International Think Tank

# Paris NASH Meeting

## July 5 & 6, 2018
Institut Pasteur

### Organized by


**Veronica Miller**
UC Berkeley School of Public Health, Washington DC, USA

**Arun Sanyal**
Virginia Commonwealth University School of Medicine, Richmond, Virginia, USA

**Lawrence Serfaty**
Hôpital Hautepierre Hôpitaux Universitaires de Strasbourg, France


### Scientific committee

Quentin Anstee
Pierre Bedossa
Jean-François Dufour
Scott Friedman
Fabio Marra
Manuel Romero-Gómez
Frank Tacke
Michael Trauner

With the partnership of

AFEF Société Française d'Hépatologie

Société Francophone du Diabète

THE FORUM For Collaborative Research℠

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# Development of a patient-reported outcomes measure (PROM) for NASH that meets regulatory standards

Dr. Maria-Magdalena Balp
Director Health Economics & Outcomes Research
Novartis Pharma AG

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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

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# 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 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

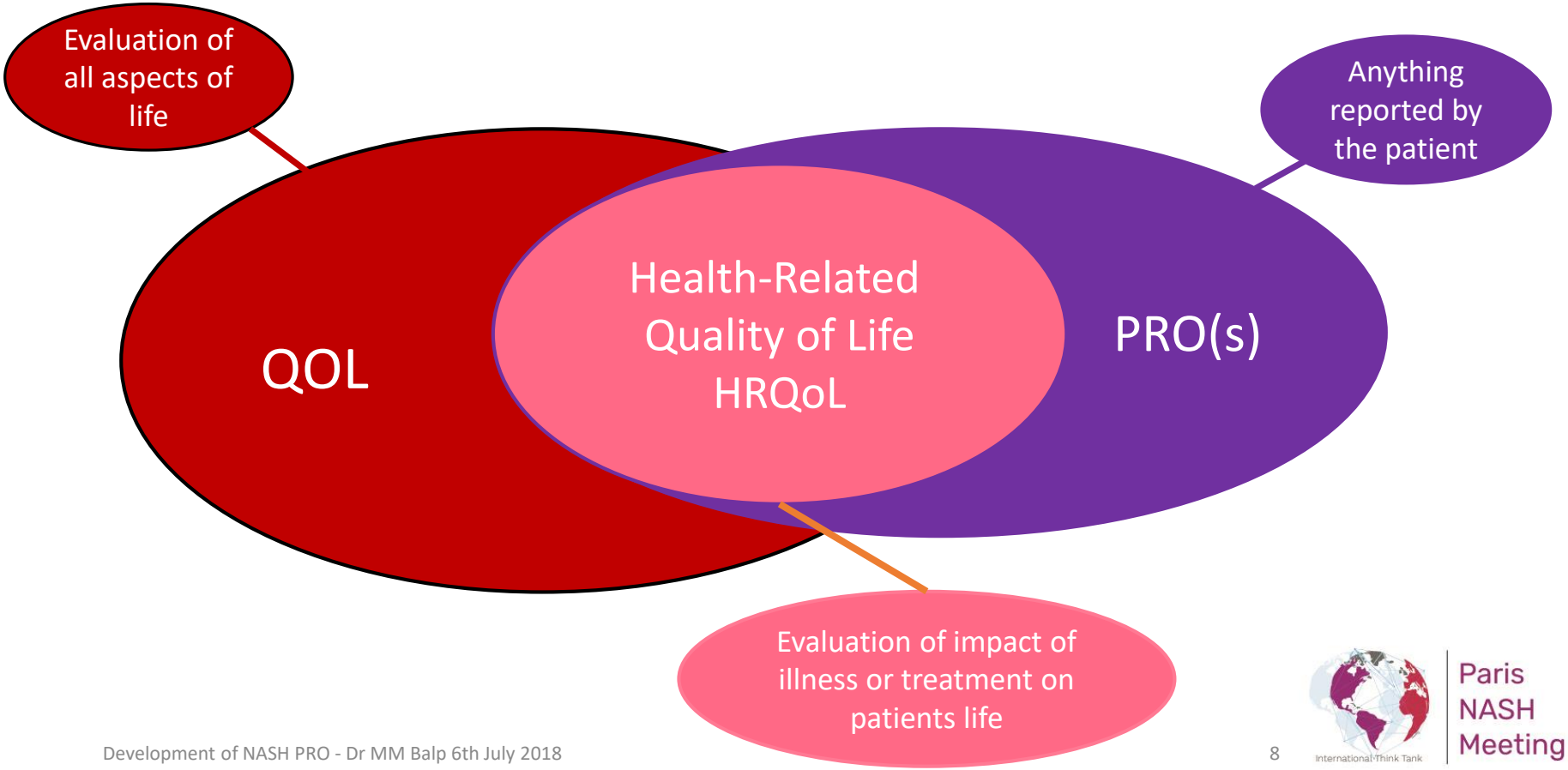
# Patient-reported outcomes (PROs)

