YALE UNIVERSITY
HUMAN INVESTIGATION COMMITTEE

Application to Involve Human Subjects in Biomedical Research
100 FR1 (2015-2)

SECTION I: ADMINISTRATIVE INFORMATION

Title of Research Project: Addiction, HIV and Tuberculosis in Malaysian Criminal Justice Settings			
Principal Investigator: Sheela Shenoi, MD, MPH		**Yale Academic Appointment: Associate Professor**	
Department: Internal Medicine, AIDS Program			
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Campus Phone: 737-6133	**Fax:**	**Pager:**	**E-mail:** sheela.shenoi@yale.edu
Protocol Correspondent Name & Address (*if different than PI*): Ahsan Ahmad			
Campus Phone: 737-6133	**Fax:**	**E-mail:**	ahsan.ahmad@yale.edu
Yale Cancer Center CTO Protocol Correspondent Name & Address (*if applicable*):			
Campus Phone:	**Fax:**	**E-mail:**	
Business Manager:			
Campus Phone :	**Fax :**	**E-mail**	

Faculty Advisor:(required if PI is a student, resident, fellow or other trainee) ☐ **NA**		**Yale Academic Appointment:**	
Campus Address:			
Campus Phone:	**Fax:**	**Pager:**	**E-mail:**

Investigator Interests:

Does the principal investigator, or do any research personnel who are responsible for the design, conduct or reporting of this project or any of their family members (spouse or dependent child) have an incentive or interest, financial or otherwise, that may affect the protection of the human subjects involved in this project, the scientific objectivity of the research or its integrity? Note: The Principal Investigator (Project Director), upon consideration of the individual's role and degree of independence in carrying out the work, will determine who is responsible for the design, conduct, or reporting of the research.

See Disclosures and Management of Personal Interests in Human Research
http://www.yale.edu/hrpp/policies/index.html#COI
o Yes Xo No

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Do you or does anyone on the research team who is determined by you to be responsible for the design, conduct or reporting of this research have any patent (sole right to make, use or sell an invention) or copyright (exclusive rights to an original work) interests related to this research protocol?

o Yes Xo No

If yes to either question above, list names of the investigator or responsible person:

The Yale University Principal Investigator, all Yale University co-investigators, and all Yale University individuals who are responsible for the design, conduct or reporting of research must have a current financial disclosure form on file with the University's Conflict of Interest Office. Yale New Haven Hospital personnel who are listed as co-investigators on a protocol with a Yale University Principal Investigator must also have a current financial disclosure form on file with the University's Conflict of Interest Office. If this has not been done, the individual(s) should follow this link to the COI Office Website to complete the form: http://www.yale.edu/coi/

NOTE: The requirement for maintaining a current disclosure form on file with the University's Conflict of Interest Office extends primarily to Yale University and Yale-New Haven Hospital personnel. **Whether or not they are required to maintain a disclosure form with the University's Conflict of Interest Office, all investigators and individuals deemed otherwise responsible by the PI who are listed on the protocol are required to disclose to the PI any interests that are specific to this protocol.**

SECTION II: GENERAL INFORMATION

1. **Performing Organizations:** Identify the hospital, in-patient or outpatient facility, school or other agency that will serve as the location of the research. Choose all that apply:

a. Internal Location[s] of the Study:

- ☐ Magnetic Resonance Research Center (MR-TAC)
- ☐ Yale Cancer Center/Clinical Trials Office (CTO)
- ☐ Yale Cancer Center/Smilow
- ☐ Yale-New Haven Hospital
- ☐ Cancer Data Repository/Tumor Registry
- ☐ Specify Other Yale Location:
- ☐ Yale University PET Center
- ☐ YCCI/Church Street Research Unit (CSRU)
- ☐ YCCI/Hospital Research Unit (HRU)
- ☐ YCCI/Keck Laboratories
- ☐ Yale-New Haven Hospital—Saint Raphael Campus

b. External Location[s]:

- ☐ APT Foundation, Inc.
- ☐ Connecticut Mental Health Center
- ☐ Clinical Neuroscience Research Unit (CNRU)
- ☐ Other Locations, Specify:
- ☐ Haskins Laboratories
- ☐ John B. Pierce Laboratory, Inc.
- ☐ Veterans Affairs Hospital, West Haven
- ☒ International Research Site (Specify location(s)): University of Malaya CERIA, Kuala Lumpur, Malaysia

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c. Additional Required Documents *(check all that apply)*: ☐ N/A

☐ *YCCI-Scientific and Safety Committee (YCCI-SSC) Approval Date:
☐ *Pediatric Protocol Review Committee (PPRC) Approval Date:
☐ *YCC Protocol Review Committee (YRC-PRC) Approval Date:
☐ *Dept. of Veterans Affairs, West Haven VA HSS Approval Date:
☐ *Radioactive Drug Research Committee (RDRC) Approval Date:
☐ YNHH-Radiation Safety Committee (YNHH-RSC) Approval Date:
☐ Yale University RSC (YU-RSC) Approval Date:
☐ Magnetic Resonance Research Center PRC (MRRC-PRC) Approval Date:
☐ *Nursing Research Committee Approval Date:
☐ YSM/YNHH Cancer Data Repository (CaDR) Approval Date:
☐ Dept. of Lab Medicine request for services or specimens form
☐ Imaging on YNHH Diagnostic Radiology equipment request form (YDRCTO request) found at http://radiology.yale.edu/research/ClinTrials.aspx)

Approval from these committees is required before final HIC approval is granted. See instructions for documents required for initial submission and approval of the protocol. Allow sufficient time for these requests. Check with the oversight body for their time requirements.

2. **Probable Duration of Project:** State the expected duration of the project, including all follow-up and data analysis activities. 5-9 years 9/1/2016-12/31/2025

3. **Research Type/Phase: (Check all that apply)**
   a. **Study Type**
   ☒ Single Center Study
   ☐ Multi-Center Study
   Does the Yale PI serve as the PI of the multi-site study? Yes ☐ No ☒
   ☐ Coordinating Center/Data Management
   ☐ Other:

   b. **Study Phase** ☐ **N/A**
   ☐ Pilot ☐ Phase I ☐ Phase II ☐ Phase III ☐ Phase IV
   ☐ Other (*Specify)*

4. **Area of Research: (Check all that apply)** Note that these are overlapping definitions and more than one category may apply to your research protocol. Definitions for the following can be found in the instructions section 4c:

☒ Clinical Research: Patient-Oriented
☐ Clinical Research: Epidemiologic and Behavioral
☐ Translational Research #1 ("Bench-to-Bedside")
☐ Translational Research #2 ("Bedside-to-Community")
☐ Clinical Research: Outcomes and Health Services
☐ Interdisciplinary Research
☐ Community-Based Research

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5. Is this study a clinical trial? Yes ☒ No ☐

NOTE the current ICMJE (International Committee of Medical Journal Editors) definition of a clinical trial: "any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes." Health-related interventions include any intervention used to modify a biomedical or health-related outcome (for example, drugs, surgical procedures, devices, behavioral treatments, dietary interventions, and process-of-care changes). Health outcomes include any biomedical or health-related measures obtained in patients or participants, including pharmacokinetic measures and adverse events"

If yes, where is it registered?

Clinical Trials.gov registry ☒ pending

Other (*Specify*)

*Registration of clinical trials **at their initiation** is required by the FDA, NIH and by the ICMJE.*

The study is currently listed on ClinicalTrails.gov and is active.

For more information on registering clinical trials, including whether your trial must be registered, see the YCCI webpage, http://ycci.yale.edu/researchers/ors/registerstudy.aspx or contact YCCI at 203.785.3482)

6. Does the Clinical Trials Agreement (CTA) require compliance with ICH GCP (E6)?
Yes ☐ No☒

7. Will this study have a billable service? *A billable service is defined as any service rendered to a study subject that, if he/she was not on a study, would normally generate a bill from either Yale-New Haven Hospital or Yale Medical Group to the patient or the patient's insurer. The service may or may not be performed by the research staff on your study, but may be provided by professionals within either Yale-New Haven Hospital or Yale Medical Group (examples include x-rays, MRIs, CT scans, specimens sent to central labs, or specimens sent to pathology). Notes: 1. There is no distinction made whether the service is paid for by the subject or their insurance (Standard of Care) or by the study's funding mechanism (Research Sponsored). 2. This generally includes new services or orders placed in EPIC for research subjects*.

Yes ☐ No☒

If answered, "yes", this study will need to be set up in OnCore, Yale's clinical research management system, for Epic to appropriately route research related charges. Please contact oncore.support@yale.edu

8.. Are there any procedures involved in this protocol that will be performed at YNHH or one of its affiliated entities? Yes ___ No __X_ *If Yes, please answer questions a through c and note instructions below. If No, proceed to Section III.*

a. Does your YNHH privilege delineation currently include the **specific procedure** that you will perform?

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b. Will you be using any new equipment or equipment that you have not used in the past for this procedure?

c. Will a novel approach using existing equipment be applied?

If you answered “no” to question 8a, or "yes" to question 8b or c, please contact the YNHH Department of Physician Services (688-2615) for prior approval before commencing with your research protocol.

Please note that if this protocol includes Yale-New Haven Hospital patients, including patients at the HRU, the Principal Investigator and any co-investigators who are physicians or mid-level practitioners (includes PAs, APRNs, psychologists and speech pathologists) who may have direct patient contact with patients on YNHH premises must have medical staff appointment and appropriate clinical privileges at YNHH. If you are uncertain whether the study personnel meet the criteria, please telephone the Physician Services Department at 203-688-2615. ***By signing this protocol as a PI, you attest that you and any co-investigator who may have patient contact has a medical staff appointment and appropriate clinical privileges at YNHH****.*

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SECTION IV:
PRINCIPAL INVESTIGATOR/FACULTY ADVISOR/ DEPARTMENT CHAIR AGREEMENT

As the **principal investigator** of this research project, I certify that:

- The information provided in this application is complete and accurate.
- I assume full responsibility for the protection of human subjects and the proper conduct of the research.
- Subject safety will be of paramount concern, and every effort will be made to protect subjects' rights and welfare.
- The research will be performed according to ethical principles and in compliance with all federal, state and local laws, as well as institutional regulations and policies regarding the protection of human subjects.
- All members of the research team will be kept apprised of research goals.
- I will obtain approval for this research study and any subsequent revisions prior to my initiating the study or any change and I will obtain continuing approval of this study prior to the expiration date of any approval period.
- I will report to the HIC any serious injuries and/or other unanticipated problems involving risk to participants.
- I am in compliance with the requirements set by the University and qualify to serve as the principal investigator of this project or have acquired the appropriate approval from the Dean's Office or Office of the Provost, or the Human Subject Protection Administrator at Yale-New Haven Hospital, or have a faculty advisor.
- I will identify a qualified successor should I cease my role as principal investigator and facilitate a smooth transfer of investigator responsibilities.

