessing all relevant parameters are unsuitable for the study.

**How is the study conducted?**

One group shall be given covidorganics orally while the second group shall be treated using the national standard of care. Treatment will be for seven (7) days Since mild to moderate cases on coronavirus will be targeted in this study, the study participants will be essentially out patients. The quantity of the coronavirus in your system will be measured while other tests will be done to assess your liver, kidney and heart functions.

**What are the risks and adverse reactions of participants in this study?**

Like all medicines, there is always the risk of side effects. However, currently we area not aware of any side effects of covicorganics. There are no adverse effects known for covidorganics yet. Nonetheless, if you experience any side effect, tell your doctor immediately.

**What are the potential benefits for participants in this study?**

Covidorganics has shown the effect of blocking the replication of New Coronavirus in the lab. Furthermore, the pilot clinical trial phase II shows that it benefited all the COVID-19-19 patients.

**Under what circumstances will the subject cease to participate in the study?**

In the event of death, serious adverse event to the drug or when clinical symptoms are worsening requiring life support and transfer to the Intensive care unit (ICU) the Clinician has the responsibility to withdraw the participant from the study.

**Expenses for participation in the study**

Participation in the study is free including medication and laboratory investigations.

**What do I need to do to participate in the study?**

1. Provide accurate medical history and current condition information.
2. Tell the study doctor about any health problems you have during the study.
3. Follow the instructions of investigators and medical staff.
4. Please feel free to ask if you have any questions.

**Will the subject's personal information be kept confidential?**

All laboratory specimens, evaluation forms, reports, study protocol, documentation, data and all other information generated will be held in strict confidence. No information concerning the study, or the data will be released to any unauthorized third party.

**Who should I contact if I have a problem or difficulty?**

This study has been approved by the ethics committee of the-------------. If you need any clarification, please contact:

PI:

Tel:

**Annex 2: Patient Consent**

I have been informed of the study background, purpose, procedures, risks and benefits of the project “Randomized Double-blind Comparator-Controlled Clinical Trial Phase III of covidorganics in the Treatment of COVID-19 Patients.”

 I have enough time and opportunity to ask questions, and I am satisfied with the answers. I have also been informed who to contact when I have additional questions or want further information. I have read this ICF and agree to participate in the study. I know that I can withdraw from the study at any time without any reason during the study. I am informed that I would receive a copy of this ICF, which contains my and the investigator's signatures.

**Name of subject: Signature of subject:**

**Tel: Date:**

**Annex 3: Investigator’s Informing Statement**

I have informed the subject of the study background, purpose, procedures, risks and benefits of the project: “Randomized Double-blind Controlled Clinical Trial Phase III of Covidorganics in the Treatment of Covid-19 Patients.” given him/her enough time to read the ICF and discuss with others, and answered the questions about the study; I have informed the subject of the contact information for any problem; I have informed the subject that he/she may withdraw from the study at any time during the study without any reason.

**Name of investigator: Signature of investigator: Witness:**

**Tel: Date: Date:**

**Annex 4: Schedule of activities**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **Day 0** |  |  |  |  |
|  | **Pre-treatment** | **Day 1** | **Day 2** | **Day 3** | **Day 4** | **Day 5**  | **Day 6** | **Day 7** |
| Medical history |  |  |  |  |  |  |  |  |
| Demography |  |  |  |  |  |  |  |  |
| Background  |  |  |  |  |  |  |  |  |
| Health diary  |  |  |  |  |  |  |  |  |
| Disease history |  |  |  |  |  |  |  |  |
| G6[D ASSAY |  |  |  |  |  |  |  |  |
| ECG |  |  |  |  |  |  |  |  |
| Chest x-ray Tb Test |  |  |  |  |  |  |  |  |
| Haematology |  |  |  |  |  |  |  |  |
| Blood chemistry |  |  |  |  |  |  |  |  |
| Uanalysis  |  |  |  |  |  |  |  |  |
| Physical exam. |  |  |  |  |  |  |  |  |
| Weight height, MA BMI |  |  |  |  |  |  |  |  |
| Vital signs |  |  |  |  |  |  |  |  |
| Adverse Events (7) |  | WHEN APPLICABLE |  |
| Concomitant medications |  | WHEN APPLICABLE |  |
| OVA & parasites |  |  |  |  |  |
| Monitor any abnormal parameters frequently until they return to baseline |  |

**Annex 5: Personal data**

RESISTRATION NUMBER: -------------------------------- DATE: -------------------------

SEX: --------------------------------------------------------------------------------------------

NAME: -----------------------------------------------------------------------------------------

MARITAL STATUS: --------------------------------------------------------------------------

ADDRESS RESIDENTIAL: -------------------------------------------------------------------

---------------------------------------------------------------------------------------------

POSTAL: --------------------------------------------------------------------------------------

-------------------------------------------------------------------------------------------------

TEL. NO: --------------------------------------------------------- FAX------------------------

NATIONALITY: ------------------------------------------------- STATE OF ORIGIN --------------

OCCUPATION: ------------------------------------------------------------------------------------

Do you smoke? |Yes/No| if you specify

Brand ----------------------------------- Quantity/work Duration (yes) --------------

Do you take alcohol? |yes/No| if yes, specify

Brand ----------------------------------- Quantity/work Duration (yes) --------------

