PROTOCOL

Protocol Number: INA-102

RESEARCH TITLE:

TUBERCULOSIS RESEARCH OF INA-RESPOND ON DRUG RESISTANCE (TRIPOD)

A Multicenter Study of the Indonesia Research Partnership on Infectious Disease (INA-RESPOND)

Sponsored by:

The Center for Health Resources and Services Research and Development, National Institute of Health Research and Development Indonesia

The National Institute of Allergy and Infectious Diseases, United States

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INA RESPOND
INDONESIA RESEARCH PARTNERSHIP ON INFECTIOUS DISEASE

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GLOSSARY

AE	Adverse Event
AFB	Acid-Fast Bacilli
ALT	Alanine Amino Transferase
AST	Aspartate Amino Transferase
BCG	Bacille-Calmette–Guérin
BMI	Body Mass Index
BW	Body Weight
CBC	Complete Blood Count
CRF	Case Report Form
DM	Diabetes Mellitus
DOTS	Directly Observed Treatment, Short course
DR-TB	Drug-Resistant Tuberculosis
DS-TB	Drug-Susceptible Tuberculosis
DST	Drug Susceptibility Testing
DNA	Deoxyribonucleic acid
EC	Ethics Committee
EOS	End of Study
ESR	Erythrocyte Sedimentation Rate
GCP	Good Clinical Practice
HIV	Human Immunodeficiency Virus
ICH	International Conference on Harmonization
ICF	Informed Consent Form
INA-RESPOND	Indonesia Research Partnership on Infectious
Disease IPR	Intellectual Property Rights
IRB	Institutional Review Board
MDR-TB	Multidrug-Resistant Tuberculosis
MGIT	Mycobacteria Growth Indicator Tube
MOP	Manual of Procedures
N	Number (typically refers to participants)
NIAID	National Institute of Allergy and Infectious Diseases
NIHRD	National Institute of Health Research and Development
NTP	National Tuberculosis Program
OHRP	Office for Human Research Protections
PBMC	Peripheral Blood Mononuclear Cell
PI	Principal Investigator
PMDT	Programmatic Management of Drug-Resistant TB
SAE	Serious Adverse Event
SoC	Standard of Care
TB	Tuberculosis
WHO	World Health Organization
XDR-TB	Extensively Drug Resistant Tuberculosis

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RESEARCH SUMMARY

Title	INA102 – Tuberculosis Research Of INA-RESPOND on Drug Resistance (TRIPOD)
Study Type	Prospective Observational Study
Principal Investigator	Dr. dr. Erlina Burhan, M.Sc, SpP(K) dr. Anis Karuniawati, SpMK,PhD
Sample Size	This study will analyze 500 participants bacteriologically confirmed TB (250 new cases and 250 previously treated cases). To obtain the numbers, we estimated that we need to enroll 1357 presumptive TB patients as participants (1000 new cases and 357 previously treated cases). These numbers were made based on our estimation that 25% of presumptive new TB cases and 70% of presumptive previously treated TB cases will be bacteriologically confirmed.
Study Population	Presumptive TB patients, ≥ 18 years old
Study Duration	Up to 4.5 years
Accrual Period	Up to 2 years
Study Design	This study is a prospective observational cohort study of TB patients who are treated or evaluated at 10 study sites. Patients presenting with cough for 2 weeks or longer with at least one additional TB symptom and a chest X-ray suggestive of TB, will be invited to be enrolled in the study. The signed informed consent will designate their willingness to participate on this study. Enrolled participants will produce the sputum for bacteriological examination of *M. tuberculosis* by AFB, culture and Xpert. The sputum will also be tested by Xpert for drug resistance test. If the culture is positive, conventional DST will be performed, and *M. tuberculosis* isolates will be stored for spoligotyping and for future research on TB. All participants treated by TB drugs regimen will be followed for outcome assessment. For all enrolled participants, chest X-Ray results, demographic data, co-morbidities, symptoms, nutritional status, treatment regimens, compliance and outcome will be collected. In addition, sputum, blood, urine, and saliva will also be collected for related TB future testing.

Primary Objective	To estimate the proportion of MDR-TB amongst new and previously treated TB cases.
Secondary Objectives	1. To evaluate accuracy of clinical diagnosis by comparing clinically defined TB to laboratory confirmed TB. 2. To compare AFB and Xpert MTB/RIF as TB diagnostic tests against culture result. 3. To estimate the sensitivity and specificity of Xpert MTB/RIF in detecting Rif susceptibility against DST. 4. To estimate the proportion of cured, completed, failed, died and lost to follow up as treatment outcomes on DS-TB and DR-TB cases 5. To evaluate the association of treatment success (cured or completed) with the following data: a. Demographics (age, sex) b. TB contact history c. Smoking habit d. Treatment seeking behavior e. Co-morbidities (HIV, DM, cancer) f. Primary and secondary drug resistance g. Symptoms h. Cavitary disease i. Nutritional status j. Treatment regimens

1. BACKGROUND

Tuberculosis (TB) continues to be a major health problem in the world, especially in developing countries. Despite the use of anti-TB treatments and Bacille-Calmette-Guérin (BCG) vaccination, TB incidence continues to rise. It was declared a global health emergency by the World Health Organization (WHO) in 1995.[1] **In 2015, WHO estimated that there were 10.4 million new TB patients with mortality rate of 1.8 million patients per year throughout the world.[2]**

Based on the WHO Report 2016, Indonesia ranked second in the world with an estimated incidence in 2015 is 1,020,000 cases with mortality number 126,000.[2] This condition is exacerbated by the increasing incidence of diabetes mellitus (DM) and Human Immunodeficiency Virus (HIV) as TB comorbidities and the growing number of cases with Multidrug- Resistant TB (MDR-TB) or even Extensively Drug-Resistant TB (XDR-TB). This situation will lead to an epidemic of TB that is difficult to manage and continues to be a major public health problem.[1,2,4] Previous TB drug resistant surveys conducted across Indonesia revealed that in Timika district, Papua (2004), 2% of new TB cases are MDR-TB cases, in Central Java province (2006), 1.8% of new TB cases and 17.1% of previously treated TB cases are MDR- TB, and in Makassar (2007) 4.1% of new TB cases and 19.2% of previously treated TB cases are MDR-TB. **WHO Report 2016 estimation in 2015 for Indonesia gave a number of incidence which are 2.9% of new TB cases and 16% of previously treated TB cases are MDR-TB cases.[2,5,7]**

The Indonesia Health Profile study reported 194,000 new TB cases in 2011 based on positive smear results.[8] TB control efforts were implemented in Indonesia starting in 1969 and Directly Observed Treatment Short-course (DOTS) began in 1995. Nevertheless, these efforts to date have not eliminated the TB burden.[9] In 2009 Ministry of Health started the implementation of Programmatic Management of Drug-Resistant Tuberculosis (PMDT) for MDR-TB patients.

Treatment success is known to be associated with several factors. These include patient related factors, such as age,[10] gender,[11] smoking habit,[12] nutritional status, comorbidities (DM and HIV). *M. tuberculosis* characteristics are also associated with outcome, including number of bacteria and *M. tuberculosis* strain (e.g Beijing strain).[13]

Data on the prevalence of drug resistance among new or previously treated TB cases is limited to several centers in Indonesia.[5-7] This study will be the first to follow new and previously treated TB patients in hospitals in Indonesia. Prevalence data for drug-susceptible and MDR-TB, along with corresponding treatment outcomes, will be beneficial to inform national tuberculosis programs (NTP). Additionally, data collected from this study

will be useful for planning future TB research studies in Indonesia, such as evaluating novel diagnostic test, evaluating markers of response to treatment and identifying new therapies.

2. RESEARCH BENEFITS

2.1 Scientific Benefits

- This study will observe and record TB, drug susceptibility profiles and treatment outcomes of new and previously treated cases.
- The study will observe and record patient demographics, smoking habits, nutritional status, clinical history, bacterial factors (the numbers of bacterial and the infecting strain), and attempt to determine the association between these factors and the success of treatment.
- The study will provide data that is useful for planning future studies in tuberculosis, e.g. basic research, improved diagnostics or clinical trials on newly developed drugs.
- The study will collect samples from participants and may lead to identification of a novel or virulent strain associated with disease and with treatment success. Such information could be extremely important for public health prevention programs.

2.2 Community Benefits

- The study may assist in the development of improved diagnostic and treatment algorithms and processes within hospitals for providing care that can improve patient outcomes.

2.3 Policy Benefits

- Results of this study may provide information that would be valuable to the Ministry of Health and the national tuberculosis program in developing a more effective strategy for treatment and prevention.

3. OBJECTIVES

3.2 Primary Objective

To estimate the proportion of MDR TB amongst new and previously treated TB cases.

3.3 Secondary Objective

- To evaluate accuracy of clinical diagnosis by comparing clinically defined TB

to laboratory confirmed TB.

- To compare AFB and Xpert MTB/RIF as TB diagnostic tests against culture result.
- To estimate the sensitivity and specificity of Xpert MTB/RIF in detecting Rif susceptibility against Drug Susceptibility Test (DST).
- To estimate the proportion of cured, completed, failed, died and lost to follow up as treatment outcomes in drug susceptible TB (DS-TB) cases and drug resistant TB (DR-TB) cases.
- To evaluate the association of treatment success (cured or completed) with the following data:
    1. Demographics (age, sex)
    2. TB contact history
    3. Smoking habit
    4. Treatment seeking behavior
    5. **Co-morbidities (HIV, DM, cancer)**
    6. Primary and secondary drug resistance
    7. Symptoms
    8. Cavitary disease
    9. Nutritional status
    10. Treatment regimens
    11. Patient reported compliance
    12. Numbers of bacteria by AFB test
    13. TB strains (e.g., Beijing)

4. METHODS

4.1 Study Plan

The brief explanation of the study plan will be captured on figure 1.

