Study Protocol:

# The Efficacy of Cognitive Remediation on Processing Speed in Patients with First Episode Psychosis

Main Researcher:

**Naniyati binti Shuib**

Co-Researchers:

**Dr. Mahadir bin Ahmad**

**Assoc. Prof. Dr. Muhammad Najib bin Mohamad Alwi**

**Dr. Zubaidah Jamil @ Osman**

**BACKGROUND**

**Introduction**

Schizophrenia is a devastating brain disorder which emphasized on avolition, chronicity and poor outcome; dissociative pathology which is fundamental and accent on negative symptoms besides reality distortion or positive symptoms (Tandon et al., 2013). It is characterized by symptoms such as hallucinations, delusions, disorganized communication, poor planning, reduced motivation, and blunted affect (Saha, Chant, Welham, & McGrath, 2005) that led to one of the major potentially severe mental illness. Kraepelin and Bleuler have revealed that cognition is important in considering schizophrenia as a diagnostic adjunct.

**Cognitive and functional deficits in Schizophrenia**

Cognitive impairments include processing speed, executive functions, attention, vigilance, learning and memory, working memory, oral comprehension, verbal reasoning and problem solving, and social cognition which have profound, disabling consequences that underlie and influence the severity of psychosocial or functional disability later in the illness. These several impairments in cognition affect the functionality particularly in community such as self-care, work, social relationships (Bowie et al., 2008; Cella, Reeder, & Wykes, 2015), difficulty with instrumental and problem-solving skills, thus it reduced the recovery success through psychosocial rehabilitation programs, and contribute most to chronic disability and unemployment (Keefe & Fenton, 2007).

In schizophrenia patients, the impaired processing speed may manifest an individual performance such as disorganization, slow speed of processing, inaccurate or inconsistent performance, self-monitoring, prone to make careless errors, fragmented skills and inefficient strategies. It thus limits an individual's ability to adequately function such as less social contact at home, in society, and struggle obtaining and sustaining employment in the workplace (Kane & Harvey, 2014; Koren, Seidman, Goldsmith, & Harvey, 2006; Velligan, Kern, & Gold, 2006), and challenges to independently living which ruined the quality of life.

**Transition through lower-level cognitive process in cognitive recovery**

Apparently, all prominent experts have consensus on enhancing cognitive functioning for better psychosocial outcomes in schizophrenia using psychosocial treatment or behavioural-training intervention of CR (Penadés et al., 2012; Eack, Greenwald, Hogarty, Cooley, DiBarry, Montrose, Keshavan, 2009). Its definition has intensely evolved to an intervention targeting cognitive

deficits using scientific principles of learning with the goal of improving functional outcomes. In fact, the outcome-oriented of recovery in CR, where the criteria consist of the following components of psychopathology, psychosocial functioning and duration its effectiveness is enhanced when provided in a context that provides support and opportunity for improving everyday functioning as concluded by the CR experts working group in 2012.

In fact, CR has shown similar efficacy in specific remediation and general remediation (CRT) in previous trial which the specific individualized remediation towards participants corresponding to their key cognitive concern of five training modules (verbal memory, visuo-spatial memory and attention, working memory, selective attention or reasoning (Franck et al., 2013) to improve particular cognitive domains. It is significantly in agreement with other findings which indicated the association with improvements across all the outcomes in cognitive performance, symptomatology and psychosocial functioning with the effect size of medium (ES=0.41), small (ES=0.28) and lower (ES=0.36) respectively (McGurk, Twamley, Sitzer, McHugo, & Mueser, 2007a).

On the other hand, the outcomes were similar across all cognitive domains although other review has revealed great improvement in the reasoning/problem solving, verbal learning and memory, and verbal working memory domains. The effect sizes for attention/vigilance and speed of processing in contrast indicated small improvement in McGurk et al.'s review (Wykes, Vyv, Cellard, Mcgurk, & Czobor, 2011), which examining the effects of CR with the effect size of d= .45 in global cognition.

The effectiveness of specific treatment mechanisms to improve the cognitive domains undeniably proven. Obviously, the field of schizophrenia research and treatment is vividly in a transitional phase, shifting from a focus on specific cognitive domain and outcomes that are measured by symptomatic remission and basic illness management to an all-encompassing outlook on real-world functional recovery (Bartholomeusz & Allott, 2012). The improvement in cognition led to improved social functioning.

Nevertheless, targeted cognitive training, particularly in the weakest domain in cognitive recovery is still lacking. It seems to be overlooked its potential in enhancing global cognition and functional outcomes, mainly at early stage of schizophrenia or in first episode psychosis. It is logical to focus on the targeted lower deficit towards the appropriate stages of illness, although it is still ambiguous. Another concern is the identification of the cognitive domains that need to be targeted to improve functioning (Penadés & Catalán, 2012) and yield durable benefits. This is consistent with the previous studies, which also suggested the chief target for intervention to bring great impact on the quality of life of an individual rather than improving performance per

se which proposed the predictive cognitive measures. Thus, adopting more strategic CR approach for global cognition and social outcome (Wykes & Van Der Gaag, 2001) with the most appropriate cognitive process should be targeted. Considerably, the need to distinguish specific from nonspecific treatment effects to identify mediators and moderators of treatment effects such as extrinsic and intrinsic motivation, mental effort, and self-perceptions are crucial. Besides, the optimal treatment strategies and cost-effective outcome (Wykes & Spaulding, 2011).

Significantly, cognitive recovery has demonstrated as the best option for psychiatric rehabilitation programs for the patients. Therefore, CR is not likely to be implemented as a stand-alone therapy, but as a part of a broader psychosocial rehabilitation program (Penadés et al., 2012) in a multidisciplinary team.


**The significance of Processing Speed in First Episode Psychosis**

Processing speed denotes the capacity to perform tasks rapidly, estimation of perceptual speed, semantic processing speed, sustained attention and speed and competency of processing the information (Koren & Harvey, 2006). It signifies the competency of individual through number of correct responses, able to execute task within a specified time as measured in digit symbol coding tasks. (David, Reichenberg, & Ph, 2010). In fact, people process information at different rates, and these differences appear to matter. Processing speed predicts automaticity, fluency, and variability of cognitive performance across a wide variety of tasks (Cepeda, Blackwell, & Munakata, 2013).

