

ISPOR Europe 2022

6th – 9th November, Vienna, Austria and Virtual

ISPOR

Europe 2022



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November

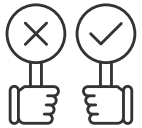
Vienna, Austria
and Virtual

A possibility of administering selected domains of existing patient-reported outcome (PRO) questionnaires to reduce patient burden and increase clinical relevance



MODERATOR

Julia Braverman (BMS, US)



SUBJECT FOR DEBATE: What are the benefits and challenges of taking a modular approach to PRO assessment selection, implementation and use in regulated clinical trials?



GOAL OF THE PANEL:

- To discuss whether a subset of domains from an existing instrument (i.e., Modular Approach) may be considered “fit for purpose”
- To gain a deeper understanding of the impact this modular approach may have in clinical trial research

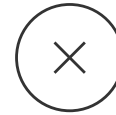


Introduction of the Issue



Most Patient-Reported-Outcomes measures contain multiple subscales/domains

- EORTC QLQ C30 contains 15 domains (e.g., fatigue, global health, insomnia, financial impact...)
- HAQ-DI contains 11 domains (dressing, eating, walking, global health...)
- SF-36 contains 8 domains (physical functioning, mental health, general health..)



Not all of those domains are equally relevant for the target population/treatment

- We don't expect the same results for all domains
- Not all domains are relevant to the given treatment/population
- Some domains are redundant across different instruments

CAN WE ADMINISTER JUST RELEVANT DOMAINS TO INCREASE RELEVANCE, AVOID REDUNDANCY AND DECREASE BURDEN?

EORTC QLQ-PR25 example



Have you had to urinate frequently during the day?
Have you had to urinate frequently at night?
When you felt the urge to pass urine, did you have to hurry to get to the toilet?
Was it difficult for you to get enough sleep, because you needed to get up frequently at night to urinate?
Have you had difficulty going out of the house because you needed to be close to a toilet?
Have you had any unintentional release (leakage) of urine?
Did you have pain when you urinated?
Have your daily activities been limited by your urinary problems?
Answer this question only if you wear an incontinence aid: Has wearing an incontinence aid been a problem for you?
Have your daily activities been limited by your bowel problems?
Have you had any unintentional release (leakage) of stools?
Have you had blood in your stools?
Did you have a bloated feeling in your abdomen?
Did you have hot flushes?
Have you had sore or enlarged nipples or breasts?
Have you had swelling in your legs or ankles?
Has weight loss been a problem for you?
Has weight gain been a problem for you?
Have you felt less masculine as a result of your illness or treatment?
To what extent were you interested in sex?
To what extent were you sexually active (with or without intercourse)?
To what extent was sex enjoyable for you?
Did you have difficulty getting or maintaining an erection?
Did you have ejaculation problems (e.g., dry ejaculation)?
Have you felt uncomfortable about being sexually intimate?

**Sexual activity
and functioning**



Subscale



**Informative for
castrate-resistant
prostate population?**

Sexual activity (2 items)

Not informative

Sexual functioning (4 items)

Not informative

Urinary symptoms (8 items)

Y

Bowel symptoms (4 items)

Y

Hormonal treatment-related
symptoms (6 items)

?

Bother due to the use of
incontinence aid (1 item)

Y

Welcome our Panellists



Paul Kluetz

Deputy Director, FDA, US

FUN FACT: Paul is playing electric guitar in a local Washington D.C. original rock band

Focus: **Fit-for-purpose**



Lauren Podger

Senior Scientist, Open Health, UK

FUN FACT: On Oct 2nd Lauren finished her first marathon (London, for Brain Research UK charity)

Focus: **Psychometric Validity**



Andrew Lloyd

Acaster Lloyd Consulting Ltd

FUN FACT: This is Andrew's 20th year of coming to ISPOR Europe

Focus: **HTA needs**

10 minutes per panelist, 25 minutes for discussion. **HAVE YOUR QUESTIONS READY!**

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Position 1: Modular Approach contributes to a relevant, non-duplicative fit-for-purpose strategy



PRO SHOULD INFORM A CLEAR RESEARCH OBJECTIVE



Efficacy or Comparative Benefit

- Drug A will have improved function compared with Drug B
- Drug A will have decreased disease symptoms compared with Drug B
- Drug A will have LESS side effect impact, improved adherence, higher on treatment functioning compared with Drug B
- *Requires inferential statistics with apriori SAP and alpha control



