Vietnam Cryptococcal Retention in Care Study (CRICS)

CASE REPORT FORMS

Ver 2.1

Identifying information:

FOA No: GH-12-008

Award Number: GH 000758

Date: 7 January, 2017

APPENDIX 1: SCREENING FORM (Phase 1 only)

Patient's name:.....**Male/Female**:.....

Date and selection criteria	
Screening date	/ / (dd/mm/yy)
Age of patient	☐ ≥18 years old (having passed 18th birthday - western calendar) ☐ <18 years old → **Patient does not meet the selection**
History of ART treatment	☐ Have never taken ARVs ☐ Has taken ARVs in the past, but has not had >4 consecutive weeks of ARVs in the past year. ☐ Has been taking ARVs for more than 4 consecutive weeks in the past 1 year →**Patient does not meet the**
History of prior / current CM (or current treatment for CM)	☐ No ☐ Yes →**Patient does not meet the selection criteria**
Receipt of systemic antifungal medication for more than 4 consecutive weeks within the past 6 months	☐ No ☐ Yes →**Patient does not meet the selection criteria**
For woman patient: Are you currently pregnant or planning to become pregnant during the next 2 years?	☐ No ☐ Yes →If CrAg positive, patient is not eligible to participate in the study.

INFORMATION FOR PATIENTS

What is cryptococcal disease?: A fungal infection that can affect the brain and other parts of the body, especially in people living with HIV

- Are you HIV positive and 18 years old or older?

- Today your CD4 is less than or equal to 100 cells/µL?

If you are HIV-positive, are at least 18 years old, and your CD4 is less than or equal to 100 cells/µL, the Vietnam Ministry of Health and the World Health Organization recommend that your blood should be screened for "Crypto," a fungal disease that can affect the brain.

Clinic staff will be taking your blood for CD4 testing. To save time and to avoid your coming back a second time to take another sample if your CD4 is ≤100 cells/µL, we will use a small amount of the blood sample remaining after CD4 or other laboratory tests to check if you have "Crypto".

For more information, please ask your nurse or clinician during this visit.

APPENDIX 2A: SCRIPT FOR INFORMING PATIENTS ABOUT CRAG SCREENING

There is an organism called Cryptococcus, or "Crypto" for short that can cause disease in people and can affect the brain, lungs, and other parts of the body. People are more likely to get Crypto if they have HIV and low immunity, i.e., CD4 counts, less than 100 cells/μL. For those who have Crypto, at the early infection stage, they may not have any clinical symptoms (called asymptomatic patients) but lately when symptom appear, they will become seriously ill. In order to prevent people from getting ill with Crypto brain and lung infections, we are testing patients who have low CD4 counts to determine if they may already have the fungus in blood. This will allow us to treat early and prevent serious illness. If the test shows that you have early Crypto, we will contact you as soon as we can to assess whether to start you on treatment.

a. "We will perform routine screening for Crypto on all patients with CD4 counts, less than 100 cells/μL and we'll be doing that from the blood that remains after CD4 testing.
b. If you have already had a CD4 test done within the last 2 weeks, the leftover plasma from other routine tests collected today will be used.
c. If no other tests are requested today, a small blood sample will be taken for CrAg screening."
d. "You will be informed of your CrAg results at the same time as your CD4 results or a separate CrAg result if you already had CD4 counts previously tested less than or equal to 100 cells/μL"
e. "If your CrAg test is positive, we will provide treatment to prevent you from developing severe disease unless your doctors think that you may be harmed due to the treatment."

Do you have any questions?

APPENDIX 3A: INFORMED CONSENT FORM

PART I: Information Sheet

Introduction

Hello. My name is ___ (name of study officer) ____. I would like to talk to you about a research study we are doing and to ask if you would want to take part in it. This study is sponsored by the United States Centers for Disease Control and Prevention (CDC). The investigators, who are doctors at National Hospital for Tropical Diseases and Tropical Diseases Hospital, will be responsible for the study. Hundreds of patients are expected to be included in the study at over 22 sites throughout Vietnam. If you do not understand something, please ask me to stop and to tell you again or to answer any questions you may have.

Purpose of the research

There is an organism called *Cryptococcus*, or "Crypto" for short, which can cause fungal disease in people, especially people with HIV. The disease can affect the brain and the breathing system. We are doing a study of people with HIV, to see if certain new ways of testing for and treating early Crypto infection with a medicine called fluconazole can help prevent patients from getting very sick. The information we learn will be used to try to help other people with HIV.

Participant selection

We are asking many patients with HIV infection if they would like to take part in this study. You are invited to take part in the study because you:

- Are aged ≥ 18 years,
- Are a patient at one of the HIV clinics in Vietnam taking part in the study
- Have advanced HIV disease (as shown by having a CD4 count less than 100 cell/μL)
- Are about to start taking medicine called ART for HIV infection

Pregnant women cannot take fluconazole because fluconazole can damage a developing fetus. If you are female, and you test positive for Crypto, you will be required to have a pregnancy test before you begin this study treatment; if it turns out that you are pregnant or if you plan to become pregnant in the next 2 years you cannot be in the study if you have crypto in your blood. If you are sexually active, we encourage you to use a modern contraceptive method, such as the contraceptive pill, during the course of the study to avoid becoming pregnant while on fluconazole.

Voluntary Participation

Taking part in this study is your choice. If you do not to take part in the study, you will receive the same care that all patients here usually get. If you decide to be in the study, you may change your mind later and stop being in the study. If you decide to stop taking part, you will receive the same care that all patients here usually get.

Study Procedures

This study will be conducted as part of routine procedures at the clinic. In addition to the information doctors will ask in order to provide care, some additional information will be required during the study. Answering these questions may take an additional 20-30 minutes each visit. For the study, we will follow you for at least 6 months and up to12 months after ART initiation and at we will collect some additional information from you at these visits. If you test positive for Crypto, you will be asked to come to the study clinic at the time you are enrolled (baseline), at 2 weeks, 10 weeks after study enrolment, and2 months, 6 months, and 12 months after ART initiation. If you test negative for CrAg, you will be asked to come to the study clinic at the time you are enrolled (baseline), at 2 months, 6 months, and 12 months after your ART initiation.

If you have a positive blood test for Crypto: This means you have a Crypto infection in the blood and are at higher risk for developing a Crypto brain infection. We will ask you some questions to see if you might have a Crypto brain infection right now. If you do, your doctor will be responsible for determining the best management of your disease according to national guidelines in Viet Nam.

If you do not have a Crypto brain infection, you still need medicine to help keep you from getting a Crypto brain infection. As part of this study, you will be given a drug called fluconazole to fight Crypto. You take this drug by mouth. First you will take 900 mg each day for 2 weeks, then450 mg each day for 8 weeks. After that, you will take 200 mg for 6 months and then 150 mg each day until your doctor lets you know it is safe to stop. This will be when you're immune system is strong enough to fight Crypto on its own.

If you have a negative blood test for Crypto: this means you probably do not have a Crypto infection at the moment. But, you might still get Crypto in the future if your immune system stays weak. Coming to the clinic for your appointments will let doctors check you for symptoms of Crypto and other diseases that people with HIV sometimes get.

General Information

If you are in this study, someone on the study team will look at your clinic medical chart to find out more about your health. Also, we will ask you some questions about yourself and your health before you came to the clinic. We will ask if you have been sick and why you came to the clinic. We will also look at your lab test records and, if you go to a hospital, your chart in the hospital. You can refuse to answer any questions you want and this will not affect the care you will get.

If you become ill during this study and your doctor thinks that you might have a Crypto brain infection, your doctor will be responsible for determining the best management of your infection in accordance with Viet Nam national guidelines.

Duration

You will come to the clinic for regular visits like all HIV patients here. At the end of 12 months, the study will be done. While the study is going on, if you are in hospital and cannot come to the clinic for an appointment, please let us know. I would like to be able to contact you, or someone who lives with you, during the year that you are in the study, to remind you about your appointments for your clinic visits.

Risks

Fluconazole is a medicine that is used around the world to treat fungal infections, including Crypto. People taking fluconazole generally feel fine, but they might sometimes have an upset stomach, loose stools, headache, or a skin rash.

High doses of fluconazole, as used in this study, should not be used during the first three months of pregnancy because it can harm an unborn baby. If you think you have become pregnant while using this medicine, stop fluconazole immediately and tell your doctor right away. For women receiving fluconazole, at each follow up visit, your doctor will ask you about your last normal menstrual period (LNMP) and contraceptive use. If your LNMP is more than 5 weeks, you will be asked to undergo a pregnancy test. If the test is positive, your treatment with fluconazole will be stopped.

