CHAPTER III

Developing and Testing Process

Research Questions

: What is the validity and reliability of the newly developed disease-specific quality of life instrument for Thai adolescents aged 10-18 years with systemic lupus erythematosus?

Research Objectives

: To develop a Quality of Life Measure for Adolescent with Lupus (QoLMEAL), a disease-specific quality of life instrument, for individual patient evaluation in Thai adolescents aged 10-18 years with systemic lupus erythematosus as well as for the comparison of patient groups with the differences in their severity

Research Methodology

A. Research design

: A multi-center descriptive study

: Four collaborating centers include:

1) Siriraj Hospital, Bangkok
2) Ramathibodi Hospital, Bangkok
3) Phamongkutklao Hospital, Bangkok
4) King Chulalongkorn Memorial Hospital, Bangkok

B. Population

1. Target population

: Thai adolescents diagnosed with SLE

2. Inclusion criteria

: Age of the patients is between 10 and 18 years

: Adolescents are diagnosed with SLE according to the American College of Rheumatology revised criteria (1997) for the classification of SLE

: Adolescents are diagnosed with SLE for at least three months

: Adolescents are fluent in spoken Thai

: At least one parent (who was also the legal guardian) is willing to participate

3. Exclusion criteria

: A known case of chronic SLE-unrelated condition(s) which likely impact QOL (e.g., asthma, symptomatic cardiac anomalies, epilepsy, thalassemia).

C. Samples

1. Sampling method

: Consecutive sampling from the Nephrology Clinic and from the hospital wards.

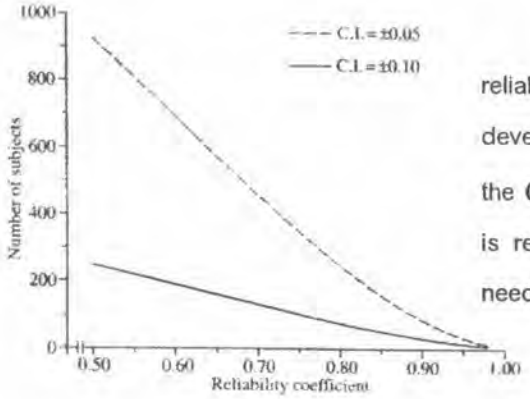
2. Sample size determination

A number of thirty adolescents are required for the stage of the questionnaire pre-testing (pilot study). The sample size determination for the stage of the field-testing uses the equations and the graph (reference from Streiner DL, Norman GF. Health measurement scale: A practical guide to their development and use. 2nd ed. Oxford University Press Inc., New York; 1995) as shown below.

$$Z'(r) = \frac{1}{2}\log_e \frac{(1+r)}{(1-r)}, \quad CI_H = Z'(r) + Z_{\alpha/2}\frac{1}{N-3}$$

Note: r = reliability coefficient; CI_H = half of the confidence interval; N = sample size

