

SCUOLA DI METODOLOGIA DELLA RICERCA CLINICA

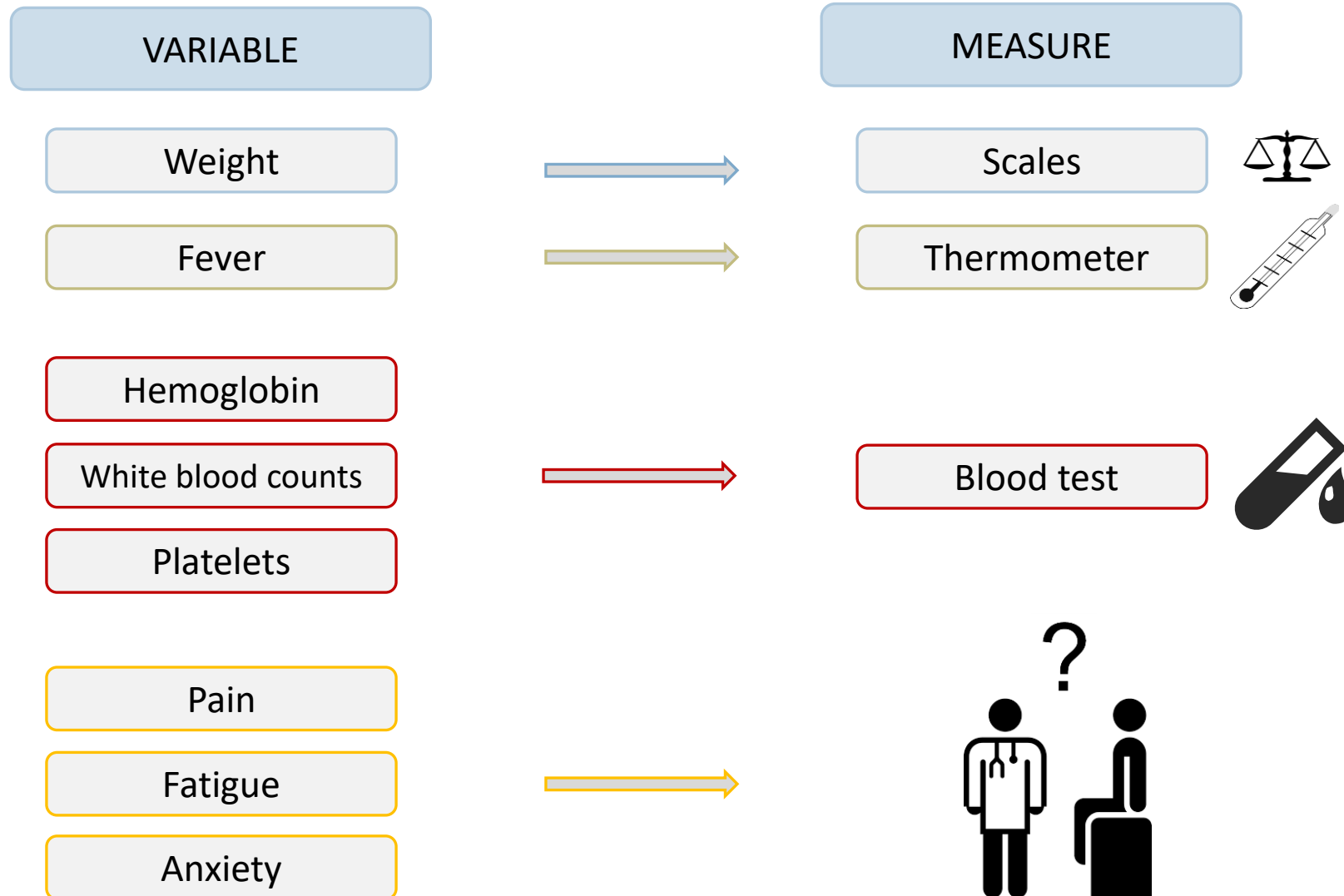


# 1° Evento Alumni della Scuola

## Definizione di PROs e tipologia di misure patient-reported

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# How to best measure variables in clinical trials and practice?



