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ORIGINAL ARTICLE

A protocol on Information-Motivation-Behavioural Skills Risk of Intensive Phase Treatment Interruption Among Pulmonary Tuberculosis Patients in Urban Districts, Selangor

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ABSTRACT

Introduction: Despite advancement of treatment modalities, Tuberculosis (TB) treatment interruption rate has globally accelerating, calling for greater framework shifting towards psychosocial intervention. Similarly, Selangor state had reported the perturbing TB treatment interruption rate, which was figured persistently above 10% in the interval year of 2014 to 2018, thus signifies an empirical assessment on Information-Motivation-Behavioural skills (IMB) determinants of TB intensive phase treatment. This study aims to determine the time to intensive phase TB treatment interruption and its prognostic factors among newly diagnosed pulmonary Tuberculosis (PTB) smear positive patients in urban district Selangor. **Methods:** A multi-centric prospective cohort study will recruit 695 newly diagnosed PTB smear positive patients at treatment centres in urban districts, Selangor. This study will utilize validated self-administered questionnaire and standardised data collection form (PROFORMA). At baseline, we will elicit information on IMB models constructs, additionally on socio-demographics, health service factors and clinical characteristics. Meanwhile, four points follow up will be executed to retrieve information on treatment status and time varying effects of body weight, treatment side effects, symptoms improvement and internalised stigma. Finally, survival analysis will be computed to identify the time to intensive phase treatment interruption and its prognostic factors. **Conclusion:** This study will enlighten IMB model determinants of intensive phase treatment interruption, hence to endeavour psychosocial elements in designing time relevant public health strategies in TB case management.

Keywords: Tuberculosis, Treatment interruption, Survival, Time to event analysis, IMB model

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INTRODUCTION

TB treatment interruption rate has increasingly recognised as a global public health concern. Despite advancement of therapeutic modalities, TB treatment interruption rate ranged from 10% to 30% across the developing countries (1-2). In the light of halting global accelerated TB treatment interruption, WHO has emphasized several strategies by means of policy and legislative framework, which include Directly Observed Treatment, Short-course (DOTS) as the core policy, fee exemption policy for anti-TB drug in developing countries and fixed-dose combination tablets for TB treatment (3-4). Likewise, the defaulter tracing and retrieval system is distinctly outlined through National Tuberculosis Control Program in Malaysia (5). Notwithstanding rigorous measures targeted to optimise acceptance and access to TB treatment, TB treatment interruption remains as a global public health challenge across the nations (6-7).

World Health Organization (WHO) has characterized TB treatment interruption as history of stopping treatment for two or more consecutive months (8). Importantly, early treatment interruption in intensive phase has been emphasized in Malaysian Tuberculosis Clinical Practice Guideline 2012, which refers to 14 days or more of treatment interruption, thus warrants treatment re-start (9).

A large and growing body of literature has investigated the devastating consequences of TB treatment interruption. Few researchers demonstrated that non-adherent patients took longer duration for culture conversion, required longer treatment regimes, and signified TB mortality through mechanism of treatment failure and drug resistance (10-11). Likewise, the delayed sputum conversion led to considerable amount of psychosocial impacts and prolonged infectiousness in the community (11-12). Importantly, TB treatment interruption significantly poses economic depletion through increase of hospital admission and prolonged course of treatment completion (13).

In the recent years, a number of researchers delicately

examined the median time to TB treatment interruption particularly in high TB burden countries (14-17). A prospective cohort study involving newly diagnosed PTB smear-positive patients in Bandung, Indonesia revealed that the median time to treatment interruption was 36 days (14). Accordingly, previous researchers (15-16) reported that the median time of TB treatment interruption was towards the completion of the intensive phase during respective assessments at Kenya and West Africa. In contrast, a systematic review which derived from temporal data demonstrated that maintenance phase was the point of exit from treatment (17). Above all, it was demonstrated that poor compliance during intensive phase was the risk factor of unfavourable treatment outcome, thus pointing out the importance of treatment adherence during intensive phase (18).

