Principles of PRO Measure Development that Apply to Sarcopenia

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PRO MEASURE DEVELOPMENT IN SARCOPENIA

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Outline

- Identify main challenges in reports from patients about their experience with sarcopenia
- Evaluate possible approaches to incorporating PROs in the endpoint strategy for evaluating treatment benefit

Patient-Focused \ Patient-Centered Outcomes

Those outcomes important to patients' survival, function, or feelings as identified or affirmed by patients themselves, or judged to be in patients' best interest by providers and caregivers when patients cannot report for themselves

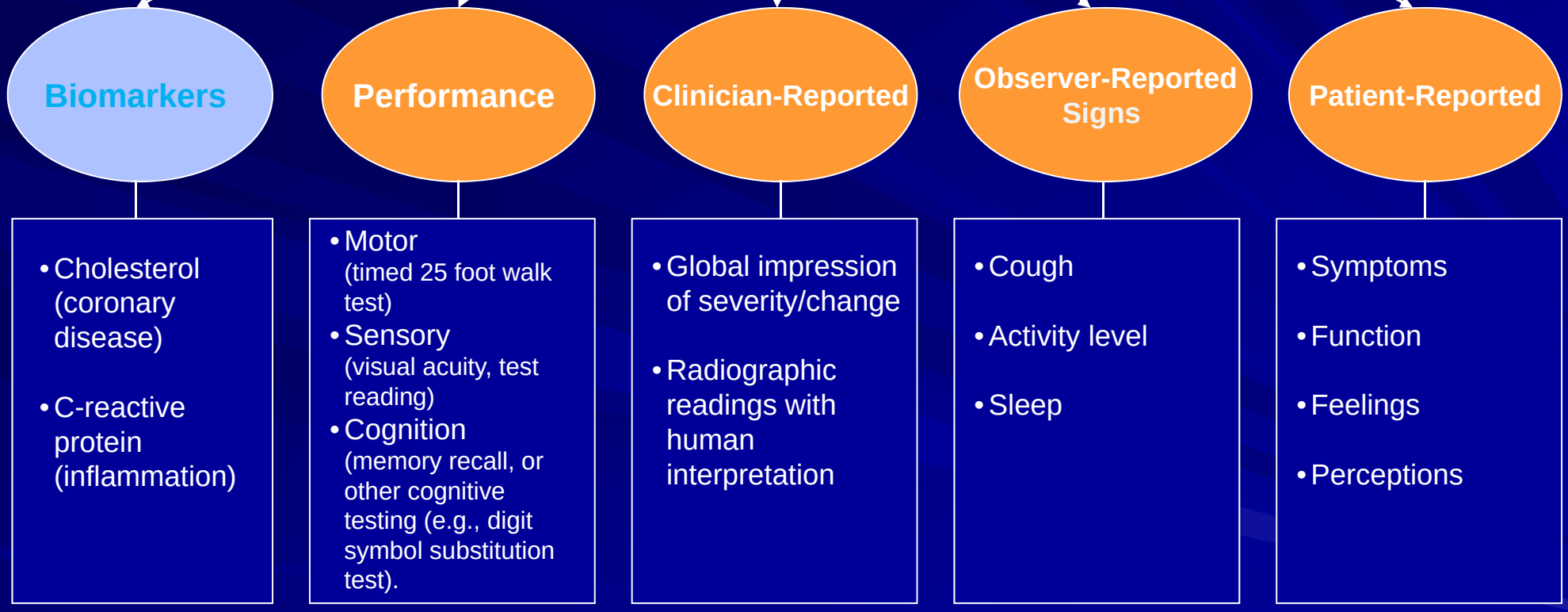
Defining Sarcopenia

Sarcopenia is the loss of muscle quality during aging characterized by a decline in muscle strength that if untreated can lead to weakness, disability, an increased risk of falls and loss of independence (Brotto, 2012)

- Clearly a patient-important issue
- Issues in relating muscle mass to function

Clinical Trial Endpoints and Examples

Orange ovals are Clinical Outcome Assessments
Blue Ovals are Survival and Biomarkers



