


# Health Outcomes in Cerebrovascular Disease Treatment Studies

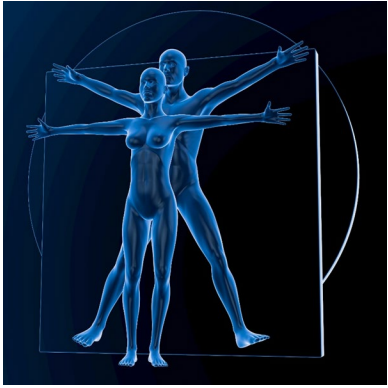
MEDCAC Meeting – 9/22/2021

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# JLS Disclosures

- ▶ Employee of the University of California. The University of California has patent rights in retrieval devices for stroke. The University of California has made the Rankin Focused Assessment freely available under a Creative Commons license and has copyright on written RFA training vignettes.
  - ▶ Unpaid site investigator in multicenter trials run by Medtronic, Stryker, Rapid Medical, and Abbott for which the UC Regents received payments on the basis of clinical trial contracts for the number of subjects enrolled.
  - ▶ Receives funding for services as a scientific consultant regarding rigorous trial design and conduct to Amgen, Abbott, BrainsGate, BrainQ, Boehringer Ingelheim (prevention only), Biogen, Medtronic, Stryker, Cerenovus, Rapid Medical, Pfizer, NuvOx, Hybernia Medical, NoNo, Neuravi, Novo Nordisc, Phaegenesis, and Phillips.
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# Talk Outline



- ▶ Distinctive Aspects of Outcome Assessment in Neurovascular Disease
- ▶ Acute Stroke
  - Timing of outcome assessment
  - **Global Disability – Modified Rankin Scale**
  - **Neurologic Deficit Severity – NIH Stroke Scale**
  - Health-Related Quality of Life
    - **Generic – EQ-5D, SF-36, NIH PROMIS 10**
    - **Stroke Specific – Stroke Impact Scale 64, SS-QoL Scale**
  - Administrative Data Measures
    - **Discharge destination**
    - **Home time during first 90 days**
    - Length of stay
    - Potentially modified Rankin Scale
- ▶ Stroke Recovery
  - Domain-specific
    - Arm Function – Fugl-Meyer UE, SIS Hand, Box and blocks
    - Leg Function – Fugl-Meyer LE, 10 meter walk speed
    - Language function, Memory, Spatial attention, etc
- ▶ Prevention
  - First/Recurrent Stroke
    - Occurrence – Questionnaire for Verifying Stroke-Free Status
    - Severity – NIHSS, mRS
    - Composite stroke, MI, vascular death
  - Administrative
    - Readmission for stroke/TIA/MI
    - All-cause readmission

# Distinctive Aspects of Outcome Assessment in Neurovascular Disease

- ▶ The disease compromises the organ that perceives and reports functioning accurately
  - Aphasia, amnesia, dysexecutive function
  - Which hemisphere is reporting?
    - Denial of illness in right hemisphere injury
    - Catastrophic response in left hemisphere injury
  - Proxy reporting from family/caregivers often required but not fully reliable
- ▶ Degree of disability comparably or more important than mortality
  - Disability much more frequent outcome than mortality
  - Breakthrough therapies, intravenous thrombolysis and endovascular thrombectomy, alter disability substantially, mortality minimally
- ▶ Acute stroke outcomes are intrinsically non-dichotomous – occur across a range of disability
  - Analytic options
    - Ordinal shift analysis – over entire disability range
    - Dichotomize – value only one of several health state transitions
    - (Continuous)
- ▶ Need to adjust for presenting stroke severity
  - The dominant determinant of outcome



# Timing of Outcome Assessment after Acute Stroke

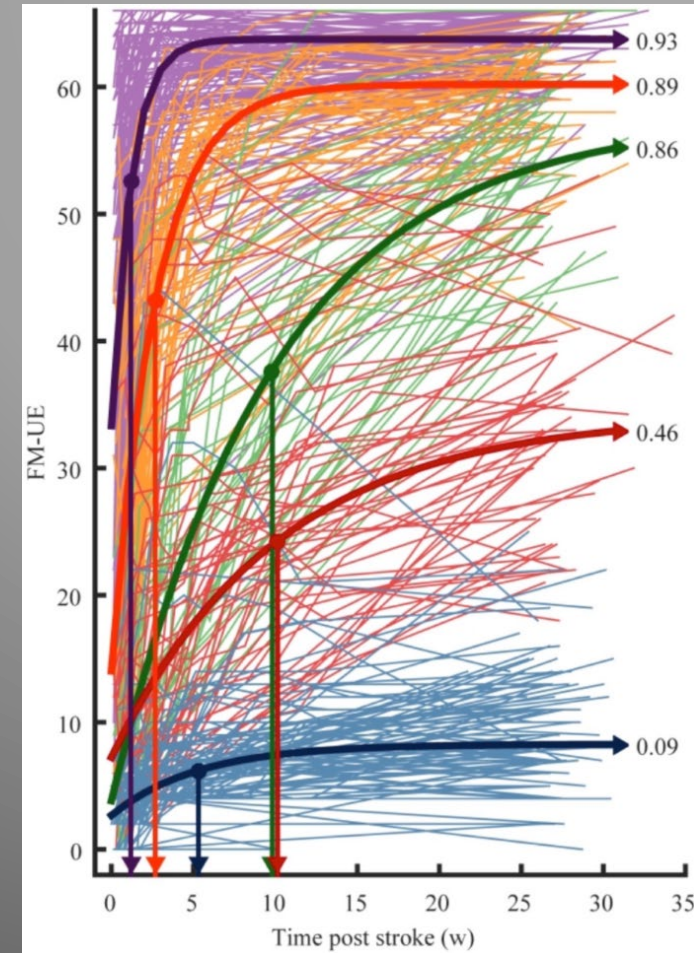
## ► Considerations

- Timing of stroke recovery
  - Most occurs during 1<sup>st</sup> 3m
  - Some additional thru 1y
- Social security administration
  - Disability determination at 3m
- Competing events (recurrent stroke, MI, etc)
  - Accrue with time

## ► Consequences

- 1m
  - Too early
- 3m
  - Generally best compromise to capture preponderance of recovery before competing events
  - Most common timepoint in RCTs
- 6m–1y
  - Sometime useful for severe strokes (e.g. ICH, SAH) in which recovery phase may be prolonged

*Timing of motor recovery on FM-UE in 412 ischemic stroke pts*



*–van der Vliet et al, Ann Neurol 2020*

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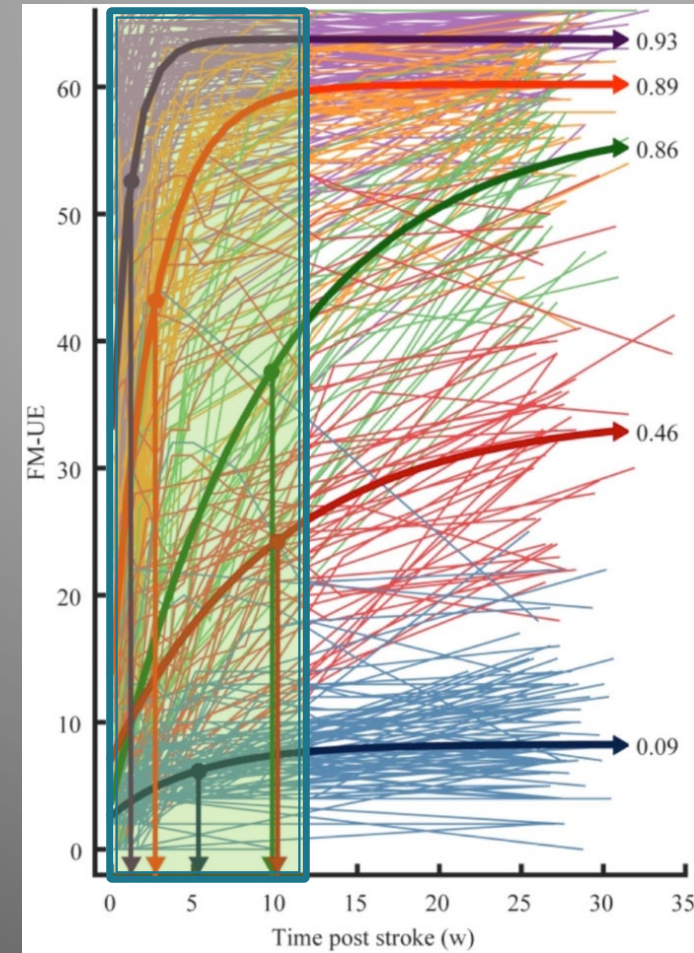
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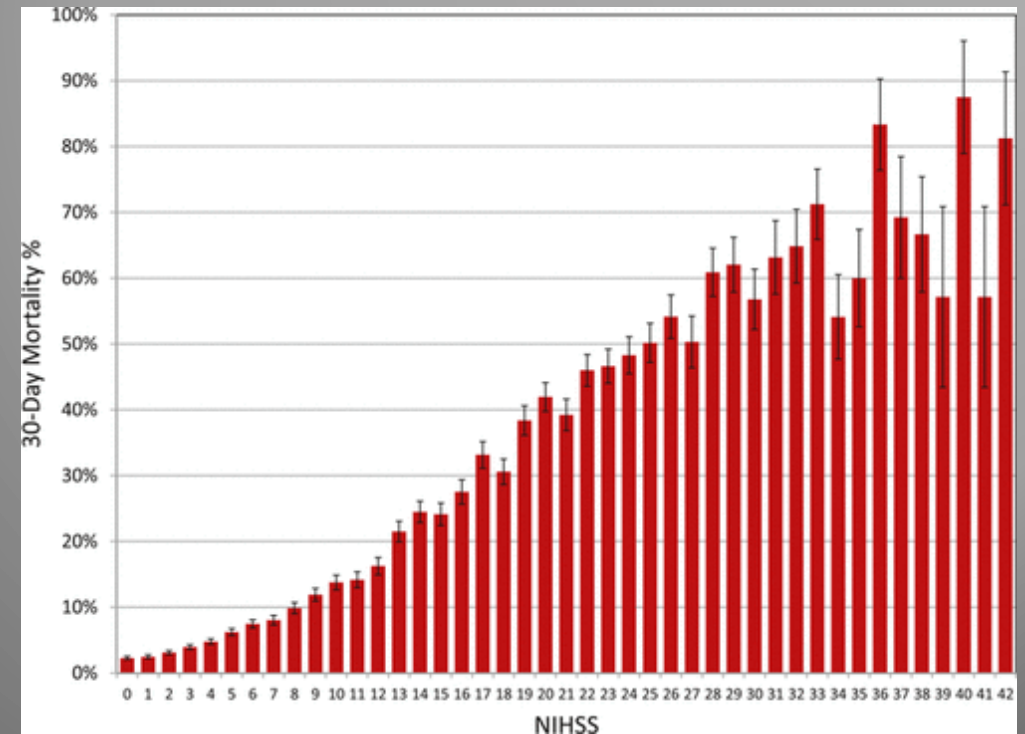


