Which outcomes to consider?

- Clinical outcome assessment (21st Century Cures Act-FDA)

  – Measurement of a patient's symptoms, overall mental state, or the effects of a disease or condition on how the patient functions

  – Includes a patient-reported outcome

- Non clinical outcome

  – Biomarker

  – Digital measures of Health

  – …

What is a clinically useful instrument?

Manta et al, *Digit Biomark* 2020

- Need to be meaningful for patients

Meaningful Aspect of Health (MAH)

Aspect of a disease that a patient
- does not want to become worse
- wants to improve
- wants to prevent

What is a clinically useful instrument?

- Need to be meaningful for patients

Meaningful Aspect of Health (MAH)

Ability to perform Ambulatory activities

What is a clinically useful instrument?

Manta et al, *Digit Biomark* 2020

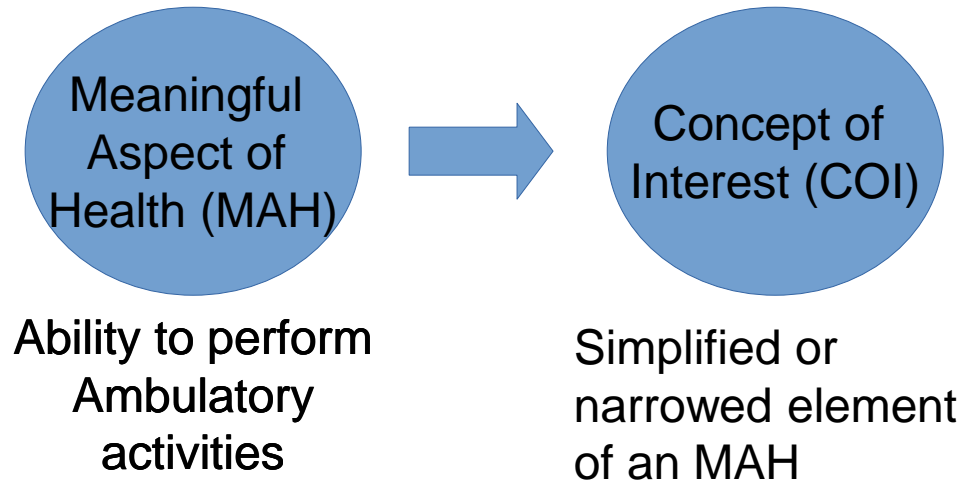- Need to be meaningful for patients

Meaningful Aspect of Health (MAH) → **Concept of Interest (COI)**

Ability to perform Ambulatory activities

Simplified or narrowed element of an MAH

What is a clinically useful instrument?

- Need to be meaningful for patients

Meaningful Aspect of Health (MAH) → Concept of Interest (COI)

