Inclusion of Patient Reported Outcomes (PROs) in NCI clinical trials

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Definitions

Health-related quality of life (HRQOL) is a multi-dimensional concept:

- Domains for physical, mental, emotional and social functioning
- Overall score provides global assessment
- Designed to assess the overall impact of disease and treatment together
- Not designed to determine a treatment effect

Patient Reported Outcome (PRO) is *any* set of survey questions completed by patients

- Symptom inventory, patient diary
- Developed to assess specific construct (symptomatic adverse events, etc)
- Item Library of survey questions (PROMIS, PRO-CTCAE)

Inclusion of PROs into NCI-sponsored Clinical Trials

HRQOL tools have been incorporated into phase 3 randomized controlled cancer trials for over 30 years

- HRQOL assessed at baseline, every 3-6 months and then annually for a year or 2
- Cumulative score for different domains compared between the randomized arms
- Most common results for chemotherapy comparison
  - Drop in scored during treatment and recovery after treatment course
  - Usually, no difference in summary scores, but specific symptom scores may differ

NCTN Groups have included HRQOL in clinical trials

- 2010 50% phase 3 trials had HRQOL endpoints
- Typically, HRQOL endpoints are published, but not with the treatment results

Alignment of NCI Approach with FDA Draft Guidance on PROs in Cancer Clinical Trials

NCI Approach Aligns with Much in FDA Guidance

NCI PRO approach for core concepts

- Hypothesis driven inclusion of PROs
- Use of any PRO measure (HRQOL, disease specific, symptomatic adverse event) all need rationale for inclusion
- Funding for PROs only for NCTN and NCORP trials
  - Primarily phase 3, but some phase 2 trials, especially randomized phase 2

NCI approach for assessment schedule and frequency

- Baseline assessment of all measures
- Different assessment frequency for each core measure used
- Not typical to have frequent (weekly) assessments for PROs in NCTN/NCORP
- PRO-CTCAE designed for weekly assessment

NCI Approach Aligns with Much in FDA Guidance (continued)

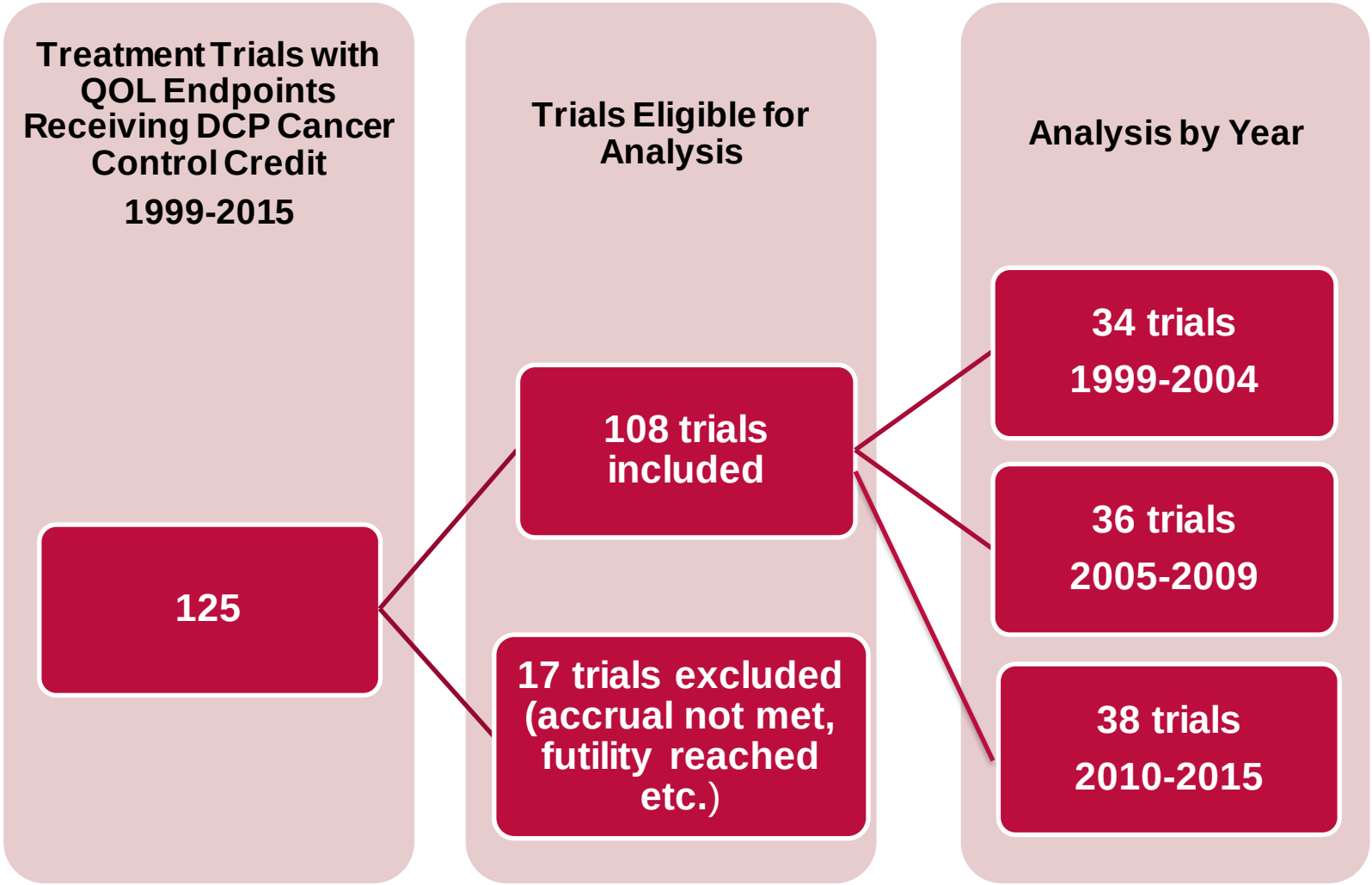
FDA draft guidance includes trial design considerations