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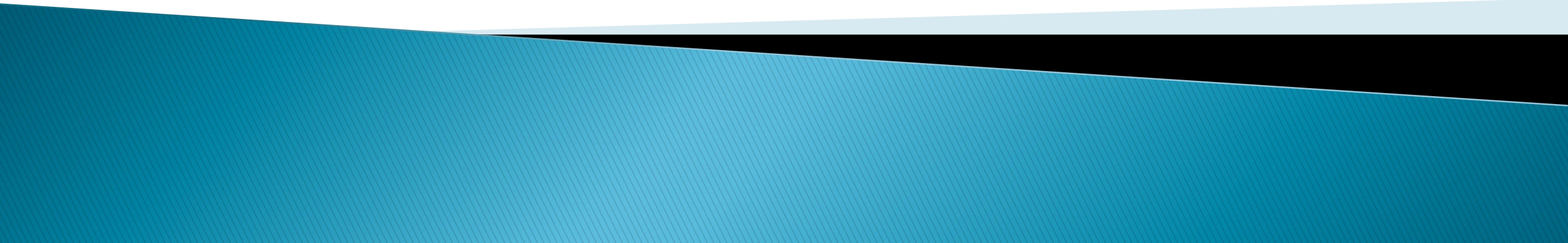
# Necessity of Adjusting for Presenting Stroke Severity

- ▶ Severity a dominant outcome predictor
  - Age also important
  - Co-morbidities much less important
- ▶ In CMS beneficiaries
  - Mortality model w/o NIHSS:  $c = 0.77$
  - Mortality model w/ NIHSS:  $c = 0.86$
- ▶ CMS recognition
  - 2014 AHA/ASA Presidential Advisory
  - 2016 – CMS pilot addition of NIHSS to ICD-10 codes
  - 2022 – anticipated CMS use of administrative NIHSS in hospital performance reporting



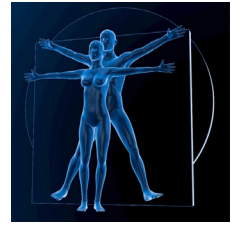
–Smith et al, *Circulation* 2010; Fonarow et al, *JAMA* 2012, Fonarow et al, *JAMA* 2012; Fonarow, *Stroke* 2014; Saber+Saver, *JAMA Neurol* 2020

# Acute Stroke Modified Rankin Scale





# Background: World Health Organization Definition of Disability



In 2001, WHO established a new definition of disability, based on human rights/social models, focuses on the interaction between a person with disability and the environment.

## DISABILITY

is an umbrella term, with three components

- ▶ ***Impairments***: problems in body function or structure
- ▶ ***Activity limitations***: difficulties encountered by an individual in executing a task or action
- ▶ ***Participation restrictions***: problems experienced by an individual's involvement in life situations

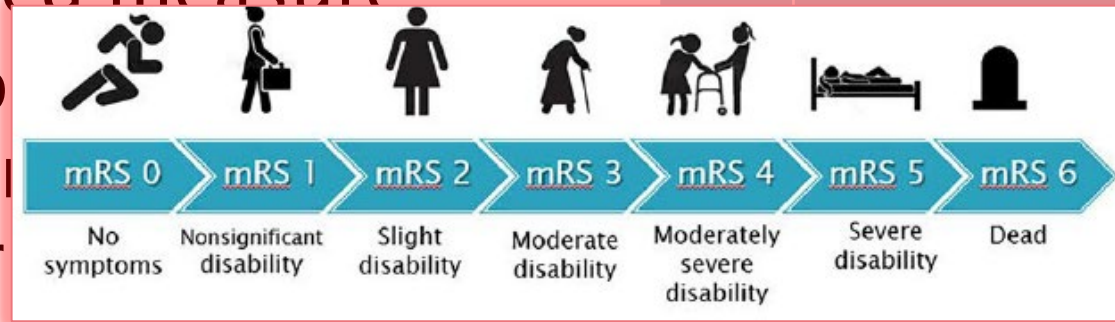
# Modified Rankin Scale (mRS)

- ▶ Measures global disability
- ▶ Clinician-reported measure
- ▶ Most common primary outcome measure in acute stroke clinical trials and clinical practice
- ▶ Assigns patient to 1 of 7 possible levels of disability

Level	Description
0	No symptoms
1	Nonsignificant disability -- despite symptoms; able to carry out all usual duties and activities
2	Slight disability -- unable to carry out all previous activities, but able to look after own affairs w/o assistance
3	Moderate disability --requiring some help, but able to walk without assistance
4	Moderately severe disability --unable to walk without assistance and unable to attend to own bodily needs w/o assistance
5	Severe disability --bedridden, incontinent and requiring constant nursing care and attention
6	Dead

# Modified Rankin Scale (mRS)

- ▶ Measures global disability
- ▶ Clinician-reported measure
- ▶ Most common post-stroke clinical trial outcome measure in clinical practice
- ▶ Assigns patient to 1 of 7 possible levels of disability



Level	Description
0	No symptoms
1	Nonsignificant disability --able to carry out all usual activities
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# Consensus Health State Descriptors for each mRS Level

Level	Can	...But	Descriptor
mRS 0	No symptoms		Normal
mRS 1	Do work/leisure/school activities fulltime	...has symptoms	Symptomatic but nondisabled
mRS 2	Live alone for >1 wk	...can't work	Disabled but independent
mRS 3	Walk+ body self-care	...can't live alone	Dependent but ambulatory
mRS 4	Not require constant nursing care	...can't walk or body self-care	Non-ambulatory or body self-care capable
mRS 5	Alive	...requires constant nursing care	Requires constant care
mRS 6		Not alive	Dead

<sup>1</sup>Saver et al, Stroke 2021 (STAIR Consensus Conference )

# Widespread Acceptance of Modified Rankin Scale

- ▶ Randomized clinical trials
  - Predominant primary outcome measure
- ▶ Consensus groups
  - US
    - Stroke Therapy Academic Industry Roundtable (STAIR)<sup>1</sup>
  - Europe
    - European Stroke Organization Outcomes Working Group<sup>2</sup>
- ▶ Regulatory agencies
  - FDA<sup>3</sup>
  - EMA<sup>4</sup>
  - NIH–NINDS Common Data Element<sup>5</sup>
- ▶ Hospital accrediting bodies
  - TJC<sup>6</sup>/DNV/HOA
- ▶ Specialty Societies
  - American Academy of Neurology<sup>7</sup>
  - American Society of Interventional and Therapeutic Neuroradiology<sup>8</sup>
- ▶ US clinical practice
  - Get with the Guidelines–Stroke

<sup>1</sup>Fisher et al, *Stroke* 2005; <sup>2</sup>Lees et al, *Stroke* 2012; <sup>3</sup>Hicks et al, *Circulation* 2018; <sup>4</sup>EMA Guideline 2014;

<sup>5</sup>Saver et al, *Stroke* 2012; <sup>6</sup>TJC Manual, 2021; <sup>7</sup>Latorre et al, *Neurology* 2017; <sup>8</sup>Higashida et al, *Stroke* 2002

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Stroke – CSC National Hospital Inpatient Quality Measures

▶ CSTK-10: Favorable modified Rankin Score at 90d (reperfusion pts)

<sup>1</sup>Fisher et al, *Stroke* 2005; <sup>2</sup>Lees et al, *Stroke* 2012; <sup>3</sup>Hicks et al, *Circulation* 2018; <sup>4</sup>EMA Guideline 2014; <sup>5</sup>Saver et al, *Stroke* 2012; <sup>6</sup>TJC Manual, 2021; <sup>7</sup>Latorre et al, *Neurology* 2017; <sup>8</sup>Higashida et al, *Stroke* 2002



# US Nationwide Quality Improvement Registry



- ▶ 2004–present
- ▶ 2356 US acute care hospitals
  - More than 6 million patient records
  - New patients added at 704,000 per year
  - More than 70% of all acute stroke admissions in US
- ▶ Modified Rankin Scale
  - At discharge
    - All GWTG–Stroke hospitals
    - All patients
  - At 90 days
    - Comprehensive and Thrombectomy Stroke Center GWTG–Stroke Hospitals
    - Patients undergoing intravenous thrombolysis or endovascular thrombectomy

# Approaches to Assigning mRS Scores

Examples	Key Features	Operationalized Scoring	Inter-Rater Consistency	Robust Data Sources – Accuracy	Ease of Use	Blinding	Assessor Type
Intuitive global judgment	–Original	---	--	++	+++	++	<i>Clinician-Rated</i>
Raters certified by video	–One training curriculum	-/+	++	+	++	++	<i>Mostly Clinician-Rated</i>
Central core lab	–Video/audio interviews	-	(+++)	--	--	+++	<i>Mostly Patient-Reported</i>
Simplified mRS Questionnaire (smRSq)	–Patient judgment	---	(-)	--	+++	-	<i>Patient-Reported</i>
mRS-9Q	–Patient yes/no	++	(+)	--	+++	-	<i>Patient-Reported</i>
mRS Structured Interview	–Structured interview	+++	+++	--	++	++	<i>Patient-Reported</i>
Rankin Focused Assessment (RFA)	–Structured rater assessment	+++	+++	+++	++	++	<i>Clinician-Rated</i>

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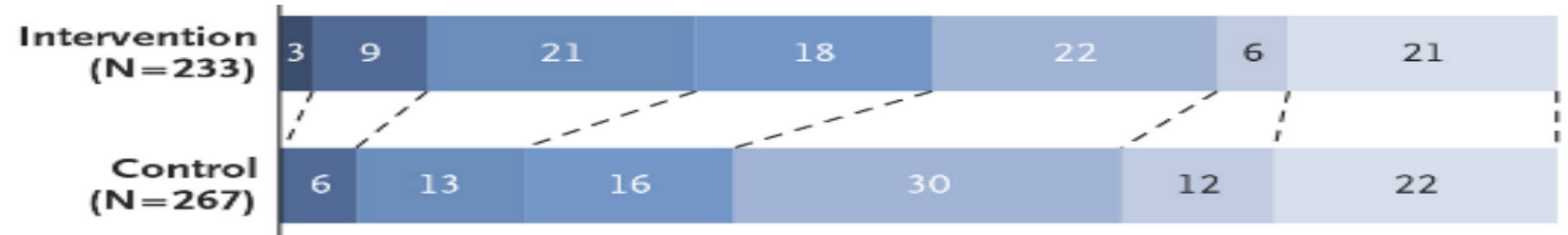
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# Analysis of the Modified Rankin Scale (mRS)

