Understanding Regulatory Guidance for PRO/eCOA in Oncology Studies

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With 11+ years of experience as a Biostatistician in Pharma, CRO, FSP environments, Roger's expertise spans, design and analysis of clinical trial data, PRO/eCOA data, regulatory-driven requirements, validation processes, and database review, with strong adherence to quality standards across different phases and indications. He has strong background in leading biostatistics and programming teams, acting as a key bridge between clients and internal stakeholders to ensure timely, high-quality deliverables. He is committed to knowledge sharing, identifying risks proactively, and fostering collaborative client relationships, all while staying dedicated to improving outcomes for patients globally.

Yogesh Sonawane, Director, Statistical Services, IQVIA RDS India Pvt Ltd

Yogesh with 20+ years experience in clinical research, having served variety of technical and strategic roles in biostatistics and programming, supporting major pharma organizations, contributing to clinical development in multiple therapeutic areas within global CRO environments. Though primarily focused on Oncology, he also supports studies in Nutrition, Neuroscience and CVGI. Yogesh currently leads a global team of statisticians supporting a top pharma company, with expert oversight, client engagement, and strategic resource planning, ensuring consistent delivery of high-value statistical insights for accelerated global programs. He drives transformation, operational efficiency, quality and compliance in the clinical development lifecycle while collaborating closely with data management, programming, clinical and regulatory writing groups to ensure timely, accurate and audit-ready deliverables. He is keen on digital innovation and spots opportunities to advance automation, analytics and technology-enabled processes that accelerate submissions.

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Agenda

- Core PRO
- General Principles to Determine Suitable PRO Instrument
- Data Collection
- Justifications Regulatory Might Require
- Endpoint Considerations
- Statistical Considerations

