# INTEGRATED MANAGEMENT OF CRYPTOCOCCAL AND OPPORTUNISTIC INFECTIONS TO IMPROVE OUTCOMES IN ADVANCED HIV DISEASE: A STRATEGY TRIAL

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**Study Sponsor: London School of Hygiene and Tropical Medicine**
**Funding mechanism: Wellcome Trust Clinical PhD Fellowship**

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# 1. IMPROVE - General information:

**STATEMENT OF COMPLIANCE**

The study will be carried out in accordance with Good Clinical Practice (GCP) as required by the following:

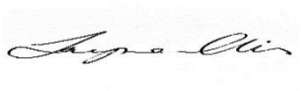
1. London School of Hygiene and Tropical Medicine research ethics committee
2. Uganda National Council of Science and Technology guidelines

All individuals responsible for the design and conduct of this study have completed Human Subjects Protection Training.

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable national regulations and ICH guidelines.

**Site investigator:** Dr Jayne Ellis

**Signed:**



**Date: 25th June 2021**

**SPONSOR**
London School of Hygiene and Tropical Medicine (LSHTM)
Sponsor Representative: TBC
Research Governance & Integrity Office
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London School of Hygiene and Tropical Medicine will act as the main sponsor for this study. Delegated responsibilities will be assigned locally.

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**FUNDING**
Wellcome Trust Clinical PhD Fellowship

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# Clinical trial sites

We will recruit participants from 2 sites in Uganda:

(1) Kampala, Kiruddu National Referral Hospital and Mulago National Referral Hospital
(2) Mbarara, Mbarara Regional Referral Hospital of Mbarara University of Science and Technology.

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# 2. IMPROVE - Protocol summary

**Title:** Integrated management of cryptococcal and opportunistic infections to improve outcomes in advanced HIV disease: a strategy trial.

**Problem statement:**

Cryptococcal meningitis remains the most common cause of HIV-associated meningitis in sub-Saharan Africa, despite ART roll-out. In Uganda cryptococcus accounts for 72% (609/842, 72%) of all cases of suspected meningitis in people living with HIV[1]. Mortality associated with HIV-associated cryptococcal meningitis remains devastatingly high (24-45%). Due to advanced immunosuppression, mortality continues in the 6 months after meningitis diagnosis, particularly in those with CD4<50 cells/mcL, some of which is due to TB. There is robust evidence that TB preventative therapy (TPT) – as recommended for all people living with HIV by the World Health Organisation (WHO) - can prevent TB deaths in advanced HIV disease, however provision of TPT has been sub-optimal globally. This study aims to determine the preferred TPT strategy for adults with HIV-associated cryptococcal meningitis, to increase the reach of TPT as an intervention, and to reduce deaths due to TB reactivation in advanced HIV disease.

**Research question:** What is the preferred strategy (safety and feasibility) for delivery of 1HP (one month of isoniazid and rifapentine) TB preventive therapy (TPT) for adults with HIV-associated cryptococcal meningitis?

**Trial design:**

(1) A nested randomised strategy trial to evaluate the safety and feasibility of two strategies for the delivery of TB preventive therapy (TPT) in HIV-associated cryptococcal meningitis: inpatient initiation (early, week 2) or outpatient initiation (standard, week 6) delivery of 1HP (one month of isoniazid and rifapentine) TPT.

The regimen received will be standard WHO-approved 1HP TPT therapy, used at their normal dose for their intended indication. The research question is when to give this therapy.

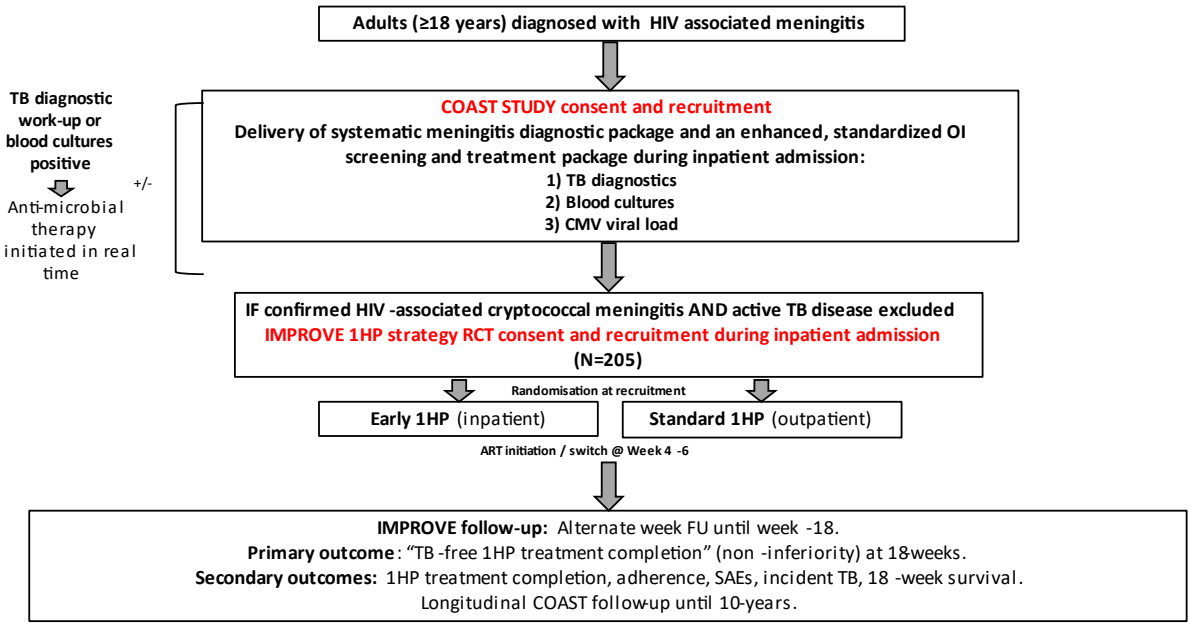
**Rationale:** Despite guidelines from the WHO, current provision of TPT in advanced HIV disease (AHD) is very limited, in part due to the inability to exclude active TB in ill patients. Improved urinary TB diagnostics (FujiLAM) may enable clinicians to more confidently exclude active TB disease in AHD removing a key barrier to TPT, and new short course TPT (one month of rifapentine and isoniazid, 1HP) offers additional opportunities to expand the use of TPT. However, amongst patients with HIV-associated cryptococcal meningitis the risk of drug-drug interactions (DDIs) and poor medication adherence due to additional pill burden need to be considered, and the optimal TPT strategy needs to be determined.

**Hypotheses:**

1) Early (inpatient initiation) 1HP TPT will be non-inferior to standard (outpatient initiation) 1HP TPT with respect to TB-disease free 1HP treatment completion in individuals in whom active TB has been excluded, and 1HP TPT is feasible (adherence and tolerability) and safe (adverse events) in patients with HIV-associated cryptococcal meningitis.

**Aim:** To generate evidence on the safety (adverse events) and feasibility (adherence and tolerability) of 1HP (one month of isoniazid and rifapentine) for TB preventative therapy (TPT) to prevent TB disease amongst adults with HIV-associated cryptococcal meningitis.
**Study population:** Adults (≥ 18 years) with a diagnosis of HIV-associated cryptococcal meningitis, with no evidence of TB disease.
**Setting:** The IMPROVE study will be nested within an ongoing IRB approved cryptococcal meningitis study (COAST) at Kiruddu National Referral Hospital, Kampala, Mulago National Referral Hospital, Kampala and Mbarara Regional Referral Hospital, Mbarara, Uganda: UNCST: HS2317, IRB: MHREC 1246.
**Description of interventions:** COAST participants in whom active TB disease has been systematically excluded will be randomized (1:1) to inpatient initiation (early, week 2) or outpatient initiation (standard, week 6) 1HP TPT.
**Study end points:** Primary outcome: TB-disease free 1HP treatment completion (non-inferiority) at 18-weeks post diagnosis of cryptococcal meningitis. Secondary outcomes: 1HP treatment completion, discontinuation, Grade 3-4 adverse events and SAEs, drug induced liver injury (DILI), incident TB, 18-week survival (post diagnosis of cryptococcal meningitis).
**Subject participation:** 18-weeks
**Study duration:** 2 years

# 3. IMPROVE - Schematic overview



# 4. List of abbreviations

AE – Adverse event
AHD – Advanced HIV Disease
aHR – Adjusted Hazard Ratio
ALT - Alanine aminotransferase
aOR – Adjusted Odds Ratio
AR - Adverse Reaction
ART – Anti-retroviral therapy
CI – Confidence interval
CRF – Case report form
HIV – Human Immunodeficiency Virus
HR – Hazard Ratio
IDI – Infectious Diseases Institute
IRIS – Immune Reconstitution Inflammatory Syndrome
LTBI – Latent Tuberculosis Infection
MDR – Multi-drug resistant
OR - Odds Ratio
PLHIV – People living with HIV
RCT – Randomised controlled trial
SAE – Serious Adverse Event
SAR - Serious Adverse Reaction
SUSAR - Suspected Unexpected Serious Adverse Reaction
TB - Tuberculosis
TB LAM – Tuberculosis lipoarabinomannan
TSC - Trial Steering committee
TPT – TB preventative therapy
UAR - Unexpected Adverse Reaction
ULN – Upper limit of normal
WHO – World Health Organisation
1HP – One month therapy of Rifapentine plus isoniazid

# 5. Background information and scientific rationale

*Cryptococcus* remains the most common cause of HIV-associated meningitis globally with an estimated 250,000 cases per year, accounting for 15% of all AIDS-related deaths[2]. The incidence of HIV-associated cryptococcal meningitis is not reducing despite widespread antiretroviral therapy (ART) roll-out[3,4]. In sub-Saharan Africa, case fatality is 24-45%, even in the context of clinical trials with delivery of rapidly fungicidal amphotericin-based regimens[5], compared to 10-15% in resource rich settings. Data suggest that co-prevalent opportunistic infections including tuberculosis (TB) are common in HIV-associated cryptococcal meningitis and may contribute to the high mortality observed in sub-Saharan Africa[6,7,8]. Recent advances in TB diagnostics including: urine TB-lipoarabinomannan (TB-LAM) lateral flow assay test (Alere, Abbott, Waltham, MA); urine Xpert Ultra MTB/RIF assay (Xpert; Cepheid, Sunnyvale, CA), and urine Fujifilm SILVAMP TB LAM (FujiLAM) will enable us to more effectively diagnose and treat, or exclude active TB disease co-infection amongst adults with HIV-associated cryptococcal meningitis in the inpatient setting.