Safety and Tolerability

- Describe symptomatic toxicities and their impact on patients
- *Can use descriptive statistics

Position 1: Modular Approach contributes to a relevant, non-duplicative fit-for-purpose strategy



Focusing on Core Patient-Reported Outcomes in Cancer Clinical Trials: Symptomatic Adverse Events, Physical Function, and Disease-Related Symptoms

Paul G. Kluetz¹, Ashley Slagle², Elektra J. Papadopoulos², Laura Lee Johnson³, Martha Donoghue¹, Virginia E. Kwitkowski¹, Wen-Hung Chen², Rajeshwari Sridhara³, Ann T. Farrell¹, Patricia Keegan¹, Geoffrey Kim¹, and Richard Pazdur¹

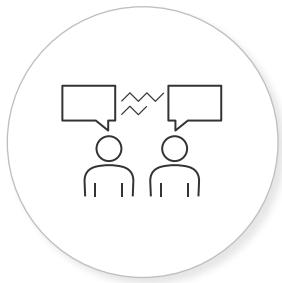


New mechanistic classes making standard QOL tools problematic

- Not assessing key toxicities
- Assessing irrelevant toxicities that were not likely to occur
- Duplicating symptoms across QOL and Disease Module Tools
- Assessing constructs that were distal to effect of the drug and disease

Clin Cancer Res (2016) 22 (7): 1553–1558. <https://doi.org/10.1158/1078-0432.CCR-15-2035>

Position 1: Modular Approach contributes to a relevant, non-duplicative fit-for-purpose strategy



Healthy Debate: A Call for a “Modular Approach”

Gronvold and EORTC QOL group

...Our recommendation... a combination of standardized patient-reported questionnaires and validated items from item libraries.

Kluetz et al in response

...Similar to Gronvold...we favor a thoughtful combination of static questionnaires and item banks or libraries to create a balanced, flexible, and modular approach to PRO assessment...

Clin Cancer Res (2016) 22 (7): 1553–1558. <https://doi.org/10.1158/1078-0432.CCR-15-2035>

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CAN WE BE MORE THOUGHTFUL?

Hypothetical Scenario



Randomized Trial of
Drug A (TKI) versus
Chemotherapy in
Non-Small Cell
Lung Cancer



Oral TKI agent given
daily continuously



Chemo administered
day 1 IV q3 week



Expected TKI toxicities
include GI toxicities
as well as ocular toxicity,
edema, taste change



Example of a “Static” Lung Cancer PRO Approach

QLQC30	LC13	NSCLC-SAQ
5 physical function	Cough	Cough
2 role function	Hemoptysis	Chest pain
4 emotional function	Dyspnea	Pain
2 cognitive function	Dyspnea	Dyspnea
2 social function	Dyspnea	Fatigue
2 QOL	Mucositis	Fatigue
Fatigue	Odynophagia	Anorexia
Fatigue	Neuropathy	
Fatigue	Hair loss	
Nausea	Chest pain	
Vomiting	Shoulder pain	
Anorexia	Pain	
Dyspnea	Medicine for pain	
Diarrhea		
Constipation		
Pain		
Pain interference		
Insomnia		
Financial		

- 50 Questions
- **Duplicates** 5 constructs involving 22 questions
- **Misses** 3 cardinal toxicities ocular, edema and taste
- **Relevance** of financial toxicity premarket?
- **Attribution to Drug Effect?** Distal Domains of emotional and social function



Example of a Modular Approach with Item Library

Functional Scales: QLQC17	Symptomatic AE Item Library	Overall Side Effect	Disease Symptom: NSCLC-SAQ
Physical function	Mucositis	GP5 ¹ or Q168 ²	Cough
Role function	Odynophagia		Chest pain
Emotional function	Neuropathy		Pain
Cognitive function	Hair loss		Dyspnea
Social function	Nausea		Fatigue
QOL	Vomiting		Fatigue
	Diarrhea		Anorexia
	Constipation		
	Blurred vision		
	Edema		
	Taste changes		
	FREE TEXT?		