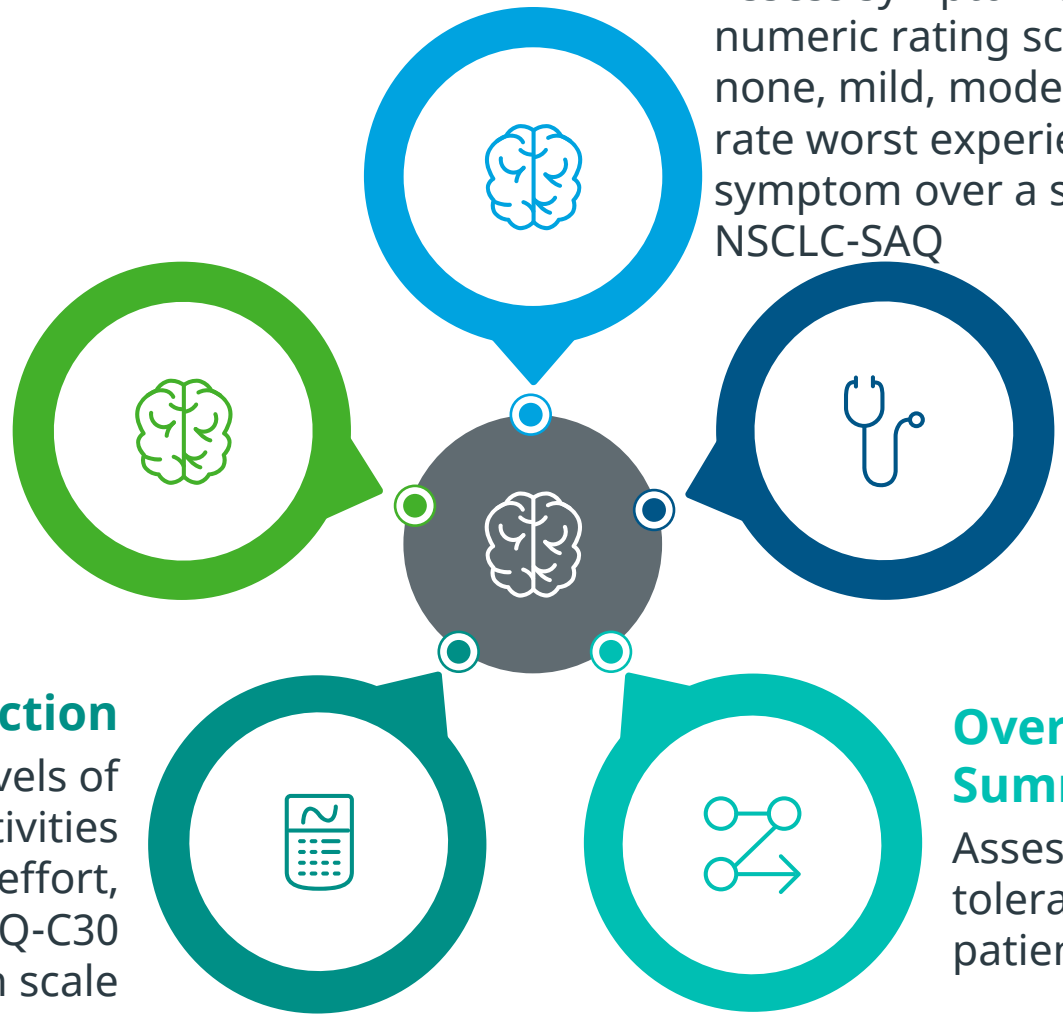
Core PRO

Disease-related Symptoms

Assess symptom severity on 11-point (i.e., 0 to 10) numeric rating scale or verbal rating scale (e.g., none, mild, moderate, severe) where patients rate worst experience of a specific disease symptom over a specified recall period, e.g., using NSCLC-SAQ

Role Function

Assess impact of a treatment on the ability to work and carry out daily activities, including leisure activities, other functional abilities, e.g., using EORTC QLQ-C30 role function scale



Symptomatic Adverse Events

Most important and/or high frequency symptomatic AEs that are expected to occur, e.g., using PRO-CTCAE

Physical Function

Assess varying levels of ability to perform activities that require physical effort, e.g., using EORTC QLQ-C30 physical function scale

Overall Side Effect Impact Summary Measure

Assess overall side effect impact for tolerability of treatment by individual patients, e.g., using FACIT GP5

General Principles to Determine Suitable PRO Instrument

Sponsors should provide support for the selection of PRO instrument(s) with available data and/or published peer-reviewed literature guided by the below principles*

Instrument is appropriate for its intended use (e.g., study design, patient population)

Appropriate

Instrument validly and reliably measures concepts that are clinically relevant and important to patients

Validity & Reliability

Data can be communicated in a way that is accurate, interpretable, and not misleading

Communicable

Data Collection: Handling Missing Data

Missing data is a major challenge to the success and interpretation of any clinical trial.

Missing data can introduce bias and interfere with the ability to compare effects in test group with control group because only a subset of the initial randomized population contributes, and these patient groups may no longer be comparable.

Protocol can increase likelihood that trial will still be informative by

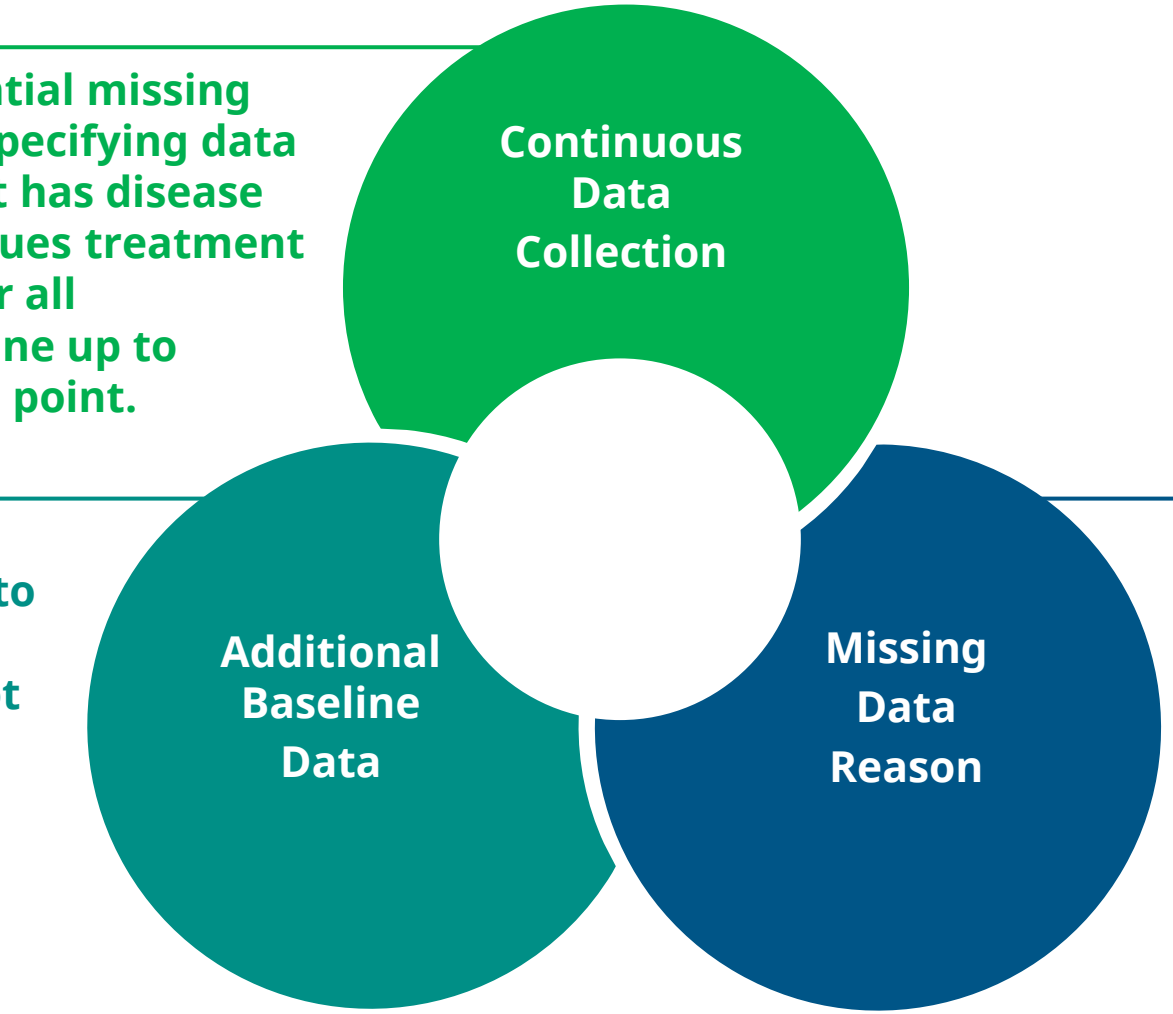
- Describing, how missing data will be handled in the analysis
- Backup plans to gather treatment-related reasons for patients failing to report at scheduled times or withdrawing from treatment or trial
- Trying to minimize patient dropouts before trial completion
- Process to obtain PRO measurement before or shortly after patient withdrawal from treatment if early withdrawal occur