Given the high burden of TB disease in Uganda (and other comparable sub-Saharan African settings) however, we hypothesise that - having excluded active TB disease - the majority of adults with HIV-associated cryptococcal meningitis will have latent TB infection (LTBI) and given the advanced state of immunocompromise associated with cryptococcal meningitis, these patients are at significant risk of TB reactivation, disease and death due to TB. There is robust evidence that TB preventative therapy (TPT) - as recommended for all people living with HIV by the World Health Organisation (WHO) - can prevent progression of LTBI to TB disease and therefore TB deaths in advanced HIV disease.Provision of TPT however, has been sub-optimal globally. This study aims to determine the preferred TPT strategy for adults with HIV-associated cryptococcal meningitis, to increase the reach of TPT as an intervention, and to reduce deaths due to TB reactivation in advanced HIV disease.

## Latent TB infection (LTBI) in cryptococcosis:

LTBI is defined as a state of persistent immune response to stimulation by *M. tuberculosis* antigens with no evidence of clinically manifest active TB[9]. It is estimated that one quarter of the world's population has had exposure to *M. tuberculosis* and may have LTBI[9]. Globally 5–10% of those with LTBI will develop active TB disease over the course of their lives, usually within the first 5 years after initial infection[10,11]; data indicate that PLHIV are about 20 times more likely to develop active TB than those without HIV infection[9].

Once active TB disease has been excluded, the World Health Organisation (WHO) recommends that PLHIV should receive TPT to prevent progression of LTBI to active TB disease[9]. There is robust evidence that TPT significantly reduces TB-associated morbidity and mortality, irrespective of CD4 count and ART status. A systematic review of 12 RCTs found that TPT reduced the overall risk for TB by 33% (relative risk (RR) 0.67, 95% CI 0.51-0.87) among the 8,578 PLHIV included[12]. The 2015 TEMPRANO randomised controlled trial (RCT) which evaluated immediate vs deferred ART Initiation with or without isoniazid

preventative therapy (IPT) for PWLH in Cote D'Ivoire demonstrated that the benefits of TPT are additive to the benefits of ART[13]; and the 2020 WHIP3 TB RCT which recruited over 4,000 PLHIV across three African countries, demonstrated conclusively that TPT is durable for at least 24 months, with no need for repeated courses even in high TB/HIV burden settings[14].

Despite this, implementation of the WHO TPT recommendations has been poor globally. In 2016, of the 30 high TB/HIV burden countries, 18 did not report any provision of TPT, and in the 12 countries that provided data, coverage among people newly enrolled in HIV care varied considerably from 2.4% in Indonesia to 73% in Zimbabwe[15]. In 2017, fewer than 1 million PLHIV received TPT, of the estimated 30 million eligible[16]. Barriers to implementation are multi-factorial and include concerns about adherence, loss to follow-up, drug toxicity and drug resistance[16].

In 2019, Swindells et al. demonstrated in a multicentre RCT that one month of isoniazid and rifapentine (1HP) was noninferior to 9-months of isoniazid (9H) for preventing TB in PLHIV [16]. Amongst 3,000 HIV-positive adults, the primary endpoint (first TB diagnosis, or death from TB or unknown cause) occurred in 2% of the 1HP group and 2% in the 9H group. Treatment completion was 97% in the 1HP group and 90% in the 9H group (p <0.001), and serious adverse events (SAEs) of any grade occurred in 6% in the 1HP group and in 7% in the 9H group (p 0.07). This short, efficacious, better-tolerated, and safe regimen is now recommended by the WHO for TPT and offers a potential breakthrough in the treatment of LTBI globally[9].

TPT with 1HP is of particular interest in cryptococcosis. In HIV-associated cryptococcal meningitis ART initiation is delayed due to the risk cryptococcal- immune reconstitution inflammatory syndrome (IRIS)[17]. The risk of unmasking TB-IRIS, however, remains following ART initiation at 4-6 weeks, most incident IRIS events occurring within the first month of ART initiation[18,19]. 1HP treatment prior to initiation of ART has the potential to reduce incidence of active TB, TB-IRIS and late deaths due to TB in HIV-associated cryptococcal meningitis [12,20]. Whilst the WHO does not currently recommend in which setting TPT should be provided, the majority of TPT is provided in the outpatient setting. We hypothesise that provision of 1HP prior to hospital discharge however, has the potential to increase the reach of the intervention and reduce the LTBI preventative care cascade (identification of at risk populations, exclusion of active TB, providing LTBI treatment, monitoring for adverse events, adherence and completion of treatment)[9]. The potential benefit of treatment should, however, be carefully balanced against the risk for drug-related adverse events for example, risk of DDIs with antifungals or ART, and poor adherence due to additional pill burden. The optimal TPT strategy to prevent TB disease in HIV-associated cryptococcal meningitis therefore needs to be determined.

# 6. Aims and objectives

**Strategic aim:** To improve outcomes in HIV-associated cryptococcal meningitis.

**Primary objectives:**

1) To generate evidence on the safety (adverse events) and feasibility (adherence and tolerability) of 1HP (one month of isoniazid and rifapentine) for TB preventative therapy (TPT) amongst adults with HIV-associated cryptococcal meningitis.
2) To generate preliminary data on potential secondary benefits (reduced loss to follow-up, reduced active TB disease, reduced mortality due to TB) of early (inpatient initiation) 1HP TPT as compared to standard (outpatient initiation) 1HP TPT amongst adults with HIV-associated cryptococcal meningitis.

# 7. Study hypothesis

1) Early (inpatient, week 2) initiation of 1HP will be non-inferior to standard (outpatient, week 6) initiation of 1HP with respect to TB-disease free 1HP treatment completion in individuals in whom active TB has been excluded, and use of 1HP as TPT is feasible (adherence) and safe (SAEs) in patients with HIV-associated cryptococcal meningitis.

# 8. IMPROVE 1HP feasibility RCT - summary of study design

Sequential consenting adults (≥18 years) **in whom active TB disease has been excluded** using TB tests (refer to COAST TB screening SOP), will be recruited (prior to the planned day of discharge) into the IMPROVE 1HP open-label feasibility RCT.

Participants will be randomized 1:1 to inpatient initiation (early, 1HP to start during week 2) or outpatient initiation (standard, 1HP to start during week 6) 1HP TPT. Amongst the inpatient 1HP intervention arm (week 2), at least one dose of HP will be given as directly observed therapy (DOT) whilst the participant is an inpatient, thereafter participants may be discharged at the discretion of the attending study physician. Amongst the outpatient 1HP intervention arm (week 6), at least one dose of HP will be given as DOT whilst the participant is in the outpatient clinic. Following hospital discharge participants will be followed-up in outpatient clinic for 18-weeks. Rifapentine, fluconazole and dolutegravir pharmacokinetic (PK) sampling will be conducted for 20 eligible participants.

**Primary endpoint:** TB-disease free 1HP treatment completion at 18-weeks (after cryptococcal meningitis diagnosis and commencement of anti-fungal therapy).

Treatment completion is defined as participant reported adherence to >90% of the study medications for the duration of the trial. TB-disease free at 18-weeks is defined as (1) not receiving a diagnosis of active TB disease for the duration of the trial and (2) a negative WHO TB symptom screen at trial completion.

**Secondary endpoints:**

i) 1HP treatment completion at 18-weeks.
ii) Discontinuation of the study drugs for ≥ 5 consecutive days for any reason.
iii) Grade 3-4 adverse events and serious adverse events (SAEs).
iv) Drug-induced liver injury defined as elevation of blood transaminase (ALT) alone ≥ 5x ULN (or ALT ≥ 3x ULN if bilirubin abnormal) or alkaline phosphatase (ALP) alone ≥2x ULN.
v) Incident active TB (defined as clinician diagnosed TB based upon clinical syndrome and/or radiological evidence and/or mycobacteriological evidence).
vi) 18-week survival.
vii) Sparse fluconazole, rifapentine and dolutegravir PK analyses (N=20).

# 9. Scientific equipoise

| **Possible benefits of early (inpatient initiation) 1HP:** | **Potential harms of early (inpatient initiation) 1HP:** |
|---|---|
| • Mortality continues post discharge in HIV-associated cryptococcal meningitis, a proportion of these deaths are due to TB. Early 1HP TPT prior to hospital discharge (and ART initiation/switch) may:<br>- Reduce TB-IRIS events<br>- Reduce active TB<br>- Reduce late death in cryptococcosis due to TB<br><br>• TPT is predominately provided in the outpatient setting. Inpatient provision may:<br>- Improve reach of the intervention i.e. clinicians providing 1HP as a to-take-away (TTA) medication prior to hospital discharge<br>- Reduce loss to follow-up within the LTBI preventative care cascade (identification of at-risk populations, exclusion of active TB, providing LTBI treatment, monitoring for adverse events, adherence and completion of treatment). | • Drug-drug interactions (DDIs) with anti-fungals (rifapentine – fluconazole) and/or ART.<br><br>• Poor tolerability of increased pill burden during acute cryptococcosis.<br><br>• Suboptimal comprehension of 1HP dosing during acute cryptococcosis.<br><br>• Increased cryptococcal relapse due to DDIs +/- non-compliance.<br><br>• Suboptimal diagnostics to definitively exclude TB in AHD, combined with the potential for symptoms of active TB disease to be masked during acute cryptococcosis and therein the risk of treating active TB disease with 1HP:<br>- TB treatment failure<br>- Development of drug resistance<br>- TB deaths |

# 10. Power calculations

The aim of the trial is to investigate the safety and feasibility of two strategies of delivery of 1HP TPT in HIV-associated cryptococcal meningitis, therefore the primary endpoint is "TB-disease free treatment completion" as a composite measure of safety and feasibility.