Researchers have found evidence of subtle cognitive impairments at the first episode of psychosis as psychosis was first formally described(Larson, Walker, & Compton, 2010). In fact, the impaired cognitive functioning is a major concern for several reasons that counting for psychosocial functioning and the ability to perform everyday life skills, an attenuated response to psychiatric rehabilitation programs such as social skills training and vocational rehabilitation besides the overall severity of schizophrenia, especially negative symptoms (Mueser, Deavers, Penn, & Cassisi, 2013)(Harvey, Wingo, Burdick, & Baldessarini, 2010). Notably, the largest deficits were reported in processing speed (–1.68), problem solving and reasoning (–1.51), sustained attention (–1.40), verbal learning and memory (–.79) while the visual learning and memory (–.63) were not much deteriorated (Mesholam-Gately, Giuliano, Goff, Faraone, & Seidman, 2009) in first-episode schizophrenia.

Significantly, slow in processing speed seemingly considered as a notable feature (Dickinson & Harvey, 2009) in schizophrenia amid cognitive functions, also at a stage of the illness, when test performance has not been influenced by potential medication or chronicity confounders

(Dickinson, Ramsey, & Gold, 2007), (Rodríguez-Sánchez, Crespo-Facorro, González-Blanch, Perez-Iglesias, & Vázquez-Barquero, 2007) and (Andersen et al., 2012). Convincingly, clinical implications has steered the focus on cognitive impairment in schizophrenia to be shifted from separable cognitive domains, and towards the construct of processing speed as a generalized measure of level of illness severity (Dickinson & Harvey, 2009; González-Blanch et al., 2011). Working memory, processing speed, and fluid intelligence are essentially connected to various aspects in daily functioning (Cassetta & Goghari, 2016). Amazingly, the processing speed and attention or working memory mediated the effects of cognitive functions on community activities and work skills, which reflects the social competence. The attention/working memory domain is associated to work skills; executive functions had a direct effect on interpersonal behaviours, while processing speed affects all three real-world behaviours. Therefore, the role played by verbal memory, working memory, and executive functioning in specific disability domains such as self-care management, family contact, vocational outcome, and social functioning were followed by interaction between processing speed and other cognitive domains (verbal memory, verbal fluency, working memory, and executive functioning) as predictors of specific functional abilities observed in schizophrenia (Sánchez et al., 2009).

Numerous reliable reviews discussed on the advantages of CR in schizophrenia patients with remarkable and promising results. The significant effect sizes were discovered in overall and separate cognitive domains based on the 26 studies (1,151 subjects) findings, including the effect sizes of d= .41 in global cognition, d= .41 in attention, d= .48 in processing speed, d= .52 in verbal working memory, and d= .47 in reasoning/problem solving (McGurk et al., 2007a).

Further inferences include the potential value of therapeutic intervention targeted towards improving impaired processing speed, since amelioration may transfer to other domains of cognitive functioning (Andersen et al., 2012). This is consistent with attention/working memory domain which directly related to work skills, executive functions with its direct effect on interpersonal behaviours and obviously processing speed for direct effects on all three real-world behaviours. The speed of processing which identified severely impaired in the early phases of psychosis (José Manuel Rodríguez-Sánchez et al., 2007) has thus justified the clinical population in this study.

In fact, speed and efficiency would be very basic components of information processing. Other studies also suggest that impaired processing speed might be a possible promising cognitive endophenotype for schizophrenia as measured primarily by the digit symbol coding task to be stable, mediate abnormal cognitive development, related to prognosis and functional outcome (Patiny, Constant, & Symann, 2015).Obviously, processing speed is related to employment

outcomes. As academic tasks and work related are normally hierarchical yet involved a lot of chain of command hence speed matters. (Koren & Harvey, 2006). Relatively, the most deteriorated cognitive deficit has identified to be promising in CR by targeting processing speed as in lower-level cognitive process for higher-level of multiple domains of cognition and more complex aspects. It will be efficient by targeting one broad-reaching domain for the most widespread benefits in cognition and everyday functioning (G, AS, HM, & LS, 2009) as an efficient mean of obtaining treatment gains. Thus, the broad associations in processing speed to other aspects of cognition and functioning seemed substantial for the treatment strategy (Vinogradov, Fisher, & de Villers-Sidani, 2012).

**Generalization to real world and adjunct psychiatric rehabilitation**

The basis of improving processing speed is to develop metacognitive strategies with guidance from a therapist, with this role being essentially dedicated to highlighting strategies and maintaining motivation through a focus on goals and support skills transfer to everyday life as revealed by (Cella, Reeder, & Wykes, 2016). Thus, a focus on metacognitive knowledge could promote better understanding and engagement as its role in CR programmes is emerging for huge benefits in schizophrenia.

In fact, (McGurk, Twamley, Sitzer, McHugo, & Mueser, 2007b) has revealed that the effects of CR on psychosocial functioning were significantly stronger (effect size=0.59, 95% CI=0.30–0.88) with adjunctive psychiatric rehabilitation than CR alone (effect size=0.28, 95% CI= –0.02 to 0.58). It was due to moderate improvements in cognitive performance and better functional outcomes when combined with psychiatric rehabilitation (supported employment or education, assertive community team, medication management, housing, coping skills, daily living and socialising).

Hence, transfer of training to community functioning is better support when integrated with other rehabilitation. It consists of strategic approaches through several key principles of learning such as (1) teaching new, efficient, information processing strategies; (2) aiding the transfer of cognitive gains to the real world; and (3) modifying the local environment of the client, which is tailored feedback methods to overcome cognitive related problems. The likelihood of successful completion of everyday life activities to be adopted will be more impactful. The broader focus was not only on the improvement of cognitive processes (Wykes et al., 2011) of the trained cognitive tasks. The goal of durability and generalization (Owen et al., 2010), (Bartholomeusz & Allott, 2012), (Cella, Preti, Edwards, Dow, & Wykes, 2016) the cognition gains, functional competence and real-world behaviour are more likely when supplemental skills training and CR

are combined (Bowie, Reichenberg, Patterson, Heaton, & Harvey, 2006).

This established therapy in producing robust improvements in neurocognition necessitates us to depict the rehabilitation practices as in transfer or generalization of cognitive skills to the real world (Wykes & Spaulding, 2011). In addition, the highlight of the importance of metacognition (Cella, Reeder, et al., 2016) without neglecting the therapist role to support the use of metacognitive strategies (Cella, Reeder, et al., 2016). It is then suggesting to more complex mediating and moderating factors which implicated in explaining the effects of the therapy (Cella et al., 2015). Moreover, working with a computer, interacting with a clinician or cognitive challenge, and discussing how the cognitive skills are used in everyday life as well as bridging strategies beneficial in transfer cognitive skills to everyday activities based on the Neuropsychological Educational Approach to Remediation (NEAR) programs and other approach (Bowie et al., 2008) (Kurtz, Seltzer, Shagan, Thime, & Wexler, 2007).

