

# FDA Workshop: Clinical Trial Design for NMIBC Patient-Reported Outcome Measures

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# PRO Measurement in Trials

Core Patient-Reported  
Outcomes in Cancer  
Clinical Trials  
Guidance for Industry

- Patient-Reported Outcome measure (PROM):  
Measurement based on report that comes directly from patient about status of patient's health condition **without amendment or interpretation of patient's response**
  - New FDA guidance for PROs in Cancer Clinical Trials in 2021
  - Trial Endpoints
    - **Primary endpoint:** palliative care/rehabilitation trials
    - **Secondary endpoint:** to support/interpret primary endpoint
    - **Tertiary endpoint:** generate hypotheses for future studies



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# Is it a PRO? Questions to Ask

- **Low Bar**

- Does it measure a health concept appropriate for direct patient report?
- Does it measure perceptions of how a patient feels or functions, beliefs about a health concept, or experience?

- **Higher Bar**

- Were items/instrument developed with patient and clinician input?
- Psychometric, validity, reliability evidence





# Common PROMs

- Symptoms
- Functional status
- Quality of life
- Self-efficacy for managing condition



# Added Value of PROs to Clinical Trials

1. Assist clinicians and patients to select the best treatment
2. Improve our understanding of the patients' experience
3. Improve future clinical trial methods
4. Inform regulatory decisions, cost-effectiveness analysis, and inform clinical guidelines and health policy

Mercieca-Bebber R, *Patient Relat Outcome Meas.* 2018;9:353-367



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# Selecting PROMS for Clinical Trials

- Consider PRO measures early in study design
- Select a primary PRO proximal to the disease or treatment
- Ensure that the PRO items are appropriate to the study
- Consider respondent burden, administration and translation
- Take a minimalist approach to ad hoc items
- Appraise evidence regarding reliability and validity

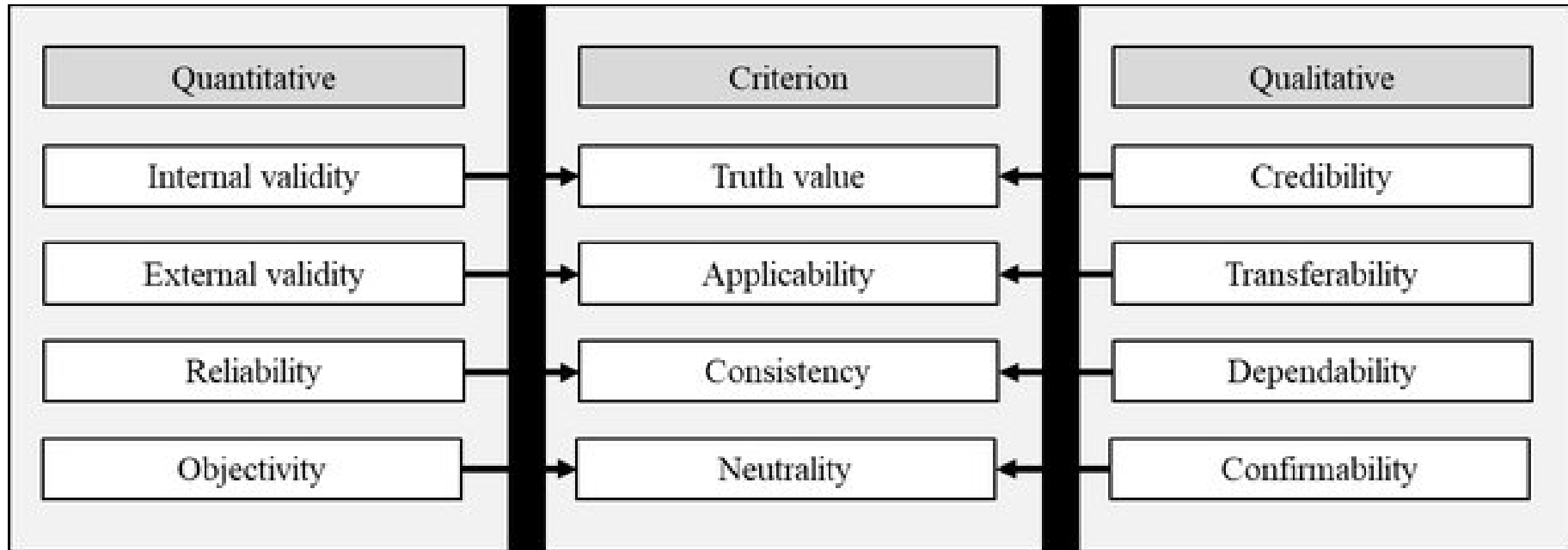
Mercieca-Bebber R, et al. *Relat Outcome Meas.* 2018;9:353-367.  
Lockett, King. *Eur J Cancer.* 2010 Dec;46(18):3149-57