Survival

Table 2 Possible biomarkers to be used in trials on sarcopenia

	Inclusion–exclusion criteria	Baseline evaluation	End-point assessment
Muscle function			
Physical performance measures	+++	+++	+++
Muscle strength measures	+++	+++	+++
Disability	+++	+++	+++
Muscle mass			
Anthropometry	+	-	-
Bioelectrical impedance analysis	+	+	+
Dual energy X-ray absorptiometry	+++	++	++
Computerized tomography	++	+++	+++
Magnetic resonance imaging	++	+++	+++
Echography	++	++	++
Electrical impedance myography	+	++	++
Mechanisms, biological confounders[a]			
Inflammation	++	++	++
Oxidative damage	++	++	++
Antioxidants	++	++	++
Apoptosis	+	++	++
Nutritional parameters (albumin, hemoglobin, urinary creatinine, etc.)	+++	++	++
Hormones (dehydroepiandrosterone, testosterone, insulin-like growth factor-1, etc.)	++	++	++

Definitions: Clinical Outcome Assessments

- **Clinical outcome assessment (COA):** measurement based on a human assessment (i.e., excluding biomarkers) and "reported" using an instrument by a patient, a clinician, or another observer

  --**Performance task outcome (PerfO):** patient is instructed to perform a defined task and some defined quantification of that performance is the measurement (e.g., distance walked in 6 minutes, number of pictorial symbols correctly matched to a key within a fixed amount of time

  - --**Clinician-reported outcome (ClinRO):** any assessment of the status of a patient's health condition based on clinician observation, reporting and\or interpretation

  - --**Observer-reported outcome (ObsRO)**: An assessment used when person unable to self-report based observable concepts (e.g., signs or behaviors); ObsROs cannot be validly used to directly assess symptoms (e.g., pain) or other unobservable concepts

  - --**Patient-reported outcome (PRO):** measurement based on a report that comes directly from the patient (i.e., study subject) about the status of particular aspects of or events related to a patient's health condition.

Roadmap to **PATIENT-FOCUSED OUTCOME MEASUREMENT** in Clinical Trials

1 Understanding the Disease or Condition

A. Natural history of the disease or condition
- Onset/Duration/Resolution
- Diagnosis
- Pathophysiology
- Range of manifestations

B. Patient subpopulations
- By severity
- By onset
- By comorbidities
- By phenotype

C. Health care environment
- Treatment alternatives
- Clinical care standards
- Health care system perspective

D. Patient/caregiver perspectives
- Definition of treatment benefit
- Benefit-risk tradeoffs
- Impact of disease

2 Conceptualizing Treatment Benefit

A. Identify concept(s) of interest (COI) for meaningful treatment benefit, i.e., How a patient:
- Survives
- Feels (e.g., symptoms)
- Functions

B. Define context of use (COU) for clinical trial:
- Disease/Condition entry criteria
- Clinical trial design
- Endpoint positioning

C. Select clinical outcome assessment (COA) type:
- Patient-Reported Outcome (PRO)
- Observer-Reported Outcome (ObsRO)
- Clinician-Reported Outcome (ClinRO)
- Performance Outcome (motor, sensory, cognition)

3 Selecting/Developing the Outcome Measure

A. Search for existing COA measuring COI in COU:
- Measure exists
- Measure exists but needs to be modified
- No measure exists
- Measure under development

B. Begin COA development
- Document content validity (qualitative or mixed methods research)
- Evaluate cross-sectional measurement properties (reliability and construct validity)
- Create user manual
- Consider submitting to FDA for COA qualification as exploratory endpoint

C. Complete COA development:
- Document longitudinal measurement properties (construct validity, ability to detect change)
- Document guidelines for interpretation of treatment benefit and relationship to claim
- Update user manual
- Submit to FDA for COA qualification as effectiveness endpoint to support claims

