

Neurocognitive Assessment in Patients with Brain Metastases



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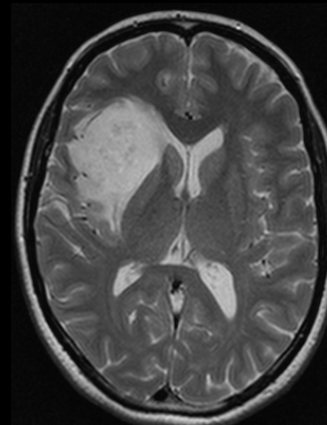


Treatment Outcomes I

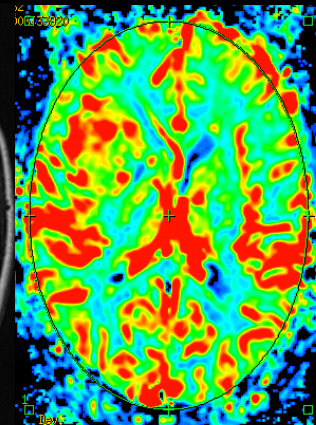
Traditional/primary endpoints of efficacy:

► Physician's point of view:

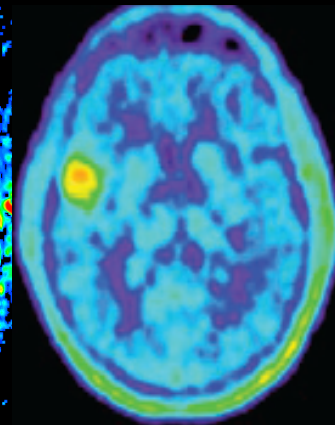
- ❑ Primary: OS
- ❑ Secondary: PFS
- ❑ Parameters of disease like MRI, rCBV, PET
- ❑ Karnofsky, Barthel



MRI T2



rCBV



FET PET



Treatment Outcomes II

Secondary/tertiary endpoints of efficacy:

- ▶ Patient's point of view (PRO): HRQOL, depression, fatigue, cognitive complaints
- ▶ Neurocognitive functioning

Challenge: balancing OS with toxic effects
(neurological symptoms, functional independence, NCF, HRQOL)



NCF in Brain Mets

- ▶ 90% of patients with brain mets have cognitive deficits at diagnosis
 - ▣ Mostly learning and memory & executive function
 - ▣ Related more to total lesion volume and location than to number of lesions
 - ▣ Associated with decreased overall survival



Relevance of NCF

- ▶ NCF as *primary* study endpoint:
 - ▣ safety endpoint with risk of neurotoxicity (e.g. time without neurocognitive deterioration – POLCA trial)
- ▶ NCF as secondary study endpoint
 - ▣ provide supporting evidence of treatment benefit
- ▶ NCF, HRQOL, and functional independence correlated
- ▶ Predictor: change in NCF before HRQOL change & functional independence



Characteristics of Cognitive Screening ≠ Formal Neuropsych Assessment

- ▶ Brief
- ▶ Suitable for bedside assessment
- ▶ Administered by non-specialist staff
- ▶ Purpose
 - ▣ Identify cognitive impairment
 - ▣ Identify nature of cognitive deficits




NCF Test Selection

► Mini-mental state examination (MMSE)

- short, 30 items, widely available
- substantial changes in MMSE: clinically significant NCF deterioration
- not sufficiently sensitive to pick up subtle relevant change, including memory

Screening Tool: The Mini-Mental State Examination (MMSE)

Patient _____ Examiner _____ Date _____

Maximum	Score	
5		Orientation
5		<ul style="list-style-type: none"> • What is the (year) (season) (date) (day) (month)? • Where are we (state) (country) (town) (hospital) (floor)?
3		Registration
3		<ul style="list-style-type: none"> • Name 3 objects: 1 second to say each. Then ask the patient all 3 after you have said them. Give 1 point for each correct answer. Then repeat until he/she learns all 3. Count trials and record. Trials _____
5		Attention and Calculation
5		<ul style="list-style-type: none"> • Serial 7s: 1 point for each correct answer. Stop after 5 answers. Alternatively spell "world" backward.
3		Recall
3		<ul style="list-style-type: none"> • Ask for the 3 objects repeated above. Give 1 point for each correct answer.
2		Language
1		<ul style="list-style-type: none"> • Name a pencil and watch.
1		<ul style="list-style-type: none"> • Repeat the following "No ifs, ands or buts."
3		<ul style="list-style-type: none"> • Follow a 3-stage command: "Take a paper in your hand, fold it in half and put it on the floor."
1		<ul style="list-style-type: none"> • Read and obey the following CLOSE YOUR EYES.
1		<ul style="list-style-type: none"> • Write a sentence.
1		<ul style="list-style-type: none"> • Copy the design shown.
		
