Patient-reported outcomes in pharmaceutical care: measurement and implementation

Huang-tz Ou,

Associate Professor,

Department of Pharmacy & Institute of Clinical Pharmacy and Pharmaceutical Sciences, College of Medicine, National Cheng Kung University

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Outline

- Importance and definition
- Tools: development and practical guidelines
- Applications from our previous studies
  - Development of your own PRO tools
    - Diabetes: DMQoL
  - Cultural adaptions of existing tools
    - Polycystic Ovary Syndrome (PCOS): Chi-PCOSQ
  - Utilization of existing local tools
    - Breast cancer: Chinese versions of EORTC QLQ-C30 and QLQ BBR-23
- Recap and Q&A

Health

- Historically, health care mainly focused on **clinical**, physiologic or surrogate outcomes
  - E.g., blood pressure for hypertension
  - The changes in patients' overall health and quality of being were overlooked
- Definition by the WHO
  - **Multi-dimensional**
  - A state of complete **physical, mental, and social well-beings** and not merely the absence of disease or infirmity

Patient-reported Outcomes (PRQs)

- **Subjective** health outcomes directly from patients
  - Health outcomes that are provided only by **patients**
  - E.g., symptom severity, perception of daily functioning, feelings of well-being, satisfaction with treatment, and **health-related quality life (HRQL)**
  - Patient Reported Outcomes Harmonization Group: www.pro-harmonization-group.com

Importance of HRQL

- An indicator of a disease and its treatment
  - **Symptomatic** diseases (no physical or physiological markers of disease activity)
    - E.g., functional gastrointestinal disorders (i.e., heartburn), pain, dermatology diseases
  - **Chronic** diseases (not be cured and need prolonged treatment)
    - E.g., diabetes, congestive heart failure
    - Improvement in HRQL as the most essential outcome
  - Disease with high morbidity and **mortality**
    - E.g., cancer, terminally ill
    - Improvement in morbidity, mortality and HRQL outcomes

Importance of HRQL

- **Treatment outcomes** directly from the patient's perspective
  - Patient's perceptions of changes with treatment on the life
- **Required document** in the regulatory approval
- Important information in **reimbursement decision**
- Promote patient benefits in Direct To Consumer (DTC) campaigns
  - Convincing communication tool to patients
  - **Marketing strategy** for pharmaceutical industries

Outline

- Importance and definition
- Tools:
  - Summary of development
  - Practical guidelines
- Applications from our previous studies
  - Development of your own PRO tools
  - Cultural adaptions of existing tools
  - Utilization of existing local tools
- Recap and Q&A

Summary of development of HRQoL Instruments

1. Identify the concepts in HRQoL

- 5 **constructs** which determine HRQL

2. Create an instrument of HRQoL

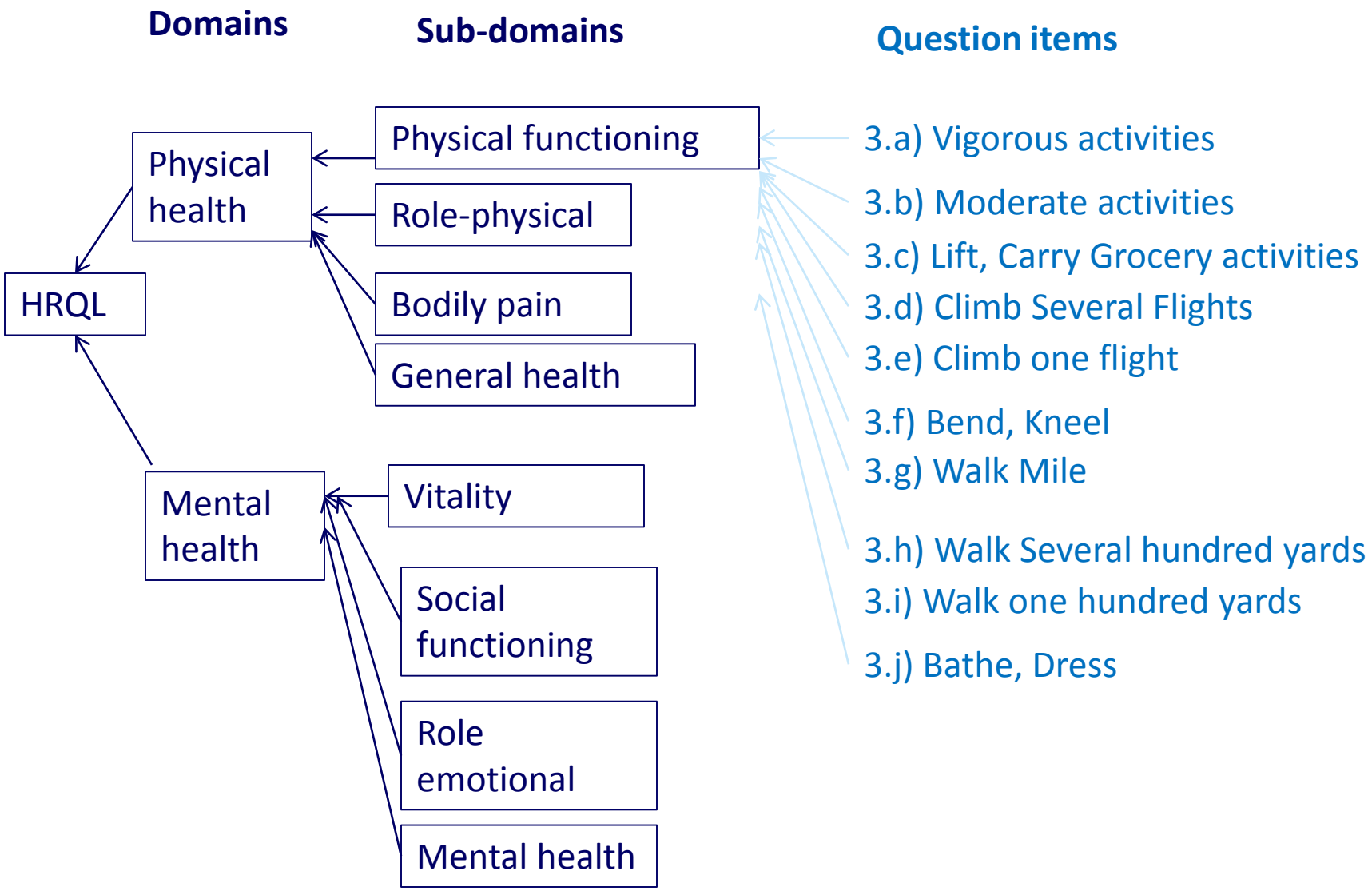
- **A set of question items** which measure the constructs
- E.g., SF-36

3. Assess **psychometric properties** of the instrument

- **Basic properties**
- The guideline for evaluating PRO instruments

4. Modify the instrument

SF-36: Domains and Sample Question Items



SF-36: Sample Question Items

3) The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

	Limited a lot	Limited a little	Not limited at all
a. Vigorous Activities, such as running, lifting heavy objects, participating in strenuous sports			
b. Moderate Activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf			
c. Lifting or carrying groceries			
d. Climbing several flights of stairs			
e. Climbing one flight of stairs			
f. Bending, kneeling, or stooping			
g. Walking more than a mile			
h. Walking several hundred yards			
i. Walking one hundred yards			
j. Bathing or dressing yourself			

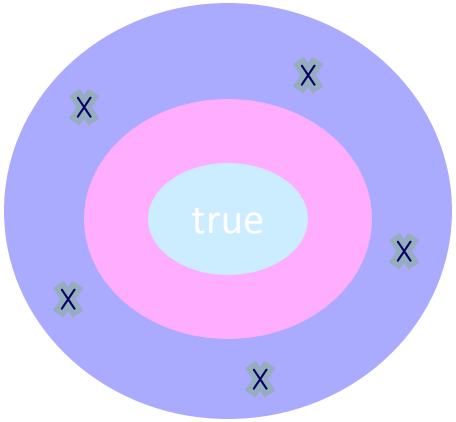
SF-36v2® http://www.qualitymetric.com/demos/TP_Launch.aspx?SID=100

Basic psychometric Properties for PRO's instruments

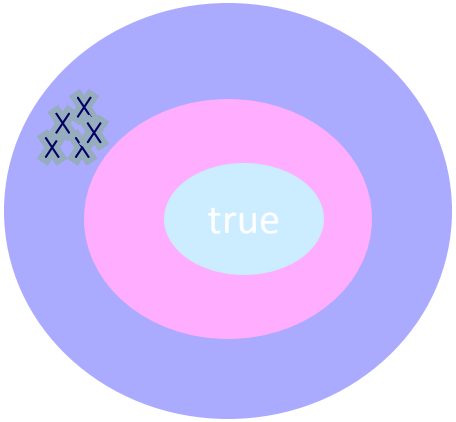
- **Reliability**
- **Validity**
- Responsiveness or sensitivity to change
- Administration burden
- Others

Reliability vs. Validity

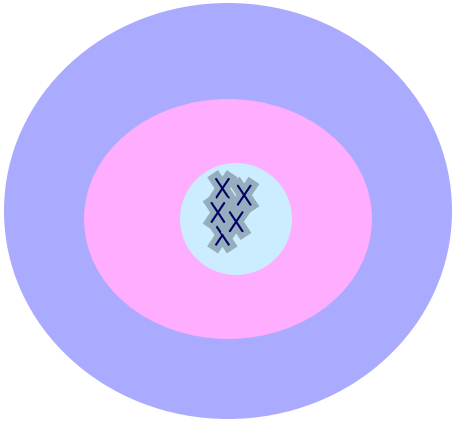
- For an instrument to be ***valid***, it must first be ***reliable (consistent)*** !



Not reliable, not valid



Reliable, not valid



Reliable, Valid

X : HRQL score

Reliability

- Definition
  - The proportion of variance attributable to the true score of the latent variable (HRQL) as reflected in the results' **reproducibility**
  - ***i.e., how consistent the result is!!!***
  - *i.e., does the instrument produce the same score on multiple administrations?*
- Three aspects
  - **Internal consistency** (Cronbach coefficient alpha, 0-1; > 0.7 as acceptable)
  - **Test-retest reliability** (invariant results over a period of time)
  - **Interrater reliability** (invariant results from different raters)

Validity

- The *validity* of the instrument is more difficult to assess than its *reliability*
  - If researchers do not get *reliable (similar) results* upon re-administration, they cannot assess if these results actually measure the underlying concept.
- Three aspects
  - Content validity
  - Criterion validity
  - Construct validity

Content Validity

- A set of items in a domain indeed represents **what it claims to represent**
  - Face validity
  - Appropriate content/items should be generated from relevant stakeholders (patient and clinician) and then be evaluated by a group of experts.
- Determined by
  - A systematic evaluation of **whether items and response options** are ***relevant*** and are ***comprehensive*** measures of the domain or construct (via Content Validity Index)

Administration Burden

- The time, effort and other demands placed on those to whom the instrument is administered (**respondent burden**) or on those who administer the instrument (**administrator burden**)
- Determined by:
  - The average and range of the time needed to complete the instrument (i.e., 10-15 minutes)
  - Reading and comprehensive level
  - Any specific requirements or requests made of respondent

Other Psychometric Properties

- Interpretability
  - The degree to which one can assign easily understood meaning to an **instrument's quantitative scores**
- Culture and language adaptation
  - Assessment of **conceptual and linguistic equivalence**
  - Evaluation of measurement properties
- The criteria for evaluating a PRO instrument
  - Scientific Advisory Committee of the Medical Outcomes Trust*

