Issues and Challenges with Integrating PROs in Cancer Trials supported by NCI-sponsored Clinical Trials Networks

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Background

- Provide an historical perspective to the incorporation of PROs in to national cooperative group trials.
- Provide an overview of the issues and challenges faced by cooperative groups to integrating PRO measures in cancer clinical trials.
- Report on the heterogeneity among cooperative groups in terms of formal and informal policies/procedures in place within each cooperative group as well as resource availability.
- Discuss the “culture” that exists within each group in regards to opinions/perspectives on the value of PROs

Definition

"A Patient Reported Outcome (PRO) is a measurement of any aspect of a patient's health status that comes directly from the patient (i.e. without interpretation of the patient's responses by a physician or anyone else)."

(U.S. Department of Health and Human Services, http://www.fda.gov/cder/guidance/, 2006)

Methods

- Survey of 12 Cooperative Groups from the US, Canada and Europe
- Potential bias….some of those who helped design the survey were also the ones who completed the survey
- 75 item survey using SurveyMonkey™ completed between June and August 2006

Results

Cooperative Groups participating

- ACOSOG
- ACRIN
- CALGB
- COG
- ECOG
- EORTC
- GOG
- NCCTG
- NCIC
- NSABP
- RTOG
- SWOG

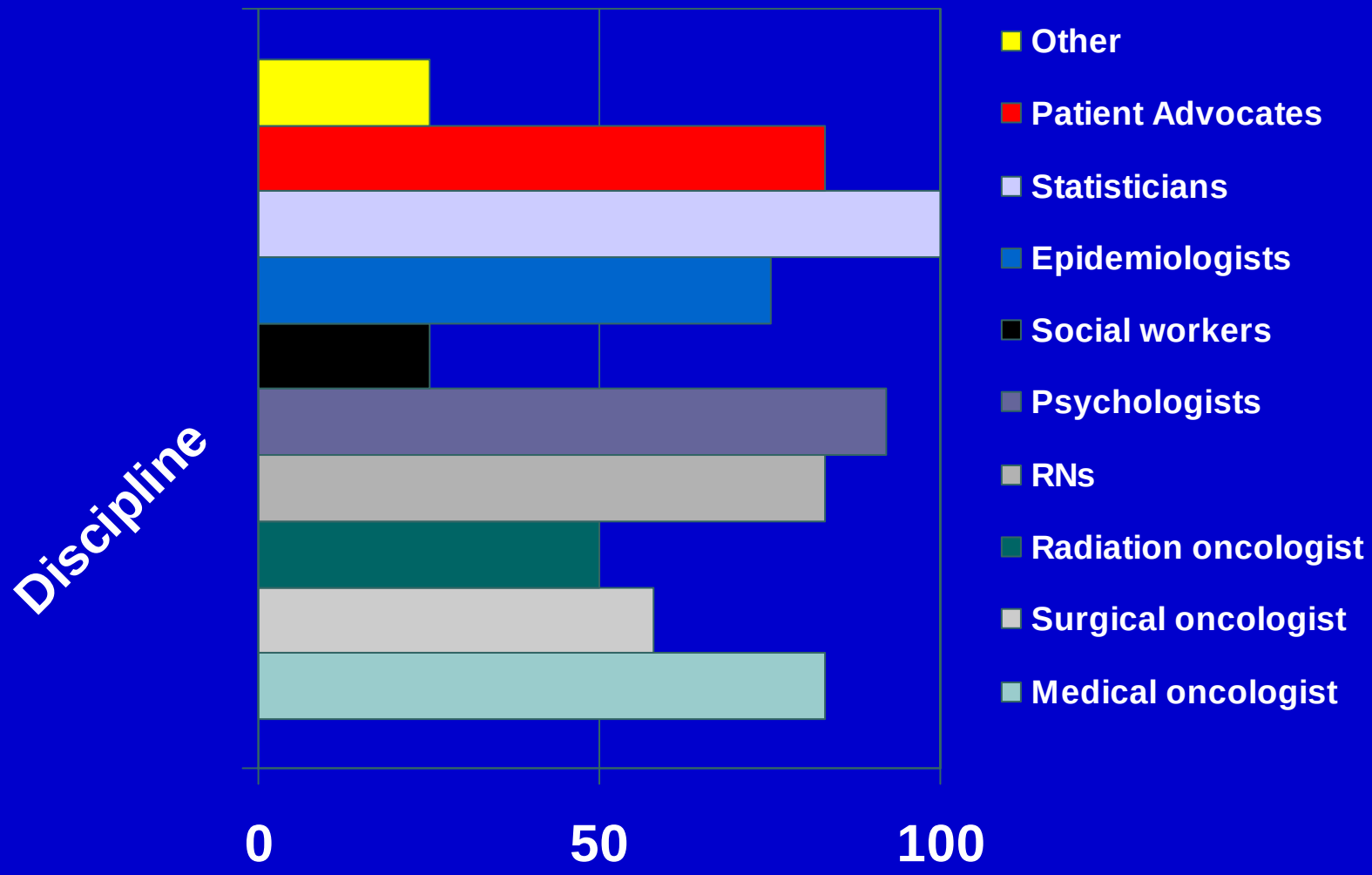
What is the name of the committee you chair?

