Study Title: Indonesia Brain Infection Study

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The investigators declare no potential conflicts of interest.

Confidentiality Statement
This document contains confidential information that must not be disclosed to anyone other than the Sponsor, the Investigator Team, host organization, and members of the Research Ethics Committee, unless authorized to do so.

Contents

Protocol Synopsis

Study Title	Indonesia Brain Infection Study (IBIS)
Study Design	Prospective cohort study
Objectives	*Aim:* To define clinical presentation, etiology, management and outcome of patients with central nervous system (CNS) infections in Indonesia *Specific objectives:* 1. To create an 'umbrella' and embed future intervention studies in CNS infection 2. To establish the etiology of CNS infections in adults, stratified by HIV status and clinical presentation (meningitis, encephalitis, brain abscess, myelitis) 3. To describe clinical, CSF and neuro-radiological characteristics of CNS infections according to etiology and HIV status, as a basis for clinical diagnostic algorithms and empiric treatment 4. To measure outcome of adult patients with CNS infections, and identify risk factors for poor outcome 5. To build a biorepository of patient samples for future study of etiology or pathogenesis of CNS infections *Note: These objectives will first be addressed in RSCM and RSHS, and selected studies may be extended to other hospitals Indonesia*
Target Population	Adult patients with suspected CNS infection (meningitis, encephalitis, brain abscess or myelitis)
Number of Subjects Planned	All consecutive suspected CNS infections recruited over a 5-year period (approximately 400 patients per year, total ~2000)
Study Location	Faculty of Medicine Universitas Indonesia (FKUI), Cipto Mangunkusumo Hospital (RSCM), Jakarta Faculty of Medicine Universitas Padjadjaran (FKUP), Hasan Sadikin Hospital (RSHS), Bandung
Duration of Study	60 months
Planned Start of Study	February 2019

<table>
<tr><td>Eligibility Criteria</td><td colspan="2">Inclusion criteria:
- Age 18 years or older
- Suspected CNS infection (meningitis, encephalitis, myelitis or brain abscess), as judged by the physician

Exclusion criteria:
- No informed consent obtained

Note: participants may refuse storage of blood or CSF samples, but may consent to research use of data obtained as part of routine care (clinical assessment, blood and CSF, CT, Chest X-ray, etc).</td></tr>
<tr><td rowspan="6">Study procedures

(not included in routine clinical practice)</td><td>Procedure</td><td>Comment</td></tr>
<tr><td>Identification and screening of potential participants</td><td>All suspected patients will be identified by emergency room or ward physicians, and screened for eligibility based on clinical assessment and routine cerebrospinal fluid (CSF) testing</td></tr>
<tr><td>Systematic collection of data and patient samples at time of presentation, hospital discharge and after 6 months</td><td>All clinical information will be collected and recorded using a digitalized standardized case report form (CRF)

If consent is given by the patient, CSF, blood and urine will be collected at predefined time points</td></tr>
<tr><td>Storage and systematic reading of radiological abnormalities</td><td>Brain CT- and MRI-scans will be read systematically; radiological findings will be linked to clinical and laboratory parameters; CT- and MRI-images will be stored for possible re-assessment</td></tr>
<tr><td>Non-routine microbiological testing</td><td>Non-routine microbiological tests, mostly batch-wise on archived samples</td></tr>
<tr><td>Storage of CSF and blood samples and isolated pathogens</td><td>Stored CSF and blood/plasma for future studies related to diagnosis, outcome or pathogenesis of CNS infections

Stored isolated pathogens for possible future(geno)typing or drug-resistance testing</td></tr>
</table>

Samples stored	• Cerebrospinal fluid • Blood for DNA extraction • Plasma (baseline) • Serum (baseline) • Urine • Throat swab and stool (for suspected viral encephalitis) • Isolated microbial pathogens

1 INTRODUCTION

1.1 Background

Central nervous system (CNS) infections (meningitis, encephalitis, brain abscess) are an important cause of morbidity and mortality in Indonesia, but their etiology has not been described well, diagnosis and treatment are often very difficult, and our understanding of risk factors and pathogenesis is incomplete.