**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

FDA Guidance, 2009. http://www.fda.gov/downloads/Drugs/Guidances/UCM193282.pdf.

# QoL ≠ HRQOL ≠ PROs



# 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

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# Value of PROs and PROMs

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

- 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

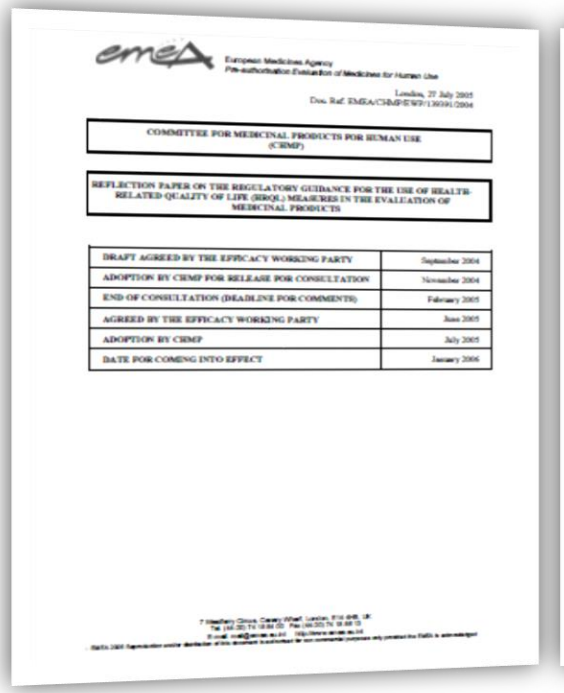
Director of FDA's Office of Hematology Oncology Products

McCallister E *et al.* BIO Century 2011

FDA, Food and Drug Administration; PRO, patient-reported outcome

# Development of PROMs follow Regulatory guidance

**2005** 2009 **2017 +**



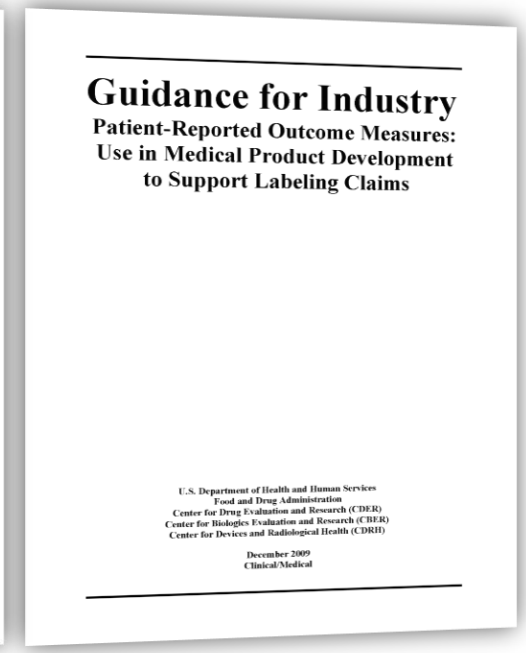
European Medicines Agency
Pre-authorisation Evaluation of Medicines for Human Use