BLOOD GROUP: ----------------------------------------- GENOTYPE ---------------------------

OCCUPATION: ---------------------------------------------------------------------------------------

OCCUPATION: ---------------------------------------------------------------------------------------

SOCIAL CLASS: ---------------------------------------------------------------------------------------

**Annex 6: Prior history**

Patient Name: ----------------------------------------------------------------------------

Patient Registration Number: -------------------------------------- Date: ----------

**Prior admissions/Hospital days: Date:-------------------- Reason (s):-----**

|  |  |
| --- | --- |
|  |  |
|  |  |
|  |  |
|  |  |
|  |  |

|  |  |  |
| --- | --- | --- |
|  **Symptons**  | **Yes** | **No** |
| 1 Fever |  |  |
| 2 Chest pain |  |  |
| 3 Shortness of breath |  |  |
| 4 Loss of taste  |  |  |
| 5 Loss of smell |  |  |
| 6 Sleepy |  |  |
| 7 Dry cough |  |  |
| 8 Others |  |  |

**Annex 7: Physical examination/vital signs, symptom monitoring**

Patient Name: ------------------------------------------------------------

Patient Registration Number: ---------------------------------------- Date: -------------------

Any crisis since last visit: ----------- Hospital Admission ------- Blood Transfusion ---

Absenteeism:----------------

 Temperature: ------------------------------ BMI: -------------------------------

 Weight: -----------------------------------

 Height: -----------------------------------

 Respiratory Rate: -----------------------------------

 Pulse Rate: ------------------------------------

 Blood Pressure: ------------------------------------

 Appearance: ------------------------------------

|  |  |  |  |
| --- | --- | --- | --- |
|  | study | absent | if present comment |
|  |  |   |
| ENT |  |  |
| Cardiovascular |  |  |
| Respiratory/Breast |  |  |
| Abdomen |  |  |
| Urogenital |  |  |
| Musculoskeletal |  |  |
| Breast |  |  |
| Neurologic |  |  |
|  | Others (vision, hearing etc) |  |  |

Comments: --------------------------------------------------------------------------------

|  |
| --- |
| **Annex 8: Cardiac studies, x – ray and ophthalmology review**Patient Name: --------------------------------------------------------------------------Patient Registration Number: ------------------------ Date:------------------- |

**Study: Baseline (pre-treatment) Study Date of comment overall Assessment Normal (N) or Abnormal (A)**

|  |
| --- |
| ECG /---/--- M D Y |
|  |
|  |
|  |
| CHEST X-RAY /------/--- M D Y |
|  |
|  |
|  |
| OPHTHALMOLOGY /-----/---- M D Y |
|  |
|  |
|  |

**Annex 9: Haematology monitoring**

Patient Name: ------------------------------------------------------------------------

Patient Registration Number: -------------------------------------------- Date: ---------------

|  |  |
| --- | --- |
|  | DATE |
|  | NORMAL |  |  |  |  |  |  |  |  |  |
|  | LAB RANGE |  |  |  |  |  |  |  |  |  |
| WBC |  |  |  |  |  |  |  |  |  |  |
| RBC |  |  |  |  |  |  |  |  |  |  |
| HB |  |  |  |  |  |  |  |  |  |  |
| HcT |  |  |  |  |  |  |  |  |  |  |
| MCV |  |  |  |  |  |  |  |  |  |  |
| MCH |  |  |  |  |  |  |  |  |  |  |
| MCHC |  |  |  |  |  |  |  |  |  |  |
| PLATELETS |  |  |  |  |  |  |  |  |  |  |
| RETICS |  |  |  |  |  |  |  |  |  |  |
| SEGS Neutrophil |  |  |  |  |  |  |  |  |  |  |
| BANDG Neutrophil |  |  |  |  |  |  |  |  |  |  |
| MONOCYTES |  |  |  |  |  |  |  |  |  |  |
| LYMPHOCYTES |  |  |  |  |  |  |  |  |  |  |
| EOSINOPHILS |  |  |  |  |  |  |  |  |  |  |
| BASOPHILS |  |  |  |  |  |  |  |  |  |  |
| NRB100WBC |  |  |  |  |  |  |  |  |  |  |
| Atyp Lymph |  |  |  |  |  |  |  |  |  |  |
| RETICULOCYTES |  |  |  |  |  |  |  |  |  |  |

**Annex 10: Microbiology monitoring**

Patient Name: -----------------------------------------------------------------------

Patient Registration Number: -------------------------------------------- Date: ---------------

|  |  |
| --- | --- |
|  | DATE |
|  | NORMAL  |  |  |  |  |  |  |  |  |
|  | LAB RANGE |  |  |  |  |  |  |  |  |
| TB Test |  |  |  |  |  |  |  |  |  |
| HIV Test |  |  |  |  |  |  |  |  |  |
| Hepatits B surface Ag |  |  |  |  |  |  |  |  |  |
| Stool Microscopy |  |  |  |  |  |  |  |  |  |
| Urinalysis  |  |  |  |  |  |  |  |  |  |
|  :PH  :SG :Glucose  :Protein  :Cells  :Gram stain :Bilirubin :Culture  |  |  |  |  |  |  |  |  |  |
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**Annex 11: Adverse experiences/concomitant treatment**