		Total Score _____
		ASSESS level of consciousness along a continuum _____
		Alert Drowsy Stupor Coma
		<small>*Mini-Mental State: A Practical Method for Grading the Cognitive State of Patients for the Clinician. Journal of Psychiatric Research, 12(3): 109-106, 1975. Used with permission.</small>
		more information on reverse ►



Phase III Trial of Prophylactic Cranial Irradiation Compared With Observation in Patients With Locally Advanced Non–Small-Cell Lung Cancer: Neurocognitive and Quality-of-Life Analysis

Alexander Sun, Kyoungghwa Bae, Elizabeth M. Gore, Benjamin Movsas, Stuart J. Wong, Christina A. Meyers, James A. Bonner, Steven E. Schild, Laurie E. Gaspar, Jeffery A. Bogart, Maria Werner-Wasik, and Hak Choy

- ▶ RTOG trial 0214 showed no OS benefit for PCI in stage III NSCLC at 12 months
- ▶ However, there was a significant decrease in brain metastases
- ▶ This analysis focuses on impact of PCI on NCF and HRQOL



Table 1. Neurocognitive and QOL Assessment Compliance

Evaluation Status by Treatment Arm and Assessment	Baseline	At 3 Months	At 6 Months	At 12 Months
MMSE				
PCI				
Expected	163	159	152	125
Dead/alive and not evaluated	0/8	4/90	7/89	27/82
Received	155	69	63	43
%	95	43	41	34
Observation				
Expected	177	172	163	139
Dead/alive and not evaluated	0/8	5/86	9/93	24/87
Received	169	86	70	52
%	95	50	43	37
Difference	0	7	2	3
<i>P</i>	1.00	.20	.72	.61
HVLT				
PCI				
Expected	163	159	152	125
Dead/alive and not evaluated	0/11	4/95	7/92	26/84
Received	152	64	60	42
%	93	40	39	34
Observation				
Expected	177	172	163	139
Dead/alive and not evaluated	0/9	5/93	9/100	24/91
Received	168	79	63	48
%	95	46	39	35
Difference, %	2	6	0	1
<i>P</i>	.44	.27	1.00	.86



Table 3. Testing of Deterioration Status From Baseline in Mini-Mental Status Examination During Follow-Up Using Reliable Change Index

Time Point (months)	Prophylactic Cranial Irradiation				Observation				P*
	Deterioration		No Deterioration		Deterioration		No Deterioration		
	No.	%	No.	%	No.	%	No.	%	
3	23	36	41	64	17	21	65	79	.04
6	17	28	44	72	17	25	52	75	.68
12	9	23	31	78	9	18	41	82	.60

*From two-sample proportional test statistic comparing the percentage of people who deteriorated since baseline.

Table 4. Testing of Deterioration Status From Baseline in Hopkins Verbal Learning Test During Follow-up Using Reliable Change Index

Component by Time Point	PCI				Observation				<i>P</i> *	Adjusted <i>P</i> †
	Deterioration		No Deterioration		Deterioration		No Deterioration			
	No.	%	No.	%	No.	%	No.	%		
3 months										
Recall	28	45	34	55	10	13	66	87	< .001	< .001
Delayed recall	25	44	32	56	7	10	64	90	< .001	< .001
6 months										
Recall	11	19	46	81	3	5	58	95	.02	.045
Delayed recall	8	15	44	85	8	14	50	86	.81	.81
12 months										
Recall	10	26	28	74	3	7	42	93	.01	.03
Delayed recall	10	32	21	68	2	5	38	95	.003	.008

*From two-sample proportional test statistic comparing the percentage of people who deteriorated since baseline.

†Adjusted using the Hommel's method; adjustment is made within time point.