In a pilot study in RSCM, a cohort of patients with suspected CNS infection was accrued. A total of 274 patients with suspected CNS infection(median age 26) presented after a median of 14 days with headache (77%), fever (78%), seizures (27%), loss of consciousness (71%) and focal signs (40%). HIV co-infection was common (54%), mostly newly diagnosed (30%) and advanced (median CD4 cell count 30/µl). Only in 30% a definite cause was established and for many patients (35%), no diagnosis could be made. In-hospital mortality was 32%, six-month mortality was 57%. Those who survived had either moderate (25%) or severe disability (11%) according to Glasgow outcome scale.

These results, recently published in Neurology Clinical Practice (Darma Imran et al, in press), underline the clinical importance of CNS infections in RSCM and highlight some of the difficulties in diagnosis and management of CNS infections.

Clinical diagnosis. Diagnosis of CNS infections depends on clinical assessment, and examination of cerebrospinal fluid (CSF), which is collected through a lumbar puncture. CNS infections may be caused by bacterial, viral, fungal, protozoal and helminth disease. Diagnostic tests for many of these diseases are not routinely performed, not available in RSCM, or not yet optimized for CSF. Improvement of current diagnostics, including for TB meningitis, use of blood or other samples (eg feces, urine, throat swabs), and recent developments in molecular diagnosis including next generation sequencing (NGS) may help increase the proportion of patients with a confirmed diagnosis[1]. Some patients with suspected infection may actually suffer from non-infectious causes of encephalitis, including autoimmune encephalitis, sarcoidosis or vasculitis[2,3].

Poor outcome of CNS infections. In the pilot study in RSCM, more than 30%of patients died within 2 weeks hospitalization, and an additional 25% during follow-up. In addition, many patients may suffer from cognitive, physical or mental sequelae of CNS infection, but this has not been studied. The high mortality and morbidity of CNS infections may be due to many factors including late presentation, late or incorrect diagnosis, drug resistance and other factors. HIV infection is an important factor. Patients with TB meningitis may die from damaging immunopathology, inadequate drug dosing, and cerebrovascular or other complications[4].

1.2 Rationale of the Study

Each year, at least 250 cases of suspected adult CNS infections are seen in RSCM Jakarta, and approximately 50% of cases are HIV-infected. Definite etiology of disease can only be established in a minority, and clinical (empiric) diagnosis is difficult. Misdiagnosis may lead to incorrect and ineffective treatment, and unnecessary morbidity and mortality. The situation in other hospitals in Jakarta may be even more difficult, as lumbar puncture and HIV testing are often not done. More insight in the etiology of CNS infections and improved clinical diagnosis will help improve treatment.

Mortality is high, but information on clinical characteristics and other factors associated with death are mostly lacking. In addition to diagnostic and therapeutic challenges, we need more insight regarding the pathogenesis of TB meningitis. This knowledge is important in order to improve the prognosis and reduce the burden of disease and help design interventions to improve outcome.

Therefore, we aim to extend the clinical cohort of CNS infections. First, we will try to establish the etiology using a combination of conventional and new laboratory methods. Together with careful clinical characterization this should help us improve clinical diagnosis and empiric treatment.

Second, careful follow-up and survival analysis will establish the functional outcome of patients and identify risk factors for poor outcome. Third, extension of the biorepository will allow future studies related to patient immunological, metabolic or genetic factors that determine susceptibility to and outcome of CNS infections[5], and secondary studies (e.g. sequencing) of isolated pathogens. This will be done using the best available platforms in RSCM/FKUI, RSHS/FKUP, IOCRL/EOCRU and Eijkman Institute and expert laboratories outside Indonesia if necessary. Finally, this cohort study will be the necessary basis for future randomized studies.

Once the IBIS cohort study is running well in RSCM and RSHS, we aim to involve other hospitals in Indonesia as much as possible in all these activities. This study is expected to improve the quality of patient care in the hospital and through dissemination of findings in other hospitals in Indonesia. IBIS can function as an 'umbrella' for sub-studies (like qualitative research focusing on barriers to care) or intervention studies related to treatment, and pave the way for RSCM and RSHS to lead or participate in future multi-center studies. The observational cohort may also be expanded to other Indonesian hospitals, sharing the research protocol and data collection tools, ideally with a centralized database.