4.2 Sites and Duration

This study will be conducted at hospitals in the INA-RESPOND network:

1. Persahabatan hospital, Jakarta
2. Prof. Dr. Sulianti Saroso Infectious Diseases hospital, Jakarta
3. Dr. Hasan Sadikin hospital, Bandung
4. Dr. Kariadi hospital, Semarang
5. Dr. Soetomo hospital, Surabaya
6. Sanglah hospital, Bali

7. Dr. Sardjito hospital, Yogyakarta
8. **Dr. Wahidin Sudirohusodo hospital, Makassar**
9. **Gatot Subroto Army hospital, Jakarta**
10. **H. Adam Malik Hospital, Medan**

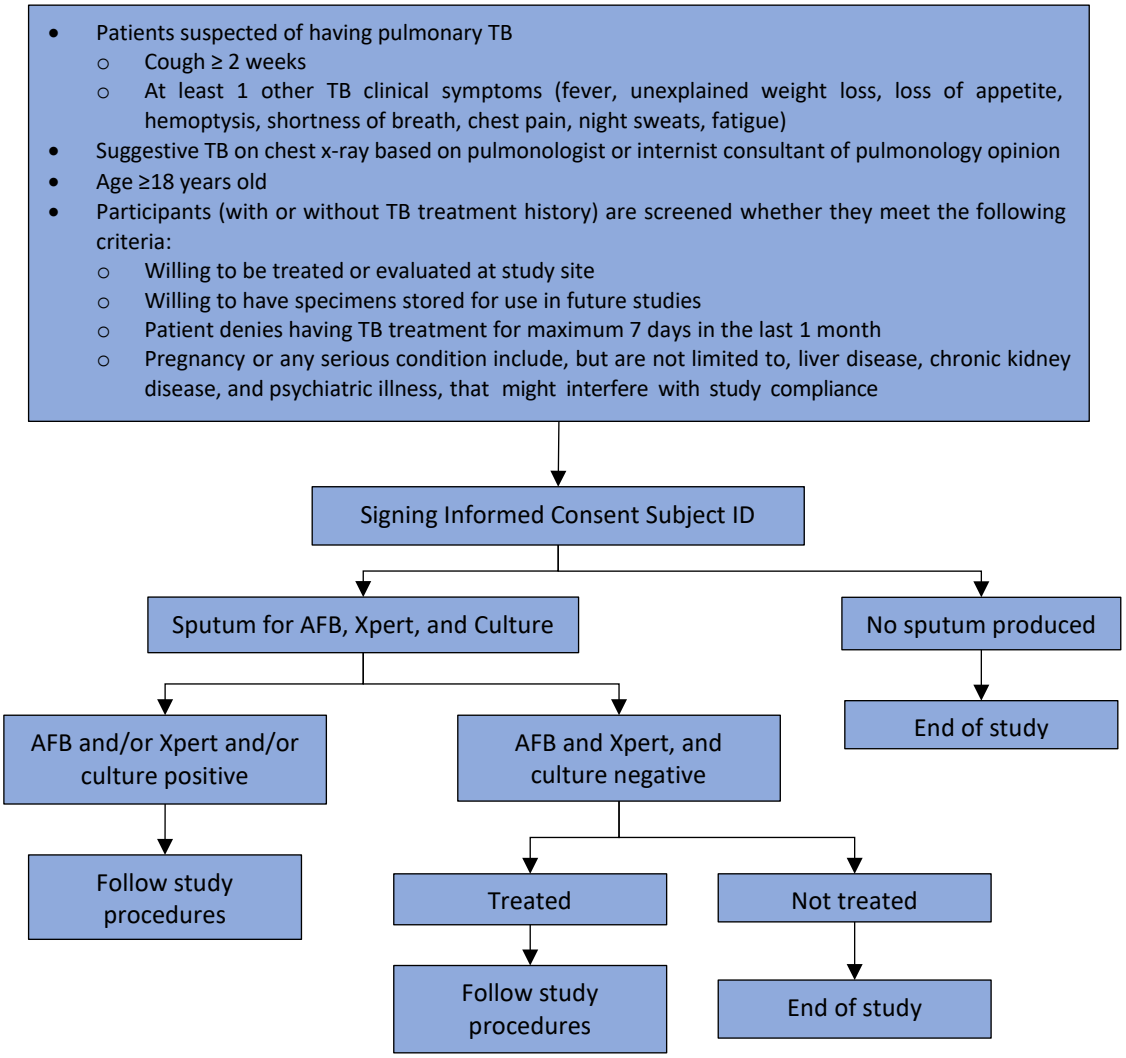

Figure 1. The Study Plan

The Study will enroll eligible participants for a period of up to 2 years. Participants will be followed up until 6 months' post treatment. **For drug susceptible TB, this will be approximately 12 months after enrollment/treatment start, but it may be longer if they have drug resistant TB or require longer treatment regimen for other reasons (e.g. Category 2 treatment, diabetes, etc). For those participants, the study will follow them for maximum 30 months after enrollment/treatment start**. Stored specimens will be investigated during the study and/or after study completion.

4.3 Type and Design of Study

This study is a prospective observational cohort study of new and previously treated TB patients. Patients will be treated as per standard of care according to national TB treatment guidelines and each study site policy by each patient' physician. This study will collect data and specimens as outlined in Appendix A. Additional blood, sputum, urine, and saliva specimens will be obtained for TB examinations and stored for related TB future testing.

Study participants will continue to be managed in accordance with the DOTS or PMDT strategy by the patients' physician. **Clinical care or treatment for all participants is provided by the healthcare facility based on the National Guidelines or clinician decisions**. **No intervention either treatment or behavior, applied for this study.**

4.4 Population and Sample Size

This is a descriptive study with the goal of estimating rates MDR in two separate cohorts (new and previously treated TB cases). WHO global report in 2013 estimated 1.9% MDR TB cases in new TB cases and 12% MDR TB cases in previously treated TB cases for Indonesia. This study will analyze 250 bacteriologically confirmed new TB participants and 250 bacteriologically confirmed previously treated participants. We estimate that 25% of presumptive new TB participants who satisfy study entry criteria will be bacteriologically confirmed TB. Similarly, we estimate that 70% of previously treated cases will be bacteriologically confirmed TB. Therefore, to obtain 500 bacteriologically confirmed TB cases, 1,000 presumptive new cases and 357 presumptive previously treated cases will be enrolled, for a total of 1,357 enrolled. The proportion of confirmed TB cases amongst new and previously treated cases is an estimation and will be re-evaluated during the course of the study. Refer to the interim analysis section below for details.

Table 4.4.1 describes the expected precision (confidence bounds and width) for observed proportion of MDR amongst previously treated cases. With 250 participants and an observed MDR proportion of 12%, the confidence interval will be (0.085, 0.162). The precision of the estimated proportion of MDR does not improve considerably when increasing the sample size to 300. The confidence interval for a sample size of 300 with an MDR proportion of 12% is (0.085, 0.162), while decreasing the sample size to 200 has a more striking impact on the bounds increasing the lower bound to 0.078 and the upper bound to 0.173.

When considering the sample size for new TB cases, we note that the precision of binomial confidence intervals based on exact Clopper Pearson method increases as the proportion gets closer to zero. As a result, we find the true MDR rate is more precisely estimated with a sample size of 250 for new TB cases (compared to previously treated cases, where the MDR rate is expected to be around 12%). With a sample size of 250

new TB cases, the expected 95% confidence interval is (0.007, 0.046). (Table 4.4.1)

Exact Clopper Pearson binomial confidence interval method formula:

$$\left(1+\frac{n-x+1}{xF\left[1-\frac{1}{2}\alpha;2x,2(n-x+1)\right]}\right)^{-1}<\theta<\left(1+\frac{n-x}{[x+1]F\left[\frac{\alpha}{2};2(x+1),2(n-x)\right]}\right)^{-1}$$

Table 4.4. 1 Expected confidence bounds based on observed MDR proportions amongst previously treated TB cases.

Sample Size	Observed proportion	Bounds of 95% confidence interval*	Actual width
150	0.12	(0.073, 0.183)	0.110
	0.15	(0.097, 0.217)	0.120
200	0.12	(0.078, 0.173)	0.095
	0.15	(0.104, 0.207)	0.104
250	0.12	(0.082, 0.167)	0.084
	0.15	(0.108, 0.200)	0.092
300	0.12	(0.085, 0.162)	0.077
	0.15	(0.112, 0.196)	0.084
400	0.12	(0.090, 0.156)	0.066
	0.15	(0.116, 0.189)	0.072

* CIs based on Exact Clopper-Pearson method

Table 4.4. 2 Expected confidence bounds based on observed MDR proportions amongst new TB cases.

Sample size	Observed proportion	Bounds of 95% confidence interval*	Actual width
150	0.01	(0.001, 0.042)	0.041
	0.02	(0.004, 0.057)	0.053
	0.03	(0.009, 0.072)	0.062
	0.05	(0.021, 0.098)	0.077
200	0.01	(0.001, 0.036)	0.034
	0.02	(0.005, 0.050)	0.045
	0.03	(0.011, 0.064)	0.053
	0.05	(0.024, 0.090)	0.066
250	0.01	(0.002, 0.032)	0.030
	0.02	(0.007, 0.046)	0.040
	0.03	(0.013, 0.059)	0.047
	0.05	(0.027, 0.085)	0.058
300	0.01	(0.002, 0.029)	0.027
	0.02	(0.007, 0.043)	0.036
	0.03	(0.014, 0.056)	0.042
	0.05	(0.028, 0.081)	0.053

400	0.01	(0.003, 0.025)	0.023
	0.02	(0.009, 0.039)	0.03
	0.03	(0.016, 0.052)	0.036
	0.05	(0.031, 0.076)	0.045

* CIs based on Exact Clopper-Pearson method

The sampling method in this study is purposive sampling. The study will stop recruiting participants when 1,000 new presumptive TB cases and 357 previously treated TB cases had enrolled.

4.5 Inclusion and Exclusion Criteria

The following inclusion and exclusion criteria are used when determining eligibility patients into the study:

4.5.1 Inclusion Criteria

- Patients suspected of having pulmonary TB
- Cough ≥ 2 weeks
- At least one other TB clinical symptom
  - Fever
  - Unexplained weight loss
  - Loss of appetite
  - Hemoptysis
  - Shortness of breath
  - Chest pain
  - Night sweats
  - Fatigue
- Suggestive TB on chest x-ray based on pulmonologist or internist consultant of pulmonology opinion
- Age ≥ 18 years' old
- Willing to be treated or evaluated at study site
- Willing to have specimens stored for use in future studies
- **Patient denies having TB treatment for more than 7 days in the last 1 month (30 days).**

4.5.2 Exclusion Criteria

Pregnancy or any serious condition includes, but not limited to, liver disease, chronic kidney disease, and psychiatric illness that might interfere with study compliance (based on the clinician judgment). In order to assess participant's pregnancy status, the attending clinician will ask the participant's first day of last menstrual period. The

final decision about participant's pregnancy status will be up to the attending clinician..