A non-inferiority analysis for the primary endpoint is planned, because as outlined in the equipoise table above, there are several potential secondary benefits associated with early 1HP (interventional arm), therefore if early 1HP can be demonstrated to be non-inferior to late (standard) 1HP with respect to safety and feasibility, then the secondary benefits associated with early 1HP TPT may make inpatient initiation of 1HP preferable.

Assuming an 80% TB-disease free completion rate in the late (standard) 1HP TPT arm, a sample size of 205 would give us 80% power, with a one sided 95% confidence interval, to determine whether early 1HP led to non-inferior TB-disease free completion rates at a 15% non-inferiority margin, allowing for an 5% rate of loss to follow-up and 10% post-randomisation mortality at 18-weeks.

**Power calculations detailing a range of possible sample sizes (overall, assuming 1:1 randomisation) depending on non-inferiority margin and TB-free 1HP completion rates.**

| | | TB-free treatment completion in standard 1HP arm (outpatient setting) | | | | |
|---|---|---|---|---|---|---|
| | | **80%** | **82%** | **84%** | **86%** | **90%** |
| **Non-inferiority margin** | **10%** | 460 | 425 | 385 | 345 | 260 |
| | **12%** | 319 | 295 | 268 | 240 | 180 |
| | **15%** | **205** | 189 | 172 | 154 | 117 |
| Sample sizes are based on 80% power, with a one sided 95% confidence interval, and allowing for 5% LTFU and 10% post-randomisation mortality at 18-weeks. | | | | | | |
| *1HP treatment completion was 97% in the Swindells et al RCT[25] | | | | | | |

The trial is not powered to detect differential incident TB events or survival between arms. Secondary TB endpoints and survival will be compared at trial completion (18-weeks).

# 11. Statistical analysis plan

Analysis will be conducted as per a pre-defined statistical analysis plan (SAP), an outline in brief is provided below.

Early 1HP (inpatient) or standard 1HP (outpatient) is the binary exposure of interest.

For each outcome, difference in the proportions with 95% confidence intervals will be reported.
**Primary endpoint:** TB-disease free 1HP treatment completion (non-inferiority) at 18-weeks.
**Secondary endpoints** (1) 1HP treatment completion (2) Discontinuation (3) Grade 3-4 adverse events and SAEs (4) DILI (5) Incident TB (6) 18-week survival.

Univariate analyses using Mantel Haenszel techniques will be used to calculate an odds ratio for each binary outcome across exposure categories. Multivariate logistic regression analyses will be presented with adjustment for possible confounders for the primary endpoint only. For the non-inferiority analysis, a generalised linear model (GLM) will be used. In this model, 1HP treatment group will be the sole predictor, using an identity-link function and binomial distribution to calculate an estimate for the (unadjusted) risk difference the treatment groups. If the upper limit of the one-sided 95% confidence interval (CI) for the risk difference falls below the non-inferiority margin of 15%, non-inferiority will be declared.

Cox regression (time to event) will be used to analyse the incident TB and 18-week survival endpoints. Both unadjusted and adjusted models will be presented.

Analyses will be done on both an intention to treat and per protocol basis.

# 12. Study population

## Participant identification

The study population will be adults (≥ 18 years) diagnosed with HIV-associated cryptococcal meningitis, **in whom active TB disease has been excluded.**

This study will be nested within an ongoing IRB approved cryptococcal meningitis study (COAST) ongoing at Kiruddu National Referral Hospital, Mulago National Referral Hospital, and Mbarara Regional Referral Hospital, Mbarara, Uganda: UNCST: HS2317, IRB: MHREC 1246. Patients presenting with suspected meningitis will be identified by ward doctors and as part of routine clinical care, potential participants will undergo an HIV test and lumbar puncture with CSF CrAg testing.

## Patient inclusion criteria

1) Adult ≥ 18 years old with a first or subsequent episode of cryptococcal meningitis (defined by CSF CrAg test positive).
2) HIV positive.
3) Written informed consent by patient or their caregiver.

## Patient exclusion criteria

1) Active TB disease (as evidenced by any positive TB screening test or taking TB therapy at time of screening)
2) Jaundice
3) Abnormal liver function tests (bilirubin > 3.5 mg/dl or ALT >200 IU/L)
4) Active hepatitis B infection (defined as hepatitis B surface antigen positive)
5) Known chronic liver disease
6) A clinical syndrome which in the opinion of the attending clinician, puts the patient at significant risk if he/she were to participate in the 1HP trial
7) Pregnant
8) Breast-feeding
9) Hypersensitivity to rifamycins or isoniazid
10) Contra-indicated medication(s) (e.g. protease inhibitor)

# 13. Screening and enrolment procedures

The IMPROVE study is nested within an ongoing IRB approved cryptococcal meningitis study (COAST) at Kiruddu National Referral Hospital, Kampala, Mulago National Referral Hospital, Kampala and Mbarara Regional Referral Hospital, Mbarara, Uganda (UNCST: HS2317, IRB: MHREC 1246).

Adults diagnosed with HIV-associated cryptococcal meningitis in whom active TB disease has been excluded, will be approached by a member of the meningitis study team trained in consent and recruitment procedures to review eligibility, to provide study information and to offer the opportunity for inclusion.

All COAST participants diagnosed with HIV-associated cryptococcal meningitis, **in whom active TB disease has been excluded** should be screened for inclusion into the nested 1HP feasibility prior to the planned day of hospital discharge.

All consenting adults (≥ 18 years) included in COAST and who do not meet any of the exclusion criteria as listed above are eligible for inclusion into the IMPROVE 1HP feasibility RCT.

## Co-enrolment guidance

Participants may be co-enrolled into other observational and interventional cryptococcal meningitis studies at the digression of the local principal investigator (PI) and regulatory board approvals.

**Special notes on co-enrolment:**

1HP therapy will begin – at the earliest - in the second week following commencement of anti-fungal therapy for cryptococcal meningitis, therefore any future interventional cryptococcal meningitis trials evaluating novel induction regimens (anti-fungal therapy delivered during the first two weeks post diagnosis of cryptococcal meningitis) should not be affected by concurrent 1HP. Co-enrolment will be at the digression of the local principal investigator (PI) and regulatory board approvals.

# 14. Informed consent procedures

Participants will be approached for their informed consent in two steps:

1) The current IRB approved parent cryptococcal meningitis study COAST (UNCST: HS2317, IRB: MHREC 1246) will approach persons for informed consent for screening for active TB disease at time of their diagnostic lumbar puncture. This consent asks for permission for CSF analyses, OI screening and management, and collection of hospital outcomes. This is IRB approved.

2) For patients in whom active TB disease has been excluded, subsequent informed consent for participation in the nested IMPROVE 1HP feasibility RCT, will be sought prior to the planned day of discharge, study day ~7-14. This consent asks for permission for participation the 1HP feasibility RCT, follow-up until 18 weeks, and additional diagnostic testing and lab safety monitoring, and sample storage in accordance with the protocol.

All members of the meningitis study team are trained in informed consent procedures. The aims, implications, potential benefits and risks associated with the study will be explained in full to all potential participants identified by screening. Information about the study will be provided in a clear and non-coercive manner, and the details of the study will be explained both verbally and via a written study information leaflet (Luganda, English or Runyankole). Information about the study will not be presented in a way which over-emphasises the benefits of being part of the study. It will be made clear to potential participants that refusal to participate in the study will not jeopardize their clinical care, and it will be made clear that consent is entirely voluntary and can be withdrawn at any time during the study.

After sufficient time for consideration, if the study staff are satisfied that the patient understands the above information, and is willing to continue, the patient will be asked to indicate their consent either by signature or by thumbprint (if the volunteer is illiterate) on the consent form. Illiterate volunteers will be asked to have a witness present (friend, family or another member of staff independent of the study team) to witness the discussion and thumbprint consent. If the volunteer is illiterate and declines to have a witness present, this will be recorded on the informed consent form. The investigator-designated research professional obtaining the consent must also sign the applicable approved informed consent forms.

Consent forms will include consent for storage of samples in accordance with Uganda National Council for Science & Technology guidelines and LSHTM Human Tissue Act Policy. Participants will be given a copy of the signed/thumb-printed consent form and an information sheet to take away if they wish.

## Consent for those who lack capacity to consent:

Given the nature cryptococcal meningitis it is anticipated that some patients will lack capacity to consent for themselves. It would be unethical and biased for these patients to be systematically excluded from the study.

Potential participants with altered mental status who are unable to consent will be enrolled into the study if their next of kin gives informed consent on their behalf. In these circumstances the legally acceptable surrogate must sign all applicable approved informed consent forms on behalf of the participant as described above. As soon as the patient's mental status improves they will be given a study information leaflet and consent obtained as above, with care taken to ensure they understand that they are free to withdraw from the study and if they do so this will not jeopardise their future care.