NCF Test Selection

► Montreal Cognitive Assessment

■ Free!

■ Mild cognitive impairment

■ Global impairment score

■ Includes some executive and visuospatial functions

■ More sensitive and specific than MMSE

■ Only takes 10 minutes

MONTREAL COGNITIVE ASSESSMENT (MOCA)

NAME: _____ Education: _____ Date of birth: _____
 Sex: _____ DATE: _____

VISUOSPATIAL / EXECUTIVE

Copy cube ☐ Draw CLOCK (Ten past eleven) (3 points) ☐

Begin 1 2 3 4 5 End A B C D E

NAMING

☐ ☐ ☐

MEMORY

Read list of words, subject must repeat them. Do 2 trials, even if 1st trial is successful. Do a recall after 5 minutes.

	FACE	VELVET	CHURCH	DAISY	RED
1st trial					
2nd trial					

ATTENTION

Read list of digits (1 digit/sec). Subject has to repeat them in the forward order. [] 2 1 8 5 4
 Subject has to repeat them in the backward order. [] 7 4 2

Read list of letters. The subject must tap with his hand at each letter A. No points if > 2 errors.
 [] FBACMNAAJ KLBFAKDEAAA JAMOF AAB

Serial 7 subtraction starting at 100 [] 93 [] 86 [] 79 [] 72 [] 65
 4 or 5 correct subtractions: 3 pts, 2 or 3 correct: 2 pts, 1 correct: 1 pt, 0 correct: 0 pt

LANGUAGE

Repeat: I only know that John is the one to help today. []
 The cat always hid under the couch when dogs were in the room. [] (N ≥ 11 words)

Fluency / Name maximum number of words in one minute that begin with the letter F []

ABSTRACTION

Similarity between e.g. banana - orange = fruit [] train - bicycle [] watch - ruler []

DELAYED RECALL

Has to recall words WITH NO CLUE

	FACE	VELVET	CHURCH	DAISY	RED
Category cue					
Multiple choice cue					

Points for UNCLUED recall only

Optional

ORIENTATION

[] Date [] Month [] Year [] Day [] Place [] City

© Z.Nareddine MD Version 7.1 www.mocatest.org Normal ≥ 26 / 30
 Administered by: _____ TOTAL Add 1 point if ≤ 12 yr edu



MOCA

- ▶ Sensitivity and specificity poor compared to formal neuropsychological assessment
- ▶ MOCA used as screening instrument in cross-sectional studies
 - ▣ Lack of psychometric data on serial use of MOCA to detect changes over time in brain mets



Brain Mets Clinical Trial Battery

- ▶ RANO working groups & International Cognition and Cancer Task Force proposed core set of cognitive tests
- ▶ Adopted by RTOG, EORTC, NCCTG, NCI-C, RTOG, MRC, EORTC, industry

Challenges relating to solid tumour brain metastases in clinical trials, part 2: neurocognitive, neurological, and quality-of-life outcomes. A report from the RANO group

Nancy U Lin, Jeffrey S Wefel, Eudocia Q Lee, David Schiff, Martin J van den Bent, Riccardo Soffietti, John H Suh, Michael A Vogelbaum, Minesh P Mehta, Janet Dancey, Mark E Linskey, D Ross Camidge, Hidefumi Aoyama, Paul D Brown, Susan M Chang, Steven N Kalkanis, Igor J Barani, Brigitta G Baumert, Laurie E Gaspar, F Stephen Hodi, David R Macdonald, Patrick Y Wen, for the Response Assessment in Neuro-Oncology (RANO) group

Used in PBT trials:

- ▶ **EORTC, NCCTG, NCI-C, RTOG, and MRC multisite clinical trials:**
 - ▣ **EORTC 26053 - 22054 RTOG 0834** - The CATNON Intergroup trial. Phase III trial on Concurrent and Adjuvant TMZ chemotherapy in non-1p/19q deleted anaplastic glioma.
 - ▣ **EORTC 26081-22086** - The CODELETED trial. Phase III Intergroup Study of Radiotherapy versus TMZ versus Radiotherapy with Concomitant and Adjuvant TMZ for Patients with Newly Diagnosed Anaplastic Oligodendroglioma or Anaplastic Mixed Glioma with Chromosomal co-deletions of 1p and 19q.
 - ▣ **EORTC 26091** - Bevacizumab in recurrent grade II and Grade III gliomas
 - ▣ **EORTC 26101** - Phase II trial exploring the sequence of bevacizumab and lomustine in patients with first recurrence of a glioblastoma