Quality of Life	58% (7)
Outcomes or Health Services Research	17% (2)
Behavioral and Health Outcomes	17% (2)
Nursing	8% (1)

Year of inception of your group compared to year 1st PRO committee was developed

Group	Inception	PRO Committee Inception	Difference
ACOSOG	1998	1998	0
ACRIN	1999	1999	0
CALGB	1956	1980	24
COG	2000	2000	0
ECOG	1955	1989	34
EORTC	1962	1981	19
GOG	1970	1991	19
NCCTG	1981	1999	18
NCIC	1980	1986	6
NSABP	1957	1992	35
RTOG	1968	1989	21
SWOG	1956	1989	33

Disciplines of PRO committee members



Name of committee currently with primary responsibility for PROs in your group

- Quality of Life 50% (6)
- Outcomes or Health Services Research 33% (4)
- CCOP/Cancer Control 8% (1)
- Behavioral 8% (1)

Areas of study that use PROs in your group

Comparison of Tx Arms	100% (12)
Quality of Life	100% (12)
Symptom Assessment	92% (11)
Survivorship	92% (11)
Symptom Management	67% (8)
Behavioral Assessments	58% (7)
Translational Research	33% (4)
CAM	33% (4)

Formal training of PRO investigators /CRAs

	MDs/PhDs	CRAs
Formal training	17% (2)	83% (10)
Formal mentorship	33% (4)	

- Methods of training

Periodic lectures/ discussions at group mtgs	83% (10)
Web-based info	33% (4)
Video	25% (3)
Lecture at orientation	17% (2)
CD	8% (1)

Use of PRO liaisons

- Do committees that focus on PROs send liaisons to other committees?
  - Yes — 100% (12)
- Are they full members of the committees to which they are assigned?
  - Always — 42% (5)
  - Usually — 33% (4)
  - Sometimes — 25% (3)

Open CTEP trials that contain PROS

Group	Number	As an estimated % of all open CTEP trials	As % of all open CTEP trials (numbers from NCI)	
ACOSOG	2	26-50%	2/10	20%
ACRIN	7	26-50%	-	
CALGB	2	1-5%	7/76	9%
COG	5	1-5%	5/101	5%
ECOG	8	6-10%	8/113	7%
EORTC	40	26-50%	-	
GOG	5	11-15%	5/77	7%
NCCTG	18	51-75%	18/86	21%
NCIC	23	51-75%	-	
NSABP	5	51-75%	5/15	33%
RTOG	**18**	**51-75%**	**18/45**	**40%**
SWOG	6	6-10%	6/133	5%

Over the past 5 years, the percentage of PRO measures on CTEP trials has been:

- Stable 33% (4)
- Increasing 33% (4)
- Decreasing 33% (4)

Open CCOP trials that contain PROS

Group	Number	As an estimated % of all open CCOP/Cancer Control trials	As % of all open CTEP CC + DCP CC + DCP Prevention trials (numbers from NCI)
ACOSOG	-	26-50%	0
ACRIN	N/A	N/A	-
CALGB	UNK	UNK	?/2
COG	5	1-5%	5/5
ECOG	-	76-100%	?/4
EORTC	N/A	N/A	-
GOG	<5	11-15%	<5/4
NCCTG	**20**	**76-100%**	**20/18**
NCIC	N/A	N/A	-
NSABP	0	0	0/3
RTOG	9	51-75%	9/3
SWOG	7	51-75%	7/8

Over the past 5 years, the percentage of PRO measures on CCOP trials has been:

- Stable 33% (4)
- Increasing 25% (3)
- N/A 17% (2)

Utilization of written PRO policies and procedures

Recommended frequency of introduction of PRO policies

- At orientation 25% (3)
- Annually 42% (4)
- Periodically 25% (3)

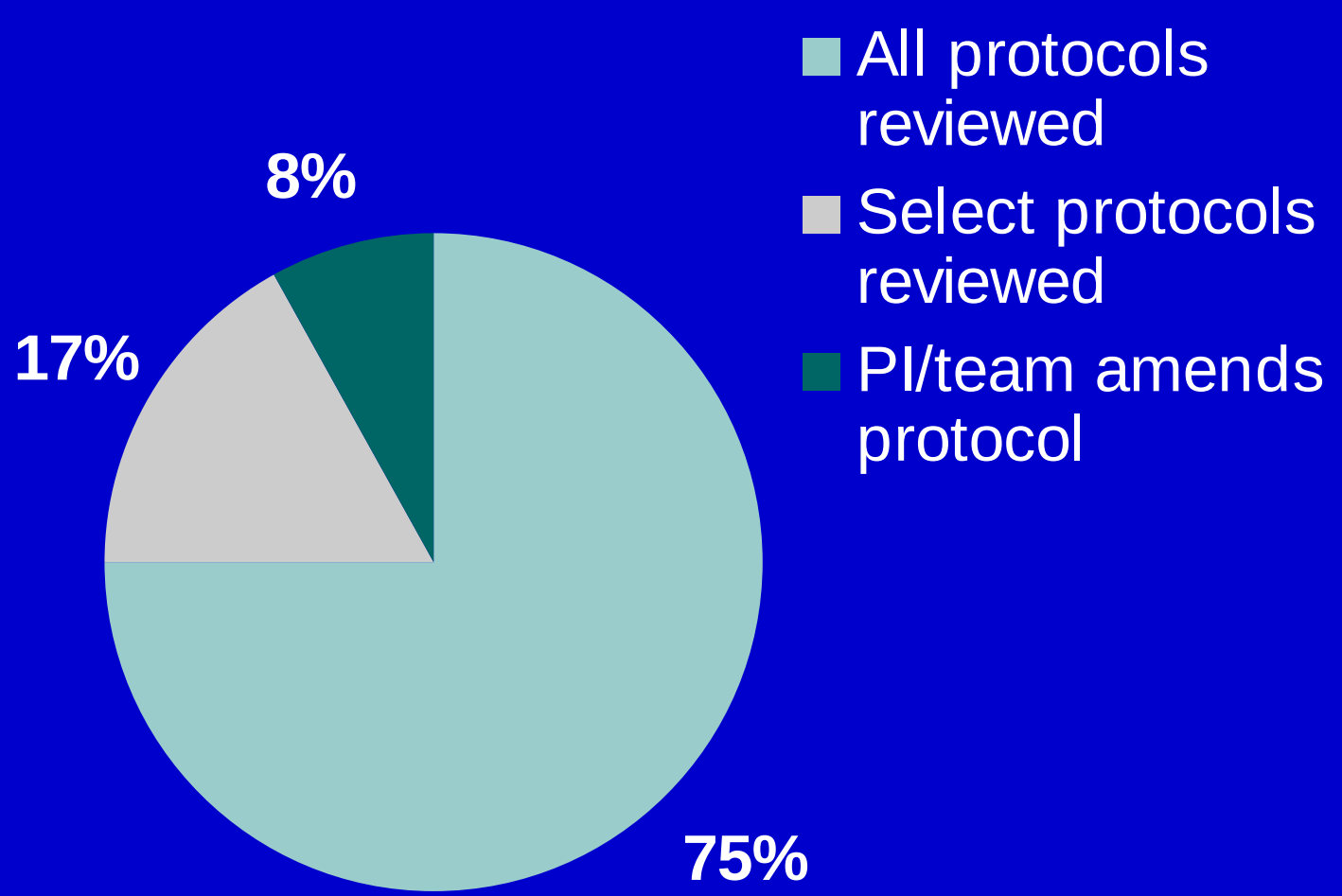
General standardized study procedures for PROs