# 15. Study procedures and schedule of events

All COAST participants diagnosed with HIV-associated cryptococcal meningitis, **in whom active TB disease has been excluded** should be screened for inclusion into the nested 1HP feasibility prior to the planned day of hospital discharge.

Participants should be screened at this stage to ensure no exclusion criteria are met. Consenting participants, will be recruited into the 1HP feasibility RCT prior to the planned day of discharge, study day ~7-14. Consent and recruitment procedures as described above to be followed.

## Randomisation procedures

Following recruitment and enrolment, participants will be randomised to either inpatient initiation (early, week 2) or outpatient initiation (standard, week 6) 1HP TPT.

Participants will be randomized on the planned day of discharge from hospital, ~7-14 days following hospital admission (the specific timing of randomisation will be participant specific as it will depend on the clinical condition of the patient as monitored by the attending study physician and their time of hospital discharge). In instances, where the participant remains an inpatient for ≥14 days, randomisation will occur on day 14 of antifungal therapy rather than on the planned day of discharge.

Participants will be randomised individually, using random block size, using a computer-generated programme.

## Schedule of events

**Intervention:** Rifapentine 600mg daily plus Isoniazid 300mg daily for one month (1HP) to be commenced either:

1) As an inpatient (week 2, intervention arm)
2) As an outpatient (week 6, standard)

Amongst the inpatient initiation of 1HP intervention arm (week 2), at least one dose of HP will be given as directly observed therapy (DOT) whilst the participant is an inpatient; participants may be discharged at the discretion of the attending study physician. Following hospital discharge participants will be followed-up every two weeks (with a visit window of +/- 5 days) until week-18.

# 16. IMPROVE 1HP open-label randomised feasibility study-map

| *Study Activity* | Day 1 | Wk 1 | Wk 2 | Wk 3 | Wk 4 | Wk 6 | Wk 8 | Wk 10 | Wk 12 | Wk 14 | Wk 16 | Wk 18 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Cryptococcal meningitis diagnosed | X | | | | | | | | | | | |
| COAST recruitment | X | | | | | | | | | | | |
| Commence anti-fungals[1] | X | | | | | | | | | | | |
| Inpatient TB screening package[2] | X | X | | | | | | | | | | |
| Recruitment into IMPROVE 1HP feasibility study[3] | | X | X | | | | | | | | | |
| Randomisation | | | X | | | | | | | | | |
| Commence 1HP in early arm[4] | | | X | | | | | | | | | |
| Hospital discharge | | | X | | | | | | | | | |
| Follow-up[5] | | | X | | X | X | X | X | X | X | X | X |
| Clinical review | | | X | | X | X | X | X | | | | X |
| Pill counts[6] | | | X | | X | X | X | X | | | | X |
| Liver function tests[7] | | | X | | X | X | X | X | | | | X |
| Safety monitoring blood tests[8] | | | X | | X | X | X | X | | | | X |
| PK sampling[9] | | | X | X | | | | | | | | |
| Standard 1HP (outpatient) | | | | | | X | | | | | | |
| ART initiation / switch[10] | | | | | X | X | | | | | | |
| Primary outcome[11] | | | | | | | | | | | | X |
| Trial completion | | | | | | | | | | | | X |
| Longitudinal COAST follow-up[12] | | | | | | | | | | | | X |

1. Participants will receive antifungal for 1-2 weeks as induction therapy for cryptococcal meningitis. Following completion of induction therapy, patients will step down to 800mg Fluconazole (continuation phase) to complete total 10-week course.
2. Clinical samples will be stored for future research
3. Consenting participants – in whom active TB disease has been excluded - will be recruited into the 1HP nested open-label randomised feasibility study.
4. 1HP = Rifapentine 600mg daily plus Isoniazid 300mg daily (plus pyridoxine)
5. Follow-up will occur on alternate weeks (with a visit window of +/- 5 days) until week-18.
6. Self-reported adherence will be assessed, and pill counts conducted.
7. Alternate week liver function tests (LFTs) will be performed to screen for anti-TB drug-induced liver injury for the duration of 1HP.
8. Safety monitoring blood tests will be taken including alternate week full blood count and renal function blood tests for the duration of 1HP. Blood will also be stored for future immunology and other studies.
9. Sparse rifapentine / fluconazole / dolutegravir PK sampling will be conducted for the first 20 participants on days 3, 5, 7 and 14 at the IDI PK unit.
10. We anticipate that ~1/3 of participants will be ART naïve, these patients will start ART at week 4-6, ~1/3 of participants will be on ART but have immunological/virological failure, these patients will switch ART at week 4-6. Patients newly started on ART (<3-months prior to their cryptococcosis diagnosis) i.e. those with unmasking cryptococcal-IRIS will continue their ART.
11. Treatment completion is defined as participant reported adherence to >90% of the study medications for the duration of the trial. TB-disease free is defined as 1) not receiving a diagnosis of active TB disease for the duration of the trial and (2) a negative WHO TB symptom screen at trial completion.
12. Following trial completion participants will be followed-up as part of the IRB approved longitudinal cryptococcosis cohort study ongoing at IDI (UNCST: HS2317, IRB: MHREC 1246).

# 17. Outpatient schedule of events

Following hospital discharge participants will be followed-up until week-18 either at the Infectious Diseases Institute Clinic in Kampala or Mbarara Hospital outpatient clinic. Follow-up visits will be harmonised with the parent IRB approved cryptococcal meningitis studies. Home visits will be possible where there are mobility problems and the patient is agreeable.

Outpatient appointments will include:

1) Clinical review with TB symptom screen and full physical examination.
2) Additional mycobateriological and/or radiological testing for active TB disease may be undertaken at the discretion of the physician with agreement of the site PI as clinically indicated.
3) 1HP adherence review with pill counts.
4) Safety monitoring blood tests for the duration of 1HP.
5) ART planning and counselling.

Participants randomised to the standard 1HP (outpatient provision) arm will commence 1HP during week 6.

Follow-up will be on alternate weeks with clinical review, pill counts, liver function tests (LFTs), unless a participant has abnormal LFTs (LFT above the upper limit of normal, which do not meet the exclusion criteria) at screening, in which case outpatient follow-up with clinical review and LFTS will be weekly. After 1HP TPT completion, follow-up appointments may be done over the phone where possible until study completion.

## Assessment of participant adherence with study drug

The initial HP treatment dose will be given as directly observed therapy (DOT) in a healthcare setting for both intervention arms (either in the hospital or in the outpatient clinic). Thereafter, participants continue 1HP as non-DOT in the hospital or in the community. Adherence to 1HP treatment will be assessed by means of patient interview and pills counts at follow up visits using an adherence and tolerability SOP.

1HP treatment completion will be defined as participant reported adherence to >90% of the study medications for the duration of the trial.

## Unscheduled visits

Participants will also be provided with the mobile number of the study team that will be answered 7 days a week. Participants will be encouraged to attend the clinic for unscheduled visits if they experience symptomatic deterioration with a particular focus on the symptoms and signs of drug induced liver injury (DILI). They will be assessed by the study doctor and adverse events reporting will be

conducted as per the adverse event SOP. If patients are sick enough to require hospital admission for investigation and management, their clinical condition will be closely managed by the meningitis study team.

Procedures to be performed during unscheduled sick visit include:

1) Interim history
2) Focused physical examination
3) Medication review
4) Laboratory evaluation as clinically appropriate

## Anti-retroviral therapy – initiation or switch

We anticipate that ~1/3 of participants will be ART naïve, these patients will start ART at week 4-6. ~1/3 of participants will be on ART but have immunological/virological failure, these patients will switch ART at week 4-6. Patients newly started on ART (<3-months prior to their cryptococcosis diagnosis) i.e. those with unmasking cryptococcal-IRIS will continue their ART. ART initiation / switch will be done in conjunction with the participant's ART clinic.

Rifapentine should not be prescribed for patients receiving protease inhibitors. Taking a protease inhibitor at baseline is an exclusion criterion for the IMPROVE 1HP RCT. If an IMPROVE study participant is started on a protease inhibitor at ART initiation / switch at week 4-6, for those in the outpatient initiation study arm, 1HP should not be started at week 6.

# 18. Study Procedures

## Treatment modifications, interruptions, and discontinuations

Study physicians may interrupt rifapentine and/or isoniazid dosing administration at physician discretion for a potentially life-threatening adverse reaction. Reversible hepatotoxicity would be the primary concern. All interruptions will be recorded on study CRFs.

Additional scenarios which would lead to treatment modifications or interruptions are as follows:

1) If a participant is diagnosed with active TB disease whilst receiving 1HP therapy, the TPT will be discontinued, and TB treatment will be commenced in line with drug susceptibility testing.
2) If a participant randomised to the outpatient initiation study arm, is diagnosed with active TB disease prior to initiation of 1HP as planned at week-6, the participant will be commenced in line with drug susceptibility testing and 1HP will not be started (as per the 1HP modification and discontinuation SOP).
3) Rifapentine should not be prescribed for patients receiving protease inhibitors, therefore if an IMPROVE study participant is started on a protease inhibitors at ART initiation / switch at week 4-6, for those in the outpatient initiation study arm, 1HP should not be started at week 6.
4) If a participant becomes pregnant whilst receiving 1HP therapy, the TPT will be discontinued.
5) If a participant randomised to the outpatient initiation study arm, becomes pregnant prior to initiation of 1HP as planned at week-6, the participant will not be commenced on 1HP (as per the 1HP modification and discontinuation SOP).
6) If any clinical event occurs such that that attending physician concludes that continuation or commencement of 1HP is not in the participants best interests, 1HP therapy may be modified or discontinued.

Participant in whom 1HP therapy is modified or discontinued due to one of the above scenarios, will continued to be followed until week-18.