- 36 Questions
- **Non duplicative**
- **Relevant**
- **Flexible Assessment**

* NOTE: Illustrative example- consult with FDA review Division early for context-specific advice

¹ GP5 - I am bothered by side-effects of treatment – an item of Functionality Assessment of Chronic Illness Therapy (FACIT) Searchable Item Library

² Q168 – To what extent have you been troubled by side-effects from your treatment? – an item of European Organisation for Research of Treatments for Cancer (EORTC) QOL Group Item Library

Position 1: Modular Approach contributes to a relevant, non-duplicative fit-for-purpose strategy



Another Benefit: Opportunity to assess different constructs at different frequencies depending on the research question

	Standard 6-month treatment period												Follow-up	
	<i>BL</i>	<i>w2</i>	<i>w3</i>	<i>w4</i>	<i>w5</i>	<i>w6</i>	<i>w7</i>	<i>w8</i>	<i>M3</i>	<i>M4</i>	<i>M5</i>	<i>M6</i>	<i>M9</i>	<i>M12*</i>
Symptomatic AE	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Single Item Side Effect Global	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Physical Function	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Role Function	x		x		x		x		x	x	x	x	x	x
Disease Symptoms	x				x				x			x		x
Other HRQOL	x								x			x		x

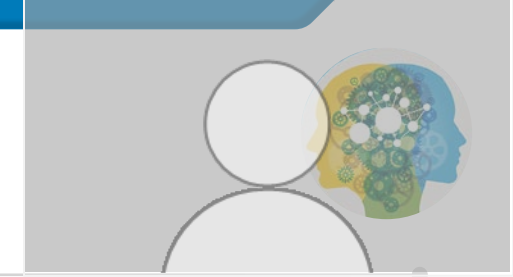
Position 1: Modular Approach contributes to a relevant, non-duplicative fit-for-purpose strategy



Change is Hard: Points of Discussion

- Logistics of differing **assessment frequencies**
- Objective selection of **expected toxicities**
- **Differing tools with different response options**
- **Disease symptoms if no clear tool (pain, anorexia, fatigue?)**
- **Role of CAT or Custom Short Forms** with Item banks?
- Potential for a **common construct across tools?**
 - EQ-5D? EORTC 2 item QOL? Physical Function?

Position 1: Modular Approach contributes to a relevant, non-duplicative fit-for-purpose strategy



CONCLUSIONS

- Modular approach can increase relevance, decrease duplication and add flexibility in assessment across objectives
- Operationalizing such a change will require discussion across international stakeholders

Panellists



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Deputy Director, FDA, US

FUN FACT: Paul is playing electric guitar in a local Washington D.C. original rock band

Focus: **Fit-for-purpose**



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Focus: **HTA needs**

Position 2: Modular approach yields unbiased measurement in most cases



Two conditions exist WRT modular sampling:

- **Condition 1 (C1):** Instrument developed to be modular
 - In which case there is no concern with modular sampling
- **Condition 2 (C2):** Instrument was developed to account for inter-domain associations
 - In which case most would conjecture there may be concern with modular sampling



Example of C1: EORTC QLQ-C30:

- Aaronson et al., 1991:
 - *"Principal components . . . Analysis was used to confirm that only one scale should be constructed from a set of items"*
 - Fatigue: Analysis supported the unidimensionality of the scale
 - Consequently, EORTC QLQ-C30 domains developed to be independent of one another
- **Under condition 1, modular approach is acceptable**

Position 2: Modular approach yields unbiased measurement in most cases



Two conditions exist WRT modular sampling:

- **Condition 1 (C1):** Instrument developed to be modular
 - In which case there is no concern with modular sampling
- **Condition 2 (C2):** Instrument was developed to account for inter-domain associations
 - In which case most would conjecture there may be concern with modular sampling



Example of C2: Anything developed to have non-independent domains:

- *Hoepken, B., Serrano, D., Harris, K., Hwang, M.C., Reveille, J., 2021*
 - Domains validated by explicitly estimating and evaluating dependencies among domains
 - Dependence between domains is quantified via correlation
 - E.g., Domain 1 (D1) explicitly dependent on Domain 2 (D2)
 - **Key question: Does modular sampling of D2 ignoring D1 alter the properties of D2?**