4.5.3 End of study criteria

- Study completion (six months after end of treatment **or six months after month 24th visit**).
- Participant desires to leave study or withdraw consent.
- **No sputum specimen for the examinations of AFB, Gene Xpert, and culture at baseline and enrollment visit.**
- **No longer treated as TB patients.**
- Treatment interruption of two months or greater.
- Death
- Transfer to other health facility where follow up/evaluation is no longer possible.
- Based on investigator's discretion it is in the participant's best interest to be discontinued from the study.
- Participants who cannot be reached to complete the 6 months' post treatment by phone or direct visit.
- Termination of study

4.6 Instruments and Data Collection'

The following instruments and data collection methods will be used in this study. Further information may be found in protocol sections 4.6.2-4.6.5.

4.6.1 Instruments:

a. Forms
   i. Informed consent
   ii. Source documents
   iii. Case report forms (CRFs)
   iv. Screening Log
   v. Enrollment Log
b. Databases
   i. OpenClinica
   ii. INA-RESPOND specimen database
c. INA-RESPOND portal

4.6.2 Eligibility determination and enrollment:

<u>Enrollment and baseline visit (visit 1)</u>

Potential participants will be referred by physicians at participating hospitals.

Following referral, research assistant will check the eligibility criteria. Thus, the potential participant will be offered information on the study. If the patient agrees, he/she will sign the informed consent document and will be considered enrolled in the study. All baseline procedures should be done in five working days, although the result may come later. Enrollment day is considered as Day 0.

Demography, clinical data, and physical examination results including body weight and height will be obtained. The initial data collection will take time about 30-60 minutes.

Participant should bring enough sputum that can be considered eligible for AFB, Xpert MTB/RIF, and culture examination. Sputum induction by inhalation medicine will be considered for participants that have difficulty to produce sputum according to site SoC. The remaining sputum will be stored for TB related future testing. Participant who cannot provide enough sputum for those examinations will be considered as end of study and stop following the study procedures.

20 cc blood will be drawn for assessment of comorbidities (HIV test and HbA1c), for other examinations needed either for study or for SoC. Such as Hb, ureum, creatinine, AST, and ALT. Left over specimen will be used for future TB related examinations and repository. Less blood volume because unanticipated problem related to blood draw such as collapsing vein would not be considered as protocol deviation. 10 cc of urine will also be collected and stored for future TB related tests. Saliva will also be collected for storage.

After the sputum culture shows positive results of M.*tuberculosis*, the *M.tuberculosis* isolate will be tested for DST and also be stored. New TB cases with Rif susceptible Xpert MTB/RIF result will be tested for first line DST, continue by second line if first line DST result shows drug resistant TB. New TB cases with Rif resistant Xpert MTB/RIF will be directly tested for first and second line DST. Previously treated TB cases will be directly tested for first and second line DST.

DS-TB participants who decide to take the TB treatment in puskesmas (primary health care) may not come to visit(s) except for study visit which the study gives compensation for participant's attendance. So that for those participants, study will provide a record, named "TRIPOD Diary", to be completed on each visit at Puskesmas. The TB program manager or designee at the Puskesmas will give their signed as a verification of this record. TRIPOD Diary will be mentioned further in MOP.

4.6.3 Ongoing monitoring and evaluation

During treatment, participants will be seen every month for 6 months and then every 2 months until end of treatment or **maximum at month 24th**. Then participants also will be assessed 6 months after end of treatment. In general, participants will have between 1 to 16 numbers of follow up visits. Study will also record the data of several participants who may need month 7 and/or month 8 and/or month 9 visits, **for example participant receiving category 2 treatment, participant with diabetes comorbid.** Study visits will occur at the same time as clinical visit. If the participant does not come for a clinical visit it will not be considered a deviation from the protocol.

Except 6 months post treatment visit, every study visit will collect data on each comorbidity include HIV, diabetes, and cancer. Study will also collect data on weight, TB symptoms, TB treatment compliance, sputum examination results (if available), and treatment regimen. Participants' compliance will be measured by counting how many medications still left in the blister pack (if available) or based on participant report if the patient does not bring the blister. **TRIPOD diary will assist the research assistant to measure participant compliance who is taking the medication in the primary health care/puskesmas.**

All participants will have follow up for treatment of TB and routine testing as mandated by the National Guidelines and provided by the hospital in accordance with Appendix A. Additional AFB tests on month 1, culture test on month 1 and 2, and chest x-ray at the end of treatment visit, will be conducted for all drug susceptible participants.

Sputum induction by inhalation medicine will be offered to participants that have difficulty to produce sputum.

4.6.4 End of treatment visit

The End of Treatment Visit will take place when the participant completes his/her prescribed TB treatment regimen. This visit approximately will be held on month 6th or 7th for participants with DS TB category 1 therapy, on month 8th or 9th for participants with DS TB category 2 therapy, and between month 18th to 24th for those with MDR. **However, the end of treatment visit might be different for some participants depend on their comorbidity or any other condition such as the new regimen for TB patient.**

The following data and evaluations will be collected and performed:

- TB related symptoms
- Treatment compliance
- Comorbidities
- Weight

- Chest X-ray
- AFB (if available)
- Sputum culture (if available)
- Store whole blood (PAXgene, PBMCs, plasma)
- Store urine
- Store sputum and Mtb isolate (if available)
- Store saliva

4.6.5 6 Months Post-Treatment Visit

The final study visit will be conducted 6 months after the participants' prescribed TB treatment is completed. The data of TB related symptoms, weight, and chest X-Ray will be obtained by direct visit. If the participants unable to come for this visit, phone call should be made to obtain the data of TB related symptoms.

4.6.6 Study Disposition Status

Study disposition status will be completed with the Research Assistant when the participants considered as end of study. The final outcome of treatment will be determined.

Participants followed until 6 months post treatment visit will be considered as completing the study procedure and end of study. The rest of the participants will be considered as end of study at the following time point:

1. Participant withdraws consent.
2. Participant who is unable to provide enough sputum at baseline/enrollment visit **for the examinations of AFB, Gene Xpert, and culture**.
3. Participant is no longer treated as TB patients.
4. Participant has treatment interruption of two months or longer after she/he starts TB treatment.
5. Participant died.
6. Participant transfers to other health facility for their TB treatment where follow up/ evaluation is no longer possible.
7. Based on investigator discretion.
8. Participant who cannot be reached to complete the 6 month post treatment by phone or direct visit.
9. Termination of study.

At this visit the final outcome **of treatment** status will be determined.

All study procedures will be outlined in Appendix A

4.6.7 TB Management

Participants who are not diagnosed with MDR-TB will be managed according

to the Indonesia MoH 2011 national TB guidelines, and those diagnosed as MDR-TB cases will be managed in accordance to Indonesia Programmatic Management of Drug- Resistant TB (PMDT) 2013. Other drug resistant TB cases will be managed in accordance to each site clinician decision. Treatment for tuberculosis is provided free of charge by the National TB Program.

4.6.8 Handling of Samples

Sputum specimen will be collected at special booth at each site. Culture and DST will be performed at laboratories which capable to perform culture, bacterial identification and DST according to international standard, and have passed Quality Assurance by TB supranational laboratory. All sputum specimen and Mtb isolate will be processed in biosafety cabinet level 2. Blood and urine specimen will be collected in Pathology Clinic at each site. Blood and urine specimen collection and handling will be up to each hospital and/or Pathology Clinic laboratory safety procedure at each site.

Transport of biological samples

As the transmission of TB can occur through contact with sputum specimens, contact and respiratory precautions will be employed by all personnel involved with sputum collecting, shipping and handling for this study.

Archived Biological Materials

Samples collected under this protocol may be used to study TB and related conditions such as spoligotyping. Participants must be willing to allow storage of sputum, Mtb isolate, whole blood (PAXgene blood, plasma, PBMC), and urine on baseline, month 1, month 2, and end of treatment visit, and saliva on baseline and end of treatment visit for use in future studies (for example, host response, spoligotyping, and genetic tests). Serum and whole blood for DNA are collected on baseline visit only.

All samples will be stored at the NIHRD, Mtb isolate, plasma, saliva and urine will also be stored at each site. Samples will be coded with a unique identifier that does not contain any information capable of linking the sample to the study participants. A code that links the unique identifier with the study sample will be kept on a locked file cabinet in a secured room. Only authorized personnel will have access to the code. Only investigators will have access to the samples. **All samples will be logged and tracked using INA-RESPOND system.**

Some of the specimens collected under this protocol will be stored for

repository. The used and destruction of the archived specimens in the future, will be determined per INA-RESPOND SOP of Specimen Ownership, Access, and Use (see appendix D).

Additional testing on study samples

Based on the clinical presentation and laboratory data the researchers will determine further testing to be done on samples. This testing could be performed for: a) existing diagnostic methods that may not have been accessible at the time of the collection of samples, b) research tests to identify and/or confirm etiologic agents, c) to study immune markers that might enable better management or prediction of outcomes for patients, d) to be used to study pathogenicity, and e) genetic testing.

IRB approval must be sought prior to any sharing of samples and/or data. Any clinical information shared about the sample would similarly require prior IRB approval. At the completion of the protocol (termination), samples and data will either be destroyed, or after IRB approval, transferred to another existing protocol.

Reporting the Loss or Destruction of Samples/Specimens/Data to the IRB

Any loss or unanticipated destruction of samples or data (for example, due to freezer malfunction) that compromises the scientific integrity of the data collected for the study will be reported to the IRB.

Additionally, participants may decide at any point not to have their samples stored. In this case, the principal investigator will destroy all known remaining samples and report what was done to both the participant and to the IRB.

4.7 Data Management and Analysis

4.7.1 Data Management

Data which are collected under this protocol may be used to study TB and related conditions. Participant will be coded with a unique identifier that does not contain any information capable of linking the data to the study participants. A code that links the unique identifier with the study participants will be kept in a locked file cabinet in a secure room. Only authorized personnel will have access to the code and the data. Data will be keyed and tracked using the OpenClinica.

Data will be periodically sent to the central data management center. Site and national data will be analyzed by all investigators.

