INCREASED INTERNALISING AND EXTERNALISING BEHAVIOURAL PROBLEMS ASSOCIATED WITH CORTICOSTEROID USAGE IN CHILDREN WITH NEPHROTIC SYNDROME: A SOUTH EAST ASIAN PERSPECTIVE

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DISSERTATION SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF MASTER OF MEDICINE (PAEDIATRICS)

UNIVESITI SAINS MALAYSIA

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ACKNOWLEDGEMENT

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- Associate Professor Dr Norsarwany binti Mohamad, Head of Department and Lecturer in Paediatric Department, School of Medical Sciences, Universiti Sains Malaysia for her approval and guidance in this study;
- My supervisor Dr Mohamad Ikram bin Ilias, Consultant Paediatric Nephrologist and Lecturer in the Department of Paediatric, School of Medical Sciences, Universiti Sains Malaysia for his advice, guidance and support throughout this study;
- My co-supervisor Associate Professor Dr Azizah Binti Othman, Clinical Psychologist and Senior Lecturer in the Department of Paediatric, School of Medical Sciences, Universiti Sains Malaysia for her guidance in data interpretation and analysis.
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- Special thanks to all my colleague and nurses in Paediatric clinic who are directly or indirectly helping me in data collection

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CHAPTER II: APPENDIX

ABBREVIATIONS

ASEBA	Achenbach System of Empirically Based Assessment
CBCL	Childhood Behaviour Checklist
CI	Confidence interval
FSGS	Focal segmental glomerulosclerosis
Hospital USM	Hospital Universiti Sains Malaysia
INS	Idiopathic Nephrotic Syndrome
MCD	Minimal change disease
SD	Standard deviation
SDNS	Steroid-dependence nephrotic syndrome
SLE	Systemic lupus erythematosus
SPSS	Statistical Package for the Social Science
SRNS	Steroid-resistance nephrotic syndrome
SSNS	Steroid-sensitive nephrotic syndrome
USM	Universiti Sains Malaysia

ABSTRAK

Tujuan: Kajian ini dilakukan untuk menilai masalah psikologi dalam kalangan kanak-kanak yang menghidap penyakit sindrom nefrotik semasa menjalani terapi steroid berbanding dengan kanak-kanak yang sihat.

Kaedah: Ini adalah kajian prospektif kohort yang dilakukan di klinik pediatrik di hospital rujukan utama. Ibu bapa kanak kanak dengan penyakit sindrom nefrotik idiopati, INS dan kumpulan kawalan yang terdiri daripada kanak-kanak tanpa penyakit kronik diminta untuk melengkapkan soal selidik menggunakan Senarai Semak Tingkah Laku Kanak-kanak (CBCL). CBCL digunakan untuk mengukur pelbagai masalah emosi dan psikologi berdasarkan umur, termasuklah tingkah laku internalisasi dan tingkah laku eksternalisasi. Analisis skor CBCL antara kumpulan dilakukan dengan menggunakan ujian Mann-Whitney.

Keputusan: Sebanyak 140 kanak-kanak terlibat dengan bilangan yang sama dari kumpulan kawalan dan kumpulan INS. Terdapat perbezaan yang signifikan dalam jumlah skor CBCL antara kumpulan INS dan kumpulan kawalan, khususnya dalam sub-domain penarikan diri, somatik, cemas dan agresif. Keputusan yang sama ditunjukkan dalam hubungan antara masalah psikologi keseluruhan dengan dos steroid. Dalam kumpulan INS, dos steroid dan ciri-ciri kegemukan, *cushingoid* didapati mempunyai kaitan positif yang signifikan dengan masalah psikologi dalaman. Begitu juga dengan dos steroid dan usia yang mempunyai kaitan yang signifikan dengan skor luaran.

Kesimpulan: Kanak-kanak INS dengan terapi steroid menunjukkan peningkatan skor internalisasi dan eksternalisasi berbanding dengan kanak-kanak yang sihat.

Kata kunci: kortikosteroid, eksternalisasi, internalisasi, sindrom nefrotik, psikologi

ABSTRACT

Aim: This study was performed to measure psychological problems in children with idiopathic nephrotic syndrome (INS) when they are on steroid therapy compared to healthy children.

Methods: It was a prospective cohort study conducted at a paediatric clinic in a tertiary hospital. The parents of participants in both the INS and control groups comprising of children without chronic illness were asked to complete questionnaires using the Child Behavioural Checklist (CBCL). CBCL measures a range of age-specific emotional and psychological problems, including Internalising and Externalising domains. Analyses of the CBCL scores between the groups were performed using the Mann–Whitney test.