2 Aim & Objectives

2.1 General Aim

To define clinical presentation, etiology, management and outcome of patients with central nervous system (CNS) infections in Indonesia

2.2 Specific Objectives

1. To create an 'umbrella' and embed for future intervention studies in CNS infection, such as patient interviews or randomized clinical trials
2. To establish the etiology of CNS infections in adults, stratified by HIV status and clinical presentation (meningitis, encephalitis, brain abscess, myelitis)
3. To describe clinical, CSF and neuro-radiological characteristics of CNS infections according to etiology and HIV status, as a basis for clinical diagnostic algorithms
4. To measure outcome of adult patients with CNS infections, and identify risk factors for poor outcome
5. To build a biorepository of patient samples for future study of etiology or pathogenesis of CNS infections

Note: These objectives will first be addressed in RSCM and RSHS, and selected studies may be extended to other hospitals in Jakarta/Indonesia

2.3 Outcome / Result

- Necessary ground work for future intervention studies to improve diagnosis and treatment of CNS infections in RSCM and RSHS, with possible collaboration with other Indonesian hospitals or in multi-center international consortia
- Etiology of adult CNS infections in an Indonesian setting
- Clinical diagnostic algorithms
- Clinical characteristics, treatment and outcome of CNS infections (including survival data, neurological sequelae and associated risk factors)
- HIV prevalence, and effect of HIV on clinical characteristics and patient outcome
- Database and biorepository (CSF, blood, bacterial isolates) for possible future research
- Scientific publications and increased research capacity
- Options for strengthening CNS infection network in Jakarta and Indonesia
- Strengthened international scientific collaboration

3 STUDY DESIGN

The study is an observational cohort study in adults with suspected CNS infection (meningitis, encephalitis, brain abscess, myelitis). Patients will be recruited at RSCM and RSHS and followed up for 6 months with assessments at enrolment, at hospital discharge, and after 6 months. Clinical care and treatment guidelines follow the current standard of care in the hospital in accordance with national guidelines

Antimicrobial treatment will be given in accordance with the hospital guidelines, and in consultation with specialists in neurology and infectious diseases. HIV treatment will follow national guidelines. Lumbar puncture will be performed before the start of treatment and later during treatment if indicated as per normal clinical care.

4 STUDY PARTICIPANTS

4.1 Study participants

All patients presenting or admitted at RSCM, Jakarta, or RSHS, Bandung, who have a clinical suspicion of CNS infection (meningitis, encephalitis, brain abscess, myelitis), as judged by the treating physician, will be eligible for the study.

4.2 Inclusion criteria

- Participant is willing and able to give informed consent for participation in the study (surrogate/family may obtain consent for unconscious or incapacitated participant).
- Male or Female, aged 18 years or above.
- Diagnosed with suspected CNS infection (meningitis, encephalitis, myelitis or brain abscess), as judged by the physician.

4.3 Exclusion criteria

The participant may not enter the study if no written informed obtained.
No other exclusion criteria will be used**.**

Note: participants may refuse storage of blood or CSF samples, but may consent to research use of data obtained as part of routine care (clinical assessment, blood and CSF, CT, Chest X-ray, etc).

5 STUDY PROCEDURES

5.1 Screening, Eligibility Assessment, Recruitment

As part of routine care, all patients with suspected CNS infection will be identified by emergency room or ward doctors, mostly residents in neurology. As per routine care patients will have a clinical assessment, including demographics, medical history, concomitant medication, physician examination, and laboratory tests, lumbar puncture and neuroimaging on indication. Only patients with clinical suspicion of CNS infections, as judged by the treating physician, will be approached to enroll in the cohort. All patients with suspected CNS infections are routinely tested for HIV, using a provider-initiated testing and counseling (PITC) approach, in line with national and hospital policy. The results of these tests will be available for study screening.

A screening log will be kept on the ward, with a record of all patients screened and how they met/did not meet the study entry and exclusion criteria. Patients who do not meet the study criteria will be informed as such and treated as per best available clinical care.