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# Qualitative & Quantitative Ways of Thinking about Validity & Reliability





# Reliability

- Degree to which PROM is free from measurement error
  - Same results in same group when assessing repeatedly
- Test-retest reliability: measure at two close points in time
  - Ability to learn math should not change much from week to week
- Internal consistency: Cronbach's alpha
- Split-half reliability



# “Is it Valid?”

- Validity and reliability are carefully constructed arguments about the amount of evidence
- Not yes/no for validity and reliability
- Instruments are valid only for a specific context
  - Validation studies are specific to the context of use (disease/population/setting)
- Helpful question: Is the instrument “Fit for Purpose”?



# Guidance for PRO Inclusion in Trials

- The SPIRIT-PRO Extension is a 16-item checklist to improve completeness of trial protocols where PROs are a primary or key secondary outcome
- Comprehensive protocol template and selected examples from existing trial protocols provided
- SPIRIT-PRO checklist items promote understanding

**SPIRIT-PRO Extension explanation and elaboration: guidelines for inclusion of patient-reported outcomes in protocols of clinical trials**

Calvert et al, JAMA 2018;319(5):483-494  
Calvert et al, BMJ Open 2021; 11:e045105.



Instrument type	Module	Domains	Domains scored individually?	
<b>General Instruments</b>				
FACT-G <sup>15</sup>	Cancer-Specific	N/A	Physical, socia/family, emotional, functional	Yes
EORTC-QLQ-C30 <sup>14</sup>	Cancer-Specific	N/A	Functional (physical/role/emotional/ cognitive/social) Symptom (fatigue, nausea, vomiting/pain) Single items (dyspnea, insomnia, appetite, constipation, diarrhea, finances)	Yes
<b>Nonmuscle-Invasive Instrument</b>				
EORTC-QLQ-NMIBC24 <sup>21</sup>	BCSI	C30	Grouped (urinary symptoms, malaise, future worries, bloating, sexual function, male sexual problems) Single items (Intravesical treatment issues, sexual intimacy, risk of contaminating partner, sexual enjoyment, female sexual problems)	
<b>Muscle-Invasive Instruments</b>				
EORTC-QLQ-BLM30 <sup>20</sup>	BCSI	C30	Single items (urinary symptoms, sexual function, urostomy issues, catheter use, body image)	No
FACT-BI-Cys <sup>22</sup>	BCSI	FACT-G	Single items (urinary symptoms, sexual interest, bowel function, body image, appetite)	No
<b>Inclusive Bladder Cancer Instrument</b>				
BCI <sup>23</sup>	BCSI	No	Grouped (blader, bowel and sexual function with function and bother subdomains for each)	Yes
FACT-BI <sup>32</sup>	BCSI	FACT-G	Single items (urinary function, sexual function, bowel function, appetite, ostomy care, body image)	No

## Assessing Symptom Burden in Bladder Cancer: An Overview of Bladder Cancer Specific Health-Related Quality of Life Instruments

Bernard J. Danna\*, Michael J. Metcalfe, Erika L. Wood and Jay B. Shah  
Department of Urology, MD Anderson Cancer Center, Houston, TX, USA

Danna et al, *Bladder Cancer* 2016:329-40.