- Yes 75% (9)
- No 17% (2)

Study specific standardized study procedures for PROs

- Never 8%
- Sometimes 59%
- Always 33%

Review process of protocols for PRO endpoints



Development of PRO secondary endpoints-when are investigators included?

- From/almost at the start of the study design — 50% (6)
- In time for NCI submissions — 50% (6)
- Added late in the study design — 25% (3)

Has this changed over time?

- Improved greatly — 42% (5)
- Improved somewhat — 50% (6)
- Has gotten worse — 8% (1)

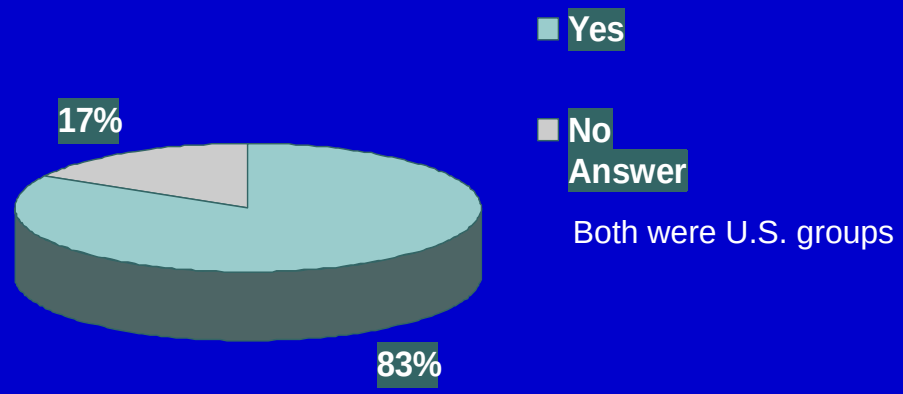
Does your group have specific psychometric criteria for validity and reliability that usually must be met in choosing a PRO measure?

- Yes 67% (8)
- No 33% (4)

Reasons for not having specific psychometric criteria for validity and reliability

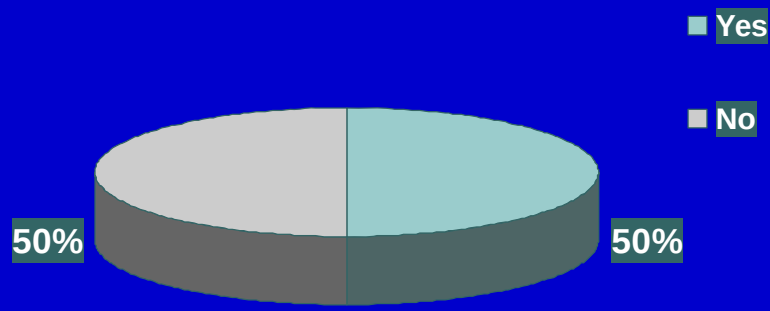
- PI included specific information in protocol
- Measure validated in other studies
- Ad hoc, based on Outcomes committee and PRO PI
- Applicability to address primary PRO endpoint

Awareness of FDA/PRO guidance?



Both were U.S. groups

Has FDA/PRO guidance been discussed in your group?



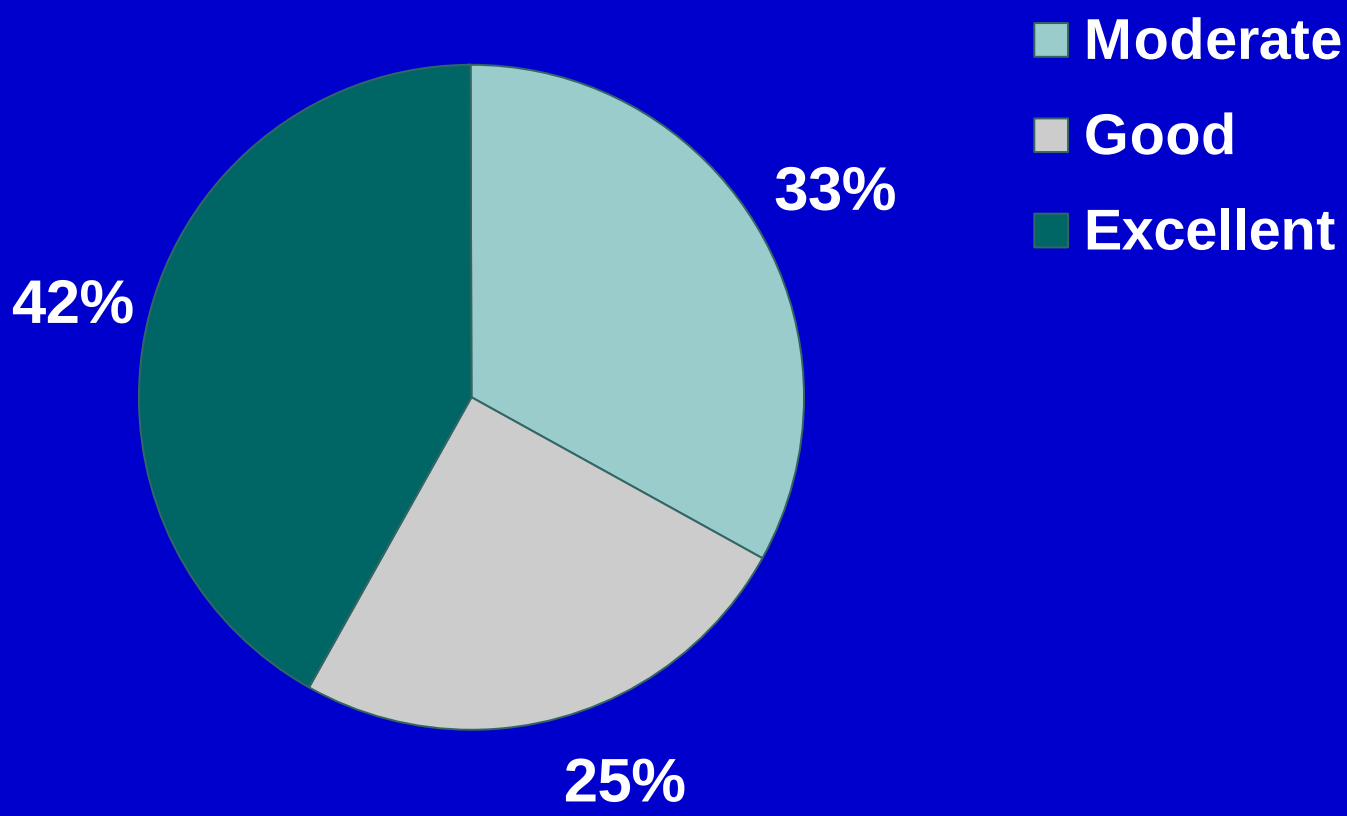
Will the FDA/PRO guidance be helpful?