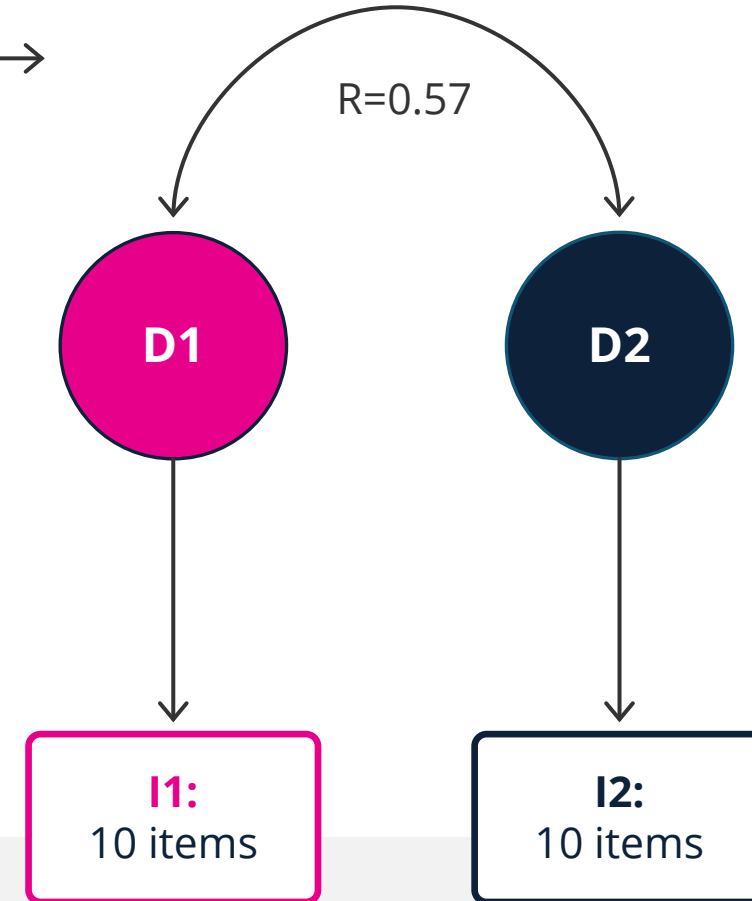
In this presentation we present a brief simulation exploring this question, thereby showing that modularity is of no statistical consequence to measurement precision

Simulation Method: Complete Sampling

Condition 2



- N=20,000 NIVS, simulated from path diagram
- Weights and response categories:
 - Weight range 0.8-3.6
 - Multinomial response distribution
 - 5 response categories per item
 - Joint Gaussian $N(0, R)$ domain distribution
 - D1 and D2 are dependent via R
 - Induces dependence in I1 and I2