_____ _____

PI Name (PRINT) and Signature Date

As the **faculty advisor** of this research project, I certify that:

- The information provided in this application is complete and accurate.
- This project has scientific value and merit and that the student or trainee investigator has the necessary resources to complete the project and achieve the aims.
- I will train the student investigator in matters of appropriate research compliance, protection of human subjects and proper conduct of research.
- The research will be performed according to ethical principles and in compliance with all federal, state and local laws, as well as institutional regulations and policies regarding the protection of human subjects.
- The student investigator will obtain approval for this research study and any subsequent revisions prior to initiating the study or revision and will obtain continuing approval prior to the expiration of any approval period.
- The student investigator will report to the HIC any serious injuries and/or other unanticipated problems involving risk to participants.
- I am in compliance with the requirements set forth by the University and qualify to serve as the faculty advisor of this project.
- I assume all of the roles and responsibilities of a Principal Investigator even though the student may be called a PI.

_____ _____

Advisor Name (PRINT) and Signature Date

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Department Chair's Assurance Statement

Do you know of any real or apparent institutional conflict of interest (e.g., Yale ownership of a sponsoring company, patents, licensure) associated with this research project?

☐ Yes (provide a description of that interest in a separate letter addressed to the HIC.)
☐ No

As Chair, do you have any real or apparent protocol-specific conflict of interest between yourself and the sponsor of the research project, or its competitor or any interest in any intervention and/or method tested in the project that might compromise this research project?

☐ Yes (provide a description of that interest in a separate letter addressed to the HIC)
☐ No

I assure the HIC that the principal investigator and all members of the research team are qualified by education, training, licensure and/or experience to assume participation in the conduct of this research trial. I also assure that the principal investigator has departmental support and sufficient resources to conduct this trial appropriately.

_____ _____

Chair Name (PRINT) and Signature Date

_____

Department

YNHH Human Subjects Protection Administrator Assurance Statement

Required when the study is conducted solely at YNHH by YNHH health care providers.

As Human Subject Protection Administrator (HSPA) for YNHH, I certify that:

- I have read a copy of the protocol and approve it being conducted at YNHH.
- I agree to notify the IRB if I am aware of any real or apparent institutional conflict of interest.
- The principal investigator of this study is qualified to serve as P.I. and has the support of the hospital for this research project.

_____ _____

YNHH HSPA Name (PRINT) and Signature Date

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SECTION V: RESEARCH PLAN

1. **Statement of Purpose:** State the scientific aim(s) of the study, or the hypotheses to be tested.

   AIM 1: To conduct several empiric studies of TB screening and treatment strategies in prisoners, including:
   - **a)** Comprehensive TB diagnostic studies, including TB symptoms, chest radiographs, tuberculin skin testing (TST), AFB smear, Gene Xpert, and sputum culture to examine best practice and alternative strategies for TB screening practices in prisons for HIV+ and HIV- prisoners;
   - **b)** A RCT of LTBI prevention strategies among HIV+ and HIV- prisoners with high prevalence of HCV using standard 26-week daily isoniazid (26H) vs short-course weekly isoniazid + rifapentine (12HR);
   - **c)** A 2-arm preference trial comparing post-release treatment completion in patients on OAT (further randomized to MMT vs ~~BPN/NLX)~~ vs no OAT in patients being treated for active or latent TB who are transitioning to the community.

   AIM 2: To use data from specific aim 1 and publicly available data to conduct agent-based modeling for comparative and cost-effectiveness analyses of TB screening and treatment strategies among prisoners with and without HIV, incorporating the contribution of LTBI and prevalent TB on community transmission post-release.

2. **Background:** Describe the background information that led to the plan for this project. Provide references to support the expectation of obtaining useful scientific data.

   Since 2003, Southeast Asia as a region has made major gains in reducing HIV infections and related morbidity and mortality by 37%, yet Malaysia is one of 4 countries in the region (all had major epidemics concentrated in PWIDs) where HIV mortality grew by >20%.[1] Drug injection, primarily of heroin, contributes significantly to evolving HIV epidemics, disability and mortality.[2] Criminalizing drug use rather than expanding risk reduction interventions has resulted in increasing imprisonment and concentration of people with HIV and opioid use disorders within prisons.[3,4] Despite the overlapping and inextricable syndemics of HIV and PWIDs, HIV transmission continues unabated.[5] Mathematical modeling studies of HIV prevention in countries where the HIV epidemic is either concentrated in or is generalizing from a PWID-driven epidemic, demonstrate that the combination of high coverage of opioid agonist and antiretroviral therapy is the best way to avert new infections,[6] irrespective of the HIV prevalence among PWIDs.[7] Opioid agonist maintenance therapies (OAT), however, are the most cost-effective.[6] Moreover, prescribing antiretroviral therapy in HIV+ patients markedly reduces the development of active TB in patients with latent TB infection (LTBI).[8,9]

3. **Research Plan:** Summarize the study design and research procedures using non-technical language that can be readily understood by someone outside the discipline. **Be sure to distinguish between standard of care vs. research procedures when applicable, and include any flowcharts of visits specifying their individual times and lengths**. Describe the setting in which the research will take place.

Study procedures: In the past 5 years, we have documented feasibility with many of the proposed procedures in prisons (e.g., TB screening pilot using diverse diagnostic options, implementing OAT in prison, prescribing study medications, interviewing participants in private study rooms that prison constructed for us with plexiglass doors, using CASI interviews, understanding and

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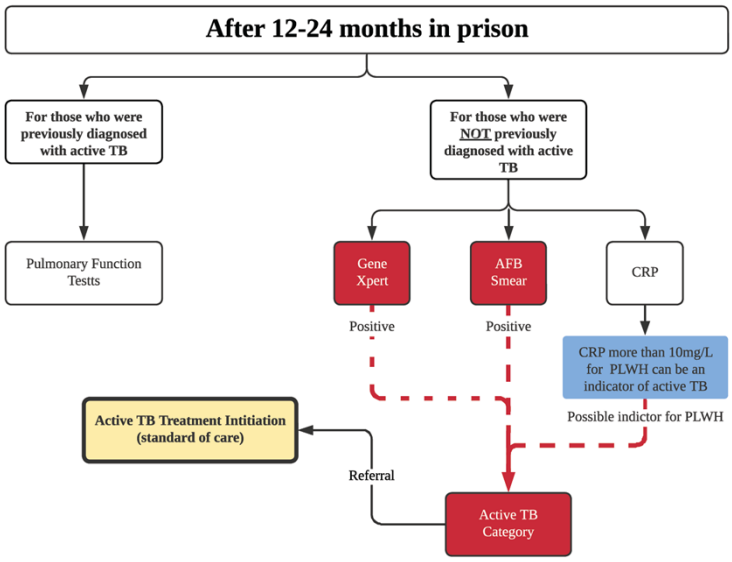
quantifying OAT preferences, etc). [10-16]

Part A: All newly admitted prisoners (80-120 on admission days and all 18 years or older) undergo a complete assessment, including a brief exam and mandatory rapid HIV test by the prison medical unit. New inmates will be pre-screened, and those who meet eligibility criteria will be invited to meet with the research staff and participate in a research study where they will be screened for TB (not currently part of standard care). Inmates interested in participating will be invited to have an individual meeting with a research team member to learn more about the study. Those interested in continuing with study activities will undergo informed consent process that will cover TB screening diagnostics, study procedures, risks, and benefits. After obtaining informed consent, research staff will administer the following study activities: a brief survey, WHO symptom assessment, tuberculin skin testing (TST) with reading after 72 hours, sputum induction on 2 consecutive mornings for AFB smear, TB culture (results back 6-8 weeks using the BACTEC MGIT 960 liquid culture gold standard), and point-of care (POC) Gene Xpert. Each person will have phlebotomy for HBV and HCV Ab, LFTs, and if HIV+, CD4 testing (all of these are POC using Alere™). For those with CD4<50, they will undergo POC low-cost, urinary TB-LAM lateral flow testing (sensitivity=67%) (Alere™ Determine) to identify disseminated TB.[17,18] Additional demographic, drug use, and TB risks will also be assessed along with prison data (release date, previous incarcerations, type of offense). Participants suspected of having active TB will then undergo CXR testing. A TB specialist will review all patients and results, ensuring that patients with suspected TB initiate treatment. All suspected or confirmed cases active TB cases in HIV+ prisoners will have ART initiated after 2 weeks of TB treatment initiation (if CNS TB not suspected) if CD4<50 and within 8 weeks for all others.

For participants with active TB, those remaining in prison after treatment completion (estimated n=40-50), research staff will administer the following study activities within 24 months of treatment completion: WHO TB symptom assessment, pulmonary function tests (PFTs), point-of care (POC) Gene Xpert, and Chest X-ray. Each person will have phlebotomy for C-reactive protein (CRP) as well. For patients living with HIV, we will perform CD4 and VL testing. For participants who did not have TB, and are still in prison (estimated n=300), research staff will administer repeat screening 12-24 months after the first screening: WHO TB symptom screen, POC Gene Xpert, AFB Smear, and Chest-X-ray. Each person will also have phlebotomy for CRP.



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Participants who previously participated in Harapan II Aim 1A who remain in the prison after 12-24 months with active TB or without active TB will be identified by their remaining sentence in prison using administrative data. These participants will be identified by prison officers using their study ID, prison ID and names (no patient names will be recorded in the data to protect confidentiality). These participants will be brought back to the CERiA clinic inside the prison for a pre-screening (to ensure eligibility), and if eligible, will be introduced by a Research Assistant to the proposed additional TB screening using the language in the Participant Information Sheet/Consent Form.

After the Research Assistant reads the Participant Information Sheet/Consent Form, the participant will be asked if he would like to voluntarily participate in the follow up TB screening. If the participant would like to voluntarily participate, he will sign the re-consent form and proceed with the follow up screening. If at any time the participant does not want to continue the follow up, he may stop with no repercussions.

Additionally, we will review prison logs and health records to determine how many patients are diagnosed with TB and HIV, start TB and HIV treatment, and the time to treatment initiation and completion (for TB only) among non-study patients to compare with outcomes study patients. We will abstract data from prison logs without identifiers and will not interact with incarcerated individuals other than the study participants. Additional structural non-patient data pertaining to service delivery, implementation of HIV guidelines, and operations in the prison may also be collected to compare prison HIV and TB care to national and global guidelines (ex. number of medical staff, whether diagnostic or monitoring tools (ex. HIV viral load), medications available on the prison formulary, etc) are available.