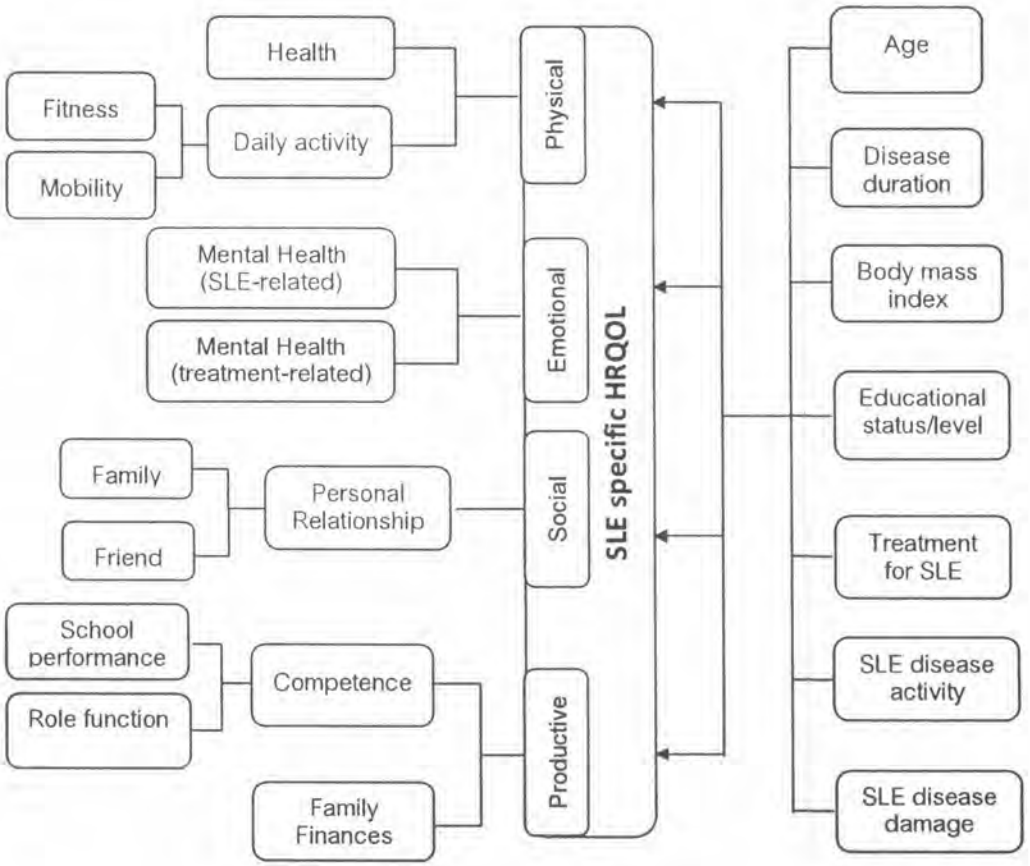
$$N = \left[\frac{Z_{\alpha/2}}{Z'(r) - Z'(r + CI_H)}\right]^2 + 3$$



As expected, the promising reliability coefficient of the newly developed questionnaire is at least 0.5. If the α level of 0.05 and CI_Hs value of 0.10 is required, a minimum of 250 cases is needed to achieve the reliability testing.

D. Tools

1. Conceptual framework



2. Variables

a) Baseline variables

: *Age, gender, weight, height, body mass index, the number of years since initial diagnosis of SLE, educational status / level, medical insurance, family financial status, hospitalization or ICU admission due to SLE and immunosuppressant use within the past month*

b) Primary outcome variables

: Scores on each item of the newly developed questionnaire, a self-report. (see appendix A)

c) Secondary outcome variables

: Scores on each item of the newly developed questionnaire, a proxy-report. (see appendix A)

: Disease activity scores

- The assigned physicians assessed SLE disease activity within the past month using the European Concensus Lupus Activity Measurement (ECLAM). It comprises 15 weighted clinical and serological items, and scores disease activity from 0 to 10. The ECLAM's validity and sensitivity have been demonstrated in childhood-onset SLE.

: Disease damage scores

- The assigned physicians assessed SLE disease damage that had been presented for at least prior 6 month using the Systemic Lupus International Collaborating Clinics/ American College of Rheumatology Damage Index (SDI). It consists of 41 items in 12 organ systems/domains and scores disease damage from 0 to 49. The SDI has been shown to have content, criterion and discriminating validity and reproducibility and has been used in pediatric studies.

3. Operational definition

- Health-related quality of life

: A multi-dimensional construct incorporating primarily the SLE patient's evaluation (and his/her caregiver's evaluation) of his/her life with respect to the domains of physical functioning, emotional well-being, social interaction and productivity

- Duration of the disease

: The period from disease onset which is defined as the time the patient fulfilled the American College of Rheumatology (ACR) criteria for SLE to the time of the study assessment.

- Disease damage

: Irreversible organ system damage resulting from either the disease process of SLE or its sequelae that has been present for at least 6 months. The damage is assessed by using the SDI (see appendix B)

- Disease activity

: Disease activity of SLE within the past month assessed by using the ECLAM (see appendix B)

- Systemic lupus erythematosus (SLE)

: The patients must meet at least four ACR criteria (see appendix B) to be classified as having SLE

E. Data collectors

1. Amount

: 2 data collectors (at least one physician included) during pre-testing in Siriraj hospital

: 2 data collectors (at least one physician included) during field-testing and the testing of discriminant validity at each collaborating center

2. Qualification and standardization

: Data collectors were appointed by the principle investigator of each collaborating site.

