FORM TECH-4. DESCRIPTION OF APPROACH, METHODOLOGY AND WORK PLAN FOR PERFORMING THE ASSIGNMENT

(For small or very simple assignments the Bank should omit the following text in Italic)

[*Technical approach, methodology and work plan are key components of the Technical Proposal. You are suggested to present your Technical Proposal (50 pages, inclusive of charts and diagrams) divided into the following three chapters:*

a) Technical Approach and Methodology,

b) Work Plan, and

c) Organization and Staffing,

a) Technical Approach and Methodology. In this chapter you should explain your understanding of the objectives of the assignment, approach to the services, methodology for carrying out the activities and obtaining the expected output, and the degree of detail of such output. You should highlight the problems being addressed and their importance, and explain the technical approach you would adopt to address them. You should also explain the methodologies you propose to adopt and highlight the compatibility of those methodologies with the proposed approach.

1. BACKGROUND

1.0. Rationale

Driven primarily by injection drug use, the HIV/AIDS epidemic in Malaysia has become one of fastest growing HIV/AIDS epidemics worldwide [1, 2]. As of 2010, nearly 70% of all HIV infections in Malaysia were among injection drug users [3]. Despite a growing HIV/AIDS epidemic driven by IDU, Malaysia continues to implement some of the most punitive drug policies worldwide. Like much of Asia, its primary approach to addressing drug use over the past decades has been to confine people who use drugs (PWUDs) or those suspected of using illicit drugs in specialized facilities referred to as compulsory centers for drug users (CCDUs) [4, 5]. Over the last decade, CCDUs have grown exponentially throughout East and Southeast Asia [6] and now detain over an estimated 400,000 individuals annually [7].

CCDUs are operated by governmental agencies, although supervising bodies differ by country [8]. Despite their intended purpose of drug rehabilitation, these centers are custodial and operated primarily by military or security personnel [6, 8]. Grounds for detention in CCDUs range from positive urine toxicology screening to suspicion of illicit drug use [8, 9] and individuals are routinely denied due process. In some cases, individuals may even be detained indefinitely [8-11]. Evidence-based therapies for substance use disorders, such as opioid-substitution therapy (OST), are unavailable in these settings. Instead, military drills, compulsory abstinence and other approaches with unproven efficacy are utilized as rehabilitation measures [8, 10, 12].

CCDUs were first introduced in Malaysia in 1978 and are operated by the National Anti-Drug Agency (AADK). In 2010, 28 detention facilities housed an estimated 6,658 individuals. According to national drug control laws, individuals who screen positive on urine toxicology for any substance classified as illicit under the Dangerous Drug Act (1952) and the Drug Dependence (Treatment and Rehabilitation) Act (1983) and deemed by a government medical officer to be drug-dependent, are mandated to two years of CCDU detention and remain under community supervision for another two years following release [13]. Post-release outcomes among detainees are uniformly poor, with 70-90% of individuals in Malaysian CCDUs relapsing to drug use within one year of release [14] and similarly high relapse rates documented throughout Asia [6, 8].

As a result of international pressure, in 2005, the Malaysian government shifted from implementing only punitive drug control measures to wide-scale expansion of harm reduction initiatives, including methadone maintenance programs and needle and syringe exchange programs (NSEPs) [14-16]. However, CCDUs remain widely utilized and PWUDs continue to be detained in these facilities without access to evidence-based treatment. More recently, however, the National Anti-Drug Agency (AADK) has begun to transition towards an evidence-based approach to drug rehabilitation. In July, 2010, AADK began opening voluntary drug treatment facilities - 'Cure and Care' (C&C) centers - that provide methadone to those who are opioid-dependent. There are currently eight such facilities, with another four slated to be open in the coming year. The creation of these facilities has signaled growing momentum for reform of Malaysia's national drug policy. However, the efficacy of this new model of care being introduced has yet to be assessed and compared against the forced rehabilitation system, Pusat Serenti, which has long been designated as the primary national drug rehabilitation system. The focus of the proposed project is thereby to compare drug-related and other health and social outcomes between opioid-dependent individuals who have undergone rehabilitation in Pusat Serenti and opioid-dependent individuals engaged in evidence-based drug treatment in the new C&C centers.

