Using modern statistical methodology for validating and reporting Patient Reported Outcomes

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joint DSBS/FMS Meeting
October 2, 2014, Copenhagen

Agenda

1. Indirect measurement

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2. Ordinal regression models with random effects
   - Item Response Theory (IRT) models
   - Probit models

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3. Example data from RCT to determine if patients with acute leukemia can benefit by a structured and supervised counseling and exercise program:

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4. Summary

Indirect measurement

1. Binet-Simon scale, first intelligence test
   - Designed for children, measured a childs 'mental age' which compared the child with his or her age group (Binet, L'Année Psychologique, vol. 12, 191-244, 1905)

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    - latent variable, can be changed

Indirect measurement

1. Karnofsky performance status
   - 0 ('Dead'), 10 ('Moribund'), 20 ('Very sick'), ..., 90 ('Able to carry on normal activity; minor symptoms'), 100

     (Karnofsky, Burchenal JH, In: MacLeod CM (ed.): Evaluation of chemotherapeutic agents. New York: Columbia University Press, pp 191-205, 1949)

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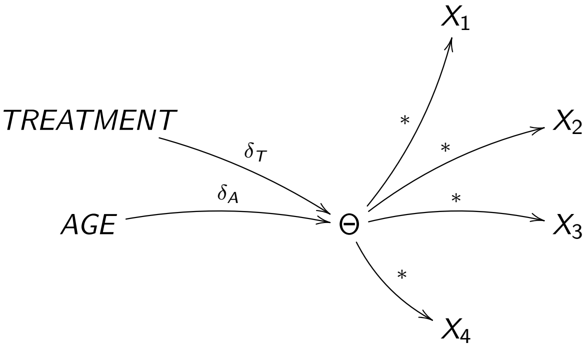
Indirect measurement

1. PRO's
   - Generic (e.g. SF36) or disease specific (e.g. FACT)
   - Sub scales consisting of ordinal items
   - Often reported as standardized (e.g. zero to 100) mean scores
   - Often analyzed using linear models or nonparametric statistics

Indirect measurement



Latent variable Θ, $X_1, \ldots, X_4$ items. [*: monotone association]

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IRT model for item response X_i

Item parameters $\bar{\beta}_i = (\beta_{i0}, \beta_{i1}, \beta_{i2}, \ldots)$

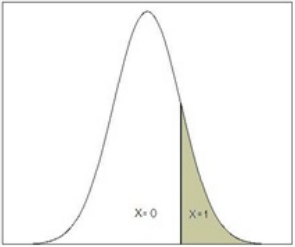
$$P(X_i = x | \Theta = \theta) = \frac{\exp(x\theta + \beta_{ix})}{K_i(\theta)} \qquad (x = 0, 1, \ldots, m_i), \quad (1)$$

where $\beta_{i0} = 0$ for convenience and

$$K_i(\theta) = \sum_{h=0}^{m_i} \exp(h\theta + \beta_{ih})$$

Alternative models for item response X_i

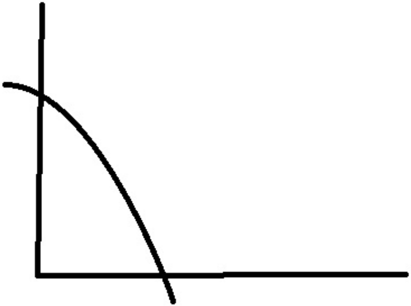
- Change linear predictor: replace $x\theta + \beta_{ix}$ with $\alpha_i(x\theta + \beta_{ix})$
- Probit model



- Regardless of these choices
  - Conditional probability of each response option given θ