Patient Name: ------------------------------------------------------------------------

Patient Registration Number: -------------------------------------------- Date: ---------------

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Adverse events | (Start) m/D/y | stop (m/D/y or 1 day: hr: min | sev (1) | Rel. to Rx (2) | action taken (3) | Outcome (4) | comments include other etiologies  |
|  |  |  |  |  |  |  |  |
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1. Severity: 1 = Mild, 2= Moderate, 3 = Severe. 4= Life Threatening 5 = Death

 2. Relationship to therapy:

 1 = Unknown: Clear cut temporal association, but other aetiologies are possible

 2 = Definite: Clear cut temporal association with + rechallenge test or lab confirmation

3 = Probable: clear cut temporal association with improvement upon medication withdrawal and not reasonable explained by the subject’s known clinical state.

4 = Possible: Less clear temporal association: other aetiologies are possible

5 = None: No temporal association; related to other aetiologies such as concomitant medications

 3. Action Taken: 1 = None, 2 = treatment required (if yes, complete concomitant medical form)

3 = Agent dose reduced, 4 = agent dosing temporarily. i/c, 5 = agent dosing permanently i/c, 6 = hospitalization required, 7 = d/c concomitant medical.

 4. Outcome: 1 = resolved, 2 = unresolved, 3 = sequelae, 4 = total, 5 = lost of follow up

Concomitant treatment (Specify) ------------------------------------------------------------Indication: -----------------------------------------------------------------

**Annex 12: Karnofsky performance scale**

|  |  |  |
| --- | --- | --- |
| Able to carry on normal activity; no special care is needed  | 100 | normal; no complaints; no evidence of disease |
|  | 90 | Able to carry on normal activity; minor signs or symptoms of disease |
|  | 80 | Normal activity with effort; some signs of symptoms or disease |
| Unable to work, above to live at home and care for most personal needs; a varying amount of assistance is needed | 70 | Cares for self, unable to carry on normal activity or to do active work |
|  | 60 | Requires occasional assistance but is able to care for most of needs |
|  | 50 | Requires considerable assistance and frequency medical car |
| Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly | 40 | Disabled; requires special care and assistance |
|  | 30 | Severely disable; hospitalization is indicted although death is not imminent |
|  | 20 | Very sick; hospitalization necessary; active supportive treatment is necessary |
|  | 10 | Moribund; fatal processes progressing rapidly |
|  | 0 | Dead  |

**Annex 13: Toxicity grading scale**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  |  |  |  |  |
|  | **GRADE 1** | **GRADE 2** | **GRADE 3** | **GRADE 4** |
| SYMPTOMS | Asymptomatic, easily tolerated, transient  | Mild tolerable symptoms, short duration, normal activity | Moderate symptoms, poorly tolerated, sustained, interferes with normal activity | Severe symptoms, intolerable, sustained, incapacitating, life treating, fatal, permanently disabling, results in congenital abnormalities, cancer, overdose.  |
| TREATMENT | Not required | Not required except when noted | Required, responds to Rx | No response to Rx, hospitalization required |
| ALLERGY | GRADE 1 | GRADE 2 | GRADES 3 | GRADE 4 |
| ALLERGIC REACTION | Transient rash, drug fever 380C, 100.4f | URTICARIA, DRUG FEVER> 380C, 100.4f, mild bronchospasm | Serum sickness, bronchospasm requiring parenteral Rx | Anaphylaxis with hypotension |
| FEVER WITH DRUG (absence of infection) | 37.1 – 38 0C100.5 – 104 0F | 38.1 - 400C100.5 – 1040F | >400C, >1040F for >24 hours despite antipyretic Rx | >400C, >1040F despite Rx for >24 hours, or any fever associated with hypotension |
| CARDIOVASCULAR | GRADE 1 | GRADE 2 | GRADE 3 | GRADE 4 |
| CARDIAC SYMPTOMS | Mild or transient  | Symptoms on exertion, recurrent or persistent; no Rx required | Symptoms at rest, requires Rx | Severe symptoms, unresponsive to Rx |
| ARRJYTHMIA | Asymptomatic, ransient, no Rx required | Recurrent or persistent, no Rx required | Requires Rx | Requires monitoring; or hypotension, or ventiricular tachnycardia, or fibrillation  |
| CARDIAC BIOPSY (Index) | 0.5 | 1.0 | 1.5 | >1.5 |
| CARDIAC FUNCTION  | Asymptomatic, decreased ejection fraction by 20% of bade | Asymptomatic, decreased ejection fraction by >20% of bade | Mild CHF, responsive to Rx | Severe refractory CHF |