- Accounting for missing data
- Reduce patient burden and electronic collection (facilitate out of clinic collection)
- Capture of other relevant data (concomitant meds, dose modifications, etc)
- Effective ways to communicate the analysis
  - (accurate, interpretable, not misleading, understandable by multiple stakeholders)

NCI approach

- Statistical section for PRO analysis needs to have process for missing data
- Primarily paper-based collection, but developing electronic means
  - Need to have mixed modality for collection
- Publication of PROs is currently the only means to communicate the results

Analysis of Publications of Health-Related Quality of Life Endpoints



Publication of HRQOL Endpoints in Cancer Treatment Trials (1999-2015)

Timeframe	Number of Trials	Parent Trial Published n (%) *	HR-QOL Published Overall	Independent HR-QOL Publication	HR-QOL Reported in Parent Publication
1999-2004	34	29 (85%)	18 (62%)	11	7
2005-2009	36	23 (64%)	14 (61%)	7	7
2010-2015**	38	6 (16%)	4 (67%)	2	2
ALL	108	58 (54%)	36 (62%)	20	16

*Percentage out of total number of trials for each timeframe

**May include trials with premature data not ready for analysis

NCI Pilot of Electronic Collection Medidata Patient Cloud (ePRO)

Collection Methods for PROs

Paper and pencil

- NCTN Groups have long history of paper booklet collection (printed booklet)
- Research staff enter patient responses into case report forms
  - Paper booklet is kept for source documentation

Electronic

- Industry standard is electronic data capture
- NCI pilot with Medidata ePRO tool
  - NCTN Groups using ePRO tool, with mixed results
  - Greater challenge at site level, but overall better data in dataset
- Two Groups had experience with electronic PRO collection before pilot
  - *Need flexibility of modalities for optimal PRO collection*

ePRO Usage Overview

Five Groups currently use ePRO on trials they conduct,

- Testers like the app; the CTSU facilitated and streamlined the use
- Several challenges in terms of syncing with cycle-based calendar, getting access to licensed tools
- Some patients do not have smart phones