London, 29 July 2005
Doc. Ref. EMEA/CHMP/EWP/139391/2004

COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

REFLECTION PAPER ON THE REGULATORY GUIDANCE FOR THE USE OF HEALTH-RELATED QUALITY OF LIFE (HRQL) MEASURES IN THE EVALUATION OF MEDICINAL PRODUCTS

| | |
|---|---|
| DRAFT AGREED BY THE EFFICACY WORKING PARTY | September 2004 |
| ADOPTION BY CHMP FOR RELEASE FOR CONSULTATION | November 2004 |
| END OF CONSULTATION (DEADLINE FOR COMMENTS) | February 2005 |
| AGREED BY THE EFFICACY WORKING PARTY | June 2005 |
| ADOPTION BY CHMP | July 2005 |
| DATE FOR COMING INTO EFFECT | January 2006 |

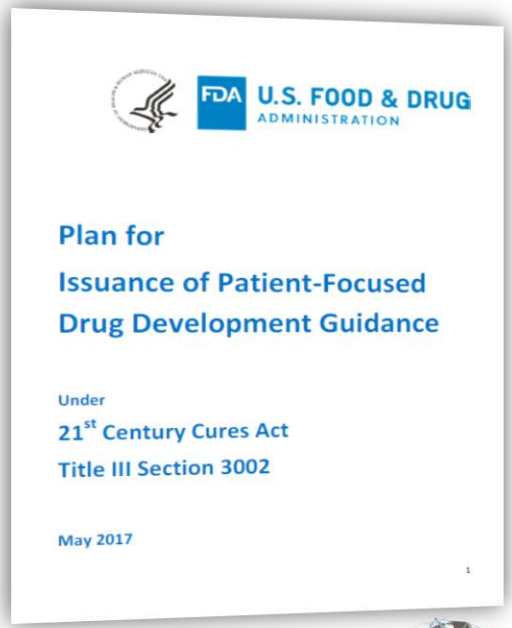


**Guidance for Industry**

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

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)