Eligibility for Part A includes:
1) Age ≥ 18 years
2) Malaysian citizen
3) Prison sentence ≥ 3 months
4) Absence of active TB within past 2 years of enrollment
5) Newly admitted prison inmate (<2 days)
6) Able to provide informed consent

Part B: Prisoners with LTBI from Aim 1 will be asked to participate in **Part B**. Our preliminary data suggest that >80% of all prisoners have TST+ and 94% of HIV+s and 63% of HIV-s are HCV Ab+.[10,12,13] We have documented both in a systematic review and using empiric data in Malaysia that few prisoners with LTBI receive preventive TB therapy and for those that do, the major factor contributing to treatment non-completion is release from prison and hepatotoxicity.[19] Consequently, WHO provides conflicting guidance on TB preventive therapy in prisoners. In its guidelines on managing TB in closed settings, preventive therapy is not recommended, yet in its HIV treatment guidelines, long-term isoniazid preventive therapy is recommended, especially if TST+. Since these recommendations, a large RCT among non-prisoners compared a once-weekly 12-week regimen of INH/rifapentine (12HR) to daily 26 weeks of isoniazid preventive therapy (IPT: 26H). In terms of TB prevention, efficacy was similar, but patients prescribed short-course 12HR had higher treatment completion rates (82.1% v.69.0%; p<0.001).[20] Since shorter LTBI preventive strategies are likely to improve completion, perhaps overturning previous recommendations based on the best science. A remaining concern, however, is the high prevalence of PWIDs with chronic HCV infection in prison, which might increase hepatotoxicity

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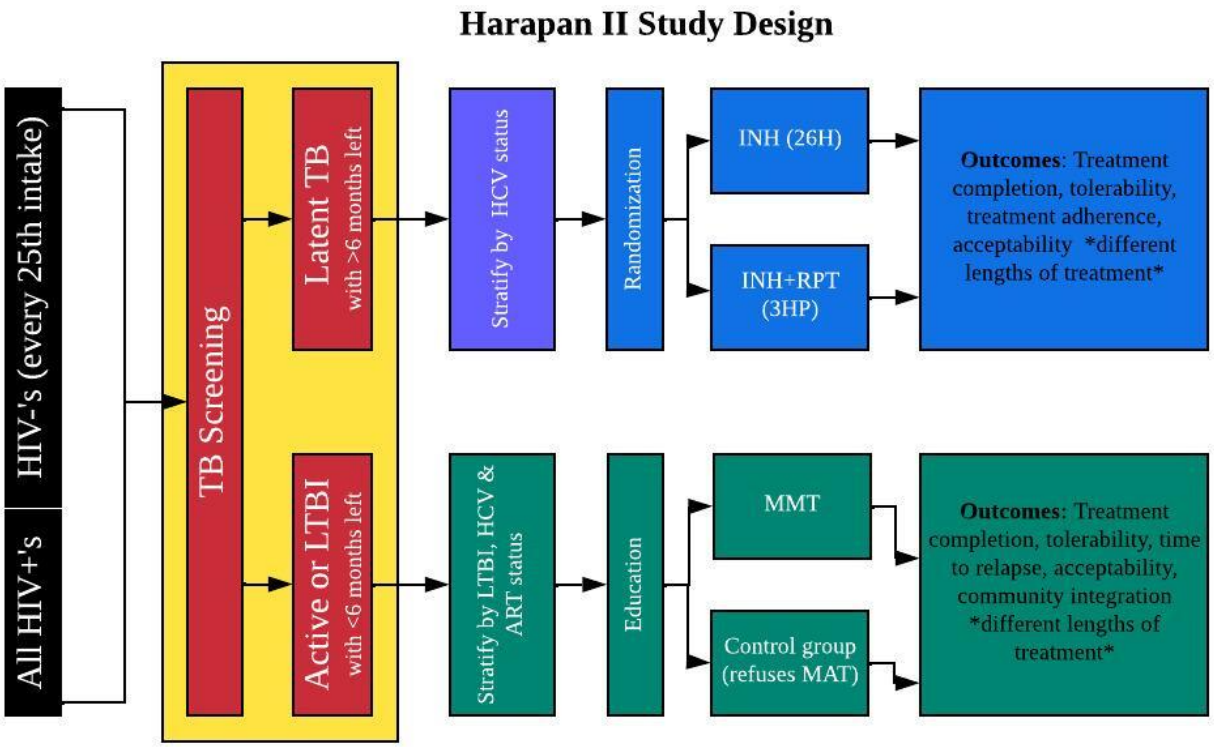
in a 12HR combination since both isoniazid and rifapentine can damage the liver; CDC is calling for studies of 12HR in prisoners, but have not yet funded research. In the absence of studies of 12HR use in prisoners, it is crucial to assess both completion rates and tolerability (especially when high HCV prevalence is present).

Eligibility for Part B includes:

1) Meets inclusion criteria for Part A
2) Has latent TB (HIV+, or TST ≥ 10mm (HIV-)) and no active TB disease
3) ≥6 months before end of sentence to ensure option for treatment completion
4) AST/ALT <5X ULN, or AST/ALT <3x ULN if TBil >2x ULN
5) Not on a protease inhibitor (drug interaction with rifapentine)
6) No known porphyria
7) Not pregnant (women only).

Enrolled participants will undergo block stratified randomization, stratifying on four factors: a) CD4<350 (if HIV+); b) HCV Ab status; c) ART status; and d) opioid dependence. After randomization and allocation to 12HR or 26H, participants will be provided 12HR weekly (12 weeks) and 26H daily (26 weeks) as directly observed therapy. Every 4 weeks, patients will be monitored for AST/ALT, adverse side effects and pregnancy. Premature treatment discontinuation will occur for any DAIDS Grade 4 toxicity, patient refusal to continue, or pregnancy (women only).

Study Design: TB Studies



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Legend: LTBI=latent TB infection; H=isoniazid; HP=isoniazid + rifapentine; MMT= methadone maintenance treatment; BPN/NLX= buprenorphine/naloxone; OAT=opioid agonist treatment; ART= antiretroviral therapy;HCV= hepatitis C virus.

Part C:

A two-arm **preference trial** (no MAT, and methadone) of prisoners with opioid use disorders who are not or are currently being treated for TB and/or HIV, and are about to transition to the community and need to continue their treatment post-release. Patients may or may not be returning to Klang Valley and within 25 km of our research site. We anticipate enrolling 25-50 participants per arm.

Once consented, study participants will be provided an informed decision-making aid that will help them decide if medication-assisted treatment, specifically Methadone, is best for them. Participants will also have the option not to enroll in medication-assisted treatment.

Informed decision-making aid:
Shared decision-making (SDM) is based on the principles of informed consent and patient-centered care, and involves patients actively partnering with their clinicians to make decisions that balance the best evidence for treatment with their personal values and preferences. Such tools using validated formal criteria have been developed in a wide variety of clinical contexts (e.g. cancer screenings, elective surgery, end-of-life care) to help guide patients in weighting risks, benefits and clarifying their values. These tools have demonstrated improved quality of decisions, satisfaction and some clinical outcomes. No such SDM tool exists in OUD treatment, and we ultimately aim to develop such a tool, pilot and evaluate its effect on clinical outcomes, especially in the initiation of and retention in OUD treatment after release from prison. At this time we will conduct focus group discussions to assess what baseline concerns, knowledge, and attitude participants have towards methadone maintenance therapy (MMT) and buprenorphine /naloxone (BPN/NLX). Although BPN/NLX is not new to Malaysia and not yet offered in prison by Ministry of Health, we will give a brief overview of BPN/NLX to the participants prior to the group session. This group discussion will guide the development of the SDM tool that will be used to help prisoners with OUDs decide if MMT is the best option for them.

We will conduct a specialized type of focus group, specifically nominal group technique (NGT), in which participants generate responses to a question and also rank the relative importance of these responses. Written notes as well as audio recording will be made. Groups will be voluntary and ***anonymous***. We will collect demographic information of group participants that will be de-identified, aggregated and decoupled from any individual responses. Data will be analyzed qualitatively for themes as well as quantitatively for frequency of themes and relative rankings across all groups. This data will reveal some of the concerns and beliefs that patients have regarding MAT on presentation and their relative importance in treatment decision making.

We will recruit adults with OUDs from CCSC Kerinchi (community MMT site), Ikhlas (needle/syringe exchange program) and from Kajang prison. Group sessions will last no longer than 1 hour, and will include 6-10 participants per session. Groups will be conducted until a

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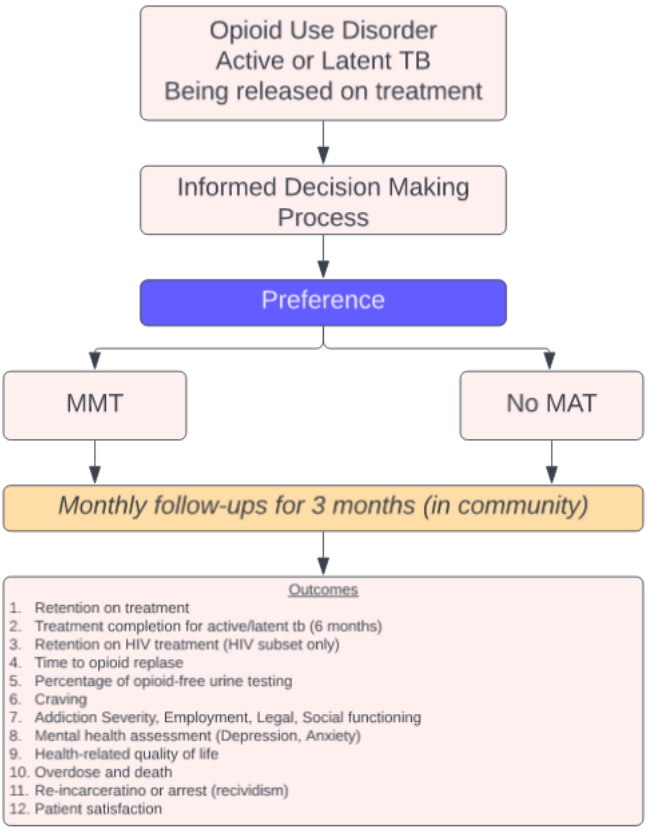
saturation of themes is reached. Participants will undergo informed consent prior to participating, and will be compensated 50RM for their time.



Upon making an informed decision using the SDM developed from the focus groups, those that choose methadone maintenance treatment (MMT) will initiate 5 mg of methadone, 3-4 months prior to release from prison. The dose will increase in 5 mg increments every 7 days (as tolerated) until the daily dose is escalated to at least 80 mg or optimal dose before the date of release. Patients prescribed MMT will receive medication daily in prison, and will receive their medications weekly in form of take-way dosing. MMT will be dispensed at the community research site. All participants will be maintained on medication-assisted treatment and will receive follow-up care for 6 months after release from prison.