5.2 Informed consent

This is not an intervention study, but patients will be approached to provide written consent to systematically record clinical data and collect and store blood, urine and CSF. Unique study numbers will be used for all CRF and patient samples, which will be devoid of identifiable data like name and address. The study participant must personally sign and date the latest approved version of the Informed Consent form before any study specific procedures are performed. Written and verbal versions of the Participant Information and Informed Consent will be presented to the participants detailing no less than: the exact nature of the study; what it will involve for the participant; the implications and constraints of the protocol; the known risks involved in taking part. It will be clearly stated that the participant is free to withdraw from the study at any time for any reason without prejudice to future care, without affecting their legal rights, and with no obligation to give the reason for withdrawal. The participant will be allowed as much time as wished to consider the information, and the opportunity to question the Investigator or other independent parties to decide whether they will participate in the study. Written Informed Consent will then be obtained by means of participant dated signature and dated signature of the person who presented and obtained the Informed Consent. If the study doctor judges that the patient does not have mental capacity to provide informed consent (for any reason, but most likely to be confusion or coma secondary to infection) they will obtain informed consent from the patient's representative (usually a relative). If consent is provided by a representative and the patient regains the capacity to consider participation during the study period, the patient should be consulted and informed consent to continue the study obtained. Patient information and informed consent form are provided in local language (Bahasa Indonesia); English and Indonesian versions of the forms are listed in **Appendix 1**. The person who obtained the consent must be suitably qualified and experienced and have been authorized to do so by the Principal Investigator. A copy of the signed Informed Consent will be given to the participant. The original signed form will be retained at the study site.

5.3 Assessment at baseline

For study participants who have signed informed consent routine data will be recorded on the baseline CRF. If necessary, additional history taking and clinical examination will be performed to complement any missing information.

Data collected as part of routine care include:

- Clinical assessment, including demographics, medical history, concomitant medication, physician examination

- Laboratory testing on CSF and blood, including complete blood count (CBC); blood chemistry, including liver function tests and renal function tests; HIV testing; CD4 cell count and cryptococcal antigen test if HIV-positive; routine CSF examinations (cells, protein, glucose with paired plasma glucose).
- Routine microbiological testing will include CSF lateral flow assay (LFA), AFB microscopy (modified technique), PCR TB, geneXpert, India-Ink microscopy and Gram-staining for bacterial meningitis.
- Radiology: chest X-ray; and brain-CT or MRI

Study-specific procedures include:

- Systematic collection of clinical data, using a standard Case Record Form;
- Additional microbiological testing for viral and bacterial etiologies (mostly batch-wise retrospectively) ;
- Collection and storage of CSF and blood samples, urine (at time of enrolment) and isolated microbial pathogens for future study.
- FujiLAM (lipoarabinomannan) testing for urine sample in both HIV positive and HIV negative subjects
- Autoimmune encephalitis panel for suspected autoimmune encephalitis cases (Glu NMDA, Glu AMPA, DPPX, Gaba B, Glycine, VGKC, LGI1, CASPR2 receptor antibodies)
- Autoimmune myelitis panel for suspected autoimmune myelitis cases (AQP4 and MOG receptor antibodies)

5.4 Follow-up

Patients will be followed up as per routine care. Additional systematic assessments will be done at the following 4 time points:

1. *Day-7 assessments*
   On day 7 after enrolment, patients will be assessed for their early clinical response in terms of body temperature, GCS, and adverse events (including decubitus ulcer, pneumonia and gastric bleeding) by the study team during hospital admission.

2. *Day-30 assessments*
   On day 30 after enrolment, patients will be assessed for their early clinical response in terms body temperature, GCS, and adverse events (including decubitus ulcer, pneumonia and gastric bleeding) by the study team. This visit may occur during hospital admission or, in case the patient has already been discharged, in the outpatient clinic.

3. *Hospital discharge or death*
   Data will be extracted from hospital records and supplemented by additional history taking if needed. Data will include clinical and functional assessment, outcome when discharged and additional procedures during hospitalization, including additional lumbar puncture, CT scan/MRI, neurosurgical procedure, admission to ICU, and the use of mechanical ventilation. Discharge diagnosis (confirmed or presumptive, see 4.4), will also be recorded. Liverpool Outcome Score and Extended Glasgow Outcome scale will be used to assess the functional outcome at discharge. For those patients that have died a presumptive cause of death will be recorded.

4. *Six months after enrolment*

The patient will be evaluated during a hospital visit by the study doctor. If no show, patients will be contacted by phone or visited at home. Data will include clinical and functional assessment, medication, and possible rehospitalisation since discharge. If patients die after discharged (but within 6 months), verbal autopsy will be done by history taking of family / household members or possible assessment of medical records.