- ▶ Ordinal

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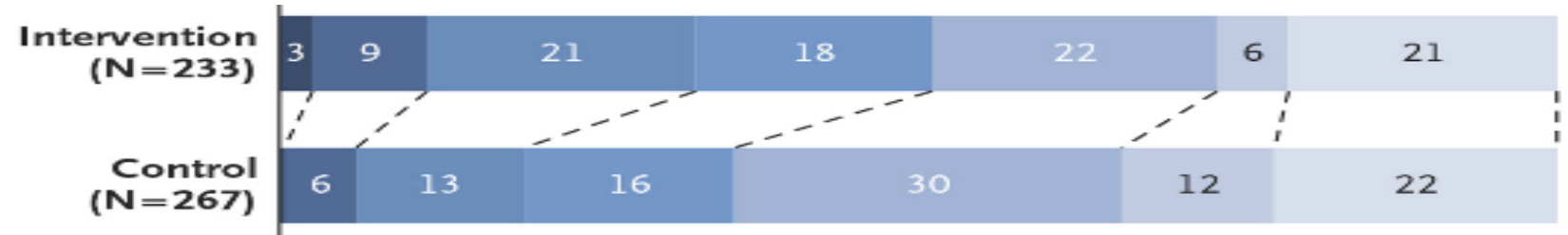
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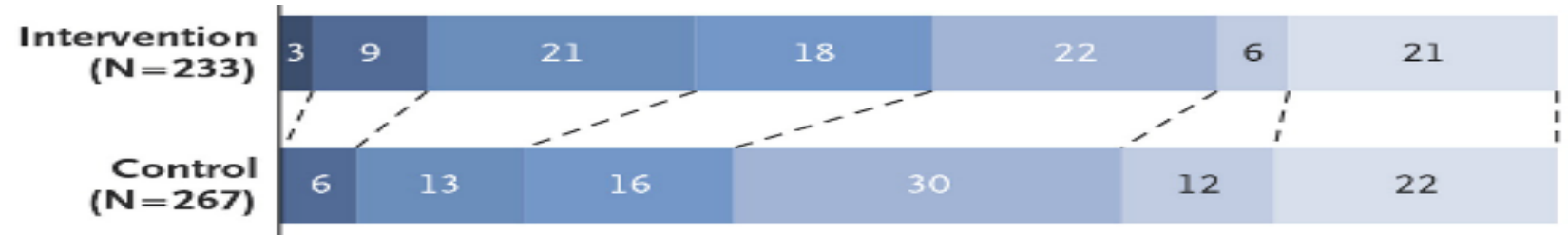
- ▶ Ordinal



- ▶ Fixed dichotomy
  - mRS 0–2

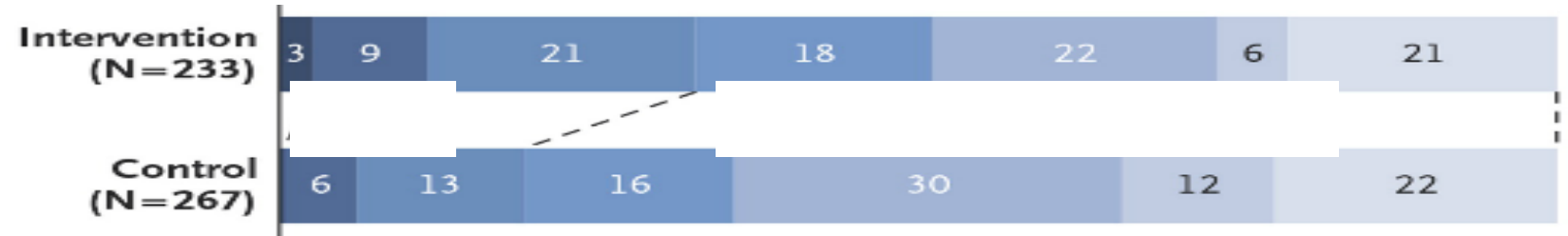
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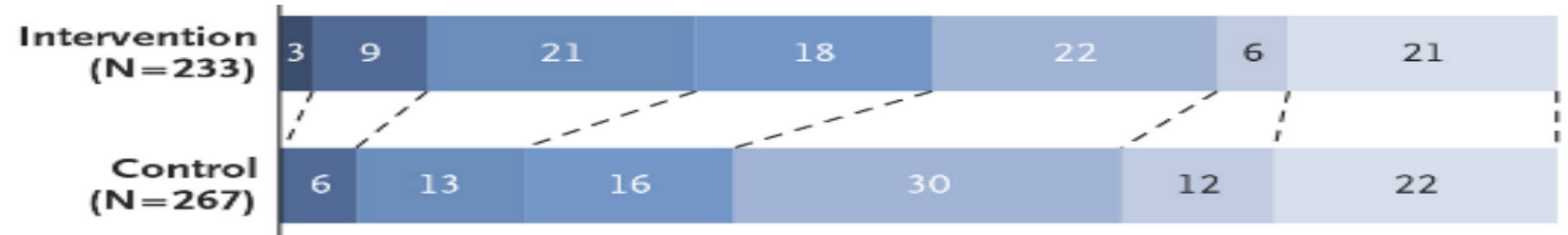
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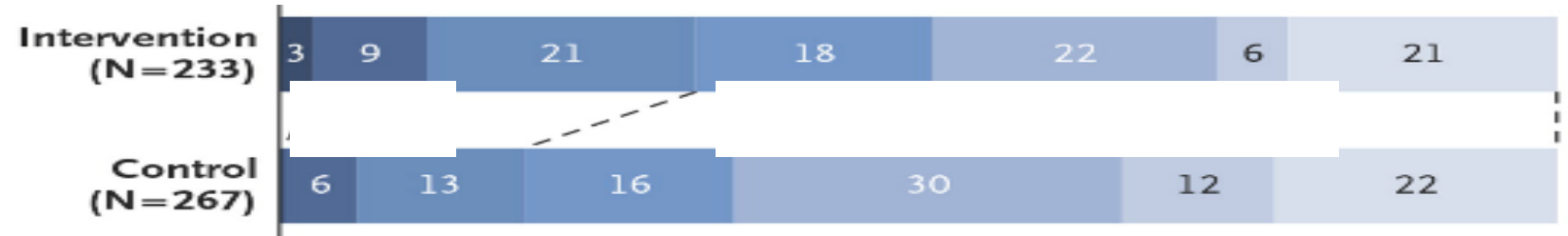
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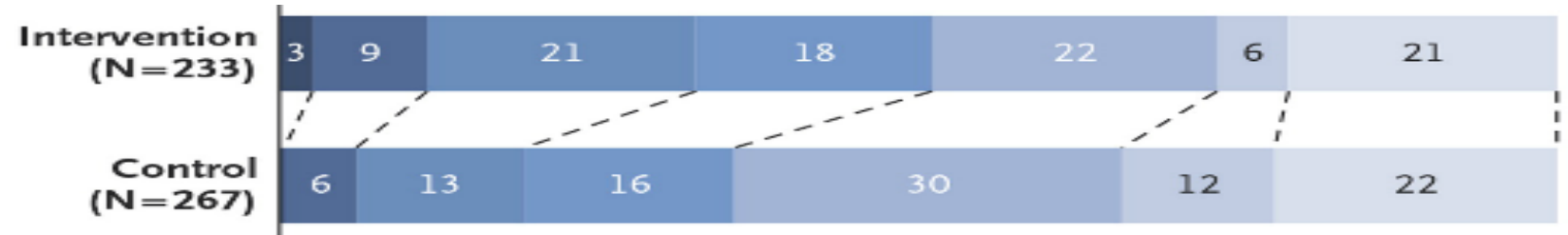
- mRS 0–2

- mRS 0–1



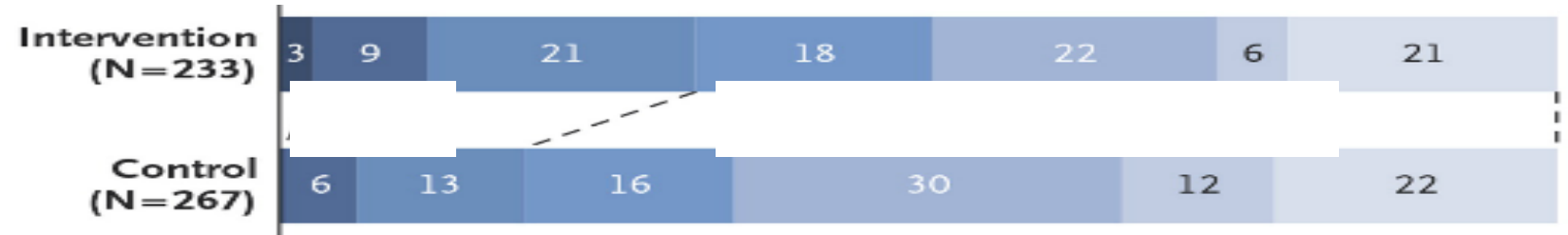
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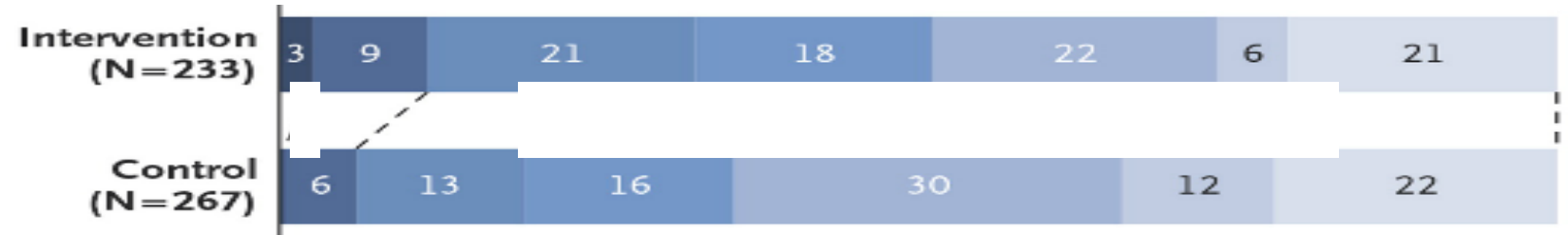


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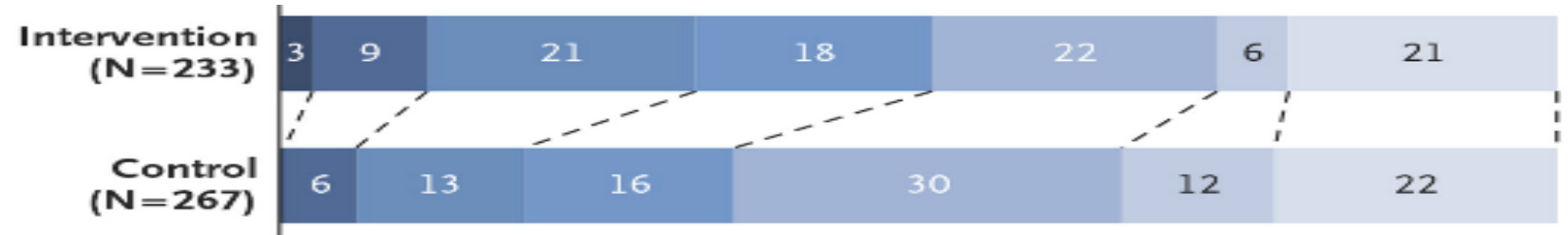