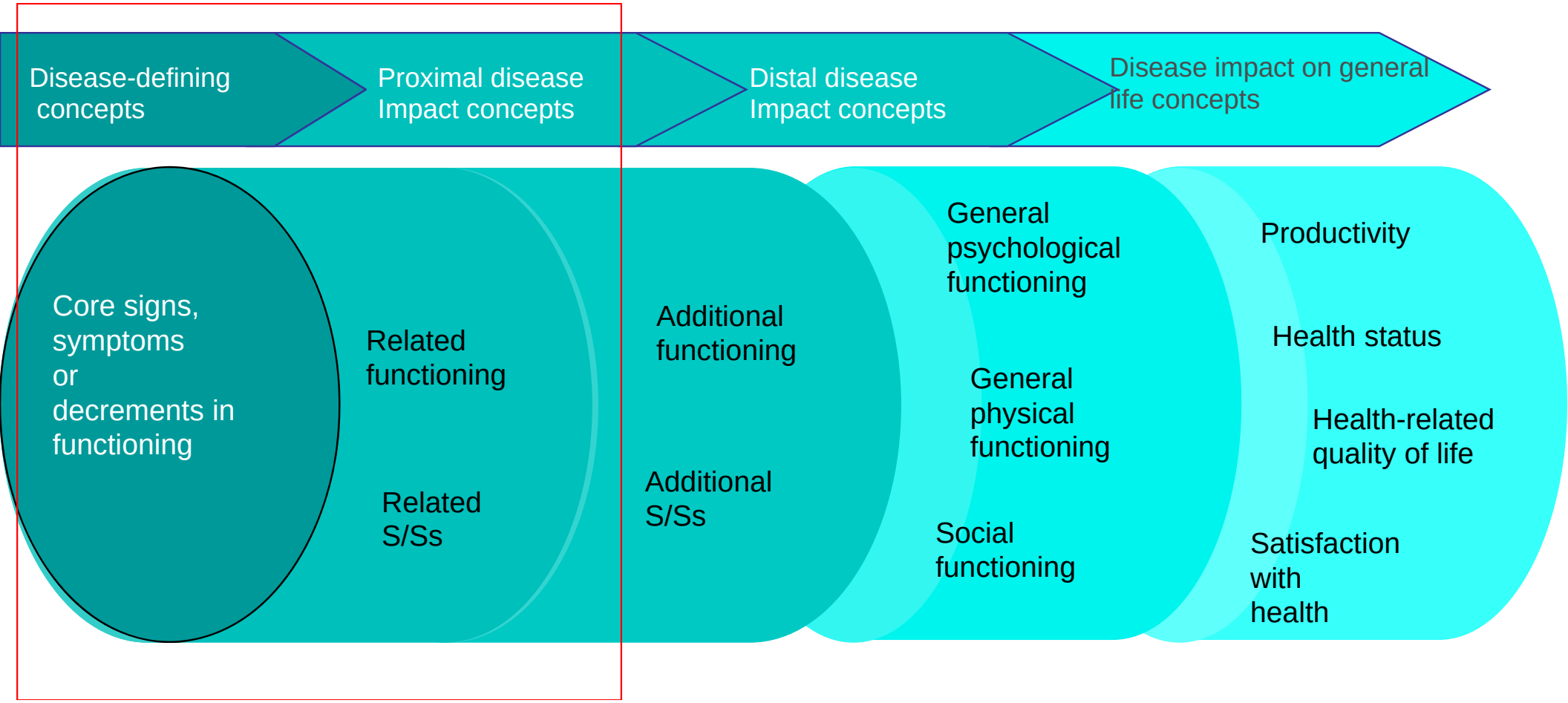
Evidence of Treatment Benefit

- **Direct evidence** of treatment benefit is derived from studies with endpoints that measure survival, or how patients feel and function in daily life.
- **Indirect evidence** of treatment benefit is derived from studies with surrogate endpoints that measure other things that are related to how patients survive, feel or function (e.g., biomarkers)

When is a COA adequate for use in *adequate and well-controlled studies*?

- Regulatory standard: *well-defined and reliable*
  - The concept of interest (COI) is measured validly and reliably in the A&WC study context of use (COU).
  - Within the stated COU, results of assessment can be relied upon to measure the COI and have a specific interpretation and application in drug development, regulatory decision-making, and labeling.
  - For COAs that do not provide evidence of how patients feel or function in daily life, the concept assessed is an adequate replacement assessment for how patients feel or function in daily life.

Concept of Interest
Direct Evidence of Tx Benefit (Proximal to Distal)




Understanding the
Disease or Condition
1

A Good Definition is Important

- Definition → trial patient selection → indication
- The definition of the condition drives the patient selection for clinical trials.
- The indication for a drug is based on the patient population that has been studied.
- The limitations of use of a drug are related, in part, to the limitations of the information that can be obtained from the studied patient population.
- Not everyone who has relatively low muscle mass has a clinical problem.

Toward an Acceptable Definition of Sarcopenia

- A work in progress to find acceptable indirect indicators of muscle mass and muscle strength to define the condition
- Is sarcopenia a “medically recognized disease or condition” with a consensus? Consensus by whom?
- A condition of high importance to people who have it and their loved ones and providers—thus the need is there to evaluate treatment benefit
- What are desirable endpoints and can we achieve them?