Meanwhile, previous longitudinal studies explicitly highlighted those clinical factors, behavioural and health service factor were prognostic factors of TB treatment interruption. Among them was HIV positive patients who had higher probability of defaulting TB treatment (16,19). Despite limited assessment of cognitive and behavioural aspect, Hill et al. (20) demonstrated that those who perceived the benefit of treatment had higher survival probability of TB treatment interruption. As for health service factor, it was evidenced in previous study that travel distance was significantly associated with higher rate of defaulting during maintenance phase mainly due to built-up cost over the time (20-21).

In Malaysia, treatment interruption rate has been persistently above 4%, in the interval year of 2013 to 2016, as compared with 2% of national target (22). Evidently, it depicts a significant economic burden to the country, as treatment interruption in Malaysia has required an additional annual projection of USD 5.3 million mainly for treatment restart, prolonged course of treatment, prolonged hospitalization and drug resistance TB treatment (23). Being the most populous and urbanized state in Malaysia, Selangor state has encountered considerable challenges in implementing TB control strategies (24). Since 2014 to 2018, TB treatment interruption rate in Selangor was accelerated and far exceeding the 2% of national target, reported as 13%, 10.8%, 9.3%, 9.0% and 11.3% for respective year (25).

The urbanization impacts on biomedical and organizational structure in health services can be hampered by disregarding individual psychosocial assessment and intervention (26). Information-Motivation-Behavioural Skills (IMB) model was originally designed to conceptualize psychosocial determinants of HIV risk and preventive behaviour via three main constructs including information, motivation, and behavioural skills (27). Conceptually, individuals who are well informed, motivated to act and possess the prerequisite behavioural skills will likely to execute the positive outcome (28). Its applicability was empirically evidenced during assessments of TB treatment adherence. During the evaluation of TB treatment interruption in Colombia, Mateus-Solarte and Carvajal-Barona (29) proposed that the motivational factor delineated the strongest impact on treatment completion. Similarly, IMB Model was used to point the possible causal mechanisms linking the risk factors and TB treatment default during assessment of treatment adherence in Morocco, hence signified the contribution of each IMB model construct onto TB treatment interruption (30).

As one of social determinant, TB stigma has potentially led to negative impact on TB control through delayed diagnosis and high drop outs from DOTS programme (31). This mechanism derives from sentiment of disgrace and blame, which lead to self-isolation as TB-infected individuals internalize their community's sceptical judgments about the disease (31-32). Despite numerous qualitative assessment of psychosocial aspect, too little attention has been paid for quantitative assessment of TB stigma impact on treatment interruption (32-33).

Therefore, this study will identify the IMB model determinants of intensive phase treatment interruption, with further conceptualization of psychosocial aspect particularly motivational factor. Beyond knowledge and attitude domain, the influence of perceived social support and internalised stigma on time to intensive phase TB treatment interruption will be empirically examined, hence adding value to the research gap. In the same boat, this study will examine the influence of socio-demographic, high risk behaviour, clinical characteristics and health service factors onto timing and survival probability of TB treatment interruption. The conceptual framework is presented in Fig. 1.

The upsurge of TB disease burden, emerging drug resistance, and unfavourable treatment outcomes in Selangor are collectively heightened the need of local, psychosocial and theory based assessment of time to treatment interruption among newly diagnosed PTB smear positive patient in urban districts, Selangor. Therefore, this study aims to identify the time to intensive phase TB treatment interruption, the survival probability and its prognostic factors among newly diagnosed PTB smear positive patients in urban district Selangor.

MATERIALS AND METHODS

Study design and study location

Selangor state is located on the west coast of Peninsular Malaysia and is administratively divided into nine districts namely Petaling, Klang, Kuala Langat, Hulu Langat, Sepang, Sabak Bernam, Kuala Selangor and Hulu Selangor (34). Meanwhile, the urban districts in Selangor are those districts governed by respective municipal council which include Petaling, Hulu Langat,