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **CARDIOVASCULAR cont** | **GRADE 1** | **GRADE 2** | **GRADE 3** | **GRADE 4** |
| OEDEMA (e.g peripheral capillary leak syndrome) also see pulmonary | Minimall ankle pitting edema | Ankle pitting edema and weight gain 5kg | Peripheral edema, weight gain 5-10kg, pleural effusion with no pulmonary function deficit | Anascara, sever pleural effusion with pulmonary function deficit, ascites, pulmonary edema, weight gain >8kg  |
| HYPOTENSION | Asymptomatic, transient increase >20mm Hg or 150/100 if previously WNL. No Rx required | Recurrent or persistent (>1 hr) increased >20mm Hg or 150/100 if previously WNL. No Rx required | Persistent increase >20mm Hg or >150/100 if previously WNL Rx required | Hypertensive crisis |
| HYPOTENSION | 10.20% decrease, systolic, no Rx required (includes transient orthostatic hypotension) | 21.50% decrease systolic, requiring fluids or other Rx but not hospitalization | 21-50% decrease systolic, requires pressors and hospitalization, resolves within 48 hours | >50% decrease systolic, requiring hospitalization, unresponsive to pressors, requires>48 hours to resolve after stopping agent |
| ISCHEMIA | Non specific T-wave flattening; stable EKG | Asymptomatic, EKG change; ST and T-wave change suggests ischaemia | New onset angina without evidence of infarction; clinical significant EKG change | Acute EKG change diagnostic for myocardial infarction |
| PERICARDIAL EFFUSION | Asymptomatic No Rx required | Pericarditis (rub, chest pain, EKG changes) | Symptomatic; large effusion, drainage required, no tamponade, responsive to drainage | Large effusion, tamponade; drainage urgently required |
| **CNS** | **GRADE 1** | **GRADE 2** | **GRADE 3** | **GRADE 4** |
| AFFECT ABNORMALITY (Mood) | Transient panic/apathy; mild anxiety/depression | Sustained panic/apathy; moderate anxiety/depression | Sustained panic/apathy; server anxiety/depression; requiring Rx | Sustained panic/apathy; unresponsive to Rx; suicidal ideation |
| ATAXIA (Cerebellar) | Mild/transient gait or limb ataxia; slight incoordination, dysdiadochokinesis | Intesion tremor, nystagmus, dysmetria | Moderate gait or limb ataxia | Disabling ataxia, cerebellar necrosis |
| AUTONOMIC DYSFUNCTION | Abnormal sweating | Impotence | Asymptomatic arrhythmia, orthostatic hypotension | Symptomatic arrhythmia, orthostratic hypotension |
| BLADDER DYSFUNCITON | - | Dysfunction not requiring catheter | Dysfunction requiring catheter | Dysfunction requiring permanent catheter |
| COGNITIVE DEFECT | Slow, accurate | Impaired memory or new learning | Global defiency | Unresponsive |
| CONSTIPATION, AUTONOMIC | Mild, n Rx required | Occasionally requiring cathartics | Daily cathartics/enema required | Abdominal distention, vomiting: lieus >96 hours |

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| --- | --- | --- | --- | --- |
| **CNS cont** | **GRADE 1** | **GRADE 2** | **GRADE 3** | **GRADE 4** |
| CORTICAL | Mild somnolence or agitation; easily arousable | Moderate somnolence or agitation; responds to loud verbal or tactile stimuli | Severe somnolence, agitation, confusion, disorientation, or hallucinationsl responds to pain only | Coma, grand mal seizures (current) toxic psychosis |
| FOCAL SEIZURES | Isolated  | ≤ 2 per day | ≤ 3 per day | Status epilepticus |
| GENERALISED SEIZURES | Isolated | ≤ per day | ≤ 3 per day | Epilepsia partialis continue |
| HEADACHE | Mild | Moderate or severe but transient  | Unrelenting and severe | --- |
| HEARING LOSS | Transient decrease, loss by audiometry only | Tinnitus, moderate loss | Interferes with function, correctable | Deaf, despite hering aid |
| LANGUAGE ABNORMALITY  | inattentiveness, slurring  | Motor or communicative aphasia 2 hours | Motor or communicative aphasia > hours | Global aphasia |
| MOTOR DEFICIT | Mild transient subjective weakness | Moderate objective weakness, ambulatory | Non-ambulatory; objective weakness | Complete paralysis |
| MOVEMENT DISORDERS | Transient abnormal limb movement | Moderate limb part disorder | Severe and reversible parkinsonism, dystonia or tremor  | Permanent parkinsonism dystonia or tremor |
| SENSORY DEFICIT | Mild paresthesias, decrease DTR’s | Mild to moderate objective sensory loss; absent; DTR’s | severe paresthesia, severe objective sensory loss; interferes with function | Complete loss of sensation  |
| SPEECH ABNORMALITY  | Mildly slurred  | Moderate sluming | Unintelligible | Mute |
| VERTIGO | Mild transient | Moderate nausea | Associated with nausea and vomiting | Disabling intractable |
| VISION ABNORMALITY | Slightly reduces acuity | Symptomatic, correctable | Symptomatic unable to correct | Blind |
|  |  |  |  |  |
| DERMATOLOGIC | GRADE 1 | GRADE 2 | GRADE 3 | GRADE 4 |
| ALOPECIA |  Partial loss | Complete loss | Non-reversible  | -- |
| CHELITIS | Chapping  | Fissures | Bleeding | Necrosis |
| SKIN REACTION | Dry skin, mild or transient rash; scattered asymptomatic macular or popular eruption or ertythema | Dry desquamation, scattered macular or popular eruption or erythema with pruritus or other associated symptoms | Moist desquamation, bullous disease, generalized symptomatic macular, popular or vesicular eruption | Exfoliative dermatitis; requires surgical Rx |