# Patient- versus physician-reporting of symptoms and health status

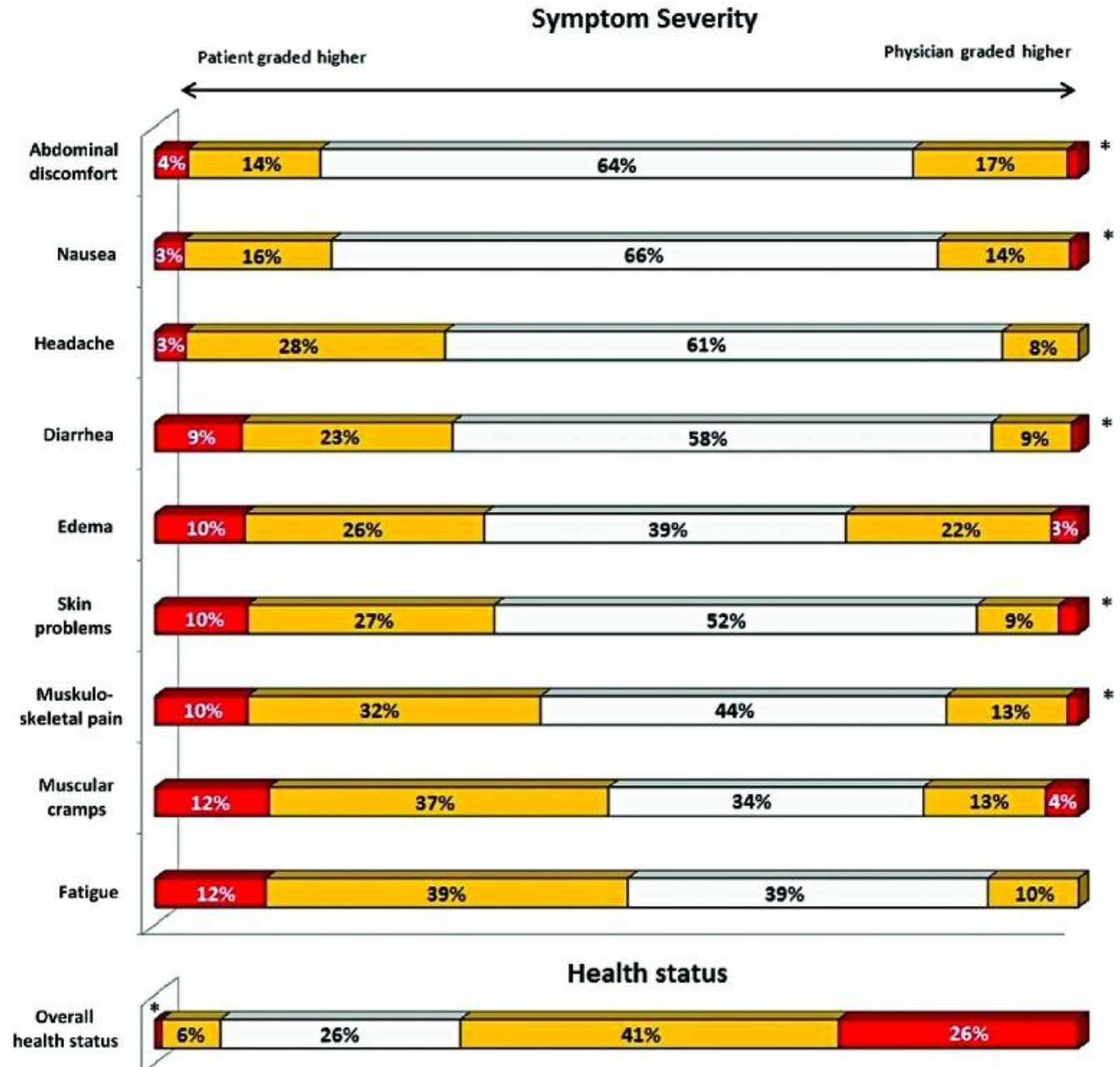
422 patients with chronic myeloid leukemia and 29 physicians completed the same questionnaire including questions on symptom severity and health status

For all symptoms, patients reported higher severity more often than their physicians

The three symptoms most frequently underestimated by physicians were **fatigue** (51%), **muscle cramps** (49%) and **musculoskeletal pain** (42%)

Health status was overestimated by physicians in 67% of the cases.

