

Quality assurance of Quality of Life (QoL): how to develop ways to ensure robustness in QoL assessment, tools, creating policies and standards of practice in instrument validation

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First of all...

このような機会をいただきありがとうございます。

(Thank you for this opportunity)

Outline

1. Introduction, glossary and a very brief (and not exhaustive) history of QoL
2. The beginning: the development of the first EORTC core questionnaire (and modules)
3. The procedure behind the development of a new questionnaire / module
4. Why do we do all this?
5. What is the utility of QoL assessments?
6. What if one would like to assess QoL in a clinical trial but no instrument satisfies the requirements?

1. Introduction, glossary and a very brief (and not exhaustive) history of QoL



FDA and NIH BeST glossary (1)

- **Clinical outcome**
 - An outcome that describes or reflects how an individual feels, functions or survives.
- **Clinical outcome assessment**
 - Assessment of a clinical outcome can be made through report by a clinician, a patient, a non-clinician observer or through a performance-based assessment.

FDA = Food and Drug Administration

NIH = National Institutes of Health

BEST = Biomarkers, EndpointS, and other Tools

<https://www.ncbi.nlm.nih.gov/books/NBK338448/>

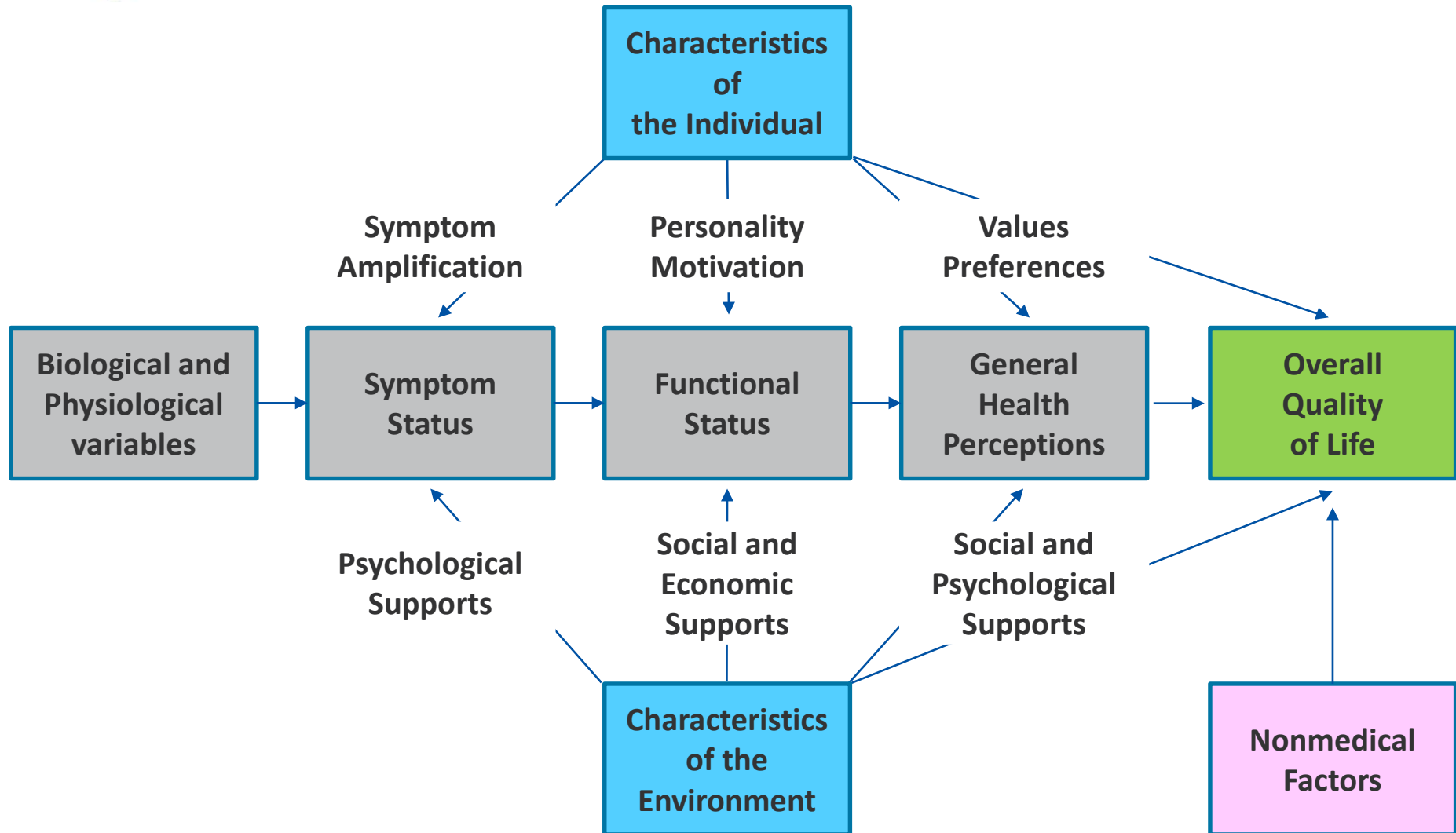
FDA and NIH BeST glossary (2)