Ability to perform Ambulatory activities
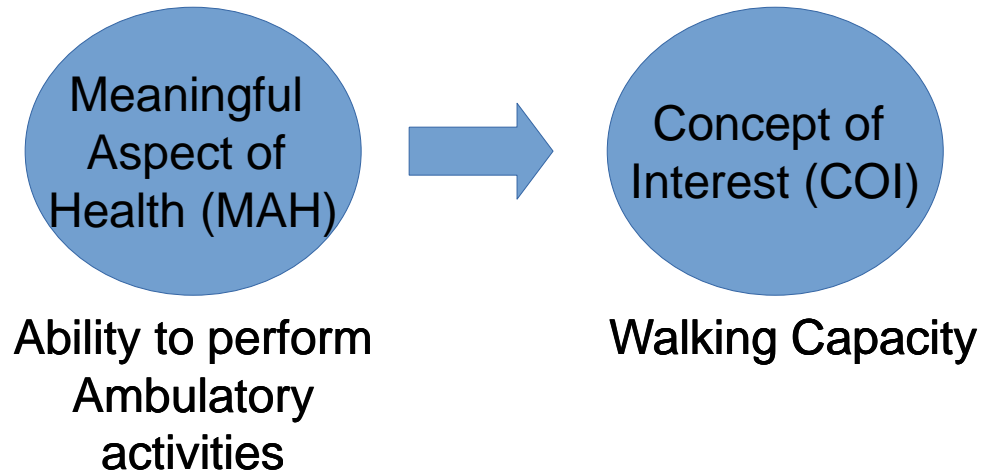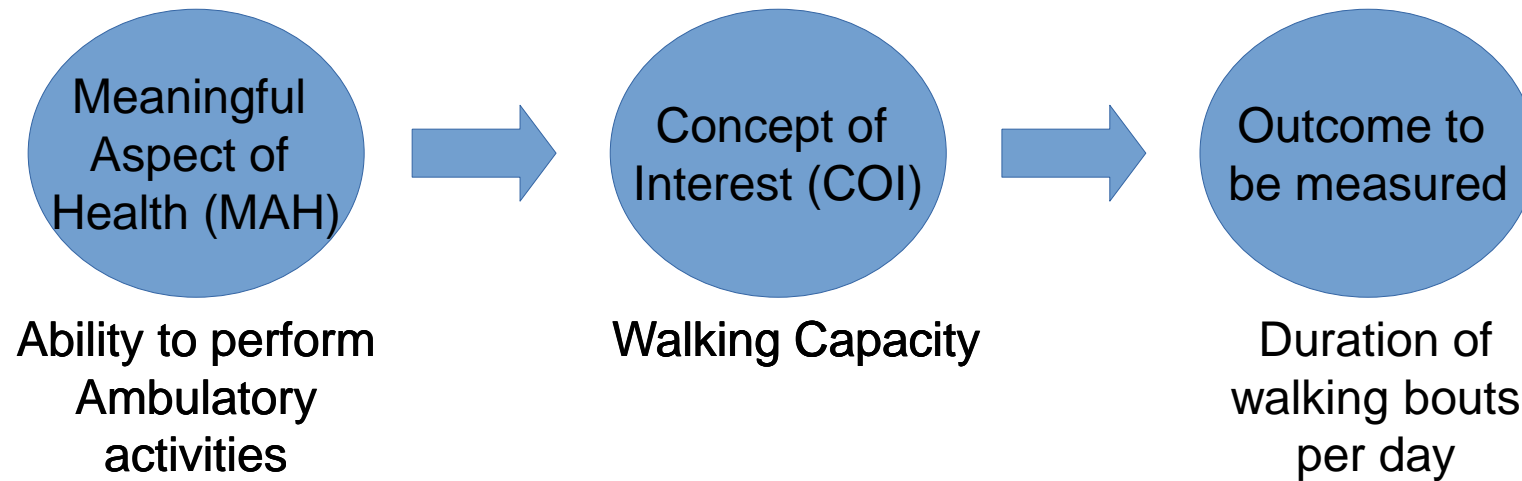
Walking Capacity

What is a clinically useful instrument?

Manta et al, *Digit Biomark* 2020

- Need to be meaningful for patients

Meaningful Aspect of Health (MAH)	→	Concept of Interest (COI)	→	Outcome to be measured
Ability to perform Ambulatory activities		Walking Capacity		Duration of walking bouts per day

What is a clinically useful instrument?