4.7.2 Analysis

This is an observational study to describe rates of MDR TB amongst new and previously treated TB cases in Indonesia. Risk factors for MDR will be evaluated as a secondary objective. Additional secondary objectives include a description of treatment outcomes (cure, failure, death, completed treatment) and evaluation of associated risk factors for poor outcome, comparison of diagnostic accuracy of AFB and Xpert MTB/RIF (relative to culture) and an estimation of Xpert MTB/RIF Rif susceptibility testing sensitivity and specificity relative to standard DST. Research objectives will be analyzed as described below.

Primary objective

1) To estimate the rate of MDR-TB amongst new and retreated TB cases. Proportions of MDR will be estimated, along with exact 95% confidence intervals based on a binomial distribution. Case definitions of MDR, new and previously treated TB are provided in Appendix B.

Secondary objective

1) To estimate treatment outcomes (cured, failed, died, treatment completion, and lost to follow up) according to susceptibility pattern. Proportions of participants within each category will be estimated along with confidence intervals. Definitions of treatment outcomes are provided in appendix B.
2) To evaluate risk/protective factors for treatment success (cured or completed treatment vs failed or died or loss to follow up). These factors include: demographics (age, sex), TB contact history, smoking habit, treatment seeking behavior, co-morbidities (HIV, DM), primary drug resistance, symptoms, no cavity in the lung, nutritional status, treatment regimens, compliance, numbers of bacteria and TB strains (e.g., Beijing). Logistic regression models will be used to describe associations of treatment success with these factors.
3) To evaluate risk/protective factors for treatment interruption (loss to follow up vs other treatment outcome). These factors include: demographics (age, sex), TB contact history, smoking habit, treatment seeking behavior, co-morbidities (HIV, DM, and other comorbidities), primary drug resistance, symptoms, cavity in the lung, nutritional status, treatment regimens, compliance, numbers of bacteria and TB strains (e.g., Beijing). Logistic regression models will be used to evaluate associations of treatment interruption with these risk factors.
4) To compare clinically defined TB against laboratory confirmed TB. Accuracy will be estimated along with 97.5% confidence intervals.
5) To compare the sensitivity and specificity of AFB and Xpert MTB/RIF relative

to culture result. Sensitivity and specificity will be estimated along with 97.5% confidence intervals. McNemar's statistic will test whether the sensitivity and specificity differ between AFB and Xpert MTB/RIF.

6) To estimate sensitivity and specificity of Rif susceptibility results in Xpert MTB/RIF against result in DST as gold standard along with 97.5% confidence intervals.

More specific plans for these analyses will be developed prior to the start of enrollment, and the plans may be adjusted during the course of the study.

Interim Analyses

Amongst presumptive new TB cases, we estimate that 25% will have confirmed TB, while amongst presumptive previously treated cases, we estimate that 70% will have confirmed TB. In order to ensure adequate numbers of TB cases, the accuracy of these estimates will be evaluated at 6 and 12 months after the study commences. Because of the expected two months waiting period for culture results, earlier looks at the data may not be informative.

5. SAFETY MONITORING AND REPORTING

5.1 Definition of an Adverse Event

An adverse event (AE) is any untoward or unfavorable medical occurrence in a human participant that occurs within 48 hours of a study-related blood draw that is possibly, probably, or definitely related to the blood draw. Any event outside of this 48 hours window period will not be considered an AE for this study.

No adverse event to be considered since sputum collection is a non-invasive procedure.

5.2 Definition of an Serious Adverse Event

Serious adverse event is any adverse event that:

- results in death;
- is life-threatening (places the participant at immediate risk of death from the event as it occurred);
- results in inpatient hospitalization or prolongation of existing hospitalization;
- results in a persistent or significant incapacity;
- results in a congenital anomaly/birth defect; or based upon appropriate medical judgment, may jeopardize the participant's health and may require medical or surgical intervention to

prevent one of the other outcomes listed in this definition.

- results in death;
- is life-threatening (places the participant at immediate risk of death from the event as it occurred);
- results in inpatient hospitalization or prolongation of existing hospitalization;
- results in a persistent or significant incapacity;
- results in a congenital anomaly/birth defect; or based upon appropriate medical judgment, may jeopardize the participant's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition.

5.3 Definition of an Unanticipated Problem

An unanticipated problem is defined as any incident, experience, or outcome that is defined as:

1. Unexpected in terms of nature, severity, or frequency in relation to:
    - the research risks that are described in the research protocol and informed consent document or other study documents; and
    - the characteristics of the participant population being studied; and
2. Related or possibly related to the participation in the research; and
3. Places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized or is an SAE.

5.4 Reporting Procedures to the IRB

All unanticipated problems and SAEs, regardless of relationship, will be reported by the site PI to the IRB within 7 working days of the investigator's awareness.

All reportable adverse events (events that occur within 48 hours of the research blood draw and are possibly, probably, or definitely related to the research blood draw) will be reported in the summary form to the IRB at the time of Continuing Review.

5.5 Study Monitoring

The study will be conducted in compliance with this protocol, International Conference on Harmonization (ICH) Guidelines for Good Clinical Practice (GCP) and any applicable regulatory requirement(s). Independent monitors, under contract by the Sponsor, will visit the clinical research site to monitor all aspects of the study in accordance with the appropriate regulations. The objectives of a monitoring visit will be:

1. To verify the prompt reporting of all data points, including reporting SAEs, and also check the availability of a signed informed consent form (ICF).
2. To review the consistency of each participant's records with the source documents.
3. To ensure compliance with the protocol, and accuracy and completeness of records.

The monitors also will inspect the clinical site regulatory files to ensure that regulatory requirements are being followed. During the monitoring visits, the site investigator (or designee) and other study personnel will be available to discuss the study progress and monitoring visit.

The site investigator (or designee) will make study documents (e.g., ICFs and CRFs) and pertinent hospital or clinical records readily available for inspection by the local institutional review board/ethics committee (IRB/EC), the local and national regulatory authorities, and the site monitors for confirmation of the study data.

5.6 Safety Monitoring Plan

The investigators will monitor protocol data that could affect patient safety or confidentiality, including AEs, documentation of patient evaluation, treatment, and disposition, and coding of patient data and samples. Additionally, independent monitors will conduct visits based on a mutually agreed schedule to monitor study documents.

6. ETHICAL CONSIDERATIONS

6.1 Informed Consent Process

Informed consent is a process in which information is presented to enable persons to voluntarily decide whether to participate as a research participant. It is an ongoing conversation between the human research participant and the researchers covering the essential information about the study which begins before consent is given and continues until the end of the participant's involvement in the research.

All volunteers will sign an ICF after discussion of essential information about the research by the study staff. This will include the purpose of the study, duration, procedures, alternatives, risks, and benefits. Participants will have the opportunity to ask questions about the study and have their questions answered.

All participants in the study will sign/thumb print an appropriate informed consent document prior to any procedures being done specifically for the study. The participants may withdraw consent at any time throughout the course of the study. A copy of the informed

consent document will be given to the participants for their records. The researcher will document the signing of the consent form in each participant's study record.

6.2 Illiterate Participant

If the volunteer is illiterate, oral consent will be obtained. The administrator of the oral consent will sign and date the form. The adult volunteers will thumbprint the consent form. An impartial witness should be present during the entire informed consent discussion and should sign and date the consent form.

6.3 Premature Withdrawal of Participant

Participants may voluntarily withdraw from the protocol at any point in the study. Attempts will be made to determine the reason that the subject wishes to withdraw.

6.4 IRB Review

Prior to the implementation of the protocol, the protocol and ICF for this study will be submitted for approval to the appropriate IRB. Any change to the protocol, ICF, will only be implemented after approval from the IRB. Records of the IRB review and approval of all the documents pertaining to the study will be kept on file by the site investigator and are subject to inspection at any time during the study. Continuing reviews or study progress report will be submitted according to the requirement of the appropriate IRB, but once a year at a minimum.

6.5 Participant Confidentiality

All records will be kept confidential to the extent provided by the law. The study monitors and other authorized representatives may inspect all documents and records required to be maintained by the site investigator, including, but not limited to, medical records. Records will be kept in a locked cabinet, and all computer entry and networking programs will be done with coded numbers only. Clinical information, attributable to the subject, will not be released without written permission of the subject, except as necessary for monitoring, the EC/IRB, or Office for Human Research Protections (OHRP).

The results of the research study may be published according to the INA-RESPOND policy, but subject names or identities will not be revealed.

6.6 Rationale for Subject Selection

Children and teenagers under age 18 are excluded from participating in the study due to concerns regarding long term study compliance.

6.7 Benefits

This study is meant to provide knowledge on the TB drug resistant in new and

previously treated TB cases in study hospitals and to identify areas of potential research in the future. It may not provide direct benefit to participants. Patients participating in this study will receive additional diagnostic and drug susceptibility testing not currently provided routinely.

The Site study team will share results with the study participants related to their medical care.

6.8 Compensation

This study will not provide any compensation for any visit schedules that are in accordance to national TB treatment guidelines. Patients who were diagnosed as DS-TB will receive Rp 150,000 as compensation at baseline visit, month 1, 2, end of treatment visit, and 6 months post treatment visit during study. Patients who were diagnosed as MDR-TB will receive Rp 150,000 as compensation at baseline visit, month 1, 2, 12, 18, end of treatment visit, and 6 months post treatment visit during study. This compensation to compensate longer time taken and any inconveniences due to more study procedures.

6.9 Risk and Discomforts

This is a minimal-risk, observational study and does not involve experimental interventions. The only study intervention is a blood draw and all other procedures are considered as part of standard care for TB patients.

The hazards of blood drawing are minimal and consist of mild discomfort and or bleeding at the venipuncture site, bruising and rarely fainting and local infection. In case of any immediate serious side effect like fainting, the patient will be stabilized by the study team if needed.

The hazards of sputum collection are minimal and consist of mild discomfort when participants tried to produce sputum to be collected.

Each drug susceptible subject in this study will undergo one additional chest x-ray at the end of study. The purpose of this x-ray is to determine if the subject has improved chest x-ray. The amount of radiation the subject will receive is 0.040 rem (which is below the guideline of 5 rem per year allowed for research participants by the NIH Radiation Safety Committee). The hazard of an additional (maximum two with 6 months interval) chest x-ray are minimal and consist of mild discomfort and radiation exposure when participants undergo the chest x-ray process.