In this study, the adjunctive CR in ReMind program with integration of other psychiatric rehabilitation may take into account which promote the real-world outcomes to boost the effect of supported employment, return to work with strategic approaches rather than drill and practice per se. It boosts better outcomes with better effect sizes, as they support transfer of training by potential bridge of metacognitive abilities (Wykes & Spaulding, 2011). As its roots in the literature on learning theory may serve as an important bridge between cognitive impairments and real-world performance. Although metacognition is related to, but separate from social cognition as it defined the ability to use existing knowledge, experience, motivations, and regulate performance or skills in new contexts (Koren & Harvey, 2006)(De Corte, 2003). It may provide the most potent form of therapy for improved functional outcomes, besides positive learning experiences through great avenue for them to prepare and rebuild their best potential and skills that eventually would also improve (McGurk et al., 2007a) the mood, self-esteem and self-efficacy for achieving realistic goals as well as negative symptoms reduction (Cella, Preti, et al., 2016).

The association among cognitive domains and resulting functional disability (self-care management, family contact, vocational outcome, and social functioning) partially attributed to the mediating effect of processing speed as stated in previous literature. The recent increasing relevance of processing speed hypothesis as a differential mediating role between the cognitive domains (verbal memory, working memory, and executive functioning) and functional disability over time and has predictive power over functional disability parameters in chronic schizophrenia. Importantly, the focus has shifted to which learning strategies may facilitate transfer process which variations in treatment with few noticeable differences; rather, they lie

along dimensions of learning support as well as support for transfer to community functioning (Cella et al., 2015). Significantly, with the early intervention may bring greater chance of improvement in quality of life and psychopathology and have greater potential in work compared to those with longer duration of untreated psychosis.

**Rationale**

Apparently, decreased processing speed is a key feature of schizophrenia with respect to cognition, functional outcome and clinical symptoms. There are several reasons to believe that processing speed deficits may be a core feature in schizophrenia as proven by Ojeda et al. (2012). The introduction of antipsychotic medications has helped people who live with schizophrenia to control the hallucinations, delusions, and other positive symptoms of psychosis, which has made it possible for many individuals to live in the community.

Unfortunately, despite antipsychotic medication, most individuals with schizophrenia continue to experience significant social, functional, and vocational disability leading to a poor quality of life (Swartz et al. 2007). The severity of current psychopathological symptoms may affect social abilities of patients with schizophrenia (Bellack et al. 1990), (Strauss, & Carpenter 1984) and most studies indicate the role of negative symptoms in this regard. Dickerson et al. (1999) reported that social functioning is associated with both negative symptoms and poor neurocognitive functions.

Hence, a primary concern of this study is to investigate the fundamental role of processing speed in enhancing cognitive and functional outcomes in the first episode psychosis. The potential of such interventions will be initiating as early as possible as the great potential in the early stage is promising. It is imperative for CR and enhancement from the trained skills that generalised the social functioning and job-related accordingly. It is evidently suggestive that the most feasible and realistic cognitive training should be adopted in reducing disability and to ameliorate functional recovery for its active ingredient to attain the treatment aims effectively (Bowie et al., 2008). The vigorous approach seems to have affirmative prognosis toward significant change in real-world functioning which manifest a holistic perspective in recovery process. This innovative neuropsychological model of remediation will be more robust with a well-articulated theoretical rationale and clearly understood, induce specific mechanisms of action that are grounded in the neuroscience of learning and cognition, robust, durable change and outcome

measures with impactful metacognitive strategies in generalisation beyond the trained task that consequently bring a meaningful improvements of functional outcome. The adjunctive psychosocial interventions in CR may vividly elevate widespread gains in schizophrenia. Therefore, a study of randomised controlled trial through adjunctive CR in ReMind program that focuses on the lower targeted deficit of Processing Speed is crucial to be conducted with the primary aim to evaluate the efficacy in patients with FEP in Klang valley, Malaysia to augment global cognition and functional outcomes. It is also promising to embrace metacognition through in enhancing cognitive performance and psychosocial for higher functioning via real-world recovery.

**Research Objective**

*Primary objective:*

To evaluate the efficacy of Cognitive Remediation to determine the efficacy of Cognitive Remediation in improving Processing Speed in patients with First Episode Psychosis

*Specific Objectives:*

1. To measure the psychosocial functions of First Episode Psychosis participants after intervention.
2. To compare the difference between psychopathology of First Episode Psychosis before and after intervention.
3. To explore the psychotic symptoms, significant changes and effect of functioning among the participants during pre and post intervention
4. To evaluate the influence of Processing Speed to predict the cognitive outcome in First Episode Psychosis.
5. To assess the efficacy of Cognitive Remediation Therapy in enhancing global cognitive domains in First Episode Psychosis and functional outcomes.
6. To ascertain the role of processing speed as mediator in enhancing global cognitive domains.

**Research Question**

1.  How is the psychosocial functions of First Episode Psychosis participants after intervention between conventional NEAR and REMIND treatment?
2.  What is the difference between psychopathology of First Episode Psychosis before and after intervention?
3.  Is there any correlation between improvements in cognitive impairment and functioning outcomes?
4.  How do the interviews with first episode psychosis participants support the quantitative results that their cognitive functioning changes during the post intervention?
5.  Is there any significant mean difference between Processing Speed in REMIND andother cognitive domains in conventional NEAR?
6.  How does Processing Speed affect the cognitive outcome in First Episode Psychosis?
7.  Is there any significant difference of efficacy towards cognitive domains performance between conventional NEAR and REMIND treatment?

**Research Hypothesis**

In the present study, the booster cognitive remediation therapy of processing speed (REMIND) will be examined whether it is superior to conventional treatment (NEAR) in improving cognitive functioning in first episode psychosis patients which the null hypothesis is no difference between the two intervention groups.

**Conceptual Framework**

*The Neuropsychological Educational Approach to Rehabilitation (NEAR) Model*

Cognitive remediation represents a broad set of activities and exercises that aim to restore or improve cognitive functioning, that is, attention, working memory, planning, and executive functions by stimulating new learning and facilitating social functioning. The ultimate goal of the intervention though is a generalization of the obtained skills in the habitual community setting. To date, several models of cognitive remediation can be assessed (Yulia Zaytseva 2013). The neuropsychological educational approach to rehabilitation (NEAR) method uses a strategy-coaching approach. After the computerized session of the training, participants elaborate and discuss in a small group the strategies that they have learned while practicing cognitive tasks and how these skills may be transposed to real life activities (A. Medalia 2009).

