IS THERE A SYSTEMATIC METHODOLOGY FOR CHOOSING TRIAL ENDPOINTS THAT INCORPORATES PATIENTS' PERSPECTIVES? WHAT MIGHT IT LOOK LIKE?

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Disclosures

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Translating endpoints into (meaningful) conclusions

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- **Questionnaire and assessment schedule**: Daily pain diary NRS (0-10) assessing "pain at its worst" in the 24 hours prior to assessment
- **Scoring**: 7-day average (i.e., pain scores collected in the 7 days prior to key study visits are averaged).
- **Endpoint**: Proportion of subjects in TX vs PBO who achieve a ≥ 3-point reduction on the pain NRS from Baseline to Time 2.
- **Result**: 75% and 25% of TX and PBP subjects achieved ≥ 3-point reduction on the pain NRS, respectively.
- **Conclusion**: Treatment T reduces pain associated with Disease D
- **Meaning**: Treatment group subjects had a reduction in their weekly average pain at its worst.

What exactly is weekly average pain at its worst*?*
Is this meaningful, relevant, and/or understandable to patients? Does it need to be? Who gets to decide?

Session expectations:
Are we using patient input as well as we could be?

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- What this session *is* designed for
  - Discuss where patient input could be (better) collected or (better) used in product development
  - Discuss barriers of using enhanced or different methods of collecting patient input
  - Foster communication and transparency in endpoint selection
- What this session is *not* designed for
  - To provide definitive "one-size-fits-all" guidance on how to select clinical trial endpoints

Regulatory Context

Perspective, documentation, and models of development

Regulatory review of a PRO questionnaires:

COA questionnaire development process

- **Applicable to all COA's including:**
  - Patient reported outcomes (PRO)
  - Clinician reported outcomes (ClinRO)
  - Observer reported outcomes (ObsRO)
  - Performance based outcomes (PerfO)

Step 1:
Concept Elicitation

Identify key concepts for measurement through:

- Targeted literature review
- Expert advice meetings
- Stakeholder meetings
- Patient interviews

Step 2:
Concept Selection & Questionnaire Construction

- Select key concepts for measurement
- Draft or modify questionnaire content

Step 3:
Questionnaire Evaluation

- Evaluate respondent understanding and ability to complete the questionnaire
- Translatability assessment (optional)
- Mode equivalence (optional)

Fit for Purpose

Step 4:
Psychometric Evaluation & Score Interpretation

- Evaluate psychometric performance
- Evaluate scoring options
- Evaluate thresholds for meaningful change

Development of a PRO instrument: an iterative process*

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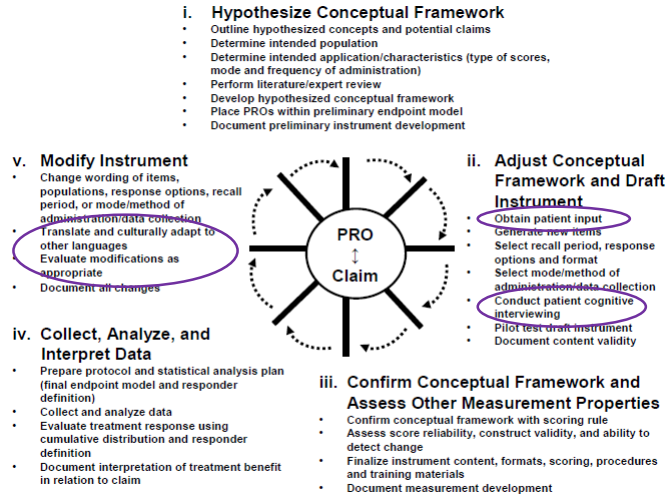

US Department of Health and Human Services, FD A (CDER, CBER, and CDRH). Guidance for Industry: Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims. 2009.