Results: A total of 140 children were recruited with equal numbers in the INS and control groups. There was a significant difference in the mean total CBCL scores between the INS and control groups, specifically in the withdrawal, somatic, anxious and aggressiveness sub-domains. Similar findings were demonstrated in the correlation between total psychological problems and corticosteroid dosage. In the INS group, steroid dose and cushingoid features were found to have a significant positive association with internalising psychological problems. Likewise, steroid dose and age were significantly associated with externalising scores.

Conclusion: Children with INS on corticosteroid therapy showed an increase in internalising and externalising scores compared to healthy children.

Keywords: corticosteroid, externalising, internalising, nephrotic syndrome, psychology

CHAPTER I:

THE TEXT

Section A:

Introduction

INTRODUCTION

LITERATURE REVIEW

Idiopathic nephrotic syndrome is the most common form of childhood nephrotic syndrome, representing more than 90 percent of cases between 1-10 years of age and 50 percent after 10 years of age[1]. The vast majority of patients with MCD (>90 percent) respond to steroid therapy. Limited data suggest that disturbances of affect and behaviour may occur in 25-50% of children receiving glucocorticoid[2]. These steroid-induced mental changes may be underrecognized in children, and yet these changes can have considerable impact on social and psychological functioning and treatment outcome.

Soliday et al conducted study regarding Behavioural Effects of Corticosteroids in Steroid-sensitive Nephrotic Syndrome (SSNS) and was published in 1999. They recruited 10 participants with the diagnosis of SSNS from the Pediatric Nephrotic Clinic at Doernbecher Children's Hospital at Oregon Health Sciences University. Out of the 10 children, 8 had normal behaviour at baseline. Out of these 8 children, 5 had Child Behaviour Checklist score above the 95th percentile for anxious/depressive behaviour and/or aggressive behaviour during relapse. Such score are in the range normally considered appropriate for referral to a mental health provider. Two children who had abnormal behaviour at baseline also experienced a worsening of their behaviour during relapse. The behavioural changes occurred almost exclusively at prednisolone doses of 1 mg/kg every 48 hours or more. Regression analysis showed that prednisolone dose was a strong predictor of abnormal behaviour, especially increased aggression.

Hall et al conducted a study regarding The Effect of Corticosteroids on Behaviour in Children with Nephrotic Syndrome from May 1999 to November 2000.

They conducted a prospective assessment of the behaviour of 12 children with newly diagnosed of nephrotic syndrome using a standardized psychological questionnaire at the time of diagnosis and again after 4 weeks of steroid therapy. A group of control children was also assessed. In their study they found a significant increase in the total behaviour score (P=0.03) and specifically in aggressive and poor attention behaviour items in the group of nephrotic children compared with the control group.

Another study regarding behavioural effect of corticosteroid on nephrotic syndrome child by Manti et al was published in 2013. They studied Psychosocial and Cognitive Function in Children with Nephrotic Syndrome: Association with Disease and Treatment Variable. Forty-one patient with Nephrotic Syndrome (23 boys, age range: 4.4-15.2 years) and 42 sex- and age- matched healthy control subjects (20 boys, age range: 4.1- 13.4 years) were involved in the study. They concluded that patients presented with more internalizing problems (P=0.015), including withdrawal (P= 0.012) and somatic complaints (P=0.011), but not more anxiety/depression or externalizing problems. A significant association was found between severity of disease and somatic complaints (P= 0.017) as well as externalizing problems (P= 0.030). Duration of illness were significantly more in those presenting with abnormal anxiety/depression (P=0.011) and externalizing problems (P=0.039). IQ was not associated significantly with disease or steroid treatment variables.

Another latest study was done by Doaa Mohammed Youssef et al in 2013 regarding Assessment of Behaviour Abnormalities of Corticosteroids in Children with Nephrotic Syndrome. In this study 30 paediatric patients with SSNS were included; known as SSNS at complete remission or low dose of prednisolone and have relapse on follow up. They found that highly significant increase in the mean values of anxiety, depression and aggression among cases starts to appear on week one and extends to

three, five and seven weeks compared to baseline. In the seventh week of follow up cases show significant positive correlation between prednisolone doses and the mean values of anxiety and depression scores and aggression.