1.1. Potential benefits of the study to participants

Participants may benefit indirectly from the possible findings of the study. Detention has been the primary approach to addressing drug use and dependence in Malaysia and should our findings support reform of this policy, it may lead AADK to focus on provision of evidence-based treatment for PWUDs rather detention and criminalization of this population. This would mean that PWUDs in Malaysia would have significantly greater access to much-needed health services, improving not only health-related outcomes but also quality of life, social stability and functioning, and community integration.

1.2. Formative research

In 2010, 100 HIV-infected detainees in two CCDU facilities were surveyed and assessed for their drug use history, addiction severity and drug-related HIV risk behaviors in addition to their access to HIV treatment and care [17]. Participants reported a lifetime mean of 3.0 prison incarcerations and 2.3 CCDU detentions. We found that pre-detention substance use disorders were highly prevalent, with 95% meeting DSM-IV criteria for opioid dependence, and 93% having substantial or high addiction severity based on the DAST-10. Heroin was the most commonly cited (94%) drug of choice; however use of multiple substances in the 30 days prior to detention was reported by 76% of participants and 40% reported daily use of multiple substances. Ninety-five percent had ever injected drugs (IDU) and 82% reported IDU in the 30 days prior to detention, with 65% reporting daily heroin injection and 22% reporting daily injection of multiple substances. Despite being detained for a mean of 7.5 months, 86% of participants reported cravings for opioids, while 58% reported cravings for methamphetamines. Concern about relapsing to drug use after release was reported by nearly all (87%) subjects. Prior experience with medication-assisted treatment was limited, with only 24% reported ever having undergone formal treatment with methadone and 15% with buprenorphine.

In the same year, a respondent-driven sampling study was conducted to assess HIV prevalence, access to HIV treatment and prevention and HIV risk behaviors among 460 adult, active injection drug users in Klang Valley, Malaysia [18]. Drug use and other drug-related characteristics were fairly similar to our sample of CCDU detainees. We found that 99.1% of individuals met DSM-IV criteria for opioid dependence, and 90% reported substantial or high addiction severity. An overwhelming 84% had ever been incarcerated in prison, with a lifetime mean of 3.7 detentions. Similarly, 61.5% had ever been detained in a CCDU with a lifetime mean of 1.7 detentions. Only 9.3% reported ever having undergone formal treatment with methadone and 12.6% with buprenorphine. These data have led us to believe the baseline characteristics between the two comparison groups in the present study may be very similar.

In addition, we are currently conducting a study examining MMT and behavioral outcomes among HIV-infected, opioid-dependent individuals being released from prison and many of the lessons learned from this study and effective operational procedures will be adapted to the present research study (unpublished findings).

We have used the implementation expertise and data gained from these prior studies to inform the conceptualization, design and implementation of the present study. These previous studies have helped us to identify key secondary factors that should be assessed in this comparative evaluation, such as frequency of police harassment, and have highlighted important operational barriers and facilitators to conducting research with CCDU detainees and active IDUs in the community. This will significantly improve the organization and implementation of the present study, particularly with regard to the procedures used to enhance retention of study participants. Additionally, relevant assessments used in previous instruments that were found to be successful will be adapted for further use in the present study.

1.3. Justification and innovation to conduct this study

This project is a fundamental and timely component to ongoing policy reform efforts in Malaysia. The study involves a direct comparison between a new, evidence-based model of care for PWUDs in Malaysia and the existing system of forced rehabilitation and would provide the first empirical evidence of their comparative efficacy. The study addresses the primary ideological and policy question currently confronting Malaysia's National Anti-Drug Agency (AADK) – to maintain their core punitive approach of forcibly rehabilitating PWUDs or move forward with implementing a new model of care – and will provide evidence specific to the Malaysian context of the differential impact of the two approaches in question.