Study-specific procedures include:

- Systematic collection of clinical data at time of hospital discharge and 6 months after enrolment, using a standard Case Report Form.

5.5 Diagnostic classification

Diagnosis will be evaluated at three time points. All diagnoses will be reviewed by the principal investigator, and final diagnostic classification will be done by consensus. Both a<u>syndromic diagnosis</u> (meningitis, encephalitis, brain abscess, myelitis) and an <u>etiological diagnosis</u> (e.g. cryptococcal meningitis, toxoplasma encephalitis), either confirmed or suspected, will be made.

1. *Initial diagnosis*

- Recorded <48 hours after presentation by the neurologist, in consultation with pulmonologist or internist as indicated, based on actual care provided (even when culture results, neuro-imaging and sometime CSF-examination is not available) (baseline CRF).
- This diagnosis is used to guide initial/empiric treatment and planned additional investigations if indicated
- This systematic baseline assessment is made by the study physician in consultation with the treating physician and study PI. It will not be changed after 48 hours to allow assessment of the diagnostic process.

2. *Discharge diagnosis*

- At time of hospital discharge or death, an updated diagnosis will be made based on more complete data from the hospitalization period (including response to treatment).
- This diagnosis is used to evaluate the diagnostic process during hospitalization and to guide treatment and follow-up after hospital discharge;
- This systematic assessment is made by the study physician in consultation with the treating physician and study PI.

3. *Final diagnosis*

- The ‘discharge diagnosis’ will be reassessed with all information available, including batch-wise retrospective microbiological testing;
- The final diagnosis will be used for epidemiological, diagnostic and prognostic analyses of the cohort data;
- The final diagnosis is made by the study PI and team using consensus.

Definitions of syndromic diagnosis

- Meningitis: a combination of any of the following: fever, headache, evidence of meningeal irritation, seizures and/or altered mental status and focal neurological signs.
- Encephalitis: a combination of altered mental status (decreased or altered level of consciousness, lethargy, or personality change) and fever, or generalized or partial seizures, with or without focal neurological signs.

- Myelitis: a combination of sensory, motor, or bladder or bowel dysfunction attributable to the spinal cord. Symptoms which progress to nadir within 4 hours to 21 days following onset are considered as acute myelitis[6].
- Brain abscess: Collection of intracranial pus as diagnosed by aspiration (confirmed) or neuroimaging procedures (probable)[7].
- No suspicion of CNS infection. Confirmed alternative diagnosis (e.g. brain tumor) or: no suspicion of CNS infection based on clinical signs and/or CSF findings and/or CT-scanning

Signs of meningitis and encephalitis can overlap, in which case the predominant presentation (headache and meningeal irritation for meningitis and behavioral/mental signs or seizures for encephalitis) is leading.

Meningitis and encephalitis can be divided into acute (acute onset and/or < 7 days duration of neurological symptoms) and subacute/chronic (subacute onset and/or >7 days symptoms). With long patient or doctor's delay, some patients with acute meningitis/encephalitis may present >7 days after start of symptoms.

Where possible, a more precise diagnosis will be made using definitions used under 'final diagnosis'