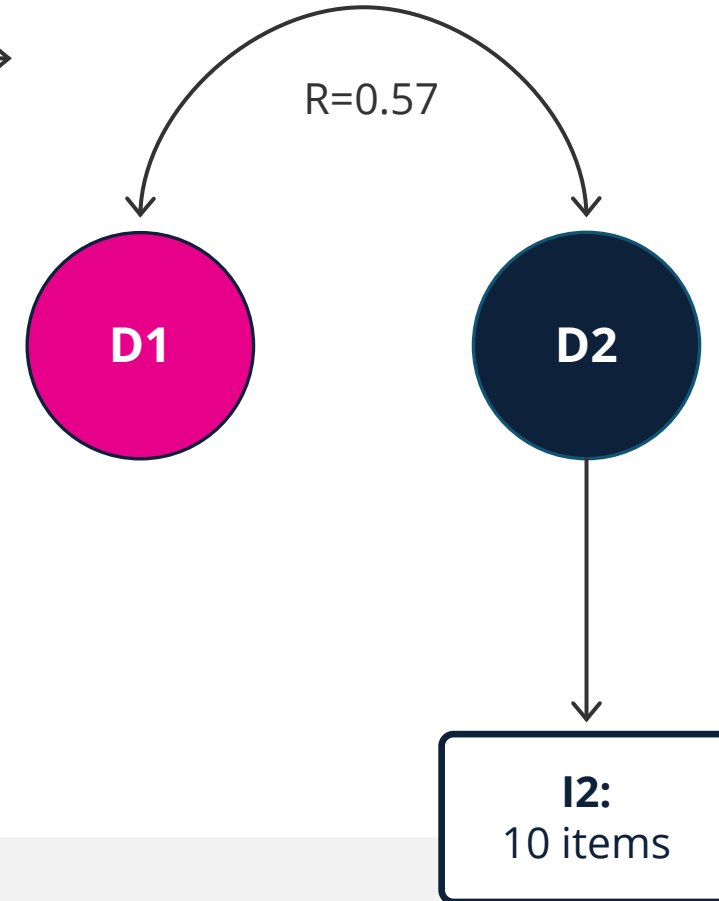


Simulation Method: Modular Sampling

Condition 2



- Simulate D1 and D2 from Complete
- Sample only I2
- Question evaluated:
 - Evaluate inter-item correlations and score mean and SD between complete and modular
 - Do they differ depending on sampling?



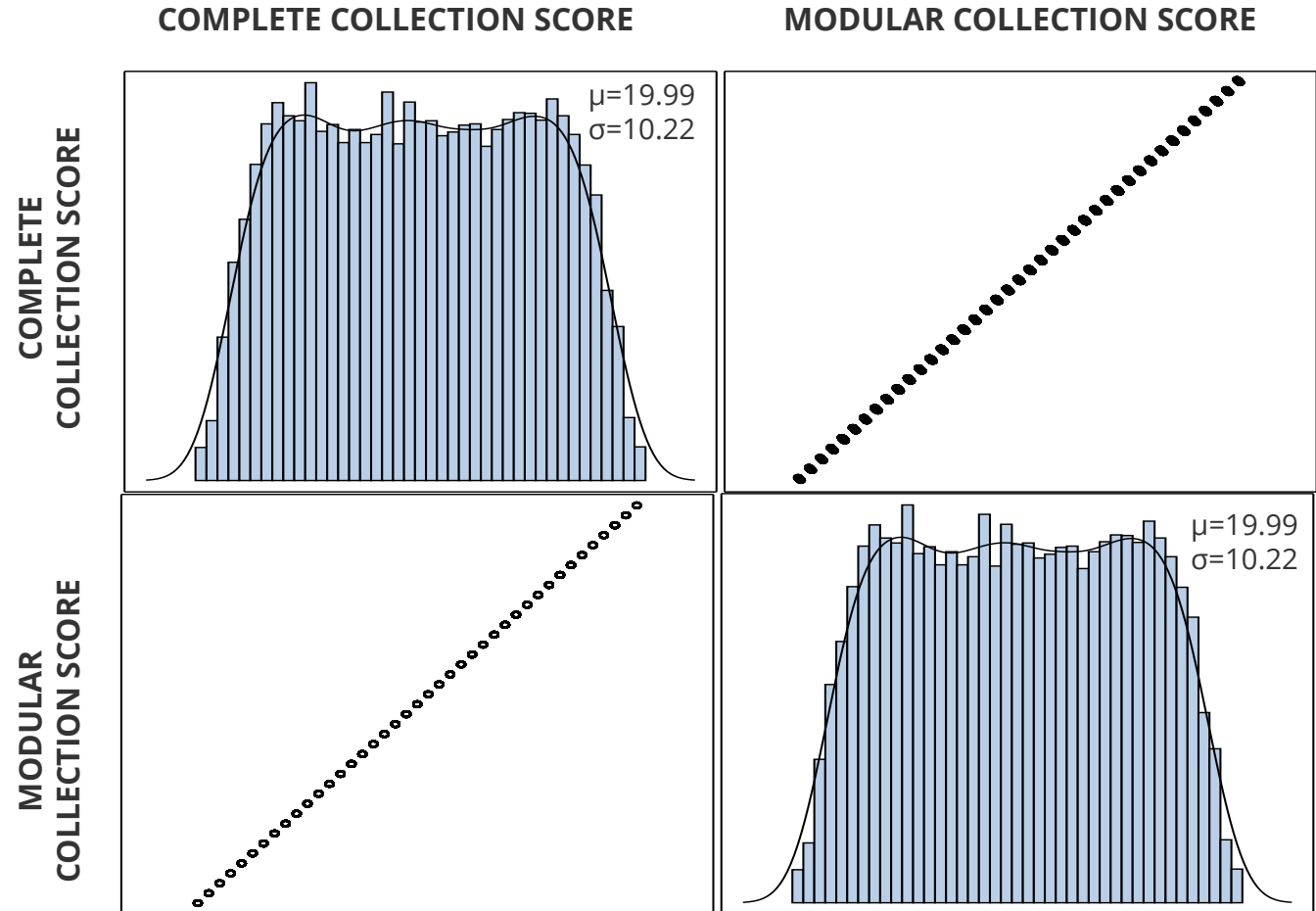
Simulation Result: Modular Sampling

Condition 2



When D2 is sampled independently:

- Score distribution, mean and SD for D2:
 - Identical whether estimated under complete or modular ($\mu=19.99$, $\sigma=10.22$)
- Correlation between complete and modular scores is 1
- No difference as a function of sampling



Position 2: Modular approach yields unbiased measurement in most cases



CONCLUSIONS

Key question:

Does using only select domains introduce measurement imprecision?

Condition 1

When domains are developed to be independent, a modular approach is acceptable

Condition 2

Simulation investigation:

- Employing a modular approach to tools that have inter-domain associations does not appear to impact measurement precision
 - Key: Except in case of **unresolved Local Dependence** (akin to correlated residuals)

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Position 3: HTA decision makers generally require more generic PRO data



Simplifying PRO data collection

- Idea of selecting specific PRO domains is appealing
 - Reduce patient burden
 - Increase relevance of data
- Consider a treatment for coeliac disease (gluten intolerance)
 - Classic symptoms include gastrointestinal problems such as chronic diarrhea, abdominal distention, malabsorption, loss of appetite, and among children failure to grow normally.
 - Symptoms could be captured using coeliac specific outcomes measure (symptom diary etc.)
 - Such a measure could support regulatory approval

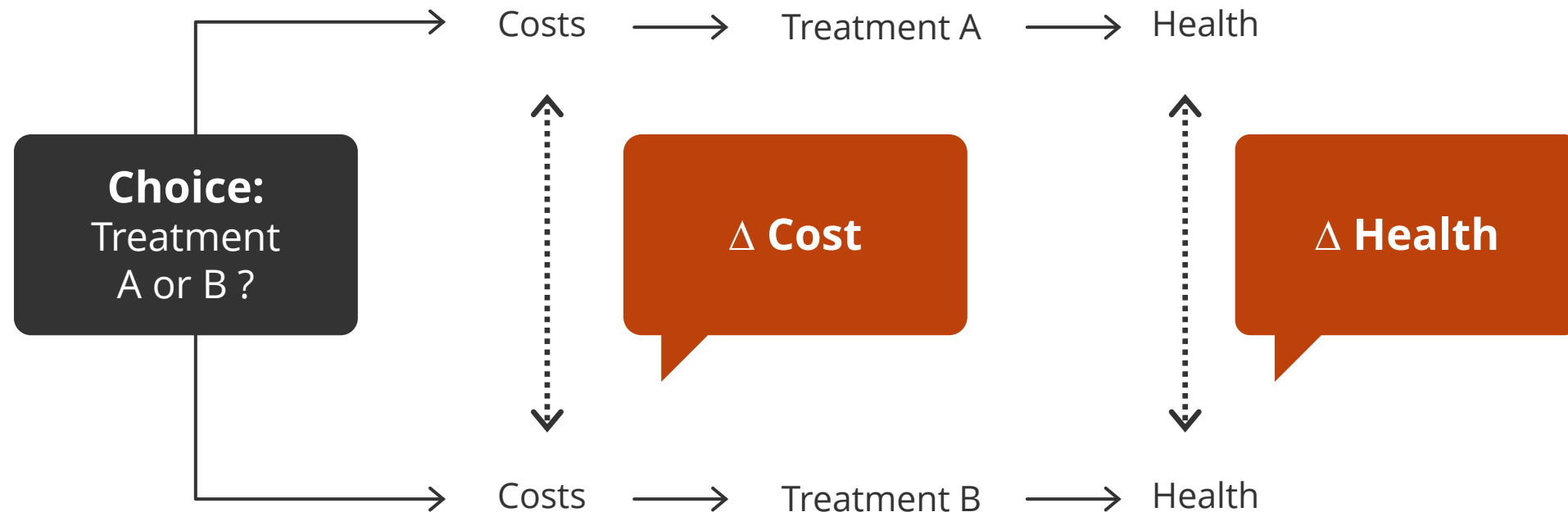
Treatment X has been shown to reduce the symptoms of celiac disease including abdominal discomfort and pain

Fasano A (April 2005). "Clinical presentation of celiac disease in the pediatric population". *Gastroenterology (Review)*. 128 (4 Suppl 1): S68-73

Position 3: HTA decision makers generally require more generic PRO data



Health Technology Assessment



Does the **extra** benefits (health) justify the **extra** cost ?