# EORTC QLQ-C30

- Cancer-specific validated questionnaire
  - Functional measures
    - Physical, social, emotional, functional
  - Symptom measure
    - Fatigue, nausea, vomiting
  - Single item measures
    - Dyspnea, insomnia, appetite, constipation, diarrhea, finances

## 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
<b>During the past week:</b>				
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4





# FACT-G

- Cancer-specific validated questionnaires
  - Physical well-being
  - Social/family well-being
  - Emotional well-being
  - Functional well-being

<u>PHYSICAL WELL-BEING</u>		Not at all	A little bit	Some-what	Quite a bit	Very much
GP1	I have a lack of energy .....	0	1	2	3	4
GP2	I have nausea .....	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family .....	0	1	2	3	4
GP4	I have pain .....	0	1	2	3	4
GP5	I am bothered by side effects of treatment .....	0	1	2	3	4
GP6	I feel ill .....	0	1	2	3	4
GP7	I am forced to spend time in bed .....	0	1	2	3	4

<u>SOCIAL/FAMILY WELL-BEING</u>		Not at all	A little bit
GS1	I feel close to my friends .....	0	1
GS2	I get emotional support from my family .....	0	1
GS3	I get support from my friends .....	0	1
GS4	My family has accepted my illness .....	0	1
GS5	I am satisfied with family communication about my illness .....	0	1
GS6	I feel close to my partner (or the person who is my main support) .....	0	1
Q1	<i>Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box <input type="checkbox"/> and go to the next section.</i>		
GS7	I am satisfied with my sex life .....	0	1

<u>EMOTIONAL WELL-BEING</u>		Not at all	A little bit	Some-what	Quite a bit	Very much
GE1	I feel sad .....	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness .....	0	1	2	3	4
GE3	I am losing hope in the fight against my illness .....	0	1	2	3	4
GE4	I feel nervous .....	0	1	2	3	4
GE5	I worry about dying .....	0	1	2	3	4
GE6	I worry that my condition will get worse .....	0	1	2	3	4

<u>FUNCTIONAL WELL-BEING</u>		Not at all	A little bit	Some-what	Quite a bit	Very much
GF1	I am able to work (include work at home) .....	0	1	2	3	4
GF2	My work (include work at home) is fulfilling .....	0	1	2	3	4
GF3	I am able to enjoy life .....	0	1	2	3	4
GF4	I have accepted my illness .....	0	1	2	3	4
GF5	I am sleeping well .....	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun .....	0	1	2	3	4
GF7	I am content with the quality of my life right now .....	0	1	2	3	4



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# EORTC NMIBC24

- The only non-invasive bladder cancer-specific measure tested in a prospective RCT
- Strong instrument – with validity and responsiveness over time
- Lacks test-retest reliability and international testing
- Recommended in comparing bladder-conserving NMIBC treatments

## During the past week:

	Not at all	A little	Quite a bit	Very much
31. Have you had to urinate frequently <b>during the day</b> ?	1	2	3	4
32. Have you had to urinate frequently <b>at night</b> ?	1	2	3	4
33. When you felt the urge to pass urine, did you have to hurry to get to the toilet?	1	2	3	4
34. Was it difficult for you to get enough sleep, because you needed to get up frequently at night to urinate?	1	2	3	4
35. Have you had difficulty going out of the house, because you needed to be close to a toilet?	1	2	3	4
36. Have you had any unintentional release (leakage) of urine?	1	2	3	4
37. Have you had pain or a burning feeling when urinating?	1	2	3	4
38. Did you have a fever?	1	2	3	4
39. Did you feel ill or unwell?	1	2	3	4
40. Did you have trouble arranging your life around the repeated bladder treatment appointments (cystoscopies or instillations)?	1	2	3	4
41. Did you worry about having repeated bladder treatments (cystoscopies or instillations)?	1	2	3	4
42. Were you worried about your health in the future?	1	2	3	4
43. Did you worry about the results of examinations and tests?	1	2	3	4
44. Did you worry about possible future treatments?	1	2	3	4
45. Did you have a bloated feeling in your abdomen?	1	2	3	4
46. Have you had flatulence or gas?	1	2	3	4



# FACT-BL

- Validated questionnaire for patients with MIBC or NMIBC
- Uses FACT-G (general) + 12 additional bladder cancer specific questions
  - Urinary, bowel, sexual function, body image, appetite, ostomy care
- Has validity, reliability, sensitivity to change over time
- Designed to COMPARE between NMIBC and MIBC patients
- Useful for studies which compare across treatment modalities and diseases (e.g. intravesical treatment vs. cystectomy)
- Lacks ability to discriminate which symptoms are most disturbing to the patient (no function/bother subscales)