Efficace F et al. Haematologica. 2014;99(4):788-93





*The* NEW ENGLAND JOURNAL *of* MEDICINE

Perspective  
MARCH 11, 2010

## The Missing Voice of Patients in Drug-Safety Reporting

Ethan Basch, M.D.

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A patient wants to know about symptoms she may have from a prescription drug she is taking. Consulting the label's "Adverse Reactions" section, she finds a wealth of data. Little does she realize that this information, largely collected during clinical trials, is based almost entirely on clinicians' impressions of patients' symptoms — not on patients' own firsthand reports of their experiences with the drug.

Basch E. N Engl J Med 2010; 362:865-869

# Definition of Patient-Reported Outcomes (PRO) by the FDA

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## 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

A PRO is any **report of the status of a patient's health condition** that **comes directly from the patient**, without interpretation of the patient's response by a clinician or anyone else.

Subjective experiences such as symptoms **are best known by the individual patient** who is best placed to optimally report the occurrence of clinically relevant adverse events.

## Added value of measuring PROs



- Help clinicians and patients to select the best treatment by providing a clearer picture of the costs and benefits of treatment.
- Enrich our understanding of the patients' experience with unique information that could not be gained from biomedical outcomes alone (eg, pain and fatigue).
- Help clinicians to timely identify symptoms or problems of their patients.
- Improve patient-physician communication.

Treatment A

Treatment B

No difference  
in OS

No difference  
in OS

Less toxicity

Better PFS

Better QoL



**HEALTH-RELATED  
QUALITY OF LIFE**

**SYMPTOMS**

E.g. fatigue, pain, diarrhea, anxiety

**SATISFACTION WITH  
CARE**

**PRO  
questionnaire**

**FUNCTIONAL STATUS**

E.g. physical, social or  
emotional functioning

**ADHERENCE TO  
TREATMENT**





## EORTC QLQ-C30 (version 3.0)

Con questo questionario vorremmo sapere alcune cose su di Lei e sulla Sua salute. La preghiamo di rispondere a tutte le domande ponendo un cerchio attorno al numero che meglio corrisponde alla Sua risposta. Non esiste una risposta "giusta" o "sbagliata". Le Sue informazioni verranno tenute strettamente riservate.

Per favore scriva solo le iniziali del Suo nome e cognome:

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Data di nascita (g, m, a):

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La data di oggi (g, m, a):

31

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	No	Un po'	Parec- chio	Moltis- simo
1. Ha difficoltà nel fare lavori faticosi, come sollevare una borsa della spesa pesante o una valigia?	1	2	3	4
2. Ha difficoltà nel fare una <u>lunga</u> passeggiata?	1	2	3	4
3. Ha difficoltà nel fare una <u>breve</u> passeggiata fuori casa?	1	2	3	4
4. Ha bisogno di stare a letto o su una sedia durante il giorno?	1	2	3	4
5. Ha bisogno di aiuto per mangiare, vestirsi, lavarsi o andare in bagno?	1	2	3	4



## Items and scales



### EORTC QLQ-C30 (version 3.0)

1. Ha difficoltà nel fare lavori faticosi, come sollevare una borsa della spesa pesante o una valigia?
2. Ha difficoltà nel fare una lunga passeggiata?
3. Ha difficoltà nel fare una breve passeggiata fuori casa?
4. Ha bisogno di stare a letto o su una sedia durante il giorno?
5. Ha bisogno di aiuto per mangiare, vestirsi, lavarsi o andare in bagno?
10. Ha avuto bisogno di riposo?
11. Ha avuto difficoltà a dormire?
12. Ha sentito debolezza?
13. Le è mancato l'appetito?
18. Ha sentito stanchezza?