This project is thereby highly innovative in that it entails a 'real-world' comparison between these two drug rehabilitation systems and observes longitudinally the health and social outcomes resulting from involvement in these systems. The study preserves fidelity to the rehabilitation principle underlying each system. Under one system, individuals are mandated to non-evidence based rehabilitation intended to, by its completion, have successfully 'treated' drug dependence, and thus, in the study, their 'treatment' outcomes will be assessed only after the completion of their 'rehabilitation.' Under the new system of care, individuals voluntarily seeking MMT at a local C&C center are provided with ongoing, evidence-based care as MMT is intended to be long-term and as needed, and thus their 'treatment' outcomes will be assessed throughout the course of their treatment. The study also allows for crossover between the two comparison groups, which would occur naturally. Additionally, the study will be the first to evaluate these domestic strategies using international standards and criteria and will employ validated instruments for measuring opioid dependence and addiction severity. This provides a critical opportunity to introduce these international standards to local systems and interventions. Importantly, a key health outcome that will be assessed will be HIV infection as participants will be regularly HIV-tested over the course of the study. The study will also involve the use of mobile phones in participant follow-up and will contribute evidence on the efficacy of using this technology to assess longitudinal health outcomes in this vulnerable, hard-to-reach population.
Findings from the proposed study would have immediate, and significant, policy implications and would highlight firmly for AADK which approach would be most effective, and most cost-effective, in meeting the agency's primary objectives: rehabilitating PWUDs and curbing the epidemic of IDU and HIV. The study also has important implications for the rest of Southeast Asia and China, where forced 'rehabilitation' systems for PWUDs continue to be the cornerstone of national drug policies. In no other country implementing CCDUs has there been direct comparison of CCDUs to an evidence-based system of care and the present study will therefore be the first of its kind internationally.

2. OBJECTIVES

2.1. Primary objective:

- To determine which rehabilitation approach is more effective in reducing time to relapse to opioid use and level of opioid use and among individuals with opioid dependence

2.2 Secondary objectives:

- To determine which rehabilitation approach is more effective in reducing opioid craving levels, opioid addiction severity, use of other illicit substances, and non-fatal overdose
- To determine which rehabilitation approach is more effective in reducing frequency of drug-related HIV risk behaviors
- To determine which rehabilitation approach is more effective in reducing incident HIV infection
- To determine which rehabilitation approach is more effective in reducing criminal activity and subsequent prison incarceration and detention in CCDUs
- To determine which rehabilitation approach is more effective in improving social stability and social functioning
- To determine which rehabilitation approach is more effective in improving health-related quality of life
- To determine which rehabilitation approach is more cost-effective
- To assess the feasibility of using mobile phone technology to assess longitudinal health outcomes in this marginalized population

3. STUDY DESIGN

3.1 Overall design

This is a prospective study assessing the comparative efficacy of forced rehabilitation and detention and voluntary, outpatient drug treatment in Malaysia's 'Cure & Care" Centers. This study plans to recruit 300 opioid-dependent individuals in Klang Valley, Malaysia, half of whom have just been released from a CCDU and half of whom have just initiated MMT in a 'Cure and Care' Clinic, and compare drug-related and other secondary health and social outcomes between the two groups.

Given that the study is intended to be a comparative evaluation of two 'real-world' interventions as they are actually administered, randomization is not possible. This may limit our ability to infer causality, as intervention effects may be attributable to baseline differences between the two comparison groups – one recruited from a confined setting and another recruited from a community-based treatment center. However, we believe the differences between these two groups may be smaller than they appear. Individuals are confined in CCDUs on the basis of a positive urine test and being designated as drug-dependent by a government medical officer. However, these criteria would also apply to those seeking to initiate MMT in a C&C center. Additionally, from our previous respondent-driven sampling study of 460 active IDUs in Klang Valley, Malaysia, nearly two-thirds had been detained previously in a CCDU (unpublished findings). Detention in a CCDU is a relatively common experience among people who use drugs (PWUDs) in Malaysia given the low criteria for entry and it is likely that many of those recruited from the C&C will have had previous detention experiences. It is possible, however, that there may still be important differences between the two groups with regard to addiction severity, years of drug use and drug injection, criminal behavior, and lifetime incarceration and detention history, and these are factors we intend to identify and control for at the analytical stage to minimize the potential effects of selection bias. However, there may still remain differences we will be unable to control for at the analytical stage.

3.2 Expected duration of subject participation

Participants from both groups will be evaluated for outcomes of interest for 12 months. For individuals recruited from the C&C, this will be 12 months from the first day of their MMT initiation and for individuals recruited from Pusat Serenti, this will be 12 months from the day of their release.

3.3 Selection of participants

3.3.1 Description of population

The study will be conducted among opioid-dependent individuals initiating MMT in C&C Centers and opioid-dependent individuals being released from Pusat Serenti who consent to participating in the study.