Conceptualizing Treatment Benefit 2

Selecting/Developing the Measure

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Selecting/Developing the Measure

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Context of Use: Endpoint Model

An Endpoint Model displays the role and hierarchy of relevant outcome concepts in clinical trials (i.e., all primary and secondary endpoints)

Endpoints		Concepts	COA/Biomarker/Survival
Primary	→	Concept A	OA 1
Secondary with Hierarchy	→	Concept B	OA 2
	→	Concept C	OA 3
	→	Concept D	OA 4
	→	Concept E	OA 5
Exploratory	→	Other concept	Other OA

Possible Endpoint Positioning: Sarcopenia

- Change in selected biomarkers
- Change in Usual Gait Speed (UGS)
- Change in Short Physical Performance Battery
- Change in Sarcopenia-related signs and symptoms
- Change in Sacrcopenia-related Impacts

Patient-Reported Outcomes (PROs): Definition

- A report directly from patients, without interpretation of the response by clinicians or anyone else
- Includes symptoms/signs, function, and quality of life (***QoL or HrQoL NOT equal to symptoms/function***)
- May also include satisfaction with care and adherence but not in regulatory context

Perceived QoL and Symptoms/Function

49. During the past 2 weeks, **I have had pain in the foot (or leg) after going to bed at night…**

All of the time	Most of the time	Much of the time	Some of the time	A Little of the time	Hardly any of the time	None of the time
☐ 6	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1	☐ 0

50. During the past 2 weeks, **pins and needles or numbness in my leg (or foot) have caused me…** *(please check one)*

- ☐ 6 A Very Great Deal of Discomfort or Distress
- ☐ 5 A Great Deal of Discomfort or Distress
- ☐ 4 A Good Deal of Discomfort or Distress
- ☐ 3 A Moderate Amount of Discomfort or Distress
- ☐ 2 Some Discomfort or Distress
- ☐ 1 Very Little Discomfort or Distress
- ☐ 0 No Discomfort or Distress

Development of a New Patient-Reported Outcome Measure in Sarcopenia

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Objective: The objective of this study was to develop a patient-reported outcome (PRO) to assess reduced muscle strength in sarcopenia.

Design: Qualitative research study.

Setting: University of Arkansas for Medical Sciences.

Measurements: Adults aged 55 years and older with sarcopenia (n=12) attended open-ended, concept elicitation interviews to characterize the functional effects of reduced muscle strength on their lives.

The resulting qualitative data were analyzed using a qualitative analysis software program (Atlas.ti [At- las.ti GmbH, Berlin, Germany]) and a common set of codes was developed to summarize the data.

Subsequently, the initial PRO measure was drafted.

Cognitive interviews were then conducted with additional sarcopenia subjects (n 5 12) to refine the measure.

Access to the Measure

Funding for this study was provided by Amgen. C-F.C., S.G. are employed by Amgen and hold stocks in Amgen. W.J.E. and W.D. received funds for recruit- ment of study participants. W.D. received a grant for data collection from Amgen. D.L.P. received honorarias for his consulting services from Amgen. C.J.E., K.A.F., W.J.E., B.R.F., W.D., L.P.F., B.D-S., and D.L.P. provided consulting services to Amgen.