After a baseline assessment, our research assistant (RA) would meet the participant at the prison on the day of release to undergo a brief assessment, urine testing and to introduce the patient to our community research site to ensure that s/he can find the site after release and take the participant home so that our research assistants can know where the person is living/residing. This process will also improve trust between the research staff and the participant. Thereafter, all participants will be seen monthly, where they will undergo urine screening and be assessed for alcohol and drug use using timeline follow-back (TLFB), appointments for HIV and/or TB, adherence to HIV and/or TB medications, assessments of legal, employment, family issues using the Lite version of the Addiction Severity Index (ASI), depressive symptoms, health-related quality of life (HRQoL), satisfaction with their treatment. They will also be assessed for diversion (and urine testing).

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The primary outcome will be the proportion completing treatment for active or LTBI. Secondary analyses will compare Kaplan Meier curves using Cox proportion hazards and time to discontinuation. TB treatment adherence will also be measured using MEMS caps and analyzed as we have done previously in TB patients in Ukraine

Eligibility for Part C includes:

1) Meets inclusion for part A, if possible
2) Opioid dependence
3) Has LTBI or active TB disease (based on screening in Part A), or no TB
4) Returning to live in Kuala Lumpur/Klang Valley region (within 25 km of Kerinchi research site), if possible
5) ≤ 6 months before end of sentence
6) AST or ALT <5X ULN
7) Not pregnant (women only).

4. Genetic Testing N/A ☒

A. Describe
   i. the types of future research to be conducted using the materials, specifying if immortalization of cell lines, whole exome or genome sequencing, genome wide association studies, or animal studies are planned
   ii. the plan for the collection of material or the conditions under which material will be received
   iii. the types of information about the donor/individual contributors that will be entered into a database
   iv. the methods to uphold confidentiality

B. What are the conditions or procedures for sharing of materials and/or distributing for future research projects?
C. Is widespread sharing of materials planned?
D. When and under what conditions will materials be stripped of all identifiers?
E. Can donor-subjects withdraw their materials at any time, and/or withdraw the identifiers that connect them to their materials?
   i. How will requests to withdraw materials be handled (e.g., material no longer identified: that is, anonymized) or material destroyed)?

F. Describe the provisions for protection of participant privacy
G. Describe the methods for the security of storage and sharing of materials

5. **Subject Population:** Provide a detailed description of the types of human subjects who will be recruited into this study.

For Aim 1 (a-c), only prisoners will be recruited. Community-based participants from methadone and needle/syringe sites will be recruited solely for the purpose of anonymous focus group discussions that will be used to develop the MAT decision making aid.

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Part A: New intakes from Kajang Prison will be recruited (80-120) per day. Mandatory HIV testing is done on all prisoners. HIV prevalence is 5%. All HIV+ prisoners upon entry will be approached for informed consent. For Part B, only prisoners who have >9 months (preferably 12 months) remaining on their prison sentence will be approached for recruitment. All subjects are expected to be Southeast Asians/Pacific Islanders. While women will represent only 10% of the sample, they will be included. The minimum age is 18 years of age, thus children 18-21 years old will be eligible for participation. Currently, only 2% of HIV+ prisoners are between 18-21 years. For part C, prisoners who have less than 90 days remaining on their prison sentence, but more than 90 days of TB treatment remaining will be approached for recruitment. They must be at least 18 years old, have latent TB infection defined by TST ≥ 5mm (HIV+), or TST ≥ 10mm (HIV-), return to live in Klang Valley (within 25 km of Kerinchi research site), and AST/ALT <5X ULN.

Aim 2 will not include Human Subjects. Data analysis only.

6. **Subject classification:** Check off all classifications of subjects that will be specifically recruited for enrollment in the research project. Will subjects who may require additional safeguards or other considerations be enrolled in the study? If so, identify the population of subjects requiring special safeguards and provide a justification for their involvement.

☐ Children	☐ Healthy	☐ Fetal material, placenta, or dead fetus
☒ Non-English Speaking	☒ Prisoners	☐ Economically disadvantaged persons
☐ Decisionally Impaired	☐ Employees	☐ Pregnant women and/or fetuses
☐ Yale Students	☐ Females of childbearing potential	

NOTE: Is this research proposal designed to enroll children who are wards of the state as potential subjects? ☐ Yes ☐ No (If yes, see Instructions section VII #4 for further requirements)

7. **Inclusion/Exclusion Criteria:** What are the criteria used to determine subject inclusion or exclusion?

Inclusion and Exclusion Criteria:
1a: inclusion:

- Above 18 years old
- Malaysian Citizen
- Newly admitted (<2 days)
- Able to provide consent
- Absence of active TB within 2 years of enrollment
- ≥ 3 month prison sentence

1b inclusion:

- Meets inclusion criteria for part A
- Has latent TB (HIV+, or TST ≥ 10mm (HIV-)) and no active TB disease
- >6 months before end of sentence to ensure option for treatment completion

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- AST or ALT <5X ULN, or AST/ALT <3x ULN if TBil >2x ULN
- Not on a protease inhibitor (drug interaction with rifapentine)
- No known porphyria
- Able to provide informed consent

1c inclusion:

- Meets inclusion criteria for Part A, if possible
- Opioid dependence
- Hast latent TB (HIV+, or TST $\geq$ 10 mm (HIV-)), or active TB infection, or no TB
- Returning to live in Kuala Lumpur/Klang Valley region (within 25 km of Kerinchi research site), if possible
- AST/ALT <5X normal
- $\leq$ 6 months remaining in prison
- Able to provide informed consent

Exclusion Criteria: Pregnant women or women planning to become pregnant will be excluded if we implement methadone or buprenorphine during pregnancy, the infant born to the mother is highly (>60%) likely to develop an infant abstinence syndrome that is avoidable by not providing MMT. If a woman becomes pregnant during the course of the study, MMT will not be discontinued if she is receiving it as withdrawal has resulted in pre-term labor. For women preferring not to be OAT, but who relapse to drug use, entry onto MMT will not be an exclusion criteria for remaining in the study.

8. How will **eligibility** be determined, and by whom?
   Eligibility will be determined by the Research Assistants (RAs) hired by the University of Malaya – CERIA to work on this study. An eligibility screening form will be developed into REDCap, a data collection and management application that will be used by the local RAs.

   Prior to enrollment, laboratory testing will be completed to ensure normal LFTs and urine testing will be completed to ensure that female participants are not pregnant.

9. **Risks:** Describe the reasonably foreseeable risks, including risks to subject privacy, discomforts, or inconveniences associated with subjects participating in the research.

For Aim 1, it is not anticipated that sensitive questions will be asked that will cause undue distress. For those who become distressed or who are identified to have an underlying psychiatric disorder, they will be seen by the Addiction Psychiatrist on this grant. For the prisoners who become distress and the psychiatrist is not IMMEDIATELY available, s/he will be referred to the onside prison doctor for evaluation and treatment according to prison protocol. During initial consent procedures, they will be fully informed about all parts of the study, including the questionnaires, will be asked to read the informed consent form, and will be asked whether they would like to participate in the study. They may choose to withdraw from the study at any point and decide not to complete the survey.

Clinical Risks Associated with Study Participation: There are no adverse clinical risks to

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participating in Aim 2. For Aim 1, because participants will be taking FDA-approved and Malaysian MoH-approved medications, the risks will primarily be for those issues directly related to the medications. Specifically for Part B of Aim 1, participants may be at increased risk for hepatotoxicity due to the high prevalence of former drug injection and HCV coinfection, which might increase the likelihood of liver damage. Though CDC and WHO do not recommend monitoring of LFTs among patients being treated for LTBI, in this case, because of the high prevalence of HCV coinfection, we will monitor for adverse side effects in Part B. The specific risks of the two approved medications for treatment of LTBI include:

Rifapentine: The major side effect in RCTs related to this medication is liver inflammation. The extent to which patients develop this complication is unknown in patients with HIV/HCV coinfection.

Hepatic Effects: Hepatitic inflammation has been described in patients taking Rifapentine. Rifapentine use in patients with abnormal liver function tests and/or liver disease should *be* when considered necessary (e.g., need for treatment of LTBI or active TB) and *only* with caution and close medical supervision. Supervision includes examining for hepatoxicity while examining for jaundice. Rifapentine should be discontinued if signs of liver disease develop or worsen (AST or ALT >5X ULN, or >3X ULN with symptoms of jaundice, nausea or fatigue,). The risk is elevated if administered with other antituberculosis agents (e.g., isoniazid, pyrazinamide) if these drugs are used with rifapentine.[1]

Hyperbilirubinemia (resulting from competition between rifapentine and bilirubin for excretory pathways in the liver) possible; such competition has been reported between rifampin and bilirubin.An isolated report of moderate increase in bilirubin and/or transaminase concentrations is not an indication to interrupt rifapentine therapy; the decision to discontinue therapy should be made after repeating the tests, noting trends in the concentrations, and considering the patient's clinical condition.

Clostridium difficile-associated Diarrhea and Colitis: Treatment with anti-infectives, including rifamycins, may permit overgrowth of clostridia though this is an extremely rare event. Consider *C. difficile*-associated diarrhea and colitis (CDAD; also known as antibiotic-associated diarrhea and colitis or pseudomembranous colitis) if diarrhea develops and manage accordingly with examination of stool and possibly starting empiric metronidazole. Some mild cases of CDAD may respond to discontinuance alone. Manage moderate to severe cases with fluid, electrolyte, and protein supplements; appropriate anti-infective therapy (e.g., oral metronidazole or vancomycin) recommended if colitis is severe.[1]Agents inhibiting peristalsis contraindicated in these patients.