## Withdrawals

Participants may withdraw from the study at any time by withdrawing subject consent. Assessment of vital status up until 18-weeks (secondary outcome) will continue via telephone calls at a minimum, unless consent is completely withdrawn. Participants may stop TPT (as above) and remain in the study for observational follow up.

## Termination of study

Reasons for study termination are study completion (week 18), withdraw of consent, death, or lost to follow up.

At study termination the study termination CRF will be completed documenting interval history, physical examination, vital status, 1HP treatment adherence/completion, adverse events, and reason for study termination.

## Loss to follow-up

Every effort will be made (for example with mobile telephone calls and financial help with travelling expenses) to obtain accurate and complete follow-up data for 18 weeks after the start of treatment.

If a patient fails to attend, the research nurse will visit the home address and make every effort to persuade the patient to attend and continue antifungal, anti-tuberculous and antiretroviral treatment.

## Trial closure

The trial will be considered closed when the last patient has completed 18 weeks in the study and all follow-up and laboratory reports have been received. Early termination could occur if there is an unacceptable level of adverse events, occurring in any of the test arms.

# 19. Study drugs (Rifapentine)

Rifapentine 600mg daily plus Isoniazid 300mg daily for one month is now recommended by the WHO as TPT to prevent TB disease in PLHIV.

**Rifapentine:**

**U.S Food and Drug Administration (FDA) summary of product characteristics for Rifapentine:**
https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/021024s009lbl.pdf

**Preparations:** Oral: 150mg tablets

**Mode of activity:** Rifapentine is a rifamycin antibiotic that inhibits DNA-dependent RNA polymerase activity in susceptible cells leading to a suppression of RNA synthesis and cell death. It is bactericidal and has a very broad spectrum of activity against most gram-positive and gram-negative organisms including susceptible strains of Mycobacterium tuberculosis

**Bioavailability:** Whilst taking Rifapentine with meals does maximise absorption, isoniazid should be taken on an empty stomach. Therefore, we recommend that 1HP are taken at the same time on an empty stomach, or with a light snack if nauseated.

**Metabolism**: Rifapentine is well absorbed when taken orally and is distributed widely in body tissues and fluids, including the CSF. It is metabolized in the liver and eliminated in bile and, to a much lesser extent, in urine.

**Tolerability:**
**Common side effects associated with rifampicin:**
Reddish discolouration of urine, sweat, sputum, tears.
Flu-like syndrome.
Gastrointestinal**:** Anorexia, nausea, vomiting, heartburn.
Hepatic: Transient increases in LFTs.
Metabolic: Hypoglycaemia, hyeruricaemia

**Serious side effects associated with rifampicin:**
Haematological: Agranulocytosis (rare), Haemolytic anaemia (rare, usually intermittent therapy), Thrombocytopaenia (rare, usually high-dose / intermittent therapy).
Hepatic: Hepatotoxicity (rare), Hyperbilirubinaemia.
Renal: Nephrotoxicity (rare).
Immunologic: Hypersensitivity.

**Contraindications and cautions:**
**Contraindications:**
Hypersensitivity**:** To rifapentine or other rifamycins.
Liver Disease: Avoid if jaundiced.

**Cautions:**
Liver Disease: Use cautiously and monitor LFTs; hyperbilirubinaemia may occur early in treatment in some patients due to competition between rifampicin and bilirubin for hepatic excretion.
Pregnancy.
Breast feeding

**Concomitant medications and potential drug-drug interactions:** Drugs not known to be contraindicated with the trial drugs will be permitted.

**Concomitant medications - precautions:**

Rifamycins induce certain cytochrome P-450 enzymes and may therefore interfere with medicines that depend on this metabolic pathway, accelerating their elimination. These include ART as well as many other medicines:

**Analgesics:** Accelerated metabolism of opiates, resulting in reduced effect (e.g. alfentanyl, codeine, fentanyl, methadone, morphine and possibly oxycodone).
**Anti-arrhythmics:** Accelerated metabolism of disopyramide.
**Antibacterials:** Reduced plasma concentrations of chloramphenicol, clarithromycin, dapsone, doxycycline and fluoroquinolones.
**Anticoagulants:** Accelerated metabolism of coumarins (e.g. warfarin).
**Anti-diabetics:** Accelerated metabolism of sulfonylureas (reduced effect).
**Antiepileptics:** Reduced plasma concentration of antiepileptics such as phenytoin.
**Antifungals**: Reduced serum concentrations of fluconazole, itraconazole and ketoconazole.
**Antipsychotics:** Accelerated metabolism of antipsychotics such as haloperidol.
**Atovaquone:** Reduced plasma concentrations of both rifapentine and atovaquone.
**Benzodiazpeines:** Reduced plasma concentrations (e.g. diazepam).
**Betablockers:** Reduced effect of betablockers; dosage adjustment maybe required.
**Calcium-channel blockers:** Accelerated metabolism of diltiazem, nifedipine, and verapamil (significant reduction in plasma concentrations).
**Ciclosporin:** Accelerated metabolism of ciclosporin (reduced plasma concentration).
**Contraceptives**: Accelerated metabolism of oestrogens and progestogens (reduced contraceptive effect). Avoid use of combined hormonal contraception (oral, patch or vaginal ring), or progestogen-only contraception (pill and implant). Suitable alternatives include barrier methods, copper-bearing intrauterine system, or progestogen-only injectable (depot medroxyprogesterone acetate, norethisterone enantate, or levonorgestrel-releasing intrauterine system, which can be continued at the usual dose and dosing/replacement interval of 12 weeks, 8 weeks and 5 years, respectively).
**Corticosteroids:** Possible accelerated metabolism of corticosteroids (reduced effect).
**Hormone Replacement Therapy (HRT):** Rifapentine would be expected to reduce the efficacy of HRT
**Levothyroxine:** Reduced effect of levothyroxine; dosage adjustment maybe required.
**Sildenafil:** Reduced plasma concentration of sildenafil.
**Sirolimus:** Potential for reduction in plasma concentration of sirolimus.

**Tacrolimus:** Reduced in plasma concentration of tacrolimus.
**Theophylline:** Accelerated metabolism of theophylline (reduced plasma concentration).
**Tri-cyclic antidepressants:** Reduced effect of tri-cyclic antidepressants; dosage adjustment maybe required.

**Data on concomitant medication**

All non-trial treatment taken by the patient will be recorded at enrolment and follow up and in the event of an SAE occurring.

## Rifapentine and fluconazole:

Reduced serum concentrations of fluconazole, itraconazole and ketoconazole can occur with prolonged concomitant use of rifamycins. Due to the short duration of 1HP, we do not recommend empirical dose adjustment of fluconazole 800mg. We will conduct rifapentine – fluconazole PK analyses for the first 20 participants recruited into the 1HP feasibility study to inform practice.

## Rifapentine and ART

Rifapentine is an inducer of CYP450 enzymes. Concomitant use of Rifapentine with other drugs metabolized by these enzymes, such as protease inhibitors and reverse transcriptase inhibitors, may cause a significant decrease in plasma concentrations and loss of therapeutic effect of the protease inhibitor or reverse transcriptase inhibitor.

**Rifapentine should not be used with saquinavir/ritonavir.**

**Rifapentine and dolutegravir**

A drug interaction study in healthy volunteers of dolutegravir with once weekly HP reported toxicities in 2 of 4 participants[21]. However subsequent results from a Phase 1/2 trial of 3HP and dolutegravir in adults with HIV reported good tolerance and viral load suppression, no adverse events of Grade >3 related to the HP, and did not indicate that rifapentine reduced dolutegravir levels sufficiently to require dose adjustment[22]. WHO guidelines recommend that rifapentine-isoniazid can be given for LTBI treatment to patients with HIV taking dolutegravir-based antiretroviral therapy, without dose adjustments[9]. Again, due to the short duration of 1HP, in line with WHO guidelines we do not recommend empirical dolutegravir dose adjustment.

# 20. Study drugs (Isoniazid):

**U.S Food and Drug Administration (FDA) summary of product characteristics for Isoniazid:**
https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/008678s028lbl.pdf

**Preparation:** 300mg once a day (oral) plus rifapentine 600mg daily for one month is now recommended by the WHO as TPT to prevent TB disease in PLHIV.

**Mode of activity:** The antimicrobial activity of isoniazid is selective for mycobacteria, likely due to its ability to inhibit mycolic acid synthesis, which interferes with cell wall synthesis, thereby producing a bactericidal effect

**Bioavailability:**
Studies have shown that the bioavailability of isoniazid is reduced significantly when administered with food. Isoniazid should be taken 30-60 minutes before food, or 2 hours after food.

**Metabolism**: Isoniazid is metabolized primarily by acetylation and dehydrazination.

**Tolerability:**
**Common side effects associated with isoniazid:**
**Neurological:** Peripheral Neuropathy. (Pyridoxine hydrochloride will be given prophylactically in all patients from the start of treatment)
**Hepatic:** Transient increases in LFTs.
**Serious side effects associated with isoniazid:**
**Dermatological**: Skin reactions e.g. urticaria (uncommon).
**Haematologic:** Agranulocytosis, megaloblastic anaemia, thrombocytopaenia.
**Hepatic:** Hepatotoxicity (rare).
**Immunological:** Drug-induced lupus (rare).
**Musculoskeletal**: Arthralgia, rhabdomyolysis.
**Neurological:** Seizure, psychosis (rare).

**Concomitant medications and potential drug-drug interactions**

**Carbamazepine:** increased plasma concentration of carbamazepine. Increased risk of hepatoxicity.

**Contraindications and cautions:**

**Contraindications:**
Hypersensitivity: To isoniazid.
**Cautions:**
Liver disease, alcohol abuse, hepatitis B co-infection: monitor LFTs closely.
Malnutrition, HIV co-infection, diabetes mellitus, and alcohol dependence**:** Increased risk of peripheral neuropathy; prescribe prophylactic pyridoxine.