For patients who have liver disease, fluconazole can damage the liver. Signs that the liver is damaged include stomach pain on the right side, nausea or vomiting, and a yellow color of the skin and eyes. Please let the study doctors know if you or a friend or family member thinks your skin color has changed or if you have stomach pain, nausea, or vomiting. If you take fluconazole, the study team will watch carefully for possible side effects of the drug at each study visit.

If you get sick or have concerns or questions between your regular visits to clinic, please let us know by coming to the clinic for a check-up.

Benefits

If your test shows that you have Crypto infection, but you do not have symptoms, you will get medicine to treat Crypto for free. If you do have symptoms, your doctor will be responsible for determining the best management of your disease in accordance with Vietnam national guidelines. We will also use the information from you and many other patients to try to improve the health of all people living with HIV.

Reimbursements

We will give you 65000 Vietnam Dong [approximately US$3]to pay for your extra time spent with us to answer questions regarding your quality of life for the study in your visit at 0, 6, and 12 months after your enrolment.

Confidentiality

Only your health care providers and the study team will know the information we collect or that you are in the study. We will not share your name or information about you with anyone else. If information is shared with other people who do not work with the study, your name will not be used and no one would be able to identify you.

Right to Refuse or Withdraw

You do not have to be in this study. If you do not want to be in this study, you can still come to this clinic and you will still get the regular care. You may stop being in the study at any time and you will not lose your rights as a patient here. Your treatment at this clinic will not be affected in any way.

Who to Contact

If you have questions, you may ask them now or later, even after the study has started. If you want to ask questions later, you can come to the clinic or you can contact any of the following: [name, address/telephone number/e-mail].

This protocol has been reviewed and approved by the Institutional Review Board (IRB) of the National Hospital for Tropical Diseases, the Tropical Diseases Hospital in Ho Chi Minh City, and the US Centers for Disease Control and Prevention in Atlanta, Georgia. This is a committee whose job is to protect people and make sure that they are not harmed in a study. If you wish to find about more about the IRB, contact National Hospital for Tropical Diseases at78 Giai Phong street – Dong Da district, Hanoi, Vietnam, Tel: (84-4).35763491

You can ask me any more questions about any part of this research study, if you wish to. Do you have any questions?

PART II: Consent Statement

I have read the information about this study or it has been read to me. I have had the chance to ask questions about it. Any questions that I have asked have been answered to my satisfaction. I would like be a part of this study. I have been offered a copy of this Consent Form.

Participant Signature	Date

If illiterate

If illiterate, a witness must sign (if possible, this person should be selected by the participant and should have no connection to the study team). Participants who are illiterate should include their thumb-print as well.

I have witnessed the accurate reading of the consent form to the potential participant, and the individual has had the opportunity to ask questions. I confirm that the individual has given consent freely.

Witness name and signature	Date	Thumb print of participant

Additional Consent for Specimen Storage for Future Use

While you are in this study, leftover blood after CrAg testing and leftover cerebrospinal fluid that maybe taken from you if you are hospitalized will be used to perform other tests about your health. If there is anything left over after we have done the required tests, we would like to ask your permission to keep the leftover blood and cerebrospinal fluid (CSF). These specimens could be useful for future research. Your specimens will be securely stored at the NHTD for future testing for 10 years with your study ID so that the specimen can be linked to your clinical information from the study; however, your name will not be on the specimens. The specific research to be done on your blood and/or cerebrospinal fluid will relate to HIV or other infections in people with HIV. To keep your information private, your blood will be labeled with a code, and your name or other personal information will not be sent outside this clinic.

It is your choice to allow your blood and/or cerebrospinal fluid to be stored for possible use in the future. No matter what you decide, it will not affect whether you can be in the study, or your routine health care. Please carefully read the statements below (or have them read to you) and think about your choice.

_____ I agree to have following samples stored and used for future testing related to HIV or other infections in people with HIV: ☐ Leftover blood ☐ Leftover CSF

_____ I do not agree to have the following samples stored and used for future testing related to HIV or other infections in people with HIV: ☐ Leftover blood ☐ Leftover CSF

Participant Signature	Date

APPENDIX 4: ENROLLMENT FORM

Study ID

Add sticker here

Date of enrollment:

____ / ____ / _____

Data collector (Full name) _____

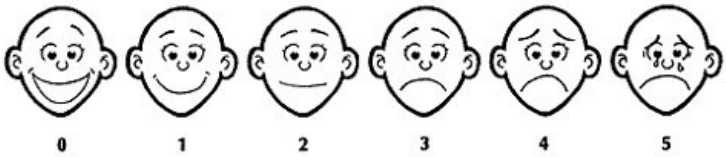
Signature _____

I	Socio - demographic information	
B01	Sex	☐1. Male ☐2. Female
B02	DOB	_____ / _____ / _____ (dd/mm/yyyy)
B03	Marital status	☐ 1. Single ☐2. Partnered ☐3. Married ☐4. Separated ☐5. Divorced ☐6. Widowed
B04	Education level *(select the highest level attained)*	☐1. No formal education ☐2. Primary school(1st to 5th grade) ☐3. Secondary school(6th to 9th grade) ☐4. High school(10th to 12th grade) ☐5. Vocational ☐6. University/College ☐7. Post graduate
B05	Occupation	☐1. School/college student ☐2. Professional/office worker ☐3. Shop worker/trader ☐4. Manual labourer ☐5. Agriculture/fishing ☐6. Housewife ☐7. Retired ☐8. Unemployed ☐9. Other (specify):_____
B06	Monthly net income from all sources	☐1. ≤600,000VND ☐ 2. >600,000-1,500,000VND ☐ 3. >1,500,000-5,000,000VND ☐ 4. >5,000,000-10,000,000VND ☐5. >10,000,000 VND
B07	Distance from home to clinic	☐ 1. ≤5 km ☐ 2. >5 – 10 km ☐ 3. >10 – 50 km ☐ 4. >50 – 100 km ☐ 5. >100 km
B77	At the point of enrolment, is the patient hospitalized?	☐1. Yes (enrolled during hospitalization) ☐2. No (enrolled from OPC)
B78	Does the patient have valid health insurance currently?	☐1. Yes ☐2. No

B79	When did the patient register with the study clinic?	_____/_____/_____ (dd/mm/yyyy)

II	**HIV Infection**			
B08	Blood specimen collection date for HIV confirmation testing(as written in the lab form presented by the patient)	_____ / _____ / _____(dd/mm/yyyy)		
B10	The most recent CD4 count	_____(cells/µL)		
B11	The most recent blood specimen collection date for CD4 count	_____ / _____ / _____(dd/mm/yyyy)		
B81	Check ALL OIs that the patient has in this visit:			
	Clinical stage 1	Clinical stage 2	Clinical stage 3	Clinical stage 4
	☐ Asymptomatic ☐ Persistent generalized lymphadenopathy	☐ Unexplained weight loss (<10% body wt) ☐ Recurrent respiratory infections ☐ Papular pruritic eruption ☐ Other, specify _____ _____	☐ Weight loss >10% body weight ☐ Pulmonary TB ☐ Unexplained diarrhea >1 month ☐ Oral candidiasis ☐ Unexplained fever >1 month ☐ Other, specify _____ _____	☐ Extrapulmonary TB ☐ Pneumocystis pneumonia ☐ Oesaphogeal candidiasis ☐ CNS toxoplasmosis ☐ Other, specify _____ _____

III	**Past History**			
B16	Diabetes	☐ 1. Yes, confirmed diagnosis	☐ 2. Yes, self-report	☐ 3. No
B17	Hypertension	☐ 1. Yes, confirmed diagnosis	☐ 2. Yes, self-report	☐ 3. No
B18	Kidney failure	☐ 1. Yes, confirmed diagnosis	☐ 2. Yes, self-report	☐ 3. No
B19	Heart failure	☐ 1. Yes, confirmed diagnosis	☐ 2. Yes, self-report	☐ 3. No
B20	Stroke	☐ 1. Yes, confirmed diagnosis	☐ 2. Yes, self-report	☐ 3. No
B21	COPD	☐ 1. Yes, confirmed diagnosis	☐ 2. Yes, self-report	☐ 3. No