LPO	# ePRO Trials	# ePRO Builds	Total ePRO Patients
NRG Oncology	12		510
Alliance	9	2	276
Theradex	4		40
ECOG-ACRIN	1		9
SWOG		1	0
		Total Patients:	835

Issues for NCI Clinical Trials Networks

Not all NCI clinical trials are done under FDA regulation

- This guidance does not apply to those trials for which no IND or IDE is planned

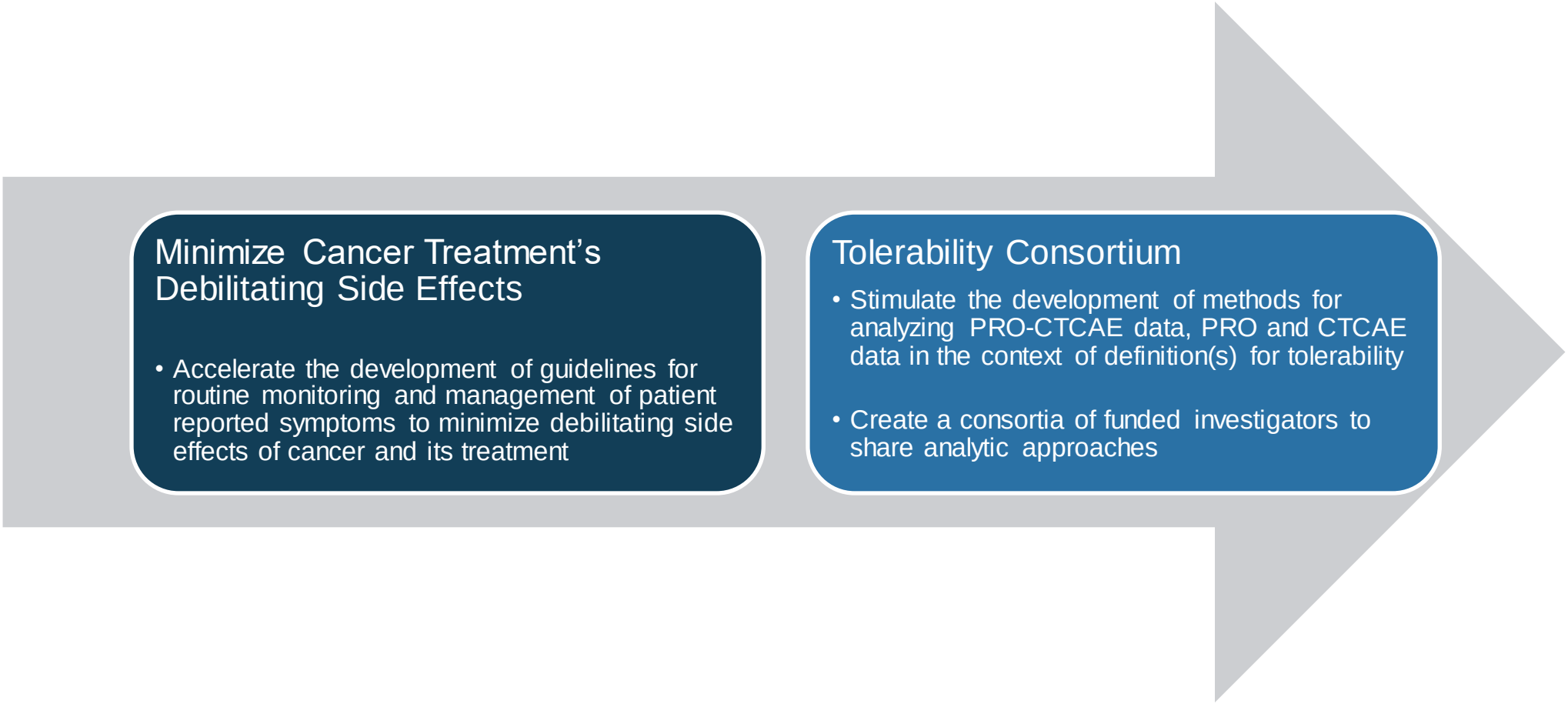
The FDA guidance is consistent with ongoing discussions between NCI and FDA, but some elements may be more challenging for NCI to implement