Newer psychosocial interventions and cognitive rehabilitation treatment approaches are framed in a positive light that are grounded in a *recovery* rather than *deficit* model. This new emphasis is based on the factors associated with improved quality of life, such as the ability to enjoy social and familial interactions, advance in educational endeavours, and performing well at work. The underlying theoretical framework comes from a developmental neuroscience perspective, which supports the idea that the brain is capable of changes and development throughout the lifespan.

Most cognitive interventions are based, in principle, on the large literature supporting the concept of brain plasticity and neurogenesis. Cognitive science assumes that skills development can occur at any age and can help advance or restore the brain's capacity for improving cognitive or social performance. Learning in a properly stimulating environment can help the patient to capitalize on brain malleability and improve functioning. In this context, cognitive remediation attempts to improve and/or restore cognitive functioning using a range of approaches (Barlati et al. 2013).
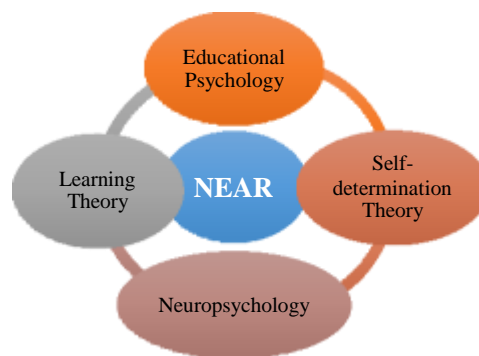


**Principles underlying NEAR**

A recent study aimed to determine the efficacy of NEAR as an early intervention in first- episode depressive and psychotic disorders. The neurocognitive remediation is an evidence- based approach that focuses on aspects such as learning and motivation when doing cognitive remediation (Glenthøj et al. 2015). Patients undergoing NEAR improved significantly more than treatment-as-usual (TAU) patients in attention, working memory, and immediate learning and memory. Similarly, the cognitive remediation group demonstrated greater improvements in psychosocial functioning. Bowie et al. (2004) evaluated the effectiveness and transfer to functional competence and everyday functioning of cognitive remediation in early course(within 5 years of first episode) and long-term (more than 15 years of illness) schizophrenia. The early course group had larger improvements in measures of processing speed and executive functions, in adaptive competence, and real-world work skills (Barlati et al. 2013). Cognitive impairment

is broadly recognized as a core feature of schizophrenia (Green et al. 2004; Keefe et al. 2006), and is widely considered to be among the most important predictorsof psychosocial outcome (Bowie et al. 2006, 2008) and quality of life (Alptekin et al. 2004). In recent years, different cognitive remediation interventions have been developed (Vita et al. 2014), and their effectiveness in ameliorating patients' cognitive performance and psychosocialfunctioning has been extensively demonstrated (McGurk et al. 2007; Wykes et al. 2011; Medalia and Saperstein 2013).

In sum, these preliminary observations (1) support the NEAR framework (a readily available, motivating, time-effective group intervention) to guide cognitive interventions in individuals with schizophrenia, (2) provide information about which specific cognitive functions could be targeted by this cognitive intervention, and (3) demonstrate that the remediation of basic cognitive deficits does appear to persist and that these effects appear to generalize to social and occupational functions.

*Processing Speed and Cognitive Dysmetria Model*

Earlier efforts to localize the symptoms of schizophrenia in a single brain region have been replaced by models that postulate a disruption in parallel distributed or dynamic circuits. Based on empirical data derived from both magnetic resonance and positron emission tomography, we have developed a model that implicates connectivity among nodes located in prefrontal regions, the thalamic nuclei, and the cerebellum. A disruption in this circuitry produces "cognitive dysmetria," difficulty in prioritizing, processing, coordinating, and responding to information. This "poor mental coordination" is a fundamental cognitive deficit in schizophrenia and can account for its broad diversity of symptoms (Andreasen 1998).

Cognitive dysmetria occurs because of disruptions in neural circuitry. A schizencephaly presumed to result from multiple hits occurring during the process of brain development. The concept of cognitive dysmetria suggests that patients suffering from schizophrenia have a misconnection syndrome that leads them to make abnormal association between mental representations and to lack the ability to distinguish between the self and not self or the important and the trivial. Perceptions or other information will be misconnected with inappropriate associations, leading to delusional misinterpretation (Andreasen 1999).

It is consistent with the study conducted by Rodriguez-Sanchez (2007) which wasdriven by the

hypothesis that deficits in cognition in schizophrenia may be determined by a slower speed of processing of cognitive performance. They compared the cognitive performance of people with schizophrenia and controls before and after controlling for the effect of speed of information processing on cognitive functioning. Interestingly, the results showed that when the influence of speed of processing was removed the cognitive deficits observed in people with first-episode schizophrenia disappeared. Moreover, the significant differences between patients and healthy volunteers in the performance of the Digit Symbol Substitution Test reveal that speed of processing is severely impaired in the early phases of psychosis.
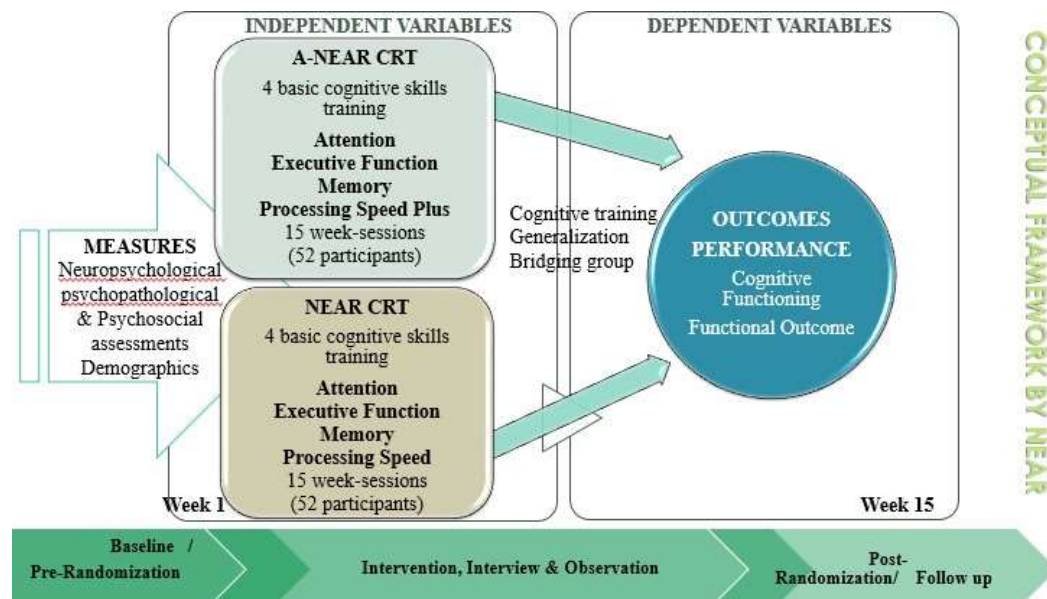