- Clinical outcome assessment: reported by
 - a clinician (skin rash severity)
 - a patient (rating scale of pain intensity) ←
 - a non-clinician observer (log of seizure episodes)
 - a performance-based outcome (6 minutes walk test)

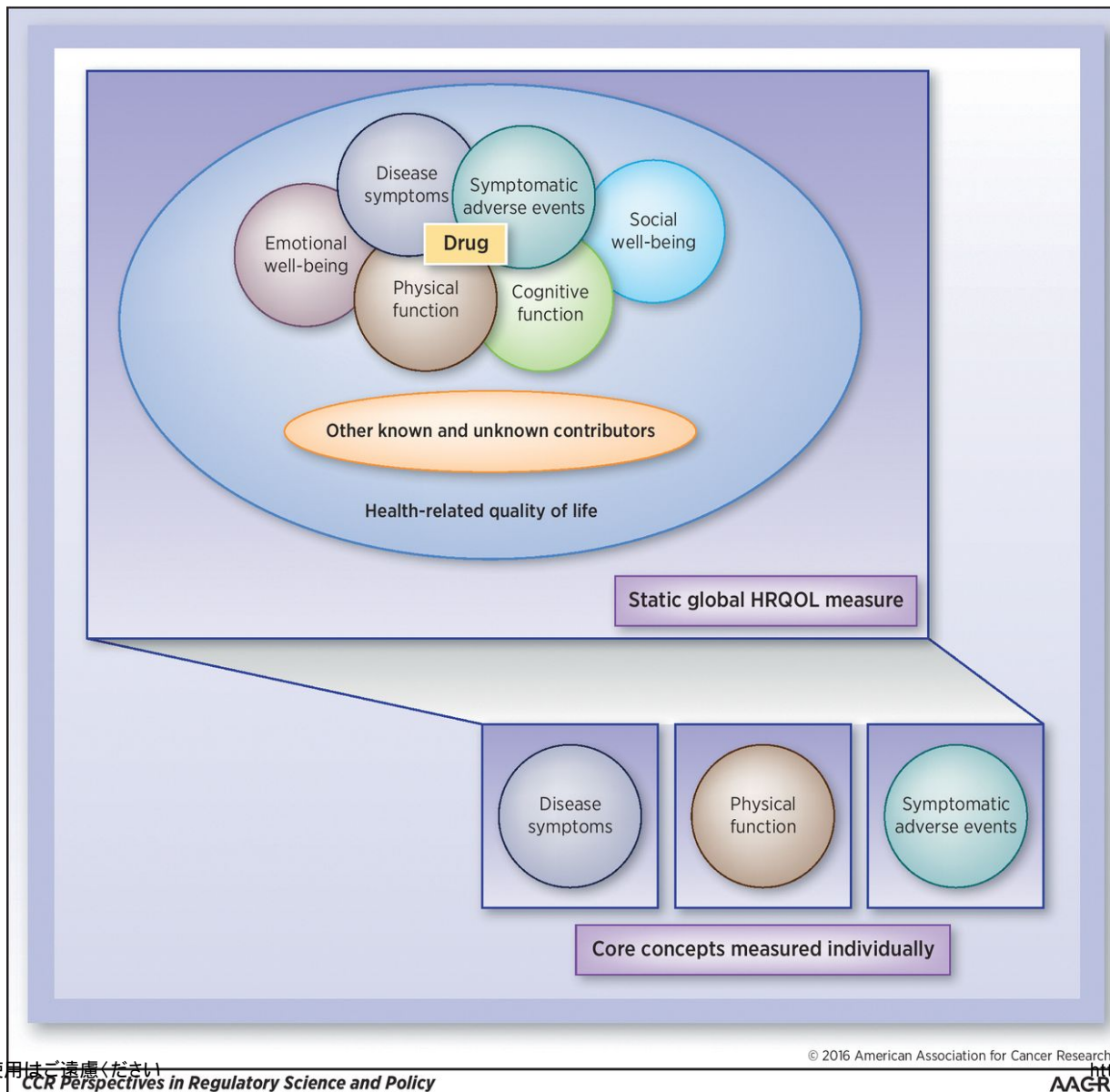
FDA and NIH BeST glossary (3)