December 2009
Clinical/Medical



U.S. FOOD & DRUG ADMINISTRATION

Plan for
Issuance of Patient-Focused
Drug Development Guidance

Under
21st Century Cures Act
Title III Section 3002

May 2017

1

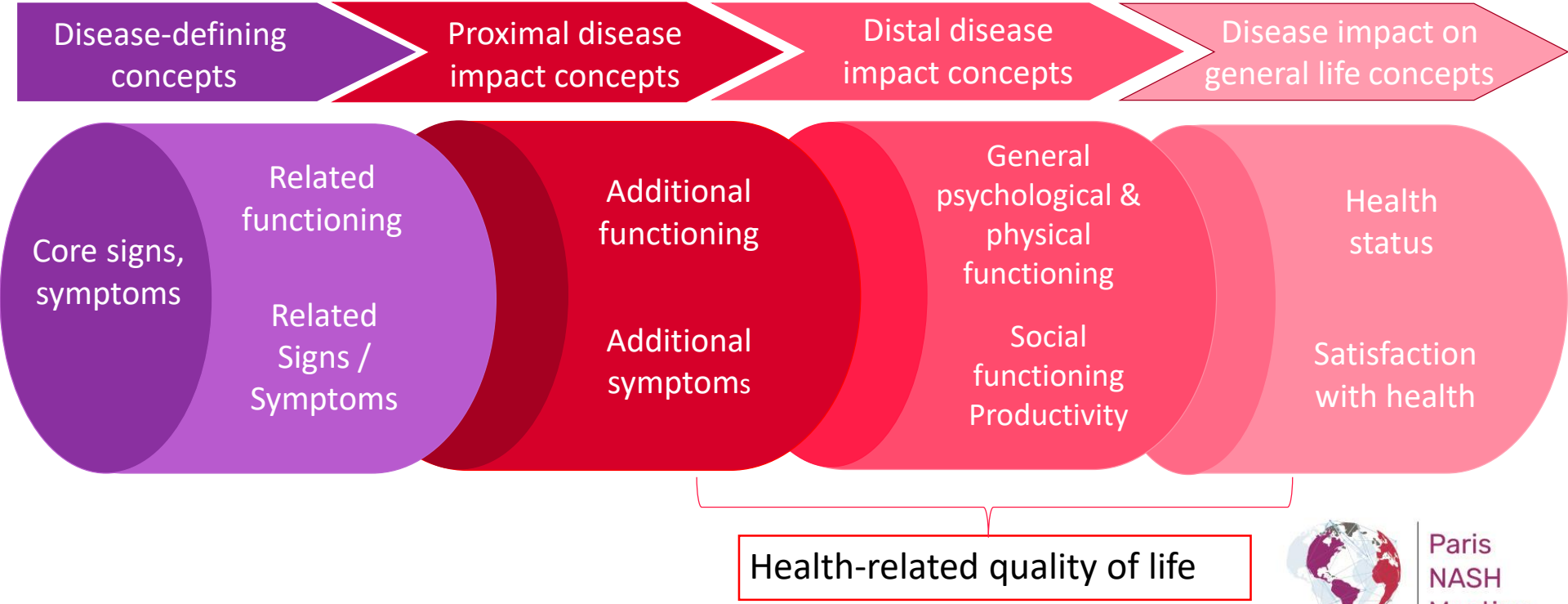
# FDA position in 2017

- **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**"*

US FDA. Plan for Issuance of Patient-Focused Drug Development Guidance. May 2017

FDA, Food and Drug Administration; PRO, patient-reported outcome

# Need to understand core & proximal disease concepts before measuring distal concepts



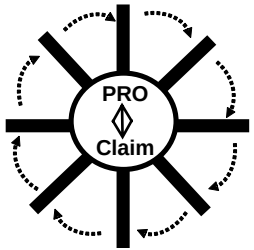
# Development of a PROM – FDA framework

Stage 1: Qualitative

Stage 2: Quantitative

## 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

## 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

## 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

# PRO label claim - only if the PRO measure is valid

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

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# Objectives

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

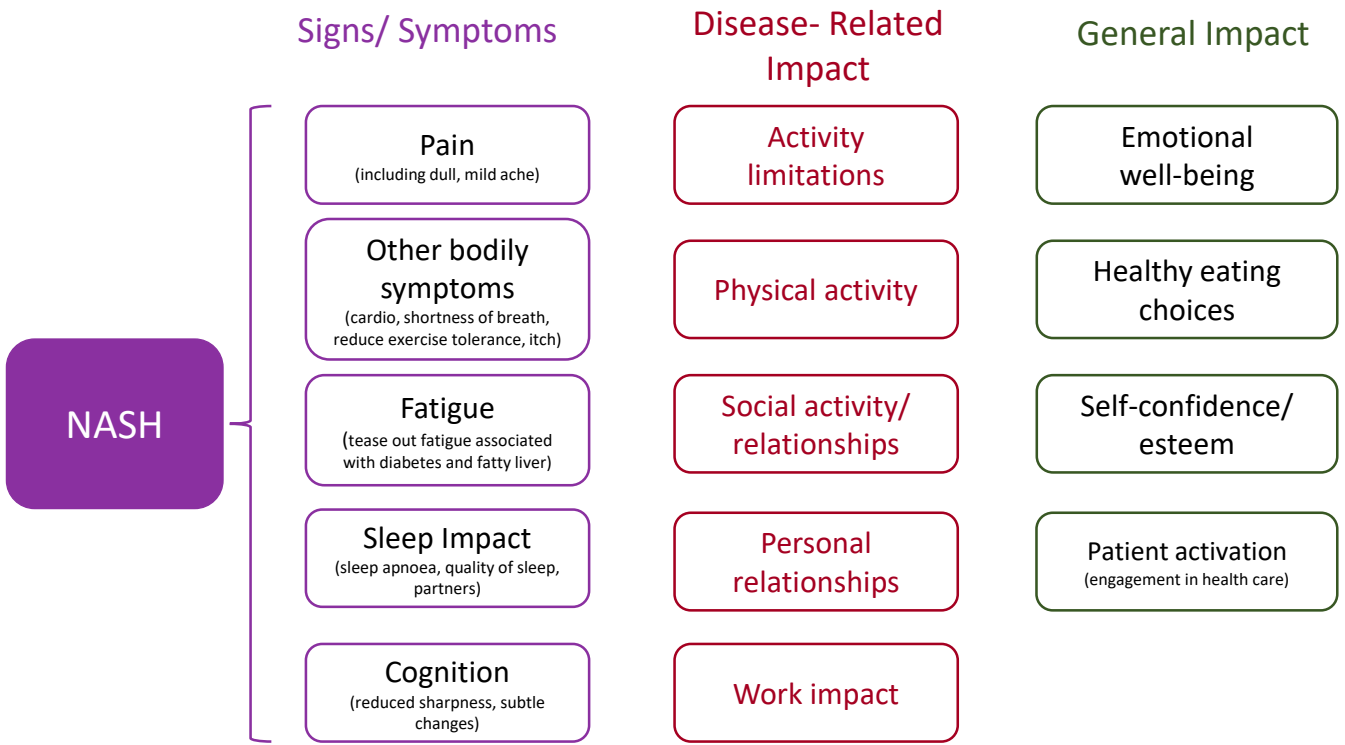
- NASH-PRO Task Force creation
  - Clinical experts
  - PRO experts
  - Patient representatives
- Targeted literature review: identify burden of NASH F1-F3 on patients and existing PROs
- Draft conceptual model framework

- 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



# Concept elicitation interviews

| | |
|---|---|
| **Objectives** | • Understand the impact of NASH from patient perspective<br>• Generate items (content) for the new PROM<br>• Construct draft PROM (response options, instructions, recall period) |