*Quality of Life Research. 2002;11, 193-

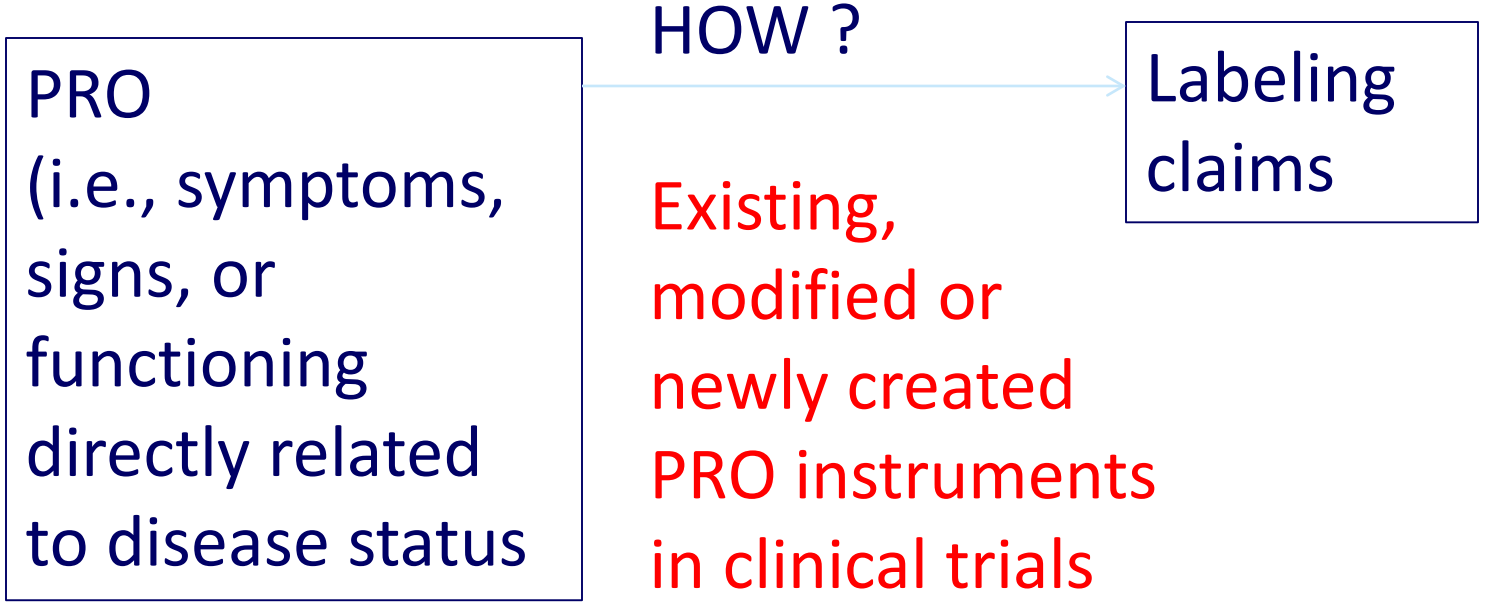
Table 1. Attributes and criteria for reviewing instruments*

Attribute	Review criteria
1. Conceptual and measurement model The rationale for and description of the concept and the populations that a measure is intended to assess and the relationship between these concepts.	– Concept to be measured – Conceptual and empirical bases for item content and combinations – Target population involvement in content derivation – Information on dimensionality and distinctiveness of scales – Evidence of scale variability – Intended level of measurement – Rationale for deriving scale scores
2. Reliability The degree to which an instrument is free from random error.	*Internal consistency* – Methods to collect reliability data – Reliability estimates and standard errors for all score elements (classical test) or standard error of the mean over the range of scale and marginal reliability of each scale (modern IRT)
Internal consistency The precision of a scale, based on the homogeneity (intercorrelations) of the scale's items at one point in time.	– Data to calculate reliability coefficients or actual calculations of reliability coefficients – Above data for each major population of interest, if necessary
Reproducibility Stability of an instrument over time (test–retest) and inter-rater agreement at one point in time.	*Reproducibility* – Methods employed to collect reproducibility data – Well-argued rationale to support the design of the study and the interval between first and subsequent administration to support the assumption that the population is stable – Information on test-retest reliability and inter-rater reliability based on intraclass correlation coefficients – Information on the comparability of the item parameter estimates and on measurement precision over repeated administrations
3. Validity The degree to which the instrument measures what it purports to measure.	– Rationale supporting the particular mix of evidence presented for the intended uses – Clear description of the methods employed to collect validity data – Composition of the sample used to examine validity (in detail) – Above data for each major population of interest
Content-related: evidence that the domain of an instrument is appropriate relative to its intended use. *Construct-related:* evidence that supports a proposed interpretation of scores based on theoretical implications associated with the constructs being measured.	– Hypotheses tested and data relating to the tests – Clear rationale and support for the choice of criteria measures

Guidance for Industry PRO Measures

- Complete guideline
  - http://www.ispor.org/workpaper/FDA%20PRO%20Guidance.pdf
- Key/practical considerations in the submission

U.S. FDA's PRO Guidance for Industry



"Recommended (***should*** do), not required"

Development of a PRO Instrument: An Iterative Process

i. Hypothesize Conceptual Framework

- Outline hypothesized concepts and potential claims
- Determine intended population
- Determine intended application/characteristics (type of scores, mode and frequency of administration)
- Perform literature/expert review
- Develop hypothesized conceptual framework
- Place PROs within preliminary endpoint model
- Document preliminary instrument development

ii. Adjust Conceptual Framework and Draft Instrument

- Obtain patient input
- Generate new items
- Select recall period, response options and format
- Select mode/method of administration/data collection
- Conduct patient cognitive interviewing
- Pilot test draft instrument
- Document content validity

iii. Confirm Conceptual Framework and Assess Other Measurement Properties

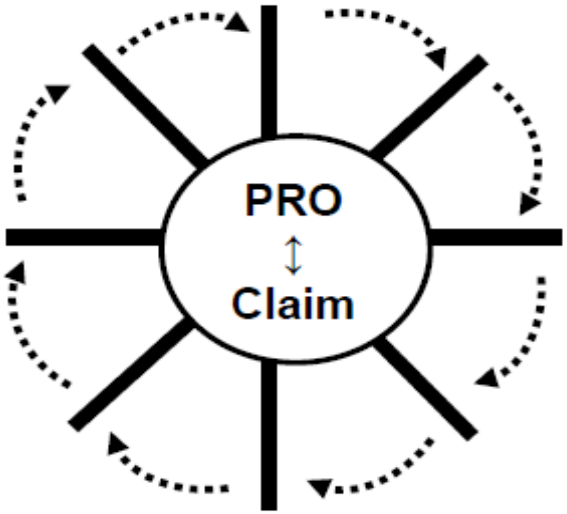
- Confirm conceptual framework with scoring rule
- Assess score reliability, construct validity, and ability to detect change
- Finalize instrument content, formats, scoring, procedures and training materials
- Document measurement development

iv. Collect, Analyze, and Interpret Data

- Prepare protocol and statistical analysis plan (final endpoint model and responder definition)
- Collect and analyze data
- Evaluate treatment response using cumulative distribution and responder definition
- Document interpretation of treatment benefit in relation to claim

v. Modify Instrument

- Change wording of items, populations, response options, recall period, or mode/method of administration/data collection
- Translate and culturally adapt to other languages
- Evaluate modifications as appropriate
- Document all changes



Key Considerations in PRO Instruments

Endpoint model

✓The relevance of the PRO to the **target population**

Clinical trial objectives and design

✓Is PRO outcome as one of study objectives?

✓How will PRO outcomes be collected and measured?

PRO instrument's conceptual framework (i.e., content validity)

- Recall period
- Response option
- Format, instructions and training
- Patient understanding
- Scoring of items and domains
- Respondent and administrator burden
- Measurement (psychometric) properties

Key Considerations in PRO Instruments

Endpoint model

✓The relevance of the PRO to the **target population**

Clinical trial objectives and design

PRO instrument's conceptual framework (i.e., content validity)

- **Recall period**
- Response option
- Format, instructions and training
- Patient understanding
- Scoring of items and domains
- Respondent and administrator burden
- Measurement (psychometric) properties

Recall Period

- The rationale and appropriateness depends on:
  - Disease
  - PRO concept (i.e., symptoms, pain): duration, frequency, intensity
  - Tested treatment
  - Population (i.e., age, memory)
- General rules
  - Short recall periods (i.e., current, recent 7 days)
  - Detail recall of experience over a period of time
    - i.e., make use of a diary for data collection
    - i.e., ask patients to respond based on their worst (or best) experience over the recall period

Key Considerations in PRO Instruments

Endpoint model

✓The relevance of the PRO to the **target population**

Clinical trial objectives and design

PRO instrument's conceptual framework (i.e., content validity)

- Recall period
- **Response option**
- Format, instructions and training
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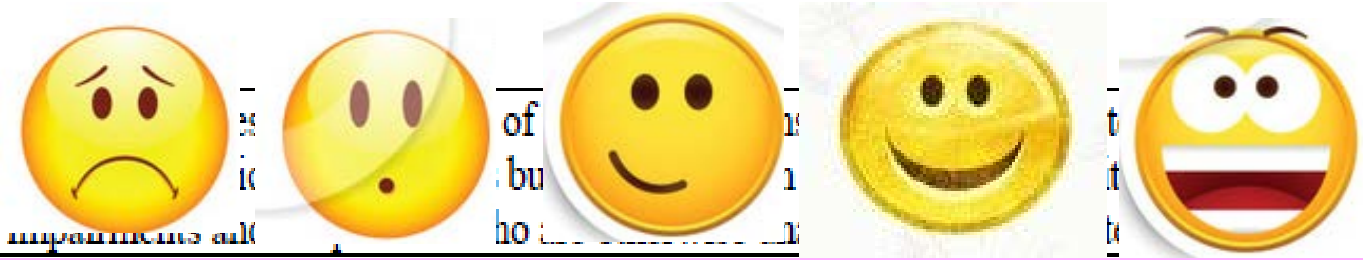
Q: In general, how do you say your health today?