- **Patient-Reported Outcome (PRO)**
 - A measurement based on a report that comes directly from the patient about the status of a patient's health condition without amendment or interpretation of the patient's response by a clinician or anyone else. Symptoms or other unobservable concepts known only to the patient can only be measured by PRO measures. PRO measures include:
 - rating scales (numeric rating scale of pain intensity)
 - counts of events (patient-completed log of emesis episodes)
- **QoL** is one type of PRO assessment
 - **Health-Related Quality of Life (HRQoL)** is one of the components of QoL

HRQoL conceptual model



HRQoL conceptual model



QoL (in general)

- What is QoL?
- Linked to several different factors
- Relative, depending on the situation
- Consequently: changing
- Most of all: subjective
- Hence: difficult to measure
- Solution: ask!
- But... how can it be objective if it is subjective?

So what?

- Just because it is not obvious to measure: should we not measure it?
- Maybe...
- ... we could make an extra effort to try to measure it in the most objective, comparable and reliable way.
- A little information is better than no information...

The early years of QoL

- QoL was a new concept for clinical groups.
- Skepticism was high.
- No robust standardized measure was available.
- And when the first measures started to appear...
- ... only a few instruments were available...
- ... and for these instruments, only a few translations were available.
- Investigators debated about the added value of QoL.
- Few studies worldwide had shown the added value of QoL.
- In a nutshell: **QoL was a challenge.**

A very brief (and not exhaustive) history of QoL

- New technology raised new questions:
 - ... *innovative and aggressive therapy/treatments have successfully extended length of life, thus generating increased demand for the evaluation of the quality of the time that has resulted from increased life expectancy...* (Pennacchini et al, 2011)
- The term QoL began to be used in the early **1960s**
- **1960**: On the quantity and quality of life (*Long, 1960*)
- The word QoL started to be used in medicine in the **1970s...**
- ... and became a keyword in MEDLINE in **1977**.

Meanwhile in Brussels...

- 1962
 - Groupe Européen de Chimiothérapie Anticancéreuse (GECA), founded by Henry Tagnon.
 - Idea: multidisciplinary approach and international cooperation in clinical research in Europe.
- 1968
 - European Organisation for Research and Treatment of Cancer (EORTC)
 - Network and a coordinating scientific and operational infrastructure based in Brussels.

A few years later...

