STUDY PROTOCOL

THE EFFICACY AND SAFETY OF FIRST LINE ANTI-EPILEPTIC DRUGS (AEDs) AS SUBSTITUTION THERAPY FOR CHILDREN WITH DRUG RESISTANT EPILEPSY

Protocol Number 22-09-1097

ABSTRACT

Background: Drug resistant epilepsy occurs around 30% of children with epilepsy. It is the failure to get seizure-free after combining two or more anti-epileptic drugs whether first- or second-line ones. Previous studies focus on the efficacy and safety between the two groups whether as add-on or substitution therapy mostly in newly diagnosed epilepsy children. However, the study that investigate first line Anti-epileptic Drugs (AEDs) as substitution therapy compared to second-line ones particularly among drug resistant epilepsy children is still lack.

Design: It is an open-label, randomized controlled trial, which will be conducted in three referral hospitals in Jakarta, Cipto Mangunkusumo, Harapan Kita, and Fatmawati Hospital, from November 2022 until April 2023. The data will be collected from electronic medical record consisting of demographic, clinical characteristics, and brain CT scan or brain MRI, and diary cards that record daily drug consumption and adverse drug reaction. Self-administered QOLCE-55 questionnaire is used to assess the quality of life of the children. Furthermore, there will be EEG and laboratory examination prior and after intervention. The data will be recorded on Case Report Form that is filled by the researcher. Ethics committee approval is obtained from The Ethics Committee of The Faculty of Medicine, University of Indonesia-Cipto Mangunkusumo Hospital. Research permits would be issued by each institution where the study will take place.

Sample: There will be 100 participants, divided into 2 groups, the intervention and control. Fifty children in the intervention group will be treated with first line AEDs as the substitution therapy, while the other 50 participants in the control group will get second-line AEDs. The sample size is calculated based on the difference proportion of two independent groups.

Duration of the study : The study will take 14 weeks as a whole that consists of 6 phases including baseline, initial, titration, maintenance, tapering-of, stopping and another maintenance phase.

Introduction

The International League Against Epilepsy (ILAE) has defined the drug-resistant epilepsy as the failure of therapy with two or more anti-epileptic drugs (AEDs) either as single or combination therapy to achieve seizure-free, occurs in around 30% of children with epilepsy.[1-3] The term seizure-free means free from all types of seizures including aura[1]. In the pediatric population, uncontrolled seizure may impair their brain's development, cause behavioral disorder, and finally impact their quality of life.[4-6]

For children, particularly, selection of the appropriate AEDs based on the type of seizure, type of epilepsy, epilepsy syndrome, and the etiology of epilepsy and comorbidities.[7] The dose of the drug is started from the minimal therapeutic dose called as initial dose, and if seizure is not controlled, it can be titrated. Furthermore, if the seizures still persist, other first-line therapy is given either as add-on or substitution therapy. Despite good compliance and adequate therapeutic dose, second-line AEDs are considered to be added if the seizure still persists.[8-10] Many factors including gender, seizure onset, family history of seizure, previous history of febrile seizure or neonatal seizure, mental and motor retardation, seizure types, history of status epilepticus, presence of a specific epilepsy syndrome or abnormal findings on EEG, radiological imaging and epileptic syndrome may contribute to drug resistant epilepsy.[8, 11]

The first line AEDs commonly used for generalized epilepsy are valproic acid, phenobarbital, phenytoin, as well as carbamazepine for focal one. They are also categorized as

older agents. On the other hand, topiramate, levetiracetam, oxcarbazepine are newer agents that are taken frequently for the second-line AEDs.[12, 13] The American Academy of Neurology (AAN) subcommittee reports in 2004 observed that newer AEDs were not different in controlling seizures but have better tolerability, particularly fewer neurotoxic adverse effect.[14-16] There have been many studies comparing the efficacy and safety between first and second-line AEDs in newly diagnosed epilepsy children, showed that first-line agents are as efficacious as second ones. Guerreiro reported that seizure freedom rate in childhood absence epilepsy treated with phenytoin did not differ from those with oxcarbazepine.[17] A study in Turki explained valproic acid, carbamazepine and phenobarbital have the same efficacy as levetiracetam for newly diagnosed epilepsy children.[18] The results was in line with that was reported by James, that valproic acid, carbamazepine as first-line agents and topiramate as the second one are equally effective to treat newly diagnosed epilepsy children.[19] While for drug-resistant epilepsy, previous research investigated that children did not get seizure-free although they have been treated with levetiracetam, known as second-line AED, as add-on therapy.[20] However, there is no robust evidence for therapeutic efficacy of first-line AEDs as substitution of second-line ones. When it comes guideline therapy, there has not been any international guideline of combination therapy for the management of drug resistant epilepsy, even though many recommendations that have been made regionally in certain countries.

In the local situation in Indonesia where the study will be conducted, there are some challenges in the management of drug-resistant epilepsy in children. Similar to those in other countries, a study at Cipto Mangunkusumo General Hospital, Jakarta, showed that around 43% and 31% did not get seizure remission children although they have been given topiramate or levetiracetam respectively.[21] Besides, from the factual situation at outpatient pediatric neurology clinic in Jakarta, the capitol of Indonesia, the number of the drugs that were covered by social insurance are limited so that sometimes patients should buy themselves the uncovered drugs that are needed. Moreover, the newer agents are sometimes not available even in the referral hospitals in other cities spreading all over the country.

Randomized studies in drug-resistant epilepsy typically involve addition of new anti-epileptic drugs. However, in clinical practice, if the patient is already taking multiple drugs, then substitution of one of the current medications commonly occurs, despite little evidence supporting this approach.[22] The choice of the substitution drug depends on the mechanism of action, the pharmacokinetic profile, drug-drug interaction, and the risk of seizure exacerbation as well as patients-related factors. The new combination is intended to maximize efficacy and minimize toxicity. However, the availability and cost-effectiveness should also be

taken into consideration since the patient would not reach the goal of ideal combination of drugs if they could not afford it nor even get the medication.[23-26] Another considerable case is one of drug resistance patterns in which at the first-time patients may not responsive to treatment yet they change into a state that is responsive to the medication.[27] The choice of substitution therapy may originate from firs-line AEDs since evidences have shown they have equal efficacy to those of second-line ones. However, there is still lack of evidence whether the drug resistance pattern occur if the substitution drug is originated from first-line AED even more if it has ever been given prior to the current drug combination.[27] The study aims to analyzed the efficacy and safety of first-line AEDs as substitution therapy in drug-resistant epilepsy children.

Primary Objective

The primary outcome of the research is to analyze the proportion of responders, who are defined as subjects who get 50% of seizure reduction.

Secondary Objectives

There are some secondary objectives of the study. The first one is to analyze the differences of improvement of quality of life, EEG feature and time to achieve seizure reduction, between the intervention and the control group. Besides, the research will describe the clinical characteristics, adverse effects of the drugs and laboratory features related to the adverse effects, among children with drug-resistant epilepsy. Furthermore, it will explain factors influencing the reduction of seizure frequency

Study Design

This protocol is intended for a multicenter open label experimental, randomized controlled trial on the efficacy and safety of using first line AEDs as substitution therapy in childhood drug-resistant epilepsy. It will prospectively follow 100 children up during 14 weeks that consist of baseline, intervention, and post-intervention phases. While the intervention consists of 6 steps, as described at the Figure 1 below.