- Not at all helpful 25% (3)
- Somewhat helpful 58% (7)

Will the FDA/PRO guidance be harmful?

- Not at all harmful 33% (4)
- Somewhat harmful 33% (4)
- Very harmful 8% (1)

Support from group chair for PRO research



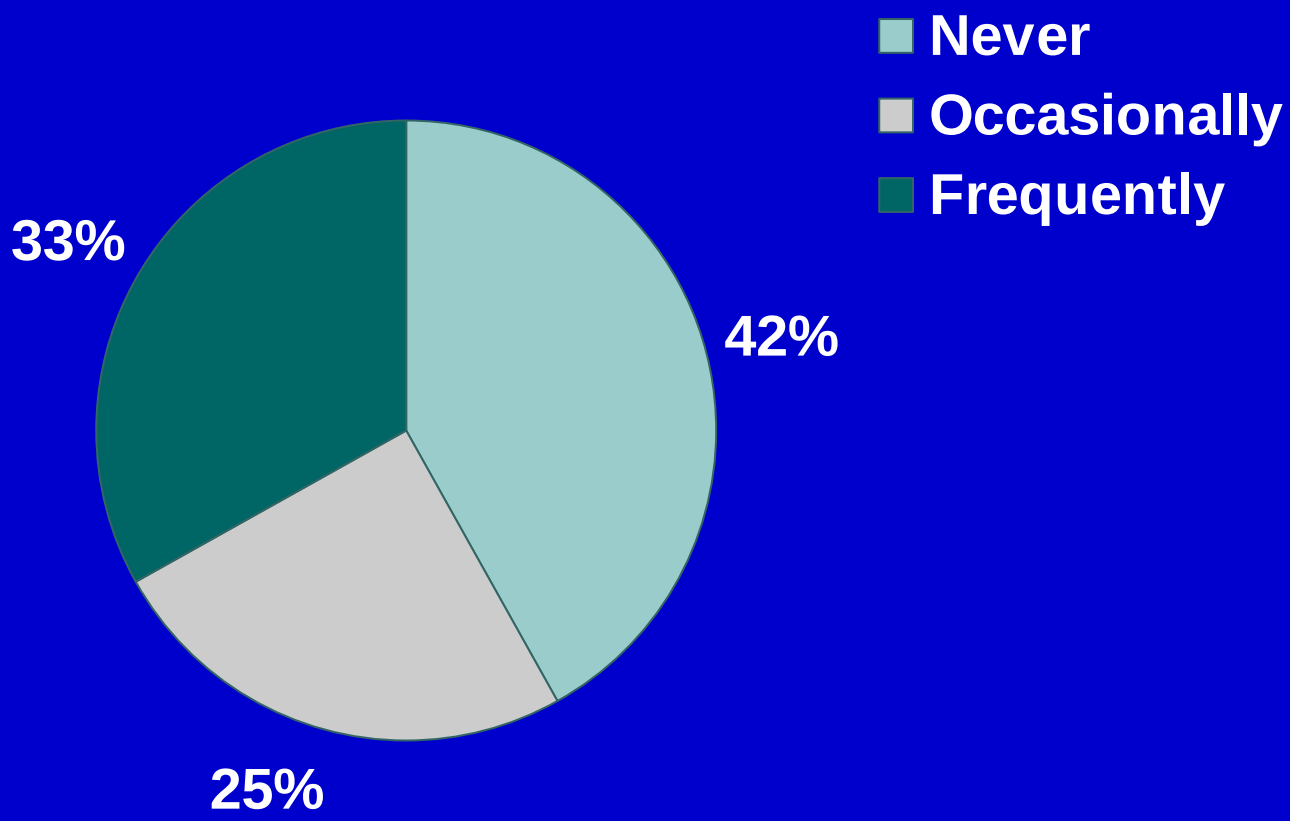
Has your group requested that you limit the number of protocols with PRO endpoints?