3.3.2 Inclusion criteria

Individuals from C&C Centers will be included in the study if they meet ALL of the following criteria:

1. Age 18 years or older
2. Meets DSM-IV criteria for opioid dependence
3. Physically and psychologically capable of understanding and undergoing informed consent process
4. Have come to the C&C to start MMT

Individuals from Pusat Serenti will be included in the study if they meet ALL of the following criteria:

1. Age 18 years or older
2. Meet DSM-IV criteria for opioid dependence
3. Physically and psychologically capable of understanding and undergoing informed consent process
4. Within 90 days of release to Klang Valley region

3.4 Recruitment and retention

3.4.1 Study Sites

Participants will be recruited from both the C&C Center in Sungai Besi and the Pusat Serenti in Serendah. All sites involved have the capacity to comply with the protocol, study-specific procedures, and all applicable regulations. Confidential interview rooms are available at all sites. CERiA will be the primary data management and storage site.

3.4.2 Recruitment

A sequential sampling method will be employed for both comparison groups. The current recruitment aim for this study is 300 opioid-dependent individuals, 150 from the C&C and 150 from Pusat Serenti.

C&C Recruitment Strategy

All individuals who have come to the C&C to initiate MMT will be referred by clinical staff to on-site research assistants (RA). Individuals will be asked by RAs if they are interested in learning more about participating in a health study and if they respond affirmatively, they will be brought to a confidential interview room where the RA will assess their eligibility and describe all aspects of the research study. If they are eligible and agree to participate, they will then undergo the informed consent process. Once informed consent is provided, they will be enrolled in the study. The RA will then provide the participant with the requisite study materials (Informed Consent Form, Study Resource Packet, mobile phone device).

Pusat Serenti Recruitment Strategy
Every two weeks, RAs will obtain from Pusat Serenti staff a list of all detainees who are within 60 days of release. Every individual on the list will be approached regarding participating in a health study. Those who are interested in participating will be further assessed for eligibility in a confidential interview room by an RA, who will describe all aspects of the research study. Eligible individuals interested in participating will then undergo the informed consent process. Once informed consent is provided, individuals will be enrolled in the study.

On the day of the participants' release from Pusat Serenti, an RA will be present at the Pusat Serenti facility and if they still wish to participate in the study, the RA will escort them to CERiA, where the RA will review the informed consent process and provide the participant with the requisite study materials that could not be provided to them during their confinement.

3.4.3 Retention

RAs will be primarily responsible for ensuring study retention. In addition, follow-up will consist of both phone and in-person interviews conducted by RAs. The use of mobile phones in the study is intended to enhance accessibility to participants and increase frequency of follow-up and retention rates (see sections 7.2.2. and 7.3.2. for phone protocol).

In general, the following retention procedures will be used: reminder calls three days in advance of the scheduled in-person appointment will be made to each participant to remind him of the data and time of the next appointment and to determine whether the participant wants to change the appointment or requires pick-up for the appointment; there will be a two-

4. STUDY PROCEDURES

4.1 Study flow chart

Table 1: Overview of Study Activities

Activity	Timeframe												
	Baseline	4 weeks	8 weeks	12 weeks	16 weeks	20 weeks	24 weeks	28 weeks	32 weeks	36 weeks	40 weeks	44 weeks	48 weeks
Type of Interview	Person	Person	Phone	Person	Phone	Phone	Person	Phone	Phone	Person	Phone	Phone	Person
Demographic Questions	X						X			X			X
Current drug use	X	X	X	X	X	X		X	X		X	X	
Drug use history	X						X			X			X
Addiction severity (DAST-10)	X	X	X	X	X	X	X	X	X	X	X	X	X
Opioid Craving Scale	X	X	X	X	X	X	X	X	X	X	X	X	X
Non-fatal overdose	X	X	X	X	X	X	X	X	X	X	X	X	X
Motivation to change drug use	X	X		X			X			X			X
Drug-related HIV risk behaviors	X	X	X	X	X	X	X	X	X	X	X	X	X
Income	X	X	X	X	X	X	X	X	X	X	X	X	X
Employment	X	X	X	X	X	X	X	X	X	X	X	X	X
Days of criminal activity	X	X	X	X	X	X	X	X	X	X	X	X	X
Police harassment	X	X		X			X			X			X
Health-related quality of life (SF-36)	X			X			X			X			X
Social support (Zimet scale)	X			X			X			X			X
MMT assessment	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine Toxicology	X	X		X			X			X			X
HIV testing	X	X		X			X			X			X
Adherence to community follow-up appointments	X	X	X	X	X	X	X	X	X	X	X	X	X

4.2 Outline

Enrollment criteria will be evaluated at a screening visit. Eligible participants who consent to participate will be enrolled immediately. In-person interviews, urine toxicology and HIV testing will be conducted at baseline and weeks 4, 12, 24, 36, 48 and phone interviews will be conducted at weeks 8, 16, 20, 28, 32, 40, 44.