Section B:

Study protocol

Documents submitted for ethical approval

Research title:

Psychological Outcomes Secondary to Corticosteroid Usage in Paediatric Nephrotic Syndrome in Tertiary Hospital

Principal investigator **: Dr Mohamad Nizam Bin Mahmud MMC 55707**

Co-researchers **: Dr Mohamad Ikram Bin Ilias MMC 40439**

: Associate Professor Dr. Azizah Binti Othman

1.0 Introduction

Idiopathic nephrotic syndrome is the most common form of childhood nephrotic syndrome, representing more than 90 percent of cases between 1-10 years of age and 50 percent after 10 years of age. The vast majority of patients with MCD (>90 percent) respond to steroid therapy. Limited data suggest that disturbances of affect and behavior may occur in 25-50% of children receiving glucocorticoid. These steroid-induced mental changes may be underrecognized in children, and yet these changes can have considerable impact on social and psychological functioning and treatment outcome.

Nephrotic syndrome in children: prediction of histopathology from clinical and laboratory characteristics at time of diagnosis. A report of the International Study of Kidney Disease in Children

Satel S. Mental status changes in children receiving glucocorticoids. Clin Pediatr. 1990;29:382–388

2.0 Problem statement & Study rationale

Problem statement/rationale:

1. This research intended to look at the psychological effect on corticosteroid among pediatric nephrotic syndrome using a validated questionnaire.
2. By analysing the result from this study we can identify the incidence of psychological problems among nephrotic syndrome children.

3.0 What is the use of your study finding?

The result from this study will benefit us in term of preparing parents and other family member regarding the potential behavioural side effect that may happen in children with nephrotic syndrome on steroid treatment.

4.0 Literature review

Elizabeth Soliday, Shannon Grey and Marc B. Lande, conducted study regarding Behavioral Effects of Corticosteroids in Steroid-sensitive Nephrotic Syndrome and was published in 1999. They recruited 10 participants with the diagnosis of SSNS from the Pediatric Nephrotic Clinic at Doernbecher Children's Hospital at Oregon Health Sciences University. Of the 10 children, 8 had normal behavior at baseline. Of these 8 children, 5 had Child Behavior Checklist score above the 95th percentile for anxious/depressive behavior and/or aggressive behavior during relapse. Such score are in the range normally considered appropriate for referral to a mental health provider. The 2 children who had abnormal behavior at baseline also experienced a worsening of their behavior during relapse. The behavioral changes occurred almost exclusively at prednisolone doses of 1 mg/kg every 48 hours or more. Regression analysis showed that prednisolone dose was a strong predictor of abnormal behavior, especially increased aggression.

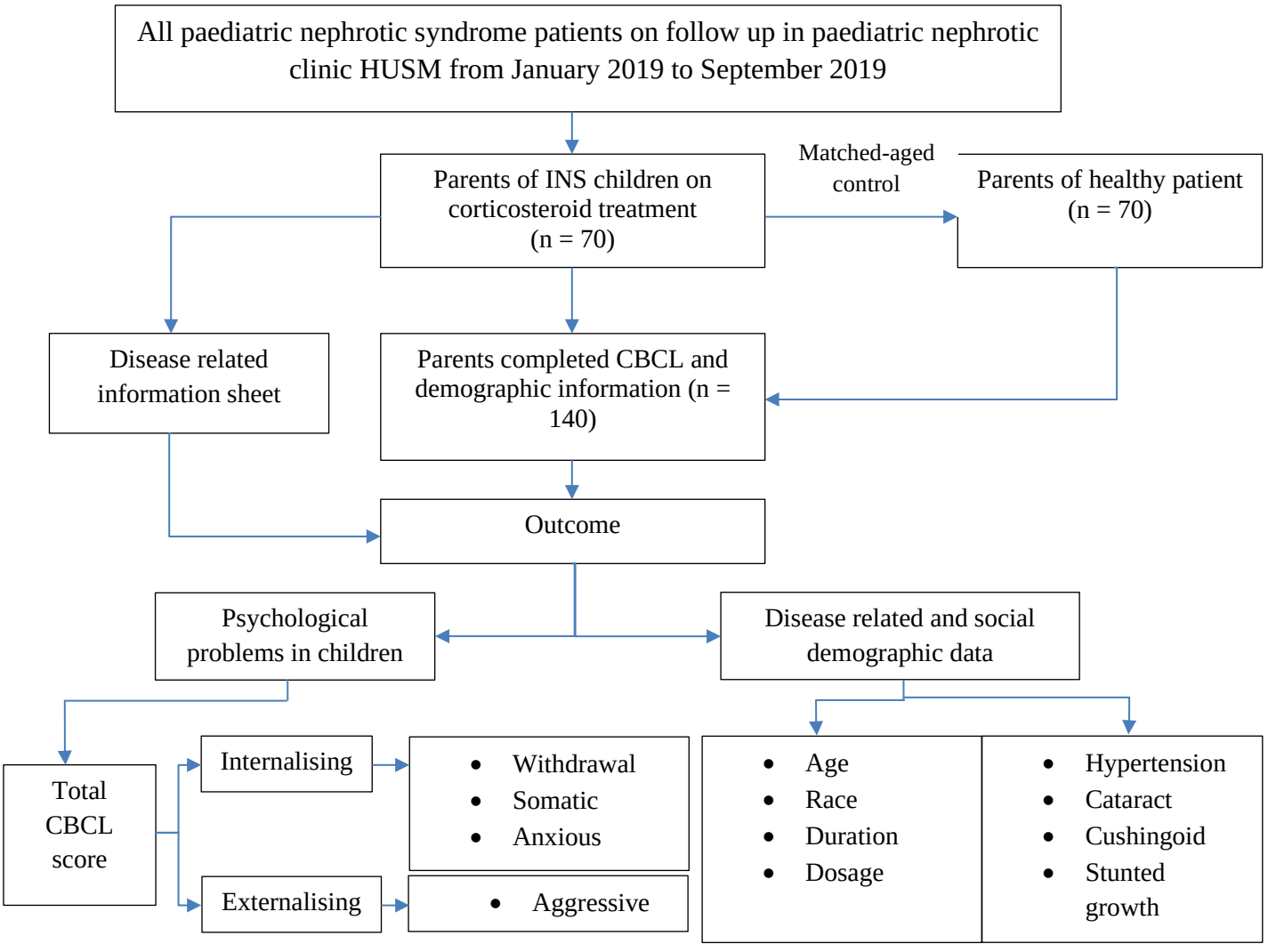
A.S.Hall, G.Thorley, P.N. Houtman conducted a study regarding The Effect of Corticosteroids on Behavior in Children with Nephrotic Syndrome from May 1999 to November 2000. They conducted a prospective assessment of the behavior of 12 children with newly diagnosed of nephrotic syndrome using a standardized psychological questionnaire at the time of diagnosis and again after 4 weeks of steroid therapy. A group of control children was also assessed. In their study they found a significant increase in the total behavior score (P=0.03) and specifically in aggressive and poor attention behavior items in the group of nephrotic children compared with the control group.