- Yes 42% (5)
- No 58% (7)

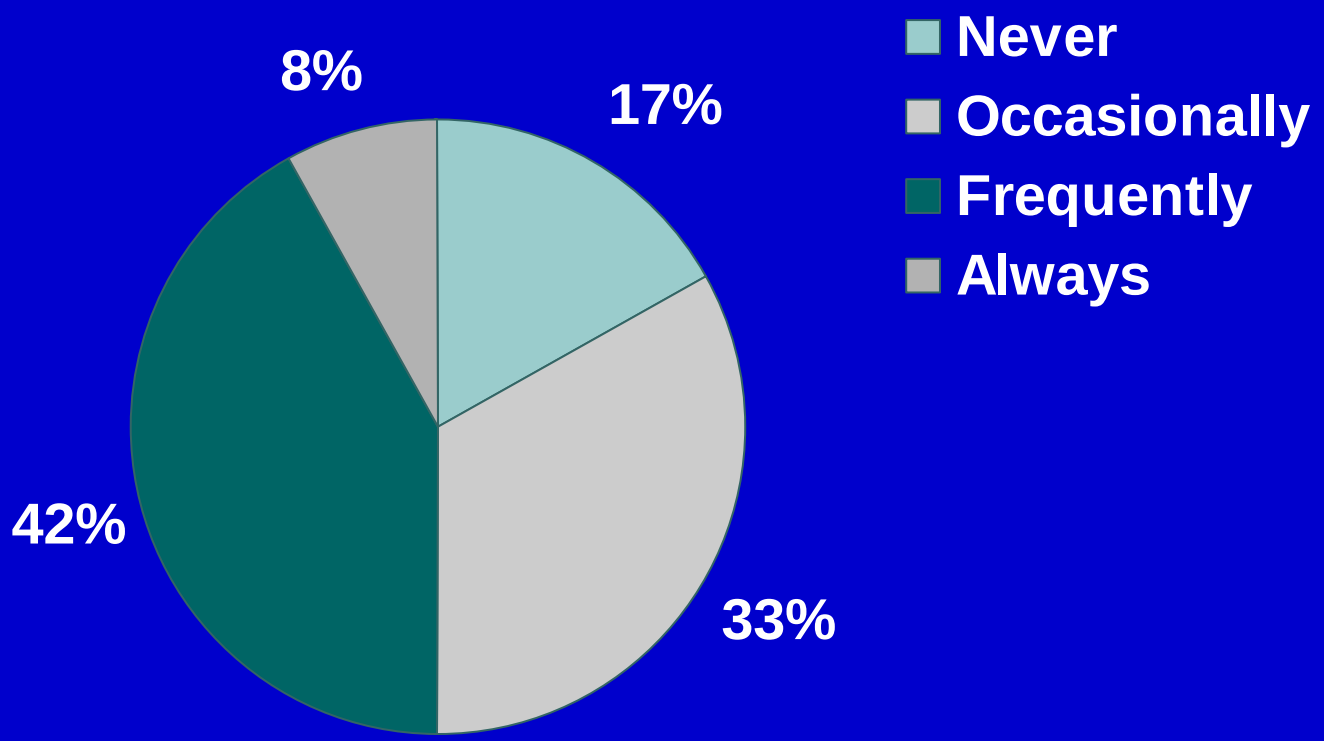
Most common PRO measures used in your group
(check all that apply)

EORTC	58% (7)
FACT/FACIT	50% (6)
SF36 (or shorter versions)	42% (5)
Other	25% (3)

Studies conducted in new PRO development?



Is PRO validation included in each study?