4.3 Screening Visit

The following procedures will be performed during screening:

Informed Consent

Obtaining informed consent is an important step in the study enrollment process. As indicated above, informed consent must be obtained prior to initiating any research activities beyond the screening process. To obtain informed consent, the RA will do the following:

1. Obtain an **Informed Consent Packet** from the Research Coordinator. This packet includes:
    a. Study Information Sheet
    b. Informed Consent Form [2 copies]
    c. Participant Screening Form
    d. Participant Locator Form
    e. Study Resource Packet
2. Provide the participant with a copy of the **Study Information Sheet**. This document provides a brief overview of the purpose, objectives, phases, and activities associated with the study. Give participant time to read the sheet and ask any questions that he may have.
3. Fill out the eligibility criteria checklist in the **Participant Screening Form** to verify that all criteria for enrollment have been met.
4. Lead the participant through the informed consent process and provide the participant with a copy of the **Informed Consent Form.** This document provides a thorough explanation of the risks and benefits a participant faces by enrolling in the study. It also explains a participant's rights as a research subject and includes all contact information that may be necessary. (For those in Pusat Serenti, a paper copy will be provided at the time of release).
5. Once the individual has reviewed the Informed Consent Form, he must sign and date the bottom of the document. Their signature is an acknowledgement of their informed consent and enrollment in the study.
6. Provide the participant with a copy of the **Study Resource Packet**, which includes information on substance abuse treatment and other related medical services in the local area. It should also information on how to contact study personnel. (For those in Pusat Serenti, a paper copy will be provided at the time of release).
7. Fill out the **Participant Locator Form** based on the contact information provided by participant.
8. The RA will then assign the participant a **Study ID Number**, which will be recorded in the **Participant Locator Form**.

9. When they are completed, the RA should place the following documents with identifying information in a locked, secure location:
   a. One copy of signed **Informed Consent Form** [2nd copy is for participant]
   b. Participant Locator Form
   c. Completed Participant Screening Form
10. The RA will also enter information from the **Participant Locator Form** and dates of all scheduled follow-up appointments in the **Participant Tracking Database.**

Additional brief review of informed consent will be conducted with individuals on the day of their release from Pusat Serenti. They will also be provided with the signed copy of the **Informed Consent Form** and **Study Resource Packet** at this point in time.

After the initial screening visit and informed consent process, all subsequent client documents will be identified only with the client's **Study ID Number.**

4.4 Mobile Phone Protocol

Following the informed consent process, the RA will provide the participant with a mobile phone and explain how the phone will be utilized in subsequent interviews, procedures to ensure confidentiality (see section 7.3.2.), and the process of reimbursement for phone interviews via transfer of phone credit.

On the **Participant Locator Form**, the RA will write down the number of the mobile device provided to the participant and identify themselves as the *Phone Contact,* as each RA will be assigned to interview the same clients over the phone during the course of the study to facilitate trust and protection of confidentiality.

To incentivize retention of mobile devices, the RA will also explain that if the device is retained at each of the in-person interviews, participants will receive an added bonus of 20 RM in addition to their normal reimbursement for each interview session.

4.5 Baseline Interview

After obtaining informed consent and providing participants with mobile devices, the RA should immediately conduct the **Baseline Interview**. All scheduled interviews will be self-administered by participants using a **Computer-Assisted Survey Instrument (CASI)** software program. Prior to initiating the CASI Baseline Interview, the RA must provide a brief tutorial on how to use the CASI tablet laptop computer. The Research Assistant must provide a quiet, confidential space for the participant to complete the interview and must remain accessible to the participant should he/she have questions.

4.6 Urine Toxicology

Following completion of the baseline interview, RAs will administer a urine test to participants. Results will be recorded immediately on the de-identified **Toxicology Report Form**, which will only have the client's **Study ID Number.** This information will then be entered into the protected study database and the paper copy will be destroyed.