6.10 Recording/Documentation

At each contact with the subject, assessment information will be elicited by appropriate questioning and examination, and they will be recorded on source documents. Source documents may include worksheets, progress notes, laboratory reports, consult

notes, and data collection tools. Data is to be transcribed onto CRFs from source documents on an ongoing basis during the study. The study monitor may review and audit all documents and records required to be maintained by the site investigator.

Any type of corrections to study documents should be initialed and dated by the person who is making the correction. The site investigator is responsible for ensuring that the data collected are complete, accurate, and recorded in a timely manner. All CRFs should be reviewed, initialed and dated by the site investigator or designee. CRFs will be maintained and kept in locked cabinets at the site for at least 5 years after study completion.

Each subject's name will be paired with a numeric code in the enrollment log. Access to data identifying participants will be kept in a locked file, accessible only by study staff. Finally, the importance of subject confidentiality will be impressed upon all research staff. The site investigator is responsible for the accuracy and completeness of the data reported.

7. PROTECTION OF INTELLECTUAL PROPERTY (IPR), MATERIAL TRANSFER AGREEMENT (MTA), AND GENETIC RESOURCES AND TRADITIONAL KNOWLEDGE (GRTK)

7.1 Protection of Intellectual Property

Publication of the results of this study will be governed by the INA-RESPOND publication policy. Any presentation, abstract, or manuscript will be made available for review by the supporters prior to submission.

7.2 Publication and Dissemination of Research Results

These will be guided by the Protection of Intellectual Property (IPR) terms as outlined in Article X and Annex I of the Science and Technology agreement between the Government of the Republic of Indonesia and the Government of the United States of America. Article X (Protection of Intellectual Property) states:

1. Provisions for the protection and distribution of intellectual property created or furnished in the course of cooperative activities under this Agreement are set forth in Annex I, which shall form an integral part of this Agreement.
2. Scientific and technological information of a non-proprietary nature resulting from cooperation under this Agreement (other than information which is not disclosed for commercial or industrial reasons) shall be made available, unless otherwise agreed, to the world scientific community through customary channels and in accordance with normal procedures of the participating agencies and entities.

And under Paragraphs III.A and III.B(1), (2)(a), (2)(b), (2)(c) of Annex I, Intellectual Protection

Rights, of the Science and Technology agreement between the Government of the Republic of Indonesia and the Government of the United States of America.

7.3 Material Transfer Agreement

Research materials used in the collaborations under this protocol may, on agreement of the participants, be transferred using Material Transfer Agreements (MTAs) as appropriate in the particular collaborations, as outlines in Article VIII of the Science and Technology Agreement.

7.4 Genetic Resources and Traditional Knowledge

The collection, conservation and exchange of genetic resources and associated traditional knowledge under this protocol shall be subject to Article VI of the S and T Agreement and will be based on the following considerations:

Obtaining informed consent from appropriate authority/institutional review board prior to accessing genetic resources collected during the conduct of this protocol.

Equitably sharing the benefits arising from the use of traditional knowledge and genetic resources.

The complete Science and Technology agreement between the Government of the Republic of Indonesia and the Government of the United States of America is in Appendix C.

8. RESEARCH TEAM

Role	Name, Institution and Location	Expertise	Contact Information
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APPENDIX A. List of Study Procedures and Timeline

Procedures	BL	Mo1	Mo2	Mo3	Mo4	Mo5	Mo6	Mo7	Mo8	Mo9	Mo10	Mo12	Mo14	Mo16	Mo18	Mo20	Mo22	Mo24	6Mos Post Tx
							End of Treatment								End of Treatment				
Screening Log	ST																		
	ST																		
Enrollment Log	ST																		
	ST																		
Informed Consent	ST																		
	ST																		
Demography	SOC																		
	SOC																		
TB history & contact history	SOC																		
	SOC																		
Smoking Habit	ST																		
	ST																		
Treatment seeking	ST																		
	ST																		
HIV, DM, cancer comorbid data	ST,IA	IA	IA	IA	IA	IA	IA	IA	IA	IA	IA	IA	IA	IA	IA	IA	IA	IA	
	ST,IA	IA	IA	IA	IA	IA	IA	IA	IA	IA	IA	IA	IA	IA	IA	IA	IA	IA	
Symptoms	ST	ST	ST	ST	ST	ST	ST	ST	ST	ST									ST
	ST	ST	ST	ST	ST	ST	ST	ST	ST	ST	ST	ST	ST	ST	ST	ST	ST	ST	ST
Treatment Compliance		ST	ST	ST	ST	ST	ST	ST	ST	ST									
		ST	ST	ST	ST	ST	ST	ST	ST	ST	ST	ST	ST	ST	ST	ST	ST	ST	
Height	ST																		
	ST																		
Weight	SOC	SOC	SOC	SOC	SOC	SOC	SOC	SOC	SOC	SOC									ST
	SOC	SOC	SOC	SOC	SOC	SOC	SOC	SOC	SOC	SOC	SOC	SOC	SOC	SOC	SOC	SOC	SOC	SOC	ST
Chest X-Ray	SOC						ST												ST
	SOC						SOC					SOC			SOC			ST	ST
AFB	ST	ST	SOC	IA		IA	SOC												
	ST	IA	IA	IA	IA	IA	IA	IA	IA	IA	IA	IA	IA	IA	IA	IA	IA	IA	
Xpert MTB/RIF	ST																		
	SOC																		
Sputum Culture	ST	ST	ST				ST												
	ST	ST	ST	SOC	SOC	SOC	SOC	SOC	SOC	SOC	SOC	SOC	SOC	SOC	SOC	SOC	SOC	SOC	
1st DST	ST																		
	SOC																		
2nd DST	ST																		
	ST																		

Procedures	BL	Mo1	Mo2	Mo3	Mo4	Mo5	Mo6	Mo7	Mo8	Mo9	Mo10	Mo12	Mo14	Mo16	Mo18	Mo20	Mo22	Mo24	6Mos Post Tx
							End of Treatment								End of Treatment				
Hb, HbA1C, HIV exams	ST																		
	ST																		
Ureum, Creatinin, AST, ALT	IA																		
	SOC																		
Stored Whole Blood (DNA)	ST																		
	ST																		
Stored Plasma	ST	ST	ST				ST												
	ST	ST	ST												ST				
Stored PBMC	ST	ST	ST				ST												
	ST	ST	ST												ST				
Stored Serum	ST																		
	ST																		
Stored Paxgene	ST	ST	ST				ST												
	ST	ST	ST												ST				
Stored Urine	ST	ST	ST				ST												
	ST	ST	ST												ST				
Stored Sputum	ST	ST	ST				ST												
	ST	ST	ST												ST				
Stored Mtb Isolate	ST	ST	ST				ST												
	ST	ST	ST												ST				
Stored Saliva	ST						ST												
	ST														ST				

*ST for HIV and DM, If available for other comorbidities

Blue : Information for DS-TB

Red : Information for MDR-TB

ST : Procedure required by study that might be different from the site SoC

SoC : Procedure must be done regularly on site

IA : Procedure might be done on site for all or some groups of participants

All available data must be recorded for study

APPENDIX B. Operational Definition

Variables	Measurement	Operational definition
New TB cases	Patient report	TB patients who never have TB treatment or already have TB treatment less than one month (4 weeks)
Previously treated TB cases	Patient report	A patient who has been treated for one month or more with anti TB drugs in the past
Presumptive TB	Clinical and X-Ray evaluation	Patient who presents with symptoms or signs suggestive of TB on the basis of X-ray suggestive TB
Bacteriologically confirmed TB	Laboratory evaluation	A participant whom a biological specimen is positive by AFB or culture or WRD (such as Xpert MTB/RIF)
Clinically diagnosed TB	Clinical and X-Ray evaluation	Participant who does not fulfil the criteria for bacteriological confirmation but has been diagnosed with active TB by a clinician or other medical practitioner who has decided to give the patient a full course of TB treatment, includes cases diagnosed on the basis of X-ray abnormalities
Pulmonary TB	Clinician judgement	Any bacteriologically confirmed or clinically TB involving the lung parenchyma or the tracheobronchial tree, including miliary TB, patient with both pulmonary and extrapulmonary TB should be classified as a case of PTB.
Extrapulmonary TB	Clinician judgement	Any bacteriologically confirmed or clinically diagnosed case of TB involving organs other than the lungs, e.g. pleura, lymph nodes, abdomen, genitourinary tract, skin, joints
Drug Sensitive/susceptible TB	By the result of Drug susceptibility test (DST)	Negative DST result
MDR TB	By the result of Drug susceptibility test (DST)	DST result positive resistant to isoniazid and rifampicin
Rif Resistance TB	By the result of Drug susceptibility test (DST)	DST result positive resistant to rifampicin

Monoresistance TB	By the result of Drug susceptibility test (DST)	DST result positive resistant to one of 1st line TB drug other than rifampicin
Polydrug resistance TB	By the result of Drug susceptibility test (DST)	DST result positive resistant to more than one of 1st line TB drugs, in addition to combination of isoniazid and rifampicin
Extensive drug resistance TB	By the result of Drug susceptibility test (DST)	DST result positive resistant to any fluoroquinolone and to at least one of three second-line injectable drugs (capreomycin, kanamycin and amikacin), in addition to multidrug resistance.
Treatment outcome DS-TB		
Cured	Attending TB team report	Smear or culture negative in the last month of treatment and on at least one previous occasion
Completed treatment	Attending TB team report	Completed treatment without evidence of failure but with no records to show that sputum smear or culture negative in the last month of treatment and on at least one previous occasion were negative, either because tests were not done or results are unavailable
Died	Attending TB team report	Died from any cause during treatment
Failed	Attending TB team report	Sputum smear or culture is positive at month 5 or later during treatment
Loss to follow up	Attending TB team report	Did not start treatment or treatment was interrupted for two consecutive months or more
Not evaluated	Attending TB team report	No treatment outcome is assigned. This include cases 'transferred out' to another treatment unit as well as cases for whom the treatment outcome is unknown.
Successfully treated	Attending TB team report	The sum of cured and completed treatment.