Measure not in the public sector; it remains proprietary

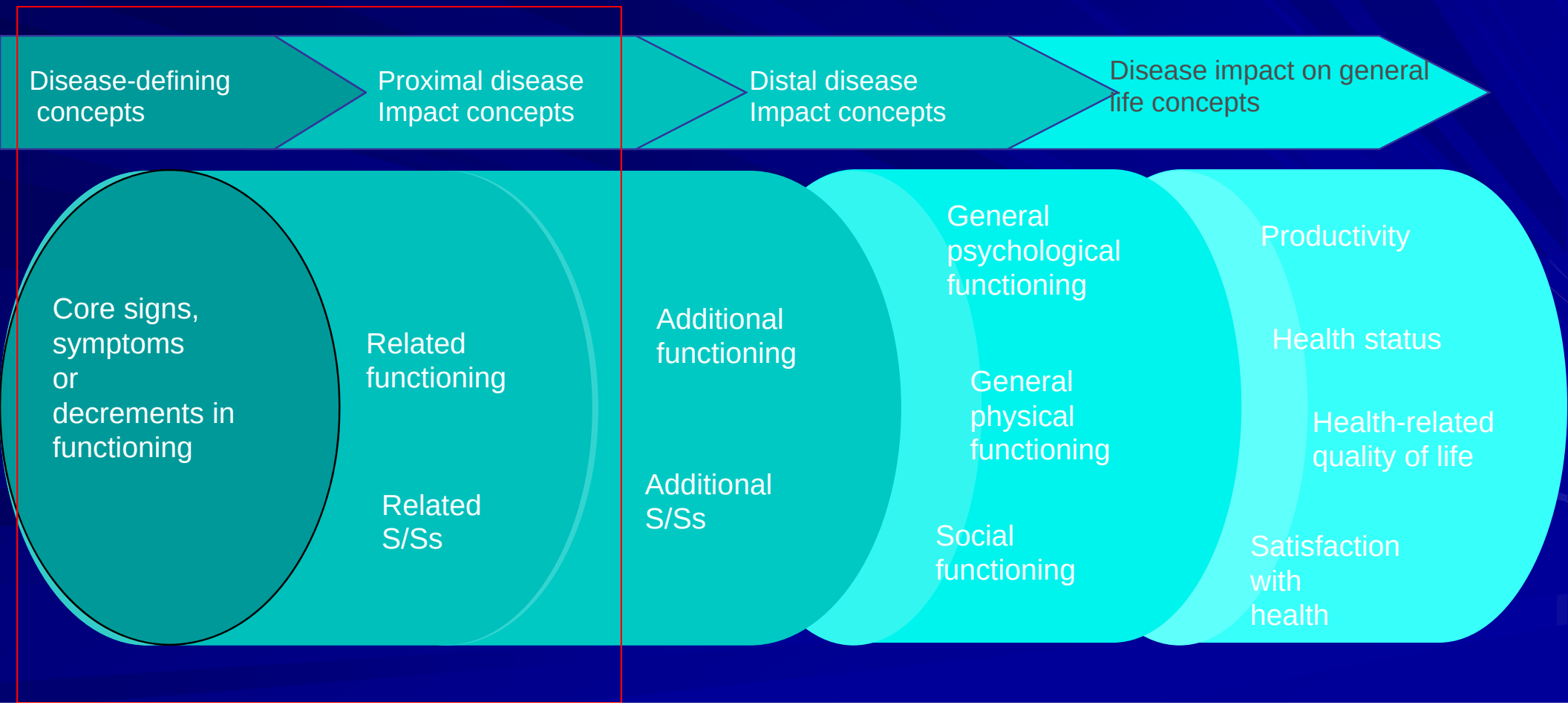
Article provides assurance that PRO development is possible

Publicly funded development and qualification possible following path of performance measures already submitted to FDA

Criteria for a Good PRO Item

- Evaluate impact of muscle wasting on an individual's life;
- Represent a single impact, rather than a multidimensional concept;
- Be relevant to most people with sarcopenia most of the time, determined by frequency of concept mentions (eg, at least 5 subjects) and importance ranking (eg, the top 10 impact rankings);
- Be easily understood;
- Measure a concept likely to change with successful treatment of the condition, determined by clinical input;
- Be unlikely to be vulnerable to ceiling or floor effects; and
- Be likely to have semantic (or at least conceptual) equiv- alence with other languages.

Concept of Interest
Direct Evidence of Tx Benefit (Proximal to Distal)



Signs and Symptoms Elicited with direct patient input

- Strength
- Energy
- Balance
- Endurance
- Coordination
- Emotional symptoms

Impacts Elicited

- Limitations in activities of daily living
- Social limitations
- Emotional limitations

Sample Items

- How much difficulty did you have walking a distance, for example, walking 100 yards or the length of a football field?
- How much difficulty did you have walking in a straight line, for example, down a hallway?
- How much difficulty did you have walking without stumbling?
- How much difficulty did you have going up and down stairs (a flight of stairs or 12 steps)?