Conditional probability of each response option given θ

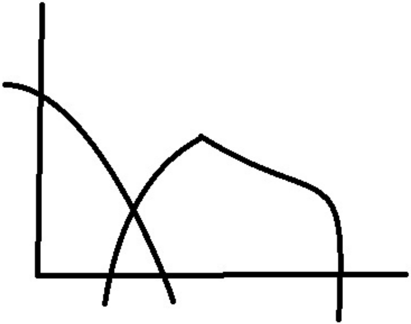
$$P(X = 0|\Theta = \theta)$$



θ

Conditional probability of each response option given θ

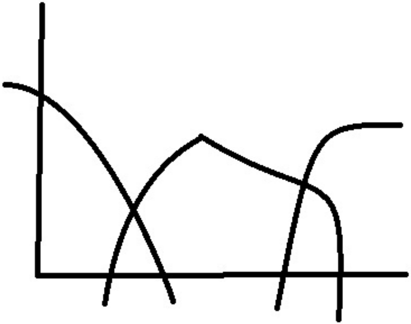
$$P(X = 1 | \Theta = \theta)$$



θ

Conditional probability of each response option given θ

$$P(X = 2|\Theta = \theta)$$



θ

Model for response vector $\bar{X} = (X_i)_{i \in I}$

Probability of observing $\bar{x} = (x_i)_{i \in I}$ is

$$P(\bar{X} = \bar{x} | \Theta = \theta) \overset{*}{=} \prod_{i \in I} P(X_i = x | \Theta = \theta) \quad (2)$$

$$= \frac{\exp(\theta \sum_{i \in I} X_i + \sum_{i \in I} \beta_{ix_i})}{\prod_{i \in I} K_i(\theta)} \quad (3)$$

Marginal probability

$$P(\bar{X} = \bar{x}) = \int P(\bar{X} = \bar{x} | \Theta = \theta) \phi(\theta) d\theta \quad (4)$$

$$= \int \frac{\exp(\theta \sum_{i \in I} X_i + \sum_{i \in I} \beta_{ix_i})}{\prod_{i \in I} K_i(\theta)} \varphi(\theta) d\theta \quad (5)$$

[*: assumption: 'local' independence]

Subjects $v = 1, \ldots, N$, T_v treatment indicator, A_v age

$$\theta_v = \delta_0 + \delta_T T_v [+\delta_A A_v] + \epsilon_v \quad (6)$$

$$L(\bar{\bar{\beta}}, \delta_0, \delta_T, \delta_A) = \prod_{v=1}^{N} \int P(\bar{X} = \bar{x} | \Theta = \delta_0 + \delta_T T_v + \epsilon_v) \varphi(\epsilon) d\theta \quad (7)$$

Implementation: PROC NLMIXED

Set of items split into two disjoint sets

$$I = I_1 \cup I_2, \tag{8}$$

with items in I_1 and I_2 measuring latent variables θ_1 and θ_2 respectively.

$$P(\overline{X} = \overline{x} | \bar{\Theta} = \bar{\theta}) \quad = \quad \frac{\exp\left(r_1\theta_1 + r_2\theta_2 + \sum_{i \in I} \eta_{ix_i}\right)}{K(\bar{\theta})} \tag{9}$$

where $r_d = \sum_{i \in I_d} x_i$, $d = 1, 2$ and

$$K(\bar{\theta}) = \left(\prod_{i \in I_1} K_i(\theta_1)\right)\left(\prod_{i \in I_2} K_i(\theta_2)\right), \quad \bar{\theta} = \begin{bmatrix} \theta_1 \\ \theta_2 \end{bmatrix}$$

Two-dimensional model, cont.

(i) θ_1 and θ_2 are distinct, but correlated latent variables,

(ii) θ_1 and θ_2 represent repeated measurements of the same latent variable

Test invariance: $(\bar{\beta}_i)_{i \in I_1}$ and $(\bar{\beta}_i)_{i \in I_2}$ identical.

Example of population models

- μ average shift in latent variable, latent correlation:

$$\bar{\theta} \sim N\left(\begin{bmatrix} 0 \\ \mu \end{bmatrix}, \Sigma\right) \quad (10)$$

- baseline means constrained to be equal across randomization groups (Liu et al, Statist. Med. vol. 28, 2509-2530, 2009):

$$\bar{\theta}_v = \begin{bmatrix} \delta_0 \\ \delta_0 \end{bmatrix} + \begin{bmatrix} 0 \\ \delta_T T_v \end{bmatrix} + \begin{bmatrix} \epsilon_{v1} \\ \epsilon_{v2} \end{bmatrix}, \quad \begin{bmatrix} \epsilon_{v1} \\ \epsilon_{v2} \end{bmatrix} \sim N\left(\begin{bmatrix} 0 \\ 0 \end{bmatrix}, \Sigma\right) \quad (11)$$