: Data collectors were appropriately trained, and had adequately the experiences in a care of adolescents with SLE. A data collector's qualifications were documented.

: Data collectors were thoroughly familiar with the investigational case record forms, protocol guidelines, written informed consent form and other involving written information to be provided to subjects.

F. Data collection procedure (5 stages)

1. Derivation of items for questionnaire content (Stage 1)

The items were derived from 1) review of the existing childhood SLE and HRQOL literature, and 2) review of other HRQOL measures. Also, the initial list of QOL items in Thai was derived from pediatric nephrologists, pediatricians and nurses, cognizant of the QOL issues and experienced in managing SLE adolescents. If new issues were proposed, details of the reasons would be recorded for subsequent justification in reports. Following the specialist interviews, a revised list of items was generated.

2. Selection of items for the draft questionnaire (Stage 2)

Item selection for the draft teen-report and parent-report questionnaires for SLE-pediatric QOL was conducted manually. These items relating to the impact of SLE on the patients' lives were organized (separated or clustered together) into groups, from which the themes emerge. The emerging themes were verified by continual reference to the literatures. Each item was carefully worded to ensure that it related specifically to SLE, and where possible the patients' terminology was used. A panel of discussants (pediatric nephrologists, pediatricians and nurses who were cognizant of the QOL issues and experienced in managing SLE adolescents, and a pediatric psychiatrist) met to consider each potential item. Items were included if they 1) were associated with the respondent's SLE, 2) were general enough to apply to the majority of potential respondents, and 3) expressed one idea only. Discussions were held until agreement was reached for each item.

Furthermore, the item organization was independently reviewed by an expert in SLE from each collaborating center. The content validity index (CVI), using ratings of item relevance by the content experts, was computed. The item which had CVI value less than 0.5 was revised or excluded. Any existing discrepancies were discussed until a consensus was reached. Based on the themes, a draft questionnaire was constructed.

The self-administered questionnaire instructions and a 5-point Likert response format were devised. The responses were "almost always", "often", "sometimes", "almost never", and "never". A 4-week time frame was chosen to correspond to that of the ECLAM which referred to disease activity in the previous month. Item response scores were totaled for each domain and the mean raw domain score was obtained by dividing the total score by the number of items in that domain. The mean raw domain score was transformed to scores ranging from 0 (best HRQOL) to 100 (worst HRQOL) by dividing by 4 (the number of Likert responses [5 responses] minus 1) and then multiplying by 100, as below:

$$\frac{\text{Mean raw domain score}}{4} \times 100 = \text{Transformed score for domain}$$

3. Pre-testing the questionnaire (Stage 3)

Pre-testing the questionnaires determines whether the questionnaires appears to measure what it is meant to measure and ensures that it is meaningful to adolescents with SLE. Purposive sampling was used to guarantee representation in terms of the inclusion criteria. The parents and the patients received written information during their outpatient visit to our nephrology clinic or during the hospitalization at the department of pediatrics, Siriraj hospital.

Adolescents and their parents independently completed the drafts of questionnaires and criticized/made comments about the design, content, structure, and response scale, in the written comments section. If the parents did not live with the patient, the draft questionnaire was mailed directly to his/her guardian who lived with him/her. This feedback was used to refine the questionnaire. They were invited to suggest items not shown in the list that may be important to them.

4. Field-testing the revised questionnaire (QoLMEAL) (Stage 4)

Field-testing the QoLMEAL necessitates multicenter collaboration. Field-testing is to confirm the acceptability, general applicability, validity, and reliability of the QoLMEAL. Patients who were attending at the collaborating pediatric nephrology units were approached during their outpatient attendance or hospitalization. Demographic and clinical information (e.g., age, gender, weight, height, duration of the disease, flare of disease activity, damage) of those who consent were recorded. They and their parents independently completed the QoLMEAL in the clinic or at ward and criticized/made comments about the design, content, structure, and response scale, in the written comments section which was similar in style to those administered during the pre-test stage.