Treatment outcome MDR-TB		
Cured	Attending TB team report	Treatment completed as recommended by the national policy without evidence of failure AND three or more consecutive cultures taken at least 30 days apart are negative after the intensive phase.
Completed treatment	Attending TB team report	Treatment completed as recommended by the national policy without evidence of failure BUT no record that three or more consecutive cultures taken at least 30 days apart are negative after the intensive phase.
Failed	Attending TB team report	Treatment terminated or need for permanent regimen change at least two anti-TB drugs because of: • Lack of conversion at the end of intensive phase; or • Bacteriologocial reversion in the continuation phase after conversion to negative; or • Evidence of additional acquired resistance to fluoroquinolones or second-line injectable drugs; or • Adverse drug reactions
Died	Attending TB team report	Died for any reason during course of treatment
Loss to follow up	Attending TB team report	Treatment was interrupted for two consecutive months or more.
Not evaluated	Attending TB team report	No treatment outcome is assigned. This include cases 'transferred out' to another treatment unit as well as cases for whom the treatment outcome is unknown.
Treatment success	Attending TB team report	The sum of Cured and completed treatment.

Demographics		
Age	Patient report	Last birthday
Sex	Patient report	male and female
Patient's history		
TB close contact	Patient report	Living in a same house with person who has TB
Smoking habit	Patient report	Smoking status of participants
Treatment seeking behavior	Patient report	History of health facility that been visited for treating these TB symptoms
Co Morbidities		
HIV	Clinical and laboratory evaluation support HIV evidence	Positive result of HIV test
Diabetes mellitus	Clinical and laboratory evaluation support diabetes evidence glucose test according to site SoC	Positive result of diabetes
Symptoms	Patient report	Presence of TB symptoms from previous visit to current visit
Nutritional status	BMI calculation based on data of Height and weight	< 18.5 : Underweight 18.5 - 24.9 : Healthy weight 25 - 30 : Overweight 30 to 35 : Obese
Treatment regiment	Source documents	Regiment of anti TB drugs given to the patients according to SoC
Compliance	Patient report or blister count	Percentage of scheduled medication minus any medication left in the blister or based on patient report

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Sample Information Sheet and Consent Form (English)

Tuberculosis Research of INA-RESPOND On Drug Resistant (TRIPOD)

Voluntary Consent for Adult Patient

INTRODUCTION

We invite you to take part in a TB study. The doctor in charge of this study at this site is (insert name of Site Investigator). Before you decide if you want to be a part of this study, we want you to know about the study.

This is an information sheet. It gives you information about the study. The study staff will inform you about the study. You are free to ask questions about this study at any time. If you agree to take part in this study, you will be asked to sign the consent form. You will get a copy of the information sheet and informed consent of this study.

WHERE AND WHY IS THIS STUDY BEING DONE?

The Indonesia Research Partnership for Infectious Diseases (INA-RESPOND) consisting of 8 hospitals: Persahabatan hospital and Penyakit Infeksi Prof. Dr. Sulianti Saroso hospital, Jakarta; Dr. Hasan Sadikin hospital, Bandung; Dr. Kariadi hospital, Semarang; Dr. Soetomo hospital, Surabaya; Sanglah hospital, Denpasar; Dr. Sardjito hospital, Yogyakarta; Dr. Wahidin Sudirohusodo hospital, Makassar; and the National Institute of Health Research and Development (NIHRD) is conducting a study on the proportion of MDR TB cases in new and previously treated TB patients.

The purposes of this study are: to find out the proportion of MDR TB in new TB and previously treated TB patients. Results of this study, proportion of MDR TB in new TB and previously treated TB patients in Indonesia, is beneficial because it can provide data for National . This study may also help to understand the factors that related to treatment outcomes in drug sensitive TB cases and MDR TB cases.

WHAT DO I HAVE TO DO IF I AM IN THIS STUDY?

1. <u>Screening</u>

This evaluation will be conducted to see whether you are eligible to take part in this study. The screening evaluation will take about 2-5 days.

You may be enrolled into this study if you meet the following criteria:

- You are eighteen years of age or older
- You have cough and at least one other TB clinical symptoms.
- You are not on TB treatment in the last 2 months
- Clinician indicates that you have pulmonary TB based on chest X-ray results

- You are willing to let us store blood, urine and result of sputum culture test for use in future studies, and willing to be treated or evaluated at the hospital that is part of our study sites.

However you may not be enrolled into this study if the clinician:

- Find out that you are pregnant
- Find out that you have liver disease and/or chronic kidney disease
- Decides you have a problem to comply with study procedure.

If you agree to join this study, you will be asked to sign this informed consent.

2. Entry (This evaluation may be combined with the Screening evaluation)

This evaluation may take about hours. At this evaluation, you will have the following done:

- We will check your TB related symptoms and you will have a physical exam including but not limited to height and weight measurement, unless these are already done by the doctor treating you.
- About 10 mL (approximately two teaspoon) of your blood will be drawn to diagnose other diseases beside TB and to test the condition of your blood. You will be told the results of these tests as soon as this information becomes available.
- The total amount of blood to be drawn will not be more than the allowed limits and the rest of the blood after being used for examination will be stored.
- About 10 ml of your urine will be collected for storage.
- About 3 containers of your sputum will be drawn to diagnose TB by culture tests and drug resistance test.

3. Study Follow-Up Visits during TB treatment

a. At month 1, 2, 3, 4, 5 (Five Visits) of treatment

This visit may take about 30 minutes. At this visit, you will have the following done:

- We will check your TB related symptoms and you will have a physical exam for weight measurement unless these are already done by the doctor treating you.
- We will count how many pills that you missed to take during treatment by counting the blister or based on your recall if you forgot to bring the blister
- About 2 containers of sputum will be collected for smear and culture

b. At month 6 (One Visit) of treatment

This visit may take about 90 minutes. At this visit, you will have the following done:

- We will check your TB related symptoms and you will have a physical exam for weight measurement unless these are already done by the doctor treating you.
- We will count how many pills that you missed to take during treatment by counting the blister or based on your recall if you forgot to bring the blister
- We will performed chest x-ray to monitor TB progress in your lung.
- About 2 containers of sputum will be collected for smear and culture.

- If this is your last clinical visit, you will be asked to drawn 6 mL of blood (approximately one teaspoon) and 10 ml of urine for storage.

c. At month 7,8,9 (Three Visits) of treatment

This visit may take about 90 minutes. At this visit, you will have the following done:

- We will check your TB related symptoms and you will have a physical exam for weight measurement unless these are already done by the doctor treating you.
- We will count how many pills that you missed to take during treatment by counting the blister or based on your recall if you forgot to bring the blister
- We will performed chest x-ray to monitor TB progress in your lung.
- About 2 containers of sputum will be collected for smear and culture.
- If this is your last clinical visit, you will be asked to drawn 6 mL of blood (approximately one teaspoon) and 10 ml of urine for storage.

d. At month 8, 10, 12, 14, 16, 18, 20, 22, 24 (Nine Visits) of treatment

This visit may take about 60 minutes. At this visit, you will have the following done:

- We will check your TB related symptoms and you will have a physical exam for weight measurement unless these are already done by the doctor treating you.
- We will count how many pills that you missed to take during treatment by counting the blister or based on your recall if you forgot to bring the blister
- About 2 containers of sputum will be collected for smear and culture.
- If this is your last clinical visit, you will be asked to drawn 6 mL of blood (approximately one teaspoon) and 1 pot of urine for storage.

Chest X-ray

You will be asked to have an x-ray of your chest. This test involves standing in front of an x-ray machine as a picture of your chest and lungs is taken. A complete x-ray exam will take about 10 minutes.

Risks of Chest X-ray

This research study involves exposure to radiation from 1 chest x-ray. This radiation exposure is not standard of care and is for research purposes only. The amount of radiation you will receive in this study is 0.040 rem (which is below the guideline of 5 rem per year allowed for research subjects by the NIH Radiation Safety Committee.) The average person in the United States receives a radiation exposure of 0.3 rem per year from natural sources, such as the sun, outer space, and the earth's air and soil.

While there is no direct evidence that the amount of exposure received from participating in this study is harmful, there is indirect evidence it may not be completely safe. There may be a very slight increase in the risk of cancer.

Unless you are pregnant, this level of radiation is generally considered safe. A pregnancy test will be performed prior to the x-ray if you are a female of child-bearing potential. If the test is positive, you will not receive a chest x-ray but you may still participate in the study.

4. Stored Samples and Future Research

During of your first and end of study visits, the result of sputum culture test, blood, and urine may be collected for future TB related tests and genetic test. In general, future research that uses your samples will not help you, but it may help us to have a better understanding about TB. This research may also help us provide better treatments for TB and improve the management of TB. Any results relevant to your care will be shared with you and communicated to your physician.

Genetic test is one of test in future studies that could be tested on your blood. This test including analysis on your several gene (carrier characteristics) to see if the TB infection that you got and the progress of the disease is related with this hereditary factor. You could choose not to participate in this genetic test and it will not affecting your enrollment in this study.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

About 1357 people will take part in this study.

HOW LONG WILL I BE IN THIS STUDY?

You will be in this study for the duration of the treatment, it depends on the diagnose of your TB, or for 24 months if your treatment duration is longer than 24 months.

WHY WOULD THE DOCTOR TAKE ME OFF THIS STUDY EARLY?

You may withdraw from the study at any time. You will not be asked for further information or collected further data.

The study doctor may need to take you off the study early without your permission if:

- The study is cancelled or terminated by the sponsors or the site's Institutional Review Board (IRB)/Ethics Committee (EC).
- You are not able to attend the study visits as required by the study.
- It will be harmful for you if you continue in this study.

WHAT ARE THE RISKS OF THE STUDY?

The researchers believe that the risks or discomforts to you are minimal and includes the risks associated with obtaining blood and producing sputum. These include slight pain and redness or bruising at the site where the blood is drawn and in rare cases, fainting and discomfort during producing sputum.

Bruising may be alleviated by a warm compress. There is a very small chance the site where the blood is drawn may become infected. This is unlikely since the person drawing the blood will clean the site with alcohol before blood is taken and use a sterile blood drawing material.

If you have difficulty to produce sputum, we could help you by providing inhalation medicine that might help you to produce sputum.

WHAT OTHER CHOICES DO I HAVE BESIDES THIS STUDY?

The alternative is not to participate in this study. If you decide not to participate in this study you still get treatment for TB symptoms.