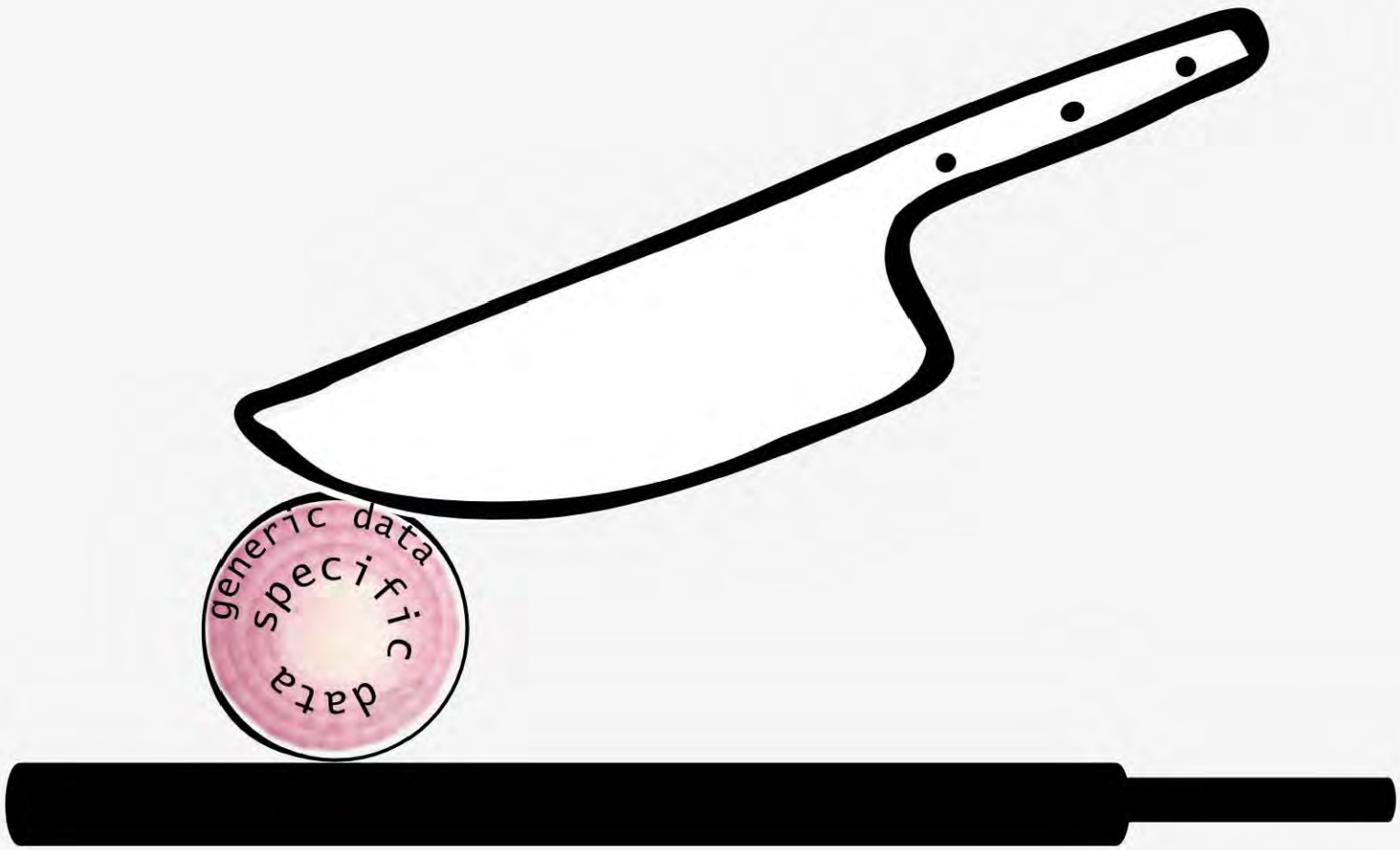
0-10 Scale of Difficulty ranging from 0= no difficulty to 10 = extreme difficulty

Implications of this Study

- Possible to conduct qualitative research sufficient to provide evidence of content validity
- Concept of interest: daily experience of muscle weakness, symptoms and impact of muscle weakness
- Focus on right concept of interest and domains remains an issue