IV	**Current Symptoms**			
B22	Headache (Please circle the correct response)			
B23	Seizure	☐1. Yes	☐ 2. No	☐ 9. Not assessed
B24	Night sweat	☐ 1. Yes	☐ 2. No	☐ 9. Not assessed
B25	Vomiting	☐ 1. Yes	☐ 2. No	☐ 9. Not assessed
B26	Nausea	☐ 1. Yes	☐ 2. No	☐ 9. Not assessed
B27	Abdominal pain	☐ 1. Yes	☐ 2. No	☐ 9. Not assessed
B28	Constipation	☐ 1. Yes	☐ 2. No	☐ 9. Not assessed
B29	Diarrhea	☐ 1. Yes	☐ 2. No	☐ 9. Not assessed
B30	Cough	☐ 1. Yes	☐ 2. No	☐ 9. Not assessed
B31	Dyspnea	☐ 1. Yes	☐ 2. No	☐ 9. Not assessed
B32	Blurred vision	☐ 1. Yes	☐ 2. No	☐ 9. Not assessed
B33	Skin rash	☐ 1. Yes	☐ 2. No	☐ 9. Not assessed
B34	Fever	☐ 1. Yes	☐ 2. No	☐ 9. Not assessed
B35	Photophobia	☐ 1. Yes	☐ 2. No	☐ 9. Not assessed

V	**Physical Examination**				
B36	Glasgow score (3-15)	_____	B37	PR (bpm)	_____
B38	BP (mmHg)	_____ / _____			
B39	Temperature (ºC)	_____	B40	Weight (kg)	_____
B41	RR (/min)	_____	B42	Height (cm)	_____
B43	Chest examination(heart and lung)	☐1. Normal ☐2. Abnormal. Specify:_____			
B44	Abdominal examination	☐1. Normal ☐2. Abnormal. Specify:_____			
B45	Neurologic examination	☐ 1. Normal ☐2. Abnormal, specify: ☐2.1. Neck stiffness ☐2.2. Kernig's sign ☐ 2.3. Cranial nerve paralysis ☐2.4. Hemiparesis ☐ 2.5. Other, specify:_____			
B46	Visual examination	☐1. Normal ☐2. Decreased ☐ 3. Fingers counting ☐4. Hand motion ☐ 5. Light perception ☐6. No light perception			

B80	☐0. Fully active, able to carry on all pre-disease performance without restriction ☐ 1. Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work ☐ 2. Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours ☐ 3. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours ☐ 4. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair

VI	**Lab Tests(Most recent in the last 2 weeks)**				**Date of testing** (dd/mm/yy)
6.1	**Full Blood Count**	**Result**	**Unit**		____ / ____ / ____
B48	Hemoglobin	_____	☐(g/L) ☐(g/dL)	☐Not available	
B49	Leukocyte count	_____	(G/L)	☐Not available	
B50	Platelet count	_____	(G/L)	☐Not available	
B51	Neutrophil (%)	_____	%	☐Not available	
B52	Lymphocyte (%)	_____	%	☐Not available	
6.2	**Biochemistry**	**Result**			____ / ____ / ____
B53	Serum creatinine	_____	☐µmol/L ☐mg/dL	☐Not available	
B54	Serum urea	_____	☐mmol/L ☐mg/dL	☐Not available	
B55	Serum glucose	_____	☐mmol/L ☐mg/dL	☐Not available	
B56	AST/SGOT	_____	(U/L)	☐Not available	
B57	ALT/SGPT	_____	(U/L)	☐Not available	
B58	Total protein	_____	☐ g/L ☐g/dL	☐Not available	
B59	Serum albumin	_____	☐g/L ☐g/dL	☐ Not available	

B60	Serum bilirubin, total	_____	☐µmol/L ☐mg/dL	☐Not available	
6.3	**Immunology**	**Result**			
B61	HBsAg	☐ 1. Negative	☐2. Positive	☐9. Not available	
B62	Anti-HCV	☐ 1. Negative	☐2. Positive	☐9. Not available	

VII	**Cryptococcus Antigen (CrAg) Test Results**	
B14	The date of OPC receiving CrAg result from the laboratory (dd/mm/yyyy)	_____ / _____ / _____
B15	CrAg result?	☐ 1. Negative → ***End*** ☐ 2. Positive

VIII	**Pregnancy test and management plan for CrAg (+)** ☐ Patient is female and of reproductive age → ***Go to B63*** ☐ Patient is male or female but menopausal or over 55 years old → ***Skip to B65***		
B63	Date of last normal menstrual period ___ / __ / _____ (dd/mm/yy)	If the patient does not remember, estimate last normal menstrual period ☐Over 5 weeks → ***Do pregnancy test and record results of the test below*** ☐Under 5 weeks → ***Go to B65*** ☐Do not know → ***Do pregnancy test and record results of the test below***	
B64	Pregnancy test	☐ 1. Negative ☐2. Positive ☐9. Not done	
B65	Was fluconazole started today (*current visit*)?	☐1. Yes →***Go to B75***	☐2. No. Please specify the reason _____ _____ →***Skip to B73***
B75	Date of starting fluconazole?	_____ / _____ / _____(dd/mm/yyyy) → ***Complete Fluconazole Log (Appendix 19)***	
B73	Hospitalization for lumbar puncture?		☐1. Yes ☐2. No → ***END***
B74	Name of the hospital		_____

APPENDIX 5: STARTING ART FORM

(These data should be transcribed from clinical notes and pharmacy prescriptions whenever ART is initiated)

Study ID

Add sticker here

Date of enrollment:

____ / ____ / _____

Data collector (Full name) _____

Signature _____

I	Treatment Information	
1.1	**Opportunistic Infection Prevention and Treatment**	
X01	Is the patient on cotrimoxazole prophylaxis?	☐1. Yes ☐2. No → ***Skip to X14***
X01a	Date of starting cotrimoxazole prophylaxis	_____ / _____ / _____
X01b	Cotrimoxazole dose per day?	☐1. 480 mg/ tablet x _____ tablet ☐2. 960 mg/ tablet x _____ tablet
X14	Is the patient on anti-TB medication?	☐1. Yes ☐2. No →***Skip to X15***
X14a	Current TB regimen (verify from the patient record)s	☐ SRHZE ☐RHZE ☐RHE ☐RH ☐ $ZEK_m(C_m)L_{fx}P_{to}C_s$ (PAS) ☐ $ZEL_{fx}P_{to}C_s$ (PAS) ☐Other:_____ ☐Unknown
X14b	Starting date of current TB regimen	_____ / _____ / _____☐Unknown
X14c	Number of anti-TB tablets taken each day	____ tablets☐Unknown
X15	Is the patient on Isoniazid prophylaxis?	☐1. Yes ☐2. No →***Skip to X02***
X15a	If yes, starting date?	_____ / _____ / _____☐Unknown
X15b	Number of isoniazid tablets per day	_____ tablets

1.2	Other drugs

X02	Is the patient on other medications(*besides anti-TB drugs, Cotrimoxazole , Isoniazid and ARVs)*		☐ 1. Yes ☐ 2. No →***Skip to 1.3***			
		OTHER DRUG1	**OTHERD RUG2**	**OTHERD RUG3**	**OTHER DRUG 4**	**OTHERD RUG 5**
X04	Name of drug					
X04a	Number of tablets per day					

1.3	**ART treatment at current visit**	
X08	Date ART started	_____ / _____ / _____ (*dd /mm/yyyy*)
X16	Dose adjustment for kidney failure patients	☐ 1. Yes ☐ 2. No
X17	ARV regimens (Dosage)	☐ TDF + 3TC + EFV
		☐ TDF + 3TC + NVP
		☐ AZT + 3TC + EFV
		☐ AZT + 3TC + NVP
		☐ ____ + _____ + _____
X18	Total number of all ARV tablets taken per day	_____ tablets

Time of visit: ____

APPENDIX 6: FOLLOW-UP FORM

Subject ID

Add sticker here

Date of Visit:

____ / ____ / _____

Data Collector (Name) _____

Signature _____

Visit type (according to appointments)

☐ 1. Routine ART visit

☐ 2. Late or missed appointment →***Complete Appendix 08 – Late Attendance, Missed Appointment Form in addition to this form***

☐ 3.Sick visit

I	**HIV Infection**			
D0A	Does the patient have health insurance?	☐ 1. Yes ☐ 2. No		
B77	At the point of enrollment, is the patient hospitalized?	☐1. Yes (enrolled during hospitalization) ☐2. No (enrolled from OPC)		
B79	When did the patient register with the study clinic?	_____/_____/_____ (dd/mm/yyyy)		
D01	Latest test CD4 result (cells/µL)	_____ (cells/µL) ☐ No result since the last testing →***Skip to D03***		
D02	Date of latest CD4 testing (check CD4 result form for date)	_____ / _____ / _____ (dd/mm/yyyy)		
D63	Check ALL OIs that the patient has in this visit:			
	Clinical stage 1	Clinical stage 2	Clinical stage 3	Clinical stage 4
	☐ Asymptomatic ☐ Persistent generalized lymphadenopathy	☐ Unexplained weight loss (<10% body wt) ☐ Recurrent respiratory infections ☐ Papular pruritic eruption ☐ Other, specify _____	☐ Weight loss >10% body weight ☐ Pulmonary TB ☐ Unexplained diarrhea >1 month ☐ Oral candidiasis ☐ Unexplained fever >1 month ☐ Other, specify _____	☐ Extrapulmonary TB ☐ Pneumocystis pneumonia ☐ Oesaphogeal candidiasis ☐ CNS toxoplasmosis ☐ Other, specify _____ _____
D05	Latest viral load result (copies/ml)	_____ (copies/ml) ☐ Not done →***Skip to D23***		
D06	Latest date of testing viral load (dd/mm/yy)	_____ / _____ / _____		

