NCI's National Clinical Trials Network (NCTN) AYA Patient-Reported Outcome (PRO) Core Battery Frequently Asked Questions (FAQs)

1. **What is the NCTN AYA PRO Task Force and how did its members come to consensus on a core PRO battery?**

   The NCTN AYA PRO Task Force includes key stakeholders involved in the measurement of health-related quality of life (HRQoL) and symptom burden in AYAs diagnosed with cancer from across the NCTN. The Task Force includes investigators with expertise in AYA HRQoL, AYA cancer clinical trial development and the inclusion and assessment of PROs in NCTN clinical trials. Members represent the Alliance for Oncology Clinical Trials, the Children's Oncology Group, ECOG-ACRIN Cancer Research Group, NRG Oncology and the SWOG Cancer Research Network. Through an iterative process, the group first identified gaps in HRQoL and symptom burden research in the AYA cancer population and subsequently identified potential approaches to fill this gap in knowledge. The guiding principles used to come to consensus on the core AYA PRO battery included: 1) focus on HRQoL domains that are important to AYAs; 2) selection of inventories previously validated in the AYA cancer population; 3) flexibility to assess a variety of HRQoL domains; 4) adaptability across different types of cancer subtypes and clinical trial designs; 5) reliance on inventories available within the public domain; and 6) minimization of patient and site burden.

2. **Why is an AYA PRO core battery being recommended for inclusion in AYA cancer clinical trials?**

   There is a paucity of research on symptom burden and the functional and psychosocial impact of cancer in AYA therapeutic trials. Lack of harmonization as to which core HRQoL domains should be assessed and which inventories should be utilized to measure HRQoL limits the ability to identify patients at high risk for poor HRQoL and develop timely interventions to improve outcomes. An AYA PRO core battery provides clinical trialists with an important tool that will standardize the measurement of HRQoL in AYAs enrolled on trials using validated instruments. Inclusion of the PRO core battery will permit the assessment of HRQoL within and across AYA cancer clinical trials to allow a more comprehensive understanding of the impact of cancer and its treatments on AYAs. As with all rare cancers, standardizing the patient-reported outcomes included in trials will allow investigators to pool findings and accelerate advancements in care.

3. **What does the AYA PRO core battery assess?**

   The AYA PRO core battery assesses key HRQoL domains including symptom burden, treatment toxicity and functional impact in AYAs diagnosed with cancer. The battery consists of two major components, the PROMIS AYA Health Status Profile, which assesses selected HRQoL domains, and the PRO-CTCAE, which assesses symptomatic adverse events important for assessing treatment toxicity and tolerability.

4. **What is the reference period or time frame for the PROMIS measure items and the PRO-CTCAE items, and can the reference period be changed?**

For most PROMIS measures, participants are asked to complete items based upon their experience "In the past 7 days". The recommended PROMIS tools have been validated using a reference period of "in the past 7 days" and this reference period cannot be changed. Similarly, the reference period for the PRO-CTCAE items is "in the past 7 days" and cannot be changed.

5. **What types of AYA cancer clinical trials should consider utilizing the AYA PRO core battery?**

   All investigators should consider utilizing the AYA PRO core battery in AYA clinical trials they are actively developing. The battery does not need to be used in its entirety and investigators can include components most relevant to their study population and anticipated toxicities.

6. **Do investigators need permission to use the AYA PRO core battery in their studies and are there charges associated with including the battery?**

   Permission is needed to use the PROMIS measures for each study to ensure the most current versions are being utilized. These measures are widely available and easily accessible. The English versions of all PROMIS measures are free and distribution fees for translated versions of PROMIS measures are waived in non-industry sponsored academic studies. The PRO-CTCAE is publicly available for use in clinical research.

