The Development and Use of Conceptual Models

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- Which clinical outcome measures are most suitable for use in our clinical trial?
- Does this measure meet regulatory standards?
- Can we use this measure as an endpoint to support a label claim?
- Usually, patient-reported outcome measures (PROs)
- Patient interviews
  - Concepts important to patients?
  - Patient experience of the disease/treatment?
- Development of a conceptual model (CM)
What is a conceptual model?

A number of definitions exist…

We tend to think of CMs as visual representations of patient experience that provide a blueprint for assessing the conceptual relevance and content validity of PRO measures.

A CM can be used to document the symptoms and impacts of a disease or condition, and can be used to propose causal linkages amongst the set of identified concepts.

Did you know…

Wilson & Cleary were the first to publish a CM for health-related quality of life (HRQoL) in 1995\(^1\).

A CM should not be confused with the term conceptual framework, which explicitly defines the concepts measured by the instrument in a diagram that presents a description of the relationships between items, domain (sub concepts), and concepts measured and the scores produced by a PRO instrument (FDA, 2009)\(^2\).

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\(^1\) Wilson IB, Cleary PD. Linking clinical variables with health related quality of life. JAMA, 1995;273;59-65.


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Conceptual Model: Wilson & Cleary, 1995

- Characteristics of the individual
  - Symptom Amplification
  - Personal Motivation
  - Values Preferences

- Biological & Physiological Variables
  - Symptom Status
  - Functional Status
  - General Health Perceptions
    - Overall Quality of Life

- Physiological Supports
  - Social & Economic Supports
  - Social & Psychological Supports

- Characteristics of the Environment
  - Non-medical Factors
Conceptual Models

Endpoint Model: FDA, 2009

Concept

Indication

Treatment of Disease X

Supportive Concepts

Improvement in symptoms/signs of Disease X

Endpoints

Primary

Physiological effect

Secondary

Symptoms diary

Signs diary

Physical exam

Physical performance

PRO assessment

Non-PRO assessment

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Conceptual models can be helpful in PRO/COA research to:

- Better/fully understand the patient/caregiver experience of a disease/condition and important concepts
- Identify potential trial endpoints (and potentially develop an endpoint hierarchy)
- Identify relationships between concepts

This information is important when developing a new PRO measure for a clinical trial.

The information can also be used to identify whether or not a suitable PRO measure already exists (through conceptual mapping).

In the PRO Guidance document (2009), the FDA highlight the importance of establishing evidence of content validity, defined as “the extent to which the instrument measures the concept of interest”. However, no specific information on the development of a CM is provided in the guidance.

Therefore, information within CMs can be used to help establish content validity of a measure.

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The aim of this work was to identify any specific guidelines on the development of CMs for use in PRO research.

- to see what methods are currently being undertaken in practice
- to help reflect on our current development of CMs
- to suggest ideas for best practice
We undertook a targeted review to identify any guidelines available on the use of CMs within PRO development within the last 10 years in humans.

For full text review of any project/disease specific publications, the authors had to include the development process for the CM and include a copy of the CM.

Search terms

- https://www.ispor.org/
- http://www.isoqol.org/

Searches were undertaken in January 2017.
No guidelines were identified that focused specifically on the development of CMs for PRO research.

The targeted hand search of relevant websites identified a number of general PRO guidance documents, which were reviewed. The use of CMs were included in some of these, often as part of the initial work around developing a PRO.
“CM provides a rationale for and description of the concepts and the populations that a measure is intended to assess”.

Inclusion of a CM is number 1 on the PRO checklist criteria developed from a systematic review by Francis et al, 2016\(^1\). No specific guidance as to how the model should be developed was included.

“A hypothesised disease model can help organize and visualize the key features of the patient population, drug mechanism of action, underlying pathophysiology, and effects of the treatment…. The model may then be used to identify and prioritize trial endpoints…and can inform the evaluation of the suitability of existing instruments for the development programme.”

Noted within the ISPOR PRO Good Research Practices Task Force paper on content validity (Patrick et al, 2011)\(^2\). This is part of determining the ‘Context of use’ section of their good practice guidelines for developing a new PRO.

“ISOQOL members were very supportive of the minimum standards described (for PRO measures), with 90% of respondents endorsing that a PRO measure should have documentation that defines the PRO construct and the intended population(s) for use…The CM provides a description and framework for the targeted construct(s) to be included in a PRO measures.”

Research conducted on behalf of ISOQOL (Reeve et al, 2013)\(^3\) to identify the minimum standards for the design and selection of a PRO measure for patient centred outcomes research.

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\(^1\) Francis D et al. Checklist to operationalize measurement characteristics of patient-reported outcome measures. Systematic reviews, 2016, 5: 2019


\(^3\) Reeve B et al. ISOQOL recommends minimum standards for patient-reported outcome measures used in patient-centered outcomes and comparative effectiveness research. Qual Life Res, 2013. DOI 10.1007/s11136-012-0344-y
The CMs were generally split into domains and sub-domains associated with disease symptoms and disease/treatment impacts.
Holloway et al. used published literature to develop a CM for systemic lupus erythematosus\textsuperscript{1}

\textsuperscript{1} Holloway et al. Patient reported outcome measures for systemic lupus erythematosus clinical trials: a review of content validity, face validity, and psychometric performance. Health and Quality of Life Outcomes, 2014, 12: 116
Devlen et al, used primary patient research (interviews and focus groups) to develop a CM for inflammatory bowel disease\(^1\)

Own example of CM (1)