Ideal scenario: Patients should remain in the trial, even if discontinued treatment and should continue to provide PRO data.

Data Collection: Handling Missing Data

Reduce amount of potential missing data in analysis by pre-specifying data collection even if patient has disease progression or discontinues treatment (due to toxicity or AE) for all assessments from baseline up to clinically justifiable time point.

Collect additional assessment at screening to reduce missing data at baseline if patients cannot complete assessments at Cycle 1 Day 1.



Ultimately, acceptability of PRO results depends on the amount and reasons for missing data.

Data Collection: Assessment Frequency

Some diseases, conditions or trial designs may necessitate more than one baseline assessment and several PRO assessments during treatment.

Schedule of PRO assessment should correspond to

1. specific research questions being addressed
2. length of recall asked by the instrument's response options
3. demonstrated instrument measurement properties
4. disease or condition's natural history
5. the treatment's nature
6. planned data analysis

Data Collection: Assessment Frequency

Based on our experience regulatory support use of standard approach to assessment frequency over the first year of therapy for consistency and interpretation across trials

Example: Assessment strategy that assesses PROs more frequently in the first 8 weeks of treatment would be suitable across most treatment administration schedules.

	Initial treatment period												Remainder of treatment period		
	BL	w 2	w 3	w 4	w 5	w 6	w 7	w 8	M 3	M 4	M 5	M 6	M 9	M12	*
Symptomatic AE[16]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Single Item Side Effect Global	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Physical Function	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Role Function	X		X		X		X		X	X	X	X	X	X	
Disease Symptoms	X				X				X			X		X	
Other HRQOL	X								X			X		X	

BL – baseline, w - week, M - month, * - context dependent long-term follow-up

16: Symptomatic AEs assessed by PROs are intended to complement, not replace, standard CTCAE safety data.

Data Collection: Pain

If plan to measure pain using EORTC QLQ-LC13 and Question 3 of BPI-SF, take into consideration potential impact of analgesic use on cancer-related pain and PRO instrument responses for these items. Consider how analgesic use could be captured and pre-specify how increases in analgesic use will be handled when analyzing patient-reported pain data.