7. **Can other domains be included in the PROMIS AYA Health Status Profile and does that alter the validity of the inventory?**

   All of the PROMIS Short Form measures were designed to be used either as standalone instruments or in combination with other measures. Study investigators can thus substitute PROMIS Short Form measures based on the HRQoL domains of interest. Additional short forms can be included (e.g., sexual function, sleep disturbances); however, investigators should limit the total number of items to minimize patient burden. Short forms should be administered in the order from most important to assess first (i.e., primary and secondary measures), followed by measures assessing exploratory endpoints. Each of the short form instruments included in the PROMIS AYA Health Status Profile is scored individually to reflect each HRQOL domain and investigators do not calculate a composite (overall) score. Investigators who plan to include one of the HRQoL domains (e.g., physical function) as a primary or secondary endpoint should consider using the 8-item version of the PROMIS measure for that domain, as the 4-item measure may not provide sufficient reliability and content validity.

   PROMIS instruments are available at: https://www.healthmeasures.net/explore-measurement-systems/promis/intro-to-promis

8. **How do I select items from the PRO-CTCAE and Ped-PRO-CTCAE measurement system?**

   Items from the PRO-CTCAE and Ped-PRO-CTCAE measurement system should be selected based on the anticipated toxicities from the planned treatment approaches. The Ped-PRO-CTCAE is a pediatric module which allow self-reporting for patients ages 7-17 years. Investigators are encouraged to limit the total number of items from the PRO-CTCAE to ~12 items to minimize patient burden. Each symptom adverse event (AE) includes items/questions that assess up to 3 of the following attributes: frequency, severity, interference, amount and/or presence/absence, and each attribute is scored separately. The PRO-CTCAE measures provide descriptive data on symptom AE toxicity. In addition to

reporting each attribute separately, algorithms have been developed to convert self-report response patterns (e.g., how an AYA answered the pain frequency, severity and interference questions) into a single, CTCAE-like grade reflecting the overall adverse effect (e.g., pain grade). [1,2]

PRO-CTCAE and Ped-PRO-CTCAE items are available at: https://healthcaredelivery.cancer.gov/pro-ctcae/

9. **When should I use the pediatric vs adult PRO measures if my target population spans both age groups? Can I use the adult HRQoL measures in adolescents or can I use the pediatric HRQoL measures in adults?**

The pediatric versions of PRO-CTCAE and PROMIS were designed for 8-17 year olds and the adult versions of the measures were designed for 18 years and older. While it is recommended to use age-specific measures, there is some evidence that adolescents as young as 16 years are mostly able to answer questions on the adult measures.[3,4] Thus, it may be feasible to use the adult PROMIS and PRO-CTCAE measures in a study that includes children as young as 16 years or to use the pediatric versions of the measures in a study that includes young adults (e.g., 18-20 years of age). A deep understanding of the target population and their capabilities (e.g., literacy levels) is recommended to guide the selection of the appropriate measures.

10. **If I collect data on the same outcome (e.g., physical function) using both the pediatric and adult versions of the PRO measure, can I simply combine all the data in a single analysis?**

Summary scores from each of the age-based versions (e.g., mean, SD) should be reported separately. The scores on the adult measures are not the same scores on the pediatric measures. If there is interest to combine data on the core HRQoL measures that include scores from both the pediatric and adult PROMIS measures, then linking metrics are available in Reeve et al 2016 and Tulsky et al 2019.[5,6]

11. **How frequently should the AYA PRO core battery be administered?**

It is important to assess changes in HRQoL throughout the cancer continuum. While there is flexibility in the timing of assessments, the Task Force recommends administering the PROMIS AYA Health Status Profile at baseline, during treatment (including key comparison points by study arm), at the end of treatment and then annually into post-treatment survivorship for a total of 3-5 assessments. Assessment of acute toxicity should be conducted at baseline, followed by time points during which toxicity is anticipated based on the agents and treatment approach utilized and then into post-treatment to assess for resolution of symptoms.

12. **Can the AYA PRO core battery be delivered electronically?**

The AYA PRO core battery can be administered electronically. AYAs are a tech-savvy population and electronic data capture is a preferred modality for AYAs and a less expensive approach to collecting data that often results in a higher response rate.[7] Electronic administration of the core battery is recommended when feasible. Safeguards are needed to ensure data completeness and quality.