**Conceptual Framework of Cognitive Remediation through NEAR model of recovery in First Episode Psychosis**

**RESEARCH METHOD**

**Study design**

This single-blinded randomised controlled trial will address the efficacy of CR therapy using NEAR model by targeting processing speed in first episode psychosis. Participants' cognition, functioning and clinical symptoms will be assessed at baseline and then randomised to treatment arm or standard care of CRT as active control for 15 sessions/ over 8 weeks. All participants will be assessed again at post-randomisation assessment with 3 months follow-up. A sequential mixed methods design is considered, in which intervention will be executed in sequence followed by in-depth interview before the data could be triangulated. There will be primary outcome of improvement in global cognition and psychosocial as secondary outcome. All procedures and reporting of primary and secondary outcomes will follow Consolidated Standards of Reporting Trials (CONSORT) 2010 guidelines.

The primary purpose of ReMind study will execute intervention of CR with the use of quantitative instruments to test the eclectic theories of neuropsychological, learning, educational psychology and rehabilitation psychology to predict the treatment effect between independent variables of additional Processing Speed in NEAR treatment and global cognitive domains and functional outcomes as dependent variables in patients with FEP.

**Randomisation and Allocation Concealment**

The randomisation will only be conducted after all the informed consent signed by the participants. The single blinded (masked) assessors will recruit the participants through demographic data and assessments. The blinding applies to ReMind training team involved in assessments, data management, data analysis, and drawing outcome conclusions except the patients and treatment providers which will not be blinded. A randomisation is performed, as the potential participants will be of the result of the process, which depends on two interrelated aspects; adequate generation of an unpredictable allocation sequence and concealment of that sequence until assignment occurs. The treatment allocation system will be set up so that the person enrolling participants does not know in advance which treatment the next person will get, a process termed allocation concealment (Douglas, Schulz, & Richard, 2014). The effective, accessible and straightforward method to conceal the randomization and maintaining allocation concealment that does not require the use of specialized technique will be using sequentially numbered, opaque sealed envelopes (SNOSE). Moreover, the methods are both reasonable to eliminate the source of bias.

**Recruitment process and study population**

**Participants**

A total of 104 participants who experienced a FEP will be assessed in cognitive and clinical assessments from Klang valley of Malaysia. There are in stable condition whether inpatients or outpatients from the psychiatric and mental health department at UKM Medical Centre, Kuala Lumpur Hospital, Kajang Hospital and Putrajaya Hospital.

**Sample size calculation**

The simplest formula for the sample size calculation were identified through continuous outcome and equal sample sizes in both groups yields (Noordzij et al., 2010), which primary outcome of this study, a priori between-group difference at 5 months with cognitive performance, BACS composite score. A difference in cognitive function of 30.6 between the treated and control group (µ1–µ2) with the SD of 49.9 (Rodríguez-Sánchez, Crespo-Facorro, González-Blanch, Perez-Iglesias, & Vázquez-Barquero, 2007) is considered as clinically relevant and specified such an effect to be detected with power of 80% power (0.80) and a two-sided alpha of 0.05 and beta of 0.20. This requires 42 participants to be randomised to each arm. Assuming 20% of attrition rate, the adjusted sample size will be involved in this intervention programme is 52 participants each arm with 104 participants in total for achieving desired statistical significance for a given hypothesis.

**Inclusion Criteria**

The inclusion criteria is established to recruit clinically stable participants according to DSM-V criteria for schizophrenia, schizophreniform disorder or schizoaffective disorder as diagnosis and presenting with cognitive deficits of young adults between 18 to 40 years. They will be provided a written informed consent and fulfil the criteria of cognitive measures, symptomatology and other functioning which to be considered as participants in this study. Moreover, they should be able to understand and/or speak a Malay language, read and write in Malay and/or English as well as able to give informed consent as considerations for being a participant in this study.

**Exclusion Criteria**

Participant can be excluded if they have previous diagnosis of mental retardation, psychotic disorder related to a general medical conditions or substance-induced psychotic disorder as well as concurrently undergo other types of CRT. The participation in the study is voluntary and

participants are free to withdraw from the study at any time for any reason without consequences for treatment possibilities. The researcher may decide to terminate the study at any time. Participants will be informed if the study is terminated and follow-up visits will be arranged if needed. They may also be withdrawn from the study at any time at the discretion of the researcher.

## Measures and Instruments

The assessments will be administered at baseline and before randomisation to corroborate inclusion and exclusion criteria. It is also to detect any changes at post-intervention.

### Socio-demographic characteristics

Socio-demographic and clinical data will be collected including gender, age, marital status, religion, education level, race, gender, occupation, with whom the patient lived, previous psychiatric history, institutional history and use of psychotropic medications.

### Clinical and Psychopathology assessment

Psychiatric symptoms: Positive and Negative Syndrome Scale (PANSS)

The 30-item PANSS is considered as an operationalized, drug-sensitive instrument that provides balanced representation of positive and negative symptoms and gauges their relationship to one another and to global psychopathology. It is a semi-structured instrument that assesses the presence and severity of psychopathological symptoms in the previous seven days. It is useful as a clinical outcome measure.