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Drug or Test	Interaction	Comments
β-Adrenergic blocking agents	Potential increased metabolism of the β-adrenergic blocking agent[1]	Dosage adjustment of the β-adrenergic blocking agent may be needed[1]
Antacids		In clinical studies, patients were advised to take rifapentine 1 hour before or 2 hours after antacids[1]
Antiarrhythmic agents (disopyramide, mexiletine, quinidine, tocainide)	Potential increased metabolism of the antiarrhythmic agent[1]	Dosage adjustment of the antiarrhythmic agent may be needed[1]
Anticoagulants, oral (warfarin)	Potential increased warfarin metabolism[1]	Adjustment of warfarin dosage may be needed[1]
Anticonvulsants (phenytoin)	Potential increased phenytoin metabolism[1]	Adjustment of phenytoin dosage may be needed[1]
Antifungals, azoles (fluconazole, itraconazole, ketoconazole)	Potential increased metabolism of the antifungal[1]	Adjustment of antifungal dosage may be needed[1]
Antiretrovirals, HIV entry inhibitors		Maraviroc: Concomitant use not recommended
Antiretrovirals, HIV protease inhibitors (PIs)	Indinavir: Decreased AUC and concentrations of indinavir; no effect on pharmacokinetics of rifapentine[1] Atazanavir, fosamprenavir, lopinavir, nelfinavir, ritonavir, saquinavir: Potential decreased concentrations of the PI[1]	Concomitant use with PIs not recommended[1 14 a] Manufacturer of rifapentine states use with extreme caution, if at all, in patients receiving PIs[1]
Antiretrovirals, nonnucleoside reverse transcriptase inhibitors (NNRTIs)	Delavirdine: Potential increased metabolism of the NNRTI[1] Delavirdine, nevirapine: HIV-infected patients receiving a NNRTI who are receiving rifapentine for TB may have a higher rate of TB relapse than those treated with other rifamycin-based regimens	Concomitant use with NNRTIs, with the exception of efavirenz, is not recommended[14 a]
Barbiturates	Potential increased metabolism of the barbiturate[1]	Adjustment of barbiturate dosage may be needed[1]
Benzodiazepines (e.g., diazepam)	Potential increased metabolism of the benzodiazepine[1]	Dosage adjustment of the benzodiazepine may be needed[1]
Calcium-channel blocking agents (diltiazem, nifedipine, verapamil)	Potential increased metabolism of the calcium-channel blocking agent[1]	Dosage adjustment of the calcium-channel blocking agent may be needed[1]
Cardiac glycosides	Potential increased metabolism of the cardiac glycoside[1]	Dosage adjustment of the

Interactions

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		cardiac glycoside may be needed[1]
Chloramphenicol	Potential increased metabolism of chloramphenicol[1]	Dosage adjustment of chloramphenicol may be needed[1]
Clofibrate	Potential increased metabolism of clofibrate[1]	Dosage adjustment of clofibrate may be needed[1]
Corticosteroids	Potential increased metabolism of the corticosteroid[1]	Dosage adjustment of the corticosteroid may be needed[1]
Dapsone	Potential increased metabolism of dapsone [1]	Dosage adjustment of dapsone may be needed[1]
Doxycycline	Potential increased metabolism of doxycycline [1]	Dosage adjustment of doxycycline may be needed[1]
Erlotinib	Possible decreased erlotinib AUC[b]	Avoid concomitant use if possible[b]
Fluoroquinolones (e.g., ciprofloxacin)	Potential increased metabolism of ciprofloxacin[1]	Dosage adjustment of the fluoroquinolone may be needed[1]
Estrogens/Progestins	Hormonal contraceptives (oral or other systemic): Potential interaction with oral or other systemic hormonal contraceptives[1]	Use nonhormonal methods of contraception[1]
Immunosuppressive agents (cyclosporine, tacrolimus)	Potential increased metabolism of the immunosuppressive agent[1]	Dosage adjustment of the immunosuppressive agent may be needed[1]
Levothyroxine	Potential increased levothyroxine metabolism[1]	Dosage adjustment of levothyroxine may be needed[1]
Macrolides (clarithromycin)	Potential increased clarithromycin metabolism[1]	Dosage adjustment of clarithromycin may be needed[1]
Opiate agonists (methadone)	Potential increased metabolism of methadone[1]	Dosage adjustment of methadone may be needed[1]
Psychotherapeutic agents (amitriptyline, haloperidol, nortriptyline)	Potential increased metabolism of the psychotherapeutic agent[1]	Dosage adjustment of the psychotherapeutic agent may be needed[1]
Quinine	Potential increased metabolism of quinine[1]	Dosage adjustment of quinine may be needed[1]
Sildenafil	Potential increased sildenafil metabolism[1]	Dosage adjustment of sildenafil may be needed[1]
Sulfonylurea antidiabetic agents	Potential increased metabolism of the sulfonylurea agent[1]	Dosage adjustment of the antidiabetic agent may be needed[1]
Theophylline	Potential increased metabolism of theophylline[1]	Dosage adjustment of theophylline may be needed[1]
Tests for serum folate	Standard microbiologic assays for serum folate and	Consider using alternative

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and vitamin B_{12}	vitamin B_{12} are inhibited by therapeutic rifampin concentrations; similar effects may occur with rifapentine[1]	assays to determine serum folate and vitamin B_{12}[1]

Concomitant use with HIV protease inhibitors (PIs) or certain HIV entry inhibitors not recommended unless there are no other choices because rifapentine decreases the therapeutic levels of these medications. Recent data by our group shows that it can be safely administered with efavirenz, the most commonly prescribed ART as first line therapy in Malaysia.

General Precautions

Discoloration of Body Tissues or Fluids

Urine, sweat, sputum, tears, and breast milk may have a red-orange coloration during rifapentine therapy. Soft contact lenses and dentures may become permanently stained. Prisoners in Malaysia do not have access to contact lens or dentures.

Patient Monitoring

In order to avoid excess hepatotoxicity, LFTs will be monitored at baseline.

Specific Populations

Pregnancy and Lactating

Rifapentine is Category C so pregnant and breast-feeding women will be excluded from treatment. Specifically, Rifampin administration during the last few weeks of pregnancy can cause postnatal hemorrhages in the mother and infant that require treatment with vitamin K. Similar effects may occur with rifapentine; appropriate clotting parameters should be evaluated if use of rifapentine is considered necessary during the last few weeks of pregnancy.

Specific Drugs and Laboratory Tests that can be affected by Rifapentine

ISONIAZID

Isoniazid (INH) is the recommended treatment for LTBI by the WHO and CDC and is one of the commonly used medications worldwide. Severe and rarely fatal hepatitis associated with INH therapy has been reported and may occur or may develop even after many months of treatment. The risk of developing hepatitis is age related and increased duration of treatment. Approximate case rates by age are: less than 1 per 1,000 for persons under 20 years of age, 3 per 1,000 for persons in the 20 to 34 year age group, 12 per 1,000 for persons in the 35 to 49 year age group, 23 per 1,000 for persons in the 50 to 64 year age group, and 8 per 1,000 for persons over 65 years of age. The risk of hepatitis is increased with daily consumption of alcohol (alcohol is NOT available to Malaysian prisoners). Precise data to provide a fatality rate for isoniazid-related hepatitis is not available; however, in a U.S. Public Health Service Surveillance Study of 13,838 persons taking isoniazid, there were 8 deaths (0.058% or 0.58 cases per 100,000) among 174 cases of hepatitis (0.012% or 126 cases per 100,000). Thus, drug-induced hepatitis is uncommon and mortality is rare.

Therefore, patients given INH should be carefully monitored and interviewed at monthly intervals. For persons 35 and older, in addition to monthly symptom reviews, hepatic enzymes

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(specifically, AST and ALT (formerly SGOT and SGPT, respectively)) should be measured prior to starting isoniazid therapy and periodically throughout treatment. Usually, enzyme levels return to normal despite continuance of medication, but in some cases progressive liver dysfunction occurs. Other factors associated with an increased risk of hepatitis include daily use of alcohol, chronic liver disease and injection drug use. A recent report suggests an increased risk of fatal hepatitis associated with isoniazid among women, particularly black and Hispanic women. No blacks or Hispanics will be enrolled. More careful monitoring should be considered in these groups, possibly as frequently as monthly. If abnormalities of liver function exceed five times the upper limit of normal, discontinuation of INH should be strongly considered. Liver function tests are not a substitute for a clinical evaluation at monthly intervals or for the prompt assessment of signs or symptoms of adverse reactions occurring between regularly scheduled evaluations. Patients should be instructed to immediately report signs or symptoms consistent with liver damage or other adverse effects. These include any of the following: unexplained anorexia, nausea, vomiting, dark urine, icterus, rash, persistent paresthesias of the hands and feet, persistent fatigue, weakness or fever of greater than 3 days duration and/or abdominal tenderness, especially right upper quadrant discomfort. If these symptoms appear or if signs suggestive of hepatic damage are detected, isoniazid should be discontinued promptly, since continued use of the drug in these cases has been reported to cause a more severe form of liver damage.

Other side effects of INH include minimal drug interactions (none expected with these study participants ... eg, some antiseizure medications), peripheral neuropathy (obviated because we provide pyridoxine), and there are no drug interactions with HIV medications.

Methadone: Methadone is the current standard of care for treating opioid use disorders in Malaysia, and will be provided as part of routine clinical care. The most concerning problem that we are likely to encounter is drug interactions with either TB medication (specifically rifampin) or HIV medications (for which there are many). All patients initiating TB or HIV medications AFTER being stabilized on MMT will be monitored daily for two weeks for symptoms of opioid withdrawal using the Clinical Opioid Withdrawal Scale (COWS). We anticipate, however, that most patients will start their TB medications before receiving OAT and precipitating withdrawal symptoms will be unlikely. For those already on OAT, MMT doses will be increased by 5mg per day for mild symptoms, 10 mg per day for moderate symptoms and 20 mg per day for severe withdrawal using the Clinical Opioid Withdrawal Scale (COWS).

Buprenorphine/Naloxone (BPN/NLX): BPN/NLX, also known by the name SUBOXONE, consists of a mixed medication of buprenorphine (BPN) and naloxone (NLX) in a 4:1 ratio by mass, respectively. BPN is a μ-opioid receptor partial agonist, which functions by partially activating opioid receptors and imitating its effects; however, BPN's effect plateaus, thus giving the user only a minimal effect. NLX is a μ-opioid receptor antagonist with slightly lower affinity to opioid receptors than buprenorphine. When administered in combination with BPN, it aids in further reducing the partial agonist effect of BPN, especially when such is injected. Together, they ameliorate the euphoric and sedative effects of opioids by binding and blocking opioid receptors to reduce cravings by inducing a less intense receptor activation. BPN/NLX is FDA approved to treat opioid use and alcohol use disorders, and is available for use under the tongue or on the inside of the cheek. BPN/NLX has sometimes been a preferred mode of MAT as it has a reduced potential for diversion or abuse, can be taken home for daily self-administration and has shown increased engagement and retention in community-based treatment. (Malta, et al., 2019). Additionally, The buprenorphine/naloxone combination tablet (BPN/NLX) was

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introduced in the Malaysian market in 2006 to reduce potential problems with diversion and abuse. When taken as directed, Naloxone does not interfere with Suboxone's primary ingredient, buprenorphine. The major ingredient in Suboxone, buprenorphine, has undergone in-depth studies since 1978, when it was originally introduced as a method of treating opiate addictions. Clinical trials sponsored by the National Institute on Drug Abuse have found buprenorphine to be effective in: alleviating withdrawal symptoms of opiate drugs, decreasing cravings, reducing illict drug use, blocking the effects of other opiates, and retaining patients in treatment programs.