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **GASTROINTESTINAL** | **GRADE 1** | **GRADE 2** | **GRADE 3** | **GRADE 4** |
| DIARRHOEA | Transient, >2-3 stools per day over baseline | Tolerable, >4.6 stools per day over baseline, or nocturnal stools, moderate cramping | Intolerable, > 7-9 stools per day over baseline, or incontinence, sever cramping | Haemorrhagic, > 10 stools per day over baseline, dehydration, requires parenteral Rx |
| NAUSEA |  Able to eat, reasonable intake | Able to eat, decreased intake | No significant intake  | -- |
| VOMITTING | 1xin 2 hours | 2-5 in 24 hours | 6 – 10 x in 24 hours | > 10x in 24 hours, or requires parenteral support |
| STOMATITIS | Milk soreness, erythema, painless ulcers | Painful erythema, patchy oedema or ulcers, but can eat | Confluent ulcers, painful erythema, oedema cannot eat | Haemorrhagic ulceraton, necrocis, requires parenteral or entereal support |
| **GENERAL** | **GRADE 1** | **GRADE 2** | **GRADE 3** | **GRADE 4** |
| MYALGIA | Myalgia | Myalgia requiring treatment | Severe, CK 2.0 – 5.0 X ULN | Intractable CK >5 X ULN |
| CHILLS | Mild | Moderate | -- | -- |
| LOCAL | Pain | Pain and swelling, inflammation or phlebitis | Ulceration | Plastic surgery indicated  |
|  |  |  |  |  |
| **HAEMATOLOGICAL**  | **GRADE 1** | **GRADE 2** | **GRADE 3** | **GRADE 4** |
| ANAEMIA (gHbg) | 10 – Normal | 8.0 – 10 | 6.5 – 7.9 | <6.5 |
| GRANULOCYTOPENIA (X 100 uL) | 1.5 – 1.9 and >20% decrease from baseline | 1.0 – 1.4 and >35% decrease from baseline | 0.5 – 0.9 and >50% decrease from baseline | <0.5 and >75% decrease from baseline |
| LEUKOPOENIA (X 100 uL) | 3.0 – 3.9 and >20% decrease from baseline | 2.0 – 2.9 and >35% decrease from baseline | 1.0 – 1.9 > 50% decrease from baseline | <1.0 and >75% decrease from baseline |
| THROMBOCYTOPOENIA X 100 uL) | 75.99 and >20% decrease from baseline | 50 – 74 and >35% decrease from baseline | 25 – 49 and >50% decrease from baseline | <25 and <75% decrease from baseline |
| HAEMORRHAGE | Petechiae, minimal blood loss, no transfusion required, mild | Gross transfusion required, 1-2 U | Gross transfusion required 3-4 U | Massive transfusion required, ≤ 4U |
|  |  |  |  |  |
| HEPATIC | GRADE 1 | GRADE 2 | GRADE 3 | GRADE 4 |
| ALKALINE PHOSPHATASE INCREASE | 1.5 – 2.5 X ULN | >1.5 – 2.5 x ULN | >5.0 – 10.0 x ULN | >10.0 X ULN |
| -- INCREASE | --- | 1.3 – 1.5 X ULN | >1.5 – 3.0 X ULN |  |
| HEPATIC SYMPTOMS | --- | ---- | Pre-coma | Hepatic comma |
| TRANSMINASE INCREASE | 1.5 – 2.5 X ULN | >2.5 – 5.0 X ULN | >5.0 – 20 XULN | >20 XULN |
| INFECTION | GRADE 1 | GRADE 2 | GRADE 3 | GRADE 4 |
| INFECTION | Mild infection, unknown origin  | Moderate infection  | Major organ infection | Disseminated infection, multi-loba pneumonia; life-threatening sepsis |
| FEVER  | 37.1 – 38OC | 38.1 – 40OC | >40OC >104OF for 24 hours despite antipyretic Rx | >40OC >104OF for 24 hours or a fever associated with hypotension  |
| **PULMONARY** | **GRADE 1** | **GRADE 2** | **GRADE 3** | **GRADE 4** |
| PLUMONARY FUNCTION ABNORMALITY | FVC 70.80% of predicted FEV, or DLCO 60.80% of predicted; 15-25% decrease from abnormal baseline | FVC 50.69% of predicted FEV, or DLCO 40.59% of predicted; 50% decrease from abnormal baseline | FVC >50% of predicted FEV, or DLCO <40% of predicted; 50% decrease from abnormal baseline | Unable to perform test due to respiratory distress |
| RESPIRATORY SYMPTOMS | Mild or transient, asymptomatic with PFT (pulmonary function tests) abnormal  | Dyspnea on significant exertion | Symptoms during normal activity; persistent dyspnea | Severe symptoms at rest, non-responsive to Rx |
| CHESTA RAY | <10% lung fields show infiltrate or effusion | 10.20% lung fields show infiltrate or effusion | 21.50% lung fields show infiltrate or effusion | <50% lung fields show infiltrate or effusion |
| ABG | PA02 <95 on room air | PA02<80 on room air | PA02<60 on room air | PA02<60 on supplemental oxygen |
|  |  |  |  |  |
| **RENAL**  | **GRADE 1** | **GRADE 2** | **GRADE 3** | **GRADE 4** |
| CREATININE INCREASE (mg/dL) | 1.25 – 2.5 X ULN | >2.5 – 5.0 X ULN | >5.0 – 10.0 X ULN | >10 X ULN; requiring dialysis ≥8.0, irreversible loss of >20% |
| CALCULATED CREATININE CLERANCE | 70-80% of baseline | 50.69% of baseline | 30.49% of baseline | <30% of baseline |
| DYSURIA | Mild | Moderate | Severe |  |
| HAEMATURIA | 6.10 RBC/HPF2 | 11.50 RBC/HPF2 | >50 RBC/HPF2 | Requires transfusion |
| PROTEINURIA | 1:<3.0g%, <3 g/л | 2.3:>0.3 – 1.Og%,3-10gl | 4:>1.OG%, >10g/л | Nephrotic syndrome |
|  |  |  |  |  |
|  | GRADE 1 | GRADE 2 | GRADE 3 | GRADE 4 |
| HYPERGLYCEMIA | 140-160mg/dL | 161-250mg/dL | 251-500mg/dL | >500mg/dL; ketoacidosis |
| HYPOGLYCEMIA | 55-64ml/dL | 40-54mg/dL | 30-39mg/dL | >30mg/dL |

