Implementation of Electronic Capture of PROs in NCI Clinical Trials

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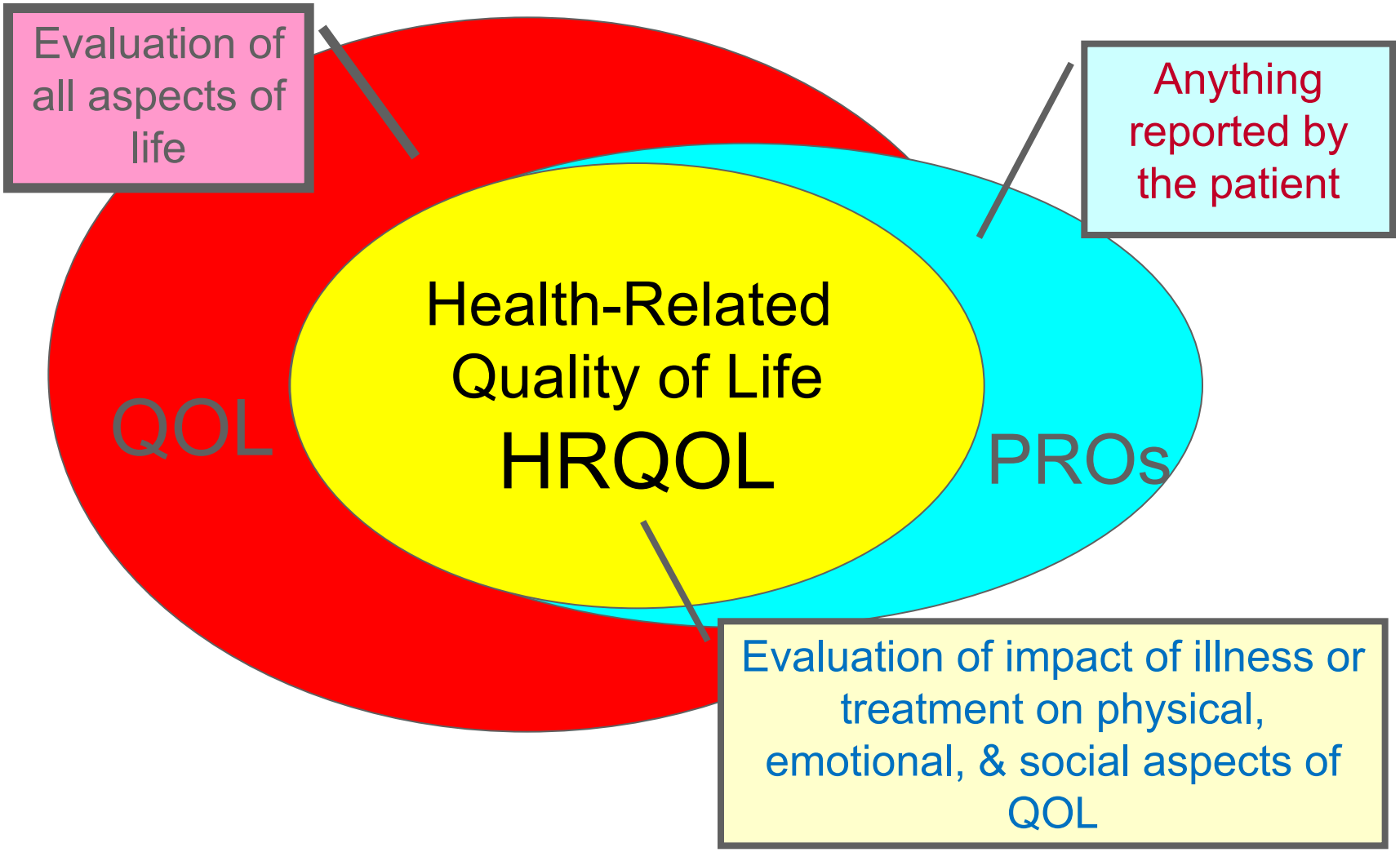
May 11, 2017