- Implementation: PROC NLMIXED

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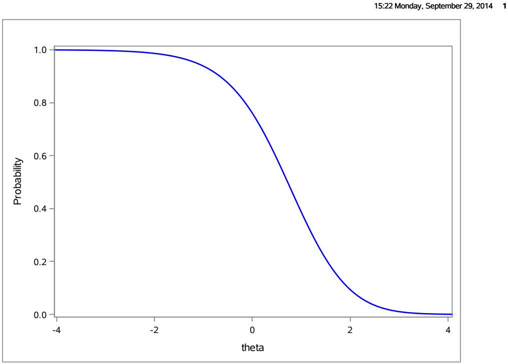
PF sub scale from SF36

- 10-item scale, measures limitations
- Items endorsed on 3-point scale ('Yes, Limited A Lot', 'Yes, Limited A Little', 'No, Not Limited At All')
  - Vigorous Activities

    ⋮
  - Walking one block
  - Bathing or dressing yourself

PF: Conditional probability given θ



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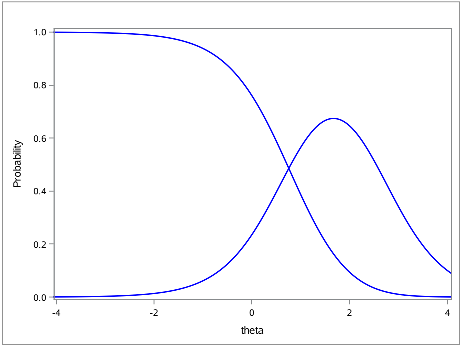

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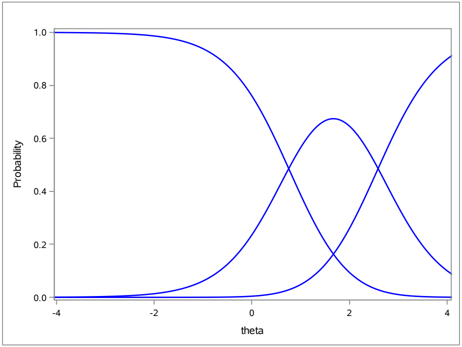
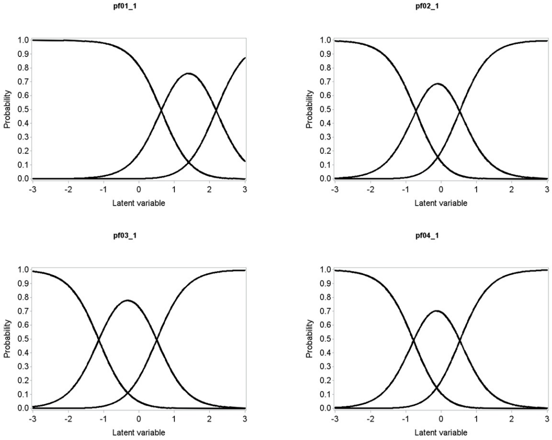


Conditional probability given θ



VT sub scale from SF36

- Widely used measure of vitality
- 4-item scale, (two positively, two negatively-worded items)
  - Did you feel full of pep?
  - Did you have a lot of energy?
  - Did you feel worn out?
  - Did you feel tired?
- Items endorsed on 6-point scale ranging from 'None of the time' to 'All of the time'

PF and VT sub scales from SF36 - linear models

Data from RCT to determine if patients with acute leukemia can benefit by a structured and supervised counseling and exercise program.

		Baseline			Twelve weeks			Change baseline to twelve weeks				Group comparison			
		N	Mean	SD	N	Mean	SD	N	D	95%	CI	D	95%	CI	p
SF36 Physical Functioning (PF)	A	34	61.9	27.5	32	82.0	21.8	32	19.1	10.0	28.1	10.4	-3.8	24.6	0.15
	B	36	66.7	24.2	30	72.7	26.3	30	8.6	-2.8	20.1				
SF36 Vitality (VT)	A	34	45.4	21.4	32	63.4	19.4	32	17.7	9.8	25.5	11.6	-0.6	23.8	0.06
	B	36	54.6	21.9	30	58.1	25.1	30	6.1	-3.7	15.9				