Type	
Visual analog scale (VAS)	|_____| Poor Excellent
	score.
Anchored or categorized VAS	|_____|_____|_____|_____|_____| Poor Excellent
Likert scale	☐ Poor ☐ Fair ☐ Good ☐ Very Good ☐ Excellent
Rating scale	☐ 0 ☐ 25 ☐ 50 ☐ 75 ☐ 100
	categories are numbered rather than labeled with words.
Recording of events as they occur	Specific events are recorded as they occur using an event log that can be included in a patient diary or other reporting system (e.g., interactive voice response system).
Pictorial scale	
Checklist	Vigorous activities (i.e., running): ☐ Yes, limited a lot ☐ Yes, limited a little ☐ No, not limited at all

Appropriate Response Options

- Adequate instructions to select options
  - Clear and appropriate wording
- Appropriate for intended population
  - More responses to capture worsening or improvement
- A clear distinction between options
  - The order of options and the interval between options
  - Not bias the direction of responses

Key Considerations in PRO Instruments

Endpoint model

✓The relevance of the PRO to the **target population**

Clinical trial objectives and design

PRO instrument's conceptual framework (i.e., content validity)

- Recall period
- Response option
- **Format, instructions and training**
  - Consistent format with the original
  - Clear instructions to patients and administrators
  - Training for standardized administration

Key Considerations in PRO Instruments

Endpoint model

✓The relevance of the PRO to the **target population**

Clinical trial objectives and design

PRO instrument's conceptual framework (i.e., content validity)

- Recall period
- Response option
- Format, instructions and training
- **Patient understanding**
  - A pilot testing (i.e., patient's own interpretation consistent with original design)
  - 6th grade reading level

Key Considerations in PRO Instruments

Endpoint model

✓The relevance of the PRO to the **target population**

Clinical trial objectives and design

PRO instrument's conceptual framework (i.e., content validity)

- Recall period
- Response option
- Format, instructions and training
- Patient understanding
- **Scoring of items and domains**
  - Numerical scores assigned to response options
  - Simple summary score vs. weighted score

Key Considerations in PRO Instruments

Endpoint model

✓The relevance of the PRO to the **target population**

Clinical trial objectives and design

PRO instrument's conceptual framework (i.e., content validity)

- Recall period
- Response option
- Format, instructions and training
- Patient understanding
- Scoring of items and domains
- **Respondent and administrator burden**
  - i.e., time needed to complete the questionnaire
  - i.e., reading and comprehensive level

Key Considerations in PRO Instruments

Endpoint model

✓The relevance of the PRO to the **target population**

Clinical trial objectives and design

PRO instrument's conceptual framework (i.e., content validity)

- Recall period
- Response option
- Format, instructions and training
- Patient understanding
- Scoring of items and domains
- Respondent and administrator burden
- **Measurement (psychometric) properties**

Outline

- Importance and definition
- Tools: development and guidelines
- Applications from our previous studies
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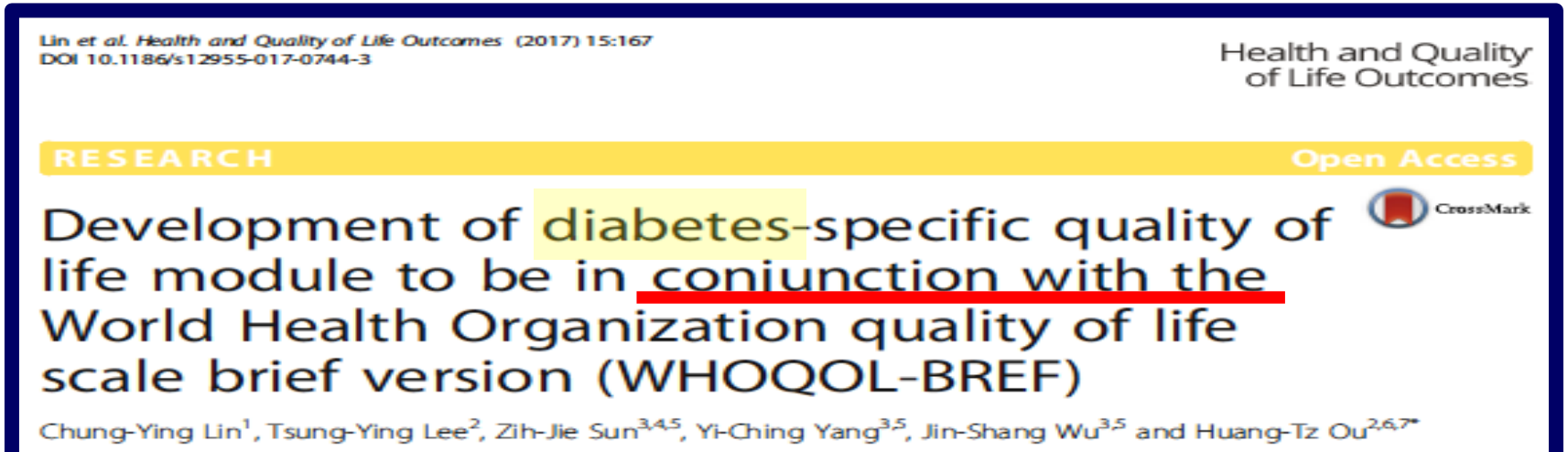
Development of PRO tools: HRQR for diabetes in Taiwan

- Problems in existing measures
  - Limited feasibility to practice due to Long length (i.e., up to 39-51 items)
  - Not distinguish items for generic and diabetes-specific
- WHOQOL-BREF
  - Short version of (i.e., 26 items)
  - Widely-used internationally and culturally
  - Less sensitive to specific disease-populations (e.g., DM)



Lin et al. Health and Quality of Life Outcomes (2017) 15:167
DOI 10.1186/s12955-017-0744-3

Health and Quality of Life Outcomes

RESEARCH Open Access

Development of diabetes-specific quality of life module to be in conjunction with the World Health Organization quality of life scale brief version (WHOQOL-BREF)

Chung-Ying Lin[1], Tsung-Ying Lee[2], Zih-Jie Sun[3,4,5], Yi-Ching Yang[3,5], Jin-Shang Wu[3,5] and Huang-Tz Ou[2,6,7*]

Development of PRO tools: HRQR for diabetes in Taiwan (process)

Literature review: 13 measures with 467 items
- ✓ Pooling of all possible items
- ✓ Removal of redundant items

66 items Expert panel (internal, 1st)

Expert panel (external)

22 items Expert panel (internal, 2nd)

Initial version for pilot testing

20 items Expert panel (internal, 3rd)

Development of response scale
(in a **5-point** Likert scale, consistent with WHOQOL-Bref)

Psychometric testing
(117 patients)

10 items

13 patients varied by:
- ✓ Ages (6 aged over 65 years),
- ✓ Educational levels (4 with college degree; 4 with high school degree; 4 with elementary school degree; 1 illiterate)
- ✓ Genders (7 males; 6 females)

Results
- ✓ in a 4-point Likert scale: how well they understood the items?
- ✓ These item descriptions were understandable to the patients (mean score = 3.69 to 4).

- Ceiling and floor effects
- Construct validity
- Internal consistency
- Concurrent validity
- Known-group validity

Property	Measure
Ceiling and floor effects	✓ The percentages of minimum (score of 1) and maximum (score of 5) ratings given by respondents. ✓ Remove the items whose ceiling/floor effect was larger than 20%, which suggests that they may not provide sufficient information
Internal consistency	✓ Cronbach's α (Ranging from 0-1.0, no to perfect homogenous. accepted value: 0.7) ✓ Item separation and person separation reliability from Rasch analysis
Construct validity	✓ Exploratory factor analysis (EFA) combined with parallel analysis (PA) ✓ Rasch analysis (i.e., Infit MnSq, outfit MnSq; 0.5-1.5: an item embedded on the latent construct)
Concurrent validity	Test the correlation between the score of DMQoL and the following scores in WHOQOL-BREF: Q1 and Q2, four domains, and total score
Known-group validity	✓ Using the laboratory data (e.g., HbA1c, cholesterol) and diabetes-related complications to differentiate patients' subgroups ✓ Hypothesis: with patients with poorer glycemic control (using HbA1c as a marker of glycemia control) or diabetes-related complications would have lower HRQoL as compared to those who had achieved the glycemic target (i.e., HbA1c ≤ 7%) or without diabetes-related complications. ✓ E.g., compare DMQoL scores of patients with a better HbA1c (≤7%) with those of patients with a worse HbA1c (>8%)

Frequency of response on each item of DMQoL

Item #: Item description	Response; n (%)				
	1	2	3	4	5
1: Overall, how much does diabetes control influence your life?	25 (21.4%)	39 (33.3%)	19 (16.2%)	21 (17.9%)	13 (11.1%)
2: How satisfied are you with the time you spend on diabetes care?	1 (0.9%)	16 (13.7%)	28 (23.9%)	66 (56.4%)	6 (5.1%)
3[a]: How satisfied are you with your expenses on diabetes care?	2 (1.7%)	5 (4.3%)	34 (29.1%)	67 (57.3%)	8 (6.8%)
4[a]: How satisfied are you with the results of glycemic control?	2 (1.7%)	36 (30.5%)	33 (28.0%)	40 (33.9%)	4 (3.4%)
5[a]: How satisfied are you with the results of the control of diabetes-related complications?	0 (0.0%)	8 (6.8%)	29 (24.8%)	63 (53.8%)	14 (12.0%)
6[a]: How much difficulty have you had in self-care in the management of diabetes?	51 (43.6%)	27 (23.1%)	13 (11.1%)	9 (7.7%)	16 (13.7%)
7[a]: How satisfied are you with your diet control?	0 (0.0%)	10 (8.5%)	38 (32.5%)	62 (53.0%)	5 (4.3%)
8[a]: How satisfied are you with your physical activities?	4 (3.4%)	28 (23.9%)	21 (17.9%)	56 (47.9%)	7 (6.0%)
9[a]: How satisfied are you with your weight control?	3 (2.6%)	22 (18.8%)	30 (25.6%)	58 (49.6%)	3 (2.6%)
10[a]: How satisfied are you with your treatment of diabetes?	0 (0.0%)	6 (5.1%)	29 (24.8%)	72 (61.5%)	5 (4.3%)
11[a]: How much can you accept that others know you have diabetes?	4 (3.4%)	12 (10.3%)	21 (17.9%)	40 (34.2%)	39 (33.3%)
12: How much have you adapted to life with diabetes?	3 (2.6%)	5 (4.3%)	27	59	23
	(60.7%)	(13.7%)	(3.4%)	(5.1%)	(16.2%)

20 items

- ✓ 8 items with **floor effects** (i.e., > 20% of the respondents rated the item as **1**)
- ✓ 2 items with **ceiling effects** (i.e., > 20% of the respondents rated the item as **5**)

- ✓ **Expert panel: remove these items**

Final 10 items for psychometric testing

Item properties in DMQoL

EFA results

- ✓ **> 0.4**
- ✓ **All items being embedded in one underlying concept**

Item #: Item description	Corrected item-total correlation	Factor loading[a]	Infit MnSq[b]	Outfit MnSq[b]
2: How satisfied are you with the time you spend on diabetes care?	0.591	0.677	0.83	0.84
3 How satisfied are you with your expenses on diabetes care?	0.506	0.575	0.88	0.87
4: How satisfied are you with the results of glycemic control?	0.574	0.623	0.94	0.97
5: How satisfied are you with the results of the control of diabetes-related complications?	0.500	0.547	1.09	1.13
7: How satisfied are you with your diet control?	0.583	0.630	0.68	0.74
8: How satisfied are you with your physical activities?	0.573	0.617	1.17	1.13
9: How satisfied are you with your weight control?	0.433	0.470	1.22	1.14
10: How satisfied are you with your treatment of diabetes?	0.526	0.578	0.77	0.81
12: How much have you adapted to life with diabetes?	0.577	0.641	1.43	1.37
15: How satisfied are you with your relationship with your family since you were diagnosed with diabetes?	0.432	0.482	0.89	0.90

[a]Using explorartory factor analysis; [b]Using Rasch anlaysis
Infit information-weighted fit statistic, *Outfit* outlier-sensitive fit statistic, *MnSq* mean square

- ✓ **All the infit and outfit MnSq values: 0.5~1.5**
- ✓ **Support EFA results**

Criterion Validity

- The correlation of the instrument score/result with **an external measure** considered to be a golden standard
- **Concurrent** validity
  - A strong correlation between **a new instrument** and another **well-accepted existing instrument** when administered to a patient at the same time
- **Predictive** validity
  - The ability of the instrument to predict future health status or disease condition

Concurrent validity of DMQoL with World Health Organization Quality of Life-short version (WHOQOL)

WHOQOL-BREF	*r* (*p*-value)	
	Pearson correlation	Partial correlation[a]
Q1: overall QoL	0.416 (< 0.001)	0.371 (< 0.001)
Q2: general health	0.479 (< 0.001)	0.457 (< 0.001)
Physical domain	0.177 (0.058)	0.283 (0.003)
Psychological domain	0.408 (< 0.001)	0.417 (< 0.001)
Social domain	0.317 (0.001)	0.336 (< 0.001)
Environment domain	0.580 (< 0.001)	0.572 (< 0.001)
Total score	0.461 (< 0.001)	0.481 (< 0.001)

[a]**adjusted for age** (Age is a potential confounder of HRQoL.)