*On track to Patient-Centered Outcome Measurement**

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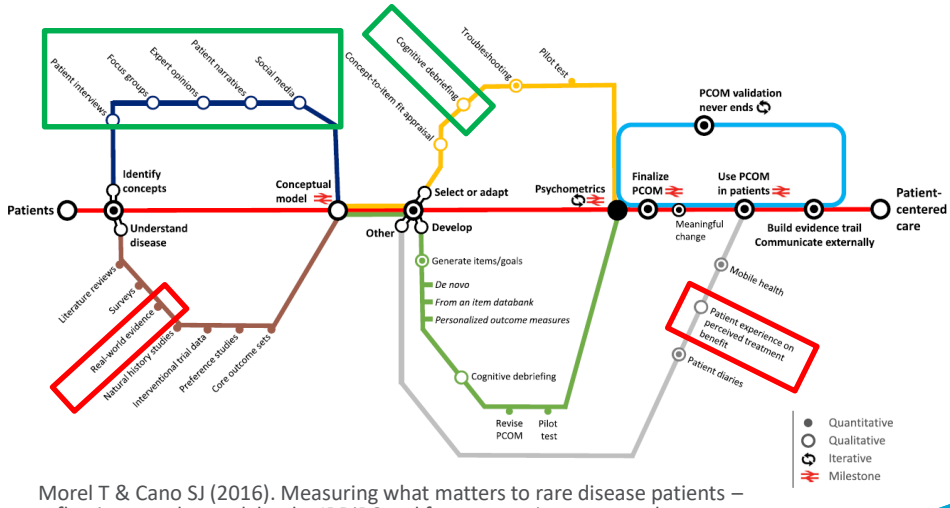

Morel T & Cano SJ (2016). Measuring what matters to rare disease patients – reflections on the work by the IRDiRC taskforce on patient-centered outcome measures. Orphanet Journal of Rare Diseases, 12, 171.

Principles of PRO endpoint selection

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- **Endpoint**: The way an assessment will be used as a study result and statistically compared among treatment groups to assess the effect of treatment.*
  - The **concept** and **outcome** is *patient centered*
    - What is being measured (and expected to change) is relevant to the disease, important to patients with the condition
  - The **questionnaire** is *content valid*
    - Questionnaire is understandable to the respondent
  - The endpoint includes **scores** that *are trustworthy* (i.e., reliable, construct valid, and sensitive)
    - The questionnaire is ***not*** what is to be concluded as "valid" or "reliable"
  - Guidance for **interpreting** *score differences or change* are available

*Clinical Outcome Assessment (COA): Glossary of Terms. (4/30/2015). http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugDevelopmentToolsQualificationProgram/ucm370262.htm

Are we using patient input as well as we could be?

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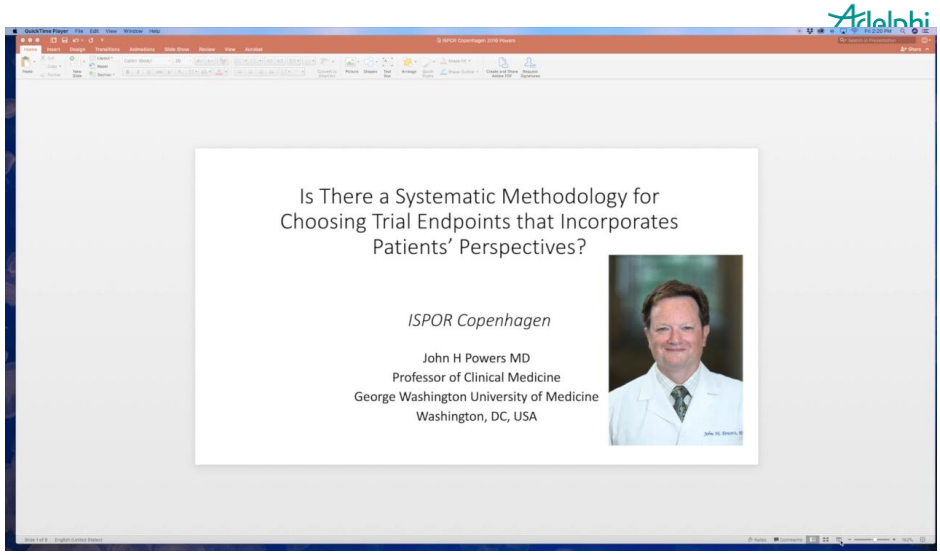
- Many places where patient input are relevant in the endpoint development process but here we are focused on better understanding the "what to measure" and "what about that concept do we want to say in terms of our products effect"
- It is not currently clear how decisions about these issues are made in regulated trials and clinical development
  - Can we use data from patient input in other ways?
  - Are PROs used often enough? Could they be used more in appropriate settings?
  - Are relevant tools available? How do we develop them and with what resources?
  - Is there enough buy in from various stakeholders?
- John Powers, MD
  - What we have done well to date
  - What we may be missing and/or could do better?
- Arthur Stone, PhD
  - Considering new pain intensity indices
- Barriers and recommendations (discussion)