PF sub scale from SF36

	T-test			IRT		
	D	(95% CI)	p	$\hat{\delta}_T$	(95% CI)	p
PF	10.4	(-3.8 to 24.6)	0.15	0.56	(-0.11 to 1.22)	0.10

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Power
N=70
N=100
N=100

PF sub scales from SF36 - linear models

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	D	(95% CI)	p	$\hat{\delta}_T$	(95% CI)	p
PF	10.4	(-3.8 to 24.6)	0.15	0.56	(-0.11 to 1.22)	0.10

Power		
N=70	$\sim$ 35%	$\sim$ 42%
N=100		
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PF sub scales from SF36 - linear models

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PF	10.4	(-3.8 to 24.6)	0.15	0.56	(-0.11 to 1.22)	0.10

Power	T-test	IRT
N=70	$\sim$ 35%	$\sim$ 42%
N=100	$\sim$ 42%	$\sim$ 49%
N=130		

PF sub scales from SF36 - linear models

	T-test			IRT		
	D	(95% CI)	p	$\hat{\delta}_T$	(95% CI)	p
PF	10.4	(-3.8 to 24.6)	0.15	0.56	(-0.11 to 1.22)	0.10

Power		
N=70	$\sim$ 35%	$\sim$ 42%
N=100	$\sim$ 42%	$\sim$ 49%
N=130	$\sim$ 53%	$\sim$ 64%

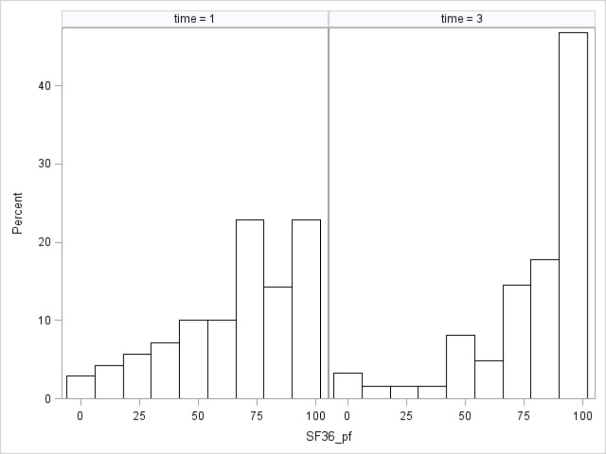
What about the VT sub scale?

	T-test			IRT		
	D	(95% CI)	p	$\hat{\delta}_T$	(95% CI)	p
PF	10.4	(-3.8 to 24.6)	0.15	0.56	(-0.11 to 1.22)	0.10
VT	11.6	(-0.6 to 23.8)	0.06			

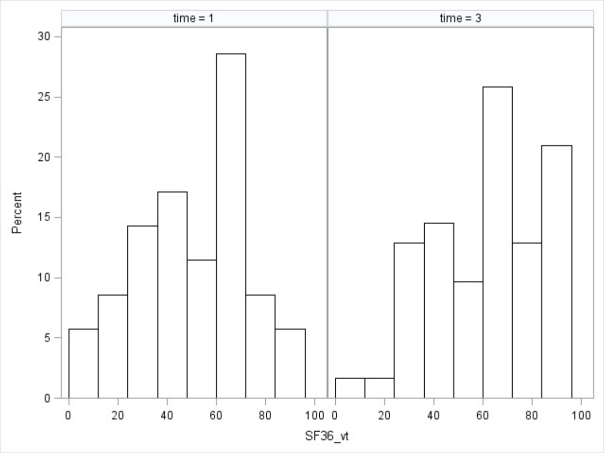
What about the VT sub scale?

	T-test			IRT		
	D	(95% CI)	p	$\hat{\delta}_T$	(95% CI)	p
PF	10.4	(-3.8 to 24.6)	0.15	0.56	(-0.11 to 1.22)	0.10
VT	11.6	(-0.6 to 23.8)	0.06	0.37	(-0.12 to 0.86)	0.14

PF sub scale from SF36



VT sub scale from SF36



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Summary

- Nonlinear random effects models yield increased power for skewed data
- Can specify model for the (unobserved) variable of interest
- Can quantify the uncertainty on change scores estimated for individual patients
- Implementation: PROC NLMIXED