Cognitive Domain	Test	Time to Administer (minutes)
Memory	Hopkins Verbal Learning Test– Revised	8
Visual-motor processing speed	Trail Making Test Part A	5
Executive Function	Trail Making Test Part B	7
Verbal fluency	Controlled Oral Word Association	5
		Total time: 25 minutes

□ Dutch, English (US, UK), French, German, Italian,
Spanish, Catalan, Hebrew, Turkish, Portuguese

□ 6 parallel versions



- Healthcare professional (e.g., nurse, psychologist) who is responsible for test administration gets certification
- Training video of test administration and data collection procedures accessible through website (MDACC)
- Post test → VUmc → certification
- Test and data recording forms are available on password-protected website (VUmc)

The collage consists of four overlapping screenshots from different web browsers. The top-left screenshot shows the MD Anderson Cancer Center website with the title 'Training Video and Test Administration Procedures - MD Anderson Cancer Center'. The top-right screenshot shows a video player titled 'Neurocognitive Training Video - M. D. Anderson Cancer Center Video' with a man in a suit speaking. The bottom-left screenshot shows a Windows taskbar and a Firefox browser window displaying the VUmc website. The bottom-right screenshot shows a Mozilla Firefox browser window displaying the VUmc website, specifically the 'Neuro-Oncology & Neurotoxicity' section, which lists various scoring forms for test administrators in multiple languages.

Practical Challenges

- ▶ NCF assessment before the start of protocol treatment crucial to establish pretreatment baseline
- ▶ Consider stratification by NCF to reduce baseline differences in trials when NCF is primary or key secondary endpoint



Practical challenges

- ▶ Timing of NCF assessments can affect interpretation of study results
 - ▣ Assessment only until time of progression prevents meaningful comparison of treatment groups
 - ▣ Changes in the time-course of expected toxicities or treatment benefit
- ▶ Timing in brain mets trials challenging
 - ▣ If too frequent confounded by practice effects
 - ▣ if too widely spaced apart might have missing data, from differential dropout or from high event rate in both groups