4.7 HIV Testing

Following completion of the baseline interview, RAs will administer an oral rapid HIV test to participants. Confirmatory testing will be done with a second finger-stick rapid HIV test. Results will be recorded immediately on the de-identified **HIV Test Results Form**, which will only have the client's **Study ID Number.** This information will then be entered into the protected study database and the paper copy will be destroyed.

4.8 Follow-up Appointments

At the end of the initial screening and enrollment interview, the RA must schedule a follow-up appointment for all participants and note the date of the next appointment in the **Participant Tracking Database.** To enhance ease of follow-up for clients, each expected follow-up appointment will have a two-week window period both before and after the expected date, so that if the scheduled time is inconvenient for the client, it can be rescheduled for another time within this window period.

The RAs are responsible for maintaining contact with study participants – this includes scheduling of their follow-up appointments. Every effort should be made to inform and remind participants of their upcoming appointments. Each participant will receive an appointment reminder by phone three days prior to the scheduled interview. If a participant fails to appear for any follow-up appointment, the Research Assistant should attempt to contact the participant through the information contained in the **Participant Locator Form**. Missed follow-ups MUST BE recorded in the **Participant Tracking Database.**

4.9 In-person interview at 4, 12, 24, 36, 48 weeks

The in-person follow-up interview consists of an in-person CASI-interview and urine toxicology.

4.10 Phone interview at 8, 16, 20, 28, 32, 40, and 44 weeks

The phone interview will be an attenuated version of the in-person interview. It will be conducted over the phone by RAs. RAs will call clients from a confidential setting at the time of their scheduled phone interview and ask clients whether they are in a comfortable location to respond to interview questions. If they are not, the interview will immediately be rescheduled so that clients are in confidential setting at the time of the call. Each client will have a unique identifier code the RA will ask for over the phone to verify the

identity of the speaker and the same RA will conduct follow-up interviews with the client over the course of the study so the client can be certain they are speaking with study personnel.

4.11 Unscheduled exit or loss to follow-up of participants

All unscheduled exists or permanent loss to follow-up of participants and any known reason for exist or loss to follow-up will be recorded in the **Particpant Tracking Database.**

4.12 Reimbursement of participants

Participants will be given 50 RM at the end of every in-person interview and will be transferred phone credit at the end of every phone interview. An additional 20 RM will be added to the normal in-person interview reimbursement if the client has retained their study mobile device at that point in time.

5. DATA SOURCES

5.1 ACASI and monthly phone interviews

Participants will take a CASI-based questionnaire at the screening visit, and also at the **4, 12, 24, 36, and 48-week** in-person interviews. All questionnaires will be self-administered by CASI in the local language. If a participant needs assistance with CASI, a study staff member will help him. The administration of questionnaires will take approximately one hour.

The **8, 16, 20, 28, 32, 40, and 44-week** phone interviews will be an abbreviated version for the in-person interview and should take between 15-30 minutes.

5.2 Urine toxicology

Urine testing for opioids will be conducted at **4, 12, 24, 36, and 48-weeks.**

5.3 HIV testing

HIV testing will be conducted at **4, 12, 24, 36, and 48-weeks.**

6. DATA MANAGEMENT AND STATISTICAL CONSIDERATIONS

6.1 Endpoints

Drug-related health outcomes as well as a wide array of social outcomes will be assessed in this study.

6.2 Drug-related and other health outcomes

The primary outcome will be time to opioid relapse. Secondary drug-related outcomes will include frequency of use of opioids and other illicit substances, opioid craving levels, opioid addiction severity, non-fatal overdose, drug-related HIV risk behaviors, drug-related police harassment and for C&C participations, self-reported use and assessment of MMT.

We are planning a study with 1 control per experimental subject, an accrual interval of 6 months, and additional follow-ups during the next 12 months after accrual. If the true median times to drug-relapse on the control and experimental treatments are 2 and 3 months, respectively, we will need to study 97 experimental subjects and 97 control subjects to be able to reject the null hypothesis that the experimental and control survival curves are equal with probability (power) of 80%. The Type I error probability associated with this test of this null hypothesis is 0.05. It is estimated that 25% of subjects will be lost to follow-up at 12 months. Adjusting for this, at the very least, a total number of 244 subjects (122 cases – C&C and 122 controls – Pusat Serenti) are required for this study. In anticipation that these estimates may differ from actual outcomes, our goal will be to recruit a total of 300 subjects (150 cases – C&C and 150 controls – Pusat Serenti)

Relapse to opioid use (self-report). We will use Cox-proportional hazards regression to assess predictors of time to relapse to opioid use.