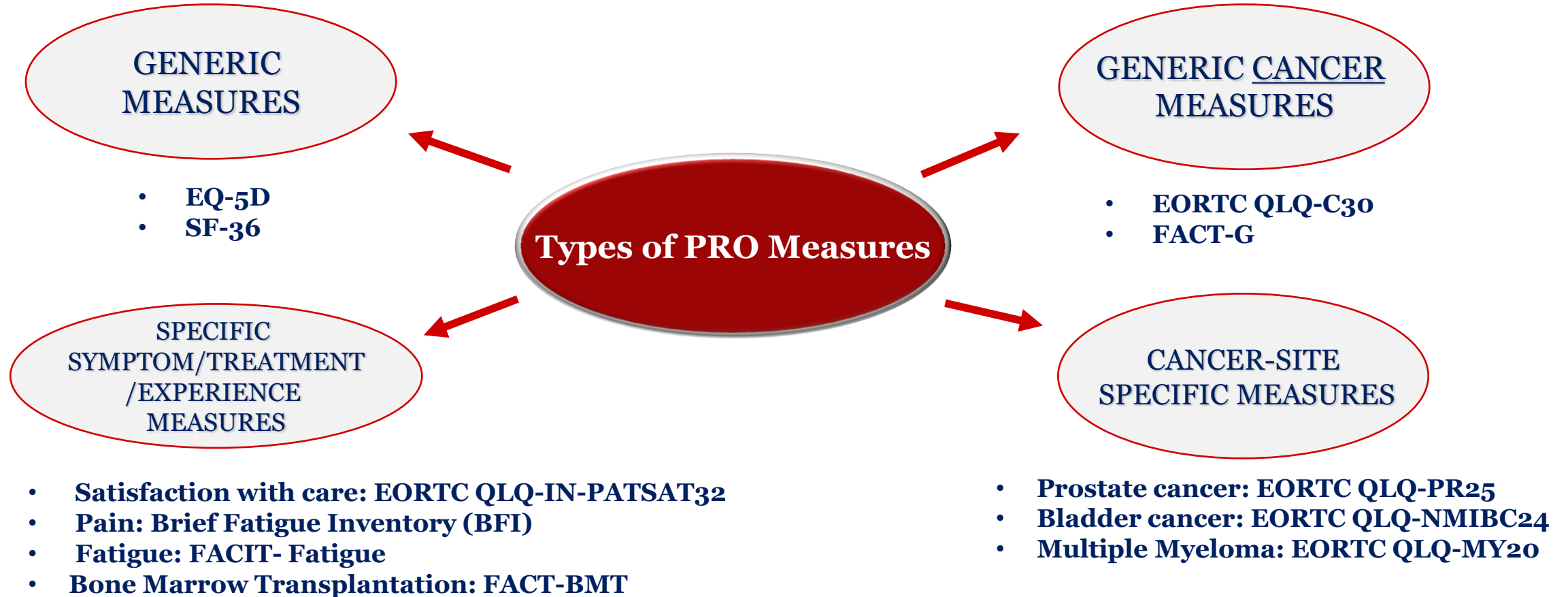
Physical functioning

Fatigue

Insomnia

Appetite loss

# Types of PRO measures



# How to select PRO measures

## 1. PRO measures should address a clinical trial research objective

**Efficacy:** Does the drug provide superior improvement in disease-related symptoms, or in fatigue, or in functional deficits, or in overall quality of life?

For example: if the objective is fatigue, select a PRO questionnaire that only measure fatigue or that contains, among the domains, a scale measuring fatigue.

**Tolerability/Safety:** Describe the patients' experience while receiving therapy.

For example: the patient-reported version of CTCAE, the PRO-CTCAE

**Satisfaction with care:** Are patients satisfied with the care they received from their physicians?

For example: the Satisfaction with Cancer Care questionnaire EORTC QLQ-PATSAT-C33

# How to select PRO measures

**2. Search the PRO questionnaire/s that measure the constructs defined in our objectives**

**Systematic reviews**

**Some catalogue of PRO measures:**

- **ePROVIDE:** <https://eprovide.mapi-trust.org/>
- **EORTC Quality of Life:** <https://qol.eortc.org/>
- **FACIT:** <https://www.facit.org/>

# How to select PRO measures

## 3. Determine the **number of PRO measures**, the **timing of assessment** and the **frequency**

Different factors need to be balanced, such as **workload** for health care personnel, **patient burden**, and aspects like **disease stage** and **current treatment** of patients.

