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With the partnership of

AFEF
Société francophone du diabète
THE FORUM
For Collaborative Research
Development of a patient-reported outcomes measure (PROM) for NASH that meets regulatory standards

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Agenda

• Are these terms synonymous?
  • Quality of Life (QoL)
  • Health-related quality of life (HRQoL)
  • Patient-reported outcomes (PROs)

• Why PROs are important?
  • Regulatory environment & guidance

• Development of a PRO measure (PROM) in NASH
Agenda

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• Development of a PROM in NASH
What is Health-related Quality of Life (HRQoL)?

HRQoL is a multidimensional construct

**FDA**
Multidomain concept that represents the patient’s general perception of the effect of illness and treatment on physical, psychological, and social aspects of life.

**EMA**
The patient’s subjective perception of the impact of his/her disease and its treatment(s) on his/her daily life, including physical, psychological, and social functioning, and well-being.

FDA Guidance, 2009; EMA reflection paper, 2005

Development of NASH PRO - Dr MM Balp 6th July 2018
Patient-reported outcomes (PROs)

A PRO - a measurement of any aspect of a patient’s health status that comes directly from the patient without interpretation from anyone else.

- Can range from symptoms (severity, frequency or duration) to more complex issues of HRQoL, activities of daily living.
- Can be assessed through direct self-report or interview administration.
- Measured through individual items, subscales, or full questionnaires.
- Administered via electronic devices or paper/pencil format.


Development of NASH PRO - Dr MM Balp 6th July 2018
Type of PRO Measures (PROMs)

• Generic – used across disease areas
  • Short Form-36 (SF-36), Work Productivity and Activity Impairment (WPAI)
  • Preference-based measures: EQ-5D

• Organ-specific
  • Dermatology Life Quality Index (DLQI)
  • Chronic Liver Disease Questionnaire (CLDQ)

• Disease specific:
  • Chronic Urticaria Quality of Life (CU-Q2oL)
  • CLDQ-NAFLD
Agenda

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• Development of a PROM in NASH
Value of PROs and PROMs

• Some symptoms and treatment effects known only to patients
• Better quantify how treatments benefit patients
• Sometimes poor correlations between clinical and PRO measures (FEV1 and asthma symptoms)
• Patient perceptions influence health seeking behaviour

PROMs

• Can be used in clinical practice to complement medical examination & ease physician-patient dialogue
• Can be implemented in drug development process:
  • Capture patients’ view about disease and treatment effect
  • Basis of a drug label claim
• Can be supportive for health-technology assessment (HTA) decisions
PROs can provide vital information to regulators

Myelofibrosis (2011)

“A PRO measure] was a secondary endpoint, but in our mind this is why we gave the application full approval. One could quibble about the importance of reduction in spleen size, but with reduction in all the symptoms, full approval was warranted.”

Richard Pazdur
Director of FDA's Office of Hematology Oncology Products

McCallister E et al. BIO Century 2011
FDA, Food and Drug Administration; PRO, patient-reported outcome

Development of NASH PRO - Dr MM Balp 6th July 2018
Development of PROMs follow Regulatory guidance

2005

2009

Guidance for Industry

Patient-Reported Outcome Measures:
Use in Medical Product Development
to Support Labeling Claims

2017 +

Plan for
Issuance of Patient-Focused
Drug Development Guidance

Under
21st Century Cures Act
Title III Section 3002

May 2017

Development of NASH PRO - Dr MM Balp 6th July 2018
FDA position in 2017

• 21st Century Cures Act: Patient-Focused Drug Development
  • The need for patient engagement in drug development
  • Define and standardize the use of patient experience data in regulatory programs
  • All new drug approvals to include a brief statement summarizing any patient experience data that was submitted and reviewed

• Workgroup Guidance 4 “will, as appropriate, revise or supplement the 2009 Guidance to Industry on Patient-Reported Outcome Measures”

FDA, Food and Drug Administration; PRO, patient-reported outcome
Need to understand core & proximal disease concepts before measuring distal concepts

- Disease-defining concepts
- Proximal disease impact concepts
- Distal disease impact concepts
- Disease impact on general life concepts