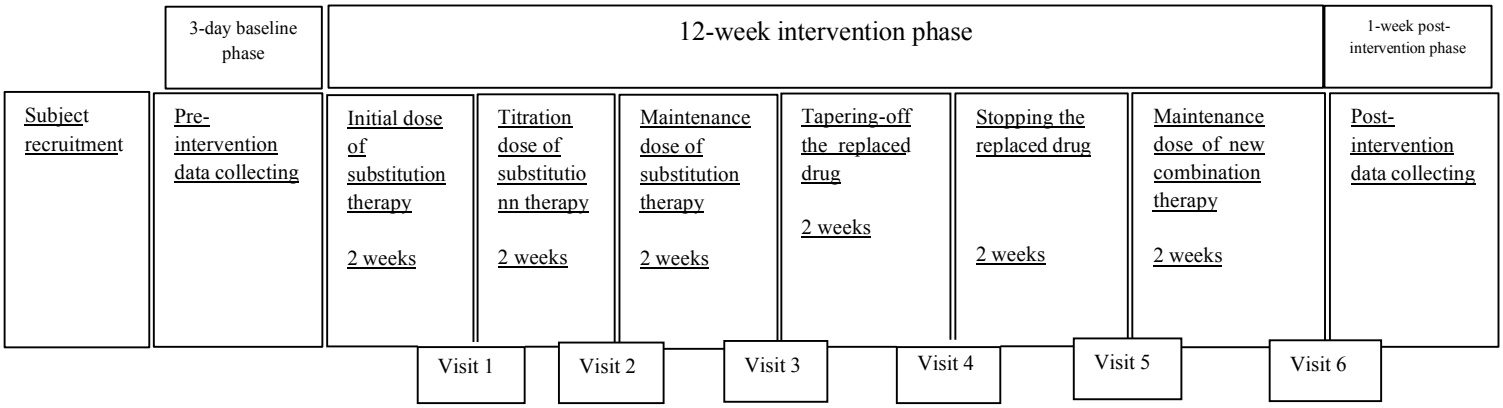

Figure 1. Timeline of the intervention phases

The study will be conducted at pediatric outpatient clinic of 3 referral hospitals in Jakarta, Cipto Mangunkusumo Hospital, Harapan Kita Hospital and Fatmawati Hospital. Children who are diagnosed with drug-resistant epilepsy receiving levetiracetam or topiramate will be enrolled in the study. Enrollment begins as soon as the research ethics committee approval is obtained from The Ethics Committee of The Faculty of Medicine, University of Indonesia-Cipto Mangunkusumo Hospital. The study will be closed after the last recruited patient has been followed up for the required 14 weeks.

All recruited children will be examined for monitoring at the hospital where the intervention is initiated. To avoid selection bias, all patients who met the inclusion criteria are divided into two groups, the intervention and control groups. Prospective participants and their parents will be provided with information related to the study. Patients will then fill out an information sheet containing demographic data, comorbidities, developmental history, school history, history of drug consumption, as well as history of seizures and patient complaints. All the data will be extracted and recorded on the case report form. Patients and their parents should be informed that participation is voluntary and they are free to withdraw from the study at any time. They should also be informed that refusal to participate or withdraw from the study will not affect the quality of treatment received. In the event of their withdrawal, it will be explained that the data collected so far is irrevocable, and we will seek consent to use such data in the final analysis if necessary.

Study procedure

Study procedures are depicted in Figure 2. The patients who are eligible for the study and have given their consents, will be enrolled, divided into 2 groups, the intervention and control, then start the 3-day baseline phase. In this phase, data such as demographic, clinical characteristic

including seizure frequency, seizure type, seizure onset, medication history, family history of seizure, and also developmental stages, will be recorded from electronic medical record. Besides, the CT-scan or MRI are also collected from the same source. After that, their quality of life will be assessed by QOLCE-55 validated questionnaire through self-guided report. Furthermore, the laboratory investigation and EEG will be performed.

The next phase is intervention phase, started from initial step and ended by the maintenance of new combination therapy, which takes with overall 12 weeks. Initially, the substitution drugs with each initial dose are consumed. The drugs consist of valproic acid for the generalized and carbamazepine for focal epilepsies. On the other hand, the control group will take lamotrigine or clobazam for generalized and oxcarbazepine for focal ones. The phase continuous to titration dose, in which, the dose is raised gradually until it causes 50% of seizure reduction, and the next step is maintained the dose for about 2 weeks.

The following is tapering-off and after that stopping the substituted drug, levetiracetam or topiramate, which is determined by considering individual condition. Yet, if the seizures increase more than one and a half time of the previous frequency during the phases, the intervention will be ended immediately. On the contrary, if the condition is better, then the children go to the maintenance of new combination, that is the substitution drug and the old drugs in which the seizures do not go up or even better keep going down. The children who complete all of the phases are categorized as responder. In case if the intervention is ended, the subjects will be given the former combination therapy with adjusted doses in order to decrease the seizures until reaching the pre-intervention condition. The subjects are categorized as non-responder, and will be dropped-out. The other criteria of drop-out are resignation, non-compliance of study procedure, and death in term of other causal not related to the study. While in term of lost to follow-up, is intended for those who do not attend the study without any possible reasons.