Another study regarding behavioural effect of corticosteroid on nephrotic syndrome child was done by Manti et al. The research was published in 2013. They study regarding Psychosocial and Cognitive Function in Children with Nephrotic Syndrome: Association with Disease and Treatment Variable. 41 patient with Nephrotic Syndrome (23 boys, age range: 4.4-15.2 years) and 42 sex- and age- matched healthy control subjects (20 boys, age range: 4.1- 13.4 years) were involved in the study. They concluded that patients presented with more internalizing problems (P=0.015), including withdrawal (P= 0.012) and somatic complaints (P=0.011), but not more anxiety/depression or externalizing problems. A significant association was found between severity of disease and somatic complaints (P= 0.017) as well as externalizing problems (P= 0.030). Years of illness were significantly more in those presenting with abnormal anxiety/depression (P=0.011) and externalizing problems (P=0.039). IQ was not associated significantly with disease or steroid treatment variables.

Another latest study was done by Doaa Mohammed Youssef et al in 2013 regarding Assessment of Behavior Abnormalities of Corticosteroids in Children with Nephrotic Syndrome. In this study 30 pediatric patients with SSNS were included; known as SSNS at complete remission or low dose of prednisolone and have relapse on follow up. They found that highly significant increase in the mean values of anxiety, depression and aggression among cases starts to appear on week one and extends to three, five and seven weeks compared to baseline. In the seventh week of follow up cases show significant positive correlation between prednisolone doses and the mean values of anxiety and depression scores and aggression.

Most of the previous literatures are study regarding the dose-related with psychological problems. However in this study, we can identify and analyse the relationship between psychological problems and demographic pattern in this community such as race and family background.

5.0 Flow Chart



6.0 Target Research Question(s)

Is the Nephrotic Syndrome patient with corticosteroid treatment experienced more or worse psychological problems?

7.0 Objective

1. **General:** To measure psychological problems in patient with NS while on steroid therapy.

2. **Specific:**

    i. To compare level of psychological problem in children with NS on steroid as compared to healthy control group.
    ii. To correlate the psychological problems with duration and dosage of the treatment.
    iii. To determine the association between psychological problems with selected demographic (age, gender, race, education level) and disease-related variables (hypertension, cataract, cushingoid, or stunted growth)

8.0 Hypothesis

Research hypothesis:

1. Children with nephrotic syndrome on corticosteroid experience more psychological problems compared to healthy children.
2. Children have more severe psychological problems (high score) if they have longer duration and high dose of corticosteroid.
3. Children with nephrotic syndrome on corticosteroid treatment with concomitant other diseases, side effect of steroid and poor social economy background experience more psychological issues.