Relapse to opioid use (based on urine testing). As a comparison to and extension of the analyses conducted using the above measure, we will use Cox-proportional hazards regression to assess predictors of time to having an opioid-positive urine test.

Addiction Severity. ASI scores will be calculated for drug use at baseline and at 3, 6, 9 and 12-month time points and will be compared between the two groups using multivariate logistic regression.

Non-fatal overdose. This variable will be measured via self-report and will be compared between the two groups using multivariate logistic regression.

Drug use. Standard measures drug use will be used. Drug use variables will be based on self-report and will be compared between the two groups using multivariate logistic regression.

Injection-related HIV risk behaviors. Standard measures for injection risk will be used. This variable will be measured via self-report and will be compared between the two groups using multivariate logistic regression.

Drug-related sexual HIV risk behaviors. Standard measures for sexual risk will be used. This variable will be measured via self-report and will be compared between the two groups using multivariate logistic regression.

Police-harassment. This variable will be measured via self-report and will be compared between the two groups using multivariate logistic regression.

Opioid Craving Scale. This variable will be measured via self-report and will be compared between the two groups using multivariate logistic regression.

Motivation to change drug use. This variable will be measured using a validated instrument assessing motivation to change drug use and will be compared between the two groups using multivariate logistic regression.

MMT use and assessment. This variable will be measured via self-report by individuals engaged in MMT at C&C Centers.

HIV infection. This measure will be assessed via administering rapid HIV tests to participants over the course of study follow-up.

6.3 Social Outcomes

Secondary social outcomes will include quality of life, social support, employment and total monthly income, days of criminal activity, and prison incarceration or CCDU detention.

Health-Related Quality of Life. This variable will be assessed using the SF-36. Mean scores on the Physical and Mental Health Subscales will be compared between the two groups using multivariate logistic regression.

Social support and integration. This variable will be measured using the Zimet social support scale.

Employment and total monthly income. Time to employment, mean days of working per month, and total monthly income will be assessed and compared between the groups using multivariate logistic regression and Cox-proportional hazards analysis.

Days of criminal activity. Days in criminal involvement will be measured using the ASI and compared between the groups using multivariate logistic regression.

Detention in Pusat Serenti/Incarceration in jail or prison. Will be assessed via report by RAs assigned to client at C&C site or accessing CCDU/prison databases.

week window period for each scheduled in-person appointment to allow for more client flexibility; at the end of every phone interview, phone credit will be transferred to the clients' phone to reinforce follow-up; if the mobile phone device is retained over the course of the study, further incentives will be provided. These incentives will have been reviewed by the study Institutional Review Boards (IRBs) to assure that they are not excessive.

Retention and follow-up rates will be assessed and reported periodically. Study coordinating meetings will include review and discussion of recruitment and retention activities, with case reviews and problem solving aimed at maximizing both.

7. HUMAN SUBJECTS CONSIDERATIONS

7.1 Institutional Review Boards/Ethics Committee

Human subjects are the focus of the work outlined in this project. Approvals from all applicable regulatory authorities will be obtained prior to initiating any study procedures. The applicable regulatory authorities include the University of Malaya, University of New South Wales and Yale University IRBs. The primary IRB for this study is the University of Malaya (UM) IRB. Prior to implementation of this study, the site must have the protocol document and the consent forms approved by the UM IRB. Amendments to the protocol will be submitted to all regulatory authorities when applicable.

7.2 Informed consent

7.2.1 Consent procedures

7.2.1.1 General procedures

Written informed consent will be obtained from each study participant prior to enrollment. Participants will be provided with copies of the signed and dated informed consent forms.

All communication with participants will be in Bahasa Malaysia. English translations of informed consents and protocols will be submitted for review in the United States and translations of informed consents and protocols to Bahasa Malaysia will be verified for accuracy by bilingual study staff. Forms will be pilot-tested among staff to assess their clarity and accuracy. After the study has been explained in detail to a potential participant, and questions answered, specially trained staff will review the informed consent with each participant. In cases of low levels of literacy, we will read the informed consent aloud.