13. Is the AYA PRO core battery available in languages other than English?

The PROMIS instruments and items included in the PRO-CTCAE and Ped-PRO-CTCAE measures have been translated in many languages. It is important to review the available languages for each instrument at the time of protocol development. Investigators should only use authenticated translations and should not use versions translated by study team members. Additional translations of the PROMIS short form measures can be requested at a modest cost.

The list of languages the PROMIS instruments, the PRO-CTCAE and the Ped-PRO-CTCAE have validated in can be accessed at:
https://www.healthmeasures.net/explore-measurement-systems/promis/intro-to-promis/available-translations
https://healthcaredelivery.cancer.gov/pro-ctcae/countries-pro.html
https://healthcaredelivery.cancer.gov/pro-ctcae/countries-ped.html

14. Who can I contact if I have additional questions about the AYA PRO core battery?

If you have additional questions about how to incorporate the AYA PRO core battery in your study, please email Dr. Susan Parsons (SParsons@TuftsMedicalCenter.org) or Dr. Michael Roth (MRoth1@mdanderson.org). The NCTN AYA PRO Task Force strongly recommends that all committees developing new AYA study concepts include an AYA PRO expert on the study committee at the earliest stages of study concept development. AYA PRO experts are available to assist within each of the NCTN Network Groups.

Alliance:	Dr. Gita Thanarajasingam Thanarajasingam.Gita@mayo.edu
	Dr. Bryce Reeve bryce.reeve@duke.edu
COG:	Dr. Susan Parsons sparsons@tuftsmedicalcenter.org
	Dr. Pamela Hinds PSHinds@childrensnational.org
ECOG-ACRIN:	Dr. John Salsman JSalsman@wakehealth.edu
	Dr. Lynne Wagner LyWagner@wakehealth.edu
NRG:	Dr. Patti Ganz pganz@mednet.ucla.edu
SWOG:	Dr. Lynn Henry norahh@med.umich.edu

References:

1. Basch E, Becker C, Rogak LJ, Schrag D, Reeve BB, Spears P, Smith ML, Gounder MM, Mahoney MR, Schwartz GK, Bennett AV. Composite grading algorithm for the national cancer institute's patient-reported outcomes version of the common terminology criteria for adverse events (PRO-CTCAE). Clinical Trials. 2021 Feb;18(1):104-14.
2. McFatrich M, Brondon J, Lucas NR, Hinds PS, Maurer SH, Mack JW, Freyer DR, Jacobs SS, Baker JN, Mowbray C, Wang M. Mapping child and adolescent self-reported symptom data to clinician-reported adverse event grading to improve pediatric oncology care and research. Cancer. 2020 Jan 1;126(1):140-7.
3. Reeve BB, McFatrich M, Pinheiro LC, Freyer DR, Basch EM, Baker JN, Withycombe JS, Sung L, Mack JW, Waldron MK, Mowbray C. Cognitive interview-based validation of the patient-reported outcomes version of the common terminology criteria for adverse events in adolescents with cancer. Journal of pain and symptom management. 2017 Apr 1;53(4):759-66.

4. Blalock DV, Lin L, Wang M, Thissen D, DeWalt DA, Huang IC, Reeve BB. Analysis of Differential Item Functioning in PROMIS® Pediatric and Adult Measures between Adolescents and Young Adults with Special Health Care Needs. Psychological Test and Assessment Modeling. 2020 Oct 1;62(4):417-28
5. Reeve BB, Thissen D, DeWalt DA, Huang IC, Liu Y, Magnus B, Quinn H, Gross HE, Kisala PA, Ni P, Haley S. Linkage between the PROMIS® pediatric and adult emotional distress measures. Quality of Life Research. 2016 Apr 1;25(4):823-33.
6. Tulsky DS, Kisala PA, Boulton AJ, Jette AM, Thissen D, Ni P, DeWalt DA, Huang IC, Liu Y, Mulcahey MJ, Slavin M. Determining a transitional scoring link between PROMIS® pediatric and adult physical health measures. Quality of Life Research. 2019 May;28(5):1217-29.
7. Flanagan SM, Greenfield S, Coad J, Neilson S. An exploration of the data collection methods utilised with children, teenagers and young people (CTYPs). BMC Research Notes. 2015;8: 61-61.