- mRS 0–1



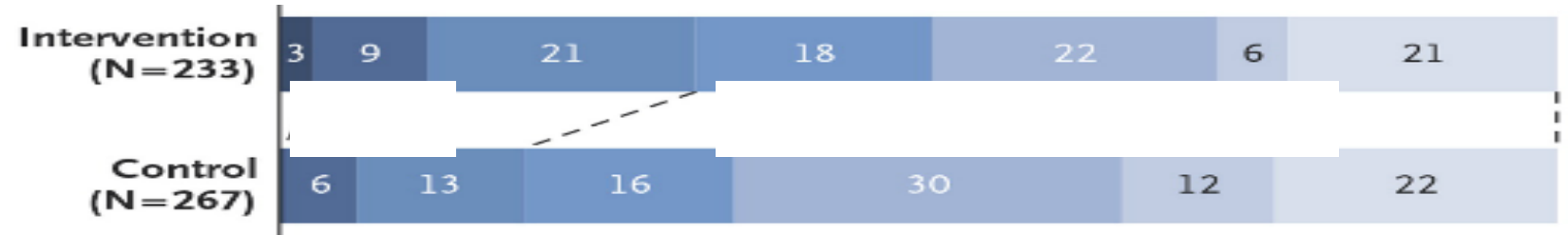
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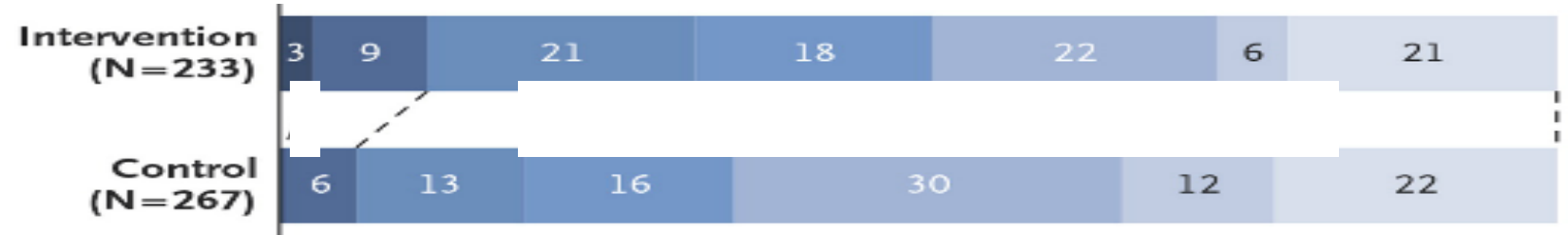


- ▶ Fixed dichotomy

- mRS 0–2



- mRS 0–1



- ▶ Weighted Ordinal

- Utility-weighted mRS



# Utility-Weighted modified Rankin Scale (UW-mRS)

–Chaisinankul et al, Stroke 2015

## Patients



- ▶ Population-based UK stroke cohort (OXVASC)
  - 1283 stroke and TIA patients
  - 1,6,12, 24 months
- ▶ Simultaneous mRS and Euro-QoL
  - mRS mapped to Euro-QoL
  - Euro-QoL previously mapped to utility
    - Via time tradeoff
  - mRS mapped to utility
- ▶ Utility weights for mRS

–Rivero-Arias et al, Med Dec Making 2010

## Providers



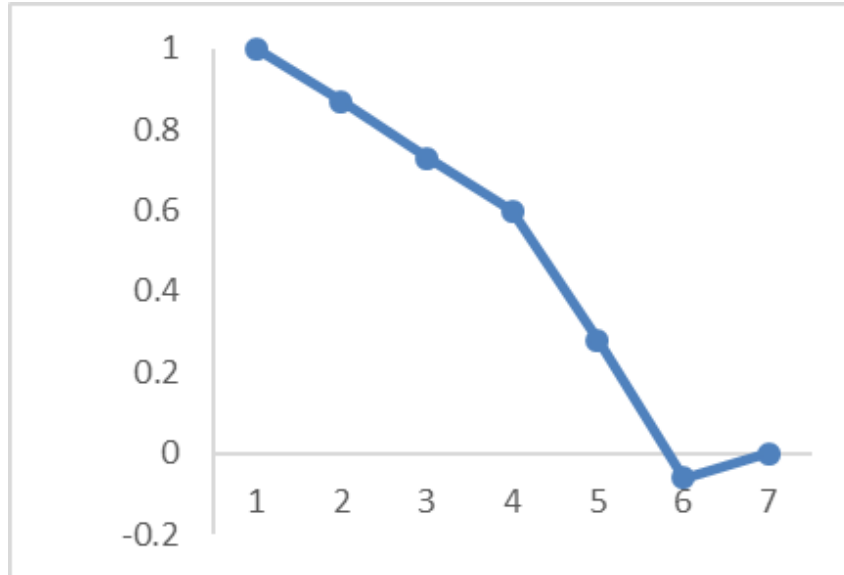
- ▶ International panel of 9 stroke physicians
  - Vas Neuro/Rehab Neuro/EM
  - US and Asia
- ▶ Vignettes of patients with mRS states
  - Person tradeoff
- ▶ Disability weights for mR

–Hong + Saver, Stroke 2009

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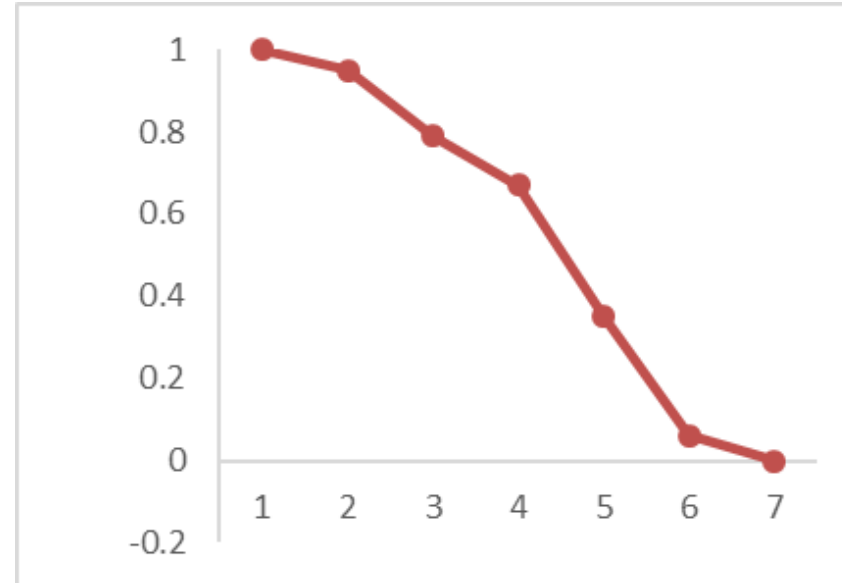
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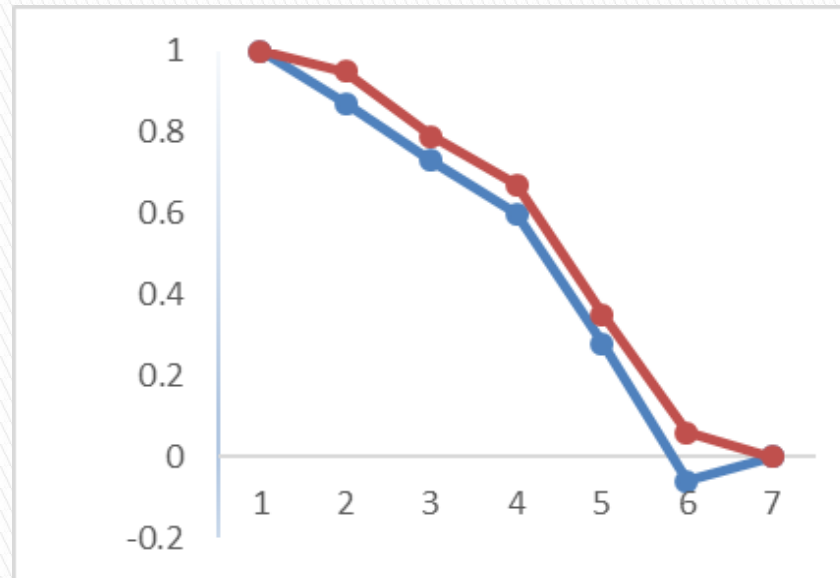
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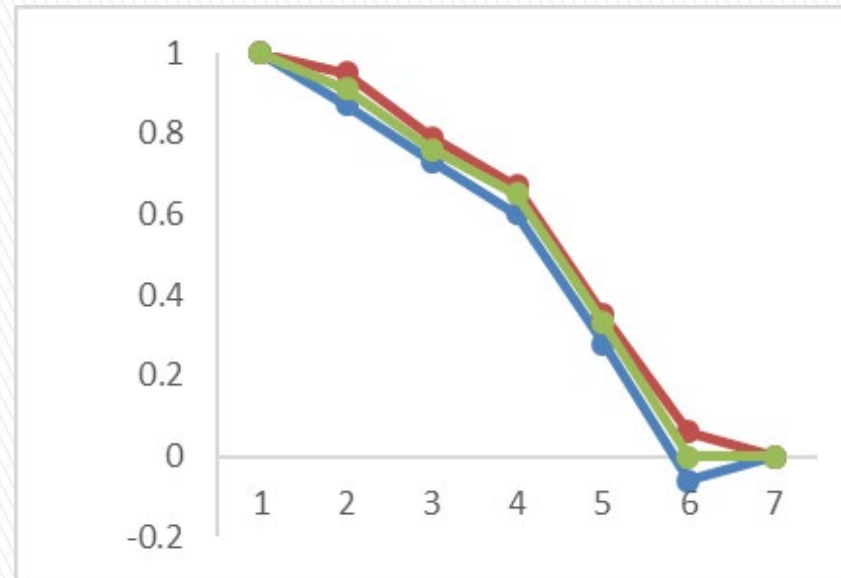
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# Utility-Weighted modified Rankin Scale (UW-mRS)

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mRS Level	Utility Weight
0	1.00
1	0.91
2	0.76
3	0.65
4	0.33
5	0
6	0