9.0 Research design

Prospective cohort study

10.0 Study area

Hospital USM

11.0 Study period

January 2019 – September 2019

12.0 Study population

Reference population	Paediatric nephrotic syndrome
Source population	Paediatric nephrotic syndrome on follow up in Paediatric Nephrology Clinic HUSM
Target population	Paediatric nephrotic syndrome on follow up in Paediatric Nephrology Clinic HUSM age 6 – 18 years old
Sampling frame	Paediatric nephrotic syndrome on follow up in Paediatric Nephrology Clinic HUSM within the study period

13.0 Subject criteria

Inclusion criteria:

1. Parents of paediatric nephrotic syndrome (newly diagnosed or with underlying nephrotic treatment) on corticosteroid treatment on follow up in Paediatric Nephrology Clinic HUSM age between 6 – 18 years old
2. Parents of healthy child without any medical/surgical problems, age between 6 – 18 years old (control group)

Exclusion criteria:

1. Patient with infantile or secondary nephrotic syndrome
2. Patient with steroid resistance nephrotic syndrome

14.0 Sample size estimation

SD	7.000
Detectable difference	3.500 (SD x effect size by Cohen)
Significant level	0.050
Power	0.800
Drop out	10%-30%
Sample size	63
Corrected sample size	70

Method that we do to calculate the sample size is 2-mean hypothesis testing.

To compare level of psychological problem in children with NS on steroid as compared to healthy control group and to determine the association between psychological problems with selected demographic and disease related variables.

This study also involves control group. Thus, we need 140 (70 x 2) sample sizes.

15.0 Sampling method, subject recruitment and withdrawal criteria.

Sampling method that will be used in this study is convenience sampling. All parents of patients with nephrotic syndrome on corticosteroid treatment that come to clinic for follow-up and parents of healthy children will be given CBCL questionnaires. Parents will be given consent form before entering the study research. Questionnaires will be given by researcher to the parents. Fifteen to twenty minutes will be given for them to complete the questionnaires.

After finished answering, the questionnaires will be collected and data will be analysed by the researcher.

16.0 Study area.

The study will be conducted in Hospital USM.

17.0 Benefit and risk to participant

Patient will benefit from the study because we could anticipate the behavioural changes when child on corticosteroid therapy. Parents can be advised about this potential side effect. Thus, all the family members can be prepared with these behavioural problems at home and at school. Early referral to psychologist or psychiatrist may be the appropriate management when the child has severe behavioural changes.

All patients will have no risk when involve in this study because they only have to answer the questionnaires. This study does not involve any invasive interventions.

18.0 Research tool

This research uses validated questionnaire from Childhood Behaviour Checklist for Age 6-18 years (CBCL 6-18). The questionnaire was translated to Bahasa Melayu. Only 4 out of 8 subscales will be tested in this study (aggressiveness, depression, attention, withdrawal). It was developed by The Achenbach System of Empirically Based Assessment (ASEBA) through decades of research and practical experience.

The inter-interviewer and test-retest reliabilities of the CBCL item scores were supported by interclass correlation of 0.93 to 1.00 for the mean item scores obtained by different interviewers and for reports by parents on 2 occasions 7 days apart. The internal consistency of ASEBA competence scales was supported by alpha coefficients of 0.63 to 0.79 on the CBCL. For the empirically based problem scales, alphas ranged from 0.78 to 0.97 on the CBCL. The scale scores were quite stable over 12- and 24-month period for the CBCL.

The criterion-related validity of the CBCL scales was supported by multiple regressions, odds ratios and discriminant analyses, all of which showed significant ($p<0.01$) discrimination between referred and nonreferred children. The construct validity of the scales has been supported in many ways, such as evidence for significant associations with analogous scales of other instruments and with DSM criteria; by cross-cultural replications of ASEBA syndromes; by genetic and biochemical findings; and by predictions of long-term outcomes.

Manual for the ASEBA School-Age Forms & Profiles; Chapter 9, Reliability, Internal Consistency, Cross-Informant Agreement, and Stability.

Manual for the ASEBA School-Age Forms & Profiles; Chapter 10, Validity.

19.0 Data analysis

Data will be analyzed using **SPSS version 22**. After data has been entered, it will be explored, checked and cleaned. Descriptive statistics will be used to summarize the socio demographic characteristics. Numerical data will be presented as mean (SD) or median (IQR) base on normality distribution. Categorical data will be presented as frequency (%).