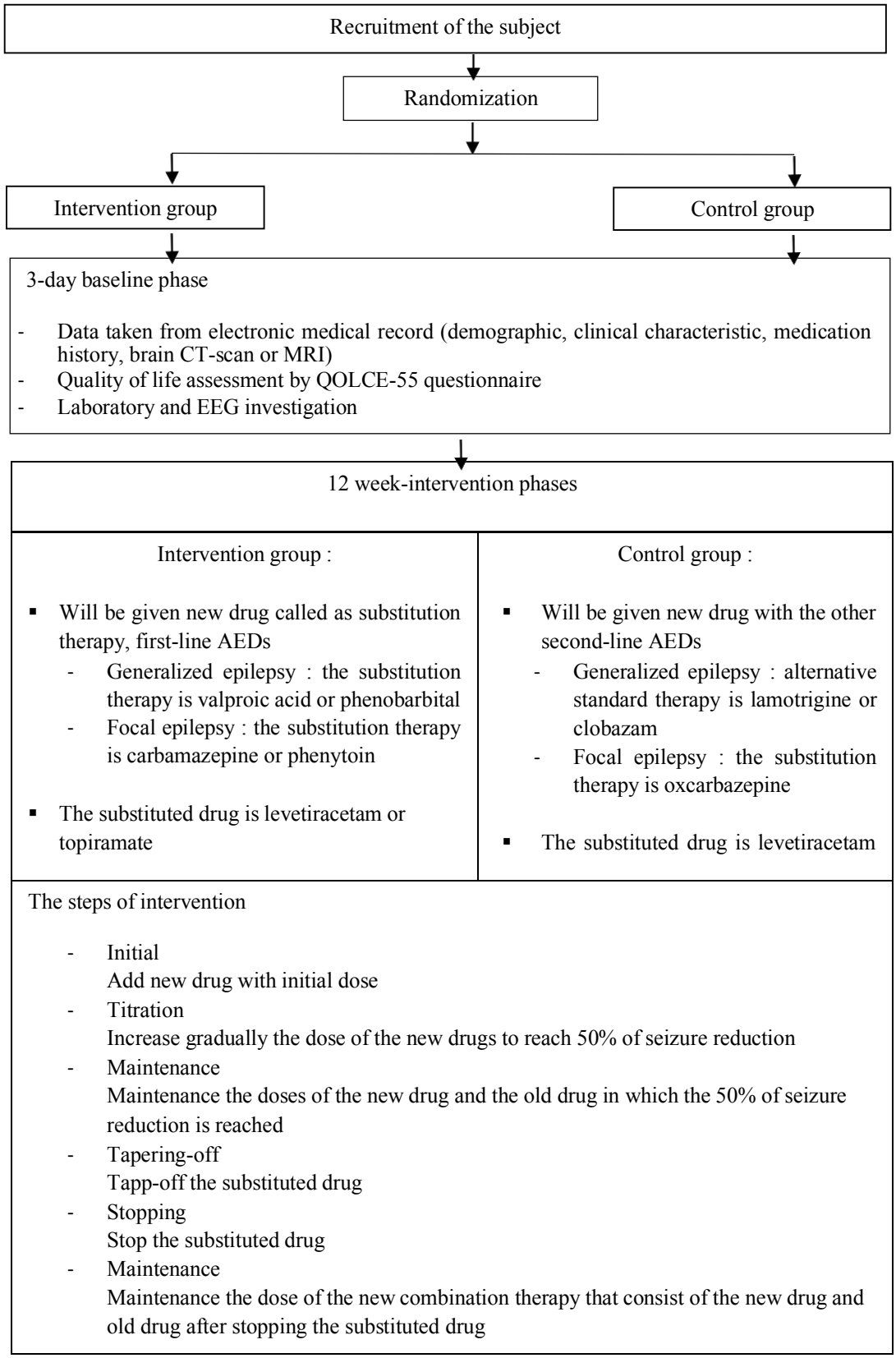

Figure 2. flow-chart of the study

Inclusion criteria

1. Children age at 1 – 18 years old
2. Children diagnosed as drug-resistant epilepsy by pediatric neurologists, diagnosis was based on the ILAE 2017 criteria
3. Children will have got at least 3 months of combination therapy that consists of levetiracetam of topiramate with optimal of therapeutic dosages

Exclusion criteria

1. Non-convulsive epilepsy
2. Suffered from status epilepticus in the prior 3 months before the study begins
3. Past medical history of idiosyncrasies or severe adverse drug reactions caused by the substitution therapy that will be given

Instrument of the study

QOLCE-55 questionnaire

Once the children are enrolled, quality of life will be assessed by using validated QOLCE-55 questionnaire. It is parent-reported and self-administered questionnaire which assess quality of life children with epilepsy age 4-18 years of age. The researcher will give a detail explanation about filling the questionnaire. It has 55 questions including cognitive (22 items), emotional (17 items), social (7 items) and also physical (9 items) function. Items are rated on a five-point Likert scale, 0 = very often, 1 = fairly often, 2 = sometime, 3 = almost never, 5 = never. The composite score is the unweighted average of the four subscales, ranging from 1-100, higher score indicates better quality of life.[28]

Diary Card

The other important thing to evaluate is subjects' adherence, seizure frequencies, and adverse drug reaction by self-reported diary card which is filled by the parents each day during the intervention phase. Besides, drug consumption compliance is also assessed by counting the tablets or powder packages during routine visits of the study.

Electronic Medical Record

Electronic Medical Record is used to collect secondary data that include demographic data, clinical characteristic, and imaging such as brain-CT or brain-MRI.

Laboratory Examination

The test is performed in hospitals' laboratory where the study take place and is done twice, at the baseline and post intervention phase. The order of the blood test consists of complete blood test, liver function test including alanine and aspartate transaminase, kidney function test

including urea and creatinine, and also blood electrolyte that consist of natrium, kalium and calcium. The laboratory professional takes the blood from vein of the arm. The subjects are seated or lying down, accompanied by the parents, while for the younger children, they seat on his/her parents' lap or position that make them feel comfortable. Older children may be asked to make a fist and then will be tied by a rubber band around his/her arms. After that, the needle is inserted the needle until the blood is drawn. The laboratory worker will take the needle since the amount of blood is enough and puts an adhesive bandage over the site. The next step is analyzes of the sample and the result will be issued for about 1-2 days both printed or provided on the electronic medical record.

Electroencephalography Examination

The EEG examination is operated two times, at the baseline and post intervention phase, with high density machine (Caldwell Easy III) is done twice, pre- and post-intervention. The machine will operate for about 45 minutes including 5 minutes each for eye-open and eye-close in every subjects. Beginning with acquisition, EEG recordings use standard parameter to analyze brain activity at various frequencies to gain good quality and artefact-free result. The printed results of the EEG is available for about 4-7 days after the examination.

Data collection

All relevant data will be recorded, by nominated member(s) of the research team, on a case report form (CRF). Each participant will have a CRF and be assigned a unique identification number.

Baseline data

At entry into the study, the following baseline information will be recorded in the CRF:

- unique patient identification number contact telephone number and/or email address
- date of entry into the study
- eligibility for study entry based on inclusion/exclusion criteria
- age at study entry, in years and months
- gender
- weight and height
- seizure type (eg, generalized tonic clonic, absence, myoclonic and partial)
- the age at diagnosis and duration of epilepsy
- seizure frequency or average number of seizures per month
- current anticonvulsant(s) with doses and formulation and its side effect (if presents)
- other medications and its side effect (if presents)

- first recognized seizure date
- prior EEG and laboratory which has been performed at the baseline phase
- physical examination

Follow-up data

Follow-up data will be collected during regularly scheduled clinic visits (per 2 weeks). This information will be obtained from the participants' diary card. Important information to be collected at follow-up will include:

- physical examination
- adverse drug reaction of the substitution therapy that happen
- seizure's frequency
- type of seizure
- complaint

Outcome evaluation

a. The difference in responders was the difference in the percentage of responders in the group that used first line OAE again as substitution therapy and those that used standard therapy. Responders are subjects who experience a decrease frequency of seizure more than or equal to 50% of the initial seizure. Frequency of seizure is the number of seizures that occur within 1 month. In previous studies, it was said that the frequency of seizures was said to have decreased significantly or was said to respond if the seizures were reduced by 50% or more from the initial seizure.[19, 29] Based on this, researchers will categorize the frequency of seizures into:

    - Responder: there is a decrease in the frequency of seizures by 50% or more than before

    - Non-responder: namely the frequency of seizures remains or decreases but not up to 50% of the initial seizure frequency or the frequency is more than before

    Furthermore, the proportion in the form of the percentage of respondents in the two groups is calculated and differentiated, therefore it is classified into two groups:

    - Different : when a significant difference is shown in difference of proportion test of the 2 unpaired groups.
    - Not different: when there is no significant difference is shown in difference of proportion test of the 2 unpaired groups.

b. Differences in quality of life: quality of life assessment using QOLCE-55 instrument. The average of each function (cognitive, emotional, social and physical functions) and the average of the total functions are assessed. This variable is categorized into:
    - Different, if there is a difference in the average quality of life
    - Not different, if there is no difference in the average quality of life

c. Differences in electroencephalography appearance

    EEG recording results are categorized into:

    - Normal : does not show of hypofunction/asymmetry/epileptiform waves
    - Abnormal: shows a picture of hypofunction/asymmetry/epileptiform waves or a combination of 1 or more of these features

    The subjects who show changes in their EEG are later grouped into groups of abnormal to normal or abnormalities that showed improvement. Abnormalities that show improvement, for example are hypofunction (slowing down) waves experience improvement or decreasing number of epileptiform waves.