<u>ADDITIONAL CONCERNS</u>		Not at all	A little bit	Some-what	Quite a bit	Very much
BL1	I have trouble controlling my urine.....	0	1	2	3	4
C2	I am losing weight.....	0	1	2	3	4
C3	I have control of my bowels.....	0	1	2	3	4
BL2	I urinate more frequently than usual.....	0	1	2	3	4
C5	I have diarrhea (diarrhoea).....	0	1	2	3	4
C6	I have a good appetite.....	0	1	2	3	4
C7	I like the appearance of my body.....	0	1	2	3	4
BL3	It burns when I urinate.....	0	1	2	3	4
BL4	I am interested in sex.....	0	1	2	3	4
BL5	(For men only) I am able to have and maintain an erection.....	0	1	2	3	4
Q2	Do you have an ostomy appliance? No ___ Yes ___ If yes, answer the following two items: ↓					
C8	I am embarrassed by my ostomy appliance.....	0	1	2	3	4
C9	Caring for my ostomy appliance is difficult.....	0	1	2	3	4



# Bladder Cancer Index (BCI)

- Designed as an all-inclusive instrument for patients with NMIBC and MIBC
- 36 items divided into 3 domains (urinary, bowel, sexual function)
- Has bother and function subscale and all domains are scored separately using a 100-point Likert scale
- Robust development with patient input
- Validated but lacks longitudinal data
- Lacks generalized instrument





# PROMIS

<http://www.healthmeasures.net>

- Patient-reported outcomes measurement information system
- Evaluates and monitors physical, mental, and social health in adults and children
- Translated into Spanish and other languages
- Uses fewer items than conventional measures, thereby decreasing respondent burden



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# PROMIS® Adult Self-Reported Health

Global Health

## Physical Health

## Mental Health

## Social Health

PROMIS Profile  
Domains

Fatigue  
Pain Intensity  
Pain Interference  
Physical Function  
Sleep Disturbance

Anxiety  
Depression

Ability to  
Participate in Social  
Roles & Activities

PROMIS Additional  
Domains

Dyspnea  
Gastrointestinal  
Symptoms  
Itch  
Pain Behavior  
Pain Quality  
Sexual Function  
Sleep-related  
Impairment

Alcohol  
Anger  
Cognitive Function  
Life Satisfaction  
Meaning & Purpose  
Positive Affect  
Psychosocial Illness  
Impact  
Self-efficacy for  
Managing Chronic

Companionship  
Satisfaction with  
Social Roles &  
Activities  
Social Isolation  
Social Support

# PRO-CTCAE

## Common Terminology Criteria for Adverse Events

- PRO Measurement System to evaluate symptomatic toxicity in patients on cancer clinical trials
- 124 items representing 78 symptomatic toxicities from the CTCAE
- Evaluate
- Validated in more than 30 languages
- <https://healthcaresdelivery.cancer.gov/pro-ctcae/>



# How to Use PRO-CTCAE

- Publicly available for clinical research
- Typically used w/ CTCAE
- Recall period is the past 7 days
- Weekly assessments during key periods in the trial
- Use a form builder to build a study-specific custom form
- Scoring Practices
  - Responses scored 0 to 4 (or 0/1 for absent/present)
  - Up to 3 scores per symptomatic toxicity (frequency, severity, interference)
  - No standardized scoring rules for how to combine attributes
  - Score for each attribute presented descriptively (e.g. summary statistics or graphical presentations)



## Form Builder

[Use Form Builder to generate a custom built form for your study.](#)





# Patient-Reported Outcomes version Of The Common Terminology Criteria

## For Adverse Events (PRO-CTCAE™)

### QUICK GUIDE TO THE ITEM LIBRARY\*

<b>Oral</b>		<b>Respiratory</b>		<b>Neurological</b>		<b>Sleep/Wake</b>		<b>Sexual</b>	
Dry mouth	S	Shortness of breath	SI	Numbness & tingling	SI	Insomnia	SI	Achieve and maintain erection	S
Difficulty swallowing	S	Cough	SI	Dizziness	SI	Fatigue	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	Rash	P	Ringing 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	Bruising	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	Muscle pain	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>Attributes</b>					
Abdominal pain	FSI	Sensitivity to sunlight	P	F: Frequency		I: Interference			
Fecal incontinence	FI	Bed/pressure sores	P	S: Severity		P: Presence/Absence			
		Radiation skin reaction	S	A: Amount					
		Skin darkening	P						
		Stretch marks	P						