### Neuropsychological assessment

### The Brief Assessment of Cognition in Schizophrenia (BACS)

Most of the neurocognitive assessment's batteries used are long and complex, adapted from clinical neuropsychology tests, which assess the entire profile of neuropsychological strengths and weaknesses in individuals. Long hours are often required to administer these batteries. The BACS (Keefe et al. 2004) on the other hand, preserves the desirable features of the RBANS but overcomes its limits, as it was specifically designed for use in schizophrenia clinical trials to detect cognitive changes in response to treatment. The BACS consists of six subtests to assess

the domains of verbal memory (list learning), working memory (digit sequencing task), processing speed (verbal fluency, token motor task, symbol coding), and executive functions/ reasoning and problem solving (Tower of London). As the BACS Malay version (BACS-M) was validated in both clinical and healthy groups in Malaysia, the likelihood of treatment-related effect with high test-retest reliability in the composite score are considered in this study for assessing cognitive change. It has proven promising useful tool with good test-retest reliability ICCs of 0.89 and required a mean of 39.27 min to complete which consistent with the original English version of the BACS that required less than 35 minutes to be completed (Keefe et al., 2006). It may aid the evaluation of cognitive within 2 weeks between assessments and before remediation strategies could be conducted. Trained psychologists to participants and controls will carry it out to the local participants.

**Functional Assessments**

In addition, improvement in a co-primary measure of either functional capacity or an interview-based measure of cognitive functioning was also specifically recommended (Buchanan et al., 2005, 2010). The Schizophrenia Cognition Rating Scale (SCoRS) is an interview-based measure of cognitive functioning. The relationship between real world functioning and performance on three measures of functional capacity will be measured including SCoRS, Social Functioning Scale (SFS), and Schizophrenia Quality of Life Scale Revision 4 (SQLS-R4).

**Schizophrenia Cognition Rating Scale (SCoRS)**
The SCoRS is a rating scale that focuses on cognitive impairment and the degree to which it affects day-to-day functioning. It consists of a 20-item interview completed by both the patient and an informant. The items are rated on a 4-point ordinal severity scale. The interviewer then generated the ratings on all items based on the results of both interviews, which represented the best judgment of the patient's true impairment, after considering the patient and informant reports. Finally, the interviewer generated a global rating that is scaled on a 10-point scale (1– 10). It helps clinicians evaluate the ties between cognitive impairment and poor functioning in both research settings and daily clinical practice. The SCoRS global ratings have been significantly correlated with psychosocial functioning and its functional capacity which is used as co-primary measures to predict real world functioning. It has excellent test-retest reliability, strong relation to cognitive performance, and proven sensitivity to treatment. Internal consistency for the scale was calculated by using Cronbach's alpha coefficient, which was found

to be 0.79 (Keefe, Poe, Walker, Kang, & Harvey, 2006).

**Social Functioning Scale (SFS)**

Social Functioning Scale (SFS) was adapted by  which developed by Birchwood et al. (1990). The scale found to be useful for diagnosing deficits of the patients' functioning and for planning of the rehabilitation procedure. The scale consists of 76 items grouped into 7 domains which comprise of Social Engagement/Withdrawal, Interpersonal Behaviour, Prosocial Activities, Recreation/Pastimes, Independence-Performance, Independence-Competence, Employment/ Education. Total score of SFS ranges between 55 to 145 points. Scoring more than 115 points means good functioning. In this study, the SFS will be employed to examine real-world functional performance. The SFS will be asked to complete by the research team rather than self-rated by participant itself to obtain information on real-world performance (Bowie et al., 2008).

**Schizophrenia Quality of Life Scale Revision 4 (SQLS-R4)**

The SQLS-R4 a fourth revision of the original SQLS developed by Wilkinson and colleagues in 2000. It measures two domains of psychosocial feelings, and cognition and vitality in individuals with a diagnosis of schizophrenia. It can be applied in clinical research and any publication due to its impressive measurement characteristics of this tool.  In this study, the SQLS-R4 which has already translated into Malay version will be used to the respondents (Taha, Ibrahim, Rahman, Shafie, & Rahman, 2012).

**Outcome measures**

The trial involves the most effective treatment to enhance the outcomes in the early stages of psychosis with the primary aim to improve the long-term cognitive functioning.

**Baseline measures**

All inclusion criteria must be met before continuing neuropsychological assessment of the BACS-M to measure the primary outcome of cognitive functioning, PANSS which will be used to assess symptomatology and psychopathology of participants, SCoRS for functional capacity, SQLS-R4, and SFS for secondary outcomes of psychosocial functions.

**Study Procedure**

The study will involve multidisciplinary team, which covers from assessment, interview, randomisation and intervention. The CR training will be required team of trained clinicians

including Clinical Psychologists with at least a master's degree, Psychiatrists, Occupational Therapists, and Nurses as the recruitment and training team. In fact, the person involved in this study have been provided with a 2-day training on CR and its process to ensure the fidelity of treatment will be sustained with thorough supervision. All the assessments and interview will be administered prior to randomisation into intervention programme and immediately after intervention. It followed by interview sessions of psychopathology, psychosocial and quality of life to participants. The three months follow up is considered after termination prior to study analysis as shown in the diagram.

**Consolidated Standards of Reporting Trials (CONSORT) flow diagram of participants through each stage of a randomized trial.**
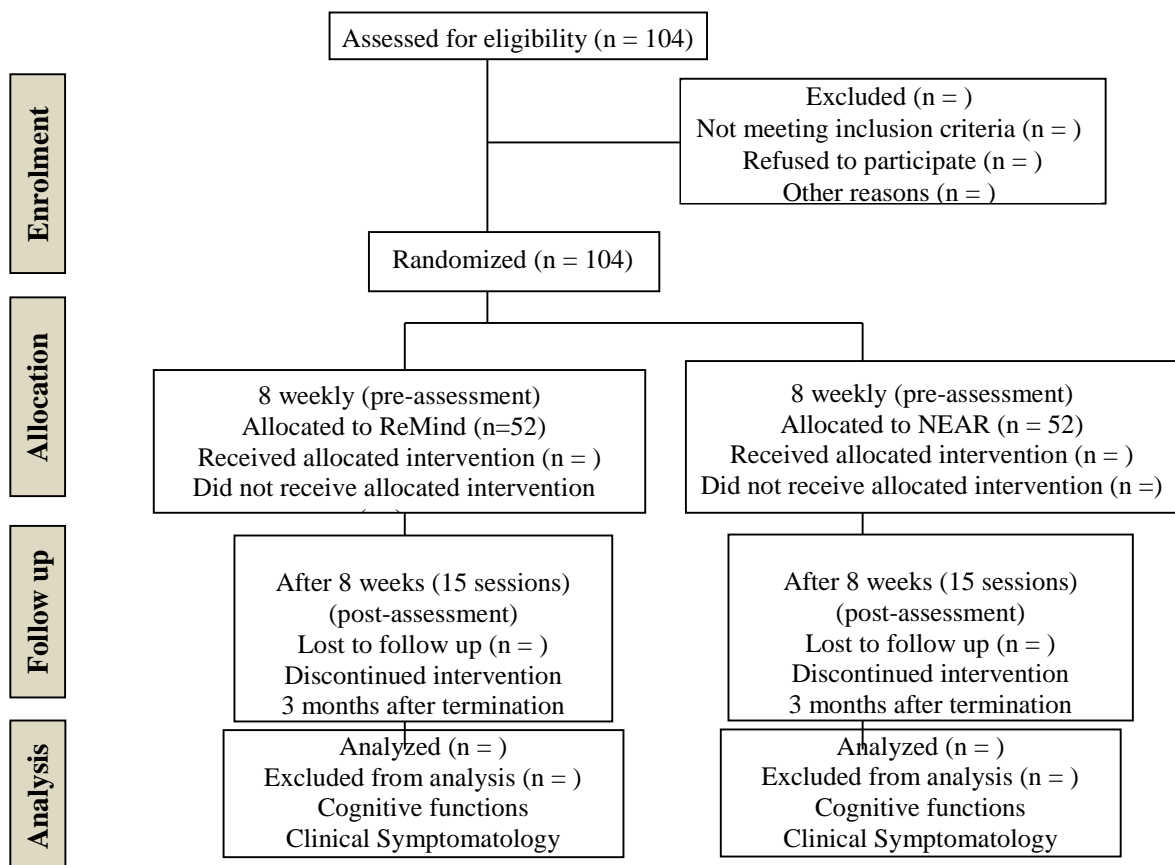
**ReMind Cognitive Training**