II	**Hospitalization**	
D23	Was the patient hospitalized	☐1. Yes

	since the last visit for which CRICS data were collected?	☐2. No ***→Go to D40***
D23A	Total number of hospitalizations since the last visit for which CRICS data were collected?	_____ (times) ***→Complete Hospitalization Form for any hospitalizations if not completed***

III	**Physical Examination**							
D40	Glasgow score (3-15)*(see Appendix)*	__	D41	Temperature (ºC)	_____	D42	Weight	_____(kg)
D43	Neurologic examination	☐1. No meningeal signs ☐2. Meningeal signs found						
D62	☐0. Fully active, able to carry on all pre-disease performance without restriction ☐ 1. Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work ☐ 2. Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours ☐ 3. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours ☐ 4. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair							

IV	**Lab Tests (The most recent if not recorded in the last CRICS visit))**				**Date of testing**
	☐1. Yes ☐2. No ***→ Skip to D53***				
5.1	**Full Blood Count**	**Result**	**Unit**		____ / ____ / ____
D44	Hemoglobin	_____	☐(g/L) ☐(g/dL)	☐Not available	
D46	Platelet count	_____	(G/L)	☐Not available	
5.2	**Biochemistry**	**Result**	**Unit**		____ / ____ / ____
D49	Serum creatinine	_____	☐µmol/L ☐mg/dL	☐Not available	
D51	AST/SGOT	_____	(U/L)	☐Not available	
D52	ALT/SGPT	_____	(U/L)	☐Not available	

VI	**Anti-retroviral Therapy (ART)**		
D53	Is patient on ART?	☐ 1. Being treated ☐2. Has not been treated yet ***→Skip to VII. Current symptoms*** ☐ 3. Starting ART at this visit ***→Skip to VII. Current symptoms and complete Form 05: Starting ART form***	
D24	Common ARV side effects	☐1. Yes. If yes, specify _____ _____ ***→ Complete Form 09: AE*** ☐2. No	
D61	Current ART regimen	☐1. Continue last regimen ***→ Skip to D54***	
		☐2. Switched to another regimen (specify below):	☐1. TDF + 3TC + EFV ☐2. TDF + 3TC + NVP ☐3. TDF + 3TC + LVP/r ☐4. AZT + 3TC + EFV ☐5. AZT + 3TC + NVP ☐6. AZT + 3TC + LVP/r ☐7. Others. Specify_____
D61a	Date of switching ART regimen		_____ / _____ / _____ (dd/mm/yy)
D61b	Reason for changing regimen	☐1. Intolerance ☐2. Treatment failure ☐3. Other, specify _____	
6.1	**ART Adherence**		
D54	Adherence based on times medications missed	☐ 1. Good (≤ 3 times/month) ☐ 2. Average (4-8 times/month) ☐ 3. Bad (> 8 times/month)	☐ 4. Not assessed If no assessment, please specify the reason:_____ _____
D55	Thinking about the past 4 weeks, on average, how would you rate your ability to take all your medications as prescribed?	☐1. Very poor ☐2. Poor ☐3. Fair	☐4. Good ☐5. Very good ☐6. No assessment, please specify the reason: _____ _____
D57	Since the last visit, have you ever missed a dose of antiretroviral medicines?	☐1. Yes ☐2. No ***→ Skip to D58***	
D58	Visual analogue scale for ART adherence (*Show the patients the VAS scale and ask the patient to rate their adherence*)	Score: _____ If the patient is CrAg-negative→ **End**	

---------- FOR CRAG-POSITIVE ONLY ----------

D64	Current place of residence	_____ _____

VII	**Current Symptoms (the timing of the closest examination)for CrAg + only**						
	Symptoms	**Present**	**Related to fluconazole adverse reactions?** *(ONLY RECORD IF THE PATIENT IS BEING TREATED WITH FLUCONAZOLE and THE SYMPTOM IS PRESENT)*				
			1. Not related	2. Unlikely related	3. Possibly related	4. Probably related	5. Definitely related
D08	Headache	☐ 1. Yes ☐ 2. No	☐	☐	☐	☐	☐
D09	Seizure	☐ 1. Yes ☐ 2. No	☐	☐	☐	☐	☐
D10	Night sweat	☐ 1. Yes ☐ 2. No	☐	☐	☐	☐	☐
D11	Vomiting	☐ 1. Yes ☐ 2. No	☐	☐	☐	☐	☐
D12	Nausea	☐ 1. Yes ☐ 2. No	☐	☐	☐	☐	☐
D13	Abdominal pain	☐ 1. Yes ☐ 2. No	☐	☐	☐	☐	☐
D14	Constipation	☐ 1. Yes ☐ 2. No	☐	☐	☐	☐	☐
D15	Diarrhea	☐ 1. Yes ☐ 2. No	☐	☐	☐	☐	☐
D16	Cough	☐ 1. Yes ☐ 2. No	☐	☐	☐	☐	☐
D17	Dyspnea	☐ 1. Yes ☐ 2. No	☐	☐	☐	☐	☐
D18	Blurred vision	☐ 1. Yes ☐ 2. No	☐	☐	☐	☐	☐
D19	Skin rash	☐ 1. Yes ☐ 2. No	☐	☐	☐	☐	☐
D20	Fever	☐ 1. Yes ☐ 2. No	☐	☐	☐	☐	☐
D21	Photophobia	☐ 1. Yes ☐ 2. No	☐	☐	☐	☐	☐

VIII	**Pregnancy test and Fluconazole Therapy for CrAg (+) patients only**	
	☐ Patient is male or female but menopausal or over 55 years old → ***Skip to D30*** ☐ Patient is female and of reproductive age → ***Go to D25***	
D25	Pregnancy ☐ Pregnancy was not diagnosed in the last visit →***Go to D25a*** ☐ Pregnancy was diagnosed in the last visit, note pregnancy status since then →***Go to D25b***	
D25a	1.Date of last normal menstrual period___ / __ / __(dd/mm/yy)	If the patient does not remember, estimate last normal menstrual period ☐ Over 5 weeks →***Do pregnancy test and record results of the test below*** ☐ Under 5 weeks → ***Skip to D30*** ☐ Do not know → ***Skip to D30***

	3. Pregnancy test	☐1. Positive ☐2. Negative ☐3. Not done	
D25b	☐1. Healthy pregnancy		
	☐2. Spontaneous abortion	Specify date (dd/mm/yy):	_____ / _____ / _____
	☐3. Medical abortion	Specify date (dd/mm/yy):	_____ / _____ / _____
	☐4. Gave birth	4a. Specify date	___ / ____ / ___(dd/mm/yy)
		4b. Congenital abnormality	☐1. Yes ☐2. No
	Fluconazole Adherence		
D30	During the past 4 weeks, basically how would you rate your ability to take all your medications as prescribed?	☐1. Very poor ☐2. Poor ☐3. Fair ☐4. Good	☐5. Very good ☐6. No assessment, please specify the reason: _____ _____
D32	Since the last attended scheduled visit, have you ever missed a dose of fluconazole?		☐1. Yes ☐2. No → ***Go to D33***
D31	During the past 4 days, how many times have you missed taking your medication (fluconazole)? (numeric response)		_____ (times)
D33	Visual analogue scale for fluconazole adherence (*Show the patients the VAS scale and ask the patient to rate their adherence*)		Score: _____

APPENDIX 7: HOSPITALIZATION FORM

Study ID

Add sticker here

Date of collection:

____ / ____ / _____

Data collector (full name) _____

Signature _____

I	Information about Hospitalization		
E0	Source of information (Check all that apply)	☐ Hospital chart ☐ Discharge certificate provided to patient ☐ Discharge summary provided to OPCs ☐ Communication with hospital clinicians ☐ Patient self-reported ☐ No information -> End of the form	
E01	Date of admission (dd/mm/yyyy)	_____ / _____ / _____	
E02	Date of discharge (dd/mm/yyyy)	_____ / _____ / _____	
E03	Name of the hospital	_____	
E05	Discharge diagnosis	☐ 1. Cryptococcal meningitis ☐ 2. ART adverse reaction ☐ 3. Fluconazole adverse reaction ☐ 4. Opportunistic infections, specify: _____ ☐ 9. Others, specify: _____	
E06	Patient's outcome at the time of discharge	☐ 1. Fully recovered ☐ 2. Partially recovered ☐ 3. Not recovered ☐ 4. Worsened ☐ 5. Dead → ***Complete Off-Study Form***	
II	**Clinical Signs and Laboratory Results**		**Date of testing**
E25	CD4 test done during current hospitalization	☐ 1. Yes ☐ 2. No → ***Skip to E08*** ☐ Unknown	

E07	CD4 count results (from sample taken during current hospitalization)	_____ (cells/μL) ☐Not available	___/ ____/ ____
E08	Meningeal signs	☐1. Yes ☐ 2. No ☐Unknown	
E09	Performing lumbar puncture?	☐1. Yes ☐ 2. No →***Go to Part IV***	
III	**CSF Analysis Results**		
3.1	**Cytology**	**Date of testing:** __ __ / __ __ / __ __ (dd/mm/yy)	
E10	WBC	_____ (cells/nm^3)	☐Not available
E11	Neutrophils	_____ %	☐Not available
E12	Lymphocytes	_____ %	☐Not available
3.2	**Biochemistry**	**Date of testing:** __ __ / __ __ / __ __ (dd/mm/yy)	
E13	CSF glucose	_____ ☐ μmol/L ☐ mg/dL	☐Not available
E14	CSF protein	_____ ☐ g/L ☐g/dL	☐ Not available
E15	Pandy reaction	☐1. Positive ☐2. Negative ☐ 9. Not available	
3.3	**Microbiology**		
E16	Indian ink stain	☐1. Positive ☐2. Negative ☐9. Not available	
E17	CSF CrAg	☐ 1. Positive ☐2. Negative ☐9. Not available	
E26	CSF culture for bacteria	☐1. Positive, specify: _____ ☐2. Negative ☐9. Not available	
E27	CSF culture for fungi	☐1. Positive, specify: _____ ☐2. Negative ☐9. Not available	
IV	**Antifungal therapy for cryptococcal meningitis**		
D20	Is the patient being treated with antifungal drugs for cryptococcal meningitis?	☐1. Yes ☐ 2. No →***End***	

E21	Induction therapy	☐1. Yes ☐2. No ***→End***			
E22	Regimen for induction therapy	**Drugs**	**Dose (mg/ day)**	**Date of starting (d/m/y)**	**Date of ending (d/m/y)**
		☐1. Amphotericin B IV	____	__/__/__	__/__/__
		☐2. Fluconazole IV	____	__/__/__	__/__/__
		☐3. Flucytosine IV	____	__/__/__	__/__/__
		☐4. Fluconazole PO	____	__/__/__	__/__/__
E23	Consolidation therapy ☐1. Yes ☐2. No ***→End***	Fluconazole PO	____	__/__/__	__/__/__
E24	Maintenance therapy ☐1. Yes ☐2. No ***→ End***	Fluconazole PO	____	__/__/__	__/__/__

APPENDIX 8: LATE ATTENDANCE, MISSED APPOINTMENT FORM

Subject ID

Add sticker here

Date of visit:

__ __ / __ __ / __ __ __ __

Data Collector (Name) _____

Signature _____

	Late Attendance, Missed Appointment	
L1	Today's date (dd/mm/yy)	_____ / _____ / _____
L2	Date of patient's original appointment(dd/mm/yy)	_____ / _____ / _____
L4	Number of phone calls before patient was successfully contacted	_____ times
L5	Number of home visits done before patient was successfully contacted	_____ times
L6	What was the main reason for missing original appointment	☐ 1. Forgot ☐ 2. Not had enough pills ☐ 3. Did not have money for transport ☐ 4. Had family emergency ☐ 5. Was away traveling ☐ 6. Could not get time off work ☐ 7. Other, specify _____ _____

Add sticker here

APPENDIX 9: AE REPORTING FORM

Vietnam Cryptococcal Retention in Care Study (CRICS)

Date of reporting: ____ / ____ / _____

Name of reporter: .....

Did the patient have any unexpected adverse event (AE) in this study? ☐Yes ☐ No *(If yes, please list all adverse events in the below table)*

Level	**Related to fluconazole?**	**Applied management related to fluconazole**	**Adverse event's outcome (AE)**	**Serious adverse event?** (If yes, complete serious adverse event form -**SAE**)
1 = Slightly **2 = Moderately** **3 = Severely**	0 = Not related: clearly explained by another, documented cause 1 = Unlikely related: more likely explained by a cause other than fluconazole 2 = Possibly related: may be related to the drug or to another cause 3 = Probably related: more likely related to the drug than to another cause 4 = Definitely related: direct association with fluconazole	1 = Not available 2 = Stop using fluconazole permanently 3 = Stop using fluconazole temporarily 4 = Reduce dose 5 = Increase dose 6 = Delay	1 = Stabilization, no complication 2 = AE is still happening - no therapy 3 = AE is still happening- being treated 4 = Still happening - not treated 5 = Still happening - was treated 6 = Death 7 = Do not know (lost to follow-up)	• Death • Life-threatening event • Hospitalization, prolongation of existing hospitalization, or re-hospitalization. • Persistent or significant disability/incapacity • An important medical event. • Pregnancy in a woman taking fluconazole • A congenital abnormality or spontaneous abortion

Adverse events relatedness to fluconazole	Date of starting	Level	Relatedness to fluconazole	Management	Adverse event's outcome	Serious adverse event?
1.						☐Yes ☐ No
2.						☐Yes ☐ No
3.						☐Yes ☐ No
Other unexpected adverse events						
1.						
2.						
3.						

Narrative Summary of AE:

FOR OPCs

APPENDIX 10A: SAE REPORTING FORM (SAE)

(Based on Serious adverse events form attached to Official Dispatch No. 6586/BYT-K2DT dated 02/10/2012*)*

Date ____ / ____ / _____

OPC:

Serious adverse events (SAE):

- ☐ Initial Report
- ☐ Follow - up report (time …)
- ☐ Final report

1. Information of patient with SAE

1. Patient ID		3. Age	
2.Sex			

2. Information about SAE

Name of SAE

Serious adverse event	
Death	☐ Yes ☐ No
Life-threatening event – this means that the participant was at immediate risk of death and required immediate medical intervention. It does not refer to an event which hypothetically might have caused death, if it were more severe	☐ Yes ☐ No
Hospitalization, prolongation of existing hospitalization, or re-hospitalization once discharged	☐ Yes ☐ No
Persistent or significant disability/incapacity (a substantial disruption of a person's ability to conduct normal life functions)	☐ Yes ☐ No
Important medical events that may not be immediate life – threatening or result in death or hospitalization but may be dangerous for the patient or requires medical intervention in order to prevent other events listed in the above definition	☐ Yes ☐ No
Taking fluconazole while pregnant	☐ Yes ☐ No
A congenital abnormality or spontaneous abortion	☐ Yes ☐ No

Describing SAE

Time (date, hour) of SAE: __ __: __ __, date ____/ ____ / _____

Clinical signs, symptoms:

……

……

Pre-clinical tests:

……

……

Why the researcher identified this is SAE:

……

Relatedness of SAE to fluconazole (as identified by researcher)

☐ Unrelated: clearly explained by another, documented cause

☐ Unlikely related: more likely explained by a cause other than fluconazole

☐ Possibly related: may be related to the drug or to another cause

☐ Probably related: more likely related to the drug than to another cause

☐ Definitely related: direct association with fluconazole

This SAE is:

☐ Expected

☐ Unexpected

(The nature, frequency and severity of adverse events in the document on product research/literature or have observed or not)

☐**Yes**→ Expected ☐**No**→ Unexpected

Severity of SAE:

☐ Death

☐ Life – threatening

☐ Not cause death or life – threatening (specify).....

3. Information about treatment/management SAE

The simultaneous drugs before appearing SAE

……

……

Drugs, medical interventions have been done to manage the study subject with SAE (specify)

……

……

The situation of study subject with SAE in the current reporting period

☐ Not recovered ☐ Recovered with sequelae ☐ Death

☐ Being recovered ☐Recovered without sequelae ☐ Unclear

4. Professional comments of local IRB/scientific council/research chair unit

……

……

……

Suggestions:

For study subject:	☐ Continuing study	☐ Stopping temporary	☐ Withdrawing from the study
For study:	☐ Continuing study	☐ Stopping temporary	☐ Withdrawing from the study

5. Principal investigator's suggestions

……

……

Reporter *(signature and mark, occupational skills)*……..