After adjusting for age, the correlation between the score of the DMQoL and that of the physical WHOQOL-BREF domain was substantially improved.

Construct Validity

- How well you translated theoretical concepts into actual measures
- Both **convergent validity** and **discriminant validity**
  - The extent to which an item correlates with other items in the same domain (**convergent validity**) but not correlate with dissimilar items in other domains (**discriminant or divergent validity**)
  - Reveal in correlation matrix
    - The items in the same domain are highly correlated (i.e., $r>0.5$) but less correlated with items in other domains (i.e., $r<0.5$)
- **Known-groups validity**

Known-Groups Validity

- To assess the differences between two patient groups **known or theorized to differ** in some way
- i.e., using a survey developed to measure anxiety related to childbirth, researchers might expect a higher level (score) of anxiety for first-time mothers than in women who already gave birth to other children

Known-group validity for DMQoL compared with that of WHOQOL-BREF

WHOQOL-Bref | **DMQoL**

		Q1[a]	Q2[a]	Physical[a]	Psychological[a]	Social[a]	Environment[a]	Total score[a]	DMQoL
		Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
CCD	Yes (*n* = 16)	3.38 ± 0.89	2.81 ± 0.91	*10.59 ± 2.11**	*11.92 ± 1.93**	11.33 ± 3.11	13.83 ± 1.82	*47.69 ± 6.43**	3.50 ± 0.37
	No (*n* = 75)	3.52 ± 0.70	3.01 ± 0.86	*12.23 ± 1.67**	*13.09 ± 1.89**	12.74 ± 3.44	14.60 ± 1.75	*52.68 ± 6.64**	3.46 ± 0.51
PVD	Yes (*n* = 4)	3.50 ± 0.58	3.49 ± 0.75	10.71 ± 2.40	12.67 ± 2.11	11.50 ± 4.51	13.67 ± 2.22	48.55 ± 10.32	3.78 ± 0.40
	No (*n* = 87)	3.25 ± 0.96	2.97 ± 0.87	12.01 ± 1.81	12.90 ± 1.94	12.55 ± 3.38	14.50 ± 1.76	51.99 ± 6.68	3.45 ± 0.49
Retinopathy	Yes (*n* = 16)	3.44 ± 0.73	2.81 ± 0.91	11.86 ± 2.00	13.00 ± 1.46	11.06 ± 5.41	14.86 ± 1.56	50.78 ± 7.44	3.44 ± 0.56
	No (*n* = 75)	3.51 ± 0.74	3.01 ± 0.86	11.98 ± 1.82	12.86 ± 2.03	12.82 ± 2.75	14.38 ± 1.82	52.07 ± 6.73	3.47 ± 0.47
Nephropathy	Yes (*n* = 34)	3.41 ± 0.70	2.82 ± 0.90	11.88 ± 2.02	12.86 ± 2.00	12.44 ± 3.60	14.54 ± 1.70	51.72 ± 7.10	3.52 ± 0.51
	No (*n* = 57)	3.54 ± 0.76	3.07 ± 0.84	12.00 ± 1.74	12.90 ± 1.92	12.55 ± 3.32	14.42 ± 1.83	51.90 ± 6.73	3.43 ± 0.47
CKD stages 3–5, eGFR <60	Yes (*n* = 11)	3.64 ± 0.67	2.55 ± 0.93	12.21 ± 2.17	12.30 ± 2.21	12.27 ± 3.52	14.83 ± 1.77	58.36 ± 4.77	3.61 ± 0.50
	No (*n* = 80)	3.48 ± 0.75	3.04 ± 0.85	11.92 ± 1.80	12.97 ± 1.90	12.54 ± 3.41	14.41 ± 1.78	57.23 ± 7.36	3.45 ± 0.48
Neuropathy	Yes (*n* = 10)	3.50 ± 0.53	3.30 ± 0.82	11.14 ± 1.69	12.27 ± 2.02	10.80 ± 3.33	14.13 ± 2.22	48.34 ± 6.62	3.40 ± 0.68
	No (*n* = 81)	3.49 ± 0.76	2.94 ± 0.87	12.06 ± 1.84	12.96 ± 1.92	12.72 ± 3.38	14.50 ± 1.73	52.28 ± 6.77	3.47 ± 0.46
HbA1c	≤ 7% (*n* = 38)	3.58 ± 0.68	3.26 ± 0.86	11.85 ± 2.40	13.05 ± 2.37	12.49 ± 2.81	14.27 ± 1.94	51.67 ± 7.48	*3.66 ± 0.47**
	> 8% (*n* = 32)	3.34 ± 0.75	3.00 ± 0.95	12.46 ± 2.08	13.10 ± 2.16	12.94 ± 3.80	14.83 ± 1.77	53.34 ± 7.77	*3.41 ± 0.53**
Cholesterol	≤ 200 mg/dl (*n* = 101)	3.55 ± 0.76	3.06 ± 0.91	12.55 ± 2.33	13.33 ± 2.19	12.86 ± 3.21	14.84 ± 1.77	53.62 ± 7.44	*3.58 ± 0.52*[#]
	>200 mg/dl (*n* = 13)	3.54 ± 0.88	3.15 ± 0.80	12.57 ± 1.19	12.97 ± 2.17	13.25 ± 3.70	13.91 ± 1.86	52.77 ± 8.14	*3.29 ± 0.47*[#]

*$p < 0.05$; [#]$p < 0.06$ *CCD* cerebral and cardiovascular diseases, *PVD* peripheral vascular diseases, *CKD* chronic kidney diseases; [a]From WHOQOL-BREF

Conclusion for DMQoL

- An efficient screening tool in routine practice for patients with diabetes
  - Stand alone: quickly screening diabetes progression in early phases (e.g., glycemic or lipid changes)
  - Combined with WHOQOL: assessing overall HRQL of patients
- A research instrument with relatively low administration burden and cost of production
  - Longitudinal pre-diabetes and diabetes cohorts in NCKUH
  - HRQL/utility parameters for cost-effectiveness studies
  - Adaption in other cultures (e.g., Iran)

Measure Health-related Quality of Life (HRQoL) in diabetes 台灣版糖尿病生活品質問卷

- 台灣糖尿病人的健康生活品質：生活品質測量工具與藥品對病患生活品質之影響(NCKUH-10408008) (NCKUH-10507015)
- 台灣糖尿病人併發症相關的花費與健康生活品質(NCKUH-10602008
- 代謝症候群高危險群世代追蹤調查之研究 (NCKUH)

1. 您滿意自己花在糖尿病照顧上的時間嗎？

□極不滿意 □不滿意 □中等程度滿意 □滿意 □極滿意

2. 您滿意自己花在糖尿病照顧上的金錢費用嗎？

□極不滿意 □不滿意 □中等程度滿意 □滿意 □極滿意

3. 您滿意自己血糖控制的結果嗎？

□極不滿意 □不滿意 □中等程度滿意 □滿意 □極滿意

4.您滿意自己糖尿病相關併發症(例如:腎病變、眼睛病變、神經病變、冠狀動脈疾病、中風等等)的控制結果嗎？

□極不滿意 □不滿意 □中等程度滿意 □滿意 □極滿意

5. 您滿意自己的飲食型態調整嗎？

□極不滿意 □不滿意 □中等程度滿意 □滿意 □極滿意

6. 您滿意自己的運動習慣嗎？

□極不滿意 □不滿意 □中等程度滿意 □滿意 □極滿意

7. 您滿意自己的體重控制嗎？

□極不滿意 □不滿意 □中等程度滿意 □滿意 □極滿意

8. 您滿意自己的糖尿病藥物治療嗎？

□極不滿意 □不滿意 □中等程度滿意 □滿意 □極滿意

9. 您能適應自己有糖尿病(的生活)嗎？

□完全不能夠 □少許能夠 □中等程度能夠 □很能夠 □完全能夠

10. 您自從有糖尿病以後，您滿意您與家人的關係嗎？

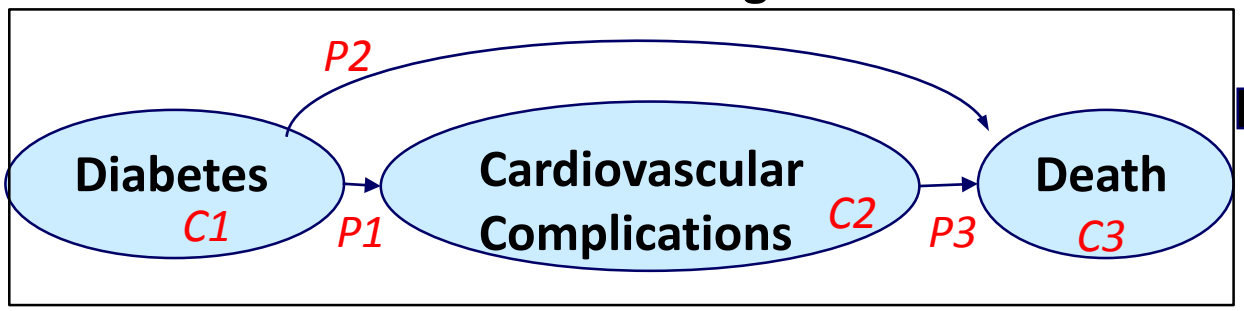
□極不滿意 □不滿意 □中等程度滿意 □滿意 □極滿意

Conduct PE in Patients with Type 2 Diabetes in Taiwan

Model parameters:

- ✓ **Effectiveness** *(i.e., P1: cardiovascular complications, P2: all-cause mortality, P3: the risk from cardiovascular complications to death)*
- ✓ **Safety** *(i.e., S: hypoglycemia risk)*
- ✓ **Costs** *(i.e., C1: event costs for diabetes (lifetime), C2: complication, C3: death)*
- ✓ **HRQL/utility** *(i.e., U1: diabetes (lifetime), U2: complication, U3: death)*

Markov model to estimate long-term outcomes



DrugA Cost

DrugA CVD averted

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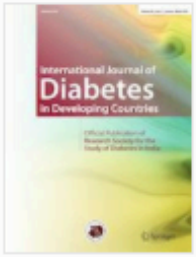
International Diabetes Federation

Comparative cost-effectiveness of metformin-based dual therapies associated with risk of cardiovascular diseases among Chinese patients with type 2 diabetes: Evidence from a population-based national cohort in Taiwan

CrossMark
http://crossmark.cross
doi=10.1016/j.diabres.
2016.03.013&domain=

Huang-Tz Ou [a,*], Yen-Ting Chen [a], Ya-Ming Liu [b], Jin-Shang Wu [c,d]

Development of PRO tools: HRQR for diabetes in Taiwan (Application 3)



International Journal of Diabetes in Developing Countries
January 2019, Volume 39, Issue 1, pp 218–227 | Cite as

Psychometric properties of Persian Diabetes-Mellitus Specific Quality of Life (DMQoL) questionnaire in a population-based sample of Iranians

Authors Authors and affiliations

Mohsen Saffari, Chung-Ying Lin, Keisha O'Garo, Harold G. Koenig, Hormoz Sanaeinasab, Amir H. Pakpour

Outline

- Importance and definition
- Tools: development and guidelines
- Applications from our previous studies
  - Development of your own PRO tools
    - Diabetes
  - Cultural adaptions of existing tools
    - Chinese version of the Polycystic Ovary Syndrome Health-related Quality of Life Questionnaire (Chi-PCOSQ)
  - Utilization of existing local tools
    - Breast cancer
- Recap and Q&A