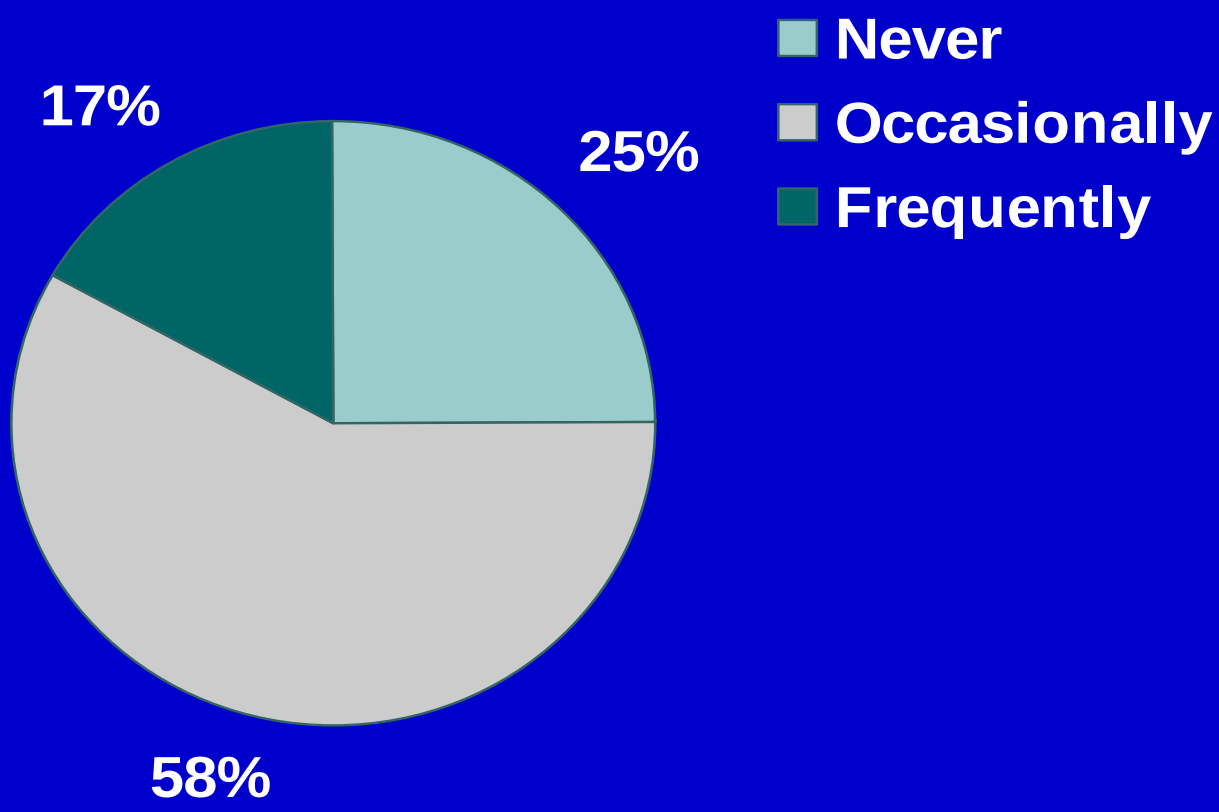


Trials including PRO endpoints

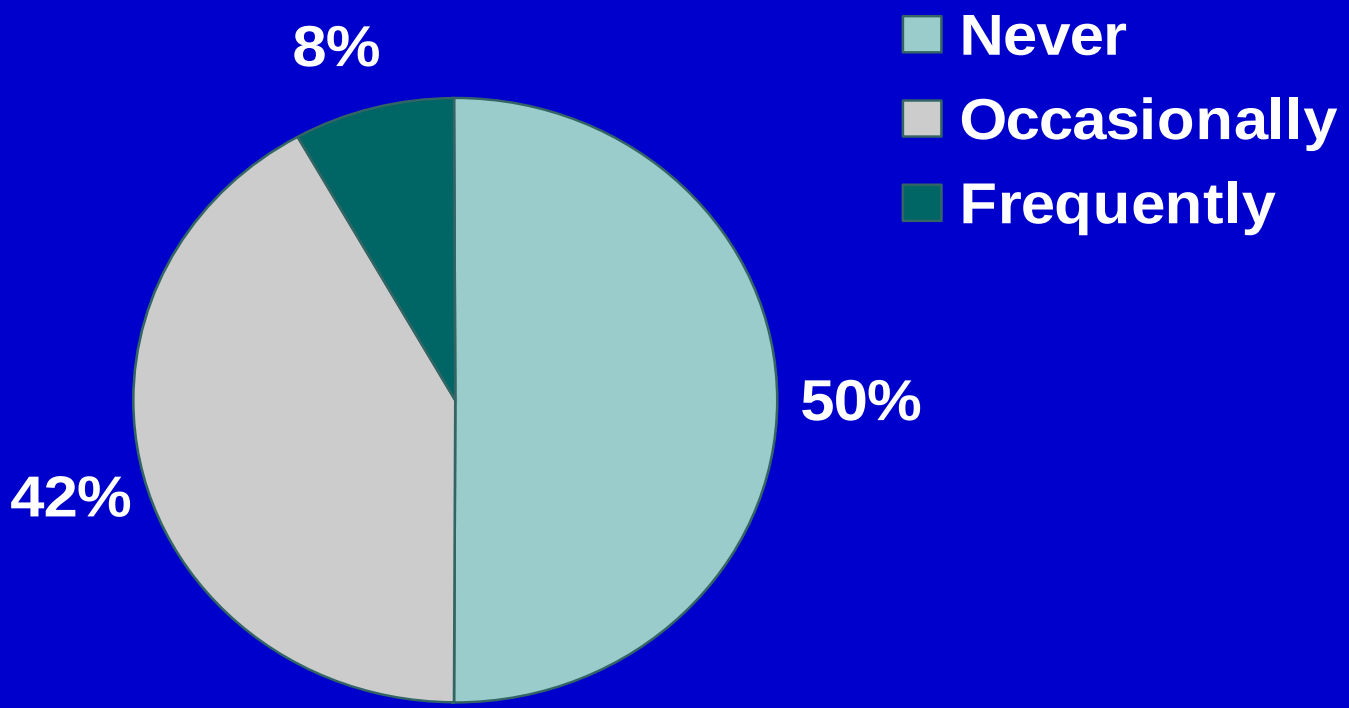
% of Cooperative Groups who include PROs by trial Phase/type

Phase I	8% (1)
Phase II	50% (6)
Phase III	100% (12)
Cancer Control	67% (8)

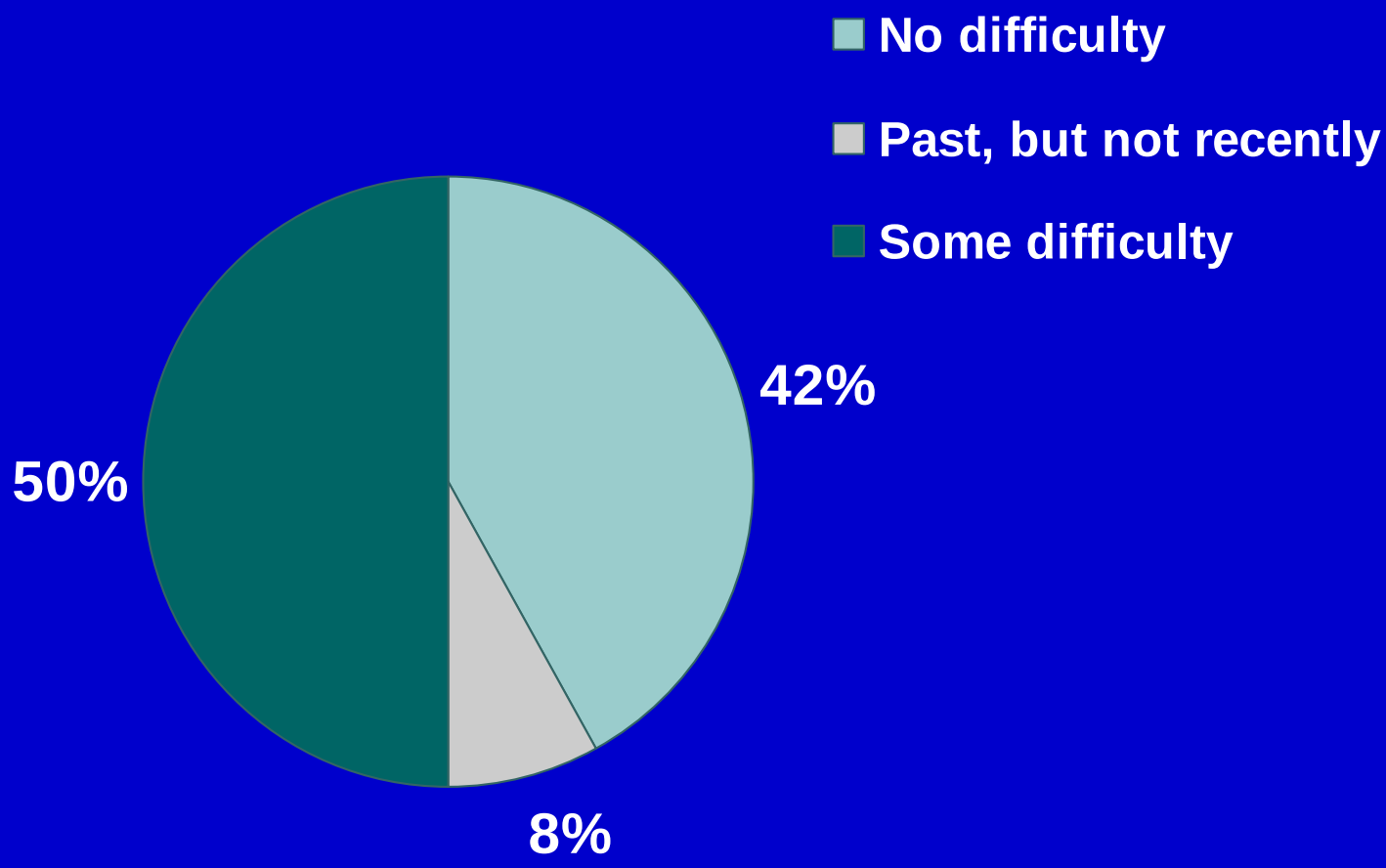
Occurrence of financial barriers to appropriate PRO endpoint inclusion