# Annex 14: Essential/Source Documents

**Before the clinical phase of the trial commences.**

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

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Title of Document** | **Purpose** | **Located in Files of** |
|  |  |  | **Investigator/****Institution** | **Sponsor** |
| **14.1** | **INVESTIGATOR’S BROCHURE** | To document that relevant and current scientific information about the investigational product has been provided to the investigator | X | X |
| **14.2**  | **SIGNED PROTOCOL AND AMENDMENTS, IF ANY, AND SAMPLE CASE REPORT FORM (CRF)** | To document investigator and sponsor agreement to the protocol/amendment(s) and CRF | X | X |
| **14.3**  | **INFORMATION GIVEN TO TRIAL SUBJECT****- INFORMED CONSENT FORM**(including all applicable translations) | To document the informed consent | X | X |
|  | **- ANY OTHER WRITTEN INFORMATION** | To document that subjects will be given appropriate written information (content and wording) to support their ability to give fully informed consent | X | X |
|  | **- ADVERTISEMENT FOR SUBJECT RECRUITMENT** (if used) | To document that recruitment measures are appropriate and not coercive | X |  |
| **14.4** | **FINANCIAL ASPECTS OF THE TRIAL** | To document the financial agreement between the investigator/institution and the sponsor for the trial | X | X |
| **14.5** | **INSURANCE STATEMENT**(where required) | To document that compensation to subject(s) for trial-related injury will be available | X | X |
| **14.6** | **SIGNED AGREEMENT BETWEEN INVOLVED PARTIES,** e.g.:- investigator/institution and sponsor- investigator/institution and CRO- sponsor and CRO- investigator/institution and authority(ies) (where required) | To document agreements | XXX | XX(where required)XX |
| **14.7** | **DATED, DOCUMENTED APPROVAL/FAVOURABLE OPINION OF INSTITUTIONAL REVIEW BOARD (IRB) /INDEPENDENT ETHICS COMMITTEE (IEC) OF THE FOLLOWING:**- protocol and any amendments- CRF (if applicable)- informed consent form(s)- any other written information to be provided to the subject(s)- advertisement for subject recruitment(if used)- subject compensation (if any)- any other documents given approval/ favourable opinion | To document that the trial has been subject toIRB/IEC review and given approval/favourable opinion. To identify the version number and date of the document(s) | X | X |
| **14.8** | **INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE COMPOSITION** | To document that the IRB/IEC is constituted in agreement with GCP | X | X(where required) |
| **14.9** | **REGULATORY AUTHORITY(IES)****AUTHORISATION/APPROVAL/****NOTIFICATION OF PROTOCOL**(where required) | To document appropriate authorisation/approval/notification by the regulatory authority(ies) has been obtained prior to initiation of the trial in compliance with the applicable regulatory requirement(s) | X(where required) | X(where required) |
| **14.10** | **CURRICULUM VITAE AND/OR OTHER RELEVANT DOCUMENTS EVIDENCING QUALIFICATIONS OF INVESTIGATOR(S) AND SUB-INVESTIGATOR(S)** | To document qualifications and eligibility to conduct trial and/or provide medical supervision of subjects | X | X |
| **14.11** | **NORMAL VALUE(S)/RANGE(S) FOR MEDICAL/ LABORATORY/TECHNICAL PROCEDURE(S) AND/OR TEST(S) INCLUDED IN THE PROTOCOL** | To document normal values and/or ranges of the tests | X | X |
| **14.12** | **MEDICAL/LABORATORY/TECHNICAL PROCEDURES /TESTS**- certification or- accreditation or- established quality control and/or external quality assessment or- other validation (where required) | To document competence of facility to perform required test(s) , and support reliability of results | X(where required) | X |
| **14.13** | **SAMPLE OF LABEL(S) ATTACHED TO INVESTIGATIONAL PRODUCT CONTAINER(S)** | To document compliance with applicable labelling regulations and appropriateness of instructions provided to the subjects |  | X |
| **14.14** | **INSTRUCTIONS FOR HANDLING OF INVESTIGATIONAL PRODUCT(S) AND TRIAL-RELATED MATERIALS**(if not included in protocol or Investigator’s Brochure) | To document instructions needed to ensure proper storage, packaging, dispensing and disposition of investigational products and trial-related materials | X | X |
| **14.15** | **SHIPPING RECORDS FOR INVESTIGATIONAL PRODUCT(S) AND TRIAL-RELATED MATERIALS** | To document shipment dates, batch numbers and method of shipment of investigational product(s) and trial-related materials. Allows tracking of product batch, review of shipping conditions, and accountability | X | X |
| **14.16** | **CERTIFICATE(S) OF ANALYSIS OF INVESTIGATIONAL PRODUCT(S) SHIPPED** | To document identity, purity, and strength of investigational product(s) to be used in the trial |  | X |
| **14.17** | **DECODING PROCEDURES FOR BLINDED TRIALS** | To document how, in case of an emergency, identity of blinded investigational product can be revealed without breaking the blind for the remaining subjects' treatment | X | X(third party if applicable) |
| **14.18** | **MASTER RANDOMISATION LIST** | To document method for randomisation of trial population |  | X(third party if applicable) |
| **14.19** | **PRE-TRIAL MONITORING REPORT** | To document that the site is suitable for the trial (may be combined with 8.2.20) |  | X |
| **14.20** | **TRIAL INITIATION MONITORING REPORT** | To document that trial procedures were reviewed with the investigator and the investigator’s trial staff ( may be combined with 8.2.19) | X | X |