# 21. Study drug procurement

The study will provide 1HP plus pyridoxine (to minimise risk of peripheral neuropathy) for all participants included in the 1HP feasibility RCT. Rifapentine will be purchased from Sanofi (or an intermediate supplier e.g. Stop TB Partnership's Global Drug Facility www.stoptb.org/gdf ), and isoniazid and pyridoxine will be purchased in country of good manufacturing practices (GMP) approved versions. These will be shipped to each of the clinical trial sites. The trial sites' pharmacists will record and sign for receipt of medication.

# 22. Study drug storage and stability

The study medication will be stored in the clinical trial sites' secure pharmacies. All drugs will be protected from light and stored at room temperature, in adherence with manufacturers' instructions and documented on a temperature log in the pharmacy. Study drug management and accountability will be described in a specific SOP.

If study medication has expired, it will be destroyed according to the local regulations. At the conclusion of the trial study medication will be destroyed. A record of study medication final accountability and destruction will be kept and filed throughout.

Clinical personnel involved in the dispensation and administration of study drugs will adhere to GCP guidelines. Compliance with the protocol will be assessed via on-going quality assurance monitoring.

# 23. Management of adverse events

The principles of ICH GCP require that both investigators and sponsors follow specific procedures when notifying adverse events or reactions in clinical trials. These procedures are described in below.

## Definitions and terms for safety reporting

| Term | Definition |
|---|---|
| **Adverse Event (AE)** | Any untoward medical occurrence in a subject to whom a medicinal product has been administered including occurrences which are **not necessarily caused by** or related to that product. |
| **Adverse Reaction (AR)** | Any untoward and unintended response in a subject to an investigational medicinal product, which is **related** to any dose administered to that subject. |
| **Unexpected Adverse Reaction (UAR)** | An adverse reaction the nature and severity of which is not consistent with the information about the medicinal product in question. |
| **Serious Adverse Event (SAE) OR Serious Adverse Reaction (SAR) OR Suspected Unexpected Serious Adverse Reaction (SUSAR)** | Respectively, any adverse event, adverse reaction or unexpected adverse reaction that:<br>1. Results in death<br>2. Is life-threatening (defined as a participant at immediate risk of death at time of the AE, e.g. anaphylaxis)<br>3. Requires hospitalisation *<br>4. Results in persistent or significant disability or incapacity<br>5. Consists of a congenital anomaly or birth defect<br>6. Other important medical event(s)** |
| * Hospitalisation is defined as an inpatient admission, regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation. Hospitalisations for a pre-existing condition, including elective procedures that have not worsened, do not constitute an SAE.<br>** Other events that may not result in death, are not life threatening, or do not require hospitalisation may be considered a serious adverse experience when, based upon appropriate medical judgement, the event may jeopardise the patient and may require medical or surgical intervention to prevent one of the outcomes listed above (excluding new cancers or result of overdose). Any unclear cases should be discussed with the site PI asap. | |

## Responsibilities of site investigators:

In the first instance the research team must act urgently to optimise the participants medical condition and minimise harm. All AEs must be systematically investigated to ascertain (1) Severity (2) Seriousness (as per definitions above) and (3) Causality (the likelihood that the AE is a response to a study drug).

## Grading the severity of AEs:

The severity of a specific event describes its intensity (i.e. mild, moderate, severe, life-threatening), and it is the intensity which is graded. Importantly, severity is *not* the same as seriousness. Seriousness, which is not graded, relates to an outcome of an AE and is a regulatory definition (as per table above).

Severity is graded in line with the Division of AIDS Table for Grading the Severity of Adult and Paediatric Adverse Events version 2.1 dated July 2017 (https://rsc.niaid.nih.gov/clinical-research-sites/daids-adverse-event-grading-tables)

**Severity Grade:**

**Grade 1 (Mild)**: event requires minimal or no treatment and do not interfere with the patient's daily activities.

**Grade 2 (Moderate)**: event results in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.

**Grade 3 (Severe):** event interrupts a patient's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually incapacitating.

**Grade 4 (Life threatening):** Any adverse drug experience that places the participant, in the view of the investigator, at immediate risk of death from the reaction as it occurred (e.g. anaphylaxis), i.e., it does not include a reaction that had it occurred in a more severe form, might have caused death (e.g. uncomplicated malaria that could be life-threatening if not treated, but it was not).

**Grade 5 (Death)**

## AE relationship to trial drugs

When reporting on serious adverse events, the trial investigator must state whether they believe that the event is causally associated with any of the trial treatments and the strength of the causal relationship.

Each AE must be classified according to the definitions as below. The trial investigator must also state whether the adverse event was expected and what if any action was taken.

| CLASSIFICATION OF ADVERSE EVENTS BY RELATIONSHIP TO STUDY MEDICATION |
|---|
| **UNRELATED**: This category applies to those AEs that are clearly and incontrovertibly due to extraneous causes (disease, environment, etc.). |
| **UNLIKELY**: This category applies to those AEs that are judged to be unrelated to the test drug, but for which no extraneous cause may be found. An AE may be considered unlikely to be related to study medication if or when it meets 2 of the following criteria: (1) it does not follow a reasonable temporal sequence from administration of the test drug; (2) it could readily have been produced by the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject; (3) it does not follow a known pattern of response to the test drug; or (4) it does not reappear or worsen when the drug is re-administered. |

| |
|---|
| **POSSIBLY**: This category applies to those AEs for which a connection with the test drug administration appears unlikely but cannot be ruled out with certainty. An AE may be considered possibly related if or when it meets 2 of the following criteria: (1) it follows a reasonable temporal sequence from administration of the drug; (2) it could not readily have been produced by the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject; or (3) it follows a known pattern of response to the test drug. |
| **PROBABLY**: This category applies to those AEs that the investigator feels with a high degree of certainty are related to the test drug. An AE may be considered probably related if or when it meets 3 of the following criteria: (1) it follows a reasonable temporal sequence from administration of the drug; (2) it could not be reasonably explained by the known characteristics of the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject; (3) it disappears or decreases on cessation or reduction in dose (note that there are exceptions when an AE does not disappear upon discontinuation of the drug, yet drug-relatedness clearly exists; for example, as in bone marrow depression, fixed drug eruptions, or tardive dyskinesia); or (4) it follows a known pattern of response to the test drug. |
| **DEFINITELY**: This category applies to those AEs that the investigator feels are incontrovertibly related to test drug. An AE may be assigned an attribution of definitely related if or when it meets all of the following criteria: (1) it follows a reasonable temporal sequence from administration of the drug; (2) it could not be reasonably explained by the known characteristics of the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject; (3) it disappears or decreases on cessation or reduction in dose and recurs with re-exposure to drug (if rechallenge occurs); and (4) it follows a known pattern of response to the test drug. |

## Reporting of AEs

Grade 3-4 AEs that are not serious and unrelated to the investigational medicinal product will be reported in aggregate in the safety reports.

All SAEs must be reported within 72 hours by the Local Investigator using the AE CRF by e-mail to the Trial Management Group (TMG).

All SAES including SUSARs must be reported to the following regulatory bodies no later than 7 days after the investigators are first aware of the reaction. Thereafter, a detailed report of the SAE should be submitted within 8 days.

## Follow-up of SAEs

In the case of an SAE the subject must be followed-up until clinical recovery is complete and laboratory results have returned to normal, or until the event has stabilised. Follow-up may continue after completion of protocol treatment if necessary. Outcomes from all SAEs must be recorded using the AE CRF.

# 24. Management of Drug Induced Liver Injury (DILI)

## Background

Medicines used for TPT to prevent TB disease regimens are generally safe and well tolerated but hepatoxicity has been associated with both rifapentine and isoniazid.

## Definition of DILI

Drug-induced liver injury defined as elevation of blood transaminase (ALT) alone ≥ 5x ULN (or ALT ≥ 3x ULN if bilirubin abnormal) or alkaline phosphatase (ALP) alone ≥2x ULN.

## DILI epidemiology

Overall DILI occurs in around 20% of HIV-positive people on TB treatment. The Ugandan National Drug Administration (NDA) actively monitors for DILI associated with isoniazid TB preventive treatment. DILI been reported by the NDA to occur between 2-weeks and 5-months after the commencement of isoniazid TB preventive treatment.

Amongst the 1488 HIV-positive adults randomised to 1HP in the Swindells et al RCT, 2% experienced elevation in liver enzymes to grade 3 or higher. The risk was higher (3%) in participants receiving 9H in comparison to those receiving 1HP[16].

The risk of DILI if higher in the following groups: history of liver disease, harmful use of alcohol, HIV infection, age > 35 years. Concomitant use of hepatoxic medications including fluconazole is also of potential concern. Therefore, specific attention must be paid to preventing DILI in our cohort.

## Baseline screening

All potential participants screened for inclusion into the IMPROVE 1HP feasibility study will have liver function tests (LFTs) and hepatitis B testing performed during week 1 (HbsAg), and results must be available prior to starting a participant on 1HP. Participants with abnormal LFTs (bilirubin > 3.5 mg/dl or ALT >200 IU/L) and/or active hepatitis B infection at baseline must not be started on 1HP as these are clear exclusion criteria. Participants will also have baseline renal function evaluated as per NDA.

## Patient education

Participants will be advised to avoid alcohol use whilst taking rifapentine and isoniazid.