Objectives

1. Provide framework for the collection of Patient Reported Outcomes (PROs) in NCI clinical trials.

2. Provide update on the implementation of the electronic capture of PROs in NCI clinical trial networks.

PRO ≠ QOL ≠ HRQOL



Vision for PROs in NCI Clinical Trials

- Incorporate patient reported outcomes into the study design to identify safe and effective interventions to treat, prevent and control cancer.
  - Evaluating impact of treatment and disease on HRQOL
  - Patient reporting of symptomatic adverse events
  - Consistent with FDA Patient Centered Drug Development

- Improve operational efficiency through the electronic collection of PROs for investigators, site staff, and patients
  - Streamline data collection and analysis with integration of PROs into the existing electronic data collection
  - Improve feasibility and usability to enhance patient participation in PRO collection

Why include PRO data?

- PRO questions can provide additional information to assess the overall risk/benefit
  - Are the symptoms of disease improving?
  - Is the functionality changing to benefit patient?
  - Are the side effects too bothersome?
  - Are the side effects exacerbated because of co-morbidities?
  - Is there a difference in Health Related Quality of Life based upon the treatment intervention?

- *Not All Studies Need to Include PROs*

What information needs to be in the protocol document?

- PRO hypothesis should be included in the study objectives
  - Why are you collecting PROs?
  - How will they inform the other study endpoints?
- Data collected reflects the clinical issue.
  - Time points for collection correspond to the rationale for inclusion of the PRO instruments
- Statistical methods are stated in the protocol,
  - Data analysis and include sample size

PRO-CTCAE™

PRO-CTCAE™

- Item Library of 78 AE items
  - Derived from CTCAE
  - Patients asked to score attributes (presence, severity, frequency, and interference) independently
  - Publicly released on April 2016
    - (https://healthcaredelivery.cancer.gov/pro-ctcae)

- Not every item is intended for use in one trial
- Designed to systematically capture symptomatic AEs from patients and complement clinician rated CTCAE

- Selected relevant PRO-CTCAE items are chosen
  - For prospective assessment
  - ***Not currently for protocol specific action***

Similar Data, *Different Purposes*

CTCAE

- Clinician reported
- Safety signal
  - Medical evaluation
- Each AE is graded 1 - 4
- Grade prompt dosing decisions
- Grades 3-5 reported descriptively,
- Tables do not account for trajectory of toxicity

PRO-CTCAE

- Patient reported
- Tolerability signal
- Each item may have 3 separate scores (frequency, severity, interference)
- Scores do not prompt dosing decisions
- Standard approach to reporting and analyzing scores not established

PATIENT-REPORTED OUTCOMES VERSION OF THE COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS (PRO-CTCAE™) ITEM LIBRARY (Version 1.0)

Oral	
Dry mouth	S
Difficulty swallowing	S
Mouth/throat sores	SI
Cracking at the corners of the mouth (cheilosis/cheilitis)	S
Voice quality changes	P
Hoarseness	S

Gastrointestinal	
Taste changes	S
Decreased appetite	SI
Nausea	FS
Vomiting	FS
Heartburn	FS
Gas	P
Bloating	FS
Hiccups	FS
Constipation	S
Diarrhea	F
Abdominal pain	FSI
Fecal incontinence	FI

Respiratory	
Shortness of breath	SI
Cough	SI
Wheezing	S

Cardio/Circulatory	
Swelling	FSI
Heart palpitations	FS

Cutaneous	
Rash	P
Skin dryness	S
Acne	S
Hair loss	P
Itching	S
Hives	P
Hand-foot syndrome	S
Nail loss	P
Nail ridging	P
Nail discoloration	P
Sensitivity to sunlight	P
Bed/pressure sores	P
Radiation skin reaction	S
Skin darkening	P
Stretch marks	P

Neurological	
Numbness & tingling	SI
Dizziness	SI

Visual/Perceptual	
Blurred vision	SI
Flashing lights	P
Visual floaters	P
Watery eyes	SI
Ringing in ears	S