- 1980
 - Quality of Life Group (QLG)
 - Different countries
 - Broad range of professionals
 - Aim:
 - to advise the EORTC headquarters and the various cooperative groups on the design, implementation and analysis of QoL studies
- **How?**

QoL on PUBMED (in the early days)

- PUBMED search with keywords "quality of life", "cancer" and "eortc" yielded following results.
 - ... *Studies of palliation, and aspects of quality of life, are also needed...* (Jones et al, 1989)
 - ... *Examples of measuring of the quality of life are Karnofsky & Burchenal's performance status which assesses the level of functional status, the Sickness Impact Profile which is a superior assessment of the general health and the "EORTC core questionnaire" which is an assessment of key factors of the quality of life adjusted specially for cancer patients...* (Klee and Sørensen, 1989)

How?

- Developing a rigorous methodological procedure to create instruments...
- ... that permit to assess the different aspects that define the QoL of a cancer patient...
- ... in the most robust, reliable and meaningful way possible.

[More on this to come]

And since 1993...

- 1993
 - Quality of Life Department (QLD)
 - Based at the EORTC Headquarters
 - Broad range of activities
 - Aims:
 - to support the development and dissemination of the questionnaires
 - to design the QoL chapter of protocols for EORTC clinical trials
 - to advise the EORTC Headquarters on how assess QoL and analyse QoL data
 - to do research (11 publications in 2017)