    Next, a proportion calculation is carried out in the form of the percentage to subjects who experience a change in the EEG and will be categorized into:

    - Different : when a significant difference is shown in difference of proportion test of the group that reuses first line OAE line as substitution therapy and those that use standard therapy/
    - Not different: when there is no significant difference is shown in difference of proportion test of the 2 groups.

d. Difference in actual failure between the groups reusing first line OAE as substitution therapy and those taking standard therapy. Description of drug side effects in the form of frequency distribution and percentage of side effects in each group. Description of laboratory results in the form of frequency distribution and percentage of side effects in each group

e. Factors contributing to decrease in seizure frequency (age, seizure onset, seizure type, family history of seizures, developmental delay, history of OAE, initial seizure frequency, initial EEG, structural brain abnormalities)

Sample size

The estimated sample size in this study was calculated using the different proportion formula for the 2 unpaired groups as follows [29] :

$$n1 = n2 = \left(\frac{Z_\alpha\sqrt{2PQ} + Z_\beta\sqrt{P1Q1 + P2Q2}}{P1 - P2}\right)^2$$

Description :

n1	number of subjects who received the new drug (First Line OAE)
n2	number of subjects receiving standard drug (Second line OAE)
Alpha	type one error (5%)
Zα	alpha standard value 5% one-way hypothesis (1,96)
Beta	type two error (20%)
Zβ	beta default value 20% (0,84)
P2	proportion of decreased seizures on standard drugs (reference) for example 0.7
Q2	1-P2 = 1-0,7 = 0,3
P1-P2	difference in the proportion of reduced seizure that is considered significant between the new drug and the standard (defined by the researcher) for example 25% (0.25)
P1	proportion of reduced seizure on the new drug (the proportion of reduced seizure on the standard drug in addition to the minimal difference that is considered significant)= 0,7 + 0,25 =0,95
Q1	1- P1 = 1-0,95 = 0,5
P	(P1 + P2) / 2 = (0,95 + 0,7) / 2 = 0,825
Q	1-P = 1-0,825 = 0,175

In this study, it was found that the proportion of seizure reduction on standard drugs was 70%.[30] Therefore the equation:

$$n1 = n2 = \left(\frac{1{,}96\sqrt{2(0{,}825)(0{,}175)} + 0{,}84\sqrt{(0{,}95)(0{,}5) + (0{,}7)(0{,}3)}}{0{,}25}\right)^2 = 49{,}56 = 50$$

$$n\ 2\ groups = 100$$

Based on the formula above, 100 research subjects are required. An additional of 10% from the total number of subjects are needed as there is a possibility of those dropping out, therefore a total of 110 subjects are needed in this study.

Statistical Analysis

1. Analysis of differences in the proportion of responders (primary outcome), differences in EEG appearance (secondary outcome) in pediatric epilepsy patients who are resistant to the combination of second line OAE between those who reused first line OAE as substitution therapy and those who used standard therapy. Data type is categorical. Data is analyzed the Chi-square statistical test, if it does not meet the requirements then an alternative test is performed, known as Fisher's multiple test. The significance level (α) is 5% and the research confidence level is 80%. If p value ≤ α is obtained, this means H0 is rejected, which means that there is a difference seen in seizure frequency between reusing first line OAE as substitution therapy and standard therapy.
2. Analysis of differences in the mean quality of life with an unpaired T test if the data distribution is normal or Mann-Whitney if data distribution is not normal
3. To assess drug effectiveness, the analysis used was the difference in actual failure between those using first line OAE as substitution therapy and those using standard therapy (primary outcome). Formula:

$$ARR = CER - EER$$

CER : the incidence of increased seizure frequency in the standard therapy group

ERR : the incidence of increased seizure frequency in the group in substitution therapy with 1st line OAE The increase in seizure frequency in this study shows therapy failure.

This test will use 2 analyses known as intention to treat analysis and per-protocol analysis. Intention to treat analysis means that all research subjects who have been randomized are included in the analysis according to their initial allocation regardless of whether or not the subject is taking the drug/therapy being tested or a placebo, or whether these subjects died before taking the drug being tested. Subjects who did not

take medication, lost to follow-up, and who moved to another group, are considered failures of their original group.

Whereas per protocol analysis only includes subjects who complete the research to the end.

4. Analysis of the difference in time to achieve a decrease in seizure frequency with the chi-square test or if it does not meet the requirements, an alternative test is performed, namely the Mann-Whitney test
5. Analysis of clinical characteristics, side effects of OAE, and laboratory findings of complete blood count (hemoglobin, hematocrit, leukocytes, platelets, and type count), liver function (SGOT and SGPT), kidney function (urea and creatinine), and blood electrolytes (sodium, potassium, calcium, chloride) in pediatric epilepsy patients who are resistant to combination second OAE who re-use first line OAE as substitution therapy and who use standard therapy (secondary outcome). All existing data is processed and presented in a table consisting of mean and standard deviation or median and inter-quartile range, as well as frequency distribution.
6. Analyzing factors that affect the decrease in the frequency of late seizures (age, seizure onset, seizure type, family history of seizures, developmental delays, history of OAE, initial seizure frequency, initial EEG, brain structural abnormalities) in pediatric patients with resistant epilepsy combination of second line OAE who re-use first line OAE as substitution therapy (secondary outcome).

   Data is categorical. Data is analyzed using Chi-square statistical test, if results do not meet the requirements then an alternative test will be performed, known as Fisher's multivariate test and further analyzed with multivariate test and logistic regression analysis. The significance level (α) is 5% and the research confidence level is 80%. Results will show statistically related if value of $p \leq \alpha$ is obtained.

Ethics and dissemination

The study will only be initiated after the protocol, consent form and the participants' information sheet are approved by The Ethics Committee of The Faculty of Medicine, Indonseia University-Cipto Mangunkusumo Hospital. We also apply for research permits at the 3 hospitals where the research will he held.

Informed Consent

Written informed consent will be obtained from the parents of participants. A potential participant whose more than 12 year-old at the time of clinic appointment will be given an informed assent. The writer will explain the details of the study and provide age-appropriate

participant information sheet to the participants and their parents. All questions about the study will be answered by the writer. Participants will be allowed sufficient time to decide whether to participate in the study or not. Before enrollment, the consent form will be signed by parents, or also by the participant who are 12 years old or above. If either the children or their parent decline to consent, they will not enter the study. The participant or their parent will keep a copy of the consent form, while the original copy will be kept by the chief writer in the recruitment file, a third copy will be kept in the patient's hospital record.

Discontinuation of study participation

Participants may choose to withdraw from the study, on their own or on the request of their parents/guardian, at any time during the course of the study. Subjects may withdraw for any reason without prejudice to his/her future medical care by the physician or at the institution. On withdrawal of consent, the date and reason for consent withdrawal will be documented. Participants' data collected up to the date of the withdrawal of consent may be included in the final analysis.

The investigator may also choose to withdraw a participant from the study if such a person does not comply with the procedure, did not participate in the study at least until the standard drug tapering-off phase, or died during the study. Withdrawn participants will not be replaced.

Study Records and Data Management

- **Case report form**

Each participant will be assigned a unique study patient identification number, for use on CRFs, other study documents, and the electronic database. CRFs will be treated as confidential documents. The writer will make a separate confidential record of the participant's name, date of birth, local hospital number and patient identification number to permit identification of all participants enrolled in the study, in case additional follow-up is required.