# For Cost Effectiveness Studies

## Deriving DALYs/QALYs from UW-mRS

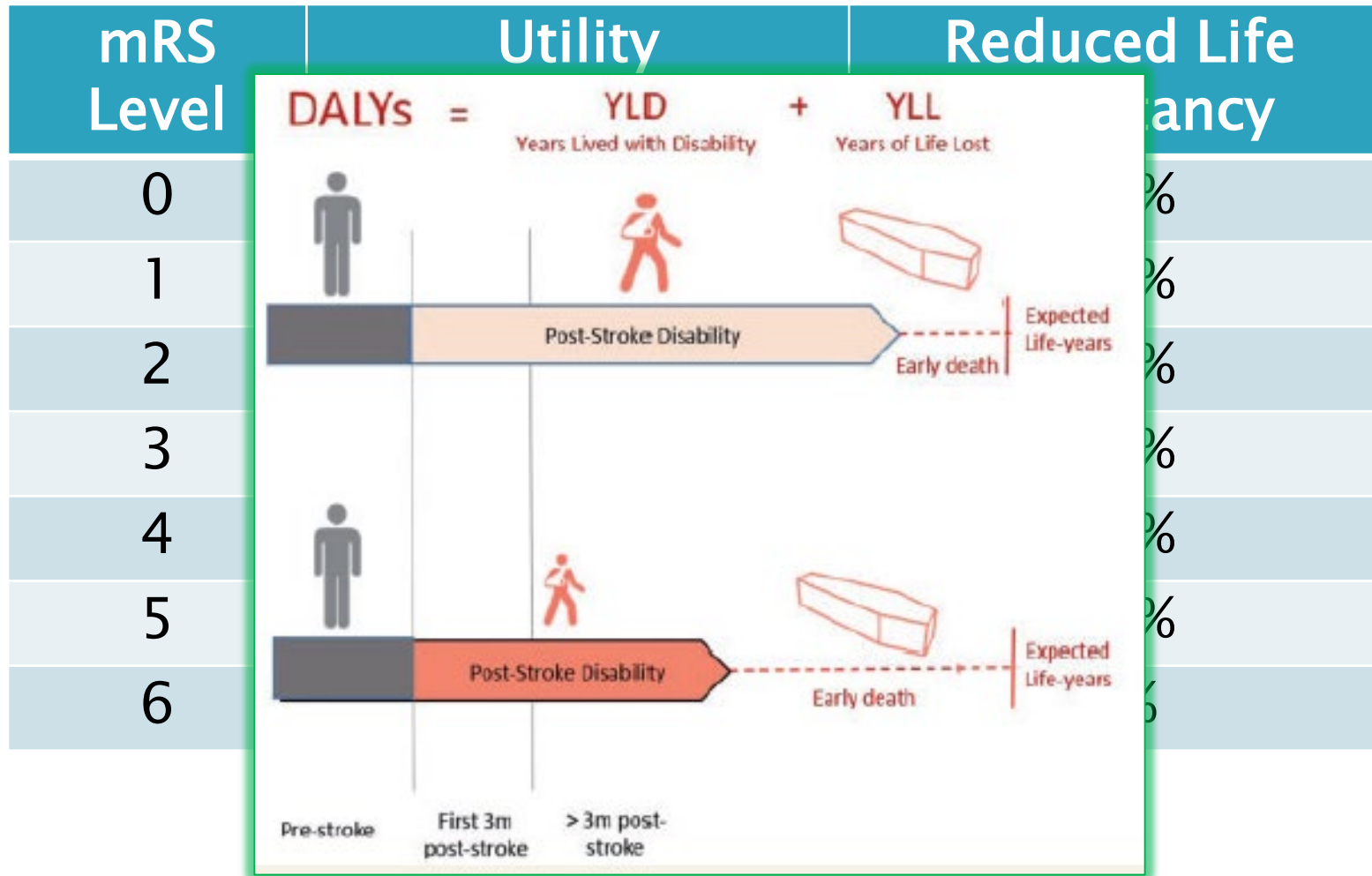
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4	0.33
5	0
6	0

## For Cost Effectiveness Studies Deriving DALYs/QALYs from UW-mRS

mRS Level	Utility Weight	Reduced Life Expectancy
0	1.00	65%
1	0.91	65%
2	0.76	46%
3	0.65	31%
4	0.33	22%
5	0	15%
6	0	0%

*-Chaisinankul et al, Stroke 2015; Hong+Saver, Stroke 2010; Saver, Brain 2017*

# For Cost Effectiveness Studies Deriving DALYs/QALYs from UW-mRS



–Chaisinankul et al, Stroke 2015; Hong+Saver, Stroke 2010; Saver, Brain 2017

# Practical Aspects of mRS Use

- ▶ Acute stroke (1<sup>st</sup> 72h)
  - Cannot use mRS change score from baseline
    - mRS not scorable during first 24h
      - Patient not attempting functional activities and functional capability can't be reliably assessed by raters
    - Instead use mRS at 3 months adjusted for baseline deficit severity (NIHSS)
      - Incorporates patient baseline state
  - Incorporating prestroke mRS
    - In most RCTs, patients with prestroke disability (mRS 2–5 or 3–5) excluded from entry
      - Dichotomous analysis (mRS 0–1, 0–2) – usually obviates need to incorporate directly into endpoint
      - Ordinal analysis/UW-mRS analysis – fine to use
    - In clinical practice and RCTs, patients with prestroke disability do receive treatment
      - Dichotomous analysis (mRS 0–1, 0–2) – need to add “or return to prestroke mRS” for patients with prestroke mRS 3,4,5 to be informative
      - Ordinal analysis/UW-mRS analysis – fine to use
- ▶ Subacute stroke (D4 forward)
  - Can use mRS change score from baseline
    - mRS is scorable at 4–7d
      - Patient attempting some functional activities and functional capability for others can be reliably assessed by raters
    - For individual patient –decrease by  $\geq 1$  point is highly clinically significant for all mRS transitions except 6 to 5
    - For group differences –decrease by  $\geq 0.12$  points exceed the MCID

# Outcome Measures Assessing Treatment Effects in Changing Patient Status Along an Outcome Continuum – Primary Analysis Statistical Approaches in Regulated Trials

Primary Statistical Analysis Modes	Aspect of Post-Stroke Global Disability Evaluated, as a Descriptive Phrase	Pivotal Acute Stroke RCTs Using this Mode for Primary/Lead mRS Analysis*		Funding and Regulatory Agencies
		Example Trials (partial listing)	Number (partial listing)	
Ordinal	Reduced Disability Level <i>(Shift Analysis)</i>	ECASS-1 / MR RESCUE / STITCH(Trauma) / FAST-MAG / MR CLEAN / ESCAPE / SWIFT PRIME / REVASCAT / EXTEND-IA / THRILL / POSITIVE / DEFUSE 3 / RIGHT 2 / PHAST-TSC / CHARM / ECASS-4 / EXTEND-IA TNK / EXTEND-IA TNK Part 2 / ENDOLOW / TENSION	<b>20</b>	FDA / EMA / NIH / DHF / MRC / ANH+MRC / HSFC+AHS / BHF
Fixed Dichotomy	Able to Return to Work <i>(mRS 0-1 vs 2-6)</i>	NINDS-tPA Part 1 / NINDS-tPA Part 2 / ECASS-3 / SYNTHESIS Expansion / EXTEND	<b>5</b>	FDA / EMA / IMA / NIH
	Able to Live Alone <i>(mRS 0-2 vs 3-6)</i>	ECASS-II / PROACT II / MELT / IMS 3 / TREVO 2 / THRACE / PISTE / Penumbra Separator 3D / COMPASS / ARISE II / ESCAPE-NA1 / TIGER	<b>12</b>	FDA / NIH / DGOS / NIHR-HTA / MHLW / CIHR
	Able to Ambulate <i>(mRS 0-3 vs 4-6)</i>	DECIMAL / HAMLET / DESTINY / MISTIE / MISTIE III / CLEAR III / ATACH II	<b>7</b>	FDA / NIH / DGOS / NHF
Weighted Ordinal	Reduced Disability Degree <i>(UW-mRS)</i>	DAWN / MOST / TESLA	<b>3</b>	FDA / NIH

FDA: Food and Drug Administration; EMA: European Medicines Agency; IMA: Italian Medicines Agency

NIH: National Institutes of Health (USA); ANH+MRC: Australian National Health+Medical Research Council; BHF: British Heart Foundation; CIHR: Canadian Institutes for Health Research; DGOS: Direction Générale de l'Offre de Soins (France); DHF: Dutch Heart Foundation (Netherlands); HSFC+AHS: Heart and Stroke Foundation of Canada and Alberta Health Services; NHF: Netherlands Heart Foundation (Netherlands); MHLW: Ministry of Health, Labor and Welfare (Japan); MRC: Medical Research Council (UK); NIHR-HTA: National Institute of Health Research - Health Technology Assessment programme (UK);

\*The following trials analyzed the mRS in multiple ways without prespecifying one way as the primary/lead, so are not included in this table: SWIFT PRIME / ASTER / ASTER 2



# mRS Minimal Clinically Important Differences

Analysis Mode	MCID Determination Methods	MCID for Treatment Group Differences
Fixed Dichotomy (e.g. mRS 0–1 or 0–2)	<ul style="list-style-type: none"><li>• Anchor-based<ul style="list-style-type: none"><li>• Survey of expert clinicians<sup>1</sup></li></ul></li><li>• Practice-based<ul style="list-style-type: none"><li>• US national practice guidelines decision-making<sup>2</sup></li></ul></li></ul>	Rate difference of 1.3%
Ordinal mRS	<ul style="list-style-type: none"><li>• Anchor-based<ul style="list-style-type: none"><li>• Survey of expert clinicians<sup>1</sup></li></ul></li><li>• Practice-based<ul style="list-style-type: none"><li>• US national practice guidelines decision-making<sup>2,3</sup></li></ul></li></ul>	mRS means difference of 0.12
UW-mRS	<ul style="list-style-type: none"><li>• Anchor-based<ul style="list-style-type: none"><li>• Smallest change perceived as beneficial by patients <sup>4,5</sup></li></ul></li></ul>	Utility value of 0.02–0.03

<sup>1</sup>Cranston et al, *Stroke* 2017; <sup>2</sup>Powers et al, *Stroke* 2019; <sup>3</sup>Chaisinankul et al, *Stroke* 2015; <sup>4</sup>Kaplan, *Chronic Obstr Pulm Dis* 2005; <sup>5</sup>Halme et al, *Value Health* 2015

# Acute Stroke NIH Stroke Scale

# NIHSS

- ▶ Most common measure of degree of neurologic deficit
- ▶ 13 items, 7 domains
  - LOC, gaze, vision, strength, coordination, sensation, language, articulation, hemineglect
- ▶ Score severity interpretation
  - Range 0–42
    - Mild: 0–4
    - Moderate: 5–15
    - Severe: 16–42

1a. Level of consciousness	0 = Alert; keenly responsive 1 = Not alert, but arousable by minor stimulation 2 = Not alert; requires repeated stimulation 3 = Unresponsive or responds only with reflex
1b. Level of consciousness questions:	0 = Both answers correct
What is the month?	1 = Answers 1 question correctly
What is your age?	2 = Answers 2 questions correctly
1c. Level of consciousness commands:	0 = Performs both tasks correctly
Open and close your eyes	1 = Performs 1 task correctly
Grip and release your hand	2 = Performs neither task correctly
2. Best gaze	0 = Normal 1 = Partial gaze palsy 2 = Forced deviation
3. Visual	0 = No visual loss 1 = Partial hemianopia 2 = Complete hemianopia 3 = Bilateral hemianopia
4. Facial palsy	0 = Normal symmetric movements 1 = Minor paralysis 2 = Partial paralysis 3 = Complete paralysis of 1 or both sides
5. Motor arm	0 = No drift
5a. Left arm	1 = Drift
5b. Right arm	2 = Some effort against gravity 3 = No effort against gravity; limb falls 4 = No movement
6. Motor leg	0 = No drift
6a. Left leg	1 = Drift
6b. Right leg	2 = Some effort against gravity 3 = No effort against gravity 4 = No movement
7. Limb ataxia	0 = Absent 1 = Present in 1 limb 2 = Present in 2 limbs
8. Sensory	0 = Normal; no sensory loss 1 = Mild-to-moderate sensory loss 2 = Severe to total sensory loss
9. Best language	0 = No aphasia; normal 1 = Mild to moderate aphasia 2 = Severe aphasia 3 = Mute, global aphasia
10. Dysarthria	0 = Normal 1 = Mild to moderate dysarthria 2 = Severe dysarthria
11. Extinction and inattention	0 = No abnormality 1 = Visual, tactile, auditory, spatial, or personal inattention 2 = Profound hemi-inattention or extinction
Total score = 0–42	