Independent t-test will be used to compare level of psychological problem in children with NS on steroid as compared to healthy control group. **Pearson correlation** is used to correlate the psychological problems with duration and dosage of the treatment. **Simple linear regression** will determine the association between psychological problems with selected demographic and disease related variables. JEPem-USM review Panel and regulatory authorities may review the study data.

20.0 Dummy table

Demographic data

Gender	No (n)	%	Total
Male			
Female			
Total			

Age (year)	No (n)	%	Total
6 - 12			
13 – 15			
16 - 18			
Total			

Race	No (n)	%	Total
Malay			
Chinese			
Indian			
Others			
Total			

Education	No (n)	%	Total
Primary school			
Secondary school			
IPT/Collage			
Total			

Family income	No (n)	%	Total
< 1000			
1000 – 5000			
5000-10000			
>10000			
Total			

Disease related data

Comorbid	No (n)	%	total
Hypertension			
Cataract			
Cushinoid			
Stunted growth			
Total			

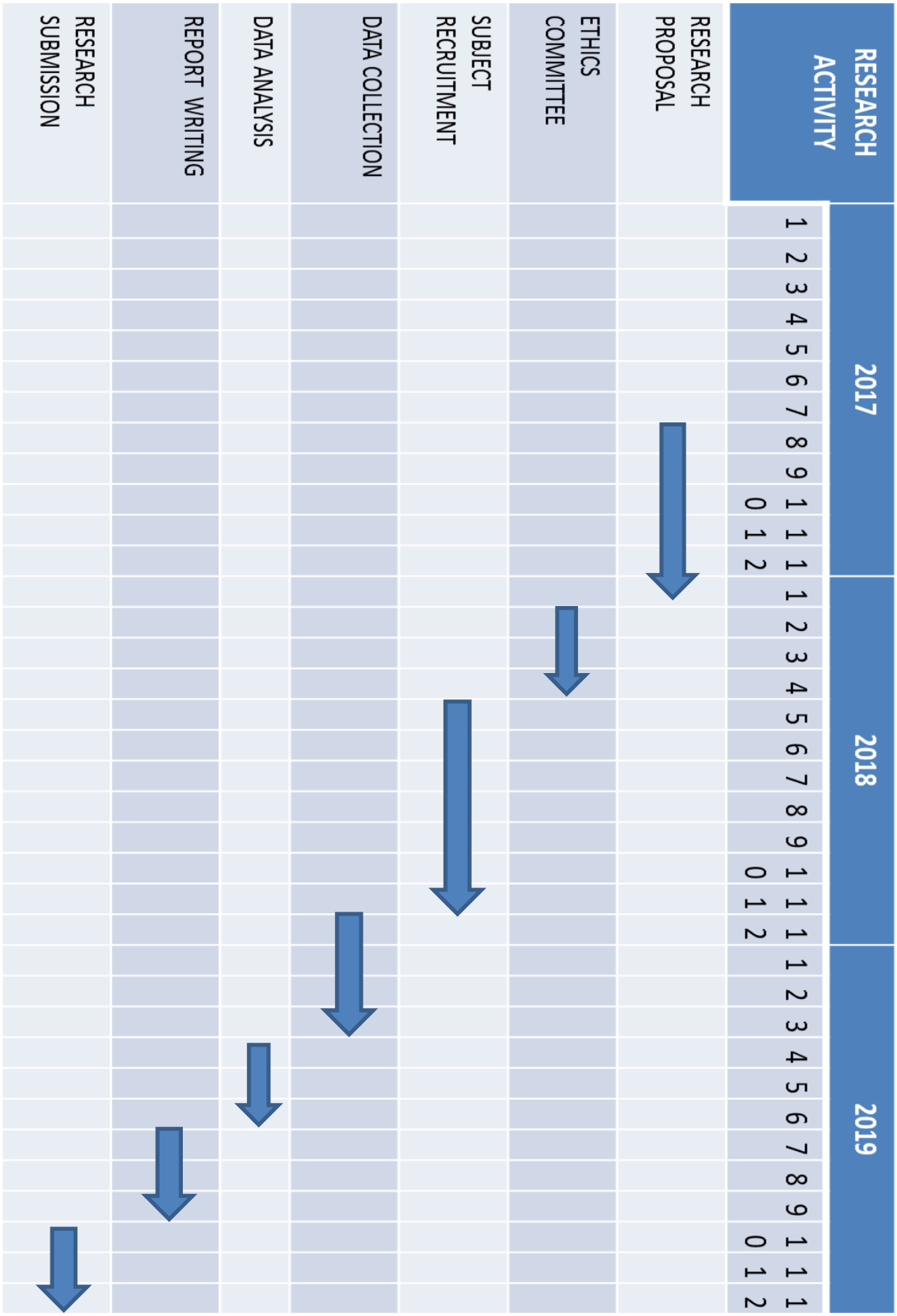
Dosage of steroid	No (n)	%	Total
Total			

Duration of steroid	No (n)	%	Total
Total			

Data analysis

Subscale	No (n)	%	Total	Score
Aggressiveness				
Anxiety/Depression				
Attention				
Withdrawal				