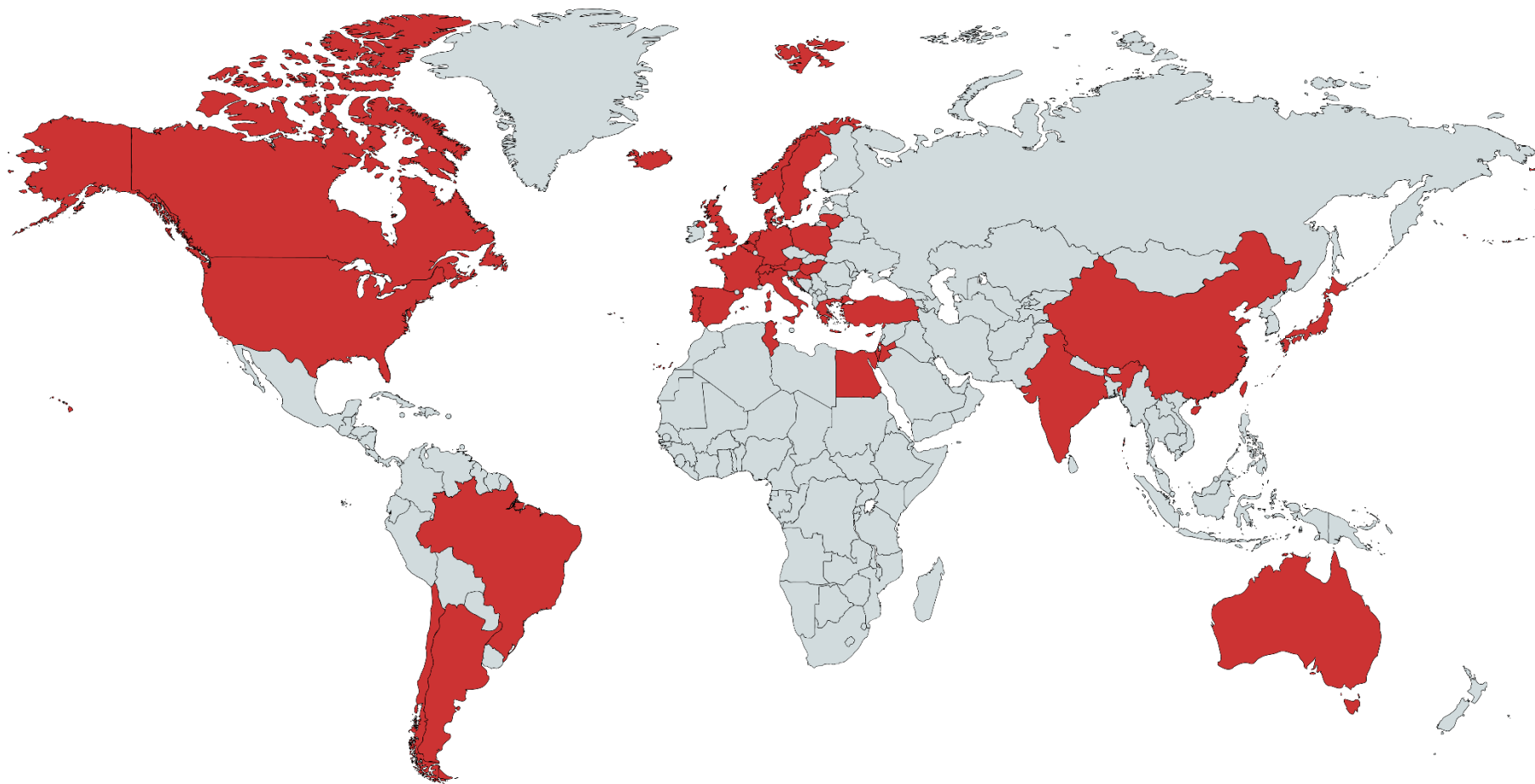
QLD

*QoL has been part of the EORTC's mission from the very start and the QLD continues to ensure that patients' voices are heard loud and clear in clinical and translational research on a daily basis
(World Cancer Day 2018)*





QLG members in the world



- www.eortc.be/qol

2. The beginning: the development of the first EORTC core questionnaire (and modules)



Definitions

- A **questionnaire** is an instrument designed to assess the different aspects that define the QoL of (a specific group of) cancer patients
 - *EORTC QoL core questionnaire*
- A **module** is an instrument that is specific to...
 - ... a disease site
 - ... a treatment modality
 - ... a QoL domain
 - *EORTC QoL core questionnaire + Lung cancer module*

Back to the story

- EORTC Quality of Life core questionnaire: requirements
 1. Sufficient degree of generalizability to **allow for cross-cultural comparison**
 2. Level of specificity **adequate for addressing research questions** of particular relevance in a given cancer clinical trial



EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials:

--	--	--	--	--

Your birthdate (Day, Month, Year):

--	--	--	--	--	--	--	--	--	--

Today's date (Day, Month, Year):

31

--	--	--	--	--	--	--	--	--	--

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a <u>long</u> walk?	1	2	3	4
3. Do you have any trouble taking a <u>short</u> walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:

	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4



EORTC QLQ-C30 (version 3)

私達は、あなたとあなたの健康状態について関心を持っています。あなたの状態に、もっともよく当てはまる番号一つを○で囲み、全設問にお答え下さい。「正しい」答えや「誤った」答え、といったものではありません。なお、お答え頂いた内容については秘密厳守とさせていただきます。

あなたの名前の頭文字を書いて下さい。 姓: ___ 名: ___ (例: 山田花子さん。姓: や 名: は)
あなたの生年月日を書いて下さい。 19___年(明・大・昭・平___年)___月___日生
今日の日付を書いて下さい。 20___年(平成___年)___月___日

	まったく ない	少し ある	多い	とても 多い
1. 重い買い物袋やスーツケースを運ぶなどの力仕事に 支障がありますか。	1	2	3	4
2. <u>長い</u> 距離を歩くことに支障がありますか。	1	2	3	4
3. 屋外の <u>短い</u> 距離を歩くことに支障がありますか。	1	2	3	4
4. 一日中ベッドやイスで過ごさなければなりませんか。	1	2	3	4
5. 食べること、衣類を着ること、顔や体を洗うこと、 トイレを使うことに人の手を借りる必要がありますか。	1	2	3	4
この一週間について:	まったく ない	少し ある	多い	とても 多い
6. 仕事をすることや日常生活活動に支障がありましたか。	1	2	3	4

Structure (briefly)

- 30 questions
- 15 scales
- Example:
 - *Did you need to rest? (q10)*
 - *Have you felt weak? (q12)*
 - *Were you tired? (q18)*
- *Fatigue*

Domains

5 functional scales:	6 singles items:
physical functioning	dyspnoea
role functioning	insomnia
cognitive functioning	appetite loss
emotional functioning	constipation
social functioning	diarrhoea
	financial problems
3 symptom scales:	
pain	1 global health scale:
fatigue	global health status / quality of life
nausea / vomiting	