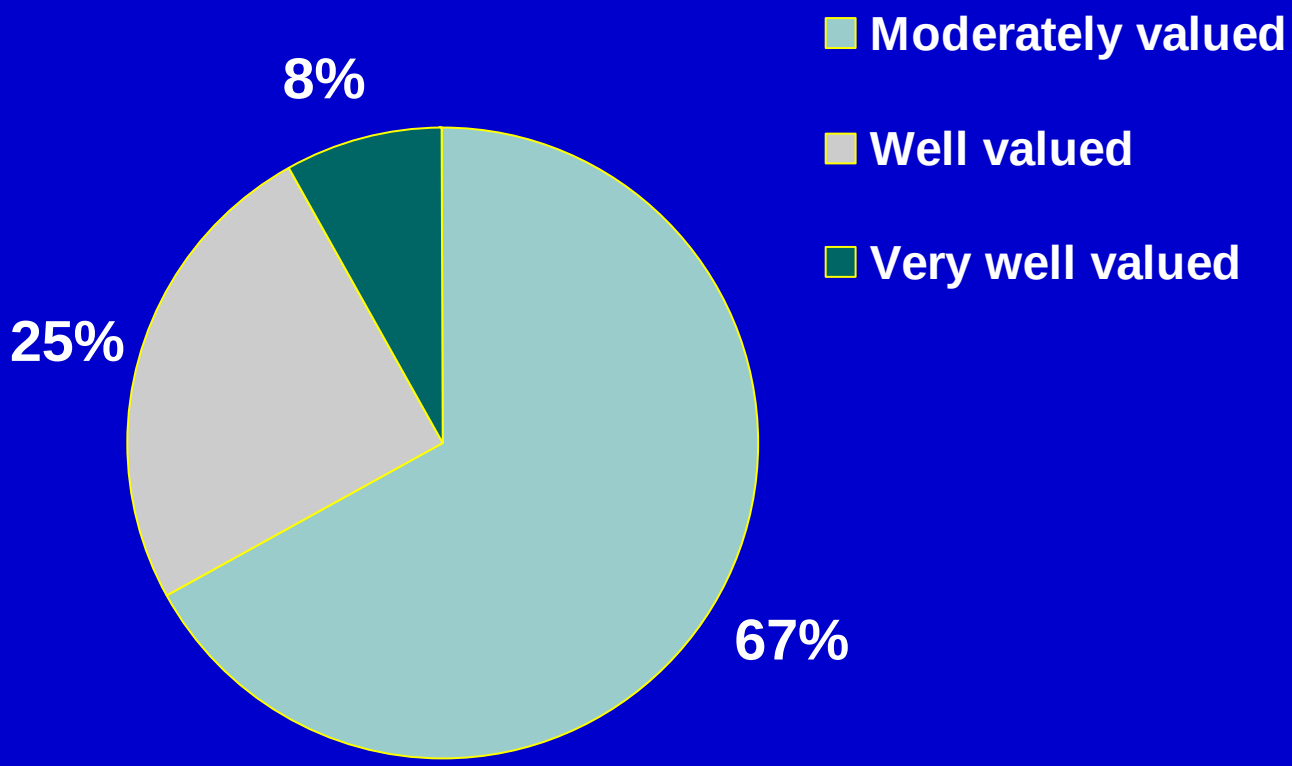
Are separate consents required for participation in PRO endpoints?



Difficulty in obtaining statisticians trained in PRO analyses?



Value of PRO endpoints compared to other outcomes



Additional comments: PRO ‘culture’ – Pros and Cons

“By and large, most clinicians support the value of PROs. There are some who do not. However, over time, we have observed positive changes.”

Additional comments: PRO 'culture' – Pros and Cons

"First was the basic belief that these PRO endpoints were ancillary to our real (funded) job of obtaining survival endpoints for CTEP. Secondly, it generally has been felt that these endpoints were too difficult to analyze statistically (i.e. doing power analyses, for trial number, worrying about our ability to deal with missing QOL data etc.). There was never a great deal of enthusiasm for them from the statistical sections and as a consequence very little statistical support for PRO endpoints as study concepts were being developed. "

Why are other measures, for example, like toxicity reporting, valued more than PROs?

46 out-pts from the Ottawa Civic Hospital Cancer Clinic

- Physician's charting of toxicities compared to pts self-report.
- Pts reported significantly more toxicities than had been recorded by their physician.
- The greatest disparity was observed for: nausea, vomiting, alopecia, and decreased performance status.
- The best-documented toxicities were: skin and mucosal reactions, and urinary symptoms.
- In 46% of cases, the physician's notes failed to identify the pt's worst symptom.
- “A self-administered questionnaire appears to be a better way of accurately identifying and reporting treatment toxicities, when compared to the oncologist's evaluation, as recorded in the patient's permanent record.”