| Approach | • Study protocol and discussion guide developed<br>• F2F interviews conducted with eligible NASH patients in a clinic in US<br>• Thematic analysis of interview transcripts<br>• Potential items to capture these concepts extracted |
| Results | • 27 patients were interviewed and 24 included in the analysis<br>• Analysis was conducted in sets of 5 - Concept saturation* was reached<br>• 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

- Fatigue
- Skin
- Cognition
- Pain
- Sleep

- “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)
- “I do have itching. Often.” (F/65)
- “I get very tired, normal activities fatigue me.” (F/48)
- “I’m forgetting things. I’m definitely foggy, really foggy. I just can’t get it together.” (F/48)
- “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)

# Key HRQOL concepts and patient quotes

- Activity Limitations
- Social Functioning
- Psychological Impact
- Work Impact
- Eating Habits

- "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<br>• Assess if the PROM includes the key dimensions important to patients<br>• Evaluate if individual items adequately capture the target dimension |
|---|---|
| Approach | • F2F interviews with other eligible NASH patients in a clinic in US<br>• "Useability" testing:<br>  • Items/wording are understood and suitable<br>  • Instructions are clear<br>  • Response options adequate<br>• Appropriateness of recall period (7days) |
| Results | • 15 patients were interviewed and audio recorded<br>• Analysis was conducted in 2 rounds<br>• 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