21.0 Gant Chart



22.0 Ethical consideration:

1. Subject vulnerability

The participants are children with newly diagnosed with nephrotic syndrome or with underlying nephrotic syndrome on treatment under Paediatric Nephrology Clinic HUSM follow up. If some subject noted to have high score on CBCL 6-18 during this study, early referral to child psychiatry or child therapies would be beneficial in order to handle their behavioral issues. Score high in CBCL 6-18 in healthy control group might be due to multifactorial issues such as family background or school performance and this will be analyzed later.

2. Declaration of absence of conflict of interest

By analysing the data, we can analyse the effect of long steroid usage towards child behaviour and some demography pattern can be analysed in this study.

3. Privacy and confidentiality

All forms are anonymous and will be entered into SPSS software. Only research team members can access the data. Data will be presented as grouped data and will not identify the respondent individually.

4. Community sensitivities and benefits

No part of this study may trigger social stigma. This study will benefit patients and family members in term of preparing themselves to face the psychological problems that may arise from the effect of treatment of nephrotic syndrome.

5. Honorarium and incentives

Nil

23.0 Principal investigator and Co investigator qualification.

Dr. Mohamad Nizam Bin Mahmud completed his Medical Degree (MD) from University Malaya in 2010. He is currently in the second year of training for the master in paediatric.

Dr Mohamad Ikram bin Ilias graduated from University of Adelaide Australia and currently he is consultant pediatric nephrology in Pediatric Department Pusat Pengajian Sains Perubatan University Sains Malaysia.

Prof Madya Dr Azizah Othman graduated from University of South Australia and she is currently consultant in child psychology in Pediatric Department Pusat Pengajian Sains Perubatan University Sains Malaysia.

Both of the investigators are a certified health care provider. The parents or participants can contact the principle investigator at any time during study period.

The study is subjected to the approval by Jabatan Etika Penyelidikan Manusia USM (JEPem-USM). Parents/patient can contact directly to the JEPem-USM secretariat if further clarifications are needed.

Operational definition

Idiopathic nephrotic syndrome	A rare primary glomerular group of diseases characterized by the triad of edema, massive, or nephrotic-range, proteinuria and hypoalbuminemia, for which there is no known cause. *Orphan.net*
Corticosteroid	Corticosteroids, often known as steroids, are an anti-inflammatory medicine prescribed for a wide range of conditions. *NHSinform.scot*
Internalising problem	Internalising behaviors reflect mood disturbance, including anxiety, depression, and social withdrawal. *Lande MB, Adams H, Falkner B, Waldstein SR, Schwartz GJ, Szilagyi PG, et al. Parental assessments of internalizing and externalizing behavior and executive function in children with primary hypertension. The Journal of pediatrics. 2009;154(2):207-12. e1.*
Externalising problem	Externalising behaviors reflect conflict with others and violation of social norms. *Lande MB, Adams H, Falkner B, Waldstein SR, Schwartz GJ, Szilagyi PG, et al. Parental assessments of internalizing and externalizing behavior and executive function in children with primary hypertension. The Journal of pediatrics. 2009;154(2):207-12. e1.*
Cushingoid features	Facial puffiness, central obesity and weight gain are typical features of a Cushingoid appearance. *Medicine.net*

References:

1. Elizabeth Soliday, Shannon Grey and Marc B. Lande, Pediatrics 1999;e51, Behavioral Effects of Corticosteroids in Steroid-sensitive Nephrotic Syndrome

2. A.S.Hall, G.Thorley, P.N. Houtman, Pediatric Nephrol 2003, The Effect of Corticosteroids on Behavior in Children with Nephrotic Syndrome

3. Manti et al (2013), Psychosocial and Cognitive Function in Children with Nephrotic Syndrome: Association with Disease and Treatment Variable

4. Doaa Mohammed Youssef et al (2013), Assessment of Behavior Abnormalities of Corticosteroids in Children with Nephrotic Syndrome