CRFs shall be restricted for approved personnel by the chief investigator only. All paper forms shall be filled in using black ballpoint pen. Errors shall be lined out but not obliterated by using correction fluid and the correction inserted, initially and dated. Personnel who fill in the CRF must affix their identity in the form of name and signature

- **Record retention and archiving**

The chief investigator will retain all records and documents for 5 years. If the responsible investigator can no longer retain these records, another person will be nominated for this purpose.

The final archiving of the study documents and databases (and associated meta-encryption codes) held by the chief investigator shall be at the secure archive facility at the University of Indonesia.

- **Publication and dissemination policy**

Participants will not be paid to participate in the study. However, they will be given transportation costs. There will be no hospital visits in excess of usual care. Findings will be published in peer-reviewed journals.

References

1. Mohammadzadeh P, Nazarbaghi S. The prevalence of drug-resistant-epilepsy and its associated factors in patients with epilepsy. Clinical Neurology and Neurosurgery. 2022;213:107086.
2. Kalilani L, Sun X, Pelgrims B, Noack-Rink M, Villanueva V. The epidemiology of drug-resistant epilepsy: A systematic review and meta- analysis. Epilepsia. 2018;59:2179-93.
3. Rohracher A, Dobesberger J, Granbichler CA, Höfler J, Kuchukhidze G, 3 MO, et al. The ILAE definition of drug resistant epilepsy and its clinical applicability compared with "older" established definitions. Journal of epileptology. 2015.
4. Fong CY, Chang WM, Kong AN, Rithauddin AM, Khoo TB, Ong LC. Quality of life in Malaysian children with epilepsy. Epilepsy Behav. 2018;80:15-20.
5. Fayed N, Davis AM, Streiner DL, Rosenbaum PL, Cunningham CE, Lach LM, et al. Children's perspective of quality of life in epilepsy. Neurology. 2015;84(18):1830-7.
6. Nawani H, Smith ML, Wheeler AL, Widjaja E. Functional Connectivity Associated with Health-Related Quality of Life in Children with Focal Epilepsy. AJNR American journal of neuroradiology. 2019;40(7):1213-20.
7. Devinsky O, Vezzani A, O'Brien TJ, Jette N, Scheffer IE, Curtis Md, et al. Epilepsy. Nat Rev Dis Primers. 2018;4:18024.
8. Tang F, Hartz AMS, Bauer B. Drug-Resistant Epilepsy: Multiple Hypotheses, Few Answers. Front Neurol. 2017;8:301.
9. Wirrell E. Rational Approach to Children with Drug-Resistant Epilepsy: Drug Resistant Childhood Epilepsy. JICNA. 2021;1(1).
10. Guery D, Rheims S. Clinical Management of Drug Resistant Epilepsy: A Review on Current Strategies. Neuropsychiatr Dis Treat. 2021;17:2229-42.
11. Dalic L, Cook MJ. Managing drug-resistant epilepsy: challenges and solutions. Neuropsychiatr Dis Treat. 2016;12:2605-16.
12. Hakami T. Neuropharmacology of Antiseizure Drugs. Neuropsychopharmacol Rep. 2021;41:336-51.
13. Reséndiz-Aparicio JC, Padilla-Huicab JM, Martínez-Juárez IE, Hernández-Martínez G, López-Correa E, Vázquez-Juárez B, et al. Clinical guideline: antiepileptic drugs of choice for epileptic syndromes and epilepsies in pediatric patients. Rev Mex Neuroci. 2019;20(2):89-96.
14. French JA, Kanner AM, Bautista J, Abou-Khalil B, Browne T, Harden CL, et al. Efficacy and tolerability of the new antiepileptic drugs I: treatment of new onset epilepsy: report of the Therapeutics and Technology Assessment Subcommittee and Quality Standards Subcommittee of the American Academy of Neurology and the American Epilepsy Society. Neurology. 2004;62:1252-60.

15. Kanner AM, Ashman E, Gloss D, Harden C, Bourgeois B, Bautista JF, et al. Practice guideline update summary: Efficacy and tolerability of the new antiepileptic drugs I: Treatment of new-onset epilepsy: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology and the American Epilepsy Society. Neurology. 2018;91:74-81.
16. Kanner AM, Ashman E, Gloss D, Harden C, Bourgeois B, Bautista JF, et al. Practice guideline update summary: Efficacy and tolerability of the new antiepileptic drugs II: Treatment-resistant epilepsy: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology and the American Epilepsy Society. Neurology. 2018;91(2):82-90.
17. Guerreiro MM, Vigonius U, Pohlmann H, Manreza MLd, Fejerman N, Antoniuk SA, et al. A double-blind controlled clinical trial of oxcarbazepine versus phenytoin in children and adolescents with epilepsy. Epilepsy Res. 1997;27:205-13.
18. Yılmaz Ü, Yılmaz TS, Dizdarer G, Akıncı G, Güzel O, Tekgül H. Efficacy and tolerability of the first antiepileptic drug in children with newly diagnosed idiopathic epilepsy. Seizure. 2014;23(4):252-9.
19. Wheless JW, Neto W, Wang S. Topiramate, carbamazepine, and valproate monotherapy: double-blind comparison in children with newly diagnosed epilepsy. J Child Neurol. 2004;19(135-41).
20. Opp J, Tuxhorn I, May T, Kluger G, Wiemer-Kruel A, Kurlemann G, et al. Levetiracetam in children with refractory epilepsy: A multicenter open label study in Germany. Seizure. 2005;14(7):476-84.
21. Ginting JB. Risk factors of success of second-line AED among children under 3 years old : a case control study. Pediatric Department of Medical Faculty of Indonesia University.2020.
22. Janmohamed M, Lawn N, Spilsbury K, Chan J, Dunne J. Starting a new anti-seizure medication in drug-resistant epilepsy: Add-on or substitute? 2021;62(1):228-37.
23. French JA, Faught E. Rational polytherapy. Epilepsia. 2009;50 Suppl 8:63-8.
24. Park KM, Kim SE, Lee BI. Antiepileptic Drug Therapy in Patients with Drug-Resistant Epilepsy. J Epilepsy Res. 2019;9:14-26.
25. Patsalos PN, Perucca E. Clinically important drug interactions in epilepsy: general features and interactions between antiepileptic drugs. Lancet Neurol. 2003;2(6):347-56.
26. Zaccara G, Perucca E. Interactions between antiepileptic drugs, and between antiepileptic drugs and other drugs. Epileptic disorders : international epilepsy journal with videotape. 2014;16(4):409-31.
27. Löscher W, Potschka H, Sisodiya SM, Vezzani A, Barker EL. Drug Resistance in Epilepsy: Clinical Impact, Potential Mechanisms, and New Innovative Treatment Options. Pharmacol Rev. 2020;73(3):606-38.
28. Conway L, Widjaja E, Smith ML, Speechley KN, Ferro MA. Validating the shortened Quality of Life in Childhood Epilepsy Questionnaire (QOLCE-55) in a sample of children with drug-resistant epilepsy. Epilepsia. 2017;58(4):646-56.
29. Madiyono B, Mz SM, Sastroamsoro S, Budiman I, Purwanto SH. Sample size estimation. In: Sastroasmoro S, Ismael S, editors. Basic Clinical Methodology. Jakarta: Sagung Seto; 2014. p. 352-`86.
30. Indonesia MKR. National guideline of medical service of epilepsy management. In: Kesehatan K, editor. Jakarta2017.