- Need to be meaningful for patients

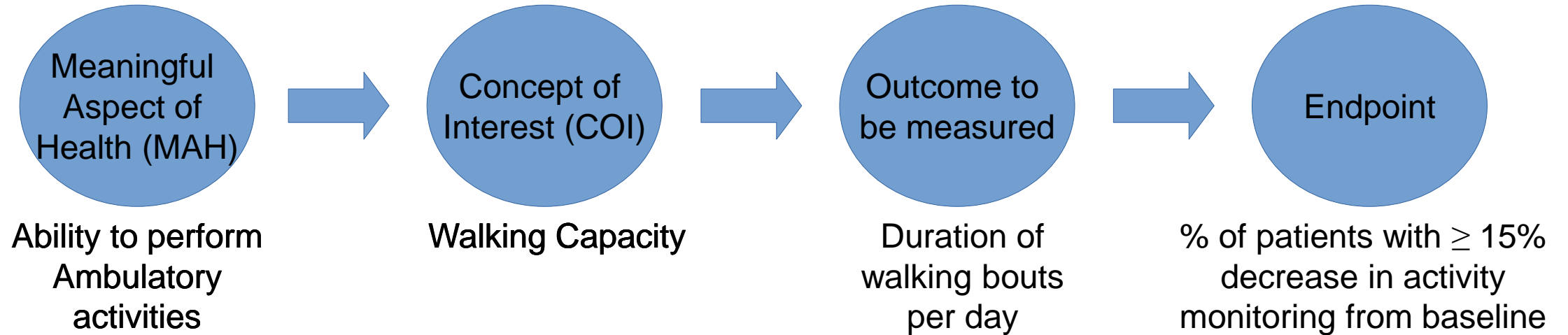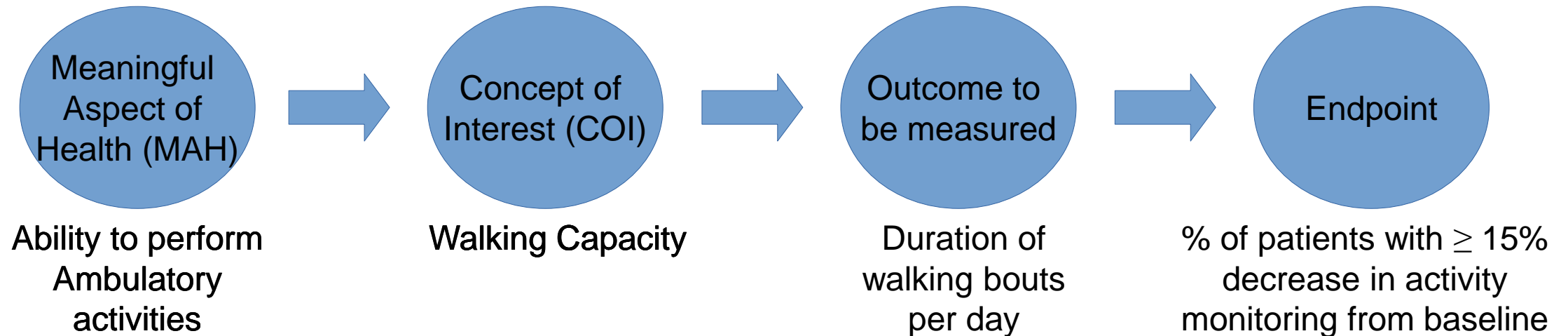| Meaningful Aspect of Health (MAH)	→	Concept of Interest (COI)	→	Outcome to be measured	→	Endpoint
Ability to perform Ambulatory activities		Walking Capacity		Duration of walking bouts per day		% of patients with $\geq$ 15% decrease in activity monitoring from baseline

What is a clinically useful instrument?
Manta et al, *Digit Biomark* 2020

- Need to be meaningful for patients

Meaningful Aspect of Health (MAH) → Concept of Interest (COI) → Outcome to be measured → Endpoint

| Ability to perform Ambulatory activities | Walking Capacity | Duration of walking bouts per day | % of patients with $\geq$ 15% decrease in activity monitoring from baseline |

- Must have demonstrate psychometric properties

    - Validity: degree to which evidence supports the performance of an instrument result for its intended purpose

    - Reliability: how reproducible is the measure?

    - Responsiveness to change

        - Statistical significant change
        - Definition of a minimal change in score considered relevant: Minimal Clinically Important Difference (MCID)

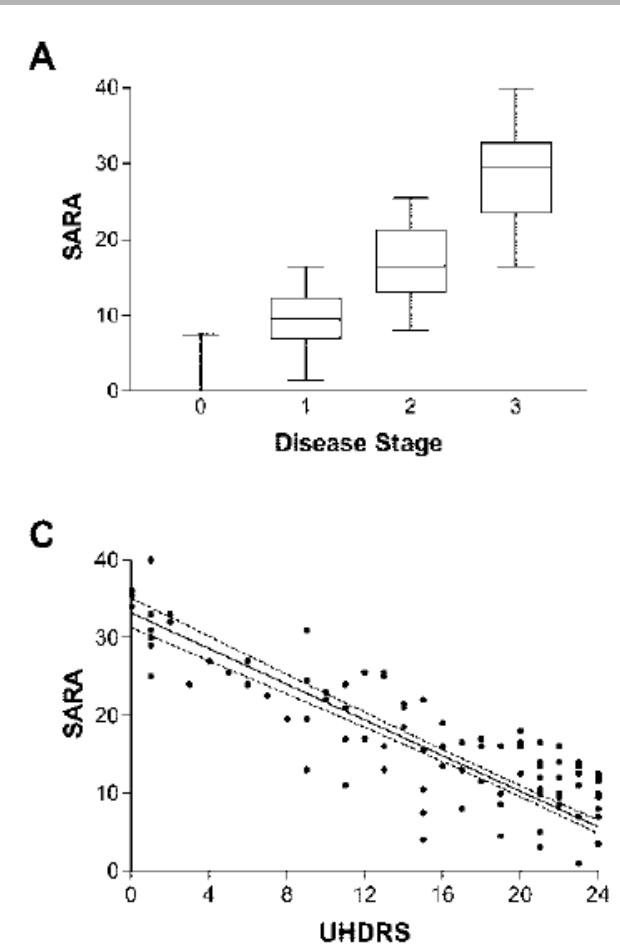# How to define the Minimal Clinically Important Difference (MCID)?