Definitions of etiological diagnosis

- TB meningitis (TBM). positive CSF microscopy, geneXpert or *M. tuberculosis* culture (definite TBM); or subacute meningitis with CSF: blood glucose ratio below 0.5 and CSF leukocytes >5/ul and exclusion of other diagnoses (probable TBM)[8]. The international TBM diagnostic criteria will also be employed[9]. Patients will be classified as 'possible TBM' if they do not fulfil criteria for definite or probable TBM or other etiology and are treated for TBM at the doctor's discretion
- Cryptococcal meningitis (CM). positive CSF India Ink or cryptococcal antigen test or *Cryptococcus* culture (definite CM); or HIV infection with subacute meningitis and positive serum cryptococcal antigen test if no lumbar puncture can be done (probable CM) [10]
- Bacterial meningitis (BM). meningitis with positive CSF Gram stain or culture (definite ABM); compatible syndrome, positive blood culture with relevant pathogen, plus 1 of the following CSF changes; >5 leukocytes/mm^3; Glucose of <40 mg/dL or CSF/blood glucose ratio <0.5 or; Protein of >100 mg/dL (probable BM); Compatible clinical syndrome, plus one of the following CSF changes; >100 leukocytes/mm^3; Glucose of < 40 mg/dL or CSF/blood glucose ratio <0.5 or; Protein of >100 mg/dL plus negative cultures or antigen for bacteria, viral, fungal, or mycobacteria (possible BM) [11]
- Neurosyphilis. Reactive CSF-VDRL or intrathecal TPHA production and elevated CSF cell countplus exclusion of alternative diagnoses[12].
- Toxoplasma encephalitis (TE). Positive CSF *toxoplasma gondii* PCR (definite TE); or HIV-infected patient andone or more cerebral mass lesions on CT or MRI andpositive serum toxoplasmosis IgG, and exclusion of an alternative diagnosis (probable TE) [13].
- Viral encephalitis. Positive CSF PCR for HSV, CMV, VZV or other neurotropic virus and altered mental status plus 2 or more of the following: fever ≥38° C; seizures; new onset of focal neurologic findings; CSF WBC count ≥5/mm^3; abnormality of brain parenchyma on neuroimaging suggestive of encephalitis[14].
- Brain abscess. Confirmed case defined as positive aerobic or anaerobic or acid-fast bacilli or fungal cultures from pus of brain abscess[7].
- Myelitis. Development of sensory, motor, or autonomic dysfunction attributable the spinal cord. Bilateral signs and/or symptoms (though not necessarily symmetric) with clearly defined

sensory level. Exclusion of extra-axial compressive etiology by neuroimaging (MRI or myelography; spinal CT not adequate)[6].

- Possible autoimmune encephalitis. Subacute onset (rapid progression of less than 3 months) of working memory impairment (short-term memory loss), altered mental status, or psychiatric symptoms; and at least one of new focal findings or unexplained seizure or CSF pleocytosis (WBC >5 cells/mm^3) or MRI features suggestive of encephalitis; and reasonable exclusion of alternative causes [2].
- Encephalitis of unknown origin. Altered mental status plus 2 or more of the following: fever ≥38° C; seizures; new onset of focal neurologic findings; CSF WBC count ≥5/mm^3; abnormality of brain parenchyma on neuroimaging suggestive of encephalitis (with negative CSF virological examination).
- CNS infection of unknown origin. Suspected CNS infection based on combination of compatible clinical signs, CSF findings and brain CT scan with no other diagnoses (based on consensus).
- No suspicion of CNS infection. Confirmed alternative diagnosis (eg brain tumor)or: no suspicion of CNS infection based on clinical signs and/or CSF findings and/or CT-scanning (consensus). Alternative diagnosis (confirmed/presumptive) will be recorded.

5.6 Description of Study Procedures

Most of the examinations done under the study are parts of routine care, therefore considered not study related.

The non-routine procedures that will be performed in this study are as follow:

a. Identification and screening of potential participants.

Patients with possible CNS infections will be identified by emergency room physicians or medical residents. A study physician will be notified, and he/she will further screen patients for eligibility, based on clinical assessment and routine cerebrospinal fluid (CSF) testing or neuroimaging (if available).

b. Systematic data collection using case record form

Signs and symptoms, risk factors, treatment data, and routinely collected clinical data (CSF, blood tests, neuroimaging etc) will be systematically recorded in a standard CRF at baseline, discharge/death and 6 months after enrolment. This information will be entered into a digital database system. For identification of data a unique research code will be used, and no patient identifiers like name or address. The key linking study number and patient identifiers will be held by the principal investigator.

c. Systematic reading of brain CT- and MRI-scans

A uniform examination protocol and reading checklist will be developed for examination of brain CT- and MRI-scan. Two experienced radiologists will independently score each scan, disagreement between reading results will be solved by consensus.

d. Non-routine microbiological testing

Non-routine microbiological tests include extensive virologic examination, mostly batch-wise on archived samples, and using different subgroups of patients (e.g. HIV-positive versus – negative, or those with a brief versus a longer disease history). This will be done using an iterative process, based on study results, published literature, and introduction of new diagnostic tests.

e. Archiving of CSF and blood samples and isolated pathogens

CSF, urine and blood/plasma at time of enrollment and plasma/serum at time of discharge will be stored at -80 C, labelled with study number and date (and no patient name) for future studies related to diagnosis, outcome or pathogenesis of CNS infections. Similarly, pathogens isolated, including *M. tuberculosis* isolates, will be stored.

f. Follow up, including tracing lost-to-follow-up

Patients started on treatment for suspected/confirmed CNS infection will be systematically assessed at time of discharge/death and 6 months after presentation. Patients not returning for follow-up will be traced by phone calls/home visits. Verbal autopsy will be done on family/household members of patients who die after hospital discharge but within 6 months.