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Bringing the Patient Perspective to the Selection of Clinical Trial Outcomes

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Disclosures: Gallup Organization; Adelphi Values
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Background

- The context for this presentation is pain intensity as an outcome measure
- History of Pain Intensity Assessment
  - 1-month to 1 week recall of pain intensity over those periods
- Considerable research suggested error and bias in patients' ability to recall even a single week
  - Memory failures
  - Summary processes
  - Cognitive heuristics

Background

- Several years ago FDA decided that Daily Diaries for collecting pain intensity would be "required" for creating outcomes
  - For characterizing a week, 7 diaries reports would be averaged
  - The question was about "Average Pain" for the day
- Somewhat mysteriously, regulatory advice then switched
  - Now the question to be averaged was "Worst Pain" of the day

Background

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- Many questions about how Pain Intensity outcomes were chosen
  - On what empirical basis was the measurement of pain intensity switched to Worst Pain?
    - Is it more able to detect Treatment effects?
      - Is that the ”right” criteria?
    - What are the alternatives that might be considered?
    - Is this the construct that is most important to Stakeholders?
      - And to which group of stakeholders?
  - And where does patient input enter the calculus?

Background

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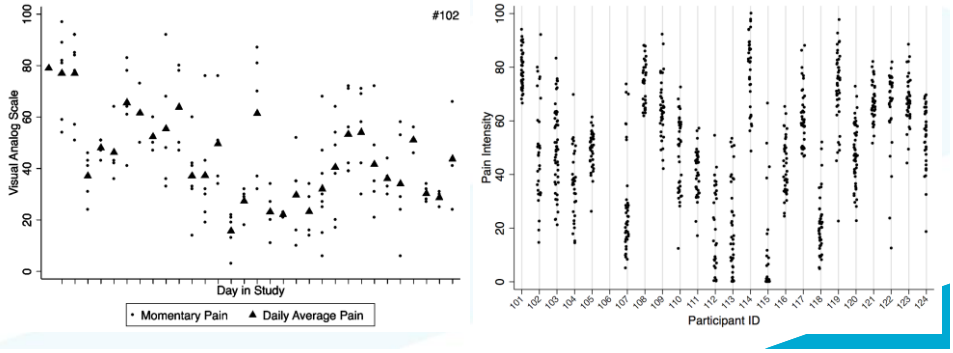
- We need to realize that Pain is quite variable over the day and over longer periods
- We can do this with momentary assessment methods such as Ecological Momentary Assessment (EMA)



USC Pain Study

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- Major objective was to develop new indices to reflect pain intensity over the course on a week
  - Based on momentary reports of pain intensity
  - In patients with clinical pain conditions
- Could these new indices reflect aspects of the pain experience that was missed by current approaches?
  - And what would patients, clinicians, and others think of them
- To collect data about the psychometrics and performance of the new indices

Broad Goals of the Studies: Focus today is on the first study

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Data about the Indices

1 **STAKEHOLDERS**

To present various stakeholder with the new indices

To determine their thoughts about the "Importance" of the indices

2 **CONSTRUCT VALIDITY**

To determine the reliability of the new indices

To determine the convergent validity of the new indices

Application of Indices

3 **CLINICAL TRIAL PERFORMANCE**

How the new indices perform in a clinical trial

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Development of New Pain Intensity Indices brought into focus the question about how trial outcomes and endpoints are chosen