Cultural adaption of PCOS in Taiwan

PCOS

- 6-10% of reproductive-age women

Polycystic Ovary Syndrome Health-related Quality of Life Questionnaire (PCOSQ)

- Well-established QoL instrument in the West

PLOS ONE

RESEARCH ARTICLE

Development of Chinese Version of Polycystic Ovary Syndrome Health-Related Quality of Life Questionnaire (Chi-PCOSQ)

Huang-tz Ou[1¤]*, Meng-Hsing Wu[2☯], Chung-Ying Lin[3☯], Pei-Chi Chen[1]

1 Institute of Clinical Pharmacy and Pharmaceutical Sciences, National Cheng Kung University College of Medicine, Tainan, Taiwan, **2** Department of Obstetrics and Gynecology, National Cheng Kung University College of Medicine and Hospital, Tainan, Taiwan, **3** Department of Public Health, National Cheng Kung University College of Medicine, Tainan, Taiwan

☯ These authors contributed equally to this work.
¤ Current address: Institute of Clinical Pharmacy and Pharmaceutical Sciences, National Cheng Kung University College of Medicine, 1 University Road, Tainan, 7010, Taiwan
* huangtz@mail.ncku.edu.tw

Cultural adaption of PCOS in Taiwan: cultural adaption

Step 1: Language translation

- ✓ **Forward** (i.e., English (1st) → translation in Chinese)
  - ✓ 2 independent translators and check consistency/discussion in expert panel (i.e., 1 pharmacist, 1 medical doctor, 1 psychometrician)
  - ✓ Both translators were English-professional fluency but from different backgrounds (i.e., medical and non-medical).
- ✓ **Backward** (i.e., translation in Chinese→ English (2nd)
  - ✓ Another 2 independent translators and check consistency /discussion in expert panel
- ✓ **Final translated version in Chinese (i.e., 26 items)**

Step 2: Pilot test and identification of culturally specific issues in PCOS patients

- ✓ 22 PCOS patients varying in educational levels (i.e., 1 high school, 18 college, 3 graduate)
- ✓ **Semi**-structured questionnaire for interview which was focused on:
  - ✓ Difficulty, confusing, and offensive on the questionnaire items
  - ✓ Other concerns that may be under-represented in the original PCOSQ
- ✓ Results:
  - ✓ All 26 original items were rated as important.
  - ✓ Additional concerns on diabetes, acne and hair loss was raised from 1/3 of patients.
- ✓ Totally **31 items (i.e., 1 diabetes, 2 acne, 2 hair loss)** as finalized by expert panel
  - ✓ i.e., growth of visible acne (or excess hair loss) is a problem

Step 3: Field testing, psychometric validation, and statistical analysis of Chi-PCOSQ

- ✓ 80 PCOS patients recruited from National Cheng Kung University Hospital

	Property	Measure
Reliability	**Factor structure**	Exploratory factor analysis (EFA) principle component analysis with varimax rotation ✓ 5 original domains and 1 additional domain on acne/hair loss ✓ Appropriate min. sample size: (1) n>= 100 or (2) a > **(2 subjects: 1 item)** ratio: 31 items-> at least **62 subjects required for EFA**
	Internal consistency	✓ Cronbach's α for individual domains (> 0.70 as acceptable) ✓ item-total correlations for all items (> 0.40 as adequate)
	Test-retest reliability	**Pearson correlation** for analysis of association between two scores collected separately from an interval of two weeks to one month (> 0.70 as adequate)
Validity	**Construct validity**	Test the correlation of the score of Chi-PCOSQ with: ✓ Two generic HRQL scores: WHOQOL-Bref, EQ-5D ✓ Four physiological indicators: BMI, waist-hip ratio (WHR), systolic blood pressure, diastolic blood pressure
	Known-group validity	✓ Subgroups by sexual experience, acne problem, hair loss, family history of diabetes statuses ✓ Hypothesis: e.g., the scores of Chi-PCOS is different between the PCOS patients with sexual experiences and those without sexual experiences.

Internal consistency, item-total correlation, and test-retest reliability

	Eigenvalue, explained %	Factor loading	Cronbach's α	Item-total correlation	Test- retest
Construct: Emotion	**11.238, 36.251%**		**0.897**		**0.861**
Q11 Low self-esteem as a result of PCOS		0.793		0.744	0.701
Q18 Self-conscious as a result of having PCOS		0.785		0.756	0.794
Q6 Moody as a result of having PCOS		0.750		0.748	0.747
Q2 Depressed as a result of having PCOS		0.748		0.722	0.713
Q17 Worried about having PCOS		0.653		0.756	0.799
Q14_1 Afraid of getting cancer		0.576		0.528	0.788
Q23 Lack of control over the situation with PCOS		0.528		0.680	0.765
Construct: Weight	**3.452, 11.136%**		**0.914**		**0.860**
Q24 Difficulties staying at your ideal weight		0.874		0.851	0.763
Q3 Concerned about being over weight		0.873		0.817	0.757
Q12 Frustration in trying to lose weight		0.866		0.849	0.794
Q10 Trouble dealing with weight		0.860		0.850	0.816
Q22 Feel unsexy because overweight		0.713		0.710	0.752
Q14_2 Afraid of getting diabetes		0.469		0.504	0.698
Construct: Body hair	**2.507, 8.086%**		**0.910**		**0.779**
Q16 Embarrassment about excessive body hair		0.822		0.818	0.719
Q26 Growth of visible body hair		0.811		0.765	0.768
Q15 Growth of visible hair on your face		0.810		0.810	0.765
Q9 Growth of visible hair on upper lip		0.788		0.774	0.671
Q1 Growth of visible hair on chin		0.768		0.733	0.644
Construct: Infertility	**2.230, 7.193%**		**0.960**		**0.825**
Q5 Concerned about infertility problems		0.863		0.920	0.812
Q25 Sad because of infertility problems		0.852		0.920	0.689
Q13 Afraid of not being able to have children		0.846		0.908	0.830
Construct: Acne & hair loss	**1.677, 5.410%**		**0.853**		**0.834**
Q29 Growth of visible acne		0.788		0.691	0.855
Q30 Feel acne is a problem		0.765		0.753	0.777
Q27 Excess hair loss		0.721		0.673	0.734
Q28 Feel excess hair loss is a problem		0.714		0.726	0.678
Q4 Tired easily		0.503		0.491	0.525
Construct: Menstrual	**1.179, 3.802%**		**0.782**		**0.726**
Q19 Abdominal bloating		0.860		0.550	0.606
Q21 Menstrual cramps		0.744		0.484	0.711
Q20 Last menstruation period		0.651		0.678	0.445
Q8 Irregular menstrual periods		0.488		0.600	0.568
Q7 Headaches		0.486		0.494	0.627

Note: Cronbach's α for total score of PCOSQ = 0.939; values for constructs are in bold.

Construct validity for Chi-PCOSQ

	r (*p*)					
	Emotion	Weight	Body hair	Infertility	Acne and hair loss	Menstrual
EQ-5D (n = 80)	0.408 (< 0.001)*	0.301 (0.007)*	0.297 (0.008)*	0.294 (0.008)*	0.349 (0.002)*	0.470 (<0.001)*
WHOQOL (n = 80)						
Physical	0.218 (0.052)	0.205 (0.07)	0.335 (0.002)*	−0.003 (0.98)	0.532 (<0.001)*	0.405 (<0.001)*
Psychological	0.293 (0.008)*	0.396 (<0.001)*	0.217 (0.053)	0.081 (0.47)	0.493 (<0.001)*	0.295 (0.008)*
Social	0.386 (<0.001)*	0.250 (0.025)*	0.331 (0.003)*	0.108 (0.34)	0.519 (<0.001)*	0.247 (0.03)*
Environment	0.347 (0.002)*	0.187 (0.10)	0.232 (0.04)*	0.231 (0.04)*	0.521 (<0.001)*	0.429 (<0.001)*
BMI (n = 80)	−0.176 (0.12)	−0.594 (<0.001)*	−0.069 (0.54)	−0.063 (0.58)	−0.044 (0.70)	−0.042 (0.71)
WHR (n = 77)	−0.093 (0.42)	−0.352 (0.002)*	0.039 (0.74)	0.099 (0.39)	−0.036 (0.76)	0.079 (0.50)
SBP (n = 79)	−0.254 (0.02)*	−0.494 (<0.001)*	−0.101 (0.38)	−0.036 (0.75)	−0.178 (0.12)	−0.066 (0.56)
DBP (n = 79)	−0.255 (0.02)*	−0.410 (<0.001)*	0.010 (0.93)	−0.112 (0.32)	−0.175 (0.12)	−0.032 (0.78)

Note: BMI = body mass index; WHR = waist-hip ratio; SBP = systolic blood pressure; DBP = diastolic blood pressure.