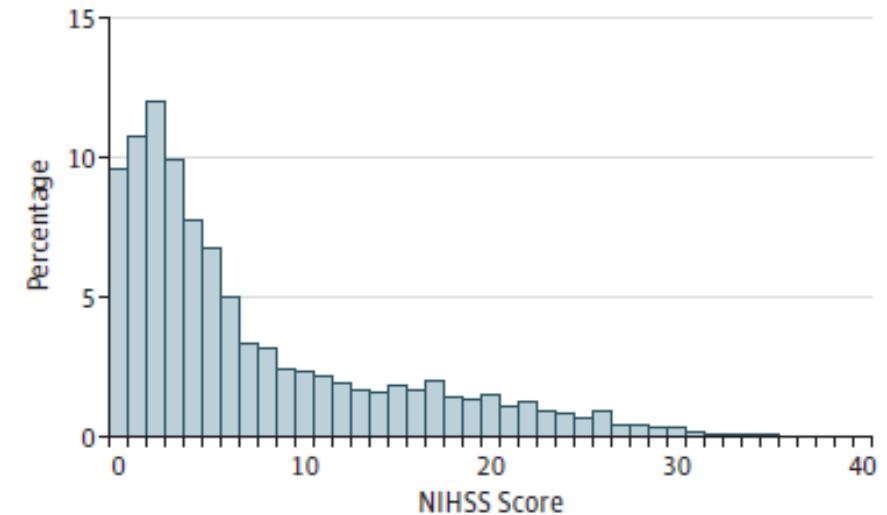
–Brott et al, Stroke 1989

# NIHSS

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- ▶ Score severity interpretation
  - Range 0–42
    - Mild: 0–4
    - Moderate: 5–15
    - Severe: 16–42
- ▶ Presenting scores in practice
  - All patients: median 4
  - IV thrombolysis pt: median 9–12
  - Endovascular thrombectomy pts: median 16–17

1a. Level of consciousness	0 = Alert; keenly responsive
	1 = Not alert, but arousable by minor stimulation
	2 = Not alert; requires repeated stimulation
	3 = Unresponsive or responds only with reflex

**Figure 1. Distribution of Administratively Recorded National Institutes of Health Stroke Scale (NIHSS) Scores in Ischemic Stroke Hospitalizations in US National Inpatient Sample**



	2 = Present in 2 limbs
8. Sensory	0 = Normal; no sensory loss
	1 = Mild-to-moderate sensory loss
	2 = Severe to total sensory loss
9. Best language	0 = No aphasia; normal
	1 = Mild to moderate aphasia
	2 = Severe aphasia
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–Brott et al, Stroke 1989

–Saber+Saver, JAMA Neurol 2020

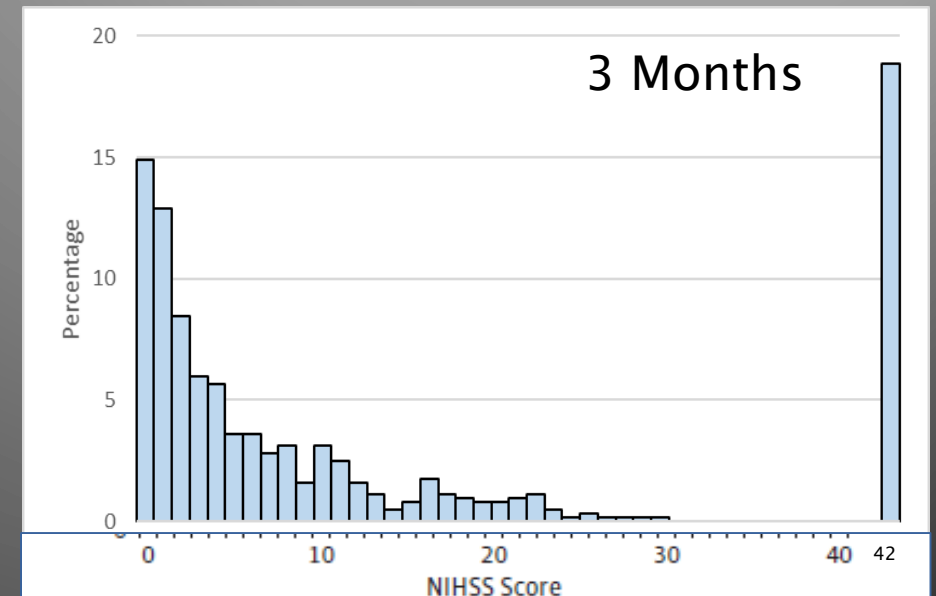
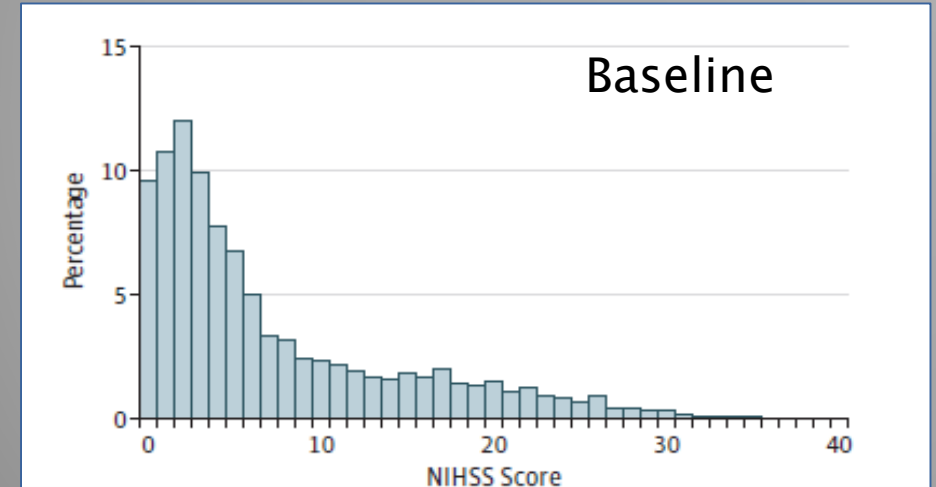
# Uses of NIHSS in Acute Ischemic Stroke

- ▶ Measure presenting severity
  - Widely accepted



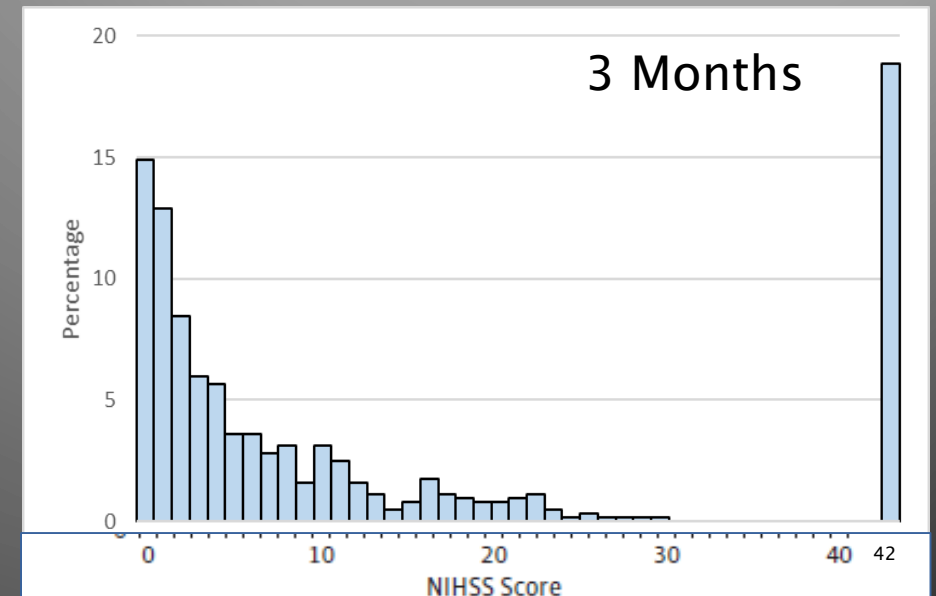
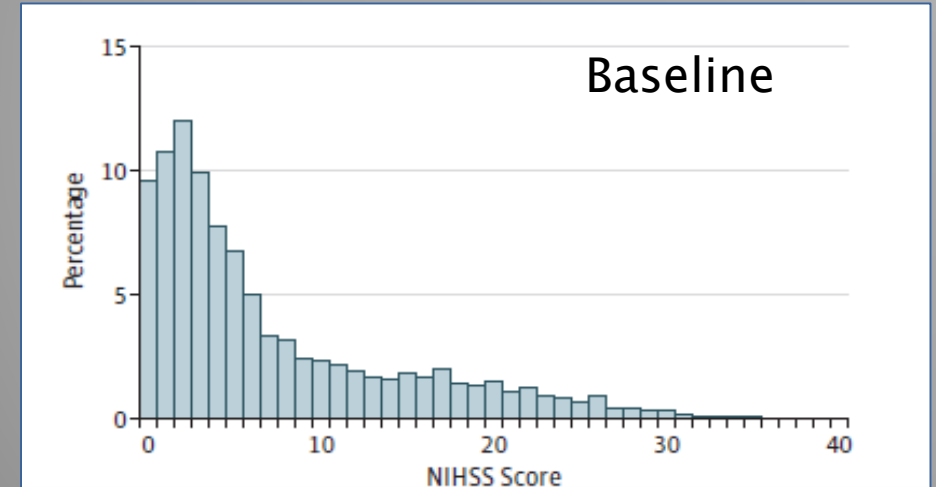
# Uses of NIHSS in Acute Ischemic Stroke

- ▶ Measure presenting severity
  - Widely accepted
- ▶ Measure long-term (eg 3m) outcome
  - Generally avoided
    - Assesses deficits rather than ability to function in the world
    - Point changes in different domains not comparable
      - E.g. weakness vs sensation
    - Highly non-linear
      - Presenting – Skewed left
      - 3 Month – Skewed bimodal