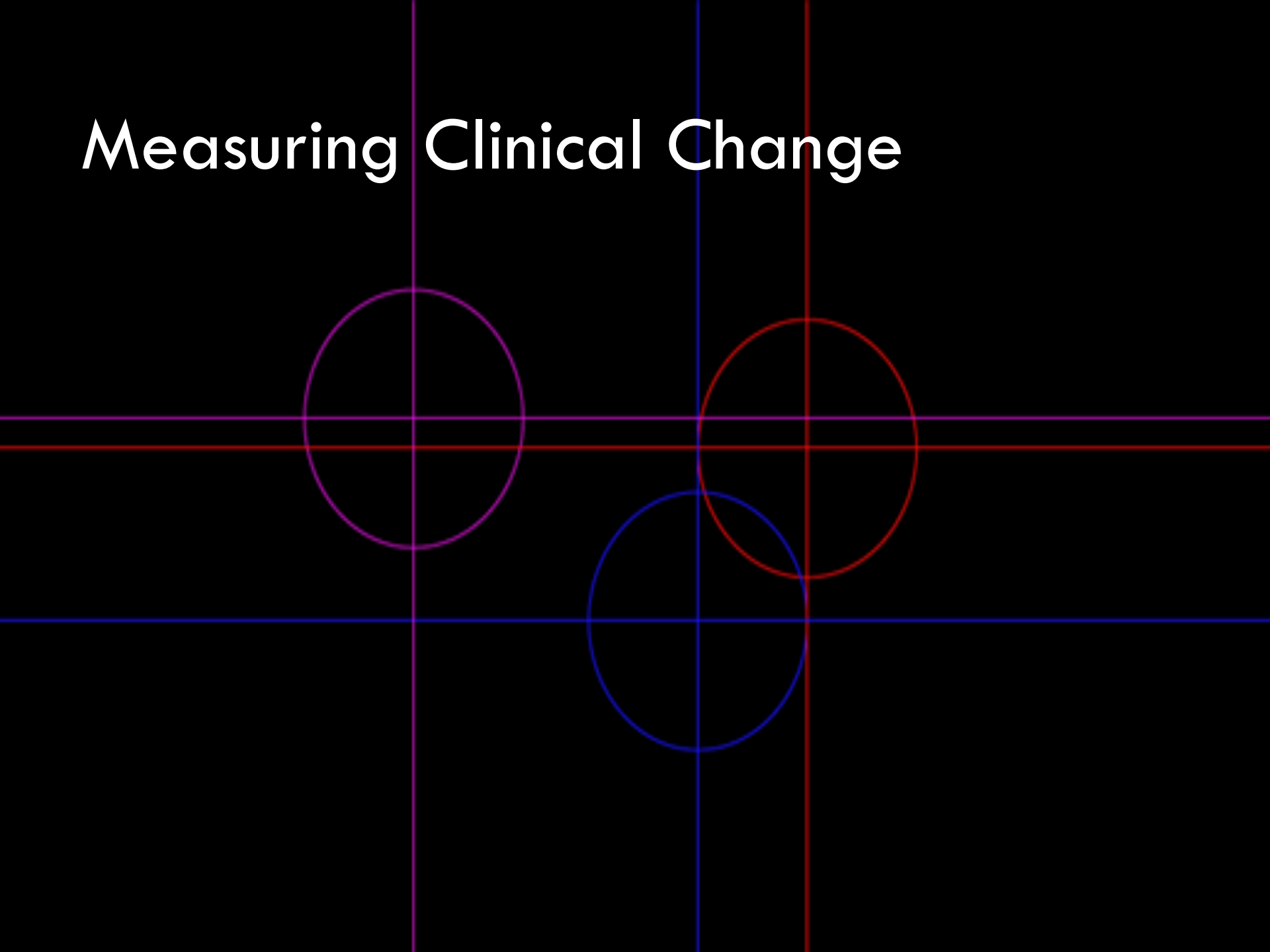


Practical Challenges

- ▶ Selective dropout can have the effect of making a treatment seem more favorable than it really is
 - ▣ Solution: require neurocognitive function tests irrespective of whether a patient is still on protocol therapy at each prespecified timepoint
 - ▣ Solution: ensure NCF testing frequent enough early in the study, which might help to detect NCF deterioration before radiological
 - ▣ Solution: require rapid submission of data and frequent data monitoring to ensure compliance with protocol scheduled assessments



Measuring Clinical Change



Measuring clinically important change is complex. Multiple methods are available with various advantages and disadvantages.

How NOT to measure clinically important change:



Two problems in brain met trials

- ▶ Small number of subjects: Clinically important differences observed in studies can be denoted as statistically non-significant and therefore be unfairly ignored as a result (type II error)
- ▶ Large number of subjects: Even the smallest difference in measurements can be proved statistically significant. Such a small difference could be of no clinical importance to patients or clinicians.

Minimal Clinically Important Difference (MCID) – 3 Solutions

- ▶ Distribution-based methods
 - ▶ Anchor-based methods
 - ▶ The Delphi method
-
- ▶ No consensus regarding the optimal technique

Distribution-based - SD, SEM, effect size

- ▶ Using the X **SD** benchmark of an outcome measure entails a MCID
- ▶ The **SEM** is the variation in scores due to unreliability of the scale or measure used. Change < SEM result of measurement error rather than a true observed change.
- ▶ **Effect size** cut off point can be used to define MCID similar to SD and SEM

Anchor-based methods

- ▶ Compares changes in scores with an “anchor” as reference
 - ▣ “Do you feel that your memory improved by your treatment?”
 - ▣ The patient is asked what minimal outcome would be necessary to undergo the proposed treatment.
- ▶ Currently no consensus on the one right question nor on the best answers

Delphi method

- ▶ Relies on a panel of experts who reach consensus regarding the MCID
- ▶ Panel provided with information on the results of a trial and are requested to provide their best estimate of MCID
- ▶ Responses are averaged, and this summary is send back with an invitation to revise their estimates
- ▶ Process is continued until consensus is achieved



Doing outcomes research is
a lot like raising children...
you always think you are
going to do a better job
next time.