**Table 1.** Recommendations for Incorporating Patient-Reported Outcomes Into the Design of CER in Adult Oncology

Recommendation
Implementation Methods
6. Limit data collection so that the average patient can complete the process as quickly as possible (ideally within 20 minutes at baseline and within 10 to 15 minutes at subsequent time points)
7. Collect patient-reported data as frequently as necessary to meet research objectives, without overburdening patients

# PRO measures in trials with patients with relapsed/refractory multiple myeloma

**Aim:** to evaluate the effect of long-term treatment with D-Rd versus Rd on PROs

## Health-related quality of life in patients with relapsed or refractory multiple myeloma: treatment with daratumumab, lenalidomide, and dexamethasone in the phase 3 POLLUX trial

Plesner T, et al. Br J Haematol. 2021 Jul;194(1):132-139.

### EORTC QLQ-C30 + EQ-5D

The image shows a screenshot of the EORTC QLQ-C30 + EQ-5D questionnaire. The form is divided into two main sections. The left section contains the EORTC QLQ-C30 (version 3) questionnaire, which includes instructions and 15 questions about various aspects of health-related quality of life, such as physical functioning, role functioning, cognitive functioning, emotional functioning, social functioning, global health status, fatigue, pain, nausea/vomiting, dyspnoea, loss of appetite, insomnia, constipation, diarrhoea, and financial difficulties. The right section contains the EQ-5D questionnaire, which includes instructions and five questions about mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The form is designed to be filled out by the patient, with checkboxes for each response option.

### EORTC QLQ-C30

- Physical functioning
- Role functioning
- Cognitive functioning
- Emotional functioning
- Social functioning
- Global health status/QoL
- Fatigue
- Pain
- Nausea/vomiting
- Dyspnoea
- Loss of appetite
- Insomnia
- Constipation
- Diarrhoea
- Financial difficulties

### EQ-5D

- Mobility
- Self-care
- Usual activities
- Pain/discomfort
- Anxiety/depression
- VAS

**Possible to compare the results with other populations, including general population**

**Disease-specific symptoms and conditions not captured**

# PRO measures in trials with patients with relapsed/refractory multiple myeloma

VOLUME 34 · NUMBER 32 · NOVEMBER 10, 2016

JOURNAL OF CLINICAL ONCOLOGY

## Health-Related Quality-of-Life Results From the Open-Label, Randomized, Phase III ASPIRE Trial Evaluating Carfilzomib, Lenalidomide, and Dexamethasone Versus Lenalidomide and Dexamethasone in Patients With Relapsed Multiple Myeloma

A. Keith Stewart, Meletios A. Dimopoulos, Tamás Masszi, Ivan Špička, Albert Oriol, Roman Hájek, Laura Rosiñol, David S. Siegel, Ruben Niesvizki, Andrzej J. Jakubowiak, Jesus F. San-Miguel, Heinz Ludwig, Jacqui Buchanan, Kim Cocks, Xinqun Yang, Biao Xing, Naseem Zojwalla, Margaret Tonda, Philippe Moreau, and Antonio Palumbo

Stewart AK et al., J Clin Oncol. 2016; 34:3921-3930.

### EORTC QLQ-C30 + EORTC QLQ-MY20

**EORTC QLQ-C30 (version 3)**

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

Please fill in your initials: \_\_\_\_\_  
 Your birthdate (Day, Month, Year): \_\_\_\_\_  
 Today's date (Day, Month, Year): 31 \_\_\_\_\_

**During the past week:**

- Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?
- Do you have any trouble taking a long walk?
- Do you have any trouble taking a short walk outside of the house?
- Do you need to stay in bed or a chair during the day?
- Do you need help with eating, dressing, washing yourself or using the toilet?
- Were you limited in doing either your work or other daily activities?
- Were you limited in pursuing your hobbies or other leisure time activities?
- Were you short of breath?
- Have you had pain?
- Did you need to rest?
- Have you had trouble sleeping?
- Have you lost weight?
- Have you lacked appetite?
- Have you felt nauseated?
- Have you vomited?
- Have you been constipated?

Please go on to the next page.