- Electronic collection to facilitate out of clinic collection
  - Improve data quality of PRO collection and reducing burden to patient and sites
  - Concern implementing effective electronic collection and not increasing missing data

- Effective ways to communicate the analysis
  - (*accurate, interpretable, not misleading, understandable by multiple stakeholders*)
  - Current method is limited to publication

Analysis
&
Graphical Displays

Cancer Moonshot℠ Research Initiatives



Moonshot RFA-CA-17-052

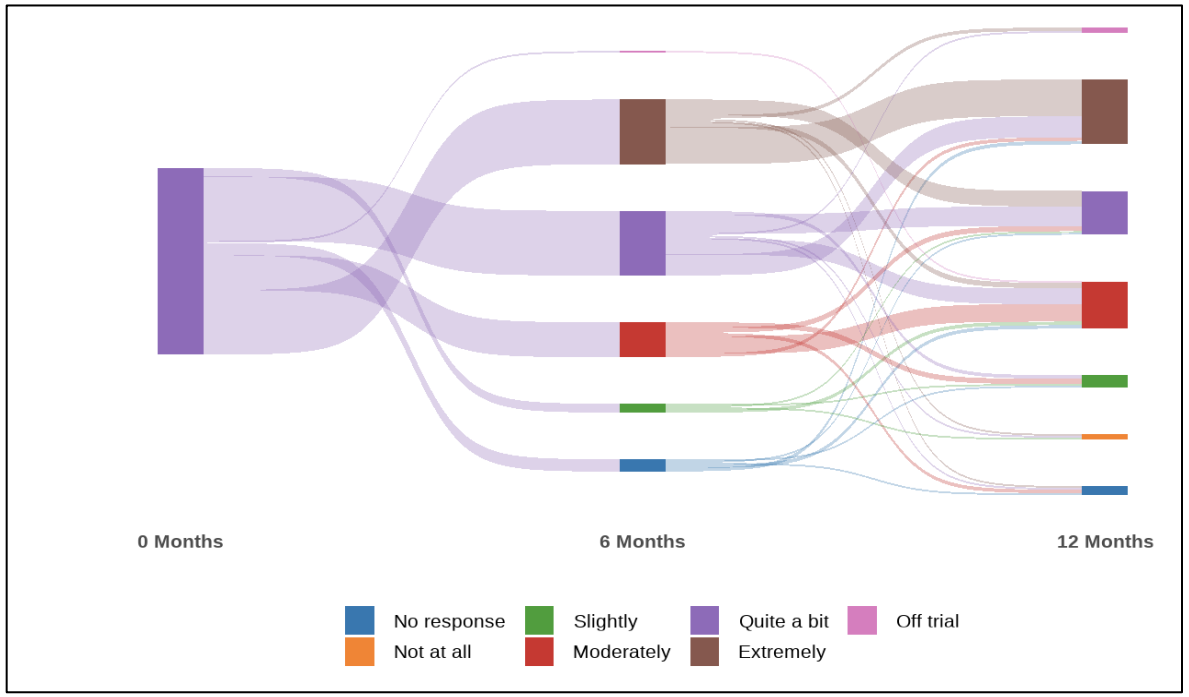
- Analyzing and Interpreting Clinician and Patient Adverse Event Data to Better Understand Tolerability