At this stage, psychometric testing of the QoLMEAL consisted of determining the construct validity and internal reliability of the measure. Construct validity evaluates the robustness of the structure and determines the domains of the QoLMEAL. Principal component analysis with oblique rotation was conducted for all remaining items. The generation of factors was confirmatory. The analysis was used as a hypothesis-generating procedure to enable the most appropriate QoLMEAL structure

from psychometric, psychosocial, and clinical perspectives. Internal reliability measured the extent to which items within a domain were conceptually related and were assessed using Cronbach's alpha coefficients. Internal reliability was perceived as acceptable for factors/domains with a Cronbach's alpha coefficient >0.7. SPSS software, version 15 was used to conduct the statistical analysis. The reduced number of items was finally composed into the QoLMEAL.

5. Testing of known-groups validity (Stage 5)

Based on the final remaining items, quality of life as well as known-groups validity was assessed during their outpatient attendance or hospitalization.

Known-groups validity or sensitivity - It is important to evaluate whether an instrument can differentiate between patients with varying degrees of disease severity. Disease severity can be captured by either disease activity using the ECLAM or damage using the SDI. The ECLAM comprises 15 weighted clinical and serological items, and scores disease activity from 0 to 10. The ECLAM's validity and sensitivity have been demonstrated in childhood-onset SLE. A urinalysis, complete blood count, estimated sedimentation rate and serum C3 level were requested according to the standard evaluation. The SDI consists of 41 items in 12 organ systems/domains and scores disease damage from 0 to 49. The SDI has been shown to have content, criterion and discriminating validity and reproducibility and has been used in pediatric studies.

G. Data management

1. Data coding

In the spreadsheets, the data is arranged in columns. The list of these columns demonstrates an explanation of what the numbers within them mean.

Column Heading	Label		
Gender	เพศ	1, ชาย	2, หญิง
RACE	เชื้อชาติ	1, ไทย	2, อื่นๆ
DOE	วันที่กรอกข้อมูล	dd/mm/yyyy; Year in Buddist era	
DOB	วันที่เกิด	dd/mm/yyyy; Year in Buddist era	

DODX	วันที่วินิจฉัยโรค	dd/mm/yyyy; Year in Buddist era				
MED_CARE	สิทธิ์การรักษา	1, จ่ายเอง; 2, ต้นสังกัดราชการ/รัฐวิสาหกิจ; 3, ต้นสังกัดเอกชน; 4, ประกันสังคม; 5, โครงการสุขภาพถ้วนหน้า; 6, ประกันสุขภาพเอกชน; 7,อื่นๆ				
EDU1	สถานะการศึกษา	1, กำลังศึกษาอยู่	2, พักการเรียน < 1 ปี		3, พักการเรียน > 1 ปี	
EDU2	ระดับการศึกษา	1, ป 4 – 6	2, ม 1 – 3	3, ม 4 – 6	4, อุดมศึกษา	
ECO	สถานะทางเศรษฐกิจ	1, มีเงินพอใช้และ มีเหลือเก็บ	2, มีเงินพอใช้ แต่ไม่มีเหลือเก็บ	3, มีเงินไม่พอใช้ แต่ ไม่มีหนี้สิน	4, มีเงินไม่พอใช้ และมีหนี้สิน	
MATE	ผู้ร่วมพักอาศัย	1, บิดามารดา	2, ปู่ย่า ตายาย	3, พี่น้อง	4, ญาติ	5. บุคคลอื่น
AP1 - AP10*	สุขภาพร่างกายวัยรุ่น	0, ไม่เลย	1, เกือบไม่เลย	2, บางครั้ง	3, บ่อยๆ	4. เกือบตลอดเวลา
AD1 – AD10*	กิจวัตรวัยรุ่น	0, ไม่เลย	1, เกือบไม่เลย	2, บางครั้ง	3, บ่อยๆ	4. เกือบตลอดเวลา
AT1 – AT12*	การรักษาวัยรุ่น	0, ไม่เลย	1, เกือบไม่เลย	2, บางครั้ง	3, บ่อยๆ	4. เกือบตลอดเวลา
AE1 – AE9*	อารมณ์วัยรุ่น	0, ไม่เลย	1, เกือบไม่เลย	2, บางครั้ง	3, บ่อยๆ	4. เกือบตลอดเวลา
AS1 – AS10*	สังคมวัยรุ่น	0, ไม่เลย	1, เกือบไม่เลย	2, บางครั้ง	3, บ่อยๆ	4. เกือบตลอดเวลา
AF1 – AF4*	ครอบครัววัยรุ่น	0, ไม่เลย	1, เกือบไม่เลย	2, บางครั้ง	3, บ่อยๆ	4. เกือบตลอดเวลา
AL1 – AL7*	การเรียนวัยรุ่น	0, ไม่เลย	1, เกือบไม่เลย	2, บางครั้ง	3, บ่อยๆ	4. เกือบตลอดเวลา
AM1 – AM3*	การเงินวัยรุ่น	0, ไม่เลย	1, เกือบไม่เลย	2, บางครั้ง	3, บ่อยๆ	4. เกือบตลอดเวลา
PP1 - PP10*	สุขภาพร่างกายวัยรุ่นฉบับพ่อแม่	0, ไม่เลย	1, เกือบไม่เลย	2, บางครั้ง	3, บ่อยๆ	4. เกือบตลอดเวลา
PD1 – PD10*	กิจวัตรวัยรุ่นฉบับพ่อแม่	0, ไม่เลย	1, เกือบไม่เลย	2, บางครั้ง	3, บ่อยๆ	4. เกือบตลอดเวลา
PT1 – PT12*	การรักษาวัยรุ่นฉบับพ่อแม่	0, ไม่เลย	1, เกือบไม่เลย	2, บางครั้ง	3, บ่อยๆ	4. เกือบตลอดเวลา
PE1 – PE9*	อารมณ์วัยรุ่นฉบับพ่อแม่	0, ไม่เลย	1, เกือบไม่เลย	2, บางครั้ง	3, บ่อยๆ	4. เกือบตลอดเวลา