**EORTC QLQ-MY20**

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 bone aches or pain?	1	2	3	4
32. Have you had pain in your back?	1	2	3	4
33. Have you had pain in your hip?	1	2	3	4
34. Have you had pain in your arm or shoulder?	1	2	3	4
35. Have you had pain in your chest?	1	2	3	4
36. If you had pain did it increase with activity?	1	2	3	4
37. Did you feel drowsy?	1	2	3	4
38. Did you feel thirsty?	1	2	3	4
39. Have you felt ill?	1	2	3	4
40. Have you had a dry mouth?	1	2	3	4
41. Have you lost any hair?	1	2	3	4
42. Answer this question only if you lost any hair: Were you upset by the loss of your hair?	1	2	3	4
43. Did you have tingling hands or feet?	1	2	3	4
44. Did you feel restless or agitated?	1	2	3	4
45. Have you had acid indigestion or heartburn?	1	2	3	4
46. Have you had burning or sore eyes?	1	2	3	4

Please turn to next page.

**Primary PRO hypothesis:** superiority of of KRd over Rd for the GHS/QoL scale

**Secondary scales of interest:** fatigue, nausea/vomiting, pain, physical functioning, role functioning, disease symptoms, adverse effects of treatment

### EORTC QLQ-C30

- Physical functioning
- Role functioning
- Cognitive functioning
- Emotional functioning
- Social functioning
- Global health status/QoL
- Fatigue
- Pain
- Nausea/vomiting
- Dyspnoea
- Loss of appetite
- Insomnia
- Constipation
- Diarrhoea
- Financial difficulties

### EORTC QLQ-MY20

- Disease symptoms (e.g. bone pain, back pain)
- Side effects of treatment (e.g. dry mouth, hair loss)
- Future perspective (e.g. worry about death and health in the future)

# PRO measures in trials with patients with relapsed/refractory multiple myeloma

## Impact of elotuzumab treatment on pain and health-related quality of life in patients with relapsed or refractory multiple myeloma: results from the ELOQUENT-2 study

David Cella<sup>1</sup> · Jan McKendrick<sup>2,3</sup> · Amber Kudlac<sup>2</sup> · Antonio Palumbo<sup>4</sup> · Abderrahim Oukessou<sup>5</sup> · Ravi Vij<sup>6</sup> · Teresa Zyczynski<sup>5</sup> · Catherine Davis<sup>5</sup>

Cella D et al., Ann Hematol. 2018;97(12):2455-2463.

**Aim:** to investigate HRQoL and whether there is a relationship between treatment response and patient-reported pain

### BPI-SF + EORTC QLQ-C30 + EORTC QLQ-MY20

The image displays three screenshots of patient-reported outcome (PRO) questionnaires used in the study:

- Brief Pain Inventory (BPI-SF):** Shows a pain scale from 0 (no pain) to 10 (worst imaginable pain) and a diagram of the human body for marking pain locations.
- EORTC QLQ-C30 (version 3):** A general health-related quality of life questionnaire with 16 items. The first five items are:
  - Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?
  - Do you have any trouble taking a long walk?
  - Do you have any trouble taking a short walk outside of the house?
  - Do you need to stay in bed or a chair during the day?
  - Do you need help with eating, dressing, washing yourself or using the toilet?
- EORTC QLQ-MY20:** A myeloma-specific questionnaire with 20 items. The first five items are:
  - Have you had bone aches or pain?
  - Have you had pain in your back?
  - Have you had pain in your hip?
  - Have you had pain in your arm or shoulder?
  - Have you had pain in your chest?

### EORTC QLQ-C30

- Physical functioning
- Role functioning
- Cognitive functioning
- Emotional functioning
- Social functioning
- Global health status/QoL
- Fatigue
- Pain
- Nausea/vomiting
- Dyspnoea
- Loss of appetite
- Insomnia
- Constipation
- Diarrhoea
- Financial difficulties

### EORTC QLQ-MY20

- Disease symptoms (e.g. bone pain, back pain)
- Side effects of treatment (e.g. dry mouth, hair loss)
- Future perspective (e.g. worry about death and health in the future)