Modules

Bone Metastases (QLQ-BM22)	Head & Neck (QLQ-H&N35)
Brain (QLQ-BN20)	Hepatocellular Carcinoma (QLQ-HCC18)
Breast (QLQ-BR23)	Information (QLQ-INFO25)
Breast Reconstruction (QLQ-BRECON23)	Lung (QLQ-LC13)
Cancer Related Fatigue (QLQ-FA12)	Multiple Myeloma (QLQ-MY20)
Cervical (QLQ-CX24)	Neuroendocrine Carcinoid (QLQ-GINET21)
Cholangiocarcinoma and Gallbladder Cancer (QLQ-BIL21)	Oesophageal (QLQ-OES18)
Colorectal (QLQ-CR29)	Oesophago-Gastric (QLQ-OG25)
Colorectal Liver Metastases (QLQ-LMC21)	Oral Health (QLQ-OH15)
Elderly Cancer Patients (QLQ-ELD14)	Ovarian (QLQ-OV28)
Endometrial (QLQ-EN24)	Prostate (QLQ-PR25)
Gastric (QLQ-STO22)	Spiritual Wellbeing (QLQ-SWB32)

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Gastric (QLQ-STO22)	Spiritual Wellbeing (QLQ-SWB32)

3. The procedure behind the development of a new questionnaire / module



Definitions (2)

- An **issue** is a generic matter that has or can have an impact on the QoL of cancer patients
 - *“Difficulties walking”*
- An **item** is a question with a timeframe and a reply scale created to assess an issue
 - *“Did you have difficulties walking?”*
 - *[During the last week]*
 - *[Not at all / A little / Quite a bit / Very much]*
- A **scale** is a group of two or more items which have been combined to assess an issue.

Phase 1

- Literature review
 - Interviews with patients
 - Interviews with health-care professionals (HCPs)
-
- At least 3 languages and countries
-
- **Outcome: generic list of issues**

Phase 2

- Conversion of generic issues into proper items
- Use of the Item Bank
- At the end of this phase: phase 1-2 report
- In view of Phase 3: translations
- **Outcome: preliminary questionnaire, to be pre-tested in Phase 3**

Phase 3

- Pre-testing on a rather small number of patients
- At least 6 languages and countries, among which a non-European one
- At the end of this phase: phase 3 report
- In view of Phase 4: additional translations
- **Outcome: semi-final questionnaire, to be further tested in Phase 4**

Phase 4

- Field-testing on a large number of patients
- Psychometric analyses
- As many countries as practical should be involved
- **Outcome: final (validated) questionnaire**

This was the theory. In practice...

Example:
the development of the
Elderly Cancer Patients
module

Phase 0: conception

- Older people with cancer have a different QoL profile (*Wright et al., 2005*)
- Elderly cancer patients are sometimes treated with a non-curative approach and may be vulnerable to treatment toxicities (*Wedding et al, 2007*)
- The specific needs of older cancer patients are often disregarded in the development, validation and use of QoL instruments (*Fitzsimmons at el, 2009*)
- A study aimed at detecting domains affecting the well-being of the healthy population reported age-related differences (*Bowling, 2011*)

But...

- ... how to define “elderly” people?



Decisional process

**Systematic
literature
review**

**Discussion
with the
EORTC QLG**

**Discussion
with the
EORTC
Elderly Task
Force (ETF)**

- **Conclusion: age 70+**

Phase 1: generation of QoL issues (1)

- (Systematic literature review)
- Review of elderly cancer patients specific measures
- Open interviews with n=9 patients from different countries
- Issues identified through review and interviews with patients were given to 17 HCPs from the EORTC ETF
- Outcome: preliminary list of issues (n=37)

Phase 1: generation of QoL issues (2)

- Open interviews with 89 patients from different countries
 - 40 patients 50-69
 - 49 patients 70+ } matched for gender and tumour site
 - QLQ-C30 → comments
 - Site-specific module → comments
- } “think aloud”
- Any extra issue was written down
- **Outcome: final list of issues (n=75 issues)**