EORTC QLQ - LC13

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.	How much did you cough?	1	2	3	4
32.	Did you cough up blood?	1	2	3	4
33.	Were you short of breath when you rested?	1	2	3	4
34.	Were you short of breath when you walked?	1	2	3	4
35.	Were you short of breath when you climbed stairs?	1	2	3	4
36.	Have you had a sore mouth or tongue?	1	2	3	4
37.	Have you had trouble swallowing?	1	2	3	4
38.	Have you had tingling hands or feet?	1	2	3	4
39.	Have you had hair loss?	1	2	3	4
40.	Have you had pain in your chest?	1	2	3	4
41.	Have you had pain in your arm or shoulder?	1	2	3	4
42.	Have you had pain in other parts of your body?	1	2	3	4
	If yes, where _____				
43.	Did you take any medicine for pain?				
	1 No 2 Yes				
	If yes, how much did it help?	1	2	3	4

Brief Pain Inventory—*Short Form*

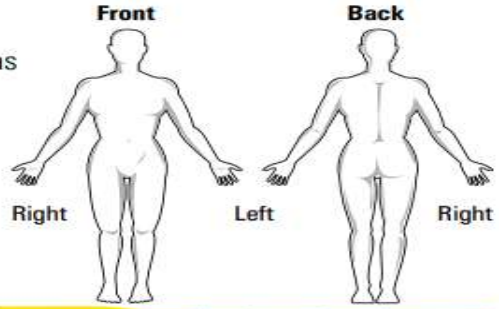
First Name _____ Date _____

Last Name _____ Time _____

1. Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these everyday kinds of pain today?

❑ Yes ❑ No

2. On the diagram, shade in the areas where you feel pain. Put an X on the area that hurts the most.



3. Please rate your pain by circling the one number that best describes your pain at its **worst** in the last 24 hours.

No pain 0 1 2 3 4 5 6 7 8 9 10 Worst pain imaginable

4. Please rate your pain by circling the one number that best describes your pain at its **least** in the last 24 hours.

No pain 0 1 2 3 4 5 6 7 8 9 10 Worst pain imaginable

Data Collection: Pain

Brief Pain Inventory—*Short Form*

First Name _____ Date _____

Last Name _____ Time _____

1. Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these everyday kinds of pain today?

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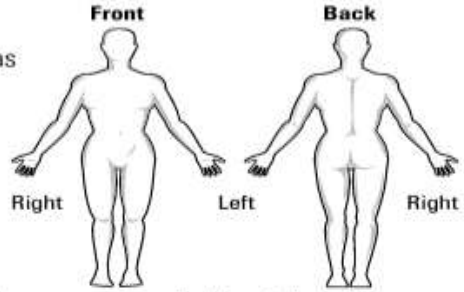

3. Please rate your pain by circling the one number that best describes your pain at its **worst** in the last 24 hours.

No pain 0 1 2 3 4 5 6 7 8 9 10 Worst pain imaginable

4. Please rate your pain by circling the one number that best describes your pain at its **least** in the last 24 hours.

No pain 0 1 2 3 4 5 6 7 8 9 10 Worst pain imaginable

5. Please rate your pain by circling the one number that best describes your pain on the **average**.

No pain 0 1 2 3 4 5 6 7 8 9 10 Worst pain imaginable

6. Please rate your pain by circling the one number that tells how much pain you have **right now**.

No pain 0 1 2 3 4 5 6 7 8 9 10 Worst pain imaginable

Brief Pain Inventory—*Short Form (cont'd)*

7. What treatments or medications are you receiving for your pain?

_____

8. In the last 24 hours, how much relief have pain treatments or medications provided? Please circle the one percentage that shows how much **relief** you have received.

No relief 0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100% Complete relief

9. Circle the one number that describes how, during the past 24 hours, pain has interfered with your:

A. General activity

Does not interfere 0 1 2 3 4 5 6 7 8 9 10 Completely interferes

B. Mood

Does not interfere 0 1 2 3 4 5 6 7 8 9 10 Completely interferes

C. Walking ability

Does not interfere 0 1 2 3 4 5 6 7 8 9 10 Completely interferes

D. Normal work (includes both work outside the home and housework)

Does not interfere 0 1 2 3 4 5 6 7 8 9 10 Completely interferes

E. Relations with other people

Does not interfere 0 1 2 3 4 5 6 7 8 9 10 Completely interferes

F. Sleep

Does not interfere 0 1 2 3 4 5 6 7 8 9 10 Completely interferes

G. Enjoyment of life

Does not interfere 0 1 2 3 4 5 6 7 8 9 10 Completely interferes

Data Collection: PRO-CTCAE Items

The tentative list of selected items from the PRO-CTCAE should include some symptomatic adverse events (AEs) that may be relevant and are likely related to treatment based on the most commonly reported AEs from the reference study.