Head of Unit *(signature and mark)*

FOR CRAs

APPENDIX 10B: CLINICAL STUDY SAE REPORT FORM

Report classification	☐ Initial report					
	☐ Follow up report	☐ #1	☐ #2	☐ #3	☐ #4	☐ Last report
Date of report:	____/_____/_____ (dd/mm/yy)					

1. Subject information

Study ID		Study site (region):	
Gender		D.O.B	_____/_____/_____
Date of enrollment	____/_____/_____	CD4 result at enrollment	_____
Serum CrAg testing	☐ Positive ☐ Negative	Date of HIV confirmation	____/_____/_____
WHO clinical stage at enrolment: ____ OIs that imply above WHO clinical stage: _____ _____		WHO clinical stage at the time of the report: _____ OIs that imply above WHO clinical stage: _____ _____	

2. SAE information

Serious adverse event	_____		
Date of occurrence	____/_____/_____	Date of notification	____/_____/_____
Alternative causality	_____	Specify: _____	

3. Event description

	Descriptions	Source of information	If other, specify or comment
Sign and symptoms			
Progression			
Possible causes/diagnosis			
Treatment/management			

4. Additional information:

_____

_____

_____

5. Additional information for CrAg (+) patients:

Treatment		Date start	Date end
Amphotericin B	☐ Yes ☐ No	____/_____/_____	____/_____/_____
Study Fluconazole – induction phase (900 mg/day)	☐ Yes ☐ No	____/_____/_____	____/_____/_____
Study Fluconazole – consolidation phase (450 mg/day)	☐ Yes ☐ No	____/_____/_____	____/_____/_____
Study Fluconazole – maintenance phase (150-200 mg/day)	☐ Yes ☐ No	____/_____/_____	[6 months after CD4 >200]
Fluconazole (150mg)– maintenance phase upon the complement of 12 month study follow-up (based on treating doctor's judgement)	☐ Yes ☐ No	____/_____/_____	____/_____/_____

6. Additional information for case of deaths:

If the patient died, specify the place of death: ☐ Home ☐ Hospital ☐ Other		If other, specify:	
If the patient died at home, was the patient discharged from hospital for palliative care within 7 days before death: ☐ Yes ☐ No. If yes:			
Date of hospitalization: _____/_____/_____ Date of discharge: _____/_____/_____		Hospital name: _____ Diagnosis on admission: _____	
Cause of death:	**Specify/comments**	**How were causes of death determined**	**Confirmatory diagnostics were performed**
Primary cause: _____	_____	_____	☐ No ☐ Yes. If yes, specify: _____
Underlying cause 1: _____	_____	_____	☐ No ☐ Yes. If yes, specify: _____
Underlying cause 2: _____	_____	_____	☐ No ☐ Yes. If yes, specify: _____
Specify OIs (using WHO AIDS-defining illness list) at the time of death :			☐ No ☐ Yes. If yes, specify: _____
Was death related to *Cryptococcus* infection?	☐ No ☐ Yes.	If yes, specify how determined: _____ If other, specify: _____	☐ No ☐ Yes. If yes, specify: _____
Underlying diseases or comorbidity at the time of death in additional to HIV: _____			

Does SAE related to study fluconazole?

☐ Yes ☐ No	Not related: clearly explained by another, documented cause
☐ Yes ☐ No	Unlikely related: more likely explained by a cause other than fluconazole
☐ Yes ☐ No	Possibly related: may be related to the drug or to another cause
☐ Yes ☐ No	Probably related: more likely related to the drug than to another cause
☐ Yes ☐ No	Definitely related: direct association with fluconazole

7. Action plan:

☐ Follow-up

☐ No action required

8. Relevant investigation data

(Recorded if the test results are within two weeks since the date of death)

Test		Unit	Date	Result	Note
Complete Blood Count			____/____/___		☐ Not available
WBC		K/μL		_____	
Neutrophils		%		_____	
Lymphocytes		%		_____	
RBC		M/μL		_____	
HGB		g/dL		_____	
PLT		K/μL		_____	
Biochemistry			_____/____/____		☐ Not available
Creatinine		μmol/L		_____	
Urea		mmol/L		_____	
Glucose		mmol/L		_____	
AST/SGOT		U/L		_____	
ALT/SGPT		U/L		_____	
Total protein		g/L		_____	
Albumin		g/L		_____	
Total Bilirubin		μmol/L		_____	
CSF analysis			_____/____/___		☐ Not available
Cell count				_____	
Cell differential				_____	
Protein		g/L		_____	
Glucose		mmol/L		_____	
Radiology					☐ Not available

Test		Unit	Date	Result	Note
Ultrasound	Abdomen				☐ Not available
Microbiology	GeneXpert		_____/____/____		☐ Not available
	Hepatitis virus				☐ Not available
	Fungal test		_____/____/____		☐ Not available
Other:			_____/____/____		☐ Not available

APPENDIX 11: OFF-STUDY FORM

Subject ID

Add sticker here

Date of Collection

____ / ____ / _____

Data Collector

(Name) _____

Signature _____

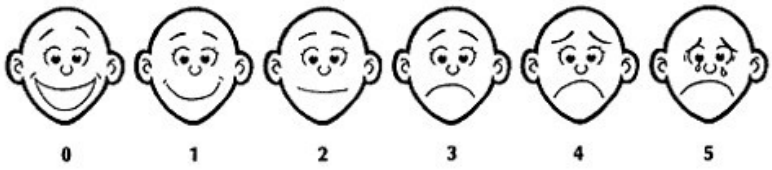
F01	Reason for going Off-Study	☐1. Completed study → ***Skip to F08*** ☐2. Lost to follow-up → ***Skip to F05*** ☐3. Withdrew consent → ***Skip to F08*** ☐4. Transferred out → ***Skip to F08*** ☐5. Death ☐6. Other, specify:_____
If the reason for off-study is Death (5)		
F02	Date of death (dd/mm/yyyy) ___ / ___/ _____	
F03	Cause of death ☐1. Confirmed cryptococcal meningitis ☐2. Suspected cryptococcal meningitis ☐3. Opportunistic infection, specify:_____ _____ ☐4. Unknown ☐5. Addiction due to overdose ☐ 9. Others, specify _____	**F03A. Source of death causes report** ☐Hospital's death documents/medical record ☐Communication with treating doctor ☐Reported by patient's family
F04	Location of death	☐1. Home ☐2. Hospital ☐9. Others, specify:_____
F05	Was patient hospitalized before death (within 1 week before the death occurred)	1. Yes → ***Complete Hospitalization Form if not recorded*** 2. No → ***End***
If the reason for off-study is Lost to follow-up (2)		
F05	Date of last attempt to contact with patient	_____ / _____ / _____(dd/mm/yyyy)
F06	Method last used to try to contact patient	☐1. Three attempts at phone contact ☐2. Home visit ☐9. Others, specify:_____

F07	Patient's status →***End***	☐1. Alive ☐2. Dead ☐ 9. Unknown
If the reason for off-study is Completed study (1), Withdraw consent (3), or Transferred out (4)		
F08	Outcome scale (explanation of activity)	☐0. Fully active, able to carry on all pre-disease performance without restriction ☐1. Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work ☐2. Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours ☐3. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours ☐4. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
If the patient returns to the initial OPC and continue take part in the study after having been lost to follow-up, Withdraw consent, or Transferred out		
F09	Date of return	___ /___ /_____. Continue follow up the patient as in the study protocol Patient's new OPC ID: _____ Patient's previous OPC ID: _____

APPENDIX 12: CLINICAL SCORING TOOLS AND WHO CLINICAL STATING OF HIV/AIDS

Sub-Appendix 1: Visual Analogue Scale (VAS) for Pain Assessment

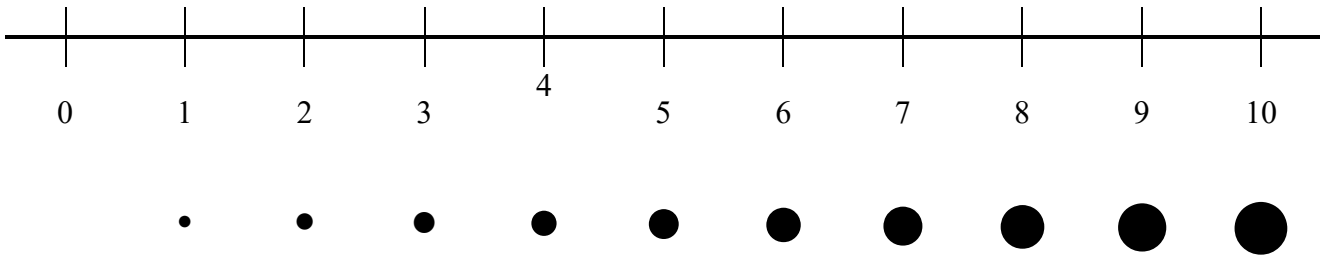
To assess the severity of pain, a six-level VAS tool is utilized. This VAS has been included in the CRFs. Following is the definition of each level of pain severity.