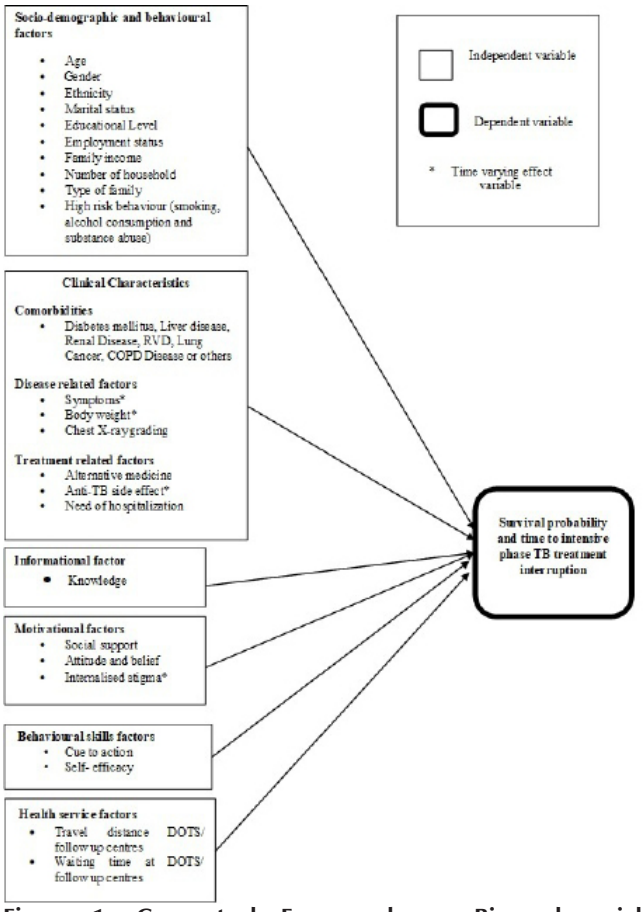

Figure 1: Conceptual Framework on Biopsychosocial Predictors of Adolescent Aggression

Klang, Gombak and Sepang (34-35). For the study purpose, a multi-centric prospective cohort study will be conducted at 40 public TB Treatment Centres One (operationally known as Pusat Rawatan Satu [PR1]) in urban districts, Selangor. TB Treatment Centres One are government hospitals or health clinics, those function as centres for TB diagnosis, treatment and scheduling TB treatment follow up.

Study population and patient selection

The study population consists of newly diagnosed PTB smear positive patients who started treatment at TB Treatment Centres One in urban districts, Selangor. In term of patient's selection, the inclusion criteria are new cases of PTB smear positive, Malaysian, aged 18 years and above, able to understand Malay or Chinese (Mandarin) language, and mentally capable. Meanwhile, patient with any of following criteria will be excluded from the study. They are TB patients who have their diagnosis changed to non-TB diagnosis, foreigners, multi-drug resistant TB patients, severely ill patients upon study recruitment, patients with pre-existing mental illness on treatment or suggestive of depressive symptoms as further verified by Patient Health Questionnaire (PHQ-9) assessment, or those identified with Malay or Chinese (Mandarin) language barrier.

Sample size estimation and sampling method

Sample size was calculated based on the formula (36) that test time-to-event data (Cox Proportional Hazard, and equivalence), which delineated as follows;

$$n = \frac{1}{p_A\, p_B\, p_E}\left(\frac{z_{1-\alpha} + z_{1-\beta/2}}{\delta - |\ln(\theta)|}\right)^2$$

Whereby:
Θ = hazard ratio
ln(θ) = natural logarithm of the hazard ratio, or the log-hazard ratio (travel distance treatment centre)
pE = overall probability of the event occurring within the study period
pA and pB = proportions of the sample size allocated to the two groups, named 'A' and 'B'
n = total sample size
δ = testing margin

Using estimation for hazard ratio, θ of 3.0 (travel distance factor, estimated for study population), pE of 0.20, pA of 0.5, pB of 0.5, δ of 0.5, power of 80%, and confidence interval of 95%, therefore the calculated sample size was 438. Finally, after adjustment for drop-out rate of 30% and non-eligibility of 10%, the estimated sample size was 695. From January to June 2018, surveillance data (*my*TB) showed a total of 853 newly diagnosed PTB smear positive patients were started TB treatment in urban districts Selangor (25). Therefore, all eligible patients those started TB treatment during the recruitment period will be included in the study.