6 DATA MANAGEMENT AND ANALYSIS

6.1 Sample Sizes

No sample size is calculated. For this explorative study, all consecutive patients within a 5-year period will be included. We expect to include ~400 patients per year, total ~2000 patients over a 5-year period, of whom around 50% will be HIV-infected. This will make it one of the largest studies in Asia[15-18].

6.2 Data Recording and Record Keeping

All data obtained during the study will be recorded using an electronic database system. For each subject enrolled, a baseline digital CRF will be completed by the study physician < 48 hours after presentation, and approved by the principal investigators. A discharge/death CRF will be completed < 48 hours after death/discharge. Each study subject and each sample (blood, CSF, cultures yielded from the specimen) will be allocated a specific 6-digit code. The key to this coding system is only accessible for the principal investigators. Patients that are re-admitted will get a new study number, but information on prior admission is noted, and the digital database allows tracking readmissions using medical record numbers (RSCM patients have one number only)

6.3 Retention of Records and Data Access

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified: protocol/amendments, CRF, IEC approval with correspondence, informed consent, other appropriate documents and correspondence. All study documents must be retained by the investigator until at least 5 years after the study. Direct access will be granted to authorized representatives from the Sponsor and host institution for monitoring and/or audit of the study to ensure compliance with regulations.

6.4 Sample Use and Storage

Samples collected will be used for the purpose of this study as stated in the protocol and stored for future use in studies not yet conceived, which may include genetic studies. Any proposed plans to use samples other than for diagnostic purposes or investigations detailed in this protocol will be submitted to the relevant ethics committees prior to any testing. Consent will be obtained from study participants for genetic testing and sample storage. Stored samples (blood/plasma, CSF, urine, microbial pathogens) will be kept under appropriate condition at the Universities of Indonesia and Oxford Clinical Research Laboratory (IOCRL), situated on the RSCM/FKUI campus, and RSHS/FKUP, for retrospective diagnostic testing. Samples will be numbered using unique digital numbering. Samples will be kept for other analyses related to meningitis or tuberculosis, or susceptibility to (tuberculous) meningitis. For investigations that cannot be performed locally, a specific MTA will be made.

6.5 Statistical Analysis of Outcome Measures

Objective 1. Etiology

Etiological diagnoses will be presented as percentage with 95% confidence interval and stratified according to HIV status. Results will be reported according to the Standards for the Report of Diagnostic accuracy studies (STARD) [19].

Objective 2. Clinical presentation and clinical diagnosis

Clinical, CSF and neuro-radiological characteristics of CNS infections will be described as percentage (95% CI) for categorical variables, and mean (SD) or median (range) for normally and non-normally distributed continuous variables. Comparisons between groups of patients with

different etiology or HIV-status will be made using Ch-square (percentages), student T or Mann-Whitney test (continuous).

The diagnostic value of selected clinical, CSF and radiological parameters will be expressed as sensitivity, specificity and negative / positive predictive value. Multivariate logistic regression and recursive partitioning will be used to develop diagnostic algorithms using clinical, CSF and neuroimaging data with reference diagnosis of CNS infections, as has been done for other infections [1,20].

Objective 3. Survival analysis

Analysis of patient factors associated with outcome will be used for logistic regression. Factors with evidence of an association with the outcome in the univariable analysis will be included in the multivariable model and retained in the model if the *P* value <0.05.Kaplan-Meier curves will be used to illustrate patient survival over time, comparing HIV-infected and non-infected patients, patients with selected disease etiology, or specific patient factors. Survival analysis will be performed where indicated.