The intervention consists of 15 sessions with the selected web based computerised cognitive training associated with homework between each session. In this program, the therapy intensity involved 2 sessions per week for 8 weeks with 15 hours to deliver an adequate treatment to improve cognitive functioning (McGurk et al., 2007a).

It also includes prominent computerised cognitive training, which leads to significant improvement concerning verbal memory, processing speed and executive function in patients with schizophrenia. During the first visit, the participant in this study will be asked to answer a set of questionnaires and to attempt a cognitive testing. Following that, participant will be randomised to one of the two arms. The arms are; Group 1: CR Therapy with targeted Processing Speed (ReMind) through selected commercial cognitive training and Group 2: standard CR.

Psychoeducation session on cognitive functions in schizophrenia will be conducted at the beginning of the program in group with discussion towards awareness on symptomatology, coping strategies and its importance in daily application. Participant will be required to attend the ReMind programme that they have been assigned to, twice a week for eight weeks with bridging group throughout the intervention. After completing eight weeks or 15 treatment sessions, whichever comes first, a set of neuropsychological, psychopathology and psychosocial questionnaires will be administered again to find out the benefits and effects that participants received from the intervention has remained at least until then. Before and after the intervention programme, they will be asked to fill up a survey questionnaire. Finally, 3 months after the intervention, the participants will be asked to come back for another follow up session.

**Treatment approach**

The strategic approaches CR adopting restorative and compensatory techniques with a transfer of training to other functional that integrated with vocational support. The use of drill and practice exercises that aim to restore cognitive functions is based on evidence for neuroplasticity and supported by evidence for functional change through targeted behavioural intervention. CR approaches may not rely solely on computerized exercises but involved therapist-guided instruction with verbal discussion to link the cognitive gains to everyday life. Furthermore, patient's motivation which is an important factor for rehabilitation success and is often utilized as a determining factor in the outcome of rehabilitation (Shapi'i, Mat Zin, & Elaklouk, 2015) particularly through computerized training.

Computers can be intimidating as well as inspiring because they can also be challenging for

participants who have difficulties with perceptual mechanisms, motor control, visual pursuit and scanning, and educational deficits, such as poor reading skills, or cognitive rigidity or inflexibility. Hence, various aspects of client skills is taken into account in dealing with computers relating to cognitive functioning. Therefore, the potential cognitive training of Lumosity are identified to be tailored for maximal benefit toward the objective of this study to enhance global cognitive domains effectively through targeted Processing Speed (ReMind) with the adopted NEAR model.

Each exercise adapts its difficulty level to the user's ability, which adaptively hierarchical with low initial difficulty level followed by progress in participant which difficulty level then will be increased for more complex stimuli, shorter time limits, provide hints or explanations. Immediate feedback of the score and accuracy of responses motivate participants. The transferability of cognitive training to unlearned areas seem crucial for its significant impact on functional outcome despite the scarce evidence (Bowie et al., 2008; Cella et al., 2015). Hence, this research established the effectiveness of potential cognitive exercises and wide array of outcome measures in schizophrenia population. On the other hand, the magnificence of CR is not merely on the cognitive training per se but its vital part of bridging group that expand the generalisation to real-world application of the training. It implies the most crucial mechanism of metacognition in translating the effects into changes in global functioning.

**Statistical Analysis**

The descriptive statistics will be used to report the participants in terms of demographic and clinical data as well as inferential analysis such as t-test analysis for mean score of the post test. Hence, the Independent Sample t-tests will be used to compare participants and controls on age, years of education and premorbid IQ. The chi-square ($\chi 2$) test will be used to compare the difference between groups in demographic characteristics. The relationship among the BACS measures will be evaluated through Pearson correlations among the composite scores by averaging all z-scores of the six primary measures. Pearson correlation for reliability and repeated measures for the validity of the test. The mixed model one-way analysis of variance (ANOVA) between and within group of intervention is expected to compare the difference between the means of pre and post treatment. The group differences on cognitive performance then analysed by the multivariate analysis of variance (MANOVA). The treatment effect on symptom and functioning outcomes will be analysed using Multiple Linear Regression (MLR) analysis. Effect sizes of the improvement in cognitive domain and psychosocial functioning will

also be calculated. The data analyses will be done using the SPSS version 22. All available data who met entry criteria will be analysed, which provided all outcomes on an intention to treat analysis (ITT) approach, assuming data which missing at random, including any significant predictors (Anaya et al., 2012).

**Ethical Consideration**

This study will be conducted in compliance with ethical principles outlined in the Declaration of Helsinki and Malaysian Good Clinical Practice Guideline. All potential participants will be enrolled in the study of cognitive remediation for first episode psychosis as defined in inclusion criteria. As the study involves UKM Medical Centre and government hospitals such as Kuala Lumpur Hospital, Kajang Hospital and Putrajaya Hospital, hence the approval from Ethics Committee of UKM and Ministry of Health (MOH) Malaysia ethical board (NMRR) have been obtained.