Arm-chaired New Indices

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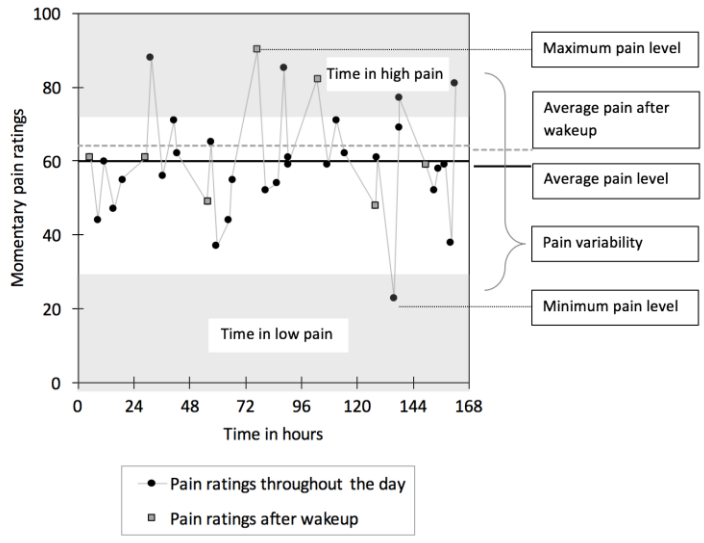
Pain Intensity Index	Definition/Explanation
Average pain intensity over a week	If we take many ratings of a patient's pain intensity during a week, add them up and then divide by the number of ratings, this would give us an average of a patient's pain during that week.
Level of pain intensity when it is at its worst during a week	If we take many ratings of a patient's pain intensity during a week, we could see what a patient's highest pain level was. This would indicate the level of pain intensity when it was at its worst.
Level of pain intensity when it is at its least during a week	If we take many ratings of a patient's pain intensity during a week, we could see what a patient's lowest pain level was. This would indicate the level of pain intensity when it was at its least.
Amount of time patient spends with no or low pain during a week	This refers to how much of the time during the week a patient didn't feel any or felt very little pain. That is, if we were to take many ratings of a patient's pain intensity, we could figure out the amount of time during a week that a patient had no pain or almost no pain.

Arm-chaired New Indices

Pain Intensity Index	Definition/Explanation
Amount of time patient spends in high pain during a week	If we were to take many ratings of a patient's pain intensity during the week, we could figure out the amount of time when a patient had ratings of pain intensity at very high levels.
How much pain intensity fluctuates or changes during a week	If we take many ratings of a patient's pain intensity during a week, we can get a sense of how much a patient's pain intensity varies from moment-to-moment or day-to-day over the week. That is, whether the intensity is more or less constant or how much a patient's pain fluctuates (that is, goes up and down).
Amount of unpredictability of pain levels during a week	This refers to the degree to which a patient's pain intensity changes for reasons that the patient can't identify. If a patient doesn't know when and why his/her pain changes, then a patient's pain levels are unpredictable.

Visualization of New Indices



Methods

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- ***How do various Stakeholders view the Importance of the Indices?***
- Stakeholder Samples
  - 32 Patients with chronic pain conditions
    - Recruited from Internet Panel (SSI); Qualified as self-report Chronic Pain condition sufferer; US-wide; $30
  - 20 Healthcare Providers
    - Recruited through Am Academy of Pain Medicine; at least 8 hours care of chronic pain patient/week; MDs, PhDs, NPs. PAs; $150-200
  - 20 Clinical Trialists (Pain)
    - Recruited from NIH Research Portfolio Online Reporting Tools; $150-200
  - [0 Regulators]

Methods

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- Interviewed by telephone for 20m
- Read definitions of Pain Indices
  - Probed for comprehension
- Rated “Importance” for each Index
  - Patients: “Most hoping to achieve from treatment”
  - Others: “Importance for evaluating treatment outcome”
  - Rankings: 1= Most important, 7=Least important
- Qualitative discussion of ratings
  - Quotations in paper and on request

Who are the respondents?

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- Patient characteristics (n=32)
  - 72% chronic back pain, arthritis, FM
  - Average years since dx: 15.5
  - 59% in current pain treatment
- Clinicians (n=20)
  - Predominately male
  - Practicing from 1-30 years
- Trialists (n=20)
  - Conducted between 1-30 trials
  - Years in clinical research: 4-40 years