- Core signs, symptoms
  - Related functioning
  - Related Signs / Symptoms
- Additional functioning
  - Additional symptoms
- General psychological & physical functioning
  - Social functioning
  - Productivity
- Health status
  - Satisfaction with health

Health-related quality of life
Development of a PROM – FDA framework

Stage 1: Qualitative

i. Hypothesize Conceptual Framework
• Outline hypothesized concepts and potential claims
• Determine intended population
• Determine intended application/characteristics (type of scores, mode and frequency of administration)
• Perform literature/expert review
• Develop hypothesized conceptual framework
• Place PROs within preliminary endpoint model
• Document preliminary instrument development

ii. Adjust Conceptual Framework and Draft Instrument
• Obtain patient input
• Generate new items
• Select recall period, response options and format
• Select mode/method of administration/data collection
• Conduct patient cognitive interviewing
• Pilot test draft instrument
• Document content validity

iii. Confirm Conceptual Framework and Assess Other Measurement Properties
• Confirm conceptual framework with scoring rule
• Assess score reliability, construct validity, and ability to detect change
• Finalize instrument content, formats, scoring, procedures and training materials
• Document measurement development

v. Modify Instrument
• Change wording of items, populations, response options, recall period, or mode/method of administration/data collection
• Translate and culturally adapt to other languages
• Evaluate modifications as appropriate
• Document all changes

Stage 2: Quantitative

iv. Collect, Analyze, and Interpret Data
• Prepare protocol and statistical analysis plan (final endpoint model and responder definition)
• Collect and analyze data
• Evaluate treatment response using cumulative distribution and responder definition
• Document interpretation of treatment benefit in relation to claim

Development of NASH PRO - Dr MM Balp 6th July 2018
PRO label claim - only if the PRO measure is valid

<table>
<thead>
<tr>
<th>VALIDITY</th>
<th>RELIABILITY</th>
<th>PRECISION</th>
<th>RESPONSIVENESS</th>
</tr>
</thead>
</table>
| Does it measure what it is meant to?  
- Content validity  
- Face validity  
- Criterion validity  
- Construct validity | Are the results stable over time when applied to the same people at different time periods?  
(Test-retest reliability) | Does the measure discriminate between different patient groups, health status, treatment? | Is the measure responsive to change when change is present? |
Agenda

• Are these terms synonymous?
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  • Health-related quality of life (HRQoL)
  • Patient-reported outcomes measures (PROMs)

• Why PROs are important?
  • Regulatory environment & guidance

• Development of a PROM in NASH
Objectives

• To develop a new NASH-specific PRO measure to assess
  o Symptoms
  o HRQOL

• Suitable for NASH patients in fibrosis stages F1 to F3
Stages of NASH-PRO development (FDA)

Stage 1 - Qualitative
- Face Validity
- Content Validity

Qualitative Study

Stage 2 - Quantitative
- Dimensionality
- Reliability
- Construct Validity
- Responsiveness
- Interpretability

Interventional phase 2 study data

Stage 3+
- Confirmation of Psychometric Properties
- Regulatory documents

Additional Studies
Qualitative development stage

- NASH-PRO Task Force creation
  - Clinical experts
  - PRO experts
  - Patient representatives
- Targeted literature review: identify burden of NASH F1-F3 on patients and existing PROs
- Draft conceptual model framework

- Concept elicitation interviews
- Items identification
- Draft PROM development
- Cognitive debriefing interviews
- Final conceptual model
- Final PROM content

- Validated translations in 16 countries/24 languages
- Pen/paper & Electronic version of the PROM
- Inclusion in a phase II interventional study
Early conceptual model in NASH
Based on literature review and discussion with the Task Force

Signs/ Symptoms
- Pain (including dull, mild ache)
- Other bodily symptoms (cardio, shortness of breath, reduce exercise tolerance, itch)
- Fatigue (tease out fatigue associated with diabetes and fatty liver)
- Sleep Impact (sleep apnoea, quality of sleep, partners)
- Cognition (reduced sharpness, subtle changes)

Disease- Related Impact
- Activity limitations
- Physical activity
- Social activity/ relationships
- Personal relationships
- Work impact