Participants will also be advised symptoms of DILI (anorexia, nausea, vomiting, abdominal discomfort, persistent fatigue or weakness, dark-coloured urine, pale stools, jaundice, confusion or drowsiness) and advised to seek urgent medical attention if they notice any of these symptoms. Participants will also be provided with the mobile number of the study team that will be answered 7 days a week. If - for

whatever reason – the participant is unable to contact a member of the study team, the participant should stop treatment immediately.

## Serial monitoring for DILI

Following commencement of 1HP TPT, participants will be undergo clinical assessment including physical examination on alternate weeks and have LFTs performed every two weeks to screen for anti-TB drug-induced liver injury (inpatient or outpatient setting) for the duration of 1HP TPT therapy. If at baseline a participant has abnormal LFTs (LFTs above the upper limit of normal, which do not meet the exclusion criteria) outpatient follow-up with clinical review and LFTS will be weekly for the duration of 1HP therapy.

## Clinical management in case of DILI

In cases of confirmed DILI (ALT alone ≥ 5x ULN (or ALT ≥ 3x ULN if bilirubin abnormal) or ALP alone ≥2x ULN) both rifapentine and isoniazid will be stopped; because the risks associated with DILI are greater than the benefits of 1HP TPT in the acute setting, rifapentine and isoniazid will not be re-introduced.

All other hepatotoxic medication including co-trimoxazole will be temporarily stopped. Fluconazole will not be routinely stopped following diagnosis of DILI due to the significant risk of relapse of cryptococcosis with cessation of anti-fungal therapy (incidence of grade 3-4 liver AEs is ~1% with fluconazole in Uganda); however, if liver function continues to deteriorate despite discontinuation of 1HP TPT, it will be at the discretion of the study physician following consultation with the site PI to decide whether fluconazole should be stopped. ART will not be discontinued following diagnosis of DILI.

Management will be described in a specific DILI SOP and will include regular clinical assessment and physical examination, plus ALT, ALP, bilirubin and INR measurement every 2 (+/-1) days. It is at the discretion of the study physician following consultation with the site PI whether to admit the participant or not for monitoring, this must be determined on a case by case basis.

# 25. Data collection procedures

## Study case report forms (CRFs)

CRFs will be the primary data collection tool. These will be completed by the study team in real-time as per the study protocol. Data collection is the responsibility of the clinical trial staff under the supervision of the site PI. The principal investigator is responsible for ensuring accuracy, completeness, legibility and timeliness of data reporting.

## Electronic data management system

Data entry will occur via the DataFax system, whereby the paper-based CRFs are scanned, emailed to a server, and data entered by intelligent character recognition. After an initial automated error-checking, secondary review for accuracy is then performed by the DataFax team at the Infectious Diseases Institute, Uganda. The DataFax system allows for automated data queries to alert for any missing data on an ongoing basis. Second, this also allows for permanent archiving and potential remote review by oversight bodies.

## Source documents

Source data are all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. The PI will retain study essential source documents for 20-years after the completion of the study, as per Ugandan guidelines. Digital images of the source documents will be retained for an indefinite period.

# 26. Laboratory procedures

All laboratory work will be undertaken in accredited laboratories with internal and external validation procedures. Refer to Laboratory SOP for protocol-related assay details.

## Storage of specimens

Participant specimens will be stored for current and future research studies related to OIs and the immune response in the IDI translational laboratory in accordance with local standards and LSHTM Human Tissue Act Policy.

# 27. Data management

## Participant confidentiality

All participant-related information (including CRFs, laboratory specimens, reports, etc.) will be kept strictly confidential. Participants will be identified only by means of a coded number specific to each participant. HIV clinic records will kept in the local HIV clinic as per local practice. All computerized databases will identify participants by numeric codes only, and will be password-protected. All paper records will be kept in a secure, locked location and only research staff will have access to the records.

## Data sharing with third parties

Upon request, participant records will be made available to the following named parties only: study sponsor, the sponsor's monitoring representative, and applicable regulatory entities, including the Uganda National Council of Science and Technology, Uganda National Drug Authority, Mulago IRB, or London School of Hygiene and Tropical Medicine. The anonymised database/protocol will be shared with the journal, if required.

# 28. Quality control and assurance

## Risk assessment

The Quality Assurance (QA) and Quality Control (QC) considerations have been based on a formal Risk Assessment, which acknowledges the risks associated with the conduct of this trial and how to address them with QA and QC processes. This Risk Assessment has been reviewed by the Sponsor (LSHTM) and will lead to the development of a Monitoring Plan.

## Site monitoring plan

Site monitoring will be conducted to ensure that the human subject protection, study procedures, laboratory, study intervention administration, and data collection processes are of high quality and meet the sponsor, ICH E6 and regulatory guidelines. A separate monitoring plan will be developed with the sponsor to describe who will conduct the internal and external monitoring, at what frequency, in what level of detail, and who will be responsible for ensuring that monitoring findings are addressed. The respective site PIs and study teams will allocate adequate time for such monitoring activities and will ensure that the monitor or is given access to all the above noted study-related documents and study related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

## Audit procedures

The study may be subject to audit by the London School of Hygiene & Tropical Medicine under their remit as sponsor, the Study Coordination Centre and other regulatory bodies to ensure adherence to GCP. The respective site PIs and study teams will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.) and study documents.

# 29. Ethics and protection of human subjects

## Informed consent

Patients will be enrolled into the study only once the conditions for informed consent have been satisfied. It will be made clear to patients that refusal to participate in the study will not jeopardize their clinical care, and it will be made clear that consent is entirely voluntary and can be withdrawn at any time during the study.

## Clinical research regulatory frameworks

This study is to be conducted according to the international standards of Good Clinical Practice (International Conference on Harmonization guidelines), Declaration of Helsinki, and International Ethical Guidelines for Biomedical Research Involving Human Subjects, applicable national government regulations, and Institutional research policies and procedures. All investigators must have received human subject protection and GCP training prior to human subject involvement.

## Institutional regulatory board approvals

The Study Coordination Centre will obtain approval from the LSHTM Research Ethics Committee, as well as the Mulago Research and Ethics Committee. Following initial approval, any future proposed amendments to the study protocol will be approved by the trial steering committee and then approval will be sought again from the respective IRBs prior to implementation.

# 30. Trial committees

## Trial management group (TMG)

A Trial Management Group (TMG) will be formed comprising the international and local Investigators. The TMG will be responsible for the day-to-day running and management of the trial and will liaise at regular intervals.

## Trial Steering Committee (TSC)

A Trial Steering Committee (TSC) will be formed, the Chairman of which will be independent of the running of the trial. The role of the TSC is to provide overall supervision for the trial and provide advice through its Independent Chairman. The ultimate decision for the continuation of the trial lies with the TSC.

Their terms of reference will be:

1. to monitor and supervise the progress of the trial towards its interim and overall objectives
2. to review at regular intervals relevant information from other sources (e.g. other related trials)
3. to consider the recommendations of the Independent Data Monitoring Committee

## Independent Data Monitoring Committee (IDMC)

There will be an Independent Data Monitoring Committee whose terms of reference will be as follows:

1. To review safety data, in particular all serious adverse events possibly attributable to the trial drugs, such as local reactions or unexpected deaths.
2. To monitor the conduct of the trial with respect to the ethical aspects of the trial.

# 31. Protocol deviations and violations

A protocol deviation is any noncompliance with the clinical trial protocol or GCP requirements without significant consequences. A protocol violation is any noncompliance with the clinical trial protocol or GCP requirements with an impact on patient safety or scientific integrity. The noncompliance may be either on the part of the participant, the investigator or study site staff. Corrective actions are to be developed by the PI and implemented promptly both with respect to protocol deviations, and violations.

Protocol deviations will be reported in aggregate as part of the required safety reports to the regulatory authorities. Protocol violations must be reported within 5 working days on the violation. All deviations must be addressed in source documents (as appropriate) and will be sent to local IRB in aggregate format. The most common expected deviation is non-adherence to TPT which is the primary endpoint of the trial and assessing adherence, tolerability, and safety is the primary objective of the trial.

# 32. Publication policy

All publications and presentations relating to the study will be authorised by the Trial Management Group. The first publication of the trial results will be in the name of the Trial Management Group, if this does not conflict with the journal's policy. Authorship of parallel studies initiated outside of the Trial Management Group will be according to the individuals involved in the project but must acknowledge the contribution of the Trial Management Group.

# 33. Conflict of interest

No conflict of interest exists by any investigator. Any investigator who develops a new conflict of interest will disclose this to their relevant institutional oversight board, to the executive committee, and to the Study sponsor.

# 34. Indemnity

All personnel involved in the trial will be expected to be indemnified by their employing authority.

# 35. Finance

Funding has been awarded the Wellcome Trust via the Wellcome Clinical PhD Programme in Global Health Research.

# 36. Ancillary studies and collaborative work

## 1. Drug-Drug Interactions caused by Rifapentine associated CYP450 enzyme induction: implications for clinical management in cryptococcal meningitis and Advanced HIV Disease.

**Background:** There are limited data on rifapentine/fluconazole DDIs, nor rifapentine/dolutegravir DDIs. Rifapentine is a rifamycin and an inducer of CYP450 enzymes. Rifapentine may therefore cause increased metabolism of both fluconazole and dolutegravir leading to decreased plasma concentrations. Current guidelines are that neither fluconazole nor dolutegravir require dose adjustment when co-administered with rifapentine however the data are sparse, and there are no data on triple therapy (rifapentine/fluconazole/dolutegravir) as may be required for patients with HIV-associated cryptococcal meningitis.

The IDI has more than 10 years experience in conducting pharmacokinetic (PK) studies and is a leading centre in sub-Saharan Africa. The IMPROVE 1HP feasibility RCT provides a novel opportunity to collect important rifapentine/fluconazole and rifapentine/dolutegravir PK samples to answer timely questions of clinical importance. This sub-study will provide important safety data to inform 1HP use in cryptococcal meningitis.