Importance Ratings

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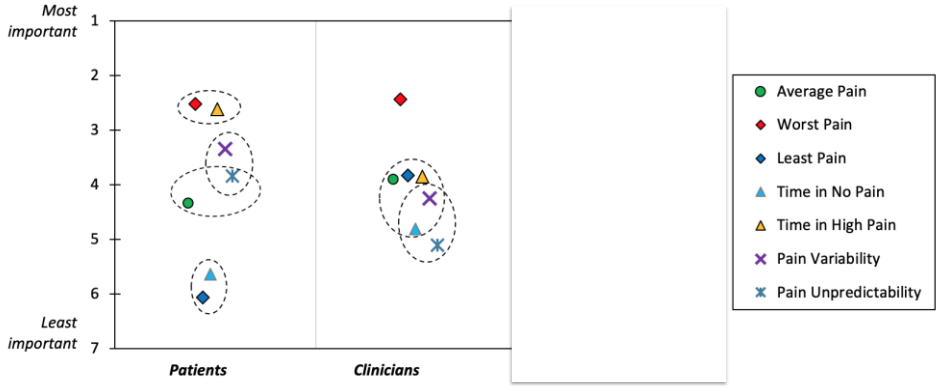
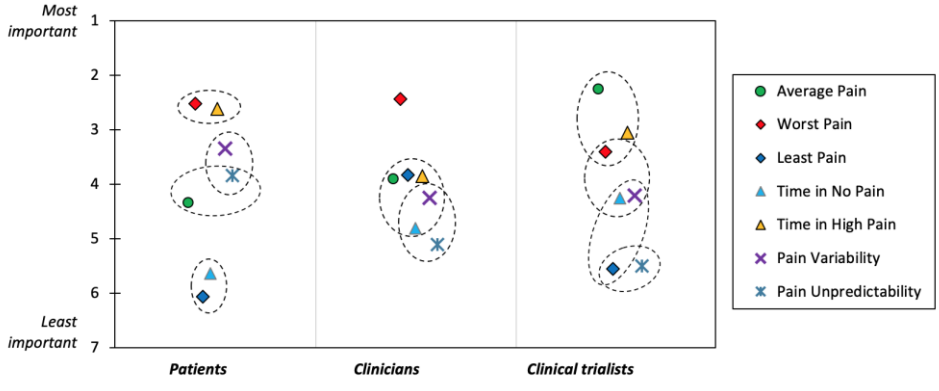
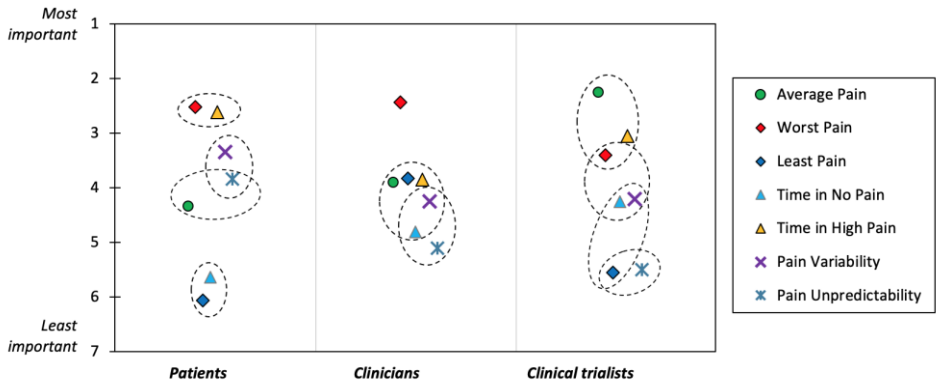
Importance Ratings



Importance Ratings



Importance Ratings



Discussion

- New momentary-based pain indices understood by stakeholders
- Clear and differing opinions expressed by stakeholders
- Worst pain preferred by Patients and Clinicians, whereas Average by Trialists
- Patients thought Variability and Unpredictability were important qualities of pain intensity
  - But Clinicians and Trialist did not agree
- Consistent with FDA approach
- Average preference by Trialists perhaps due to historical precedents, but not clear
- Duration in High Pain important to Patients, but not Clinicians

Discussion

- These data show the importance of considering the opinions of multiple stakeholders, *including Patients*, in considering an outcome measure.
- They also highlight the importance of seriously considering the construct and the multiple ways it could be measured.
- They highlight the need for a systematic and transparent approach to the development and selection of outcomes.

Conclusions and discussion

Conclusions

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- Trial researchers use patient input in a number of ways to inform endpoints used in clinical studies to test new product efficacy
- There may be other ways in which the patient voice can inform endpoint development in the product development lifecycle
- The methods by which patient input is incorporated into endpoint development can be extended to yield a more comprehensive portrait of the patient experience
- Barriers exist to integrating these methods

Barriers

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- I didn't even think about it
  - Incorporating patients into the design of the trial does not even come up (hopefully less common)
- Precedent (even if its bad precedent)
  - "It 'got approved' before" or this is how the other guys did it
  - Antithesis to innovation
  - . Old school paternalism - doctor (or company executives) know best - we don't need patient input
- Regulatory "black hole"
  - "we submitted our PRO for review and haven't heard back".
- Lack of funding
  - No resources or initiatives not seen as worth the investment
- Drug development company positions
  - "We're a conservative company"
- Differentiating consultant good advice from bad advice