Known-group validity for Chi-PCOSQ

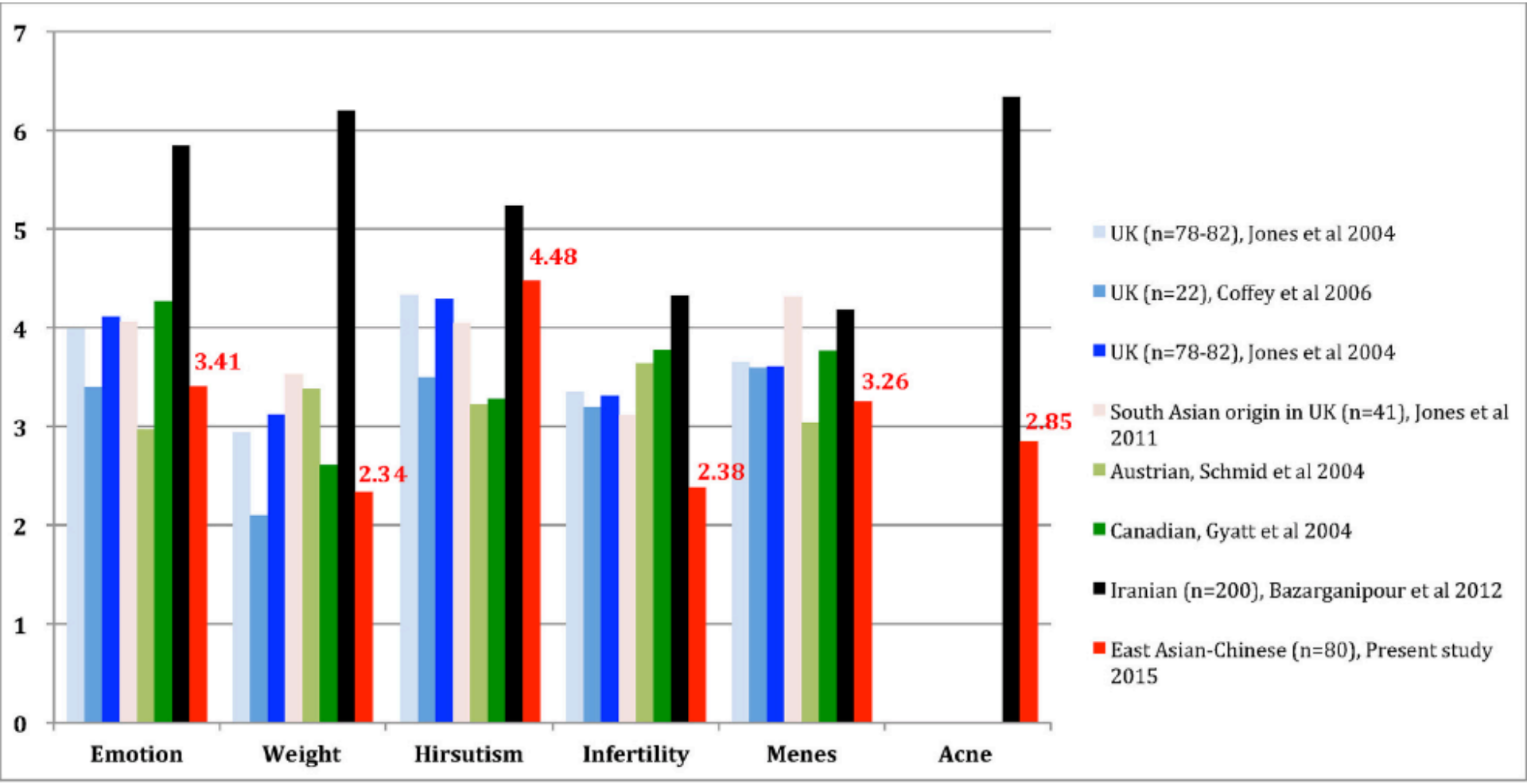
	Domain score: Mean (standard deviation)					
	Emotion	Weight	Body hair	Infertility	Acne and hair loss	Menstrual
Sexual experience						
No (n = 24)	3.64 (1.48)	2.39 (1.64)	4.27 (1.40)	3.61 (1.77)	3.50 (1.55)	3.59 (1.45)
Yes (n = 56)	3.32 (1.57)	2.32 (1.73)	4.57 (1.66)	1.86 (1.82)	3.15 (1.61)	2.53 (1.44)
t (p)	0.836 (0.41)	0.162 (0.87)	0.755 (0.45)	3.981 (<0.001)*	0.891 (0.38)	3.018 (0.003)*
Acne						
No (n = 31)	3.45 (1.64)	2.47 (1.38)	4.65 (1.55)	2.03 (1.89)	4.06 (1.21)	2.97 (1.40)
Yes (n = 44)	3.33 (1.50)	2.18 (1.81)	4.44 (1.59)	2.67 (2.02)	2.64 (1.51)	2.64 (1.46)
t (p)	0.329 (0.74)	0.755 (0.45)	0.565 (0.57)	1.391 (0.17)	4.355 (<0.001)*	0.990 (0.33)
Hair loss						
No (n = 32)	3.80 (1.35)	2.67 (1.51)	4.89 (1.10)	2.81 (1.88)	4.07 (1.33)	3.09 (1.57)
Yes (n = 42)	3.18 (1.66)	2.15 (1.77)	4.30 (1.84)	2.10 (2.01)	2.70 (1.51)	2.56 (1.35)
t (p)	1.741 (0.09)	1.348 (0.18)	1.708 (0.09)	1.564 (0.12)	4.074 (<0.001)*	1.545 (0.13)
Family history of diabetes						
No (n = 30)	3.45 (1.57)	2.78 (2.07)	4.37 (1.70)	2.09 (2.05)	3.42 (1.47)	3.31 (1.53)
Yes (n = 50)	3.39 (1.54)	2.08 (1.37)	4.54 (1.52)	2.56 (1.92)	3.16 (1.67)	2.57 (1.45)
t (p)	0.165 (0.87)	1.663 (0.10)	0.464 (0.64)	1.037 (0.30)	0.705 (0.48)	2.145 (0.04)*

Conclusion for Chi-PCOS

- Language and cultural adaptions
  - Internally consistent and culturally acceptable
- Preliminary psychometric assessment
  - Reliable and valid
- Application and further psychometric refines
  - Cross-culture comparison on HRQL of patients with PCOS
  - Further validation in a large sample population of PCOS
  - In routine services for caring PCOS patients in NCKUH

Cultural adaption of PCOS in Taiwan: Application on cross-cultural comparison

Comparisons across ethnicities in HRQoL of PCOS women measured using PCOSQ



Cultural adaption of PCOS in Taiwan: Further psychometric refine/assessment

- Assess the responsiveness, longitudinal validity, and measurement invariance of Chi-PCOSQ

Participants characteristics at baseline (n=102 from NCKUH)

	For responsiveness and longitudinal validity (n = 50)	For confirmatory factor analysis (n = 102)
Age (year) (mean ± SD)	30.40 ± 5.57	29.57 ± 5.50
Educational level (≥ college)	38 (76.0%)	85 (83.3%)
Currently smoker (yes)	3 (6.0%)	4 (4.0%)
Currently drinker (yes)	8 (16.0%)	24 (23.5%)
Sexual experience (yes)	37 (74.0%)	69 (67.6%)

PLOS ONE

RESEARCH ARTICLE

Validation of Chinese Version of Polycystic Ovary Syndrome Health-Related Quality of Life Questionnaire (Chi-PCOSQ)

Chung-Ying Lin[1], Huang-tz Ou[2¤]*, Meng-Hsing Wu[3], Pei-Chi Chen[2]

1 Department of Rehabilitation Sciences, Faculty of Health and Social Sciences, The Hong Kong Polytechnic University, Hung Hom, Hong Kong, **2** Institute of Clinical Pharmacy and Pharmaceutical Sciences, National Cheng Kung University College of Medicine, Tainan, Taiwan, **3** Department of Obstetrics and Gynecology, National Cheng Kung University College of Medicine and Hospital, Tainan, Taiwan

¤ Current address: Institute of Clinical Pharmacy and Pharmaceutical Sciences, National Cheng Kung University College of Medicine, 1 University Road, Tainan 7010, Taiwan
* huangtz@mail.ncku.edu.tw

Responsiveness

- Interchangeable with *Sensitivity to Change*
- Ability to detect a **minimally clinically important difference over time**
  - The smallest change in HRQL score that is considered meaningful or important by patients, their caregivers or providers
- Minimally important difference (MID)
  - Related to applications within specific populations; not an inherent or fixed property of an instrument
  - i.e., asthma HRQL (7-point response points)*: MID:0.5, moderate change: 1.0, a large change: 1.5

*J Clin Epidemiol. 1994;47(1), 81-87.

Two Aspects of Responsiveness

- **Internal** responsiveness
  - The ability of a measure to change **over a particular pre-specified time frame**
  - i.e., to detect a clinical change **before and after** a known efficacious treatment
- **External** responsiveness
  - The extent to which changes in a measure over a specified time frame relate to corresponding **changes in a reference measure** of health status
    - The relationship between change in the measure and the change in the standard
    - The measure is shown to adequately capture the change in the standard (is a replacement for a standard measure?)

Responsiveness of Chi-PCOSQ and WHOQOL-BREF (n=50)

Instrument (Domain)	Pretest score mean (SD)	Posttest score mean (SD)	*t* (*p*); *df* = 49	SRM
Chi-PCOSQ	**24.66 (5.94)**	**27.36 (6.36)**	**5.20 (< 0.001)**	**0.74**
(Menstruation)	3.67 (1.51)	4.41 (1.41)	3.63 (0.001)	0.51
(Infertility)	3.59 (1.99)	4.22 (2.00)	3.56 (0.001)	0.50
(Emotions)	4.15 (1.52)	4.60 (1.56)	3.78 (< 0.001)	0.53
(Body weight)	3.41 (1.57)	3.81 (1.48)	2.72 (0.009)	0.39
(Hair growth)	5.28 (1.66)	5.40 (1.70)	0.88 (0.39)	0.12
(Acne & hair loss)	4.54 (1.57)	4.94 (1.26)	3.41 (0.001)	0.48
WHOQOL-BREF	**55.29 (6.72)**	**56.15 (8.11)**	**1.81 (0.08)**	**0.26**
(Physical)	14.53 (1.88)	14.99 (2.09)	2.63 (0.011)	0.27
(Psychological)	12.67 (2.25)	12.88 (2.51)	1.28 (0.21)	0.18
(Social)	14.12 (1.90)	14.12 (2.07)	0.00 (1.00)	0.00
(Environment)	13.97 (1.83)	14.15 (2.23)	1.04 (0.30)	0.15

Abbreviations: SD: standard deviation, Chi-PCOSQ: Chinese version of Polycystic Ovary Syndrome Health-related Quality of Life Questionnaire, *df*: degree of freedom, SRM: standardized response mean, which was computed as the mean change scores divided by the standard deviation of the change.

Interval between pre-and post-treatment: 3.60 +/- 1.96 months

SRM values calculated as the mean change scores divided by the standard deviation (SD) of the change

SRM < 0.2 is trivial, 0.2 to 0.5 is small, **0.5 to 0.8 is medium, and > 0.8 is large**.

Longitudinal validity of Chi-PCOSQ (n=50)

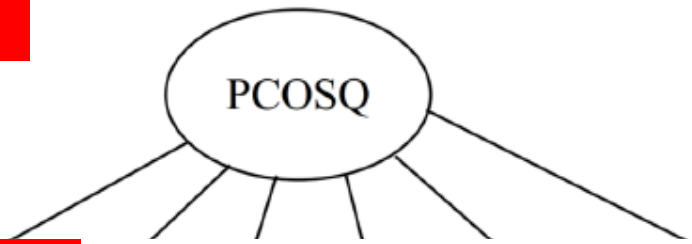
Change of Chi-PCOSQ score	Change of 2-hour glucose *r* (*p*)	Change of 2-hour insulin *r* (*p*)
Chi-PCOSQ total score	–0.57 (< 0.001)*	–0.29 (0.045)*
Menstruation	–0.45 (0.001)*	–0.12 (0.40)
Infertility	–0.07 (0.64)	–0.05 (0.75)
Emotions	–0.26 (0.07)	–0.07 (0.65)
Body weight	–0.33 (0.02)*	–0.23 (0.10)
Hair growth	–0.40 (0.004)*	–0.23 (0.10)
Acne & hair loss	–0.54 (< 0.001)*	–0.36 (0.009)*

*$p < 0.05$

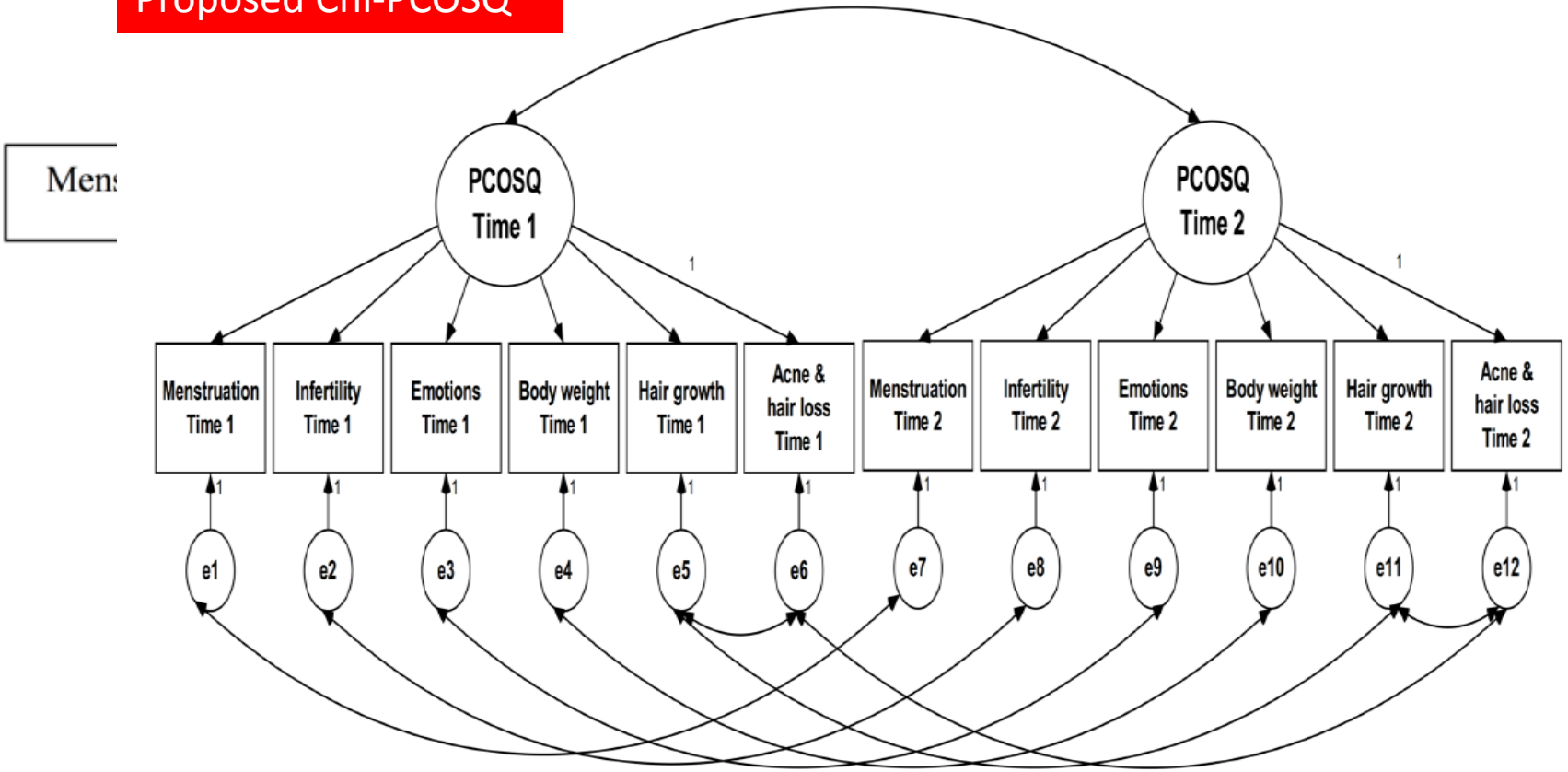
Except for two domains (Infertility and Emotions), all the changes of domain scores and the total scores were negatively and significantly correlated with the change of 2-hour glucose.