General Impact
- Emotional well-being
- Healthy eating choices
- Self-confidence/ esteem
- Patient activation (engagement in health care)
### Concept elicitation interviews

| Objectives | • Understand the impact of NASH from patient perspective  
|            | • Generate items (content) for the new PROM  
|            | • Construct draft PROM (response options, instructions, recall period) |

| Approach | • Study protocol and discussion guide developed  
|          | • F2F interviews conducted with eligible NASH patients in a clinic in US  
|          | • Thematic analysis of interview transcripts  
|          | • Potential items to capture these concepts extracted |

| Results | • 27 patients were interviewed and 24 included in the analysis  
|         | • Analysis was conducted in sets of 5 - Concept saturation* was reached  
|         | • Interview transcripts were coded based on the conceptual model |

| Key Outcome | Draft 1 NASH-PRO Instrument suitable for content validity evaluation |

*Guest et al 2006
Key Symptoms and patient quotes

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Description</th>
<th>Patient Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>“I would say I probably have constant dull ache in my right upper quadrant that radiates to my back. And sometimes it goes up to my like shoulder” (F/Age 36)</td>
<td>F/Age 36</td>
</tr>
<tr>
<td></td>
<td>“I do have itching. Often.” (F/65)</td>
<td>F/65</td>
</tr>
<tr>
<td></td>
<td>“I get very tired, normal activities fatigue me.” (F/48)</td>
<td>F/48</td>
</tr>
<tr>
<td></td>
<td>“I’m forgetting things. I’m definitely foggy, really foggy. I just can’t get it together.” (F/48)</td>
<td>F/48</td>
</tr>
<tr>
<td></td>
<td>“Memory and retention. I’ll go to say something and I’ll just completely forget where I was at and that aggravates me.” (F/45)</td>
<td>F/45</td>
</tr>
<tr>
<td>Skin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cognition</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sleep</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Key HRQOL concepts and patient quotes

- “It limits my activities. I can’t do a lot of things that I was doing, sports and working; working is the main thing.” (F/age 48)
- “Just drive to work is a pain .... Sometimes before I get there my head’s nodding .... and if you drive ... got to be so alert.” (M/51)
- “I used to walk 5 miles a day and I was riding a bicycle during the summer too. I can’t do any of it now. I just feel like everything’s been deprived from you” (F/58)
- “Like if I try to vacuum ... I get out of breath.” (F/61)
- “I changed ..., stopped drinking sodas, no fatty foods and I went gluten-free, wheat-free, basically meat-free except for chicken, and salads and nuts and fish and water.” (F/48)
First draft of the NASH-PRO based on CE

- The Task Force team agreed on the proposed draft items, instructions, recall period and response options for 3 ‘logical’ scales
  - Symptoms – 16 items
  - Day-to-day Activities – 9 items
  - Emotions and Lifestyle – 27 items
- Total items - 52
- Recall period 7 days
- Draft 1 contained some duplicate items for review during CD interviews
- The NASH-PRO was named NASH-CHECK
# Cognitive debriefing interviews

| Objectives | • Evaluate content validity  
| • Assess if the PROM includes the key dimensions important to patients  
| • Evaluate if individual items adequately capture the target dimension |

| Approach | • F2F interviews with other eligible NASH patients in a clinic in US  
| • “Useability” testing:  
| • Items/wording are understood and suitable  
| • Instructions are clear  
| • Response options adequate  
| • Appropriateness of recall period (7days) |

| Results | • 15 patients were interviewed and audio recorded  
| • Analysis was conducted in 2 rounds  
| • Changes made after the first round (removal of duplicates and rewording) |

| Key Outcome | Draft 2 NASH-CHECK suitable for translation and inclusion in an interventional phase II clinical trial |
Changes to the NASH-PRO during/after CD

Draft 1.0 (Round 1)
- Symptoms
  - 16 items
- Life Impact (Activities)
  - 9 items
- Life Impact (Emotions and Lifestyle)
  - 27 items
  **52 item measure**

Draft 1.1 (Round 2)
- Symptoms
  - 10 items
- Life Impact (Activities)
  - 8 items
- Life Impact (Emotions and Lifestyle)
  - 16 items
  **34 item measure**

