

NCI Cooperative Group Phase 3 Treatment Trials

Historical Accrual Experience of Trials Activated 2000-2010

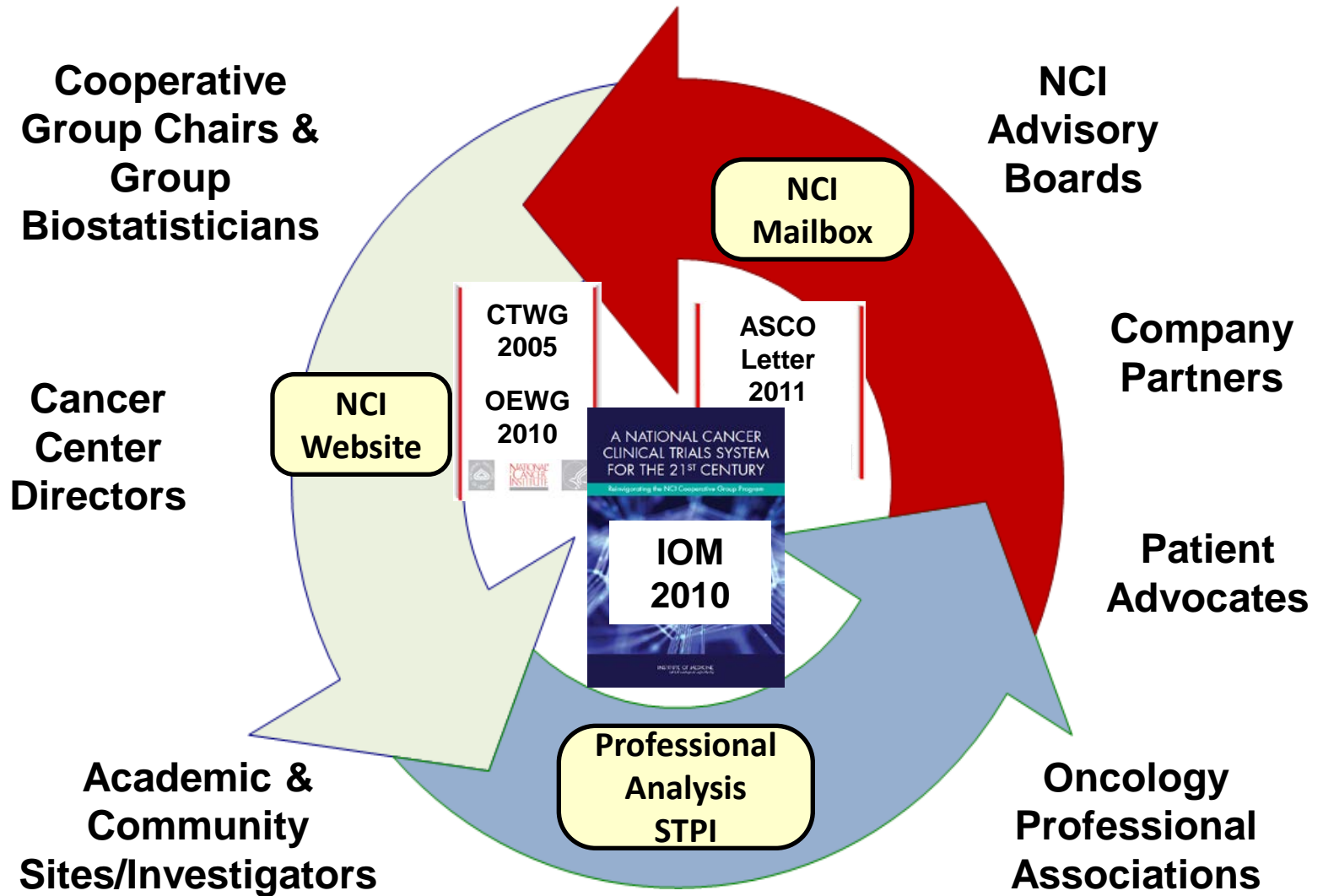
and

Preliminary Assessment of the DCTD/CTEP Slow Accruing
Guidelines for Phase 3 Treatment Trials