Study outcome

The outcome of interest is intensive phase treatment interruption. It is defined as treatment interruption for 14 days or more, or loss to follow up (9). Besides, this outcome is binary variable with zero (0) is when the subject is censored and one (1) is when the subject has event occurred (intensive phase treatment interruption). Patients will be considered censor if (1) they have not experienced the event (intensive phase treatment interruption) at day 60 of TB treatment; or (2) died regardless the cause; or (3) move away or transfer to other treatment centre outside the study location.

Each consented patient will be followed up throughout the intensive phase, generally to elicit the survival times and the survival probability. Zero time is the date of starting TB treatment. Meanwhile, the end point is day 60 of treatment day. In term of survival time, it refers to the days from the day one (1) of TB treatment until the last day of recorded treatment before treatment interruption occurs, or loss to follow up, or until when the data is censored.

David Kleinbaum (37) denotes survival probability or survival function 'is the probability that a person survives longer than specified time, t'. In this assessment, it reflects on the probability of surviving from the date of treatment initiation until day 60 of treatment. Hence, the survival probability at baseline, second, fourth, sixth, and eight week are referred to the percentage of patients who still

at treatment at baseline, week 2, week 4, week 6 and week 8 respectively, since the TB treatment is initiated.

Study recruitment and study procedure
The recruitment period will take place for six (6) months duration. During this interval period, all newly diagnosed PTB smear positive patients who started TB treatment at involving treatment centres one (PR1) will be included in the study. The list of patients who diagnosed with PTB smear positive will be retrieved on daily basis from TB patient registration book that is available at each treating centre. Therefore, all newly diagnosed PTB smear positive patients who presented to medical wards and TB clinics will be screened for eligibility. Upon recruitment, enumerators will discuss with site investigator (treating physician) whether the patient meets the inclusion criteria. Reasons for exclusion and possible refusals will be recorded.

At baseline (upon treatment initiation), a self-administered questionnaire is filled up by respondents to collect data on socio-demographic and behavioural factors, informational (knowledge), motivational factors (attitude and belief, social support, internalised stigma), behavioural skills factors (cue to action and self-efficacy) and health service related factors. Meanwhile, clinical characteristics will be retrieved to complete a standardised data collection form (PROFORMA).

Following baseline assessment, patients will be followed up at four (4) time points which at week 2, week 4, week 6, and week 8 after initiation of treatment. Apart from event or censoring status, time varying effect for symptoms improvement, anti-TB side effect, internalised stigma and latest recorded body weight will be elicited at each point of follow up. A flow chart describing the study procedure is demonstrated in Fig. 2.

Data collection method
This study will use a self-administered questionnaire and a standardised data collection form (PROFORMA), both to be applied during baseline and follow up assessment. PROFORMA will be used to collect data on co-morbidities history (chronic pulmonary obstructive disease, diabetes mellitus, chronic renal disease, chronic liver disease, HIV status and lung cancer), chest x-ray grading upon diagnosis, body weight and treatment status. These information will be abstracted from patient's medical record and TBIS forms. TBIS is the TB disease surveillance system in Malaysia, comprises of 32 formats on recording and reporting of TB treatment history and outcome (9). As for occurrence of loss to follow up, the ascertainment of event is conducted via calling of patients or next of kin. Meanwhile, if patient died during the course of treatment, the date of death in the medical record and TBIS form will be recorded as the date of censoring. For those who move or transfer out from study location, the last day of treatment will be the date of censoring. Among those who are censored, the