Position 3: HTA decision makers generally require more generic PRO data



Health Technology Assessment (HTA) context

- Much greater focus on generic measurement of health
- Outcomes (benefit) assessed using quality adjusted life years (QALYs)
 - QALYs are life years weighted by a quality of life index (EQ-5D)
 - Single index score is preference weighted
 - EQ-5D scores
 - 1 = Full health
 - 0 = Dead
 - EQ-5D scores reflect the value of a health state

Position 3: HTA decision makers generally require more generic PRO data



- EQ-5D is a generic measure of quality of life
- Favoured by many HTA bodies

(You cannot score the measure unless all 5 dimensions are completed)

By placing a tick in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

- ☐ I have no problems in walking about
- ☐ I have slight problems in walking about
- ☐ I have moderate problems in walking about
- ☐ I have severe problems in walking about
- ☐ I am unable to walk about

Self-Care

- ☐ I have no problems washing or dressing myself
- ☐ I have slight problems washing or dressing myself
- ☐ I have moderate problems washing or dressing myself
- ☐ I have severe problems washing or dressing myself
- ☐ I am unable to wash or dress myself

Usual Activities (e.g., work, study, housework, family or leisure activities)

- ☐ I have no problems doing my usual activities
- ☐ I have slight problems doing my usual activities
- ☐ I have moderate problems doing my usual activities
- ☐ I have severe problems doing my usual activities
- ☐ I am unable to do my usual activities

Pain/Discomfort

- ☐ I have no pain or discomfort
- ☐ I have slight pain or discomfort
- ☐ I have moderate pain or discomfort
- ☐ I have severe pain or discomfort
- ☐ I have extreme pain or discomfort

Anxiety/Depression

- ☐ I am not anxious or depressed
- ☐ I am slightly anxious or depressed
- ☐ I am moderately anxious or depressed
- ☐ I am severely anxious or depressed
- ☐ I am extremely anxious or depressed

Position 3: HTA decision makers generally require more generic PRO data



Coeliac symptom diary

- Accurately assesses the burden and impact of *symptoms of coeliac* disease
- Has validity and is sensitive to treatment effects



EQ-5D

May measure some aspects of coeliac disease

- Pain/discomfort
- But not diarrhea, bloating etc.

Position 3: HTA decision makers generally require more generic PRO data, Simple conclusions



- We need both measures to meet needs of regulators and HTA
- There seems little scope to drop measures or domains
- So trials should collect both measures
- **But is this conclusion correct?**

Position 3: HTA decision makers generally require more generic PRO data, **example:** Coeliac disease