ARE THERE BENEFITS TO TAKING PART IN THIS STUDY?

The study will covered all the tests cost during treatment that are not paid by the government. This study will provide xxxx at the beginning and end of study for your time spent and incoveniences. The study will not provide costs for routine care or hospitalization that are required by the government. The results of this study may help your clinician to provide better treatments and improve the management of your TB infection.

WILL I RECEIVE ANY PAYMENT?

You will receive no payment for taking part in this study.

WHAT ABOUT CONFIDENTIALITY?

All information about you will be kept confidential and will not be shared with anyone who is not responsible for your care. Your medical record will only be reviewed by those who are working on this study.

All the research documents and samples will be labeled using your study number. Your name will not be used for labeling samples and your name will not appear in study related reports or scientific publications.

WHAT HAPPENS IF I AM INJURED?

We will provide immediate medical care for study related injuries e.g. an infection where blood has been taken. The study cannot pay for long term disability that may have resulted from the subject's illness.

WHAT ARE MY RIGHTS AS A RESEARCH PARTICIPANT?

Your participation in this study is completely voluntary. If you do not want to participate, you will still get standard treatment. You may discontinue your participation in this study at any time you choose.

We will tell you about new information from this or other studies that may affect your health, welfare, or willingness to stay in this study. If you want the results of the study, let the study staff know.

WHAT DO I DO IF I HAVE QUESTIONS OR PROBLEMS?

If you have questions regarding this study, you may contact:

- insert name of the investigator or other study staff
- telephone number of above

SAMPLE ADULT CONSENT FORM

Tuberculosis Research of INA-RESPOND On Drug Resistant

I have read the study information sheet or this information sheet has been read to me. I have had the opportunity to ask questions about it and any questions I have asked have been answered to my satisfaction. I have been explained that I may withdraw from this study at any time.

I freely and voluntarily choose to participate in this study. I will be given a copy of this information sheet and signed consent form to keep for my reference.

I agree to the storing of my result of culture test from my sputum for genetic testing to see whether specific genetic factors play a role in the occurrence of TB and its progression.

___YES ___NO

Name of Subject: _____ Age: _____

Signature*: _____ Date: ____/____/____
(dd/mm/yy)

*A thumb print can be used of the patient who cannot write.

Name of the Investigator: _____ Signature: _____

Date: ____/____/____
(dd/mm/yy)

Name of Witness: _____ Signature: _____

Date: ____/____/____
(dd/mm/yy)

Appendix D: Contoh Lembar Penjelasan dan Formulir Persetujuan (Bahasa Indonesia)

Penelitian Tuberculosis oleh INA-RESPOND Mengenai Kekebalan Obat

Persetujuan untuk ikut dalam penelitian dengan sukarela, untuk pasien dewasa

PENGANTAR

Kami mengharapkan anda untuk ikut serta dalam suatu penelitian mengenai TB karena anda saat ini sedang dicurigai menderita TB. Dokter yang bertugas untuk penelitian ini di RS ini adalah Dr ……..(tuliskan nama peneliti). Sebelum anda memutuskan untuk ikut dalam penelitian ini, kami mengharapkan anda untuk mengetahui terlebih dahulu mengenai penelitian ini.

Ini adalah lembar penjelasan dimana berbagai informasi mengenai penelitian ini akan diterangkan. Seorang petugas pada penelitian ini akan memberikan informasi mengenai penelitian ini. Anda dapat dengan bebas untuk bertanya mengenai penelitian ini kapan saja. Jika anda setuju untuk ikut serta, anda akan diminta untuk menandatangani formulir persetujuan. Anda akan mendapatkan salinan dari lembar penjelasan ini dan formulir persetujuan.

DIMANA DAN MENGAPA PENELITIAN INI DILAKSANAKAN?

Kemitraan dalam Penelitian Penyakit Infeksi Indonesia (dalam bahasa Inggris dikenal sebagai "*The Indonesia Research Partnership for Infectious Diseases*"/INA-RESPOND) yang terdiri dari 8 rumah sakit: RS Persahabatan dan RSPI Prof. Dr. Sulianti Saroso, Jakarta; RS Dr. Hasan Sadikin, Bandung; RS Dr. Kariadi, Semarang; RS Dr. Soetomo, Surabaya;, RS Sanglah, Denpasar, RS Dr. Sardjito, Yogyakarta, RS Dr. Wahidin Sudirohusodo, Makassar dan Badan Penelitian dan Pengembangan Kesehatan, Kementerian Kesehatan Republik Indonesia akan melaksanakan suatu penelitian mengenai proporsi kasus TB *Multi Drug Resistant* (*TB-MDR*) pada pasien TB baru dan pasien TB yang pernah diobati sebelumnya.

Tujuan dari penelitian ini adalah untuk mengetahui proporsi kasus *TB-MDR* pada pasien TB baru dan pasien TB yang pernah diobati sebelumnya. Hasil dari penelitian ini, proporsi kasus *TB-MDR* pada pasien TB baru dan pasien TB yang pernah diobati sebelumnya, adalah berguna karena bisa memberikan data untuk Nasional. Penelitian ini juga dapat membantu mengerti faktor-faktor yang berhubungan dengan hasil terapi pada kasus TB dan *TB-MDR*.

APA YANG HARUS SAYA LAKUKAN JIKA IKUT PADA PENELITIAN INI?

1. <u>Skrining</u>

Pertama-tama akan dilakukan penapisan untuk melihat apakah anda memenuhi kriteria untuk ikut dalam penelitian ini. Evaluasi untuk skrining ini berlangsung sekitar 2-5 hari.

Anda dapat ikut dalam penelitian ini jika :

- Anda berusia 18 tahun atau lebih.
- Anda menderita batuk dan setidaknya satu gejala klinis TB lainnya.
- Anda tidak sedang dalam pengobatan TB dalam 2 bulan terakhir.
- Klinisi menyatakan bahwa anda menderita TB paru berdasarkan hasil ronsen dada
- Anda mengijinkan kami untuk menyimpan darah, air seni dan hasil dari kultur dahak untuk digunakan dalam penelitian-penelitian di masa depan, dan bersedia untuk diterapi atau dievaluasi di rumah sakit-rumah sakit yang ikut serta dalam penelitian ini.

Anda tidak dapat ikut dalam penelitian ini jika dokter yang merawat anda :

- Menyatakan anda sedang hamil
- Menyatakan anda menderita penyakit hati dan/atau penyakit ginjal menahun
- Berpendapat anda akan mengalami kesulitan dalam mengikuti prosedur penelitian.

Jika anda memenuhi kriteria dan setuju untuk ikut serta dalam penelitian ini, anda akan diminta untuk menandatangani formulir persetujuan ini.

2. Evaluasi saat awal penelitian

Evaluasi ini akan berlangsung kira-kira beberapa jam. Saat evaluasi ini akan dilakukan hal-hal berikut ini:

- Kami akan memeriksa gejala-gejala yang berhubungan dengan TB serta melakukan pemeriksaan fisik termasuk namun tidak terbatas pada pengukuran tinggi dan berat badan, kecuali jika hal ini sudah dilakukan oleh dokter yang menangani anda.
- Kira-kira sebanyak 10 ml (kira-kira dua sendok teh) darah akan diambil untuk pemeriksaan diagnosa penyakit lain selain TB dan mengetahui kondisi darah anda. Anda akan diberitahukan hasilnya segera setelah hasil pemeriksaan tersedia.
- Jumlah darah yang diambil tidak akan melampaui yang diijinkan dan sisa darah setelah yang digunakan untuk pmeriksaan, akan disimpan.
- Sekitar 10 ml wadah air seni akan dikumpulkan untuk disimpan.
- Sekitar 3 wadah dahak akan diambil untuk mendiagnosa TB melalui pemeriksaan kultur, dan uji kekebalan obat.

3. Kunjungan-kunjungan penelitian selama terapi TB:

a. Terapi bulan 1, 2, 3, 4, 5 (Lima kunjungan)

Kunjungan ini mungkin memakan waktu sekitar 30 menit. Pada kunjungan ini, anda akan mengalami pemeriksaan sebagai berikut:

- Kami akan memeriksa gejala-gejala yang berhubungan dengan TB dan melakukan pengukuran berat kecuali ini telah dilakukan oleh dokter yang memeriksa anda.

- Kami akan menghitung berapa banyak pil yang anda lupa untuk minum selama terapi dengan menghitung bungkus atau berdasarkan ingatan anda jika anda lupa membawa bungkus obat
- Sekitar 2 wadah dahak akan diambil untuk pemeriksaan hapus dan kultur.

b. Terapi bulan 6 (Satu kunjungan)

Kunjungan ini mungkin memakan waktu sekitar 90 menit. Pada kunjungan ini, anda akan mengalami pemeriksaan sebagai berikut:

- Kami akan memeriksa gejala-gejala yang berhubungan dengan TB dan melakukan pengukuran berat kecuali ini telah dilakukan oleh dokter yang memeriksa anda.
- Kami akan menghitung berapa banyak pil yang anda lupa untuk minum selama terapi dengan menghitung bungkus atau berdasarkan ingatan anda jika anda lupa membawa bungkus obat
- Kami akan melakukan ronsen dada untuk mengetahui perkembangan penyakit TB di paru-paru anda.
- Sekitar 2 wadah dahak akan diambil untuk pemeriksaan hapus dan kultur.
- Jika ini adalah kunjungan terakhir anda, maka anda akan diminta untuk mengumpulkan 6 mL darah (sekitar satu sendok teh) dan 10 ml seni untuk disimpan.

c. Terapi bulan 7,8,9 (Tiga kunjungan)

Kunjungan ini mungkin memakan waktu sekitar 90 menit. Pada kunjungan ini, anda akan mengalami pemeriksaan sebagai berikut:

- Kami akan memeriksa gejala-gejala yang berhubungan dengan TB dan melakukan pengukuran berat kecuali ini telah dilakukan oleh dokter yang memeriksa anda.
- Kami akan menghitung berapa banyak pil yang anda lupa untuk minum selama terapi dengan menghitung bungkus atau berdasarkan ingatan anda jika anda lupa membawa bungkus obat
- Kami akan melakukan ronsen dada untuk mengetahui perkembangan penyakit TB di paru-paru anda.
- Sekitar 2 wadah dahak akan diambil untuk pemeriksaan hapus dan kultur.
- Jika ini adalah kunjungan terakhir anda, maka anda akan diminta untuk mengumpulkan 6 mL darah (sekitar satu sendok teh) dan 10 ml seni untuk disimpan.

d. Terapi bulan 8, 10, 12, 14, 16, 18, 20, 22, 24 (Sembilan kunjungan)

Kunjungan ini mungkin memakan waktu sekitar 60 menit. Pada kunjungan ini, anda akan mengalami pemeriksaan sebagai berikut:

- Kami akan memeriksa gejala-gejala yang berhubungan dengan TB dan melakukan pengukuran berat kecuali ini telah dilakukan oleh dokter yang memeriksa anda.
- Kami akan menghitung berapa banyak pil yang anda lupa untuk minum selama terapi dengan menghitung bungkus atau berdasarkan ingatan anda jika anda lupa membawa bungkus obat
- Kami akan melakukan rontgen dada untuk mengetahui perkembangan penyakit TB di paru-paru anda.
- Sekitar 2 wadah dahak akan diambil untuk pemeriksaan hapus dan kultur.