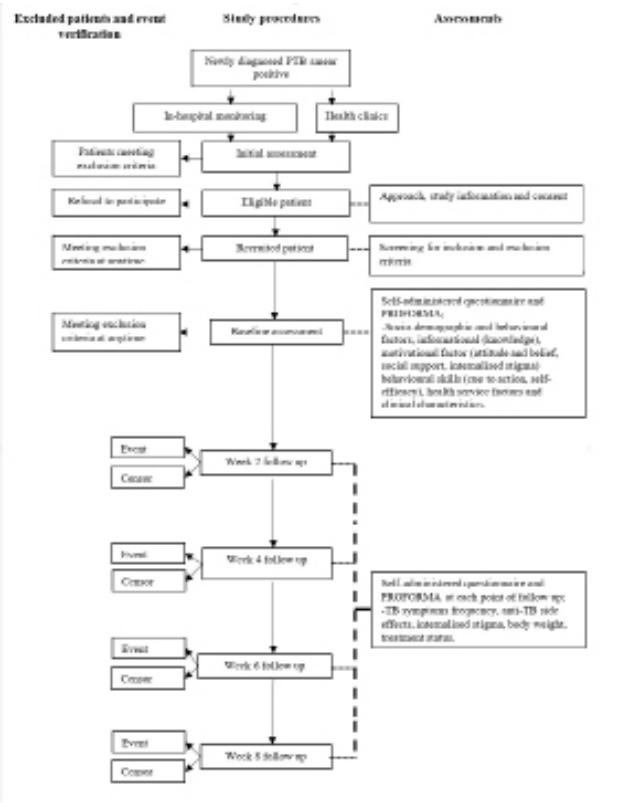

Figure 2: Methodology Framework of Mixed Methods Study on Adolescent Aggression

data obtained prior to censoring dates will be retained.

In the meantime, five appointed enumerators will assist on the data extraction from medical records and TBIS forms. A serial of training will be provided to the enumerators which covers on study overview, roles and responsibilities of enumerators, methodological approach including data collection skills, study instrument contents, and frequently asked questions (FAQ).

Study measures
Upon treatment initiation, baseline assessment will be executed via self-administered questionnaire, which operationally prepared in Malay and Chinese language. This baseline assessment is delineated in the frameworks of IMB Model, with adding on evaluation of socio-demographic factors, behavioural factors, health service factors and clinical characteristics. Operationally, it can be divided into following sections;

Section A: Socio-demographic factors
Section A will elicit on socio-demographic factors including age, gender, ethnicity, marital status, educational level, employment status, family income, number of household, and type of family.

Section B: High risk behaviour
Section B will elicit on respondents' smoking status, history of substance abuse and alcohol consumption, regardless of type or quantity.

Section C: Symptoms assessment, traditional or alternative remedies and health service factors

For above purposes, this section will elicit on self-report of TB symptoms, alternative or traditional remedies practice, travel distance and waiting times spent at DOTS at treatment centres. In term of TB symptoms, it will assess on the symptoms frequency (5-points Likert scale ranging from 1 as never and 5 as always) experienced by the respondent in the past one week. As for alternative traditional medicine practice, it refers to respondents' self-report on the practice of traditional healer, herbal remedies, cupping, traditional massage, acupuncture, Yoga, Ayurveda, homeopathy, Islamic practice, supplementary product or other alternative or traditional practice specified by the respondent. Those selecting one or more from listed options, will be considered as practicing alternative or traditional medicine.

Section D: Informational factor (knowledge)

For this section, knowledge scale is adapted from previous studies (38-39). It consists of 18 items, which operationalize general knowledge on TB treatment, regime and drugs utilization, specific requirement for compliance, potential anti-TB drug side effect or interaction, as well as faulty heuristic that created the negative decision towards adherence (27-28). The answer options are 'true', 'false' or 'not sure'. Each question is given one (1) mark for correct answer, zero (0) mark for wrong or not sure. Question 19(iii), 19(xiv), 19(xvi), 19(xvii) and 19(xviii) are the negative statements, therefore reverse scoring is performed. The total knowledge score ranging from 0 to 18. The higher the score indicates the better knowledge towards TB treatment.

Section E: Motivational factors

In this section, it will assess the attitude and belief towards TB treatment, internalised stigma, and perceived social support. For attitude and belief, the scale is adapted from previous study (39) which can be further divided into subscales of perceived susceptibility (5 items), perceived severity (5 items), perceived benefits (5 items) and perceived barrier (16 items). All subscales obtained good internal consistency in previous study (39) and will be rated through 4-point Likert scale (from 1 as strongly disagree and 4 as strongly agree). As for perceived susceptibility, perceived benefit and perceived severity, a total score ranging from 5 to 20 for respective scale, whilst for perceived barrier, the total score is 16 to 64. The higher the score indicates the higher attitude towards TB treatment.