10. **Minimizing Risks:** Describe the manner in which the above-mentioned risks will be minimized.

Informed Consent: Informed consent will be obtained by the local RAs using an information sheet approved by the Medical Ethics Committee of the University of Malaya Medical Centre. Participants will also complete a standard consent form for the University of Malaya Medical Centre.

Face-to-Face Interviews and surveys/questionnaires: There are minimal risks expected from participating in interviews, such as feeling uncomfortable with certain topics being discussed. As mentioned previously, all participants for interviews will be reminded that their refusal to participate will in no way negatively affect their professional relationship with any of the participating agencies or clinics. If participants do feel uncomfortable about certain questions asked, subjects will be able to choose not to answer the question that makes them uncomfortable. All interviews and consultations will occur in private rooms, to ensure confidentiality. All data will be stored in secure locations. Everyone will be told that the meeting is confidential.

Recruitment: Recruitment procedures are designed to reduce the risk of confidentiality loss for participants. Patients will not be targeted for recruitment in this study. They will visit participating prisons for their routine medical care. They will be reassured that their participation is voluntary and confidential. For participants in Aim 1, recruitment will take place in a private prison room.

Monitoring Adverse Side Effects:
For patients in Aim 1, Part B (trial of 26H vs 12HR) and Part C (MMT, vs. no MAT), patients will be seen monthly clinically for symptoms of hepatitis or neuropathy and LFTs shall be monitored. Anyone whose LFTs increase to >5X ULN, or >3X ULN with symptoms of jaundice, nausea or fatigue, will be stopped from receiving medications and LFTs will be monitored weekly to ensure that LFTs are decreasing. Similarly, if patients develop Grade 3 or higher peripheral neuropathy, they will be discontinued. Of note, LFTs will be measured at baseline and monthly for 3 months for 12HR and monthly x 6 months for 26H.

MMT patients will be seen daily for the first month and may have their medications dispensed less frequently if they have no evidence of using illicit drugs by self-report or urine testing.

11. **Data and Safety Monitoring Plan:** Include an appropriate Data and Safety Monitoring Plan (DSMP) based on the investigator's risk assessment stated below. (Note: the HIC will make the final determination of the risk to subjects.) For more information, see the Instructions, page 24.

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a. What is the investigator's assessment of the overall risk level for subjects participating in this study?
b. If children are involved, what is the investigator's assessment of the overall risk level for the children participating in this study?
c. Include an appropriate Data and Safety Monitoring Plan. Examples of DSMPs are available here http://www.yale.edu/hrpp/forms-templates/biomedical.html for
    i. Minimal risk
    ii. Greater than minimal

Aim 1parts (a-c) requires a DSMB.

Data and Safety Monitoring Board

We will comprise a full Data and Safety Monitoring Board (DSMB), that will include three voting members from colleagues in the field. The PI on this grant is familiar with the implementation of a DSMB; he is currently serving as one of the board members of the NIDA Clinical Trials Network studies examining routine HIV testing among drug users.

The key elements of a DSMB include the following:

1) Selecting experts in the field (HIV, TB, Substance abuse) who will serve as members of the board. If funded, we will select two U.S. and one Malaysian experts to serve on the DSMB. As in other NIDA trials, we will work with NIDA staff to select these individuals. Individuals from NIDA will be responsible for the final invitation to participate on the Board. During the first six months of the study, while final implementation is being conducted, the DSMB will convene to go over their charge, examine the guidance set forth by the study team and to question the PI and biostatisticians about pre-defined endpoints. Once these outcomes and stopping rules are defined, the Board will reconvene at regularly scheduled times to assess outcomes.

   Defining stopping rules. For Aim 1, part B, we will be examining completion and tolerability of two LTBI prevention strategies. The study is not powered to reduce development of active TB, but to establish safety in prisoners who have high prevalence of HCV infection. Tolerability (discontinuation from study medication) will be the primary outcome. All discontinuations will be reviewed by the PI and the team. Death will be brought to the DSMB within 24 hours if medication related (though most deaths are related to TB itself). If the discontinuation rate is 3-fold higher in either group, either in the interim analysis when 50% is enrolled or at any time within study assessment, the study will be stopped for safety purposes and a press release will be made. For Part B, we anticipate a difference between the control group and the two intervention groups of about 40%.
2)
3) Assessment of possible adverse consequences of the various interventions. No specific guidance is available for DSMBs for these kinds of interventions; however, we have considerable experience with CHRP, Project PLUS, Project TRUST, Project CONNECT, Project BEST and other community research studies to provide a specific plan. In fact, in order to collect information about the "safety" of the intervention, we intend to hire a research assistant to gather safety information from three independent sources. These include the weekly study meeting where all active participants are discussed, daily conversations with the Health Educators and weekly conversations with the subject

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comes in for HHRP sessions. These data are rich and include an impressive amount of information to guide an appropriate safety plan for this intervention. The types of information captured below are a number of items that potentially could be an adverse event for participation in this study. The findings from our study will also be reported to the DSMB for them to review and provide feedback, and if necessary, halt or refine the study. These include, but are not limited to:

a. Breaches of confidentiality: To date, we have had one subject refuse to participate in the intervention for fear that someone within his community would recognize him coming to the mobile van on a daily basis and therefore be identified as being HIV+. Two others expressed similar concerns a priori, however these concerns were dispelled as soon as the subject met the DAART-SP who introduced them to the mobile van staff an operation procedures.
b. Severe adverse events associated with increased adherence to ART or TB medications: It is possible that non-adherent subjects will develop severe adverse side effects from properly adhering to a regimen. Positive Transitions, for the subset of subjects who ultimately receive HAART, may have increased levels of adherence and therefore more adverse side effects. We have learned from two examples of this type of experience. One pregnant women developed severe drug-related hepatitis while taking her medications properly. In this case, experience with DAART actually improved her outcome because her community HIV clinician could only reach this patient through our research program to ask her to discontinue her medications. A second case may have died as a consequence of increased adherence to ART. He initially was quite symptomatic and ill from advanced HIV/AIDS with a baseline CD4 = 4. With time and adherence to ART, his CD4 rose and he became asymptomatic and felt better. He began to feel so well that he is believed to have relapsed to drug use (he previously felt too poorly to use drugs) and may have overdosed. Our team pursued an autopsy in this case and learned that an opiate overdose was not the etiology of his death. The cause of death is currently unknown.
c. Assessment of adverse consequences: Several different research staff members will assess subjects in both the MMT and IPT interventions. For those on MMT who receive either HAART or TB Treatment, we will monitor for symptoms of opioid withdrawal. Alternatively, we will monitor for overdose in these subjects, diversion or drug interactions with MMT. We would also monitor for breaches of confidentiality in PT subjects. An initial investigation would be undertaken and simultaneously reported to the IRB using standard university procedures.
d. Confidentiality of research data: Breaches of confidentiality regarding research data are more difficult to detect. For that reason, we have in place a number of safeguards including double-locked doors, locked file cabinets, confidential and dedicated fax machine and double password-protected computers. In accordance with federal and university policy, all research personnel are compliant with HIPAA training. If any breach of data confidentiality were detected, we would use similarly detailed procedures for report to the PI and IRB simultaneously.

e. Complications from MMT: In this study, we will monitor for adverse consequences in a standard way. First, drug interactions between buprenorphine and HIV antiretrovirals have not been extensively evaluated. Efavirenz and nevirapine have been associated with reductions in methadone levels, and precipitated clinical withdrawal. In cases where we can detect symptoms of opiate withdrawal, we will increase the methadone dose to treat the symptoms of withdrawal. Dr. Altice was the first clinician to report cases of opiate withdrawal among patients receiving HAART and methadone and is currently investigating other pharmacokinetic interactions between methadone and buprenorphine with antiretroviral drug interactions. Methadone may

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result in opiate excess. Patients are observed daily by the methadone nurse who will refer any subject noted to have excess sedation to the physician to assess dosing. Moreover, we will assess drug interaction with methadone and NNRTIs and rifampin through administration of the COWS for up to three weeks after any two medications are combined that are known to impact opiate levels. Last, we will recommend that all women use barrier contraceptives to prevent pregnancy. For women receiving MMT and who become pregnant, we will continue to monitor them and their newborn infant for adverse consequences. Any such adverse events will be reported to our IRB, and when indicated, to the drug manufacturer if a pharmacokinetic drug interaction is identified.

d. For multi-site studies for which the Yale PI serves as the lead investigator: N/A
   i. How will adverse events and unanticipated problems involving risks to subjects or others be reported, reviewed and managed?
   ii. What provisions are in place for management of interim results?
   iii. What will the multi-site process be for protocol modifications?

12. **Statistical Considerations:** Describe the statistical analyses that support the study design.

Analytical Plan for Aim 1

Part A: International guidelines recommend TB screening for prisoners, but they do not offer any specific guidance on how to most effectively screen them, especially given restricted budgets (especially for prisoners) in resource-constrained settings. We hypothesize that HIV+ prisoners should be prioritized for screening since TB incidence is minimally 10% per year (higher in Malaysian prisoners based on our previous pilot data) vs 10% lifetime in HIV-s. We also hypothesize that a number of screening methods are available, but will have differential impact on prevalence, incidence and transmission to others (including to prison staff). Precision in the estimates will be used for calculations in Aim 2. All analyses will conform to the STARD guidelines for diagnostic accuracy reporting (www.stard-statement.org/). Using standard measures for establishing prevalence and incidence of active and LTBI, frequencies will be calculated for categorical variables and median with standard deviation (SD) or interquartile range (IQR) for continuous variables depending on whether the data were normally distributed or not, respectively. Chi square and Student t-tests will compare between Xpert-negative/culture-positive and Xpert-positive/culture-positive groups. Sensitivity, specificity, positive (PPV) and negative (NPV) predictive values of the Xpert and their respective 95% confidence intervals (95% CI) will be calculated compared to the results of active TB defined using the gold-standard MGIT 960 liquid culture.[39,40] For variables identified as being strongly collinear with each other (age, duration of drug use and duration of cigarette smoking), final models for diagnostic accuracy will be based on the most optimal goodness-of-fit using the Akaike Information Criterion (AIC). When combining results from multiple screening tests (e.g., symptoms + CXR or symptoms + Gene Xpert), we will examine multiple thresholds using pair measures, or Receiver Operator Curves (ROC), where sensitivity and specificity (or even predictive values) differ across thresholds. Such methods provide better discriminative power when adjusting the threshold (e.g., varying levels of TB symptoms).[41] Using estimates of LTBI of 84% and active TB 10-15% with a 95% CI and SE=0.025 among a cross-sectional population of ~4800 HIV+ prisoners, a sample size of 214 HIV+ and 214 HIV- participants would be needed. Thus, a sample of 250 HIV- and 250 HIV+ prisoners (N=500) should be more than adequate. No loss to follow-up is expected because sentenced prisoners must serve at least 90 days and can easily complete screening procedures.