Draft 2 (Post CD)
- Symptoms
  - 10 items
- Life Impact (Activities)
  - 8 items
- Life Impact (Emotions and Lifestyle)
  - 13 items
  **31 item measure**

**Instrument was considered comprehensive (nothing missing)**

Instructions / Recall Period / Response Options
- Minor changes to instructions
- No changes to recall period or response options

Development of NASH PRO - Dr MM Balp 6th July 2018
Final conceptual model framework

NASH (F1 to F3)

Symptoms
- Pain
- Fatigue
- Itch
- Cognition
- Sleep impact

Activity Limitations
- Physical Mobility
- ADLs (+ personal care)
- iADLs

Social Impact
- Social Functioning
- Personal Relationships
- Relationships (Friends)

Psychological Impact
- Emotional Impact
- Self Confidence

Economic Impact
- Work Productivity
- Ability to Work
- Cost of Medication
- Cost of Lifestyle Mng

Risk Factors
- Diabetes
- High BMI

Psychological Risk Factors
- Attitude
- Motivation
- Eating Habits

Development of NASH PRO - Dr MM Balp 6th July 2018
### Symptoms

The following questions ask about your symptoms you may have experienced related to your fatty liver disease.

Instructions: For each of the following questions, please choose the one response that best represents the symptom at its worst over the past 7 days. If you did not experience the symptom in the past 7 days, answer 0.

1) At its worst, how would you rate the severity of any pain you have had in the upper part or right side of your abdominal (stomach) area over the past 7 days?

<table>
<thead>
<tr>
<th>No Pain</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>Worst</th>
</tr>
</thead>
</table>

2) At its worst, how would you rate the severity of any abdominal (stomach) bloating you have had over the past 7 days?

<table>
<thead>
<tr>
<th>No Bloating</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>Worst</th>
</tr>
</thead>
</table>

3) At its worst, how physically fatigued have you felt over the past 7 days?

<table>
<thead>
<tr>
<th>No Physical Fatigue</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>Worst</th>
</tr>
</thead>
</table>

4) At its worst, to what extent have you felt the need to lay down and rest over the past 7 days?

<table>
<thead>
<tr>
<th>No Need To Rest</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>Worst</th>
</tr>
</thead>
</table>

5) At its worst, to what extent have you had difficulty sleeping over the past 7 days?

<table>
<thead>
<tr>
<th>No Difficulty Sleeping</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>Worst</th>
</tr>
</thead>
</table>

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### Day-to-Day Activities

The following questions ask about how your fatty liver disease affects your day-to-day activities.

Instructions: Please select the answer that best describes what you were able to do during the past 7 days. Please select one answer for each question.

1) Bending over (e.g., to put on your socks and shoes or to pick something up from the ground)

<table>
<thead>
<tr>
<th>Not at all</th>
<th>A little</th>
<th>Quite a lot</th>
<th>Very much</th>
</tr>
</thead>
</table>

2) Doing light chores around the house (e.g., dusting, cooking, light gardening)

<table>
<thead>
<tr>
<th>Not at all</th>
<th>A little</th>
<th>Quite a lot</th>
<th>Very much</th>
</tr>
</thead>
</table>

3) Doing heavy chores around the house (e.g., changing bed linens, vacuuming, taking the trash out, heavy gardening)

<table>
<thead>
<tr>
<th>Not at all</th>
<th>A little</th>
<th>Quite a lot</th>
<th>Very much</th>
</tr>
</thead>
</table>

4) Lifting or carrying heavy objects (e.g., a large bag of groceries)

<table>
<thead>
<tr>
<th>Not at all</th>
<th>A little</th>
<th>Quite a lot</th>
<th>Very much</th>
</tr>
</thead>
</table>

5) Taking a short walk on level ground (e.g., walking for less than 5 minutes)

<table>
<thead>
<tr>
<th>Not at all</th>
<th>A little</th>
<th>Quite a lot</th>
<th>Very much</th>
</tr>
</thead>
</table>

6) Taking a long walk on level ground (e.g., walking for more than 20 minutes)

<table>
<thead>
<tr>
<th>Not at all</th>
<th>A little</th>
<th>Quite a lot</th>
<th>Very much</th>
</tr>
</thead>
</table>

7) Taking a brisk walk on level ground

<table>
<thead>
<tr>
<th>Not at all</th>
<th>A little</th>
<th>Quite a lot</th>
<th>Very much</th>
</tr>
</thead>
</table>

8) Walking up a flight of stairs

<table>
<thead>
<tr>
<th>Not at all</th>
<th>A little</th>
<th>Quite a lot</th>
<th>Very much</th>
</tr>
</thead>
</table>

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### Emotions and Lifestyle

The following questions ask about how you feel.