Attention/Memory	
Concentration	SI
Memory	SI

Pain	
General pain	FSI
Headache	FSI
Muscle pain	FSI
Joint pain	FSI

Sleep/Wake	
Insomnia	SI
Fatigue	SI

Mood	
Anxious	FSI
Discouraged	FSI
Sad	FSI

Gynecologic/Urinary	
Irregular periods/vaginal bleeding	P
Missed expected menstrual period	P
Vaginal discharge	P
Vaginal dryness	S
Painful urination	S
Urinary urgency	FI
Urinary frequency	PI
Change in usual urine color	P
Urinary incontinence	FI

Sexual	
Achieve and maintain erection	S
Ejaculation	F
Decreased libido	S
Delayed orgasm	P
Unable to have orgasm	P
Pain w/sexual intercourse	S

Miscellaneous	
Breast swelling and tenderness	S
Bruising	P
Chills	FS
Increased sweating	FS
Decreased sweating	P
Hot flashes	FS
Nosebleed	FS
Pain and swelling at injection site	P
Body odor	S

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

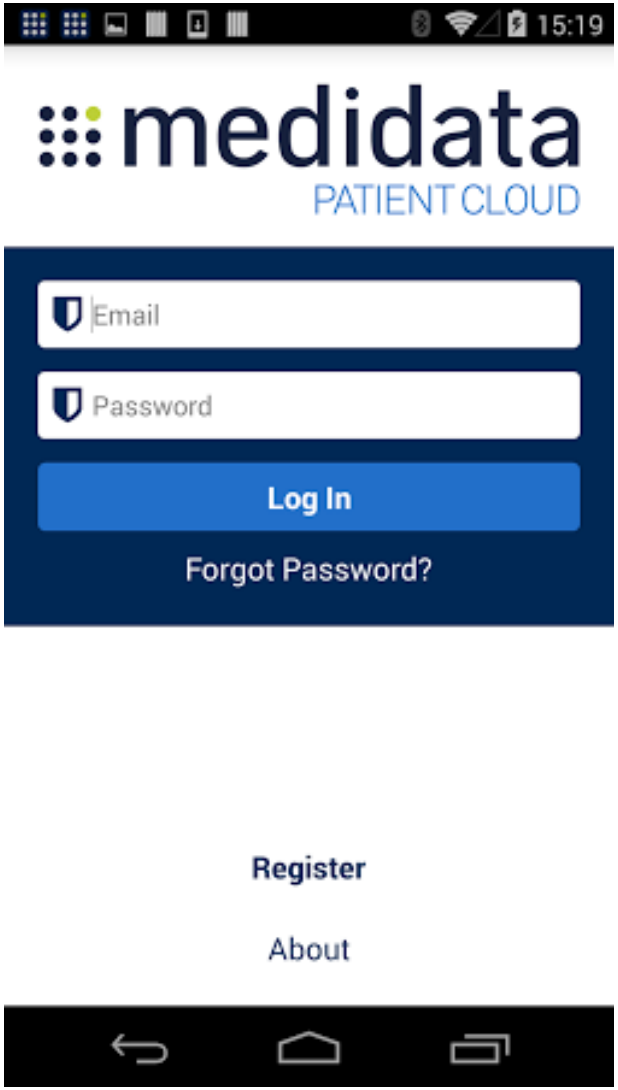
Collection Methods for PROs

- **Paper and pencil**
  - Long history of paper booklet collection
- **Telephone**
  - Some Groups have central telephone collections
  - IVRS useful
- **Electronic**
  - Industry using electronic direct patient capture methods
  - Increasingly being used, often with device provided by study
  - RTOG has used VisionTree for electronic data collection (a few trials)
  - ACRIN has used EASEEPRO for ePRO collection for COMET
  - Alliance has begun work with Medidata ePRO