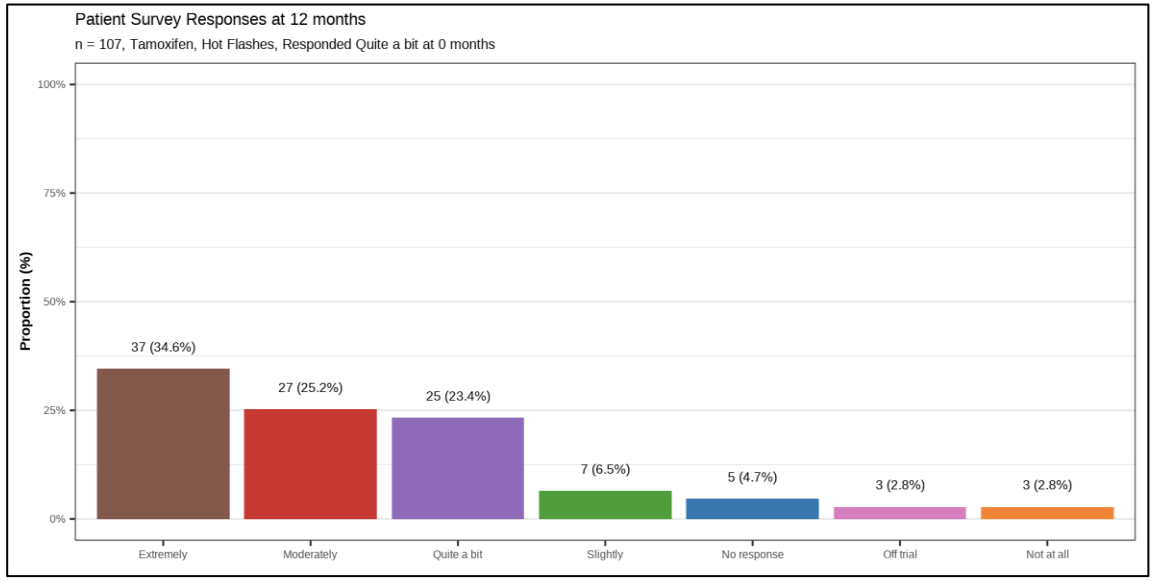
  - Using PRO-CTCAE with CTCAE data together with other clinically relevant data to determine tolerability
  - Evaluating associations of baseline symptoms (with pharmacologic or other laboratory data) with emerging symptomatic AEs over time
  - Using different approaches to address missing PRO-CTCAE data, e.g., characterizing missingness, gauging bias
  - Create a consortium to share analytic approaches

- Develop graphic displays to facilitate the *understanding and interpretation* of patient and clinician generated data

Visualize: Example (Symptom Explorer from Andre Rogatko Team)

There were a total of 107 patients with "Hot Flashes" who responded "Quite a bit" at 0 months treated with Tamoxifen.





Among those 107 patients at 12 months:

5 (4.7%) responded "No response"
3 (2.8%) responded "Not at all"
7 (6.5%) responded "Slightly"
27 (25.2%) responded "Moderately"
25 (23.4%) responded "Quite a bit"
37 (34.6%) responded "Extremely"
3 (2.8%) were "Off trial"

Translation and Validation of Patient Reported Outcome Measures

Supporting Clinical Trials Diversity: Translated PROs

- Enhance the ability of non-English speakers in DCP's clinical trials
  - Translation efforts need are not limited to PROs
  - Other patient facing materials (instructions, study calendar, etc)

- Access to existing translated PRO measures can be challenging
  - Permissions for use
  - Assuring consistent alignment of the translated questions

- Need a solution that promotes ease of use by patients, sites, and researchers

NCORP Meeting on PRO Challenges and Lessons Learned

Challenges:

- Data accessibility (missing data, resources for analysis, etc)
- Protocol development timelines and data issues for opening trials
- Ensuring that investigators work with PRO experts to design endpoints
- Certified translations for PROs and other related materials
- Lack of proactive emails to remind patients/sites for PRO completion
  - Relying on standard monitoring through RAVE is insufficient

Lessons:

- Early adoption of PROs into study design
- Patients are willing and able to participate, but want to know that it matters
- Technology can be leveraged to enhance data collection

Summary

NCI's approach is fundamentally aligned with the new FDA draft guidance for inclusion of PROs in cancer clinical trials

Two key areas for NCI to provide greater resource investment for those trials that are conducted under an IND

- Enhance infrastructure for the collection of PRO data to reduce missingness
- Enhance resource support for the analysis and distribution of the PRO results

The CTAC Clinical Trials Working Group has identified operational efficiency as a key aspect for the improved collection of PROs

NCI PRO Team for Review and Development

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DCCPS

- Sandra Mitchell

Thank you