- Jika ini adalah kunjungan terakhir anda, maka anda akan diminta untuk mengumpulkan 6 mL darah (sekitar satu sendok teh) dan 10 ml air seni untuk disimpan.

Ronsen dada

Anda akan diminta untuk dilakukan foto ronsen di dada. Pemeriksaan ini meliputi berdiri di depan mesin ronsen saat gambar dada dan paru-paru anda diambil. Pemeriksaan foto ronsen akan berlangsung sekitar 10 menit.

Resiko Ronsen dada

Penelitian ini meliputi paparan terhadap radiasi dari 1 kali foto ronsen. Paparan radiasi ini tidak termasuk dalam pemeriksaan standar dan hanya untuk keperluan penelitian. Jumlah radiasi yang anda terima dalam penelitian ini 0,040 rem (yang mana di bawah batas 5 rem per tahun yang diperbolehkan untuk peserta penelitian oleh Komite Keselamatan Radiasi Institut Kesehatan Nasional Amerika Serikat.) Rata-rata seseorang di Amerika Serikat menerima paparan radiasi sebesar 0,3 rem per tahun dari sumber alami sepert matahari, luar angkasa, serta air dan tanah di bumi.

4. Sampel yang disimpan dan penelitian selanjutnya

Pada kunjungan pertama dan akhir penelitian, hasil kultur dahak, darah dan air seni mungkin akan diambil untuk dilakukan pemeriksaan yang berhubungan dengan TB dan pemeriksaan genetik pada penelitian dimasa yang akan datang. Secara umum, penelitian yang menggunakan sampel anda dan dilakukan di masa yang akan datang tidak akan membantu anda, namun akan membantu kami untuk lebih mengetahui dengan baik mengenai TB. Penelitian ini juga dapat membantu kami untuk memberikan pengobatan yang lebih baik untuk TB dan memperbaiki pengelolaan TB. Semua hasil yang berhubungan dengan perawatan anda akan diinformasikan kepada anda dan dikomunikasikan kepada dokter anda.

Pemeriksaan genetik merupakan salah satu jenis pemeriksaan pada penelitian dimasa yang akan datang yang mungkin dilakukan pada darah anda. Pemeriksaan ini meliputi analisa beberapa *gen* (pembawa sifat) anda untuk melihat apakah infeksi TB yang anda dapatkan dan *perjalanan* penyakit tersebut berhubungan dengan faktor keturunan ini. Untuk pemeriksaan genetik ini anda dapat memilih untuk tidak ikut dan ini tidak akan mempengaruhi keikutsertaaan anda dalam penelitian ini.

BERAPA JUMLAH ORANG YANG AKAN IKUT SERTA DALAM PENELITIAN INI?

Sekitar 1357 orang akan ikut serta pada penelitian ini.

SAMPAI KAPAN KEIKUTSERTAAN SAYA PADA PENELITIAN INI?

Anda akan ikut dalam penelitian selama masa terapi, tergantung pada diagnosa TB anda, atau selama 24 bulan jika lama terapi anda melebihi 24 bulan.

MENGAPA DOKTER MENGHENTIKAN KEIKUTSERTAAN SAYA DALAM PENELITIAN INI LEBIH AWAL DARI YANG DIJADWALKAN?

Anda boleh mengundurkan diri dari penelitian ini kapan saja. Jika anda berhenti, anda tidak akan diminta informasi atau data tambahan untuk penelitian ini.

Dokter pada penelitian ini dapat pula menghentikan keikutsertaan anda tanpa persetujuan anda, jika:

- Penelitian ini dihentikan, atau dibatalkan oleh pihak penyandang dana atau lembaga komisi etik penelitian.
- Anda tidak dapat hadir pada kunjungan yang telah dijadwalkan oleh penelitian.
- Akan berbahaya untuk anda jika melanjutkan penelitian ini.

APAKAH RESIKONYA IKUT PENELITIAN INI?

Peneliti-peneliti meyakini bahwa resiko atau ketidaknyamanan yang akan anda alami adalah sangat ringan, yaitu misalnya keadaan-keadaan yang berhubungan dengan pengambilan darah seperti sakit sedikit, kemerahan atau lebam pada tempat pengambilan darah. Lebam dapat dikurangi dengan kompres hangat. Ada kemungkinan terjadi infeksi pada tempat pengambilan darah, namun karena petugas akan membersihkan tempat pengambilan darah dengan alkohol dan alat-alat yang digunakan adalah steril, kemungkinan ini sangat kecil untuk terjadi.

Jika anda mengalami kesulitan dalam mengeluarkan dahak, kami mungkin membantu anda dengan menyediakan obat hirup yang bisa membantu anda untuk mengeluarkan dahak.

APAKAH SAYA MEMPUNYAI PILIHAN LAIN DISAMPING IKUT DALAM PENELITIAN INI?

Alternatif yang anda miliki adalah untuk tidak mengikuti penelitian ini. Jika anda memutuskan untuk tidak ikut dalam penelitian ini, anda tetap akan diterapi untuk gejala TB.

APAKAH ADA MANFAATNYA UNTUK IKUT DALAM PENELITIAAN INI?

Penelitian akan membayar semua biaya pemeriksaan selama terapi TB anda yang tidak ditanggung oleh pemerintah. Penelitian ini akan memberikan Rp 150,000; pada awal dan akhir penelitian untuk waktu yang terpakai dan ketidaknyamanan anda. Penelitian ini tidak akan menanggung biaya perawatan rutin atau rawat inap yang telah dijadwalkan oleh pemerintah. Hasil dari penelitian ini dapat membantu dokter anda untuk memberikan perawatan yang lebih baik dan memperbaiki tata cara pengelolaan TB.

APAKAH SAYA AKAN MENDAPAT BAYARAN?

Anda tidak mendapat bayaran untuk ikut serta dalam penelitian ini.

BAGAIMANA DENGAN KERAHASIAAN?

Semua informasi tentang anda akan dijaga kerahasiaannya dan tidak akan diberikan pada orang yang tidak bertanggung jawab untuk perawatan anda. Rekam medis anda hanya akan dipelajari oleh mereka yang bekerja untuk penelitian ini.

Semua dokumen dan sampel yang berhubungan dengan penelitian akan diberi label sesuai dengan nomor penelitian anda. Nama anda tidak akan dicantumkan pada label sampel, pada laporan penelitian maupun pada publikasi ilmiah.

APA YANG AKAN TERJADI JIKA SAYA TERLUKA?

Kami akan menyediakan dan membayar biaya perawatan yang segera harus dilakukan jika terjadi luka yang berhubungan dengan penelitian, misalnya infeksi setelah pengambilan darah. Namun, penelitian tidak dapat membayar kecacatan yang disebabkan oleh penyakit yang anda derita.

APAKAH HAK-HAK SAYA SEBAGAI PESERTA PENELITIAN?

Ikut sertanya anda dalam penelitian ini bersifat sukarela. Jika anda tidak ingin ikut dalam penelitian ini, anda tetap akan mendapatkan perawatan standar yang sama dengan mereka yang ikut dalam penelitian. Anda boleh berhenti kapan saja dari penelitian ini.

Kami akan memberitahu anda mengenai informasi baru dari penelitian ini atau dari penelitian lain yang dapat mempengaruhi kesehatan anda, kesejahteraan atau keinginan anda untuk tetap ikut serta dalam penelitian ini. Jika anda menginginkan hasil penelitian ini anda dapat memberitahu kepada petugas penelitian.

APA YANG HARUS SAYA LAKUKAN JIKA SAYA MEMPUNYAI PERTANYAAN ATAU MASALAH ?

Jika anda mempunyai pertanyaan yang berkaitan dengan studi, anda dapat menghubungi:

-Cantumkan nama peneliti atau staff peneliti lainnya.

-Cantumkan nomor telepon peneliti atau staff peneliti diatas

CONTOH FORMULIR PERSETUJUAN UNTUK ORANG DEWASA

Tuberculosis Research of INA-RESPOND On Drug Resistant

Saya telah membaca formulir persetujuan ini, atau formulir persetujuan ini telah dibacakan kepada saya. Saya telah mendapatkan kesempatan untuk bertanya, dan pertanyaan-pertanyaan yang saya ajukan telah dijawab dengan memuaskan. Saya telah dijelaskan bahwa saya dapat mengundurkan diri dari penelitian ini kapan saja.

Saya, tanpa tekanan apapun dengan sukarela memilih untuk ikut dalam penelitian ini. Saya akan diberikan salinan dari lembar penjelasan dan formulir persetujuan yang telah ditanda tangani untuk arsip saya.

Saya setuju untuk menyimpan hasil dari pemeriksaan kultur dahak saya untuk pemeriksaan genetik (keturunan) tertentu untuk melihat apakah faktor keturunan berperan untuk terjadinya infeksi ini dan perkembangan penyakit ini.

___YA ___TIDAK

Nama peserta: _____ Umur: _____

Tanda tangan*: _____ Tgl: ____/____/____
(tgl/bln/thn)

*cap jempol dapat digunakan untuk yang tidak dapat menulis

Nama peneliti: _____ Tanda tangan: _____

Tgl : ____/____/____

(tgl/bln/thn)

Nama saksi: _____ Tanda Tangan: _____

Tgl : ____/____/____
(tgl/bln/thn)