Challenges to Using Patient Report

- Achieving consensus on disease definition
- Focussing on both the proximal and distal
- Developing relationship between endpoints in the evaluation of treatment benefit
- Meeting the measurement challenges with a well-developed PRO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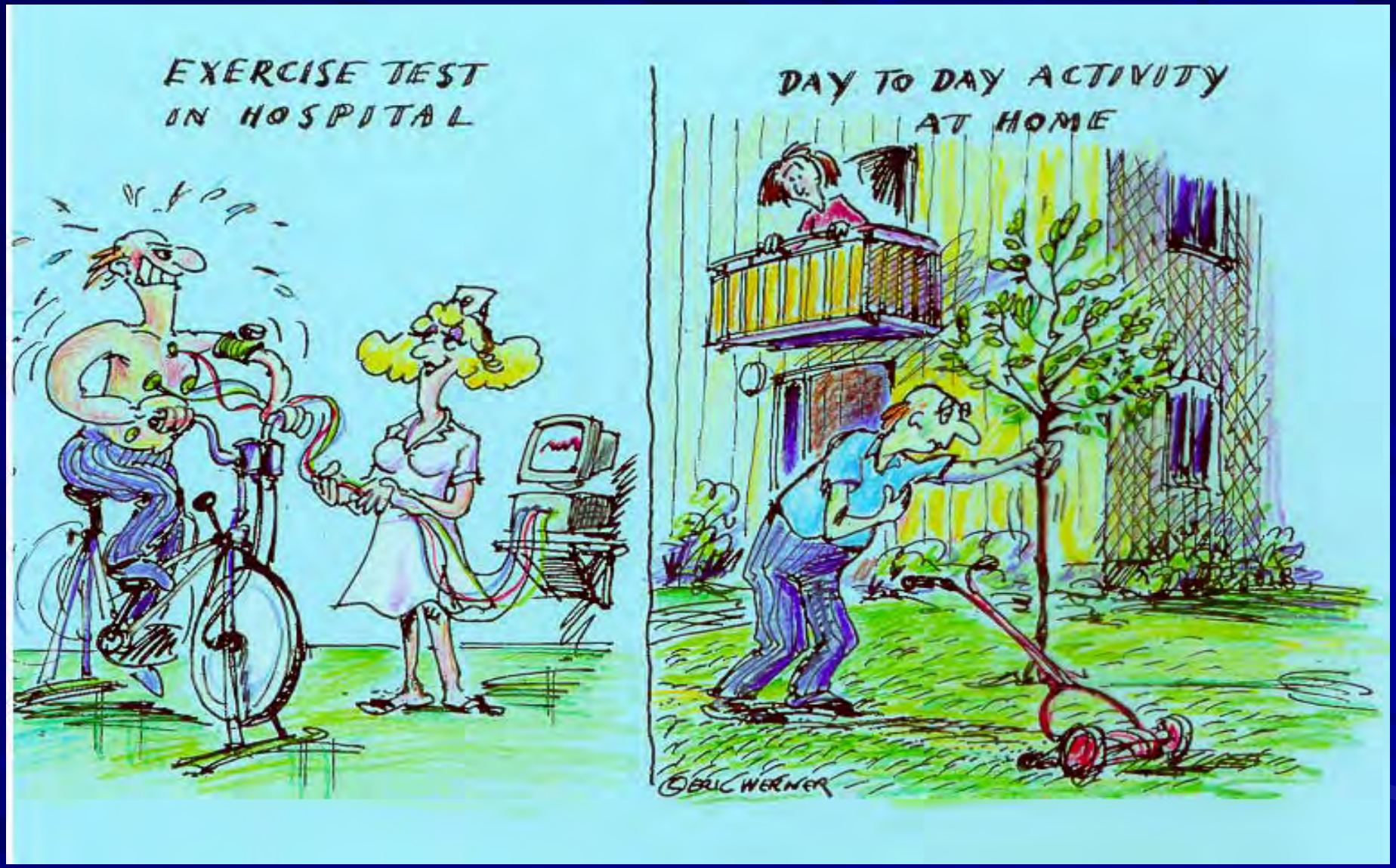
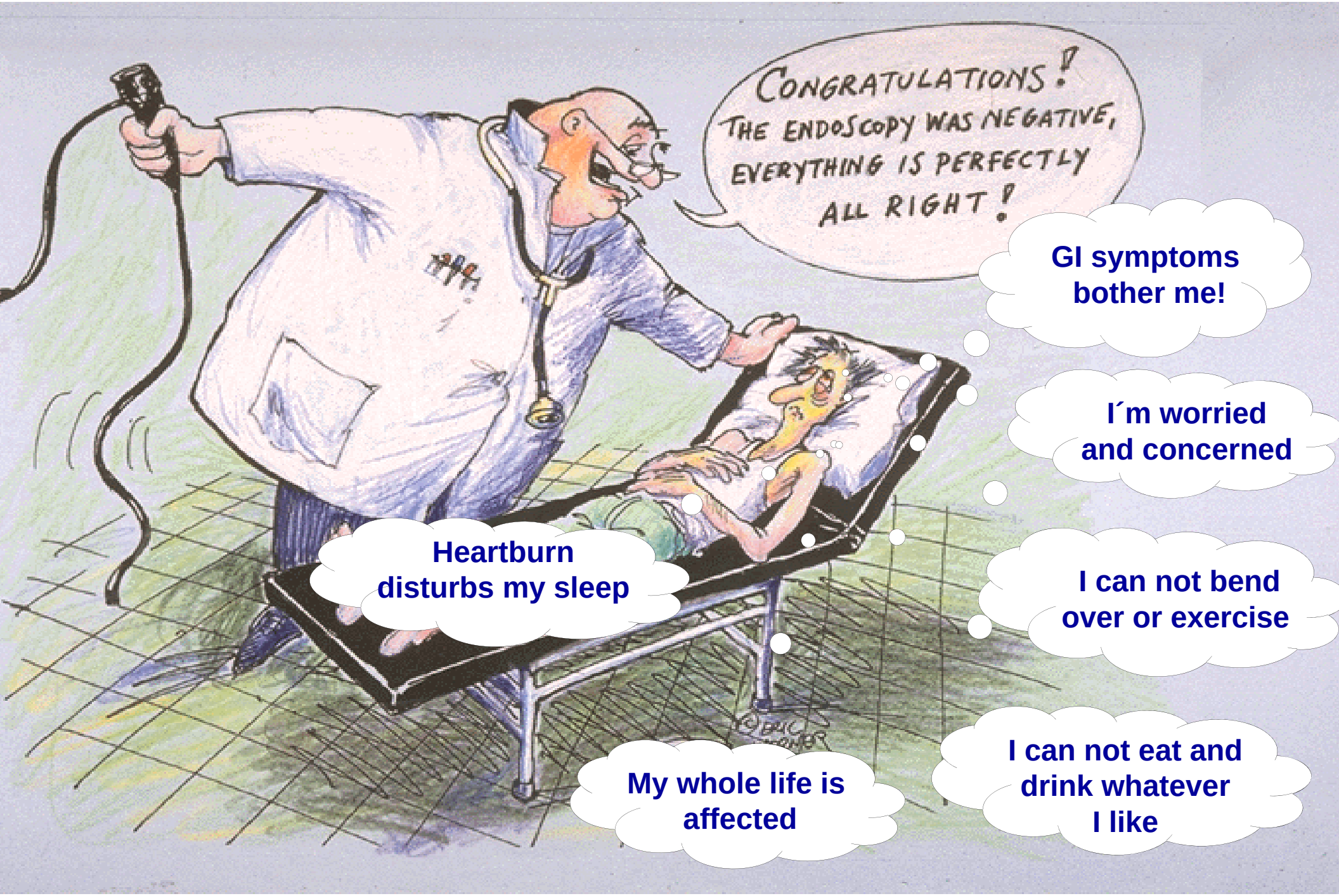