Flexibility for Multiple Modalities is key

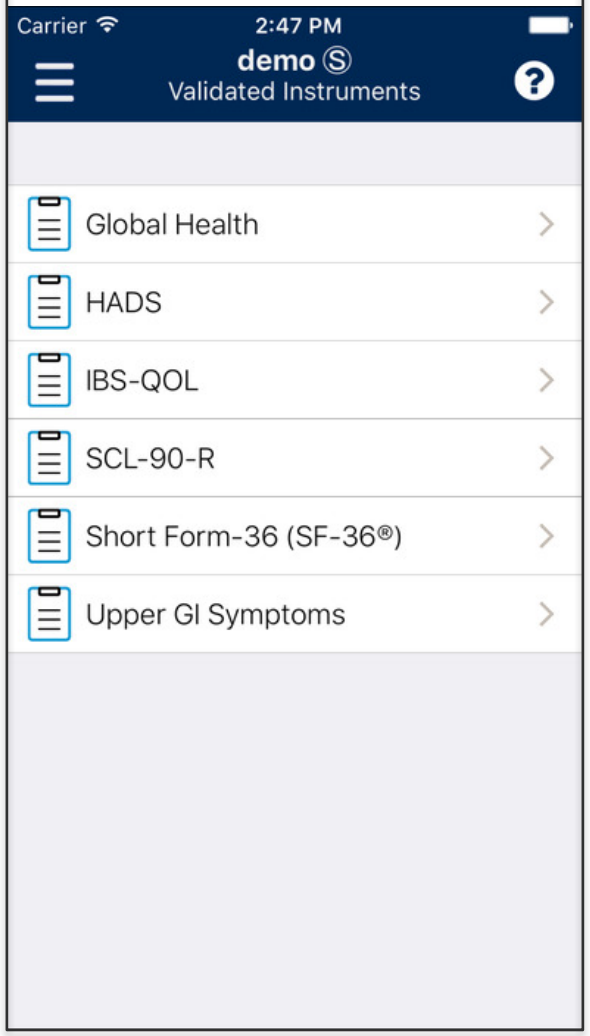
Patient Cloud ePRO Overview

- What is Patient Cloud ePRO?
  - A mobile app that collects patient responses to questionnaires / diaries and transfers data to the Medidata Clinical Cloud
  - Self-service setup and execution via intuitive role-based user interface
  - Fully integrated with Rave EDC to leverage the entire Medidata platform
  - Available for Android and iOS mobile devices