Phase 2: construction of the provisional module

- Issues were reviewed according to predefined rules, and then analyzed to remove duplicates and combine issues that were very similar. Some issues were reworded.
- Retained issues were converted into items, using the Item Library where possible
- Items were translated into the languages needed for phase 3, following the EORTC QLQ translation guidelines
- **Outcome: preliminary module (n = 45 items)**

Phase 3: testing the preliminary module (1)

- The aim of this phase was to assess the content, acceptability and relevance of the preliminary module
- 182 patients from different countries
 - 85 patients 50-69
 - 95 patients 70+ } matched for tumour site and stage
- QLQ-C30 + preliminary module
 - fill out
 - rate each item for importance and relevance
 - debriefing interview

Phase 3: testing the preliminary module (2)

- Item list was reviewed according to predefined rules and patient feedback
- The remaining 15 items were grouped into hypothesized scales (to be further tested in phase 4)
- **Outcome: semi-final module: QLQ-ELD15**



EORTC QLQ-ELD14

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week:

	Not at All	A Little	Quite a Bit	Very Much
31. Have you had difficulty with steps or stairs?	1	2	3	4
32. Have you had trouble with your joints (e.g. stiffness, pain)?	1	2	3	4
33. Did you feel unsteady on your feet?	1	2	3	4
34. Did you need help with household chores such as cleaning or shopping?	1	2	3	4
35. Have you felt able to talk to your family about your illness?	1	2	3	4
36. Have you worried about your family coping with your illness and treatment?	1	2	3	4
37. Have you worried about the future of people who are important to you?	1	2	3	4
38. Were you worried about your future health?	1	2	3	4



EORTC QLQ-ELD14

患者さんから以下のような症状や問題を抱えているという訴えが時々あります。この1週間に、以下のような症状や問題をどの程度経験されましたか。ご自身に最もよく当てはまる数字に○をつけてお答え下さい。

この1週間について：	まったく ない	少し	かなり	とても多い
31. あなたは、段差や階段で困難だったことはありますか。	1	2	3	4
32. あなたは、自分の関節にトラブルがあったことがありますか（例えば、こわばり、痛み）。	1	2	3	4
33. あなたは、自分の足元に不安定さを感じましたか。	1	2	3	4
34. あなたは、掃除または買い物などの家の雑用の助けが必要でしたか。	1	2	3	4
35. あなたは、自分の病気について家族に話すことができると感じたことがありますか。	1	2	3	4
36. あなたは、自分の病気と治療に対する家族の対処を心配したことがありますか。	1	2	3	4
37. あなたは、あなたにとって大切な人々の将来を心配したことがありますか。	1	2	3	4

4. Why do we do all this?



QoL data are *special*

- Umbrella concept (covers a wide range of concepts)
- Subjective
- Self-reported

Why do we have guidelines

- Importance of involving HCPs and patients
- Importance of being consistent
- Importance of cross-cultural applicability
- Importance of validation

What does validation mean?

- Content validity
 - Internal validity
 - Questions related to one domain should agree strongly (convergent validity)
 - Questions related to different domains should agree less (divergent validity)
 - External validity
 - Compare against another 'accepted' standard

A good instrument...

- ... will measure what we want to measure.
- How can we know if this is happening?
 - Test-retest (reliability)
 - Know-group comparison
 - Responsiveness to changes (in clinical status over time)

Interpretation

- How to interpret the score of a patient?
- The QLQ-C30 and its modules have been designed to evaluate **change** of QoL in clinical trial settings. As such, a single individual score is not considered to be informative. Scores are only informative in a comparative setting:
 - comparing different patient groups (reference data)
 - comparing changes within one group over time
 - comparing changes between different patient groups over time

Statistical vs. clinical significance

- When comparing scores, one should take into account that statistically significant differences do not necessarily imply clinically relevant differences. For the QLQ-C30, a change in any scale of at least 10 points is considered to be clinically relevant. (*Osoba et al, 1998*)
- P-values are a measure of statistical significance but not of clinical relevance.
- Statistical significance should not be the only reference value.