(Parliament et al IJRBOP;11(3):603-8:1985)

Toxicity Criteria have Rarely Undergone Reliability or Validity Testing

- Recent Pubmed search unable to find any studies of validity, and only one study of reliability
- Japanese study evaluated the reliability of CTC v 2.0
- 5 CRAs independently reviewed med. records from 17 pts and graded toxicities
- At completion of toxicity grading coordinators discussed each case, and a consensus was reached for final toxicity grading
- The proportion of agreement for each toxicity criteria were as follows:
  - diarrhea; 0.59 (95%CI 0.35-0.82)
  - nausea; 0.47 (0.23-0.71)
  - stomatitis/pharyngitis; 0.59 (0.35-0.82)
  - vomiting; 0.71 (0.49-0.92)
  - febrile neutropenia; 0.88 (0.73-1)
  - infection; 0.82 (0.64-1)
  - sensory neuropathy; 0.65 (0.42-0.87).

(Kaba et al 31(8):1187-92:2004)

Differences in Toxicity Ratings and PROs

- An analysis of three NCCTG trials of symptom control regimens found a number of discrepancies between CTC ratings and PRO's (n=121)
- 10% percent of patients with no CTC reported diarrhea self-reported four or more diarrhea-related problems on the bowel function questionnaire
- 4% reported rectal bleeding on the questionnaire without a corresponding CTC toxicity rating
- 14% of lung cancer patients reported fatigue with no CTC-recorded fatigue (Varricchio & Sloan, 2002)

Differences in Toxicity Ratings and PROs

- Assessment of RTOG prostate trial that included toxicity ratings and PROs found that discordance between PROs on the FACT scale and physician ratings on the RTOG acute toxicity rating scale of the same symptoms ranged from 13% (for dysuria) to 45% (for diarrhea and erectile dysfunction) at 3 months f/u

  (Bruner et al IJROBP;33(4): 1995)

- Another RTOG trial examined sexual outcomes following RT ± androgen deprivation therapy in 471 prostate cancer pts and showed physician and pt assessment of the pt's ability to have an erection differed up to 47% of the time

  (Bruner et al Quality of Life Research, 7(7): 1998)

Differences in CTC vs PROs

- RTOG 97-09 assessed effect of pilocarpine during RT on salivary flow, xerostomia, mucositis, and QOL
- 245 evaluable patients were randomized to pilocarpine or placebo
- Pts provide stimulated and unstimulated samples of saliva and completed U Wash H&N Scale before treatment, at end of treatment, and 3 and 6 months after completion of RT
- Following completion of RT, the average unstimulated (but not stimulated) salivary flow was statistically greater in the pilocarpine group
- There was no effect on mucositis
- Results of the QOL scales did not reveal any significant difference between the pilocarpine and placebo groups with regard to xerostomia and mucositis.
- "The significant difference in unstimulated salivary flow supports the concomitant use of oral pilocarpine to decrease radiation-associated xerostomia. However, the absent correlation between improved salivary flow and QOL scores is of some concern (though not a new finding) and may be related to the existence of comorbidities and the lack of effect on mucositis."

Scarantino et al J Support Oncol. 4(5): 2006

Differences in CTC vs PROs

- RTOG 98-01: study of amifostine to reduce chemoRT-induced esophagitis and evaluate effect on QOL and swallowing
- Amifostine did not significantly reduce esophagitis as per CTC >/= grade 3 in pts receiving hyperfractionated RT/chemo
- In contrast, PROs suggested a possible advantage to amifostine. Overall QOL was not significantly different between the two arms
- However, there was a benefit in terms of pain control, with the amifostine arm showing more clinically meaningful improvement and less deterioration at 6 wks f/u vs. pretreatment (p = .003)

(Movsas et al JCO;23(10): 2005)

Prognostic Value of Self-reported QOL

- Baseline EORTC QLQ showed global QoL is a strong prognostic factor for survival (P<0.0001) in pts with NSCLC treated with radical or curative RT (Langendijk et al Radiother Oncol;55(1):2000)
- Esophageal ca pts EORTC QLQ scores pre-RT showed physical fx was significant survival predictor. At 2 mos after RT, dysphagia symptom scale was most significant survival predictor. 2-yr survival rate was 54.5% for pts without dysphagia 2 mos after RT compared with 14.3% for those with dysphagia (p <0.001) (Fang et al IJROBP; 58(5): 2004)
- Baseline FACT-Cervix prognostic of survival in GOG trial (Monk et al JCO;23(21):2005)
- MVA of EORTC QLQ indicated performance status (P<0.001) and appetite loss (p=0.005) as prognostic for survival in metastatic breast cancer (Efficace et al Eur J Cancer;40(7):2004)
- HRQoL was independent prognostic factor for survival in advanced bladder cancer; Predictors of longer survival included high physical fx, low role fx, and no anorexia. (Roychowdhury et al JCO; 21(4):2003)

Conclusion

- All cooperative groups surveyed include PROs in clinical trials
- Most PRO endpoints are on Phase III trials
- Wide variation in # and % of trials per group with PRO endpoints… with a range of 2-40
- Wide variation in policies, procedures and criteria for choosing PROs
- Resource barriers to incorporating PROs cited by all groups either in terms of financial or statistical support
- Most groups report PROs are not valued at level of other clinical endpoints
- Most groups report improvement in group culture related to acceptance of PROs

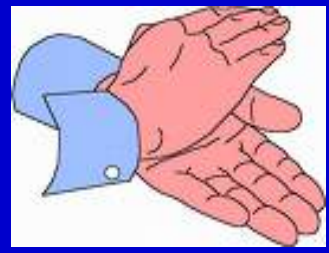
Conclusion

- There are significant opportunities to assess “Best Practices” and PROductivity among the groups
- Hopefully this will be the first in a more formal coming together of cooperative group PRO leadership to continue the dialogue

Conclusion

CTC and PROs should be used as STANDARD complimentary reporting in clinical trials to assess the objective and subjective components of treatment- and disease-related toxicity.

Many Thanks to Contributors



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