For ethical purposes, it is important to ensure participants that their data will be kept confidential and will be used only for the purpose of the research and will not be utilized for any personal purpose. The participants will receive information on the trial both verbally and in written form. Written informed consent will be obtained from each participant before inclusion. It is emphasised that participation in the study is voluntary and that the participant can withdraw his or her consent at any time without consequences for treatment possibilities. The sponsor may decide to terminate the study at any time. Participants will be informed if the study is terminated and follow-up visits will be arranged if needed.

There are no known risks for this treatment. Other treatments that already received (if any) should be continued as usual and they will not affect the treatment programme. There may or may not be any benefits to them. Study procedures will be provided at no cost to the participants. Information obtained from this study will help improve the treatment or management of other patients with the same disease or condition.

**Publication**

The final study results will be submitted as a manuscript for publication. No restrictions on publication exist. This information will be made available to the recruitment clinics and research participants.

**Discussion and Conclusion**

The result of the study promotes further evidence for integrated treatments that indicate the prognosis of adjunct CR by adding targeted cognitive process of processing speed through ReMind to enhance cognitive functioning and functional outcomes in patients with FirstEpisode Psychosis with the use of strategies and other approaches for recovery. The prospective cognitive training exercises is highly recommended to optimize variance and viable tools in ReMind programme in Malaysia for global cognitive gains besides the effect in symptomatology and functional capacity. The metacognitive mechanism, which the highlights despite the main study could be the active ingredients of the most effective recovery strategies to produce real-world functioning in future. Moreover, fidelity of delivery remains as one of the concerns in this study to make it evidence-based clinical practice.

**Timeline**

It is important to demonstrate that the project has been completed within the time allocated. Timeline considers all phases of the project including conducting a literature review, obtaining ethical clearance, writing up results and final reports.

**Competing interests**

There is no potential conflict of interest in relation to this article.

# GANTT CHART FOR PhD COMPLETION

| TASK TO BE PERFORMED/ YEAR | 2015/2016 SEM 1 | | | | | | 2015/2016 SEM 2 | | | | | | 2016/2017 SEM 3 | | | | | | 2016/2017 SEM 4 | | | | | | 2017/2018 SEM 5 | | | | | | 2017/2018 SEM 6 | | | | | | 2018/2019 SEM 7 | | | | | |
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| | 9 | 10 | 11 | 12 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 1 | 2 |
| Identify Research Area/ Problem identification | █ | █ | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Analysis & Justification | █ | █ | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Literature review | █ | █ | █ | █ | █ | █ | █ | █ | █ | █ | █ | █ | █ | █ | █ | █ | █ | █ | █ | █ | █ | █ | █ | █ | █ | █ | | | | | | | | | | | | | | | | |
| Developing objectives and hypotheses | █ | █ | █ | █ | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Choose variable | █ | █ | █ | █ | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Choose type of study & sampling technique | | █ | █ | █ | █ | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Formulate Research (questions, design & strategy) and select methods | | █ | █ | █ | █ | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Write research proposal | | █ | █ | █ | █ | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Negotiate access | | █ | █ | █ | █ | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Submit proposal | █ | █ | █ | █ | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Defence Proposal | | | | | █ | █ | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Ethical consideration | | | | | | | █ | █ | █ | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Applying research grant/ fund | | | | | █ | █ | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Pre-testing (Pilot Study) & Sampling | | | | | | | | █ | █ | █ | █ | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Preparing 1st journal publication | | | | | | | █ | █ | █ | █ | █ | █ | █ | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Validation study/ NEAR software development | | | | | | | | | █ | █ | █ | █ | █ | █ | █ | █ | █ | █ | █ | █ | █ | | | | | | | | | | | | | | | | | | | | | |
| Data collection | | | | | | | | | | █ | █ | █ | █ | █ | █ | █ | █ | █ | █ | █ | █ | █ | █ | █ | █ | █ | █ | █ | █ | █ | | | | | | | | | | | | |
| Follow up | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | █ | █ | | | | | | | |
| Data analysis & Preparing 2nd journal publication | | | | | | | | | | | | | | | | | | | | | | | | | █ | █ | █ | █ | █ | █ | █ | █ | █ | █ | █ | | | | | | | |
| Thesis Report writing 1st draft | | | | | | | | | | | | | | | | | | | | | | | | | █ | █ | █ | █ | █ | █ | █ | █ | █ | █ | █ | █ | | | | | | |
| 2nd draft report | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | ▒ | ▒ | ▒ | | | | | | | | | |
| Viva Voce | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | █ | ▒ | ▒ | ▒ | ▒ | ▒ | ▒ | ▒ | ▒ | ▒ | | | |
| Thesis Correction & Final submission | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | █ | ▒ | | | | | | ▒ | ▒ | ▒ | ▒ | ▒ | ▒ |

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## BUDGET OF THE STUDY

| PORTION OF BUDGET | | | |
|---|---|---|---|
| **MAIN ITEM** | **JUSTIFICATION** | **AMOUNT/ QUANTITY** | **AMOUNT (RM)** |
| *Research Material & Supply* <br> 1) Kertas, Alatulis, Bateri | Untuk kerja-kerja perkeranian, penyelidikan dan pengumpulan data | RM 1500 | RM 1500 |
| 2) Ink | Untuk mencetak instrument dan borang berkaitan penyelidikan dan laporan | RM 2500 | RM 2500 |
| 3) Upah dan Elaun | Pengumpulan Data, Transkrip dan kemasukan data | 1 GRA x 24 bulan | RM 43200 |
| 4) Perisian Kognitif | Pembangunan Perisian *Processing Speed* | RM 7000 | RM 7000 |
| 5) Mesin Cetak | Untuk mencetak pelbagai instrumen dan borang penyelidikan | RM 500 | RM 500 |
| 6) Penilaian Psikologi | Untuk pentadbiran dan penilaian bagi skala klinikal | RM 5000 | RM 5000 |
| *Transportation* <br> Kutipan Data dan Mesyuarat/ Perbincangan dengan agensi luar | Memastikan kajian berjalan lancar dan diselaraskan dengan sempurna <br> Memenuhi KPI bagi penyelidikan | RM 1500 | RM 1500 |
| Menghadiri Persidangan | | RM 3000 | RM 3000 |
| | | **JUMLAH RM :** <br> *TOTAL RM* : | RM 64, 200.00 |

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