- ## Anchor-based methods

  – Examine the relationship between a measure with another measure of clinical change (the anchor)

  – Anchor can be derived from clinical outcomes or Patient-Reported Outcomes

- ## Distribution-based methods

  – Use statistical properties of the distribution of outcomes scores

- ## Opinion-based methods

  – Based on Delphi methods: consensus between experts

Crosby et al, *J Clin Epidemiol* 2003

Anchor-based methods – Type: Cross-sectional

Method	Instrument evaluated in relation to:	Advantages	Disadvan...
Comparison to disease-related criteria	Disease severity or diagnosis	Disease Staging Disease groups (genotype)	• May n... • Groups... variabl...
Comparison to non disease-related criteria	Impact of life events	• Easy to obtain Stressfull event ...ernal basis for interpretation	• May n... • Groups... variabl... • Relatio...
Preference ratings	Pairwise comparisons of health states	All health states are compared	• May n... • Hypoth... • Time c...
Comparison to known population(s)	Functional or dysfunctional populations	Uses normative information	• Norma... availab... • Amount of change needed not specified

Anchor-based methods – Type: Longitudinal

Method	Instrument evaluated in relation	Advantages	Disadvantages
Global ratings of change	Patients clinicians of impro...		...le
Prognosis of future events	Those experien... not expe... some fu...		...t
Changes in disease related outcome	Changes outcome	outcome measure • Known psychometric properties	precision • Assumes strong Instrument – outcome correlation

Schmitz-Hübsch et al, *Neurology* 2010

Standardized response mean

	Whole sample (n = 171)	PGI: Worse (n = 120)	PGI: Stable (n = 43)
SARA	Converters	0.59	0.21
INAS	0.26	0.33	0.17

Crosby et al, *J Clin Epidemiol* 2003

Distribution-based methods

Method	Calculation	Advantages	Disadvantages
Paired t-statistic	Difference/SE mean change	None	Increases with sample size
Growth curve analysis	Slope/SE slope	• Not limited to pre-test and post-test scores • Uses all of the available data	• Increases with sample size • Requires large sample sizes • Assumes data missing at random
Effect size (ES)	Difference/Pre-test SD	• Standardized units • Benchmarks for in • Independent of sa	• Decreases with increased baseline ...sample ...variability of ...mong samples
Standardized response mean (SRM)	Difference/SD of change	• Standardized units • Independent of sa • Based on variability of change	...of effectiveness of

Chan et al, *Mvt Disord* 2011

Scale	Effect size	Standardized response mean
CCFS	0.117	0.320
SARA	0.140	0.411

SD: standard deviation
SE: standard error

Crosby et al, *J Clin Epidemiol* 2003

Distribution-based methods

Method	Instrument evaluated in relation to:	Advantages	Disadvantages
Responsiveness statistic	Difference/SD of change in a stable group	• Standardized units • More conservative than effect size • Independent of sample size • Takes into account spurious change due to measurement error	Data on stable subjects frequently not available
Standard error of measurement (SEM)	$\frac{ES}{\sqrt{1-r}}$ where r = reliability measure	• Relatively stable across populations • Takes into account the precision of the measure • Cutoffs based on confidence intervals	Assumes measurement error to be constant across the range of possible scores
Reliable change index	$\frac{difference}{\sqrt{2(SEM)^2}}$	• Relatively stable across populations • Takes into account precision of measure • Cut-offs based on confidence intervals	Assumes measurement error to be constant across the range of possible scores

SD: standard deviation
SE: standard error

Crosby et al, *J Clin Epidemiol* 2003

Conclusions

- Define Meaningful Aspect of Health (MAH) and Concept of Interest (COI) of the outcome to be sure that it is related to a patient meaningful aspect

- Define the Minimal Clinical Important Change (MCID) to be able to interpret changes

- Use combined Anchor and distribution methods