The enrollment informed consent process will include an assessment of each potential participant's understanding of concepts essential to the informed consent decision prior to the participant signing the informed consent. Participants who are not able to

demonstrate adequate understanding of key concepts after educational efforts will not be enrolled in the study. Assessments of participant understanding will be repeated throughout the accrual period; results will be used to identify participants who need additional counseling regarding the study. Participants who are able to comprehend the study and want to participate will be asked to sign an informed consent form. Additionally, a study staff member will sign the informed consent form to document the consent process and their belief that the participant understands the informed consent form.

In addition to the informed consent forms, RAs will work with other study staff and community representatives to develop locally appropriate information materials about the study and a standardized approach to the informed consent process to be implemented at the study sites. The process and materials will be pilot-tested prior to study start-up to ensure cultural appropriateness.

7.2.2 Key elements of the informed consent

The informed consent process will cover all elements of informed consent required by research regulations. In addition, the process will specifically address the following topics of importance to this study:

1. The real yet limited benefits of study participation.
2. The right to withdraw from the study at any time.

7.2.3 Stage of informed consent

Screening and enrollment consent

Before enrollment, a private informed consent session will be held with each individual participant, in which the study will be explained in detail. Specially trained staff will read the informed consent and approved supporting educational material to each potential participant. The consent form will outline the study procedures, including specimen collection, and specific topics that will be covered during interviews. It is of utmost importance that participants understand the key concepts of the study; only after this is demonstrated can written informed consent be obtained.

7.3 Risks

As with all studies with human subjects, there are potential risks. The investigation team will go to great efforts, however, to ensure that risks are minimized. This is particularly true as we intend to conduct this project with a vulnerable population.

7.3.1 Risks associated with loss of confidentiality

As with all research, there is a risk of potential breaches of confidentiality. We intend to do everything possible to reduce this risk. These measures are further described below (See Section10.5 - Participant confidentiality)

7.3.2 Sensitive information
Participants may feel uncomfortable with the sensitive nature of some of the CASI and counselor's questions.

7.4 Benefits
Participants may benefit indirectly from the possible findings of the study. Detention has been the primary approach to addressing drug use and dependence in Malaysia and should our findings support reform of this policy, it may lead AADK to focus on provision of evidence-based treatment for PWUDs rather detention and criminalization of this population. This would mean that PWUDs in Malaysia would have significantly greater access to much-needed health services that would likely improve not only health outcomes but also quality of life, social stability and functioning, and community integration.

7.5 Participant confidentiality
This study is confidential and not anonymous. All project staff will be trained in procedures for maintaining confidentiality.

All study-related information will be stored securely at the study site. Names and other identifying information will be collected only on consent forms and contact-tracing forms. All survey instruments, administrative forms, urine toxicology and HIV testing results will be identified only by a unique participant **Study ID Number** to maintain participant confidentiality. Records that contain names or other personal identifiers, such as locator forms and informed consent forms, will be stored separately from study records identified by code number. All participant information will be stored in locked file cabinets in areas with access limited to study staff. All local databases will be secured with double password-protected access systems. Only de-identified data will be sent to Yale University collaborators for analysis.

Importantly, all in-person and phone interviews will be conducted by trained research assistants in a private, confidential setting to minimize breaches in confidentiality. Research assistants will call clients at the time of their scheduled phone interview and ask clients whether they are in a comfortable location to respond to interview questions. If they are not, the interview will immediately be rescheduled so that clients are in confidential setting at the time of the call. Each client will also have a unique identifier code the RA will ask for over the phone to verify the identity of the speaker and the same RA will conduct follow-up interviews with the client over the course of the study so the client can be certain they are speaking with study personnel.

7.6 Monitoring for data and operational issues
The principal investigator, co-investigators and the project director and project manager will meet at least monthly to review data and operational issues such as enrollment, data quality, retention, and protocol violations.

7.6.1 Quality assurance/quality control procedures

Internal audits will be performed as part of quality assurance (QA) procedures. These audits will evaluate study conduct and compliance with protocol.

7.7 Study discontinuation

The On-Site Principal Investigator may pause or stop the study in emergency situations, for instance involving personal safety of the study site staff.

7.8 Disenrollment / study completion

When a participant has been lost to follow-up, no longer wishes to participate, is deceased, is suspended from services due to behavioral issues, or has reached the end of the study, the RA must record this using the **Participant Tracking Database.** The documentation must include the reason for discharge. Except in the case of death, the On-Site Principal Investigator or a designee must notify the client in writing about discharge from services.

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