Faculty of Medicine of Indonesia University – General Hospital of Dr. Cipto Mangunkusumo

HEALTH RESEARCH ETHICS COMMITTEE

Guidelines of Information Sheet for Prospective Research Subjects

INFORMATION SHEET FOR CANDIDATES (REVISION 1)

I, Dr. Roro Rukmi Windi Perdani from the Faculty of Medicine, Indonesia University, will conduct a study entitled Efficacy and safety of reusing first line OAE as substitution therapy in pediatric epilepsy patients who are resistant to a combination of second line OAE

I wish you to inform you the possibility of your children in taking part of this research study. All information will be provided.

Your participation in this study is voluntary. If you do not want to be in this study, you do not have to enroll. Your refusal to participate will not result in penalties or loss of benefits that you would otherwise be entitled to. In addition, if you decide to participate, you may withdraw from the study at any time. You also have the right to receive the latest information from us regarding the treatment being tested, if any. Withdrawing from this study will not affect the relationship you have, if any, with the researcher or affect the hospital services. If you have questions regarding this consent form, you may contact researcher.

1. **Purpose of Study**

   Observing and assessing the efficacy and safety of reusing first line OAE as a replacement drug in pediatric epilepsy patients who do not respond to second line OAE combination drugs

2. **Participation in research**

   Overall, the study will run for 14 weeks. If you decide that your child will participate in this research, you will be asked to agree to follow our schedule and ensure that you can comply with this schedule. This research will involve several interview sessions and filling out questionnaires. In addition, in this study, we ask for your willingness to fill out daily therapy diaries to monitor side effects and adherence to taking medication from research subjects. We would like to ask for your children's participation to have an EEG and blood laboratory examination before and after administering a replacement drug which is 3 months apart, and to make regular visits every 2 weeks.

3. Reasons for choosing Mr/Ms/Brother

The reason for choosing your child as a subject in this study is based on the criteria we have previously set. These criteria are children with epilepsy aged 1 – 18 years who have been diagnosed with drug-resistant epilepsy by a pediatric neurologist consultant pediatrician according to the 2017 ILAE criteria and receive combination therapy for 3 months or more consisting of 2 OAEs or more where one of them is topiramate or levetiracetam.

4. Study procedure

The study procedure consists of the following steps:

1. Your son/mother/sibling comes for the first visit when the patient comes for a follow up at the Children's Neurology Polyclinic at General Hospital Dr. Cipto Mangunkusumo Jakarta, the Children's Neurology Polyclinic at Harapan Kita Hospital Jakarta, and the Children's Neurology Polyclinic at Fatmawati Hospital, Jakarta.
2. You will be asked for your child's consent to be part of this research. If your child is 12-18 years old, the child will also be asked to fill out a consent form to be part of this research.
3. If you are willing to be part of this research, you will collect initial data in the form of blood laboratory tests and EEG examinations. You will also be interviewed by the research team for information regarding : identity, history of illness, history of drug use and frequency of seizures in the past month
4. You will be given instructions to fill in daily medical record consisting frequency of seizures (type, duration, drugs used to stop seizures if any), notes on taking medication (hours, doses), and notes on side effects what happened to the patient (if any).
5. Your children will be allocated into 2 groups; treatment group or control group randomly. Each group will receive a different replacement drug and will be adjusted to the needs of each patient.
6. In this research, your child will undergo several phases (stages) of research, namely:
   a. Baseline phase (initial data collection) for 3 days
   b. Initial dose phase (replacement drug administration stage with initial dose) for 2 weeks,
   c. Dose titration phase (the dose of the replacement drug is increased) for 2 weeks,
   d. Replacement drug maintenance dose phase (replacement drug maintenance dose phase) for 2 weeks,
   e. Tapering-off phase for 2 weeks
   f. Discontinuation dose phase (replaced drug discontinued phase) for 2 weeks
   g. Maintenance of the new OAE dose phase (no medication stage) for 2 weeks

7. During the initial dose to maintenance dose phase, patients come once every 2 weeks to the pediatric neuro polyclinic at the hospital where the study was conducted. During the visit, the researcher will evaluate filling in the daily medical record.
8. During the initial dose phase to the maintenance dose, monitoring will be carried out:
    - The researcher will remind you to fill out the daily medical record by follow up calls if there have been seizures or side effects every once a week.
    - If there are severe side effects such as severe allergies, representative must immediately report to the researcher by phone. The researcher will explain regarding severe allergic reactions and signs that can be recognized by you or people who live in the same house as the patient. In addition to reporting to the researchers, you are advised to immediately take your child to the emergency room of the nearest hospital or the nearest health facility if a severe allergic reaction occurs to get emergency assistance.
    - The researcher will stop administering the drug in this study if a severe allergic reaction occurs and the subject is categorized as treatment failure.
9. After the maintenance dose phase, your child will enter the final data collection stage at week 13. The data will be collected through laboratory tests, EEG and interviews as well as filling out a questionnaire given by the researcher.
10. EEG examination procedure
    a. You will receive a letter of introduction for the EEG examination from the neurosurgery where the research was carried out.
    b. Representative will bring a letter of introduction to register your child to the EEG department at the hospital where the research was carried out
    c. Representative will have to register online according to the schedule given by the EEG department at the hospital where the research was carried out
    d. Children are tried to sleep naturally by means of the night before the examination
    e. Children are to sleep at 23.00 (11 pm) and wake up at 4.30 am. If this method is not successful, an alternative is to consume a sleeping drug , chloralhydrate at a dose of 50 mg/kg body weight by drinking assisted by officers at the polyclinic.
    f. Hair and scalp should be washed to prevent grease

11. Laboratory examination procedures
    a. Patients come to the hospital laboratory where the research is carried out according to the schedule given by the poly doctor
    b. The patient will be subjected to the process of taking blood with a syringe by the laboratory staff of the hospital where the research was carried out
    c. Patients do not need to fast before the blood collection process

5. Risks, side effects and management

This study requires consumption of valproic acid or phenobarbital or carbamazepine or phenytoin or lamotrigine or clobazam or oxcarbazepine in children with epilepsy who does not respond to second-line OAE for 12 weeks. This drug has been circulating in the community and is used as an anti-epileptic drug. The use of this drug is classified as safe. However, the use of drugs can cause allergic reactions or side effects.

Drug side effects are categorized into:

- Serious side effects (severe allergic reactions, or other reactions that are dangerous or life threatening)
- Mild side effects (flush, lightheadedness, drowsiness, etc.)

If you find that your child is experiencing one of the side effects mentioned above or other side effects, you can immediately contact the researcher to report the situation and immediately seek help at the emergency room or the nearest health facility . Researchers will always be responsible for providing full assistance in the care of patients who experience side effects related to this study.

6. Benefit

There are potential benefits by taking part in this research. Your child will get routine check-ups therefore any potential health problems can be early discovered or prevented. The medicine we provide may not actually be successful in preventing seizures in your child. However, this study can help us find drugs that are has more worse side effects than second line OAEs used as standard treatment today

7. Compensation

Your child will get a laboratory examination and EEG to find out the condition of your child for free. If your child experiences mild side effects or serious side effects during the study, your child will receive the necessary medical treatment and medicines and health financing will be met by the researcher.

You will also receive travel expenses of IDR 100,000 for every daily visit during this research and additional of IDR 200,000

8. Cost

All costs required in this study were borne by the researchers.

9. Confidentiality

The information you provide and your test results are confidential and will be handled so that no unauthorized person can access them. All presentations will present information on a group level and your identity will remain always confidential. Neither your name nor your initials will be collected in the study.