Score	Definition of pain severity
0	No pain at all
1	Very mild pain
2	Mild pain
3	Moderate pain
4	Very severe pain
5	The worst pain ever

Sub-Appendix 2: Visual Analogue Scale (VAS) for Adherence

To assess ART and fluconazole adherence, a VAS tool is utilized in combination with other measures. The following VAS is to show the data collector how to use this tool. A large version printed in a plastic-wrapped A4-sized paper is used during interviewing the patient for their adherence.



Ask the patient: to think back over the past month and identify the times when he or she either missed a dose or took it at the wrong time. Show the patient this VAS. Tell the patient that if he/she had taken all medicine doses, he/she would point to 10 (biggest round); and if he/she had missed all the doses, he/she would point to 0 (no round). Now give the patient an opportunity to point out their level of adherence. Write the score in the blank.

Sub-Appendix 3: Glasgow coma scale

Category	Response	Grade
Eyes	Opens eyes spontaneously	4
	Opens eyes in response to speech	3
	Opens eyes in response to painful stimuli	2
	Does not open eyes	1
Motor	Obeys	6
	Localize	5
	Withdrawal	4
	Abnormal flexion	3
	Abnormal extension	2
	No motor response	1
Verbal	Orientated	5
	Confused (Disoriented)	4
	Inappropriate words	3
	Incomprehensive sounds	2
	No response 1	1
	Total:	**15 points**

Assess the severity of a brain injury using Glasgow coma scale:

15 points: Normal
9-14 points: Light unconsciousness
6-8 points: Heavy unconsciousness
4-5 points: Deep coma
1-3 points: Very deep coma, very poor chance of recovery

Sub-Appendix 4: WHO clinical staging of HIV disease in adults and adolescents

Clinical stage 1
Asymptomatic or Persistent generalized lymphadenopathy
Clinical stage 2
Moderate unexplained weight loss (<10% of presumed or measured body weight)
Recurrent respiratory tract infections (sinusitis, tonsillitis, otitis media, pharyngitis)
Herpes zoster
Angular cheilitis
Recurrent oral ulceration
Papular pruritic eruption
Fungal nail infections
Seborrheic dermatitis
Clinical stage 3

Unexplained severe weight loss (>10% of presumed or measured body weight)
Unexplained chronic diarrhoea for longer than 1 month
Unexplained persistent fever (intermittent or constant for longer than 1 month)
Persistent oral candidiasis
Oral hairy leukoplakia
Pulmonary tuberculosis
Severe bacterial infections (such as pneumonia, empyema, pyomyositis, bone or joint infection, meningitis, bacteraemia)
Acute necrotizing ulcerative stomatitis, gingivitis or periodontitis
Unexplained anaemia (<8 g/dl), neutropenia (<0.5 × 10^9/l) and/or chronic thrombocytopenia (<50 × 10^9/l)
Clinical stage 4
HIV wasting syndrome
Pneumocystis (jirovecii) pneumonia
Recurrent severe bacterial pneumonia
Chronic herpes simplex infection (orolabial, genital or anorectal of more than 1 month's duration or visceral at any site)
Oesophageal candidiasis (or candidiasis of trachea, bronchi or lungs)
Extrapulmonary tuberculosis
Kaposi sarcoma
Cytomegalovirus infection (retinitis or infection of other organs)
Central nervous system toxoplasmosis
HIV encephalopathy
Extrapulmonary cryptococcosis, including meningitis
Disseminated nontuberculous mycobacterial infection
Progressive multifocal leukoencephalopathy
Chronic cryptosporidiosis
Chronic isosporiasis
Disseminated mycosis (extrapulmonary histoplasmosis, coccidioidomycosis)
Lymphoma (cerebral or B-cell non-Hodgkin)
Symptomatic HIV-associated nephropathy or cardiomyopathy
Recurrent septicaemia (including non-typhoid *Salmonella*)
Invasive cervical carcinoma
Atypical disseminated leishmaniasis

APPENDIX 13: Invitation to participate in Cryptococcal Antigen Screening Program

NHTD/TDH/CDC/VAAC

CRAG Screening Program

RE: Invitation to participate in Cryptococcal Antigen (CrAg) Screening Program

Dear Dr.

In 2011, the World Health Organization (WHO) recommended that patients with low CD4 be screened for CrAg and, if positive, be preemptively treated with oral fluconazole before starting ART to reduce mortality from undiagnosed infection. In the same guidance, WHO recommends discontinuation of primary prophylaxis with fluconazole as an intervention in the prevention of cryptococcal meningitis (CM).CrAg screening has been shown to be cost-effective where the prevalence of CrAg positivity in persons living with human immunodeficiency virus (PLHIV) with CD4<100 cells/μL exceeds 0.6 to 3%, depending on the setting. The prevalence of CrAg in PLHIV in Vietnam is not clearly known. However a study conducted on archived specimens showed that the prevalence is2% in the North and 6% in the South. The prevalence in the middle of Vietnam is not known. Information from this study will help the Vietnam Administration of HIV/AIDS Control **(**VAAC) decide whether to implement the WHO guidelines in Vietnam.

To this end, the National Hospital for Tropical Diseases (NHTD) in collaboration with the Tropical Diseases Hospital (TDH), the United States Centers for Disease Control and Prevention (CDC) and the VAAC is about to begin rollout of a program to screen PLHIV with CD4<100 for cryptococcal antigen. We want to know if the screening PLHIV with CD4<100 for cryptococcal disease using a lateral flow assay (LFA) and preemptively treating those who are CrAg-positive with oral fluconazole 900 mg daily for 2 weeks followed by a consolidation dose of 450 mg daily for 8 weeks, followed by 200 mg for maintenance reduces mortality and improves retention in care. We will also assess the costs associated with such screening at in Vietnam

To help VAAC and the Ministry of Health (MoH) rollout the intervention, we will ask clinics to start screening all patients with CD4 ≤ 100 cells/μL for CrAg. Your clinic is one of those identified to participate in this evaluation.

This letter is to invite you to work with us to answer the question of whether screening for CrAg among PLHIV with severe immunodeficiency helps reduce mortality and improve retention in care.

With your participation, we hope the lessons learned will benefit practitioners in Vietnam and other countries in the region that are contemplating similar screening to provide the best care for their patients.

If you have any questions or want to know more, please contact Assoc. Prof Nguyen Van Kinh – National Hospital for Tropical Diseases or Dr Le Manh Hung – Tropical Diseases Hospital - Ho Chi Minh City representing the study team and VAAC.

FOR OPC

APPENDIX 14A: SCREENING LOG FOR OPC

Clinic name:……

No.	Participant name	OPC ID	Year of birth	Gender	Screening date	Specimen code	CD4 result (cell /µL)	CrAg result	Be pregnant /plan to be pregnant	CrAg released Date	Staff
1.				☐ Male ☐ Female				☐ Positive ☐ Negative ☐ Not done	☐ Yes ☐ No		
2.				☐ Male ☐ Female				☐ Positive ☐ Negative ☐ Not done	☐ Yes ☐ No		
3.				☐ Male ☐ Female				☐ Positive ☐ Negative ☐ Not done	☐ Yes ☐ No		
4.				☐ Male ☐ Female				☐ Positive ☐ Negative ☐ Not done	☐ Yes ☐ No		
5.				☐ Male ☐ Female				☐ Positive ☐ Negative ☐ Not done	☐ Yes ☐ No		
6.				☐ Male ☐ Female				☐ Positive ☐ Negative ☐ Not done	☐ Yes ☐ No		
7.				☐ Male ☐ Female				☐ Positive ☐ Negative ☐ Not done	☐ Yes ☐ No		

FOR OPC

APPENDIX 14B: ENROLLMENT LOG FOR OPC

Clinic name:……

No.	Participant name	Year of birth	Gender	Phone number of participant	OPC ID	CD4 result (cell /µL)	CrAg result	Agree to participate in the study	Enrollment date	Study ID	Note
1			☐ Male ☐ Female				☐ Positive ☐ Negative	☐ Yes ☐ No			
2			☐ Male ☐ Female				☐ Positive ☐ Negative	☐ Yes ☐ No			
3			☐ Male ☐ Female				☐ Positive ☐ Negative	☐ Yes ☐ No			
4			☐ Male ☐ Female				☐ Positive ☐ Negative	☐ Yes ☐ No			
5			☐ Male ☐ Female				☐ Positive ☐ Negative	☐ Yes ☐ No			
6			☐ Male ☐ Female				☐ Positive ☐ Negative	☐ Yes ☐ No			
7			☐ Male ☐ Female				☐ Positive ☐ Negative	☐ Yes ☐ No			
8			☐ Male ☐ Female				☐ Positive ☐ Negative	☐ Yes ☐ No			

CRICS study #15 CrAg testing request form – Ver 2.1

APPENDIX 15: TESTING FORM

Specimen:…….