8. PRO-CTCAE® Symptom Term: Decreased appetite				
a. In the last 7 days, what was the SEVERITY of your DECREASED APPETITE at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe
b. In the last 7 days, how much did DECREASED APPETITE INTERFERE with your usual or daily activities?				
O Not at all	O A little bit	O Somewhat	O Quite a bit	O Very much

9. PRO-CTCAE® Symptom Term: Nausea				
a. In the last 7 days, how OFTEN did you have NAUSEA?				
O Never	O Rarely	O Occasionally	O Frequently	O Almost constantly
b. In the last 7 days, what was the SEVERITY of your NAUSEA at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe

10. PRO-CTCAE® Symptom Term: Vomiting				
a. In the last 7 days, how OFTEN did you have VOMITING?				
O Never	O Rarely	O Occasionally	O Frequently	O Almost constantly
b. In the last 7 days, what was the SEVERITY of your VOMITING at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe

Data Collection: PRO-CTCAE Items

The tentative list of selected items from the PRO-CTCAE should include some symptomatic adverse events (AEs) that may be relevant and are likely related to treatment based on the most commonly reported AEs from the reference study.

15. PRO-CTCAE® Symptom Term: Constipation				
a. In the last 7 days, what was the SEVERITY of your CONSTIPATION at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe

49. PRO-CTCAE® Symptom Term: Headache				
a. In the last 7 days, how OFTEN did you have a HEADACHE?				
O Never	O Rarely	O Occasionally	O Frequently	O Almost constantly
b. In the last 7 days, what was the SEVERITY of your HEADACHE at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe
c. In the last 7 days, how much did your HEADACHE INTERFERE with your usual or daily activities?				
O Not at all	O A little bit	O Somewhat	O Quite a bit	O Very much

Justifications Regulatory Might Require

PRO-CTCAE	Dyspnea Composite Score	Clinically Meaningful Change
▪ Justification if the tentative list of selected items from the PRO-CTCAE does NOT include some symptomatic AEs that may be relevant and are likely related to treatment based on the most commonly reported AEs from the reference study.	▪ Justification if dyspnea symptom score composed from question 8 of EORTC QLQ-C30 and question 33,34,35 of EORTC QLQ-LC13 as this approach is not validated.	▪ Justification to support the definition of clinically meaningful change. ▪ If claim of superiority in PRO endpoints is sought, pre-specify clinically meaningful change at the patient level in PRO scores.

Justification for selection of week x for the PRO endpoints.

Justifications Regulatory Might Require

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 long walk?	1	2	3	4
3.	Do you have any trouble taking a short 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
7.	Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8.	Were you short of breath?	1	2	3	4
9.	Have you had pain?	1	2	3	4
10.	Did you need to rest?	1	2	3	4
11.	Have you had trouble sleeping?	1	2	3	4

EORTC QLQ - LC13

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.	How much did you cough?	1	2	3	4
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	If yes, where _____				
43.	Did you take any medicine for pain?				

Endpoint Considerations

Global Health Status

- Regulators generally caution against use of Global Health Status or generic Health Related Quality of Life as a PRO endpoint of interest.
- This concept is subject to confounding by non-treatment/non-disease factors which makes it difficult to ascertain the effect of treatment.
- May include EORTC QLQ-C30 GHS/QoL scale as a key secondary endpoint at sponsor's discretion.

Dyspnea Composite Score

- Dyspnea symptom score composed from one item in EORTC QLQ-C30 and 3 items from EORTC QLQ-LC13: this approach is not validated.
- Reconsider using dyspnea symptom score only from EORTC QLQ-LC13 (3 items).

Pain Measurement

- If plan to measure pain using EORTC QLQLC13 and Question 3 of BPI-SF, take into consideration potential impact of analgesic use on cancer-related pain and PRO instrument responses for these items.
- Consider how analgesic use could be captured and pre-specify how increases in analgesic use will be handled when analyzing patient-reported pain data.

Statistical Considerations

Analysis Population

- PRO efficacy analysis should be based on ITT population, not PRO analysis set.
- This helps avoid potential bias when making direct comparisons between treatment arms.

Missing Data

- Approach for handling missing data in PRO analyses
- Strategies to minimize potential missing data during study conduct
- Measures to reduce missing data at baseline

MMRM vs GEE

- Based on our experience, regulatory guidance does not support the use of GEE approach to analyze PRO endpoints as its MCAR assumption is unlikely in cancer trial setting and have different summary measures.
- Consider using MMRM approach for all PRO endpoints.

References

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BPI SF: https://static.medicine.iupui.edu/divisions/rheu/content/physicians/BRIEF_PAIN_INVENTORY.pdf

NCI PRO-CTCAE: https://healthcaredelivery.cancer.gov/pro-ctcae/instruments/pro-ctcae/pro-_english.pdf

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