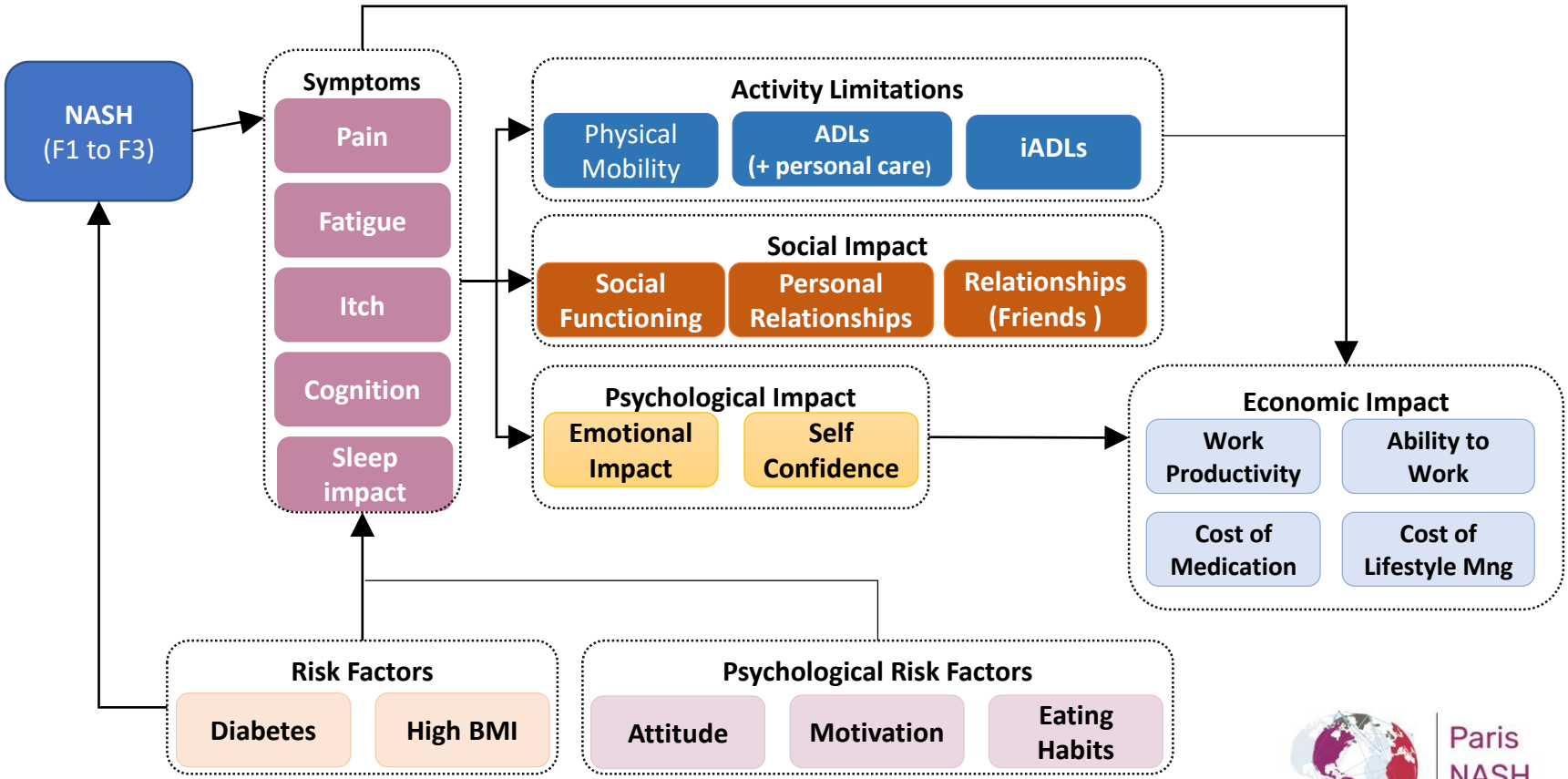
**31 item measure**

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

### Instructions / Recall Period / Response Options

- Minor changes to instructions
- No changes to recall period or response options

# Final conceptual model framework



# Assessment of symptoms and health-related quality of life in non-alcoholic steatohepatitis (NASH)

NASH-CHECK

This questionnaire asks about your experience of living with fatty liver disease. We are interested in the symptoms that you may have experienced and how these may have affected your day-to-day life and emotions.