**Annex 15: During the Clinical Conduct of the Trial**

In addition to having on file the above documents, the following should be added to the files during the trial as evidence that all new relevant information is documented as it becomes available

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Title of Document** | **Purpose** | **Located in Files of** |
|  |  |  | **Investigator/****Institution** | **Sponsor** |
| **15.1** | **INVESTIGATOR’S BROCHURE UPDATES** |  To document that investigator is informed in a timely manner of relevant information as it becomes available |  X | X |
| **15.2** | **ANY REVISION TO:**- protocol/amendment(s) and CRF- informed consent form- any other written information provided to subjects- advertisement for subject recruitment(if used) | To document revisions of these trial related documents that take effect during trial | X | X |
| **15.3** | **DATED, DOCUMENTED APPROVAL/FAVOURABLE OPINION OF INSTITUTIONAL REVIEW BOARD (IRB) /INDEPENDENT ETHICS COMMITTEE (IEC) OF THE FOLLOWING:**- protocol amendment(s)- revision(s) of:- informed consent form- any other written information to be provided to the subject- advertisement for subject recruitment(if used)- any other documents given approval/favourable opinion- continuing review of trial (where required) | To document that the amendment(s) and/or revision(s) have been subject to IRB/IEC review and were given approval/favourable opinion. To identify the version number and date of the document(s). | X | X |
| **15.4** | **REGULATORY AUTHORITY(IES) AUTHORISATIONS/APPROVALS/NOTIFICATIONS WHERE REQUIRED FOR:**- protocol amendment(s) and other documents | To document compliance with applicable regulatory requirements | X(where required) | X |
| **15.5** | **CURRICULUM VITAE FOR NEW INVESTIGATOR(S) AND/OR SUB-INVESTIGATOR(S)** | (see 8.2.10) | X | X |
| **15.6** | **UPDATES TO NORMAL VALUE(S)/RANGE(S) FOR MEDICAL/ LABORATORY/ TECHNICAL PROCEDURE(S)/TEST(S) INCLUDED IN THE PROTOCOL** | To document normal values and ranges that are revised during the trial (see 8.2.11) | X | X |
| **15.7** | **UPDATES OF MEDICAL/LABORATORY/ TECHNICAL PROCEDURES/TESTS**- certification or- accreditation or- established quality control and/or external quality assessment or- other validation (where required) | To document that tests remain adequate throughout the trial period (see 8.2.12) | X(where required) | X |
| **15.8** | **DOCUMENTATION OF INVESTIGATIONAL PRODUCT(S) AND TRIAL-RELATED MATERIALS SHIPMENT** | (see 8.2.15.) | X | X |
| **15.9** | **CERTIFICATE(S) OF ANALYSIS FOR NEW BATCHES OF INVESTIGATIONAL PRODUCTS** | (see 8.2.16) |  | X |
| **15.10** | **MONITORING VISIT REPORTS** | To document site visits by, and findings of, the monitor |  | X |
| **15.11** | **RELEVANT COMMUNICATIONS OTHER THAN SITE VISITS**- letters- meeting notes- notes of telephone calls | To document any agreements or significant discussions regarding trial administration, protocol violations, trial conduct, adverse event (AE) reporting | X | X |
| **15.12** | **SIGNED INFORMED CONSENT FORMS** | To document that consent is obtained in accordance with GCP and protocol and dated prior to participation of each subject in trial. Also to document direct access permission (see 8.2.3) | X |  |
| **15.13** | **SOURCE DOCUMENTS** | To document the existence of the subject and substantiate integrity of trial data collected. To include original documents related to the trial, to medical treatment, and history of subject | X |  |
| **15.14** | **SIGNED, DATED AND COMPLETED****CASE REPORT FORMS (CRF)** | To document that the investigator or authorised member of the investigator’s staff confirms the observations recorded | X(copy) | X(original) |
| **15.15** | **DOCUMENTATION OF CRF CORRECTIONS** | To document all changes/additions or corrections made to CRF after initial data were recorded | X(copy) | X(original) |
| **15.16** | **NOTIFICATION BY ORIGINATING INVESTIGATOR TO SPONSOR OF SERIOUS ADVERSE EVENTS AND RELATED REPORTS** | Notification by originating investigator to sponsor of serious adverse events and related reports in accordance with 4.11 | X | X |
| **15.17** | **NOTIFICATION BY SPONSOR AND/OR INVESTIGATOR, WHERE APPLICABLE, TO REGULATORY AUTHORITY(IES) AND IRB(S)/IEC(S) OF UNEXPECTED SERIOUS ADVERSE DRUG REACTIONS AND OF OTHER SAFETY INFORMATION** | Notification by sponsor and/or investigator, where applicable, to regulatory authorities and IRB(s)/IEC(s) of unexpected serious adverse drug reactions in accordance with 5.17 and 4.11.1 and of other safety information in accordance with 5.16.2 and 4.11.2 | X(where required) | X |
| **15.18** | **NOTIFICATION BY SPONSOR TO INVESTIGATORS OF SAFETY INFORMATION** | Notification by sponsor to investigators of safety information in accordance with 5.16.2 | X | X |
| **15.19** | **INTERIM OR ANNUAL REPORTS TO IRB/IEC AND AUTHORITY(IES)** | Interim or annual reports provided to IRB/IEC in accordance with 4.10 and to authority(ies) in accordance with 5.17.3 | X | X(where required) |
| **15.20** | **SUBJECT SCREENING LOG** | To document identification of subjects who entered pre-trial screening | X | X(where required) |
| **15.21** | **SUBJECT IDENTIFICATION CODE LIST** | To document that investigator/institution keeps a confidential list of names of all subjects allocated to trial numbers on enrolling in the trial. Allows investigator/institution to reveal identity of any subject | X |  |
| **15.22** | **SUBJECT ENROLMENT LOG** | To document chronological enrolment of subjects by trial number | X |  |
| **15.23** | **INVESTIGATIONAL PRODUCTS ACCOUNTABILITY AT THE SITE** | To document that investigational product(s) have been used according to the protocol | X | X |
| **15.24** | **SIGNATURE SHEET** | To document signatures and initials of all persons authorised to make entries and/or corrections on CRFs | X | X |
| **15.25** | **RECORD OF RETAINED BODY FLUIDS/ TISSUE SAMPLES (IF ANY)** | To document location and identification of retained samples if assays need to be repeated | X | X |