5. Nephrotic syndrome in children: prediction of histopathology from clinical and laboratory characteristics at time of diagnosis. A report of the International Study of Kidney Disease in Children

6. Satel S. Mental status changes in children receiving glucocorticoids. Clin Pediatr. 1990;29:382–388

7. Manual for the ASEBA School-Age Forms & Profiles; Chapter 9, Reliability, Internal Consistency, Cross-Informant Agreement, and Stability

8. Manual for the ASEBA School-Age Forms & Profiles; Chapter 10, Validity

9. Lande MB, Adams H, Falkner B, Waldstein SR, Schwartz GJ, Szilagyi PG, et al. Parental assessments of internalizing and externalizing behavior and executive function in children with primary hypertension. The Journal of pediatrics. 2009;154(2):207-12. e1.

10. Barnett H. Early identification of frequent relapsers among children with minimal change nephrotic syndrome. J Pediatr. 1982;101:514-8.

Ethical approval

UNIVERSITI SAINS MALAYSIA

JAWATANKUASA ETIKA PENYELIDIKAN MANUSIA

Jawatankuasa Etika
Penyelidikan Manusia USM (JEPeM)
Human Research Ethics Committee USM (HREC)

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9th July 2018

017-5396879

Dr. Mohamad Nizam Mahmud
Department of Paediatrics
School of Medical Sciences
Universiti Sains Malaysia
16150 Kubang Kerian, Kelantan.

Protocol Title : Psychological Outcomes Secondary to Corticosteroid Usage in Paediatric Nephrotic Syndrome in Tertiary Hospital.

Dear Dr.,

We wish to inform you that your study protocol has been reviewed and is hereby granted approval for implementation by the Jawatankuasa Etika Penyelidikan M[redacted]laysia (JEPeM-USM). Your study has been assigned study protocol co[redacted]which should be used for all communication to the JEPeM-USM related to this study. This ethical clearance is valid from **9th July 2018** until **8th July 2019.**

Study Site: Hospital Universiti Sains Malaysia.

The following researchers also involve in this study:

1. Dr. Mohamad Ikram Ilias
2. Assoc. Prof. Dr. Azizah Othman

The following documents have been approved for use in the study.

1. Research Proposal

In addition to the abovementioned documents, the following technical document was included in the review on which this approval was based:

1. Parental Information Sheet and Consent Form (Malay version) – Study Group
2. Parental Information Sheet and Consent Form (Malay version) – Control Group
3. Child Behavior Checklist for Ages 6-18

Attached document is the list of members of JEPeM-USM present during the full board meeting reviewing your protocol.

While the study is in progress, we request you to submit to us the following documents:

1. Application for renewal of ethical approval 60 days before the expiration date of this approval through submission of **JEPeM-USM FORM 3(B) 2017: Continuing Review Application Form.** Subsequently this need to be done yearly as long as the research goes on.
2. Any changes in the protocol, especially those that may adversely affect the safety of the participants during the conduct of the trial including changes in personnel, must be submitted or reported using **JEPeM-USM FORM 3(A) 2017: Study Protocol Amendment Submission Form.**

CERTIFIED BY: National Pharmaceutical Regulatory Agency (NPRA) | Forum for Ethical Review Committees in Asia & Western Pacific Region

3. Revisions in the informed consent form using the **JEPeM-USM FORM 3(A) 2017: Study Protocol Amendment Submission Form.**
4. Reports of adverse events including from other study sites (national, international) using the **JEPeM-USM FORM 3(G) 2017: Adverse Events Report.**
5. Notice of early termination of the study and reasons for such using **JEPeM-USM FORM 3(E) 2017.**
6. Any event which may have ethical significance.
7. Any information which is needed by the JEPeM-USM to do ongoing review.
8. Notice of time of completion of the study using **JEPeM-USM FORM 3(C) 2017: Final Report Form.**

Please note that forms may be downloaded from the JEPeM-USM website: **www.jepem.kk.usm.my**

Jawatankuasa Etika Penyelidikan (Manusia), JEPeM-USM is in compliance with the Declaration of Helsinki, International Conference on Harmonization (ICH) Guidelines, Good Clinical Practice (GCP) Standards, Council for International Organizations of Medical Sciences (CIOMS) Guidelines, World Health Organization (WHO) Standards and Operational Guidance for Ethics Review of Health-Related Research and Surveying and Evaluating Ethical Review Practices, EC/IRB Standard Operating Procedures (SOPs), and Local Regulations and Standards in Ethical Review.

Thank you.

"ENSURING A SUSTAINABLE TOMORROW"