CFA Models for Chi-PCOSQ

Prior structure of PCOSQ



Proposed Chi-PCOSQ



Measurement invariance of Chi-PCOSQ across time

Model	χ^2 (*df*)	*p*	CFI	RMSEA	SRMR
Model at pre-test	17.17 (8)	0.03	0.930	0.107	0.064
Model at post-test	16.22 (8)	0.04	0.951	0.101	0.052
Model 1 (Configural)	77.62 (45)	0.002	0.970	0.085	0.088
Model 2 (Metric invariance)	81.20 (50)	0.003	0.971	0.079	0.088
Model 3 (Scalar invariance)	92.52 (56)	0.002	0.966	0.080	0.087
Model comparisons	$\Delta\chi^2$ (Δdf)	*p*	ΔCFI	ΔRMSEA	ΔSRMR
Models 2 and 1	3.58 (5)	0.61	−0.001	0.006	−0.0002
Models 3 and 2	11.31 (6)	0.08	0.005	−0.001	0.0004

Notes: The uniqueness of the Hair growth domain was correlated to that of the Acne & hair loss domain in all models.

Model 2 constrained all domain loadings to be invariant across pre- and post-test.

Model 3 constrained all domain intercepts to be invariant across pre- and post-test.

Abbreviations: CFI: comparative fit index, RMSEA: root-mean-square error of approximation, SRMR: standardized root mean square residual.

- ✓ All fit indices of the models examining measurement invariance were satisfactory, except for the slightly high SRMR values (0.087 to 0.088).
- ✓ The model comparisons (nonsignificant Δχ2 tests, ΔCFI > −0.01, ΔRMSEA and ΔSRMR < 0.02) indicate that the measurement invariance of Chi-PCOSQ is supported across time.

Conclusion for Validation for Chi-PCOSQ

- Chi-PCOSQ is sufficiently sensitive in detecting clinical changes and its measurement structure is suitable for Chinese women with PCOS.
- It is thus a promising tool for assessing the HRQoL of ethnic Chinese women with PCOS.

Cultural adaption of PCOS in Taiwan: In routine services for caring PCOS patients

Main finding:

Metformin might improve QoL of PCOS women by ameliorating psychological disturbances due to acne, hair loss and infertility problems, especially for overweight and hyperandrogenic patients.

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Health and Quality of Life Outcomes

RESEARCH Open Access

Metformin improved health-related quality of life in ethnic Chinese women with polycystic ovary syndrome

Huang-Tz Ou[1*], Pei-Chi Chen[1], Meng-Hsing Wu[2] and Chung-Ying Lin[3]

Mixed effect model analysis of metformin effect on specific PCOS QoL outcome measured via Chi-PCOSQ

Chi-PCOSQ		Subgroups			
	Total Coefficient (SE)	Normal weight Coefficient (SE)	Overweight Coefficient (SE)	Non- hyperandrogenism Coefficient (SE)	Hyperandrogenism Coefficient (SE)
Total scores					
Treatment time					
Visit 2 (reference = visit 1)	0.44 (0.56)	0.75 (0.86)	0.20 (0.75)	−0.58 (0.89)	0.61 (0.66)
Visit 3 (reference = visit 1)	1.25 (0.56)	1.77 (0.84)	0.80 (0.78)	0.11 (0.92)	1.45 (0.66)*
Weight domain					
Treatment time					
Visit 2 (reference = visit 1)	−0.06 (0.14)	0.11 (0.22)	−0.18 (0.19)	−0.04 (0.28)	−0.07 (0.17)
Visit 3 (reference = visit 1)	0.12 (0.15)	0.15 (0.21)	0.10 (0.20)	−0.01 (0.29)	0.15 (0.17)
Infertility domain					
Treatment time	*p = 0.043*				*p = 0.048*
Visit 2 (reference = visit 1)	0.25 (0.18)	0.34 (0.23)	0.15 (0.29)	−0.06 (0.33)	0.32 (0.21)
Visit 3 (reference = visit 1)	0.46 (0.18)*	0.34 (0.24)	0.59 (0.28)*	0.12 (0.34)	0.52 (0.21)*
Menstrual domain					
Treatment time					
Visit 2 (reference = visit 1)	0.10 (0.18)	0.21 (0.29)	0.02 (0.24)	0.26 (0.39)	0.08 (0.20)
Visit 3 (reference = visit 1)	0.19 (0.18)	0.36 (0.27)	0.04 (0.25)	0.58 (0.41)	0.11 (0.20)
Emotions domain					
Treatment time					
Visit 2 (reference = visit 1)	0.07 (0.15)	0.15 (0.21)	0.01 (0.21)	0.82 (0.33)*	0.04 (0.18)
Visit 3 (reference = visit 1)	0.14 (0.15)	0.30 (0.21)	0.003 (0.21)	0.43 (0.29)	0.13 (0.18)
Body hair domain					
Treatment time					
Visit 2 (reference = visit 1)	0.03 (0.14)	0.18 (0.19)	−0.08 (0.20)	−0.34 (0.20)	0.10 (0.17)
Visit 3 (reference = visit 1)	0.02 (0.14)	0.24 (0.18)	−0.16 (0.21)	−0.37 (0.21)	0.10 (0.17)
Acne & Hair loss domain					
Treatment time	*p = 0.008*		*p = 0.043*		*p = 0.007*
Visit 2 (reference = visit 1)	−0.51 (0.28)	−0.10 (0.19)	0.01 (0.20)	−0.46 (0.18)*	−0.55 (0.35)
Visit 3 (reference = visit 1)	0.45 (0.26)	0.08 (0.19)	0.33 (0.21)	−0.28 (0.19)	0.71 (0.32)*

Outline

- Importance and definition
- Tools: development and guidelines
- Applications from our previous studies
  - Development of your own PRO tools
    - DMQoL (diabetes)
  - Cultural adaptions of existing tools
    - Chi-PCOS (PCOS)
  - Utilization of existing local tools
    - Breast cancer: Chinese version of EORTC QLQ-C30 and BBR-23

Recap and Q&A

Utilization of existing local tools: Breast cancer

Aim: Assess the QoL associated with patients' characteristics and different cancer treatments among women with breast cancer in Taiwan

- Demographics (e.g., age at diagnosis)
- Socioeconomics (e.g., education and income levels)
- Breast cancer related (e.g., cancer stage)
- Cancer treatments (e.g., chemotherapy, hormone therapy, radiotherapy, mastectomy)

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ORIGINAL ARTICLE

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Health-related quality of life associated with different cancer treatments in Chinese breast cancer survivors in Taiwan

Huang-Tz Ou[1,2,3] | Wei-Pang Chung[4] | Pei-Fang Su[5] | Tzu-Hsuan Lin[5] | Ji-Ying Lin[1] | Yao-Chun Wen[6] | Wei-Tse Fang[6]

Study design and measures

- Cross-sectional survey in 2017
- HR-positive/HER2-negative metastatic breast cancer

Aspect	Measure	Description
QoL	EORTC QLQ-C30	Generic **QoL for cancer**
	EORTC QLQ-BR23	**Breast cancer** specific QoL
	EQ-5D-5L	Generic QoL EQ-5D descriptive system EQ visual analogue scale (VAS)
Patient characteristics	Demographics and social economics	Age at QoL assessment, marital status, education, income
	Caner specific	Duration from cancer diagnosis, family history of breast cancer, menopausal status, cancer stage
	Treatment	Cancer treatment, chemotherapy, radiotherapy, mastectomy

Results of descriptive analyses

- 193 patients included
- Mean age of 55.52±9.00 years at QoL assessment
- Mean time since cancer diagnosis of 5.38±3.89 years
- 88.3% of patients at post-menopausal status
- Distributions of stage at breast cancer diagnosis

Overall (n=193)	Stage at diagnosis				
	0 (n=22, 11.40%)	I (n=51, 26.42%)	II (n=71, 36.79%)	III (n=38, 19.69%)	IV (n=4, 2.07%)