A difference is a difference...

- ... when it makes a difference!
- This holds for
 - efficacy endpoints
 - toxicity endpoints
 - **QoL endpoints**

5. What is the utility of QoL assessments?



Impact on clinical trials?

- As already mentioned, the QLQ-C30 and its modules have been designed to evaluate change of QoL in clinical trial settings.
- These changes might be statistically significant and have a clinical meaning, and yet not have an impact on the outcome of the trial.
- However, changing the standard of care should not be the only reason for assessing.
- QoL results could be not enough to change the standard of care; but could be enough to improve the QoL of patients (if taken into account).

There is the big picture; but there is also a smaller one

- Knowing that some patients are more at risk than other can allow HCPs to monitor and manage symptom burden
- Psychosocial interventions prior to treatment have been shown to improve some aspects of QoL before and after treatment (*Parker at al, 2009*)
- As these interventions have a cost, identifying the populations that could benefit from receiving support is important; studying health-related problems helps to identify these populations

It's costly. It's time consuming. What is the point?

- Not as costly and time consuming as one might think
- Use in clinical trials
- Use in clinical practice
- QoL as a prognostic factor
 - A global analysis of multitrial data investigating quality of life and symptoms as prognostic factors for survival in different tumor sites (*Quinten et al, 2014*)
- QoL as a stratification risk factor
 - Poor preoperative patient-reported quality of life is associated with complications following pulmonary lobectomy for lung cancer (*Pompili et al, 2017*)

6. What if one would like to assess QoL in a clinical trial but no instrument satisfies the requirements?



The research question

- For a trial the research question is new every time and, therefore, unique set of questionnaires/items may have to be created to cover the research question
- Adding items is always possible; but it is important to keep in mind that the new structure will not be validated (unless one validates it)

The proposed solution

- From static to dynamic instruments: Item Banks / Libraries
- New tools to create individualized measures and ad hoc checklists
- Several measurement systems with different scopes
 - PRO-CTCAE → symptom measurement
 - PROMIS → QOL and symptoms but not cancer specific
 - EORTC Item Library → cancer specific QoL and symptoms

The EORTC Item Library

- Started in the 90s as the EORTC QLQ Item Bank
- Item Bank = database of all questions and translations
- New version in 2009; then 3.0 in 2016 and further development in 2017
- Item Bank → **Item Library**

What is inside the Item Library?

**QLQ-C30
(+ > 110
translations)**

**Stand-alone
instruments**

Modules

**Previous
versions**

**Computer
Adaptive
Testing
(CAT)**

What can be done with the Item Library?

- New EORTC QLQ group strategy supports a comprehensive strategy combining static and flexible measures
- Currently over 900 items from over 60 questionnaires
- Up to 100 language versions per item
- Possibility to adapt existing measures and create ad hoc item lists → **filling in the gaps**
- **Core +/- Module +/- Item Library based item list**
- Guidelines currently in preparation (expected: end 2018)

Advantages

- Can reduce patient burden by minimizing number of measures required
- Increased content validity
- Increased flexibility and efficiency
 - More tailored to the needs of specific treatments and populations
- Can identify important gaps and inspire future development of measures

Access

- <http://www.eortc.be/itemlibrary/>

EORTC Quality of Life Group Item Library

The Item Library is a database of items used in fully and partially validated EORTC quality of life questionnaires.

This tool has been created by the EORTC Quality of Life Group with the primary aim of being used during the development of new instruments.

Developers can access it to see how items were formulated in previous questionnaires and to reuse existing validated items and their translations.

Access to the Item Library can also be granted to academic and commercial users as a reference tool.

[Request access](#)



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Conclusions

- Have a clear research question
- Use a validated instrument (if possible)
- Keep in mind that a difference is a difference when it makes a difference
- But also remember that what could be a small difference from the clinical point of view could be a big difference for a patient

ありがとうございました。

Thank you