PS1 – PS10*	สังคมวัยรุ่น ฉบับพ่อแม่	0, ไม่เลย	1, เกือบไม่เลย	2, บางครั้ง	3, บ่อยๆ	4, เกือบตลอดเวลา
PF1 – PF4*	ครอบครัววัยรุ่น ฉบับพ่อแม่	0, ไม่เลย	1, เกือบไม่เลย	2, บางครั้ง	3, บ่อยๆ	4, เกือบตลอดเวลา
PL1 – PL7*	การเรียนวัยรุ่น ฉบับพ่อแม่	0, ไม่เลย	1, เกือบไม่เลย	2, บางครั้ง	3, บ่อยๆ	4, เกือบตลอดเวลา
PM1 – PM3*	การเงินวัยรุ่น ฉบับพ่อแม่	0, ไม่เลย	1, เกือบไม่เลย	2, บางครั้ง	3, บ่อยๆ	4, เกือบตลอดเวลา
ECLAM	Disease activity	Score 0-10				
SDI	Disease damage	Score 0-49				

*Items subject to change during the development process

2. Data exploration:

a) The item in each domain was scored from 0 to 4 and linearly transformed to a 0-100 scale, with higher values corresponding to worse QOL.

b) To transform to scores ranging from 0 (best HRQOL) to 100 (worst HRQOL), mean raw domain score was divided by 4 (the number of Likert responses [5 responses] minus 1) and then multiplying by 100, as below:

$$\frac{\text{Mean raw domain score}}{4} \times 100 = \text{Transformed score for domain}$$

c) To create Scale Scores, the mean was computed as the sum of the items over the number of items answered. If the items in the scale were missing, the Scale Score was not computed.

H. Data analysis

Initial descriptive analyses were performed on all variables. All variables were examined to ascertain the data distributions and assess normality.

a) Item-Level Analysis

Feasibility was determined from the percentage of missing values for each item and the distribution of item responses. Multitrait scaling analysis was conducted to determine the extent to which individual items correlated with hypothesized scale construct rather than with other scale. Spearman's rank correlations

were used to determine relationships. Multitrait scaling analysis was summarized via tests of individual item scaling success, defined as the number of times an item correlated higher with its hypothesized scale construct rather than with another scale by ≥ 2 standard errors, which provided an approximation of scaling success. The percentage of item scaling successes relative to the total number of item scaling tests was calculated for each scale.

b) Scale-Level Analysis

Range of measurement was based on the percentage of scores at the extremes of the scaling range, which was, the maximum possible score (ceiling effect) and the minimum possible score (floor effect).