This section will also cover on internalised stigma evaluation using The Internalised Stigma Mental Illness (ISMI) scale (40). This scale had previously underwent adaptation and psychometric validation in the context of assessing stigma among TB patients (32). It comprises of 10 items (4-point Likert scale, from 1 as 'strongly disagree' to 4 as 'strongly agree') which are conceptualized based on alienation, stereotypes endorsement, perceived discrimination and social withdrawal dimension. The total score ranging from 10 to 40. The higher the score, indicates the higher stigma that perceived by the respondents.

As for social support assessment, this assessment will use Interpersonal Support Evaluation List shortened version-12 items (ISELS-S) (41). It comprises of 12 items (4-point Likert scale, from 0 as definitely false to 3 as definitely true) and evaluated on appraisal support, belonging support and tangible support. The total score for ISELS-12 ranged from 0 to 36. The higher the score, the higher social support gained. In previous psychometric assessment, this scale was validated among English-and Spanish-speaking Hispanics/Latinos respondents from the Sociocultural Ancillary Study via confirmatory factor analysis which showed model fit of data (42).

Section F: Behavioural skills

Behavioural skills domain is measured via cue to action and self- efficacy scales. Both scales are adapted from previous study (38- 39). For cue to action subscale, it consists of 8 items (5-point Likert scale, from 1 as strongly disagree to 5 as strongly agree) with total score ranging from 8 to 40. Meanwhile for self-efficacy subscale, it consists of 16 items (5-point Likert scale, from 1 as strongly disagree to 5 as strongly agree) with the total score ranges from 16 to 80.

Section G: Clinical characteristics

This section is to retrieve information on date of starting treatment, history of hospitalization upon treatment initiation, baseline body weight, comorbidities (diabetes mellitus, chronic obstructive lung disease, chronic renal disease or chronic liver disease) and chest x-ray grading, mainly to be elicited from medical records and TBIS form.

Upon follow up assessment, a self-administered questionnaire and PROFORMA will be used to evaluate the time varying effects of TB symptoms improvement, anti-TB side effects, internalised stigma and body weight, as well as their influence onto treatment interruption. Section A will cover on the TB symptoms frequency and anti-TB side effects. In addition, while section B will elicit on internalised stigma assessment. Finally, section C will retrieve information on the latest body weight and treatment status, which can be established through medical records and TBIS forms.

Quality Control

First and foremost, the questionnaire will be translated (forward and backward translation) in Malay and Chinese Language by native speakers, who are proficient in respective languages (43). In the meantime, an expert group, consists of public health physician, clinician and

psychologist will perform content validity assessment of study instruments, in regards with relevance and cultural equivalence of respective construct. Likewise, face validity will be conducted among 10 TB patients, who will not be included in the study, essentially to assess their understandings and phrasing of items. Finally, Exploratory Factor Analysis will be conducted among 150 PTB smear positive patients to explore and test underlying dimensions of construct, as well as factors' internal consistency. As for reliability assessment, internal consistency of pre-test questionnaire will be tested using Cronbach's alpha in IBM SPSS (Version 25.0). In the meantime, the PROFORMA will be tested among 10% of estimated sample size, which is on 80 medical records.

Data management and statistical analysis

Data will be analysed using IBM SPSS (Version 25.0). Descriptive statistic of variables will be presented as frequency, percentage for categorical data, mean and standard deviation for normally distributed data, or median and inter-quartile range for not normally distributed data. Some of the independent variables will be re-categorized when necessary.

Importantly, survival analysis will be computed to assess the relationship between explanatory variables with the outcome variable. Kaplan Meier analysis will be used to estimate and graphically plot the survival probabilities using a product limit formula. As the result, the median survival time will be computed, and survival pattern for various groups can be compared. Meanwhile, the log-rank test will statistically compare the overall differences between estimated survival curves of two or more groups of subjects. Subsequently, univariate Cox proportional hazards (PH) analysis will be performed for all independent variables, in order to predict which variable that giving the prognostic significance. Subsequently, multivariate Cox PH regression will be computed to identify the independent prognostic variables of intensive phase treatment interruption (37).