10. Obligations of research subjects

If you agree that your child will take part in this research, then as research subjects, you and your child are obliged to follow the rules or research instructions as written above. If any information is not clear, you can ask further questions to the research team. During the study, no drugs or herbs can be taken other than those given by the researchers.

11. Withdrawal from study

You or your family have the right to refuse to participate in this research. You or your family also have the right to withdraw from this research, even if you have signed a consent form. If you or your family choose to refuse or withdraw from the study, we guarantee that you will still receive the best treatment according to standards while being treated at this hospital.

12. Post-trial access

After this study is completed, we will continue to provide subjects with the best follow-up treatment according to the management of the subject's disease.

13. Additional information

Ask if anything is unclear, the research team will answer any questions you have. You will be provided with sufficient time to take your decision. If you decide to take part in this research study please contact us through the contact details below. If at any time side effects occur or require further explanation, you may contact Dr. Roro Rukmi Windi Perdani, at no. HP 081373679940 at the Division of Neurology, Department of Pediatrics, Faculty of Medicine, Indonesia University – General Hospital of Dr. Cipto Mangunkusumo, Jakarta

INFROMED CONSENT FORM

For research subjects .....who participate in the study: Efficacy and safety Reuse of 1st-line OAEs as substitution therapy in pediatric epilepsy patients resistant to combination 2nd-line OAEs

I declare that I have read this patient information sheet. I declare that I have been informed of the nature of the study, its purpose, its duration, any risks and benefits and what is expected from me. I have taken note of the information document and the appendices to this document. I have had sufficient time to think about it and discuss about it. I agree to allow my child to receive therapy according to the research protocol. that my participation in this study is voluntary and that I am free to end my participation in this study at any time, without justification and without this affecting my relationship with the therapeutic team in charge of my child's health.

I, as the PARENT/GUARDIAN of..... AGREE to participate in this research.

Date

Signature of Parent/Guardian Name of Parent/Guardian

Witness signature

Witness Name : .....

: ..... : ....

: ..... : ....

Researcher Information:
Main Researcher: Dr. Roro Rukmi Windi Perdani

Mobile Number : 081373679940 / email : rororwp@gmail.com KEPK
Faculty of Medicine Indonesia University-General Hospital of Dr Cipto Mangunkusumo : Salemba Street 6, Central Jakarta, 10430

Contact Number: 021 3157008 Email: ec_fkui@yahoo.com

Informed Consent and Assent Guide For Pediatric Patients

(Usage of language must customized to age and development child)
This format is made for children age teenager.

Notes for researcher:

1. The informed assent form consists of from two parts, namely: sheet information and certificate of approval (assent).
2. Do not be too fixated to the length of this format. This format is made long as it contains guide and explanation for you and will not be included in the informed assent you will make later and submit to subject / participant in your study.
3. This format contains example of possible key questions asked at the end of every session to ensure that the information provided is completely understood, especially if study is complex. This just a number of examples and input , each researcher must change question key based on their respective research .
4. In this format:
   - The square brackets signify a specific information that should be attached.
   - Printed thick letters signify parts or the best letters included
   - Standard letter is used to give explanation to researchers and doesn't have to be included in the approval form (assent) later. Advice questions are written in bold to help subjects improve understanding.

WRITING FORMAT IS AVAILABLE ON THE FOLLOWING PAGE

Informed Assent form could not replace form consent that has been signed by parents or guardian. Assent is complementary to consent and signify willingness of child to participate in a study.

[Informed Assent Form for_____]

The form is intended for children aged 12-18 years who visits Pediatric Neurology Polyclinic at General Hospital Dr. Cipto Mangunkusumo Jakarta, Pediatric Neurology Polyclinic at Harapan Kita Hospital Jakarta, and Pediatric Neurology Polyclinic at Fatmawati Hospital Jakarta and we were invited for follow participate in study "Efficacy and safety use back first line OAE as substitution therapy for epilepsy resistant patient with second line OAE combination."

dr.Roro Rukmi Windi Perdani
Department of Pediatric
(Faculty of Medicine of Indonesia University –
General Hospital of Dr. Cipto Mangunkusumo)

Efficacy and safety use back first line OAE as substitution therapy for epilepsy resistant patient with second line OAE combination

Form This Informed Assent consists from two part :

- **Information Sheet (information about study this)**
- **Certificate Approval (Assent) (on sheet you will have to sign as agreement to participate in study this)**

You will be given one copy of This Informed Assent .

Part I: Introductory Information Sheet

My name is Dr. Roro Rukmi Windi Perdani. I am a researcher and currently doing research on anti - epileptic drugs (OAE) to know it's efficacy and safety of the first line anti - epileptic drugs (OAE) to replace second line therapy for the pediatric patient with epilepsy child that a resistant to the medication. We think that study this could give the answer .

I will inform you about this study and would like you to participate. You may choose to participate or decline. We have discussed with your parent / guardian about study this and they are aware that we are asking for your agreement. If you are ready for participate in this study your parents would also agree. However, if you do not wish to participate in study, you do not have to enroll despite the agreement of your parents.

You may discuss all the information that is given in this form this with your parents , friends, or whoever you feel comfortable with. You may slowly decide to participate after discussion.

There are terms and words used that you may not understand. You may ask me directly to answer all your worries and curiosity.

Purpose :

To observe and assess efficacy as well as security in reusing first line anti- epileptic drug as drug replacement for the patient with epilepsy who does not respond to second line anti-epileptic drug. Therefore, we will have to do the study in order to know the effect.

Election subject / participant study:

I have done this trial drug to children with epilepsy who does not respond to second line anti-epileptic drug aged 1 to 18 years – at General Hospital Dr. Pediatric Neurology Polyclinic Cipto Mangunkusumo Jakarta, Pediatric Neurology Polyclinic at Harapan Kita Hospital Jakarta, and the Pediatric Neurology Polyclinic at Fatmawati Hospital, Jakarta. This trial is done to children who suffer epilepsy and shows no response to second line drug and currently is under combination treatment of topiramate or levetiracetam .

Participation characteristic volunteer

You don't have to follow study if you do not wish to join. All decision is given to you. If you do not wish to join , this will not affect anything. The hospital will still accept you and nothing will change. If you agree to say "yes" now, you can still change your decision anytime.

If any changes occurred, and I still want you to participate in this study, I will speak to you beforehand.

- ***Example question to test understanding:*** *: If you decide to not join this study, do you know what are the choices that you have taken? Do you know that this is not a compulsory? If you do not wish to join ? Do you have any questions?*

I have confirmed with the patient and he/she understood that participation in study is voluntary (initials)

Information about Tested Drugs
Valproate acid/phenobarbital, carbamazepine / phenytoin, *lamotrigine/ clobazam* dan *oxcarbazepine*

What is this drug, and do you know anything about this drug?

The drugs I will be using in this study are: valproate / phenobarbital, carbamazepine / phenytoin, lamotrigine / clobazam and oxcarbazepine

This drug has been circulating in the community and is used as anti-epileptic dru . In study this, I will be doing research towards patients who have no response towards combination therapy consisting either topiramate or levetiracetam.

The use of this drug is classified as safe. However, the use of drugs can cause allergic reactions or side effects. As a researcher, I will try to prevent this from happening to you by not giving you drugs that are known to have side effects. In addition, if side effects appear, then I will provide treatment and stop using drugs towards you.

Procedure:
I will start by giving the tested drug according to your condition. You will know what medicine you will be receiving until the end of this study.

If you decide to take part in this research, three things will happen.