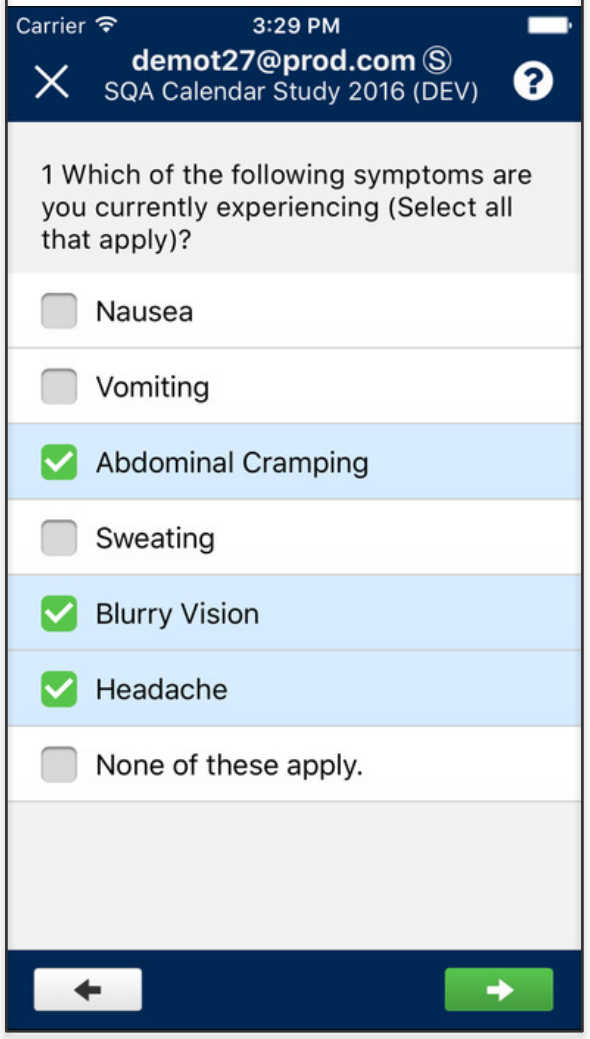


Patient Cloud ePRO Overview

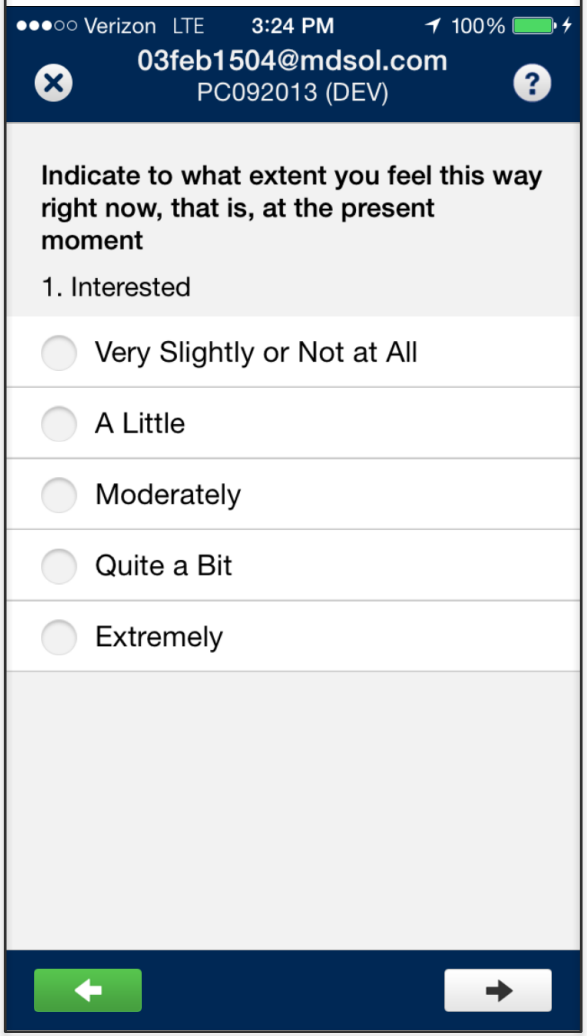
List of Instruments



Patient Questionnaire



PRO-CTCAE



ePRO Implementation Project

- Start with pilot
  - Collaborative process with the Groups
    - Protocol developers, data managers
  - Understand logistical and workflow issues for PROs and unique aspects for electronic collection

- Currently we have identified 13 clinical trials for inclusion
  - Anticipate 10-15 trials for NCTN and NCORP
    - Any PRO tool that has verified for electronic platform
  - Anticipate 4-5 trials for ETCTN

- Generate data from the use of PRO-CTCAE in clinical trials for the next step of its development
  - Both in early and late phase trials

How are PROs Funded in NCI Clinical Trials Networks?

- PROs captured in Cancer Prevention and Control Trials
  - *Division of Cancer Prevention funded **NCORP Grant***
  - *PROs may be the primary endpoint for cancer control trials*
  - *Cancer Control Credits*

- PROs captured in Cancer Treatment Trials
  - *Division of Cancer Treatment and Diagnosis funds the **NCTN Grant***
  - *Cancer Control Credits for hypothesis driven PROs*
    - *Cancer Control Credits from DCP NCORP Grant*

- All Endpoints in Cancer Trials undergo scientific review
  - Biospecimen collection need prospective analytic plan
  - PROs also must have a prospective analytic plan
    - *One exception is PRO-CTCAE*

Who works with PROs in the Alliance?

- Health Outcomes Committee
  - Home for developing PRO questions for inclusion with trials
  - Reviews Correlative Studies which include HRQOL and PROs
- Symptom Management Committee
  - Design studies that may have PRO primary endpoints
- Disease Committees
  - Consider the inclusion of PROs into disease specific protocols
- Patient Advocates
  - Perspective for information to be collected and patient burden
  - Perspective on feasibility of capturing different kinds of information
    - Alliance ePRO pilot study

Summary

- NCI is committed to including the patient voice through the inclusion of PROs in clinical trials
- Multiple different PROs instruments are used across the NCI clinical trials networks
  - HRQOL, PRO-CTCAE, others
  - Need hypothesis and analytic plan for inclusion
  - All PROs undergo scientific review
- Electronic collection of PROs is being implemented in a way consistent with other electronic clinical trial data
- PRO-CTCAE is a newly developed instrument
  - Systematic capture of patient reported symptomatic adverse events (*still under construction*)

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