6.6 Ancillary studies

1. IBIS 1: Focus on CNS infection etiology (*IBIS 1: Studi eksplorasi etiologi infeksi otak*)

CNS infections cases associated with high number of morbidity and mortality, especially in Indonesia with emerging number of HIV cases. Establishing a diagnosis of CNS infections is often difficult, as lumbar puncture still considered as high risk procedure to patients/family and even healthcare workers. Based on previous study in RSCM, definite diagnosis can only be found in 30% subjects, clinical diagnosis in 36%, and unknown diagnosis in 34%. Even when definite diagnosis is made, treatment is also challenging as CNS infections patients came in advanced stage.

One barrier in establishing diagnosis in CNS infections is limited diagnostic capacity, especially micobiological tests. With high TB burden in Indonesia, TB diagnostic panel as first line initial diagnostic in all patients with suspected CNS infections is recommended. This study is funded by Dana Hibah Riset IPTEKKES 2019, and **will only be eligible for Jakarta site (RSCM)**.

2. Sub-study: Identifying tuberculosis meningitis (TBM) patients' pathways and the associated out-of-pocket costs prior to hospital admission in Indonesia

Details on sub-study are available under Appendix 3.

7 Ethical considerations

7.1 Declaration of Helsinki

The Investigators will ensure that this study is conducted in accordance with the principles of the Declaration of Helsinki.

7.2 Guidelines for Good Clinical Practice

The Investigators will ensure that this study is conducted in accordance with relevant regulations and with Good Clinical Practice.

7.3 Approvals

The protocol, informed consent form, participant information sheet and any proposed advertising material will be submitted to the Research Ethics Committee (REC) of the Faculty of Medicine Universitas Indonesia and Oxford Tropical Research Ethics Committee (OxTREC) for written approval. The Investigator will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents.

7.4 Reporting

The PI shall submit once a year throughout the study, or on request, an Annual Progress report to the ethics committee and Sponsor. In addition, an End of Study notification and final report will be submitted to the same parties.

7.5 Participant Confidentiality

The study staff will ensure that the participants' anonymity is maintained and that their identities are protected from unauthorized parties. All data related to the study subjects is considered to be confidential. The participants will be identified only by a participant ID number on all study documents and any electronic database, with the exception of the CRF, where participant initials may be added. All documents will be stored securely and only accessible by study staff and authorized personnel. The study will comply with the Data Protection Act, which requires data to be anonymized as soon as it is practical to do so.

7.6 Risks and Benefits

There is no clear direct benefit to the study participant, although patients may receive more comprehensive and precise examination and monitoring than routinely done. This is not a clinical trial, and there is no specific risk involved. Blood and cerebrospinal fluid will be taken as per clinical routine. One additional blood tube and urine will be taken for storage.

The study may improve the general standard of care for CNS infection, in terms of performance of health staff, laboratory procedures and clinical SOPs.

The study will have a scientific benefit, both in terms of data collected in this particular study as well as in terms of research capacity building, and networking and collaboration with other institutes.

7.7 Funding

IBIS ancillary study, titled as IBIS 1: Focus on CNS infection etiology exploration, is funded by Dana Hibah Riset IPTEKKES 2019, ministry of health, Indonesia. This fund will only be eligible for Jakarta site (RSCM), and valid for subject recruitment until end of 2019.

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APPENDIX 1: INFORMED CONSENT FORMS

APPENDIX 2: AMENDMENT HISTORY

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made
1	1.3	15 Oct 2019	Dr. Kartika Maharani, SpS Dr. Darma Imran,SpS(K)	• Funding: IBIS ancillary study, titled as IBIS 1 is funded by Dana Hibah Riset IPTEKKES 2019. • FujiLAM (lipoarabinomannan) urine testing for HIV positive subjects • Additional assessment: Autoimmune encephalitis panel and Autoimmune myelitis panel
2	2.0	03 Feb 2020	Dr. Darma Imran, SpS(K)	• FujiLAM testing for both positive and negative HIV subjects • *Day-7* clinical assessment • *Day-30* clinical assessments • Sub-study: Identifying tuberculosis meningitis (TBM) patients' pathways and the associated out-of-pocket costs prior to hospital admission in Indonesia

List details of all protocol amendments here whenever a new version of the protocol is produced. This is not necessary prior to initial REC submission.