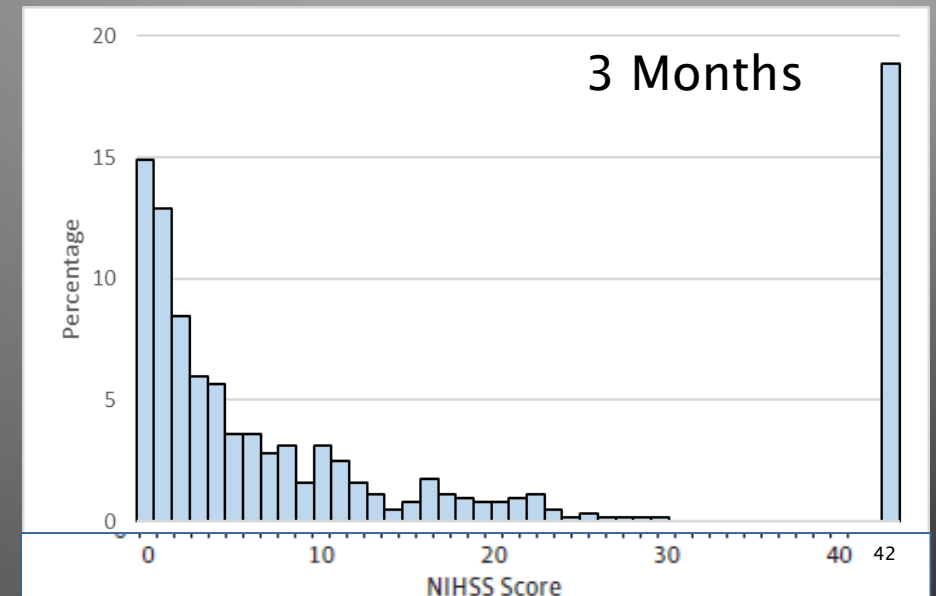
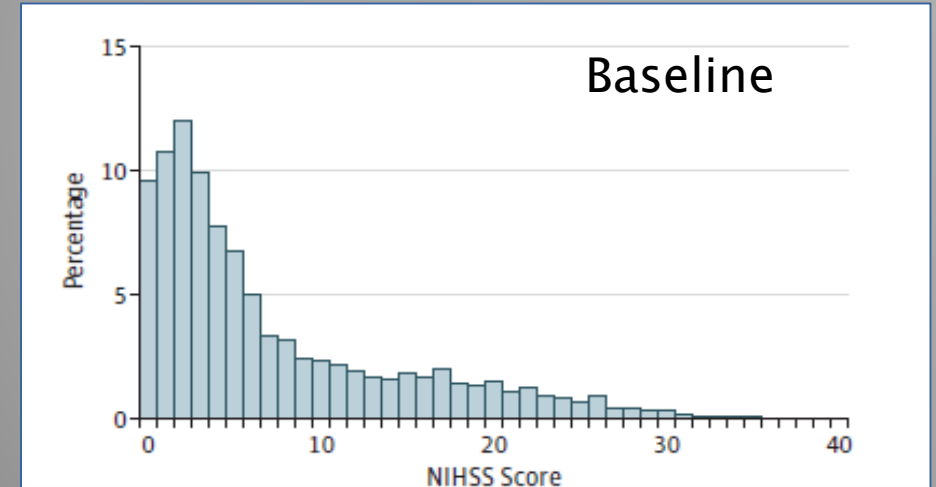
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  - Useful – correlates w/ 3m mRS
    - Change BL to 24h, BL to 72h, abs or %



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      - 3 Month – Skewed bimodal
- ▶ Measure early tx response
  - Useful – correlates w/ 3m mRS
    - Change BL to 24h, BL to 72h, abs or %
    - Also useful – mRS at discharge



# NIHSS Minimally Clinically Important Differences\*

Baseline NIHSS	MCID
0–4	1
5–10	2
11–42	4

*\*JLS Estimate*

# Acute Stroke Health Related Quality of Life



# Health-Related Quality of Life

## ▶ Generic

- Brief
  - EQ-5D-5L
  - NIH PROMIS 10
- Extended
  - SF-36

## ▶ Stroke-Specific

- Stroke Impact Scale
  - SIS 64 – All domains
  - SIS 16 – Physical function
- Stroke-Specific QoL Scale (SS-QoL)

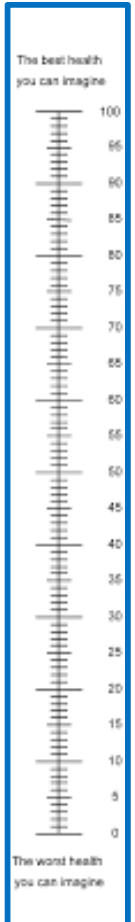


# European QoL 5 Domain 5 Level EQ-5D-5L

- ▶ Patient-reported outcome
  - 5 domains, 1 item each
    - Mobility, Self-Care, Usual Activities, Pain, Mood
    - Likert scales of magnitude of problems – 5 levels
  - Health visual analog scale
- ▶ Maps to health utility values
- ▶ Can use to generate QALYs
  - Cost effectiveness
- ▶ MCID 0.03

Under each heading, please tick the ONE box that best describes your health TODAY

<b>MOBILITY</b>	
I have no problems in walking about	<input type="checkbox"/>
I have slight problems in walking about	<input type="checkbox"/>
I have moderate problems in walking about	<input type="checkbox"/>
I have severe problems in walking about	<input type="checkbox"/>
I am unable to walk about	<input type="checkbox"/>
<b>SELF-CARE</b>	
I have no problems washing or dressing myself	<input type="checkbox"/>
I have slight problems washing or dressing myself	<input type="checkbox"/>
I have moderate problems washing or dressing myself	<input type="checkbox"/>
I have severe problems washing or dressing myself	<input type="checkbox"/>
I am unable to wash or dress myself	<input type="checkbox"/>
<b>USUAL ACTIVITIES</b> (e.g. work, study, housework, family or leisure activities)	
I have no problems doing my usual activities	<input type="checkbox"/>
I have slight problems doing my usual activities	<input type="checkbox"/>
I have moderate problems doing my usual activities	<input type="checkbox"/>
I have severe problems doing my usual activities	<input type="checkbox"/>
I am unable to do my usual activities	<input type="checkbox"/>
<b>PAIN / DISCOMFORT</b>	
I have no pain or discomfort	<input type="checkbox"/>
I have slight pain or discomfort	<input type="checkbox"/>
I have moderate pain or discomfort	<input type="checkbox"/>
I have severe pain or discomfort	<input type="checkbox"/>
I have extreme pain or discomfort	<input type="checkbox"/>
<b>ANXIETY / DEPRESSION</b>	
I am not anxious or depressed	<input type="checkbox"/>
I am slightly anxious or depressed	<input type="checkbox"/>
I am moderately anxious or depressed	<input type="checkbox"/>
I am severely anxious or depressed	<input type="checkbox"/>
I am extremely anxious or depressed	<input type="checkbox"/>



–Golicki et al, Qual Lif Res 2015; de Graaf et al, Clin Rehab, 2020; Kaplan, Chronic Obstr Pulm Dis 2005

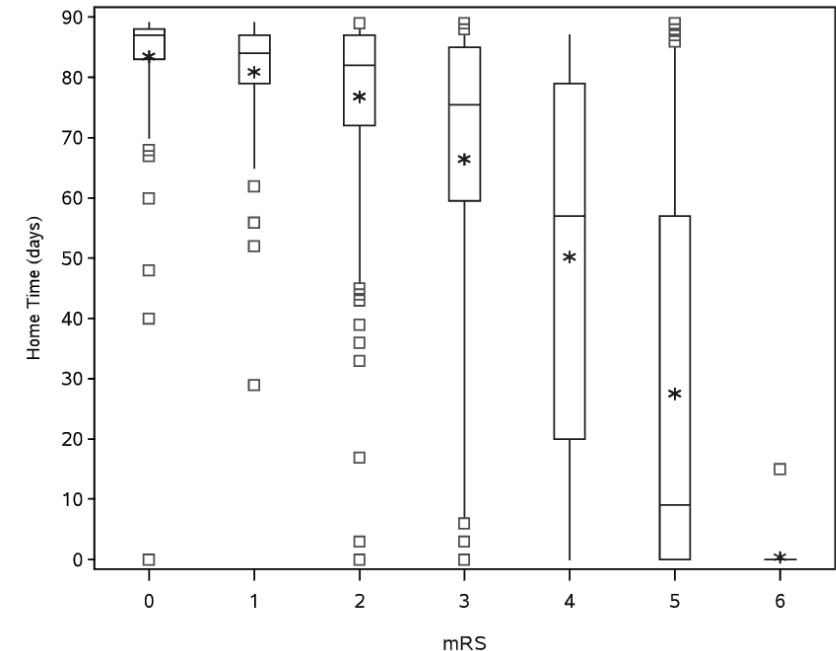
# Acute Stroke Administrative Measures

# Administrative Claims Data Outcomes

- ▶ Discharge destination
  - Ordinal 4 levels
    - Home/Inpatient Rehabilitation/Skilled Nursing Facility/Hospice-Death
  - Dichotomized
    - Home vs Other
      - Approximates mRS 0-1 vs 2-6
    - Home or Inpt Rehab vs Other
      - Approximates mRS 0-2 vs 3-6

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- ▶ Home-time
  - Days not in a facility (Acute hosp, IRF, SNF)
    - 90 days (30 days, 1 year)
    - CMS as payor has information on all sites
    - Maps well to mRS

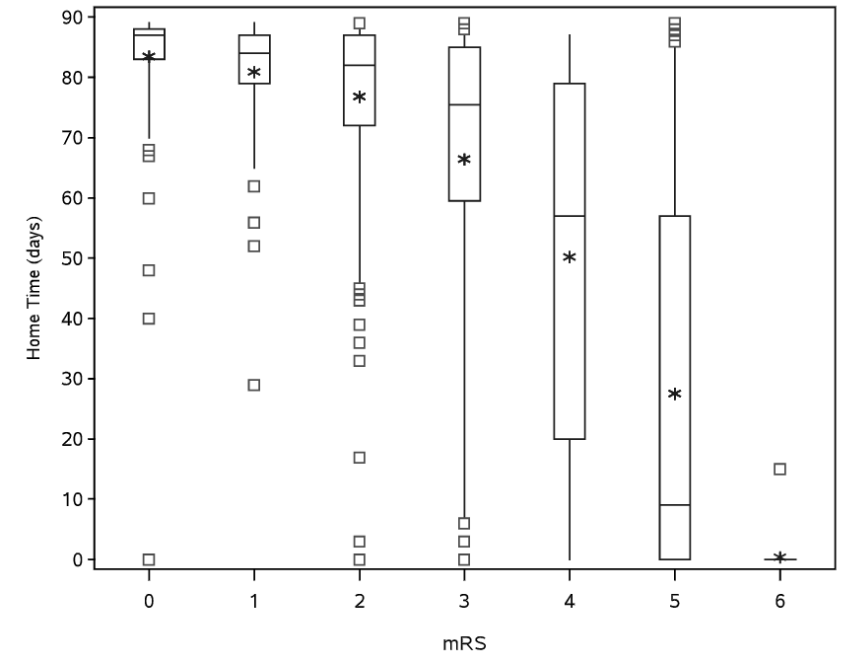


*Box plot of 90d home-time vs 90d modified Rankin Scale in 815 CMS beneficiaries*