### BPI-SF

- Pain severity
- Pain interference
- Worst pain



# FROM A TRADITIONAL PRO APPROACH

## STATIC MEASURES

**GENERIC**

**EQ-5D  
SF-36**

**CANCER  
GENERIC**

**EORTC QLQ-C30  
FACT-G**

**DISEASE-  
SPECIFIC**

**FACT-Leu  
EORTC QLQ-CML24**

## PAPER QUESTIONNAIRES



# TOWARD A MORE FLEXIBLE AND PERSONALIZED APPROACH

## PRO ITEM LIBRARIES

### PRO-CTCAE Library

<https://healthcaresdelivery.cancer.gov/pro-ctcae/instrument-pro.html>

### EORTC Item Library

<https://itemlibrary.eortc.org/>

### FACIT Item Library

<https://wizard.facit.org/>

### MDASI Symptom Library

<http://www.mdanderson.org/symptom-research>  
> Symptom Assessment Tools

## ELECTRONIC PROs



# Patient-Reported Outcomes version Of The Common Terminology Criteria For Adverse Events (PRO-CTCAE™)

## QUICK GUIDE TO THE ITEM LIBRARY\*

Oral	Respiratory	Neurological	Sleep/Wake	Sexual
Dry mouth S	Shortness of breath SI	Numbness & tingling SI	Insomnia SI	Achieve and maintain erection S
Difficulty swallowing S	Cough SI	<b>Dizziness</b> SI	<b>Fatigue</b> SI	Ejaculation F
Mouth/throat sores SI	Wheezing S	<b>Visual/Perceptual</b>	<b>Mood</b>	Decreased libido S
Cracking at the corners of the mouth (cheilosis/cheilitis) S	<b>Cardio/Circulatory</b>	Blurred vision SI	Anxious FSI	Delayed orgasm P
Voice quality changes P	Swelling FSI	Flashing lights P	Discouraged FSI	Unable to have orgasm P
Hoarseness S	Heart palpitations FS	Visual floaters P	Sad FSI	Pain w/sexual intercourse S
<b>Gastrointestinal</b>	<b>Cutaneous</b>	Watery eyes SI	<b>Genitourinary</b>	<b>Miscellaneous</b>
Taste changes S	<b>Rash</b> P	Ring in ears S	Irregular periods/vaginal bleeding P	Breast swelling and tenderness S
Decreased appetite SI	Skin dryness S	<b>Attention/Memory</b>	Missed expected menstrual period P	<b>Bruising</b> P
Nausea FS	Acne S	Concentration SI	Vaginal discharge A	Chills FS
Vomiting FS	Hair loss A	Memory SI	Vaginal dryness S	Increased sweating FS
Heartburn FS	Itching S	<b>Pain</b>	Painful urination S	Decreased sweating P
Gas P	Hives P	General pain FSI	Urinary urgency FI	Hot flashes FS
Bloating FS	Hand-foot syndrome S	Headache FSI	Urinary frequency FI	Nosebleed FS
Hiccups FS	Nail loss P	<b>Muscle pain</b> FSI	Change in usual urine color P	Pain and swelling at injection site P
Constipation S	Nail ridging P	Joint pain FSI	Urinary incontinence FI	Body odor S
Diarrhea F	Nail discoloration P			
<b>Abdominal pain</b> FSI	Sensitivity to sunlight P			
Fecal incontinence FI	Bed/pressure sores P			
	Radiation skin reaction S			
	Skin darkening P			
	Stretch marks P			

Attributes	
F: Frequency	I: Interference
S: Severity	P: Presence/Absence
A: Amount	

Version date: 3/11/2020



\*Complete library of items available at: <https://healthcaredelivery.cancer.gov/pro-ctcae>

<https://healthcaredelivery.cancer.gov/pro-ctcae/item-library.pdf>



**Clinical utility in**

**In phase II trials**

- to minimize patient burden
- preliminary collection of anticipated AEs and symptoms when little is known about the treatment

**Trials investigating novel drugs**

- to complement PRO measures

# Adoption of electronic PROs in clinical practice

Patients complete ePROs in the hospital before visits, at home, wherever they want



ePRO monitoring may help physician to identify symptomatic AEs and facilitate communication with patients