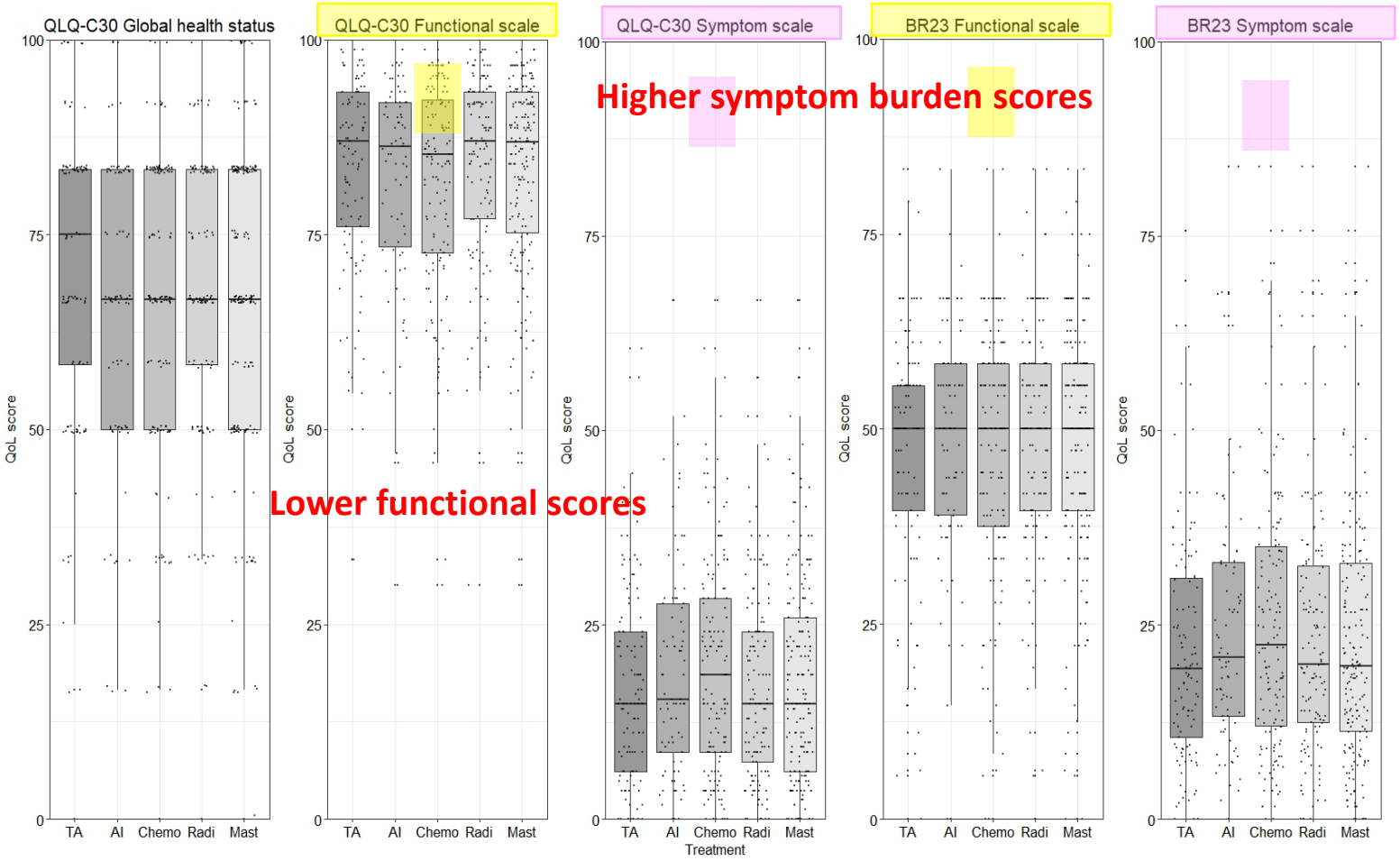
QoL for early- (i.e., I or II) vs. late-stages of breast cancer patients

Early stage women had better functional status, lower symptom burden on their QoL, and better overall well-being as measured by EQ-5D.

	(n=193)		0 (n=22)		I (n=51)		II (n=71)		III (n=38)		IV (n=4)	
QoL	n	Mean (SD) or %	n	Mean (SD) or %	n	Mean (SD) or %	n	Mean (SD) or %	n	Mean (SD) or %	n	Mean (SD) or %
QLQ-C30 global health	189	68.4 (21.1)	22	70.8 (20.2)	50	68.2 (23.1)	70	68.7 (18.6)	37	67.3 (24.5)	4	64.6 (21.9)
QLQ-C30 functional scale	193	83.1 (13.6)	22	86.7 (11.9)	51	86.5 (9.7)	71	80.6 (14.5)	38	82.2 (16.9)	4	75.1 (7.5)
QLQ-C30 symptom scale	193	18.0 (13.4)	22	14.4 (10.8)	51	16.3 (11.1)	71	19.1 (13.7)	38	20.3 (17.1)	4	21.0 (4.2)
QLQ-BR23 functional scale	192	48.5 (15.9)	22	51.5 (13.2)	51	50.7 (15.1)	70	47.7 (14.2)	38	43.6 (19.4)	4	44.3 (15.7)
QLQ-BR23 symptom scale	192	23.2 (16.5)	22	17.9 (12.9)	51	19.3 (13.3)	70	26.0 (18.4)	38	27.0 (18.2)	4	19.7 (11.7)
EQ-5D-5L utility score	182	0.92 (0.09)	22	0.93 (0.06)	48	0.94 (0.06)	65	0.91 (0.10)	37	0.91 (0.12)	3	0.91 (0.03)
VAS score	182	79.3 (15.0)	22	76.1 (18.1)	49	83.0 (9.4)	64	76.8 (16.8)	37	79.9 (16.1)	3	85.0 (13.2)

Utilization of existing local tools: Breast cancer

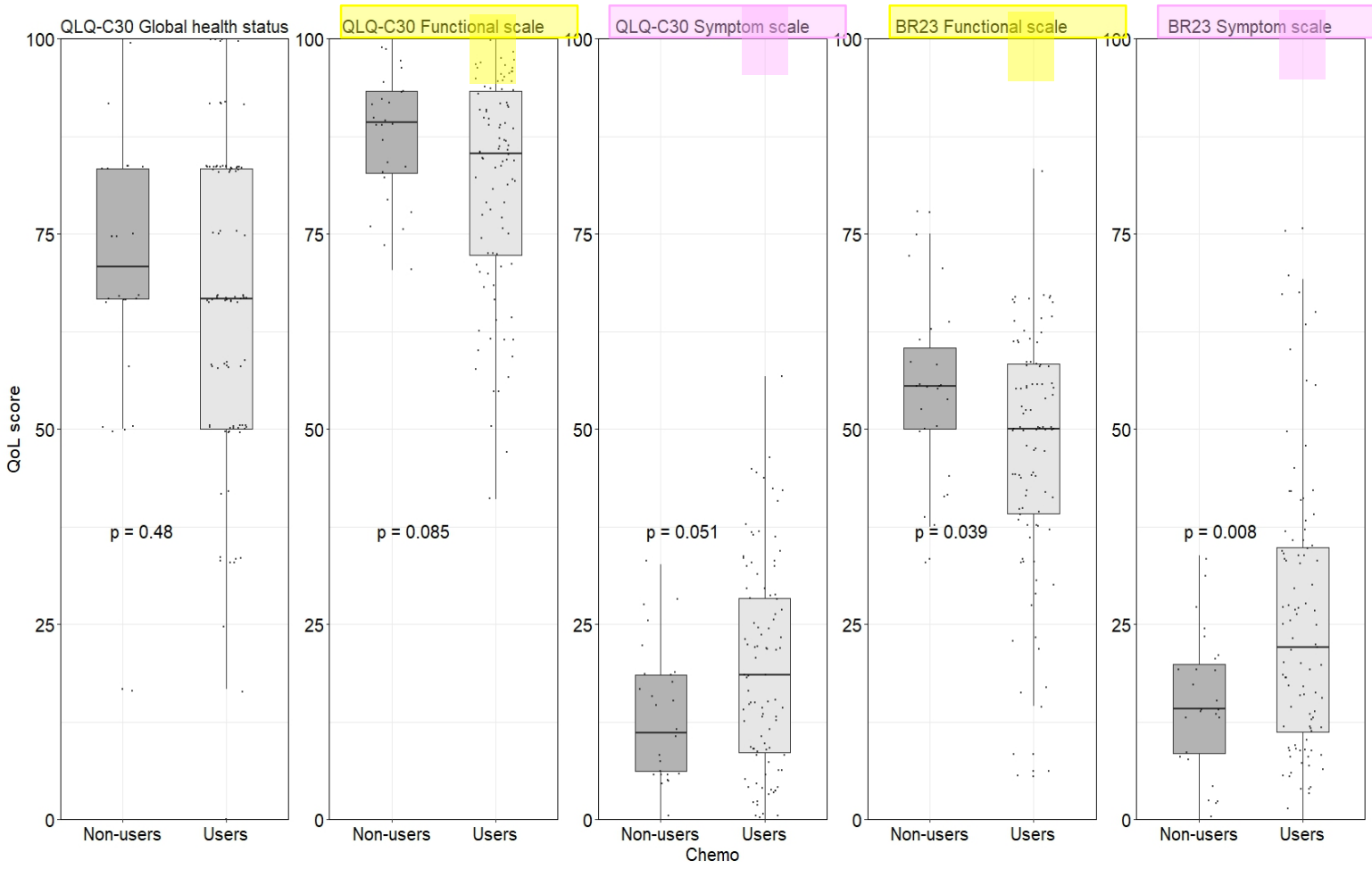
QoL for patients with breast cancer in Taiwan stratified by type of breast cancer treatment



- The chemotherapy users had poor QoL (with **a lower QLQ-C30 functional score** and **higher QLQ-C30 and QLQ-BR23 symptom scores**), compared to patients undergoing other types of breast cancer treatment

Utilization of existing local tools: Breast cancer

QoL for women with breast cancer stages I or II (n=122):
chemotherapy users ('users") vs. chemotherapy non-users ("non-users")



Chemotherapy users v.s. non-users:

- **Lower health utility (by EQ-5D-5L)**

Lower functional scores
(i.e., cognitive and sexual functioning**)**

Higher symptom burden scores
(i.e., dyspnea, constipation, systemic therapy side effects)

Results of univariate analyses

- Cancer stage and chemotherapy use were significantly associated with the QLQ-C30 functional score and the QLQ-BR23 functional and symptom scores.
- Chemotherapy use was significantly associated with the QLQ-C30 symptom score.
- Educational level was significantly associated with the VAS score.
- Radiotherapy and mastectomy were significantly associated with the utility score.

Results of multivariate analyses

	QLQ-C30		QLQ-BR23			EQ-5D utility	VAS score
	Global health	Functional scale	Symptom scale	Functional scale	Symptom scale		
	(n=176)	(n=188)	(n=188)	(n=178)	(n=178)	(n=179)	(n=178)
Variables	Estimate (SE)	Estimate (SE)	Estimate (SE)	Estimate (SE)	Estimate (SE)	Estimate (SE)	Estimate (SE)
Intercept	66.26***	86.64***	13.94***	57.34***	16.13***	0.939***	73.74***
	(5.64)	(3.68)	(3.52)	(4.20)	(4.47)	(0.024)	(4.56)
Tamoxifen (ref. non-users)	4.42	-0.66	-0.36	-2.98	-0.30	0.004	-1.93
	(3.61)	(2.40)	(2.27)	(2.73)	(2.91)	(0.016)	(2.69)
Aromatase inhibitors (ref. non-users)	-2.76	-1.44	1.15	0.69	1.06	-0.020	-3.35
	(3.61)	(2.41)	(2.28)	(2.74)	(2.92)	(0.016)	(2.70)
Chemotherapy (ref. non-users)	-0.79	-4.26	7.01**	-6.72*	8.11*	-0.027	2.26
	(3.81)	(2.75)	(2.40)	(3.17)	(3.38)	(0.016)	(2.79)
Radiotherapy (ref. non-users)	4.07	4.39	-2.49	0.28	-0.63	0.023	1.27
	(3.98)	(2.71)	(2.51)	(3.07)	(3.27)	(0.017)	(2.88)
Mastectomy# (ref. partial)	-1.86	0.64	0.09	-3.17	-1.50	-0.011	-1.68
	(3.67)	(2.57)	(2.30)	(2.92)	(3.11)	(0.016)	(2.64)

Conclusions for QoL of breast cancer patients in Taiwan

- Implications
  - Designing clinical strategies to alleviate the short- and long-term adverse effects of chemotherapy on the QoL of cancer patients
    - Women with early-stage of breast cancer should be carefully considered in clinical practice because chemotherapy is frequently used as an adjuvant treatment in these patients.
  - Developing new treatment strategies with less side effects

Recap

- Importance and definition
- Tools:
  - 4-steps for development of PRO measures
  - Practical guidelines
    - Scientific Advisory Committee of the Medical Outcomes Trust
    - US FDA guidelines for PRO measures and data
- Applications from our previous studies
  - Development of your own PRO tools: DMQoL
  - Cultural adaptions of existing tools: Chi-PCOSQ
  - Utilization of existing local tools: Chinese versions of EORTC QLQ-C30 and QLQ BBR-23
- Recap and Q&A

Many Thanks to Your Time and Attention

Comments and Questions