**Research questions:** Does co-administration of rifapentine lead to decreased plasma concentrations of fluconazole and/or dolutegravir in adults with HIV-associated cryptococcal meningitis?

**Study population:** 20 study participants with HIV-associated cryptococcal meningitis taking 1HP, fluconazole and dolutegravir.

**Study design:** Consenting adults with HIV-associated cryptococcal meningitis who are able to attend the IDI PK unit for a full day, will be invited to attend for PK sampling. Sparse PK sampling will be performed on day 3, 5 and 14 of 1HP. Fluconazole and dolutegravir concentrations will be measured at 2, 4, 6, 8 and 24 hours using liquid chromatography-tandem mass spectrometry approach.

**Analysis plan:** Non compartmental analysis (Cmax, Cmin, AUC)

**Study outputs:**

1. Data to inform fluconazole dosing when co-administered with rifapentine for patients with HIV-associated cryptococcal meningitis.
2. Data to inform dosing of dolutegravir when co-administered with rifapentine.
3. Whilst this data is specific to patients with HIV-associated cryptococcal meningitis, it will also be informative with respect to other patients with advanced HIV disease in whom dolutegravir may be co-administered with rifapentine.

# 37. Supplementary information

## IMPROVE 1HP feasibility RCT patient information sheet

**Patient information**

You are invited to take part in this research trial. Before you decide, it is important for you to understand why the research is being done and what it will involve. Please take your time to read through the following information carefully. Ask any questions you may have. Take time to decide whether or not you wish to take part.

**What is the purpose of the study?**

This study aims to improve survival for patients with HIV and cryptococcal meningitis. In addition to treatment for your HIV and cryptococcal meningitis, it is recommended that patients with HIV receive anti-infective treatment to treat tuberculosis (TB) infection and prevent TB disease. This is because TB infection is very common and there is good evidence that early treatment of TB infection prevents more severe TB disease. TB remains the most common cause of death in patients with HIV. We wish to understand the best strategy for providing treatment for TB infection in patients with cryptococcal meningitis.

**Why have I been chosen?**

You have been chosen because you have been diagnosed with cryptococcal meningitis and HIV, and we have found no evidence of active TB disease.

**Do I have to take part?**

You decide whether or not to take part. If you do decide to take part, you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part you are still free to withdraw at any time and without giving a reason. This will not affect the standard of the care you receive.

**What will happen to me if I decide to take part?**

You will receive treatment for your cryptococcal meningitis and be cared for by our specialist meningitis research team. In addition to the standardised care for cryptococcal meningitis that is the norm, you will receive additional treatment with 2 drugs (rifapentine and isoniazid) to treat TB infection. The duration of this treatment will be for one month, and you will be required to take the treatment every day.
We wish to understand the best strategy for providing treatment for TB infection in patients with cryptococcal meningitis, therefore we will ask you to take the rifapentine and isoniazid as an inpatient

(early treatment) OR as an outpatient (late treatment). This will be decided at random and we do not know which allocation you shall receive at this stage.

If you take part in the study you will be followed-up for 18-weeks. Once you have been discharged from hospital, you will have to return to our outpatient clinic for alternate week follow-up visits to review your progress with our doctors and nurses. You will be reimbursed for each of these visits to pay for transport to/from the hospital based on the cost 2 mini-buses or a mini-bus/bicycle taxi for transport. You will only be reimbursed if you have been discharged from hospital and need transportation to attend the follow-up visit. If you decide to take part, you will also need to provide alternate week blood samples for safety monitoring.

**What are the possible disadvantages and risks of taking part?**

There is the possibility of side effects from the drugs used in the study.

Rifapentine is a antibiotic tablet for treatment of TB infection. Rifapentine is generally safe and well tolerated but side effects have been reported. Most patients taking rifapentine will notice that their urine, tears, sweat and sputum turns red. This is temporary side effect whilst you are taking the drug, and the colour will return to normal once you stop taking the rifapentine. Some patients report feeling generally unwell when taking rifapentine with flu-like symptoms or nausea, loss of appetite and low blood sugar but these symptoms are again temporary and not generally harmful.

Serious complications associated with rifapentine use can occur and include liver dysfunction, kidney dysfunction, or abnormalities with your blood cells. This is rare, and the risk is small. You will be reviewed regularly by our specialist team to monitor you, and you will have weekly blood tests. Another rare complication which has been reported with rifapentine treatment is an allergic type reaction called a hypersensitivity reaction. We will observe you when you take the first dose of rifapentine to make sure you do not have a reaction.

Isoniazid is the second drug you will take to treat TB infection. Isoniazid is generally very well tolerated but can also rarely be associated with liver dysfunction, again we will monitor you closely for this. Abnormalities with your blood cells can also occur with isoniazid treatment which we will monitor for, and skin and nerve reactions have also been reported. We will provide you with a vitamin (pyridxone) to minimise the risk of nerve reactions.

As part of the study, you will need to have blood tests on alternate weeks. On occasion a blood test can be associated with some discomfort but only a small volume of blood is taken which will cause no harm to the body.

**What are the possible benefits of taking part?**

The aim of this study is to improve treatment of TB infection and improve survival in HIV and cryptococcal meningitis. By taking treatment for TB infection, we anticipate you will have reduced chances of developing active TB disease or dying from TB. If you decide to take part, you will be cared for by our specialist meningitis research team and be reviewed daily by our doctors and nurses on the ward. You will be able to regularly ask questions about your health and care as you wish.

**What happens when I leave hospital?**

When you are well enough, you are able to leave hospital. As an outpatient you will need to continue to take treatment for your cryptococcal meningitis and the study treatment for TB infection. You will subsequently be seen in our outpatient department to review your progress with our doctors and nurses. At the follow up visits we will continue to collect information about your progress for 18 weeks to compare the safety and effectiveness of the different TB infection treatments. Counsellors will also talk to you about treatment for HIV.

**What if something goes wrong?**

If you are harmed by taking part in this research project you will be cared for until your condition improves or becomes stable. London School of Hygiene and Tropical Medicine has Clinical Research Insurance to cover the legal liability of the University to research participants. In the unlikely event that you are harmed it is possible to seek compensation through **TBC.** If you wish to complain or have any concerns about any aspect of the way you've been approached or treated during the course of this study, please contact: the study Doctor or study nurse on this number **TBC**

**What will happen to any samples I give?**

If you consent, some of your blood and urine samples will be stored for current and future research studies related to infection and the body's immune response. The aim is to better understand co-infections amongst patients with cryptococcal meningitis, and to improve survival. Samples may be analysed outside of this country. Any samples will have only an identification number and the results will be anonymous.

**Confidentiality**

All information which is collected about you during the course of the research will be kept strictly confidential. Any information about you that leaves the hospital will have your name and address removed so that you cannot be recognised from it. Upon request, participant records will be made available to applicable regulatory entities for study monitoring purposes.

**What will happen to the results of the research study?**

The results from this study will be used to better understand TB and other secondary infections in patients with HIV and cryptococcal meningitis, and will be used in the future to inform improved management strategies for patients.

**Who has reviewed the study?**

This study has been reviewed and approved by the following regulatory and ethics boards: Uganda National Council for Science and Technology, Mulago Research and Ethics Committee and The London School of Hygiene and Tropical Medicine.

**Contact for further Information**

If you have any questions relating to this study, if you should have a research related injury or suffer additional medical problems while you are in the study, please talk to your study nurse or doctor.

**The 24-hour telephone number,** through which you can reach your study doctor or study nurse is **TBC.**

**In case of any questions regarding:**

- Your welfare and rights as a research participant,
- Any questions or complaints not being answered by your study doctors
- You want to talk to someone besides the research team.

you should contact:

- Dr. Nakwagala Frederick Nelson, the Chairman of the **Mulago Research and Ethics Committee (MREC)** on telephone 0414-554008 (mobile: 0772325869), or
- **Uganda National Council for Science and Technology (UNCST)**, Plot 3 Kimera Road; Ntinda, Kampala on telephone 0414-705-513.

If you have any questions about this research study, you can ask them now or contact the above doctors later. The study doctors will see you while in hospital.

**For More Information**

A description of this clinical trial will be available on www.ClinicalTrials.gov, as required by United States Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

# IMPROVE 1HP feasibility RCT consent form

The patient or next of kin should complete the whole of this form themselves

**Please cross out as necessary**

Have you read the patient information sheet? YES/ NO

Have you had an opportunity to ask questions and discuss the study? YES/ NO

Have you received satisfactory answers to all of your questions? YES/ NO

Have you received all of the information which you require? YES/ NO

Do you understand that you are free to withdraw yourself from the study:

At any time
Without having to provide a reason
And without affecting your future medical care YES/ NO

Do you agree to take part in this study? YES/ NO

**The following IS optional, answering "No" will not affect your ability to participate in the study**

Do you agree that your samples (blood and urine) may be used as part of this study to understand secondary infections in patients with cryptococcal meningitis, and that these samples may be stored for this use either in Uganda or outside of the country.

YES/ NO

CONSENT

Your signature below indicates that you have voluntarily decided to participate (or voluntarily decided that your next of kin to participate) in this study after having read and understood all the information in this form. A signed copy of this form will be made available for your/your next of kin's personal records.

_____ _____ _____

PATIENT NAME (Print) Date Signature/Thumbprint

_____ _____ _____

NEXT OF KIN NAME (Print) Date Signature
(If patient unable to consent)

_____ _____ _____

WITNESS NAME (Print) Date Signature
(If patient thumbprint)

_____ _____ _____

NAME OF PERSON TAKING CONSENT (Print) Date Signature

*When completed 1 for volunteer, 1 for research file (both original signatures)*

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