“Objective” **“Subjective”**

Exercise test versus physical functioning, r = 0.40

h://.../hserv5842010/session 1.1

Wiklund I et al.
Clin Cardiol 1991;14


CONGRATULATIONS! THE ENDOSCOPY WAS NEGATIVE, EVERYTHING IS PERFECTLY ALL RIGHT!
GI symptoms bother me!
I´m worried and concerned
I can not bend over or exercise
I can not eat and drink whatever I like
My whole life is affected
Heartburn disturbs my sleep

Well-defined and Reliable:
MEASUREMENT PROPERTIES found adequate to measure the CONCEPT OF MEASUREMENT in the CONTEXT OF USE

- Measurement Properties:
  - Content validity
  - Construct validity
  - Reliability (particularly test-retest)
  - Ability to detect change
    - Information to support interpretation of change

The Way Forward

- Multidisciplinary efforts like the one today
- Possible consortia of private sponsors through the Critical Path Institute and PRO Consortium
- Possible multi-center development through NIH funding
- Incremental incorporation of existing measures through exploratory endpoints
- The need for sarcopenia-specific measures

Summary

- Science of measurement the same for all types of COAs
- Patient-reported outcomes augment other endpoints in hierarchy used to evaluate treatment benefit
- A PRO cannot be chosen or developed without a well-defined context of use and targeted concept of measurement based on understanding the condition