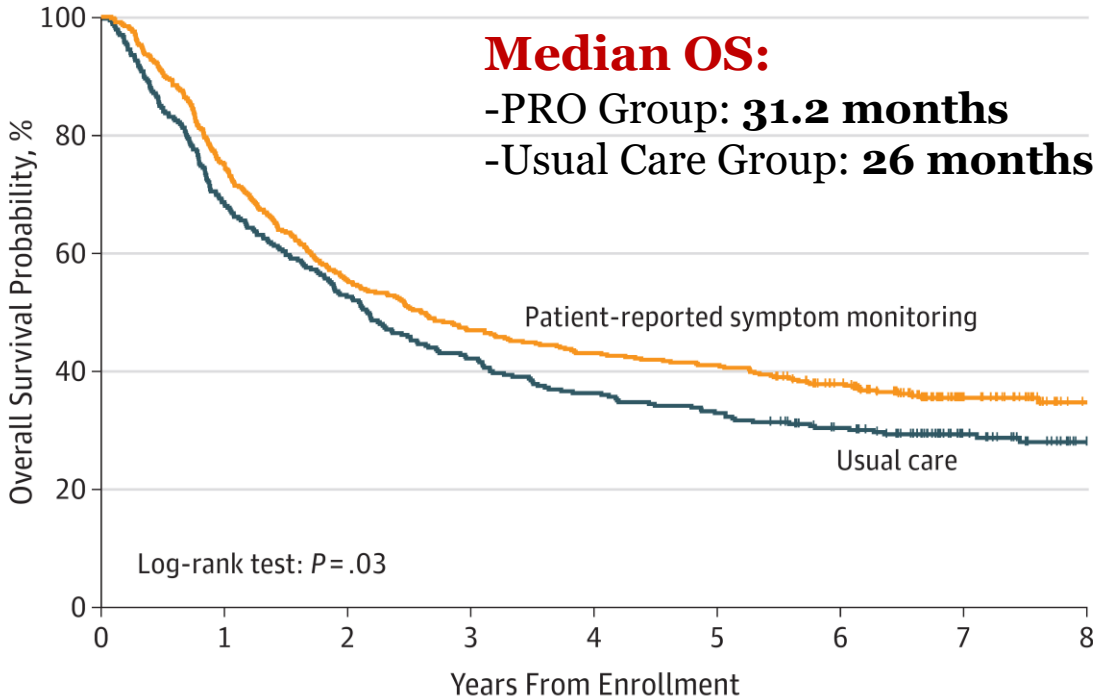


If a **clinically important problem or symptom** is reported, the system trigger an **alert to the physician**



**In a randomized controlled trial, the integration of electronic PROs into the routine care of patients with metastatic cancer was associated with increased survival compared with usual care**

Figure. Overall Survival Among Patients With Metastatic Cancer Assigned to Electronic Patient-Reported Symptom Monitoring During Routine Chemotherapy vs Usual Care



No. at risk	0	1	2	3	4	5	6	7	8
Patient-reported symptom monitoring	441	331	244	207	190	181	148	65	33
Usual care	325	223	171	137	118	107	89	50	27

Basch E, et al. JAMA. 2017;318(2):197-198.

# Personalized questions based on specific condition

103 questionnaires, 1028 questions

- |               |                       |                        |
|---------------|-----------------------|------------------------|
| Back pain     | Emotional functioning | Social functioning     |
| Pain          | Role functioning      | Medication adherence   |
| Fatigue       | Physical functioning  | Nausea                 |
| Insomnia      | Cough                 | Sore eyes              |
| Muscle cramps | Weight loss           | Fever                  |
| Diarrhea      | Blurred vision        | Financial difficulties |
| Edema         | Constipation          | Cognitive functioning  |
| Dyspnoea      | Rash                  | Future perspective     |

<https://itemlibrary.eortc.org/>



## Conclusions

- Including **PROs** (e.g. quality of life and symptom burden) in a clinical trial has the great potential of providing important information to **facilitate clinical decision-making** and **improve healthcare quality**.
- Use validated PRO measures
- Item libraries now allows for flexibility in PRO measurement, but guidelines should be followed (i.e. Piccinin C et al. Lancet Oncol. 2023;24:e86-95) to ensure a rigorous use of this new approach

**Grazie per l'attenzione**