Part B: In CDC's original non-inferiority trial of 26H v 12HR, treatment completion differed significantly (67.0% v 82.1%); however, there were no HIV+s (and therefore no ART prescribed)

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and HCV infection was <3%. Therefore tolerability for a longer exposure to 26H may decrease completion further. We will compare the proportion completing TB preventive therapy (no adverse side effects) for the two groups and control for any confounders that may differ after randomization. Using an alpha=0.05 and power=0.8 and a 20% difference (most conservative), we would need 118 per arm. We hypothesize, however, that 26H will be tolerated even less based on studies of IPT hepatoxicity in a RCT of isoniazid in prisoners (21% in with HCV)[42] and HCV+ patients (correlated with longer IPT exposure).[43-45] Thus, even increasing the difference in treatment completion to 20% (still conservative), the sample size would need to be 164. Thus, we will conservatively enroll 177 per arm or 354 patients total. We will analyze the data two ways, including ITT as a difference in proportion of treatment completion used in RCTs. In order to discern factors associated with differences in treatment completion, we will treat the entire recruited sample as a cohort and using Cox regression, examine time to treatment discontinuation between the two groups using Cox Proportion Hazards as well as examine the independent factors associated with treatment discontinuation (e.g., being on ART, HCV status, baseline AST/ALT, CD4 strata, etc).

Part C: Eligibility will be having no TB disease, TB disease or LTBI, on TB medications that must be completed after release, and meet pre-incarceration DSM-V criteria for opioid dependence. We will compare a control group of prisoners choosing no OAT and compare them to OAT patients. Even though we anticipate 15-20% attrition, we will count missing=failure to be conservative and will censor the data based on the mid-point between the last and the missed visit. The primary outcome will be the proportion completing treatment for active or LTBI. Secondary analyses will compare Kaplan Meier curves using Cox proportion hazards and time to discontinuation. TB treatment adherence will also be measured using MEMS caps and analyzed as we have done previously in TB patients in Ukraine.

For the FGDs, data will be analyzed qualitatively for themes as well as quantitatively for frequency of themes and relative rankings across all groups. This data will reveal some of the concerns and beliefs that patients have regarding MAT on presentation and their relative importance in treatment decision making.

SECTION VI: RESEARCH INVOLVING DRUGS, BIOLOGICS, RADIOTRACERS, PLACEBOS AND DEVICES

If this section (or one of its parts, A or B) is not applicable, state N/A and delete the rest of the section.

A. DRUGS, BIOLOGICS and RADIOTRACERS

1. **Identification of Drug, Biologic or Radiotracer:** What is (are) the **name(s)** of the drug(s) biologic(s) or radiotracer(s) being used? Identify whether FDA approval has been granted and for what indication(s).
Rifapentine and Isoniazid. Both are approved by the FDA.
Methadone is an FDA-approved medicine currently in Malaysia, and standard of care in Prison

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B. DEVICES

1. Are there any investigational devices used or investigational procedures performed at Yale-New Haven Hospital (YNHH) (e.g., in the YNHH Operating Room or YNHH Heart and Vascular Center)? ☐Yes ☒No *If Yes, please be aware of the following requirements*: NOT APPLICABLE

a

SECTION VII: RECRUITMENT/CONSENT AND ASSENT PROCEDURES

1. Targeted Enrollment: Give the number of subjects:

a. targeted for enrollment at Yale for this protocol__80-120 per day will be recruited; 300-375 will be enrolled in parts b & c_

b. If this is a multi-site study, give the total number of subjects targeted across all sites__N/A_

2. Indicate recruitment methods below. Attach copies of any recruitment materials that will be used.

☐ Flyers	☐ Internet/Web Postings	☐ Radio
☐ Posters	☐ Mass E-mail Solicitation	☐ Telephone
☐ Letter	☐ Departmental/Center Website	☐ Television
☐ Medical Record Review	☐ Departmental/Center Research Boards	☐ Newspaper
☐ Departmental/Center Newsletters	☐ Web-Based Clinical Trial Registries	
☐ YCCI Recruitment database	☐ Clinicaltrials.gov Registry (do not send materials to HIC)	
☒ Other (describe): Information sessions		

3. Recruitment Procedures:

a. Describe how potential subjects will be identified.

AIM 1:
Part A: Recruitment will take place among all new prison intakes as noted above. Informed consent procedures will occur in our private room in the prison medical unit with a closed door but plexiglass window so that we can assure the prison staff that security regulations are not being breached. The risks and benefits of the study will be described. The risks are minimal and include phlebotomy of 30cc of blood (2 tbsp), chest radiograph (minimal radiation exposure) and expectoration of sputum.

Part B: Among those in Part A who have LTBI and who otherwise meet eligibility criteria, they will undergo informed consent in the private research room at the prison with a plexiglass door in a similar manner as done for Part A.

Part C: Among those in Part A who have LTBI or active TB, 6 months or less remaining in prison and who otherwise meet eligibility criteria, they will undergo informed consent in the private research room at the prison with a plexiglass door in a similar manner as done for Part A.

Participants in Parts A and B will NOT be compensated for ANY research activities while within the prison. This is done to avoid any real or perceived level of coercion. Participants in Part C, however, will receive mobile flip phones, with calling minutes added every month of follow-up. The mobile phones will be used to communicate with participants to facilitate scheduling follow-up appointments post-prison release. Participants who already have their own personal mobile phone prior to prison

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release can use their personal devices and will still be offered to have minutes added to their phone each month. To thank participants for participating in our study they will be offered the option to keep the mobile phone at the end of the study or receive the monetary equivalent of the mobile phone (RM50 or ~16.67).

AIM 2: No human subjects will be used.

b. Describe how potential subjects are contacted.

Subjects will be contacted in the prison and asked if they would like to learn more about the project.

c. Who is recruiting potential subjects?

Part A: New intakes from Kajang Prison will be recruited daily. Mandatory HIV testing is done on all prisoners. HIV prevalence is 5%. All prisoners that meet pre-screening eligibility and who are interested in participating in the study will be approached for informed consent. For Part B, only prisoners who have >6 months (preferably 12 months) remaining on their prison sentence will be approached for recruitment. For Part C, prisoners who have less than 6 months remaining on their prison sentence will be approached for treatment.

Subjects will be recruited by local research assistants.

4. Screening Procedures

a. Will email or telephone correspondence be used to screen potential subjects for eligibility prior to the potential subject coming to the research office? ☐ Yes ☒ No

b. If yes, identify below all health information to be collected as part of screening and check off any of the following HIPAA identifiers to be collected and retained by the research team during this screening process.

HEALTH INFORMATION TO BE COLLECTED:

HIPAA identifiers:

☒ Names

☒ All geographic subdivisions smaller than a State, including: street address, city, county, precinct, zip codes and their equivalent geocodes, except for the initial three digits of a zip code if, according to the current publicly-available data from the Bureau of the Census: (1) the geographic unit formed by combining all zip codes with the same three initial digits contains more than 20,000 people, and (2) the initial three digits of a zip code for all such geographic units containing 20,000 or fewer people is changed to 000.

☒ Telephone numbers

☒ Fax numbers

☒ E-mail addresses

☒ Social Security numbers

☒ Medical record numbers

☐ Health plan beneficiary numbers

☒ Account numbers

☒ All elements of dates (except year) for dates related to an individual, including: birth date, admission date, discharge date, date of death, all ages over 89 and all elements of dates (including year) indicative of such age, except that such ages and elements may be aggregated into a single category of age 90 or older

☐ Certificate/license numbers

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☐ Vehicle identifiers and serial numbers, including license plate numbers
☐ Device identifiers and serial numbers
☐ Web Universal Resource Locators (URLs)
☐ Internet Protocol (IP) address numbers
☐ Biometric identifiers, including finger and voice prints
☐ Full face photographic images and any comparable images
☐ Any other unique identifying numbers, characteristics, or codes

5. Assessment of Current Health Provider Relationship for HIPAA Consideration:

Does the Investigator or any member of the research team have a direct existing clinical relationship with any potential subject? N/A – HIPAA is not applicable.
☐ Yes, all subjects
☐ Yes, some of the subjects
☒ No

If yes, describe the nature of this relationship.

6. Request for waiver of HIPAA authorization: (When requesting a waiver of HIPAA Authorization for either the entire study, or for recruitment purposes only. Note: if you are collecting PHI as part of a phone or email screen, you must request a HIPAA waiver for recruitment purposes.)

The research will be conducted in Malaysia where HIPAA does not apply.

Choose one:
☐ For entire study
☒ For recruitment purposes only
☐ For inclusion of non-English speaking subject if short form is being used

i. Describe why it would be impracticable to obtain the subject's authorization for use/disclosure of this data;
ii. If requesting a waiver of **signed** authorization, describe why it would be impracticable to obtain the subject's signed authorization for use/disclosure of this data;

By signing this protocol application, the investigator assures that the protected health information for which a Waiver of Authorization has been requested will not be reused or disclosed to any person or entity other than those listed in this application, except as required by law, for authorized oversight of this research study, or as specifically approved for use in another study by an IRB.

Researchers are reminded that unauthorized disclosures of PHI to individuals outside of the Yale HIPAA-Covered entity must be accounted for in the "accounting for disclosures log", by subject name, purpose, date, recipients, and a description of information provided. Logs are to be forwarded to the Deputy HIPAA Privacy Officer.

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7. **Required HIPAA Authorization:** If the research involves the creation, use or disclosure of protected health information (PHI), separate subject authorization is required under the HIPAA Privacy Rule. Indicate which of the following forms are being provided:
   - ☐ Compound Consent and Authorization form
   - ☐ HIPAA Research Authorization Form

HIPPA not relevant to international studies.

8. **Process of Consent/Assent:** Describe the setting and conditions under which consent/assent will be obtained, including parental permission or surrogate permission and the steps taken to ensure subjects' independent decision-making.