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

Version date: 3/11/2020



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# NMIBC Endpoint Survey

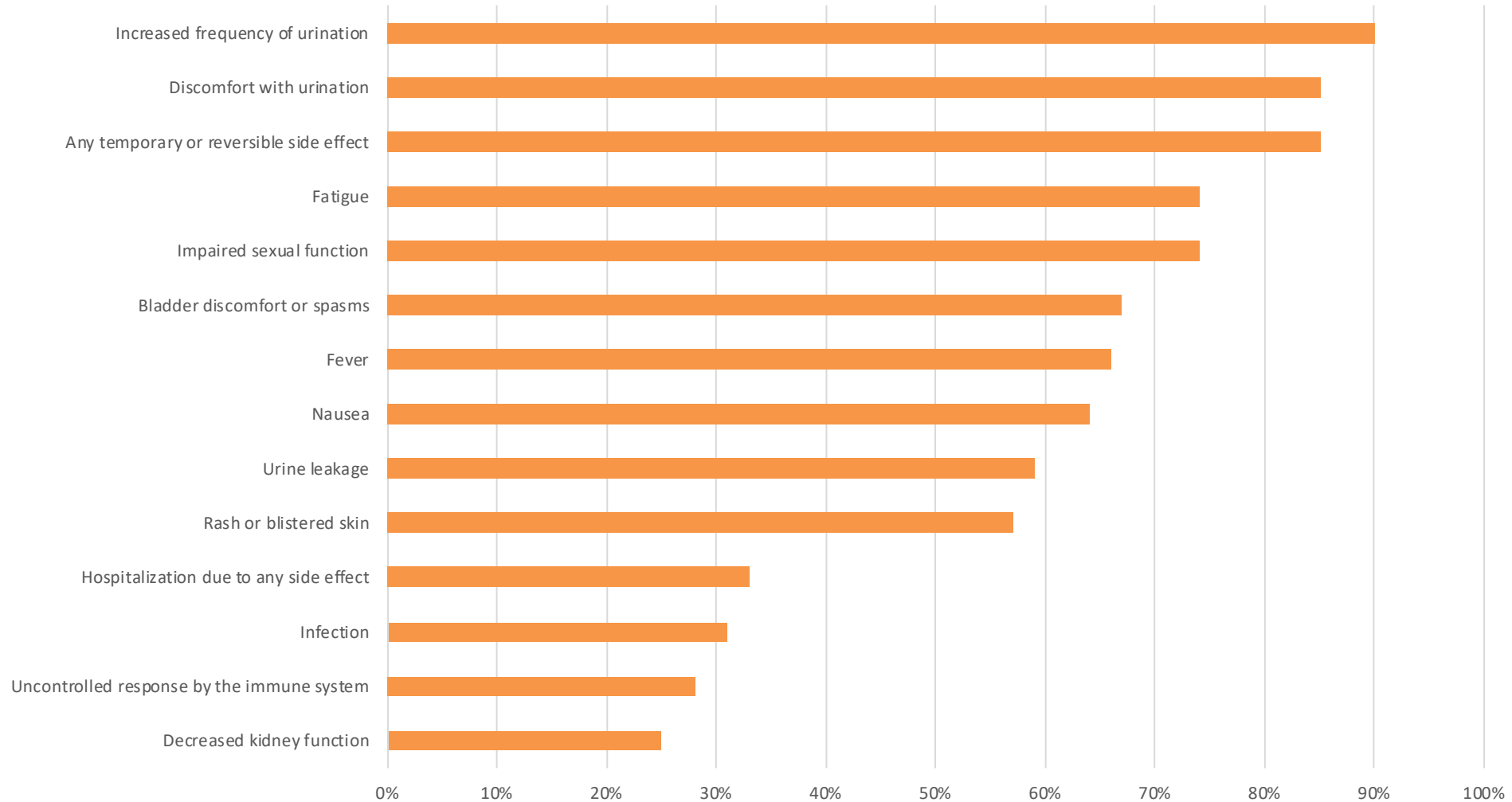


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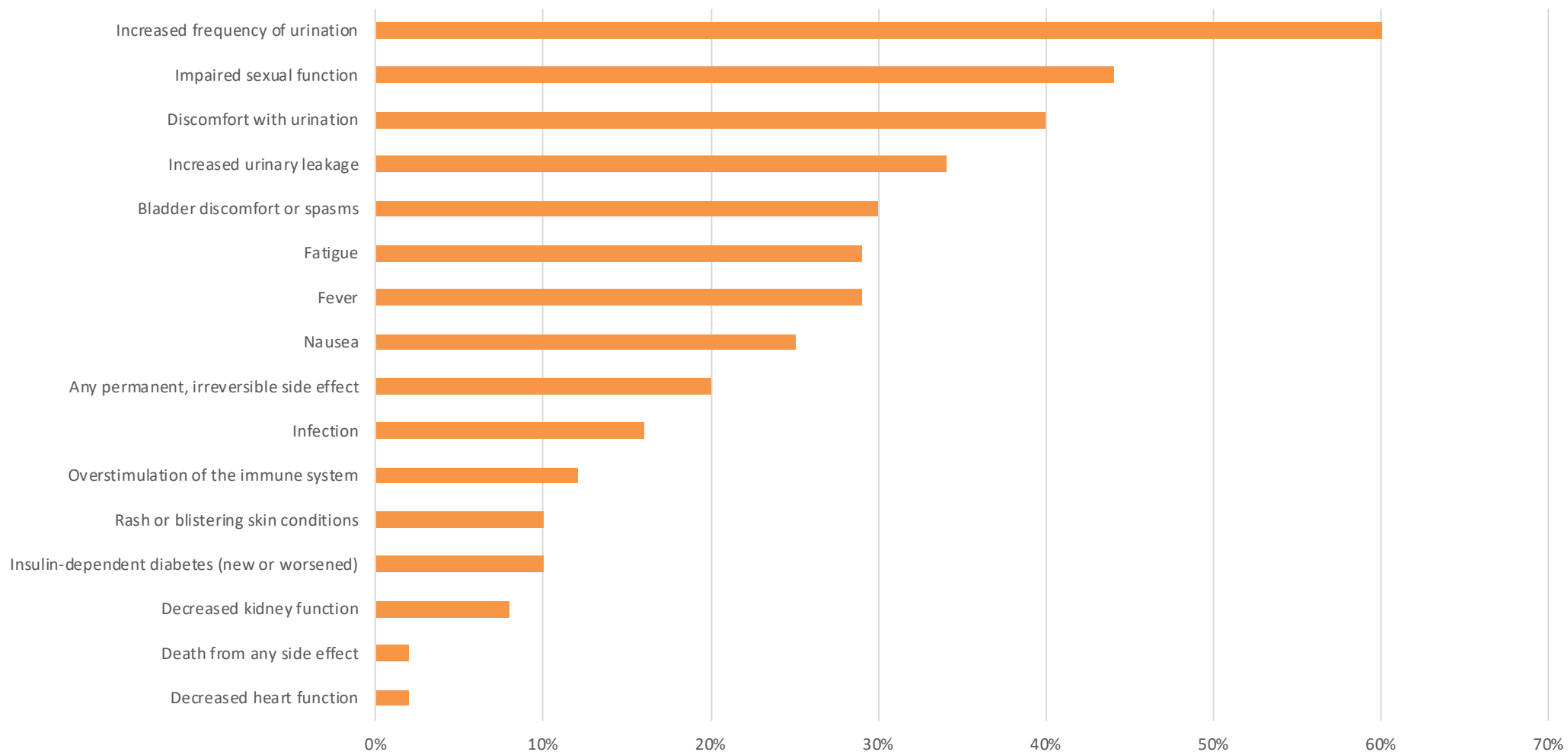
## Percentage of Respondents Who Would Accept a Reversible Side Effect from a New Therapy



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## Percentage of Respondents Who Would Accept an *IRReversible* Side Effect from a New Therapy



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# PROs in NMIBC: Thinking Outside the Box

- Does your intervention:
  - Avoid procedures such as TURBT?
  - Conserve the bladder?
  - Decrease cost?
  - Reduce healthcare utilization?
  - Permit earlier return to work?
  - Reduce caregiver burden?



# NMIBC-Relevant PROs (a snapshot)

- Time off work: WPAI
- Financial toxicity: COST
- Healthcare utilization: HCUP
- Decision regret: Decision Regret Scale
- Caregiver burden: CareGiver Oncology Quality of Life





# Final Considerations for PROs in Clinical Trials

- Mode of administration
- Timing/frequency of questionnaires
- Respondent burden
- Missing PRO data



# Thank You!



Photo credit: Sam Kittner '85

# Questions?

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