*For mRS 0-2: c index 0.84*

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  - Confounded by social support, non-medical determinants
  - Correlates poorly with 3 month functional outcomes

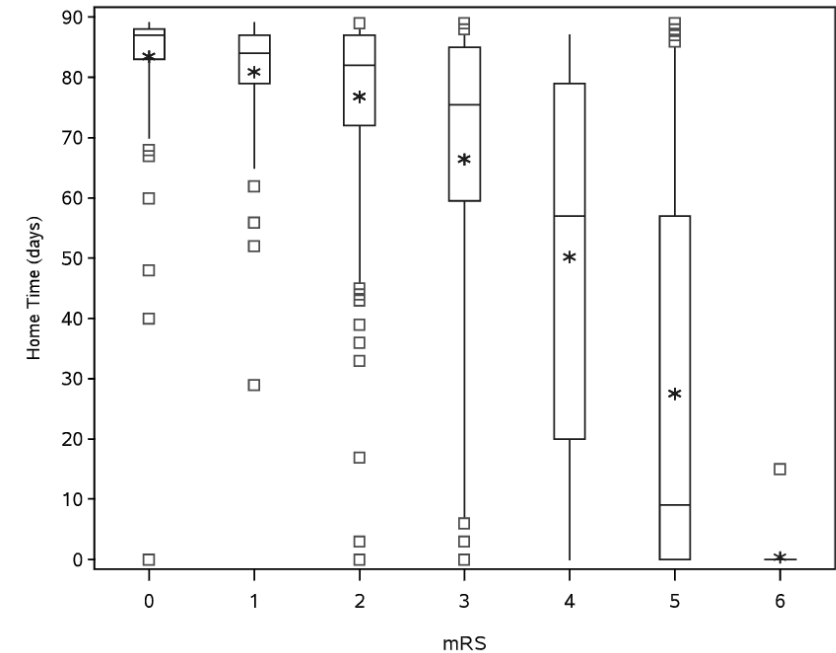


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  - Correlates poorly with 3 month functional outcomes
- ▶ (Potentially in future – Discharge modified Rankin Scale
  - Can be reliably scored
  - Already being documented in >80% of patients
  - Would require new administrative field)



*Box plot of 90d home-time vs 90d modified Rankin Scale in 815 CMS beneficiaries*

*For mRS 0–2: c index 0.84*



# Stroke Recovery Outcome Measures

# Features of Stroke Recovery Measures

- ▶ Importance of domain-specific measures
  - Therapies are domain target
    - Arm weakness–function/leg weakness–walking language/memory/vision/sensation/hemispatial attention, etc
- ▶ Measures of functional change
  - Somewhat stable/stable baseline
    - Subacute (3d–6m) – “proportional recovery rule” in controls
    - Chronic (>1y) – no major change in controls
  - Analytic approaches
    - Change scores, median/mean
    - Percentile change, median, mean
    - Proportion of patients with >MCID additional improvement

*--Cramer et al, Stroke 2007; Kwakkel et al, Neurorehab Neural Rep 2017; Balkaya et al, JCBFM 2019; Wallace et al, Int J Stroke 2019*

Domain Examples	Clinician– Rated/Examined	Patient–Reported Outcome	Functional Testing
Arm+Hand Function	<ul style="list-style-type: none"> <li>Fugl–Myer UE Motor</li> </ul>	<ul style="list-style-type: none"> <li>SIS Hand Domain</li> </ul>	<ul style="list-style-type: none"> <li>Action Research Arm Test</li> <li>Box and blocks</li> <li>Nine hole peg</li> <li>Hand dynamometry</li> </ul>
Leg Function	<ul style="list-style-type: none"> <li>Fugl–Myer LE Motor</li> </ul>	<ul style="list-style-type: none"> <li>SIS Mobility</li> </ul>	<ul style="list-style-type: none"> <li>10 meter walking speed</li> </ul>
Language	<ul style="list-style-type: none"> <li>Western Aphasia Battery</li> </ul>	<ul style="list-style-type: none"> <li>Stroke and Aphasia Quality of Life Scale (SAQOL39)</li> <li>SIS Communication</li> </ul>	<ul style="list-style-type: none"> <li>The Scenario Test</li> </ul>

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Standardized Measurement of Sensorimotor Recovery in Stroke Trials: Consensus-Based Core Recommendations from the Stroke Recovery and Rehabilitation Roundtable\*

*Kwakkel et al, Neurorehab Neural Rep 2017*

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A core outcome set for aphasia treatment research: The ROMA consensus statement

*Wallace et al, Int J Stroke 2019*



# Fugl-Myer Upper Extremity Motor

- ▶ Detailed assessment
  - Wrist movement
  - Hand movement
  - Shoulder-elbow movement
  - Coordination + speed
- ▶ 33 movements/tasks
  - Each rated unable/partial/full
  - Total 66 points
- ▶ Takes 15 minutes to administer

<b>B. WRIST</b> support may be provided at the elbow to take or hold the starting position, no support at wrist, check the passive range of motion prior testing		none	partial	full
<b>Stability at 15° dorsiflexion</b> elbow at 90°, forearm pronated shoulder at 0°	less than 15° active dorsiflexion dorsiflexion 15°, no resistance tolerated maintains dorsiflexion against resistance	0	1	2
<b>Repeated dorsiflexion / volar flexion</b> elbow at 90°, forearm pronated shoulder at 0°, slight finger flexion	cannot perform volitionally limited active range of motion full active range of motion, smoothly	0	1	2
<b>Stability at 15° dorsiflexion</b> elbow at 0°, forearm pronated slight shoulder flexion/abduction	less than 15° active dorsiflexion dorsiflexion 15°, no resistance tolerated maintains dorsiflexion against resistance	0	1	2
<b>Repeated dorsiflexion / volar flexion</b> elbow at 0°, forearm pronated slight shoulder flexion/abduction	cannot perform volitionally limited active range of motion full active range of motion, smoothly	0	1	2
<b>Circumduction</b> elbow at 90°, forearm pronated shoulder at 0°	cannot perform volitionally jerky movement or incomplete complete and smooth circumduction	0	1	2
<b>Total B</b> (max 10)				

<b>C. HAND</b> support may be provided at the elbow to keep 90° flexion, no support at the wrist, compare with unaffected hand, the objects are interposed, active grasp		none	partial	full
<b>Mass flexion</b> from full active or passive extension		0	1	2
<b>Mass extension</b> from full active or passive flexion		0	1	2
<b>GRASP</b>				
<b>a. Hook grasp</b> flexion in PIP and DIP (digits II-V), extension in MCP II-V	cannot be performed can hold position but weak maintains position against resistance	0	1	2
<b>b. Thumb adduction</b> 1-st CMC, MCP, IP at 0°, scrap of paper between thumb and 2-nd MCP joint	cannot be performed can hold paper but not against tug can hold paper against a tug	0	1	2
<b>c. Pincer grasp, opposition</b> pulp of the thumb against the pulp of 2-nd finger, pencil, tug upward	cannot be performed can hold pencil but not against tug can hold pencil against a tug	0	1	2
<b>d. Cylinder grasp</b> cylinder shaped object (small can) tug upward, opposition of thumb and fingers	cannot be performed can hold cylinder but not against tug can hold cylinder against a tug	0	1	2
<b>e. Spherical grasp</b> fingers in abduction/flexion, thumb opposed, tennis ball, tug away	cannot be performed can hold ball but not against tug can hold ball against a tug	0	1	2
<b>Total C</b> (max 14)				



# Action Research Arm Test

- ▶ Task-based, 19 item observational measure
- ▶ Four subscales
  - Grasp
  - Grip
  - Pinch
  - Gross movement
- ▶ Equipment
  - Wooden blocks of various sizes
  - Washer and bolt
  - 2 glasses
  - Sharpening stone
  - Marbles
  - Ball bearings
  - Ball (cricket size)
  - Metal tubes
- ▶ 10 minutes to administer



# Stroke Impact Scale – Hand Domain

- ▶ Daily life hand–tasks
  - 5 items
  - Rate difficulty for each on 5 level Likert scale from no difficulties to can't do at all
- ▶ Total score 5–25
- ▶ Patient–reported outcome
  - Proxy if pt unable to report

Not difficult at all	A little difficult	Somewhat difficult	Very difficult	Could not do at all
5	4	3	2	1

**7. In the past 2 weeks, how difficult was it to use your hand that was most affected by your stroke to...**

a. Carry heavy objects (e.g. bag of groceries)?

b. Turn a doorknob?

c. Open a can or jar?

d. Tie a shoe lace?

e. Pick up a dime?

# Stroke Prevention Outcome Measures

# Assessing First/Recurrent Stroke in Clinical Trials

## ▶ Stroke Detection

- Non-interventional neurologist assessor
  - Avoid bias of performing surgeon/interventionalist
  - Neurologic history
  - Neurologic examination
- Imaging
  - Confirm symptomatic infarcts
  - Detect covert cerebral infarcts
- Stroke symptom questionnaire
  - Detects events that may have resolved after days/weeks before return visit
  - Avoids “ascertainment bias”
  - Triggers further history, exam, imaging
  - Questionnaire for Verifying Stroke-Free Status (QVSS)
    - 2 “Were told” items – stroke/TIA
    - 6 “Suddens” items
      - Weakness, numbness, visual loss one-both eyes, visual loss-half of space, trouble speaking, trouble understanding
- Event adjudication
  - Central CEC preferable to site judgment

## ▶ Stroke Severity

- Neurologic deficit – NIHSS
- Global disability – mRS at 3 months

### 8-Item Questionnaire for Verifying Stroke Free Status with Pictograms.

Have you ever been told by a doctor that you had a stroke?  
Yes ☐ No ☐ Don't know ☐

Have you ever been told by a doctor that you had a mild stroke or almost had a stroke (TIA)?  
Yes ☐ No ☐ Don't know ☐

Have you ever had sudden painless weakness on one side of your body?  
Yes ☐ No ☐ Don't know ☐

Have you ever had sudden numbness or a dead feeling on one side of your body?  
Yes ☐ No ☐ Don't know ☐

Have you ever had sudden painless loss of vision in one or both eyes?  
Yes ☐ No ☐ Don't know ☐

Have you ever suddenly lost one half of your vision?  
Yes ☐ No ☐ Don't know ☐

Have you ever suddenly lost the ability to understand what people are saying?  
Yes ☐ No ☐ Don't know ☐

Have you ever suddenly lost the ability to express yourself verbally or in writing?  
Yes ☐ No ☐ Don't know ☐



# Administrative Measures To Detect First/Recurrent Stroke / Vascular Events

- ▶ Cerebrovascular event admissions/observations
  - Admission for ischemic stroke
  - Admission for hemorrhagic stroke
  - Admission/Observation for TIA
  - Sensitivity + Specificity
    - High for moderate–severe events
    - Moderate for mild events
- ▶ Other vascular event admissions
  - Myocardial infarction
  - Vascular death
  - Composite nonfatal stroke, nonfatal MI, vascular death