Informed Consent: Patients in Aim 1 will undergo informed consent as we have done in all of our previous HIV and TB studies. Our previous experience has been high (near 100%) for participating in TB screening studies. Of note, HIV testing is mandatory for prisoners and their status will already be known. The Prisons Department has provided our team with dedicated research space for both our HIV and TB studies, including well-ventilated rooms for conducting interviews. Each room has a large plexiglass window built into the door so that prisoners can enter the room with research staff and a prison guard can watch, but not hear the any informed consent procedures nor receipt of any interview data. Research assistants who are NOT employed by the prison will perform all informed consent procedures. Any Information or advertising information sheets will be approved by the IRBs at both Yale and the University of Malaya. All participants will be reminded that their refusal to participate will in no way negatively affect their relationship with the prison officials, the prison health system or any participating medical sites in the community either during the conduct of the research or into the future. For Aim 1B, 1C and the FGD an information sheet and separate consent document approved by the University of Malaya Medical Center will be used to consent the inmates.

9. **Evaluation of Subject(s) Capacity to Provide Informed Consent/Assent:** Indicate how the personnel obtaining consent will assess the potential subject's ability and capacity to consent to the research being proposed.

The study interviewers are trained in interviewing and will assess the subject's understanding through verbal responses and non-verbal cues. Interviewers will ask open ended questions while introducing the details of the study to the subject such as "Can you tell me what you understood from our discussion?" or "What should you do if you want to stop participating in this study?" and will use IRB approved consent forms during informed consent procedure. If the interviewer determines that the subject does not fully comprehend the study purpose and his or her role as a participant, the subject will not be consented and will not be eligible for the study.

10. **Documentation of Consent/Assent:** Specify the documents that will be used during the consent/assent process. Copies of all documents should be appended to the protocol, in the same format that they will be given to subjects.
An Information Sheet and separate consent form, approved by the University of Malaya Medical Center, will be used for each eligible participant.

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11. Non-English Speaking Subjects: Explain provisions in place to ensure comprehension for research involving non-English speaking subjects. If enrollment of these subjects is anticipated, translated copies of all consent materials must be submitted for approval prior to use.

All documents including data collection instruments and informed consent forms will be translated into Bahasa Malaysia and administered by research assistants who speak the language.

12(a) As a limited alternative to the above requirement, will you use the short form* for consenting process if you unexpectedly encounter a non-English speaking individual interested in study participation and the translation of the long form is not possible prior to intended enrollment?
YES ☐ NO ☒

Note* If more than 2 study participants are enrolled using a short form translated into the same language, then the full consent form should be translated into that language for use the next time a subject speaking that language is to be enrolled.

Several translated short form templates are found on our website at: http://www.yale.edu/hrpp/forms-templates/biomedical.html. If the translation of the short form is not available on our website, then the translated short form needs to be submitted to the IRB office for approval via amendment prior to enrolling the subject. ***Please review the guidance and presentation on use of the short form available on the HRPP website.***

If using a short form without a translated HIPAA Research Authorization Form, please request a HIPAA waiver in the section above.

12. Consent Waiver: In certain circumstances, the HIC may grant a waiver of signed consent, or a full waiver of consent, depending on the study. If you will request either a waiver of consent, or a waiver of signed consent for this study, complete the appropriate section below.

☒ **Not Requesting a consent waiver**
☐ **Requesting a waiver of signed consent**
☐ **Requesting a full waiver of consent**

A. Waiver of **signed** consent: (Verbal consent from subjects will be obtained. **If PHI is collected, information in this section must match Section VII, Question 6**)

☐ **Requesting a waiver of signed consent for Recruitment/Screening only**

If requesting a waiver of signed consent, please address the following:
a. Would the signed consent form be the only record linking the subject and the research?
☐ Yes ☐ No
b. Does a breach of confidentiality constitute the principal risk to subjects?
☐ Yes ☐ No

OR

c. Does the research activity pose greater than minimal risk?
☐ Yes ***If you answered yes, stop. A waiver cannot be granted.*** Please note: Recruitment/screening is generally a minimal risk research activity
☐ No

AND

d. Does the research include any activities that would require signed consent in a non-research context? ☐ Yes ☐ No

☐ **Requesting a waiver of signed consent for the <u>Entire Study</u> (**Note that an information sheet may be required.)

If requesting a waiver of signed consent, please address the following:
a. Would the signed consent form be the only record linking the subject and the research?
☐ Yes ☐ No
b. Does a breach of confidentiality constitute the principal risk to subjects?
☐ Yes ☐ No

OR

c. Does the research pose greater than minimal risk? ☐ Yes ***If you answered yes, stop. A waiver cannot be granted.*** ☐ No

AND

d. Does the research include any activities that would require signed consent in a non-research context? ☐ Yes ☐ No

B. **<u>Full waiver</u>** <u>of consent:</u> (No consent from subjects will be obtained for the activity.)

☐ **Requesting a waiver of consent for <u>Recruitment/Screening</u> only**

a. Does the research activity pose greater than minimal risk to subjects?
☐ Yes ***If you answered yes, stop. A waiver cannot be granted.*** Please note: Recruitment/screening is generally a minimal risk research activity
☐ No
b. Will the waiver adversely affect subjects' rights and welfare? ☐ Yes ☐ No
c. Why would the research be impracticable to conduct without the waiver?
d. Where appropriate, how will pertinent information be returned to, or shared with subjects at a later date?

☐ **Requesting a full waiver of consent for the <u>Entire Study</u> (Note: If PHI is collected, information here must match Section VII, question 6.)**

If requesting a full waiver of consent, please address the following:

a. Does the research pose greater than minimal risk to subjects?
☐ Yes ***If you answered yes, stop. A waiver cannot be granted.***

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☐ No
b. Will the waiver adversely affect subjects' rights and welfare? ☐ Yes ☐ No
c. Why would the research be impracticable to conduct without the waiver?
d. Where appropriate, how will pertinent information be returned to, or shared with subjects at a later date?

SECTION VIII: PROTECTION OF RESEARCH SUBJECTS

Confidentiality & Security of Data:

a. What protected health information (medical information along with the HIPAA identifiers) about subjects will be collected and used for the research?

b. How will the research data be collected, recorded and stored?

AIM 1: For Parts (A-C), all interview data will be recorded using a PC tablet and uploaded directly into REDCap, a data collection system using wireless internet (available within our prison research offices). All clinical data will be returned to the prison clinic and to the research staff and recorded directly in the participant database. All study interviews, done through REDCap, will be recorded without personal identifiers and only the PIs, study coordinator, and data managers will have access to the Link File to study number and identifiers. Uploaded data will go directly into the REDCap database. The data will be cleaned by the Data Management team.

c. How will the digital data be stored? ☐ CD ☐ DVD ☐ Flash Drive ☐ Portable Hard Drive ☒ Secured Server ☒ Laptop Computer ☐ Desktop Computer ☐ Other

d. What methods and procedures will be used to safeguard the confidentiality and security of the identifiable study data and the storage media indicated above during and after the subject's participation in the study?
Do all portable devices contain encryption software? ☒ Yes ☐ No
If no, see http://hipaa.yale.edu/guidance/policy.html

All research staff members have undertaken Human Subjects' training and know the importance of maintaining confidentiality of the participants' information. Staff members refer to study subjects by study number to maintain their privacy. All data and study instruments which are recorded by study number only are maintained in secure password-protected computers and locked cabinets at Ceria at the University of Malaya and at the Yale AIDS program.

e. What will be done with the data when the research is completed? Are there plans to destroy the identifiable data? If yes, describe how, by whom and when identifiers will be destroyed. If no, describe how the data and/or identifiers will be secured.

The data will be stored in the manner noted above for at least seven years after completion of the study. Storage will be without individual identifiers. These data will be analyzed so that the findings can contribute to scientific literature that could be used to develop effective interventions for prisoners with LTBI or active TB disease.

f. Who will have access to the protected health information (such as the research sponsor, the investigator, the research staff, all research monitors, FDA, Yale Cancer Center Data and Safety Monitoring Committee (DSMC), SSC, etc.)? (please distinguish between PHI and de-identified data)

The Principal Investigator and research staff will have access to collected data.

g. If appropriate, has a Certificate of Confidentiality been obtained? The research is covered by a CoC since it is NIH-funded.

h. Are any of the study procedures likely to yield information subject to mandatory reporting requirements? (e.g. HIV testing – reporting of communicable diseases; parent interview -incidents of child abuse, elderly abuse, etc.). Please verify to whom such instances will need to be reported.

We plan to report any infectious disease we identify (eg, HIV, TB) to the local authorities in accordance with the local reporting requirements.

SECTION IX: POTENTIAL BENEFITS

Potential Benefits: Identify any benefits that may be reasonably expected to result from the research, either to the subject(s) or to society at large. (Payment of subjects is not considered a benefit in this context of the risk benefit assessment.)

The benefits for AIM 1 are numerous. For Part A, identifying the optimal TB screening strategy for prisoners, will guide prison care worldwide, but especially in LMICs. For Part B, the potential benefits are that we may identify that providing a SHORT-COURSE INH/RIFAPENTINE (12HR) course results in INCREASED LTBI completion rates and LOWER or even SIMILAR toxicity. As such, it would greatly improve LTBI treatment strategies for HIV+ prisoners who are at profoundly high risk for developing active TB. For Part C, the benefits of participating in this study include being better informed about available medication-assisted treatment options, receiving a medication-assisted treatment of their choice to manage their opioid use disorder, and receiving healthcare for TB management.

SECTION X: RESEARCH ALTERNATIVES AND ECONOMIC CONSIDERATIONS

1. **Alternatives:** What other alternatives are available to the study subjects outside of the research?

The alternative to participation in the study is non-participation. Subjects who do not wish to participate in this study may obtain healthcare, drug treatment, and other services through standard means in the prison.

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2. **Payments for Participation (Economic Considerations):** Describe any payments that will be made to subjects, the amount and schedule of payments, and the conditions for receiving this compensation.

   Participants in Parts A , B and C will NOT be compensated for ANY research activities while within the prison. This is done to avoid any real or perceived level of coercion. Participants in Part C, however, will be paid for their time for research interviews **post-release only** (RM50 or ~$16.67 per interview). This amount is intended to cover their time and transportation costs to attend the interview.

3. **Costs for Participation (Economic Considerations):** Clearly describe the subject's costs associated with participation in the research, and the interventions or procedures of the study that will be provided at no cost to subjects.

   Participants will not have any costs associated with this research.

4. **In Case of Injury:** This section is required for any research involving more than minimal risk.
   a. Will medical treatment be available if research-related injury occurs?
   b. Where and from whom may treatment be obtained?
   c. Are there any limits to the treatment being provided?
   d. Who will pay for this treatment?
   e. How will the medical treatment be accessed by subjects?

   Any possible adverse drug experiences will be referred to and evaluated by a licensed clinician at the prison. If needed, the subject will be referred to an infectious disease specialist for treatment. Costs for treatment will be the same as the cost for any other treatment provided at the prison. In cases when the prison clinicians cannot be contacted, the client will be assessed and treated with backup from the site Co-I who is a medical doctor.

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