In considering the time varying effects exerted over time, symptoms improvement, side effects occurrence, internalised stigma scoring and body weight change will be entered as the time-dependent covariates into Cox PH regression model. In this time dependent model, the covariate allows incorporation of a time interaction function mainly to quantify whether the predicting effects exerted by these variables are independent of time changes throughout the intensive phase of TB treatment.

Ethics

This study has obtained permission and approval from National Medical Research and Ethics Committee (NMREC) of National Institute of Health, Ministry of Health Malaysia (Reference number:NMRR-18-1635-42371) and Ethic Committee for Research Involving Human Subject Universiti Putra Malaysia (JKEUPM). Besides, respondents' consent will be executed prior to questionnaire distribution with additional provision of the information sheet explaining on study objectives and methodology. Meanwhile, the confidentiality of information will be held in strictest confidence, in which their names and identification information will be kept anonymous throughout the data analysis.

RESULTS

Data collection activity has been commenced and the findings are estimated to be published in the following year. The finding is expected to yield in benefits to the target population and the relevant authorities. First and foremost, this study will provide a local update on risk factors of intensive phase TB treatment interruption. In the framework of IMB model, this study will endeavour the empirical evidences of psychosocial factors in TB treatment interruption, hence to drive the integration of psychosocial elements in TB management.

In this assessment, the advantage of taking account on 'censored observations' in survival analysis is to avoid an underestimation of survival probability beyond the fixed time-point, which may lead to undermine the valuable information on patients survival (44). Importantly, through survival analysis, this study will identify the time-points of intensive phase TB treatment interruption hence to assist the local authority and policy maker in planning time relevant and impactful adherence strategy.

DISCUSSION

The utmost importance of intensive phase in TB treatment is meant to render patient to non-infectious state, hence to curb TB transmission rate in the community (45). In the same boat, the relationship between TB treatment interruption and risk of death was higher during intensive phase of treatment, thus patient with intensive phase treatment interruption should be retrieved on priority basis (46). Therefore, this temporal assessment aims to elicit the time to intensive phase treatment interruption, hence prompting rigour assessment of the risk factors of early treatment interruption.

While previous studies had primarily concentrated on biomedical aspect, psychosocial context has been echoed by WHO to be crucially explored in TB treatment interruption (6-8). Some interventions were not evaluated sufficiently for motivational and mediating factors such as comorbidities, and psychosocial aspect. Therefore, this assessment will be framed based on IMB Model in order to refine the motivational factors and to tailor a better understanding of psychosocial influence in TB treatment interruption. IMB model provides a relatively simple explanation for complex behaviour that fundamental for successful treatment adherence

among patients with chronic diseases (47).

Beyond attitude and belief, this study will delineate TB stigma characterization among newly diagnosed PTB smear positive patients in urban districts, Selangor. Given the temporal sensitivity of stigma measurement, it is recommended for stigma evaluation to be conducted serially (48). Having said that, previous studies were mainly conducted in cross-sectional design whereby the new and old TB patients were assessed together. By the time of evaluation, some of the defaulters might not be captured as they already defaulted, giving the possible reason of 'underestimate' and non-significant impact of TB stigma on TB treatment interruption (49). Similarly, most of the investigators had only considered the baseline value of the covariate during previous assessment of body weight, TB symptoms and anti-TB side effect, which however failed to consider the relation of the survival outcome as the function of covariate change over time. Instead, the evaluation should be conducted serially as its effect on the outcome may not constant over the follow-up time, which can lead to violation of the proportional hazards assumption (50) As such, the time dependent model will be the best method to describe the data. Therefore, the prospective cohort design in this study will assemble newly diagnosed patients, through which the latter variables can be assessed longitudinally via five time points assessments, thus to elicit time varying effect on the TB treatment interruption.

CONCLUSION

In parallel with biomedical evidence, this study will enlighten the determinants of TB treatment interruption in the lens of IMB model, giving emphasize on longitudinal psychosocial assessment, hence to gratify informed policy and strategy in TB treatment monitoring.

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