**Annex 16: After Completion or Termination of the Trial**

After completion or termination of the trial, all of the documents identified in sections 8.2 and 8.3 should be in the file together with the following

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Title of Document** | **Purpose** | **Located in Files of** |
|  |  |  | **Investigator/****Institution** | **Sponsor** |
| **16.1** | **INVESTIGATIONAL PRODUCT(S) ACCOUNTABILITY AT SITE** | **To document that the investigational product(s) have been used according to the protocol. To documents the final accounting of investigational product(s) received at the site, dispensed to subjects, returned by the subjects, and returned to sponsor** | **X** | **X** |
| **16.2** | **DOCUMENTATION OF INVESTIGATIONAL PRODUCT DESTRUCTION** | **To document destruction of unused investigational products by sponsor or at site** | **X****(if destroyed at site)** | **X** |
| **16.3** | **COMPLETED SUBJECT IDENTIFICATION CODE LIST** | **To permit identification of all subjects enrolled in the trial in case follow-up is required. List should be kept in a confidential manner and for agreed upon time** | **X** |  |
| **16.4** | **AUDIT CERTIFICATE**(if available) | **To document that audit was performed** |  | **X** |
| **16.5** | **FINAL TRIAL CLOSE-OUT MONITORING REPORT** | **To document that all activities required for trial close-out are completed, and copies of essential documents are held in the appropriate files** |  | **X** |
| **16.6** | **TREATMENT ALLOCATION AND****DECODING DOCUMENTATION** | **Returned to sponsor to document any decoding that may have occurred** |  | **X** |
| **16.7** | **FINAL REPORT BY INVESTIGATOR TO IRB/IEC WHERE REQUIRED, AND WHERE APPLICABLE, TO THE REGULATORY AUTHORITY(IES)** | **To document completion of the trial** | **X** |  |
| **16.8** | **CLINICAL STUDY REPORT** | **To document results and interpretation of trial** | **X****(if applicable)** | **X** |

1. Wichmann D, Sperhake JP, Lütgehetmann M, et al. Autopsy Findings and Venous Thromboembolism in Patients With COVID-19: A Prospective Cohort Study. Ann Intern Med. 2020 May 6. doi: 10.7326/M20-2003. [↑](#footnote-ref-1)
2. Chan, J.F., et al., Broad-spectrum antivirals for the emerging Middle East respiratory syndrome coronavirus. J Infect, 2013. 67(6): p. 606-16. [↑](#footnote-ref-2)