1. First, your parents will be interviewed related to your condition and be given a questionnaire related to the evaluation of your quality life
2. Later, there will be several examination that will be conducted such as laboratory blood test and EEG examination.
3. On the appointed day , I will be doing several procedure which consist of several stages (phases), namely the baseline phase (collection of initial data) for 3 days, the initial dose phase (the stage of administering the drug with the initial dose) for 2 weeks, the dose titration phase (adjustment stage drug dose) for 2 weeks, maintenance dose phase (drug taking stage at a fixed dose) for 2 weeks, tapering-off dose phase (drug dose reduction stage) for 2 weeks, dose discontinuation

phase (drug discontinuation stage) for 2 weeks and the maintenance dose phase (the stage of not taking the drug) for 2 weeks and at the end there is final data collection for 1 week.

4. Every 2 weeks , you will be asked to come for a regular follow up.
5. If results have met my expectations, then you can proceed to the next research phase, where I will reduce the dose of the drug you have been receiving until you can stop taking the drug. Conversely, if the number of your seizures increases or there are dangerous side effects, the drug given to you will be stopped and you will get treatment according to the side effects or conditions that you are experiencing. Previously, side effects and dangerous conditions had been prevented as best as possible so that they did not occur.

- ***Example question to test understanding*** Can you say how many times you will return to the clinic to complete your treatment? How many times do you have to make additional visits to the clinic if you are willing to take part in this study? How many injections will you receive? How many tablets? How much blood will be drawn from your veins, using needles and syringes? In how many weeks? Etc. Do you have any other questions? Do you want me to explain the procedure again

I have confirmed with the patient and he/she understood that participation in study is voluntary (initials)

Risk: Is this bad or dangerous for me?

You will feel like there is no difference. This drug may not really work to prevent seizures from occurring in you. But this research can help us to find drugs that work not worse than the drugs used as standard treatment today. There are some good things that you will receive if you participate in this research. You will get regular check-ups with the nurses so if you are sick we will be able to find out quickly and this is actually important.

I have confirmed with the patient and he/she understood that participation in study is voluntary (initials)

Reimbursement: What will I get if I follow this research

Because you need to come to the hospital several times, I will give your parents travel expenses to be able to pay for your trip to this place and give additional fees as a form of my gratitude for your willingness to take part in this research.

Example question to test understanding: Can you tell me if you have correctly understood the benefits that you/you will get if you take part in this research? Did you know that this research will reimburse your travel expenses and time, and how much will be reimbursed? Do you/you have any other questions?

Benefits : Is there the benefits for me ?

You will feel like there is no difference. This drug may not really work to prevent seizures from occurring in you. But this research can help us to find drugs that work not worse than the drugs used as standard treatment today. There are some good things that you will receive if you participate in this research. You will get regular check-ups with the nurses so if you are sick, we will be able to find out quickly and this is actually important.

I have confirmed with the patient and he/she understood that participation in study is voluntary (initials)

Reimbursement: What will I get if I follow this research

Because you need to come to the hospital several times, I will give your parents travel expenses to be able to pay for your trip to this place and give additional fees as a form of my gratitude for your willingness to take part in this research

- **Example question to test understanding:** *Can you tell me if you have correctly understood the benefits that you/you will get if you take part in this research? Did you know that this research will reimburse your travel expenses and time, and how much will be reimbursed? Do you/you have any other questions?*

Confidentiality: Will everyone know this?

I will not tell other people that you participated in this research and I will not share information about you with anyone who is not involved in this research. After this research is complete, you and your parents will be informed of the type of drug you received and how it went.

The information I receive about you during this research will be stored and no one else will be able to see it except the research team. All information about you will be coded with a number and your name will not be included. Only the research team will know your number and we will lock that information with a lock and key. It will not be shared with anyone except me, your doctor, and data security.

- ***Example question to test understanding :*** *Are you familiar with the procedures that we will use to maintain the confidentiality of all information that the research team collects about you? Do you/you have any other questions?*

Compensation: What if I become sick ?

If you become sick while participating in this study caused by the administration of drugs in this study, I will take care of you and all costs of treatment will be my responsibility. I have provided additional information to your parents about what to do if you become sick during this study.

Sharing the results of research: Will you tell me about the results?

When you are done with this research, I will sit with you and your parents and I will explain to you about what I have learned during this research. I will also give you a paper containing the results of this research. After that we will share the results like other researchers, about our findings. We will do this by writing and sharing a report on this research and by attending several meetings with people who are interested in our work.

Right to refuse or withdraw: Can I choose not to participate in this study? Can I change my mind later?

You are not required to take part in this research. No one will scold you or be disappointed with you if you decide not to. This is completely your choice. You can think about it in advance and tell me later. You can say "yes" now and it's okay if you change your mind later.

Who to contact: Who can I contact if I have questions?

You can ask questions now or later. You can also ask the nurses. I've written down a number and address where you can call, or if you're around here, you can come see me. It doesn't matter if you want to talk about this with other people such as your teacher, doctor or your aunt.

If you decide to participate in this research, I will provide you with a copy of this paper to keep for yourself. You can ask your parents to keep it if you want

- **Sample questions to test understanding:** Did you know that you are not obligated to take part in this research if you don't want to? You can say “No” if you want it?
- Did you/you know that you can ask me later if you want? Do you know that I have provided information about who you/you can contact if you/you want to know more about this research? Etc.

Part 2: Certificate of Approval (Assent)

I understand that this study intends to test drugs for epilepsy. I understand that I will receive medication and that I will come monthly to the hospital polyclinic where I will provide my blood sample and EEG examination.

I have read this information (or this information has been read to me). I have received an answer to my question and I understand that I may ask additional questions later.

I agree to participate in this study

OR

I do not agree to participate in this study and I have not signed the inform *assent* below ____(*initial*)

Only if the child gives consent (assent):

Child's name: _____

Child's Signature: _____

Date: _____
Date/Month/Year

If the child subject is illiterate:

I have witnessed the reading of the assent form to the child accurately, and the child has been given the opportunity to ask questions. I confirm that the child has given his or her consent freely.

Name (Other than child's parents)_____AND Child's Finger Print

Signature_____

Date_____
Date/Month/Year

To be signed by the researcher:

I have carefully read or witnessed the accurate reading of the consent form (assent) to the candidate research subject/participant, and the child has been given the opportunity to ask questions. I confirm that the child is given to consent freely.

Name of Researcher: Dr. Roro Rukmi Windi Perdani

Signature of Researcher:_____

Date___
(day/month/year)

Declaration by researchers/consent seeker

I have read the information sheet accurately to the subject/participant candidate, and ensured to the best of my ability that the child understands that the following things will be done:

1. **Interview and filling out the questionnaire that will be conducted with the child's parents/guardians**
2. **I will provide medicine to my patient for 12 weeks**
3. **I will carry out daily check-ups at the polyclinic every month and will carry out examinations in the form of blood tests with blood samples taken by injection and EEG examinations at the beginning and end of treatment with a distance of 12 weeks**

I confirm that the child has been given the opportunity to ask questions about this research, and ensure that all questions are answered to the best of my ability. I confirm that there is no coercion in giving assent, and assent is given freely and voluntarily.

One copy of this consent form has been given to the subject/participant.

Name of researcher/ consent seeker (assent)_____

Signature of researcher/consent seeker (*assent*)_____

Date _____
day/month/year

Copies are given to subjects/participants_____(given the initials by the researcher/assistant)

Parents/Guardians have signed an informed consent form_____Yes_____No_____(given initials by researcher/assistant