Symptoms pre-diagnosis
- Lump/ bumps; neck/ head
- Swollen lymph nodes
- Swallowing problems (changes to and/or difficulty swallowing)
- Pain in mouth
- Cough
- Change in voice
- Sore throat
- Loss of appetite / eating less
- Weight loss
- Impact on range of movement
- Tiredness
- Dry neck skin
- Hearing problems
- Tongue ulcer
- Breathing difficulties
- Difficulty speaking
- Difficulty chewing food
- Enlarged tonsils
- Ear pain
- Nasal bleeding
- Headaches

Symptoms side effects during treatment
- Diagnosis
- Unable to differentiate*
- Emotional/ psychological impacts
- Surgery
- Swallowing problems
- Taste problems
- Weight loss
- Dry mouth
- Swelling
- Tooth damage/ removal
- Tiredness/ fatigue/ exhaustion
- Weakness
- Breathing difficulties
- Scarring
- Radiation
- Swallowing problems
- Oral inflammation/ burning sensation
- Soreness
- Difficulty speaking
- Cough
- Loss of voice
- Numbness
- Dry/ peeling neck skin
- Radiation burns
- Tooth damage/ removal
- Bleeding
- Abdominal bloating
- Impact on range of movement
- Chemotherapy
- Peripheral Neuropathy
- Psychadelic dreams
- Difficulty sleeping through the night
- Diarrhoea
- Dizziness
- Immunotherapy
- Pain
- Fatigue
- Fluid retention
- Emotions/ Psychological impacts
- Missing food/ not enjoying food/ feeling hungry
- Bothered/ embarrassed by appearance
- Depression/ demotivation/ feeling hopeless
- Fear/ concern/ worry
- Felling drained/ worn down
- Feeling irritated/ annoyed/ frustrated
- Feeling isolated
- Feeling overwhelmed
- Upset/ miserable

Impacts on lifestyle
- Impact on physical function
  - Difficulty eating/ drinking
  - Increased resting/ napping
  - Difficulty with self-care
  - Difficulty carrying
  - Difficulty standing
  - Difficulty walking
- Difficulty sleeping through the night
- Unable to drive
- Unable to care for dependents
- Unable to work/ reduced work
- Unable/ limited to continue socialising/ taking part in hobbies
- Financial burden
- Reliance on partner/ others
- Issues with verbal communication

Cited in Degboe et al. Qualitative interviews to understand the patient experience of squamous cell carcinoma of the head and neck and explore the content validity of patient reported outcome measures. Presented at ISPOR 22nd Annual International Meeting, May 20-24, 2017, Sheraton Boston Hotel and the John B. Hynes Veterans Memorial Convention Center, Boston, MA, USA.
### Own example of CM (2)

<table>
<thead>
<tr>
<th>Pre-diagnosis symptoms</th>
<th>Most frequently reported concepts</th>
<th>Most common impacts on patient functioning and HRQoL</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acute</strong></td>
<td>• Neck lump/ swelling</td>
<td>• Difficulty eating/ drinking</td>
</tr>
<tr>
<td></td>
<td>• Difficulty swallowing</td>
<td>• Difficulty speaking</td>
</tr>
</tbody>
</table>

#### Surgery side effects

- Acute
  - Numbness
  - Difficulty speaking
  - Pain
  - Soreness
  - Swelling
- Chronic
  - Tooth damage/ removal
  - Loss of mobility

#### Chemotherapy and/or radiation side effects

- Weight loss
- Tiredness/ fatigue
- Taste problems
- Pain
- Dry mouth/ lack of saliva
- Nausea

#### Radiation side effects

- Swallowing problems
- Soreness
- Dry skin at radiation site
- Radiation burns

### Quotes

- “I had a lump on my neck... I noticed it for maybe two months, it did not bother me, did not hurt, I just could feel it when I touched it, there was a lump there” (01-06-M-57)
- “I first had a... noticed a difference in my swallow, it was really a sore throat but it was something that was different” (01-04-M-59)
- “I couldn’t talk. My friends would call and family to see how I was and it was very difficult talking on the phone initially” (01-14-F-61)
- “My face looked like I had two footballs on the sides. I think it took a week for me to look” (01-07-F-66)
- “Well at that point I couldn’t eat. I mean they were just feeding me through a tube” (01-07-F-66)
- “…the easiest way to sum up when I started chemotherapy...It feels like somehow it’s just a nightmare, literally a nightmare” (01-10-M-35)
- “Everything goes on hold. You don’t do anything, you don’t go to the gym, you don’t work out, you don’t socialise, you can’t drink any alcohol, and you can’t eat, so you become very isolated” (01-03-M-55)
- “…radiation was shooting round my neck, so my throat was very sore, and I couldn’t eat...” (01-06-M-57)
- “So at that point in time I’ve lost 35 pounds, and you are very depressed, can’t eat through your mouth, everything goes through the feeding tube, you try to eat foods that they taste horrific, things that you like don’t taste at all like you remember them” (01-03-M-55)
Conclusions

From the publications reviewed, there are similarities between the final models developed.

CMs play an important role in the development of new PROs and for establishing whether suitable PROs already exist for use in clinical trials.

No guidelines were identified that provide guidance on the best methods for developing CMs for PRO use.

The method for development can vary; however, including data from patients will provide a more robust blueprint as to what concepts are important to them. This is especially true where literature in a certain disease area is lacking or unclear.

A two-step process of involving patients and/or clinicians during model development, and validation following model development may also be useful to ensure that all viewpoints are considered.
Any questions?

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