Specimen code:……

OPC code:……..

- Participant name:

YOB:…… Gender:……...

- Referral Unit:

- Diagnosis: ……

TYPE OF TEST	TEST RESULT
CrAg Antigen (if CD4 ≤100cell/μL)	

Date… month … year 201…

Doctor

Full name:…….

Date… month… year 201...

Head of lab Department

Full name:…….

CRICS study

#15CrAg testing request form Ver 2.1

TESTING FORM

Specimen:…….

Specimen code:……

OPC code:……..

- Participant name:

YOB:…… Gender:……...

- Referral Unit:

- Diagnosis: ……

TYPE OF TEST	TEST RESULT
CrAg Antigen (if CD4 ≤100cell/μL)	

Date… month … year 201…

Doctor

Full name:…….

Date… month… year 201...

Head of lab Department

Full name:…….

APPENDIX 16: CRAG TESTING LOG

FOR LABORATORY

Laboratory name:

No.	Participant name	Year of birth	Gender	Specimen referral Unit	Specimen receiving date	Specimen code	CD4 result (cell /µL)	CD4 indication	CrAg result	CrAg released Date	Screening conductor	Note
1			☐ Male ☐ Female					☐ New enrollment ☐ Routine monitoring ☐ Presumed treatment failure	☐ Positive ☐ Negative ☐ Not done			
2			☐ Male ☐ Female					☐ New enrollment ☐ Routine monitoring ☐ Presumed treatment failure	☐ Positive ☐ Negative ☐ Not done			
3			☐ Male ☐ Female					☐ New enrollment ☐ Routine monitoring ☐ Presumed treatment failure	☐ Positive ☐ Negative ☐ Not done			
4			☐ Male ☐ Female					☐ New enrollment ☐ Routine monitoring ☐ Presumed treatment failure	☐ Positive ☐ Negative ☐ Not done			
5			☐ Male ☐ Female					☐ New enrollment ☐ Routine monitoring ☐ Presumed treatment failure	☐ Positive ☐ Negative ☐ Not done			
6			☐ Male ☐ Female					☐ New enrollment ☐ Routine monitoring ☐ Presumed treatment failure	☐ Positive ☐ Negative ☐ Not done			
7			☐ Male ☐ Female					☐ New enrollment ☐ Routine monitoring ☐ Presumed treatment failure	☐ Positive ☐ Negative ☐ Not done			

APPENDIX 17: HEALTH-RELATED QUALITY OF LIFE FORM

Study ID

Add sticker here

Date of enrollment:

__ __ / __ __ / __ __ __ __

Data collector (full name) _____

Signature _____

Q	Quality of life					
	TODAY	**1. Unable to do**	**2. Severe problems**	**3. Moderate problems**	**4. Slight problems**	**5. No problems**
Q01	Mobility	☐	☐	☐	☐	☐
Q02	Self-care	☐	☐	☐	☐	☐
Q03	Usual Activities (e.g. work, study, housework, family or leisure activities)	☐	☐	☐	☐	☐
		1. Extremely	**2. Severely**	**3. Moderately**	**4. Slightly**	**5. None**
Q04	Pain / Discomfort	☐	☐	☐	☐	☐
Q05	Anxiety / Depression	☐	☐	☐	☐	☐
Q06	We would like to know how good or bad your health is **TODAY**. This scale is numbered from 0 to 100. **100 means the best health you can imagine; 0 means the worst health you can imagine.** Please indicate how is your health to day?				……..points	

APPENDIX 18. PATIENT'S VISITS LOGBOOK

Patient's ID: _____________

Date of appointment	Actual date of visit	Medication pick-up	Number of days for which ARVs were given	Any OIs since the last visit (using WHO clinical stages)	
				List all test-based OIs diagnosed since the last visit	List all clinical OIs diagnosed without any investigations since the last visit
__ / ___ / ____	__ / __ / ___	☐ Patient ☐ Family member			
__ / ___ / ____	__ / __ / ___	☐ Patient ☐ Family member			
__ / ___ / ____	__ / __ / ___	☐ Patient ☐ Family member			
__ / ___ / ____	__ / __ / ___	☐ Patient ☐ Family member			
__ / ___ / ____	__ / __ / ___	☐ Patient ☐ Family member			
__ / ___ / ____	__ / __ / ___	☐ Patient ☐ Family member			
__ / ___ / ____	__ / __ / ___	☐ Patient ☐ Family member			
__ / ___ / ____	__ / __ / ___	☐ Patient ☐ Family member			
__ / ___ / ____	__ / __ / ___	☐ Patient ☐ Family member			
__ / ___ / ____	__ / __ / ___	☐ Patient ☐ Family member			
__ / ___ / ____	__ / __ / ___	☐ Patient ☐ Family member			

APPENDIX 19. Fluconazole (pre-emptive treatment) log

Patient's ID:……………………………….

Phase	**Start date (Date of medication was given to the patient)**	**End date (Date of next appointment)**	**Dosage (mg/day)**	**Formulation**	**Comments**
Initial phase (2 weeks)				☐ 150 mg x ___ tablets (___ tablets) ☐ 50 mg x ___ tablets (___ tablets)	
				☐ 150 mg x ___ tablets (___ tablets) ☐ 50 mg x ___ tablets (___ tablets)	
Continuation phase (8 weeks)				☐ 150 mg x ___ tablets (___ tablets) ☐ 50 mg x ___ tablets (___ tablets)	
				☐ 150 mg x ___ tablets (___ tablets) ☐ 50 mg x ___ tablets (___ tablets)	
				☐ 150 mg x ___ tablets (___ tablets) ☐ 50 mg x ___ tablets (___ tablets)	
				☐ 150 mg x ___ tablets (___ tablets) ☐ 50 mg x ___ tablets (___ tablets)	
Maintenance				☐ 150 mg x ___ tablets (___ tablets) ☐ 50 mg x ___ tablets (___ tablets)	
				☐ 150 mg x ___ tablets (___ tablets) ☐ 50 mg x ___ tablets (___ tablets)	
				☐ 150 mg x ___ tablets (___ tablets) ☐ 50 mg x ___ tablets (___ tablets)	
				☐ 150 mg x ___ tablets (___ tablets) ☐ 50 mg x ___ tablets (___ tablets)	
				☐ 150 mg x ___ tablets (___ tablets) ☐ 50 mg x ___ tablets (___ tablets)	
				☐ 150 mg x ___ tablets (___ tablets) ☐ 50 mg x ___ tablets (___ tablets)	
				☐ 150 mg x ___ tablets (___ tablets) ☐ 50 mg x ___ tablets (___ tablets)	
				☐ 150 mg x ___ tablets (___ tablets) ☐ 50 mg x ___ tablets (___ tablets)	
				☐ 150 mg x ___ tablets (___ tablets) ☐ 50 mg x ___ tablets (___ tablets)	
				☐ 150 mg x ___ tablets (___ tablets) ☐ 50 mg x ___ tablets (___ tablets)	

End of therapy: Date __ __ / __ __ / __ __ __ __

Pre-emptive fluconazole therapy is ongoing at the time the patient completed study participation:

☐ Yes ☐ No

Reason to stop fluconazole(choose one item below):

- ☐ CD4 count ≥ 200 for more than 6 months
- ☐ Viral load less than 1000 copies/mL(suppressed) in patient on ART for more than 6 months
- ☐ Adverse drug reaction related to fluconazole
- ☐ Other. Specify:

Appendix 20: Script informing patients of reimbursement

As you have agreed to join this study, we want to interview you about your feelings and some questions about your quality of life. Additionally, since you are spending some of your time with us for this interview, we'll reimburse you for this time. You will be reimbursed 65,000 Vietnam Dong for the extra time spent at the facility for study-related activities, including the time which is used to for answering the Quality of Life questionnaire. We pay you at the time of enrollment (baseline visit), and at 6 and 12 month), however you will not receive any reimbursement for your previous visits to OPC.

APPENDIX 21: COST STUDY DATA COLLECTION TOOLS

See Excel files enclosed