Instructions: Please think about how much each statement has applied to you over the past 7 days. Please select one answer for each statement.

19. I worry about my fatty liver disease

<table>
<thead>
<tr>
<th>Not at all</th>
<th>A little</th>
<th>Quite a lot</th>
<th>Very much</th>
</tr>
</thead>
</table>

20. My fatty liver disease makes me feel down

<table>
<thead>
<tr>
<th>Not at all</th>
<th>A little</th>
<th>Quite a lot</th>
<th>Very much</th>
</tr>
</thead>
</table>

21. I get angry with myself because of my fatty liver disease

<table>
<thead>
<tr>
<th>Not at all</th>
<th>A little</th>
<th>Quite a lot</th>
<th>Very much</th>
</tr>
</thead>
</table>

22. I feel like others may judge me for my fatty liver disease

<table>
<thead>
<tr>
<th>Not at all</th>
<th>A little</th>
<th>Quite a lot</th>
<th>Very much</th>
</tr>
</thead>
</table>

23. My illness affects my relationships with my friends and family

<table>
<thead>
<tr>
<th>Not at all</th>
<th>A little</th>
<th>Quite a lot</th>
<th>Very much</th>
</tr>
</thead>
</table>

24. I feel I miss out on everyday activities with my family and friends

<table>
<thead>
<tr>
<th>Not at all</th>
<th>A little</th>
<th>Quite a lot</th>
<th>Very much</th>
</tr>
</thead>
</table>

25. I feel I miss out on family life

<table>
<thead>
<tr>
<th>Not at all</th>
<th>A little</th>
<th>Quite a lot</th>
<th>Very much</th>
</tr>
</thead>
</table>

26. I feel like I am a worry to my family

<table>
<thead>
<tr>
<th>Not at all</th>
<th>A little</th>
<th>Quite a lot</th>
<th>Very much</th>
</tr>
</thead>
</table>

27. My illness affects my intimate relationships

<table>
<thead>
<tr>
<th>Not at all</th>
<th>A little</th>
<th>Quite a lot</th>
<th>Very much</th>
</tr>
</thead>
</table>

28. I don’t go out to socialize with friends

<table>
<thead>
<tr>
<th>Not at all</th>
<th>A little</th>
<th>Quite a lot</th>
<th>Very much</th>
</tr>
</thead>
</table>

29. My illness restricts the things I can do in my spare time

<table>
<thead>
<tr>
<th>Not at all</th>
<th>A little</th>
<th>Quite a lot</th>
<th>Very much</th>
</tr>
</thead>
</table>

30. My illness affects my ability to work or study

<table>
<thead>
<tr>
<th>Not at all</th>
<th>A little</th>
<th>Quite a lot</th>
<th>Very much</th>
</tr>
</thead>
</table>

31. I feel restricted in the foods I can eat

<table>
<thead>
<tr>
<th>Not at all</th>
<th>A little</th>
<th>Quite a lot</th>
<th>Very much</th>
</tr>
</thead>
</table>
Next steps

• Work as a team in Liver Investigation: Testing Marker Utility in Steatohepatitis

• Psychometric validation of NASH-CHECK based on phase II study data

• Inclusion of NASH-CHECK in other interventional and non-interventional studies

• Qualitative work to explore content validity in patients with NASH and cirrhosis
Thank you

NASH-PRO Task Force

- Arun Sanyal
- Donna Cryer
- Maria-Magdalena Balp
- Clifford Brass
- Quentin Anstee
- Judi Rhys
- Lynda Doward
- James Twiss

Development of NASH PRO - Dr MM Balp 6th July 2018
Supporting publications