## 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 sym **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?

☐ 0 No Pain ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 1 W Pos P

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

☐ 0 No Bloating ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 1 W Pos Bloa

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

☐ 0 No Physical Fatigue ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 1 W Pos Phy Fat

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

☐ 0 No Need To Rest ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 1 Extr Nee Re

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

☐ 0 No Difficulty Sleeping ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ Ext Diff Sle

## 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 de the past 7 days. Please select one answer for each

Over the past 7 days, how much difficulty have you

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

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

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

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

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

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

17) Taking a brisk walk on level ground

18) Walking up a flight of stairs

## 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.

| | Not at all | A little | Quite a lot | Very much |
|---|---|---|---|---|
| 19. I worry about my fatty liver disease | ☐ | ☐ | ☐ | ☐ |
| 20. My fatty liver disease makes me feel down | ☐ | ☐ | ☐ | ☐ |
| 21. I get angry with myself because of my fatty liver disease | ☐ | ☐ | ☐ | ☐ |
| 22. I feel like others may judge me for my fatty liver disease | ☐ | ☐ | ☐ | ☐ |
| 23. My illness affects my relationships with my friends and family | ☐ | ☐ | ☐ | ☐ |
| 24. I feel I miss out on everyday activities with my family and friends | ☐ | ☐ | ☐ | ☐ |
| 25. I feel I miss out on family life | ☐ | ☐ | ☐ | ☐ |
| 26. I feel like I am a worry to my family | ☐ | ☐ | ☐ | ☐ |
| 27. My illness affects my intimate relationships | ☐ | ☐ | ☐ | ☐ |
| 28. I don't go out to socialize with friends | ☐ | ☐ | ☐ | ☐ |
| 29. My illness restricts the things I can do in my spare time | ☐ | ☐ | ☐ | ☐ |
| 30. My illness affects my ability to work or study | ☐ | ☐ | ☐ | ☐ |
| 31. I feel restricted in the foods I can eat | ☐ | ☐ | ☐ | ☐ |

# Next steps

- Work as a team in LITMUS
  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



International Think Tank
Paris NASH Meeting

*Thank*

NASH-CHECK

**NASH-PRO Task Force**

*you*

- Arun Sanyal

- Quentin Anstee

- Donna Cryer

- Judi Rhys

- Maria-Magdalena Balp
- Clifford Brass

- Lynda Doward
- James Twiss

# Supporting publications


- Doward LC, Balp MM, Twiss J, Slota C, Cryer D, Langford A, Collen R, Agashivala N, Brass C, Anstee QM, Sanyal A. Measuring what matters to patients: the development of the NASH-CHECK, a new patient-reported outcome instrument for non-alcoholic steatohepatitis. *Submitted to EASL International Liver Conference, 2018*.
- Twiss J, Balp M, Doward L, Slota C, Cryer D, Langford A, Collen R, Agashivala N, Brass C, Sanyal A, Anstee QM. Development of a new patient-reported outcome measure for non-alcoholic steatohepatitis: NASH-check. Poster presented at the ISPOR 20th Annual European Congress; November 7, 2017. Glasgow, Scotland.
- Doward LC, Balp M-M, Twiss J, Slota C, Cryer D, Langford A, Collen R, Agashivala N, Brass CA, Anstee QM, Sanyal AJ. Understanding the patient-perceived impact of nonalcoholic steatohepatitis: raising the volume on a silent disease. Poster presented at the 2017 AASLD Liver Meeting; October 23, 2017. Washington, DC. [abstract] Hepatology. 2017 Jul; 66(1 Suppl):1182A.
- Doward LC, Balp MM, Stewart KE, Cryer D, Langford A, Twiss J, Agashivala N, Brass C, Anstee QM, Sanyal A. Exploring the patient perceived impact of non-alcoholic steatohepatitis. Poster presented at the 2017 EASL International Liver Conference; April 2017. Amsterdam, The Netherlands. [abstract] J Hepatol. 2017 Apr; 66(1 Supplement):S422-3.