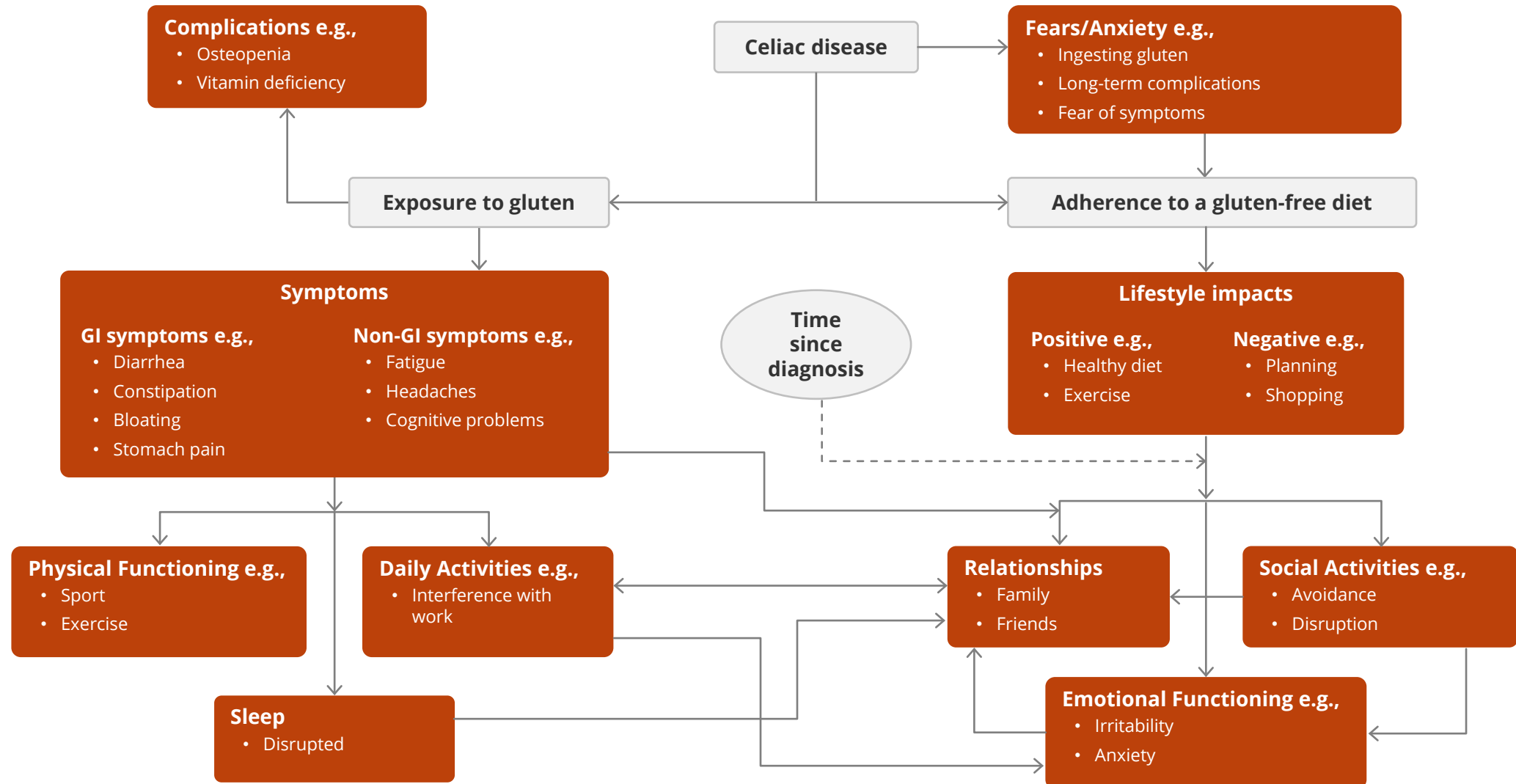


Classic symptoms include gastrointestinal problems such as chronic diarrhoea, abdominal distention, malabsorption, loss of appetite, and among children failure to grow normally

- Wrong to classify this condition this simply
- Leffler et al explored patients experience of coeliac disease using qualitative methods
- The disease has a much more complex impact on people
- It affects many different areas of people's health

Leffler DA et al. A Novel Patient-Derived Conceptual Model of the Impact of Celiac Disease in Adults: Implications for Patient-Reported Outcome and Health-Related Quality-of-Life Instrument Development. Value Health. 2017 Apr;20(4):637-643.

Position 3: HTA decision makers generally require more generic PRO data, **example:** Coeliac disease



Position 3: HTA decision makers generally require more generic PRO data



CONCLUSIONS

- Measurement of patient outcomes should be targeted and efficient
- Many trials in GI disease either have no PRO tools or far too many
- The clinical assumptions regarding how disease affects people may be incomplete
 - This suggests a wider coverage is needed
- HTA decision makers generally require more generic PRO data



Summary of Positions



Modular Approach is Preferable

- Modular approach opens opportunities for flexible, tailored (for content and frequency) and non-duplicative assessment of patient-reported outcomes (Paul K.)
- Modular sampling does not bias domain score/psychometric properties of the instrument (Lauren P.)



Modular Approach is NOT Preferable

- The clinical assumptions regarding how disease affects people may be incomplete
 - This suggests a wider coverage is needed (Andrew L.)