The questionnaire factor structure was examined via multitrait-multi method (MTMM) analysis of the domains and factor analysis of the questionnaire items. MTMM assumes that heterotrait-monomethod correlations (e.g, correlations among domains within self-report and proxy-report) should be lower than monotrait-heteromethod correlations (e.g, concordance between self-report and proxy-report for the same Domain). Correlations were designed as weak (0.10-0.29), medium (0.30-0.49), and strong (≥ 0.50). Given shared method variance and that the questionnaire items were developed to measure an integrated multidimensional construct, it was expected that heterotrait-monomethod correlations among the domains would be medium to large (r ≥ 0.40). Parent / adolescent concordance for the same domain was expected to demonstrate medium to large effect sizes, but not so large that adolescent and parent reports would be redundant. Principal component analysis with oblique rotation was conducted for all remaining items to test the questionnaire underlying dimensions.

Scale internal consistency reliability was determined by calculating Cronbach's coefficient alpha.

$$\alpha_{Cronbach} \equiv \frac{m}{m-1}\left(1-\frac{\sum Var(xi)}{Var(S)}\right)$$

When m, number of items; Var(x_i), variance of *i* th item; S, Σx_i

Scales with reliabilities of 0.70 or greater are recommended for comparing patient groups, whereas a reliability criterion of 0.90 is recommended for analyzing individual patient scale scores. Cronbach's alphas and item-to-total correlations were used for item reduction. If Cronbach's alpha changed little when an item was omitted, that item was a candidate for removal from the scale.

Construct validity was determined utilizing the known-groups method. The known-groups method compared scale scores with groups known to differ in the health construct being investigated. In this study, groups differing in known health status according to ECLAM and SDI were computed, using Spearman's range correlation. It was hypothesized the lower score of ECLAM or / and SDI the patients were assessed, the poorer in their QOL (higher score in our instrument). SPSS software, version 11 was used to conduct the statistical analysis.

I. Ethical considerations

: There are many instruments measuring QOL, physical function and health status in children, but the existing measures largely focus on impact of physical function, which are more applicable in diseases such as juvenile arthritis causing impairment of physical function.*(31-37)* Most of them were not developed specifically for SLE and therefore present different limiting features when considered in the context of pediatric SLE. Recently, a novel pediatric SLE-specific QOL tool titled, Simple Measure of the Impact of Lupus Erythematosus in Youngsters© (SMILEY©) was developed to reflect QOL issues in children with SLE in pediatric practice.*(38)* However, the questionnaire may be inappropriate for Thai adolescents because of the cultural differences. The indices of the HRQOL in Thai adolescents with SLE have never been evaluated. This study will be valuable for the future related studies and the development of promising intervention for these adolescents.

: Each question was carefully worded to ensure that it did not threaten, depress or embarrass the patients and the parents.

: The patients and the parents joined in the study voluntarily and did not receive any bounties for enrolling in this study.

: There was no further medical expense for doctor charge or laboratory investigations for the patients who enrolled in this study.

: These patients might gain medical health benefit from the promising quality of health care.

: The study was started after the approval of the institute ethic committee.

: The voluntary consent was absolutely required prior to a subject enrolment. A principle investigator or assigned co-investigators informed the parents and the child regarding to the objectives of the study, the study process and the confidentiality of subject data. During the course of the study, the child and parents were at liberty to withdraw from the study. Informed consent was obtained according to the Declaration of Helsinki.

J. Limitation

Due to limitation of the study period as well as a small number of the patients per day of the clinic, every patient who visited the clinic was asked whether they decided to enroll in the study. This consecutive sampling might result in the selection bias.

K. Obstacles

: Interference on the completion of pre-testing and field testing

Preventive strategies

1. The questionnaires were completed before the respondents completed any other health data forms and before they saw their physician or healthcare provider.

2. The parent and child completed the questionnaires independently of one another.

3. The questionnaires administrators were trained in the administration of questionnaires according to the protocol guideline.

: Interference on the completion of ECLAM and SDI

Preventive strategies

- The assigned physicians were trained how to score ECLAM and SDI.