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Extensive Review & Stakeholder Input on Revising NCI's Late-Phase Clinical Trials System



Consensus Goals for a Transformed System

- ❑ Improve speed & efficiency of development & conduct of trials
- ❑ Incorporate innovative science and trial design
- ❑ Improve trial prioritization, selection, support, & completion
- ❑ Ensure participation of patients & physicians in system

Consensus Goals for a Transformed System

□ Improve speed & efficiency of development & conduct of trials

- Instituted Operational Efficiency Working Group Timelines for Protocol Development with Results Previously Reported

Implementation of Timeline Reforms Speeds Initiation of National Cancer Institute–Sponsored Trials, Abrams JS et al, J Natl Cancer Inst (2013) 105 (13): 954-959

- Now Concentrating on Activities to Support Ensuring Accrual Goals to Trials are Reached Once Trial is Opened

Accrual Experience of NCI Cooperative Group Phase 3 Trials Activated 2000 to 2007, Korn EL et al, J Clin Oncol (2010) 28:5197-5201

-----> *Updated Analysis*

Analysis of Accrual for NCI Cooperative Group Phase 3 Trials Activated 2000-2010

N=254 Trials (activated 2000-2010)

Accrual not over	51
\geq 90% accrued so far	41
<90% accrued so far	10
Accrual over	203
\geq 90% accrued	119
<90% accrued	84

Reasons<90%

interim monitoring	18
external information	11
drug supply issues	2
unacceptable toxicity	3
achieved sufficient number of events	1
inadequate accrual rate	53

Background on Analysis

N=254 Trials (activated 2000-2010)

Projections -- All trials

21.1% of trials will end with <90% accrual because of inadequate accrual rates

1.6% of patients will be on trials that end with <90% accrual because of inadequate accrual rates

Projections -- Non-pediatric trials

24.4% of trials will end with <90% accrual because of inadequate accrual rates

1.8% of patients will be on trials that end with <90% accrual because of inadequate accrual rates

Comparison Updated Analysis to Previously Published Figures

Activated:

Years

2000-1010

2000-2007

All trials

of trials

254

191

Trials <90% accrued

21.1%

22.0%

Patients on these trials

1.6%

1.7%

Non-pediatric trials

of trials

199

149

Trials <90% accrued

24.4%

26.7%

Patients on these trials

1.8%

2.0%

Preliminary Analysis of Primary Reasons Trials With <90% of Targeted Accrual Closed

Accrual over	203
≥ 90% accrued	119
<90% accrued	84

Reasons <90%

interim monitoring	18
external information	11
drug supply issues	2
unacceptable toxicity	3
achieved sufficient number of events	1
inadequate accrual rate	53

50 Adult Cancer Trials and 3 Pediatric Cancer Trials

Primary Reason Inadequate Accrual – Closed Trials for Adult Cancer Patients (Trials Activated 2000 to 2010)	# Trials (50)	Cancer Type	% Trials with Inadequate Accrual
Challenging Randomization: +/- Modalities			36%
Observation vs Chemotx or vs Early Intervention	3	APL, CLL, Prostate	
Surgery vs RT	1	Prostate	
Surgery with ChemoRT vs ChemoRT	1	Gyne	
+/- Transplant	1	Hodgkins Lymphoma	
+/- RT	7	Brain, Breast, H&N, Lung (2), Pancreas, Sarcoma	
+/- Chemotx or ChemoRT	4	Breast, Gyne, Lung, (Germinoma-CNS)	
+/- Hepatic Infusion Catheter	1	CRC	
+/- In-patient Tx of Pleural Effusions	1	Lung	

Primary Reason Inadequate Accrual – Closed Trials for Adult & Pediatric Cancer Patients (Trials Activated 2000 to 2010)	# Trials (53)	Cancer Type	% Trials with Inadequate Accrual
Challenging Randomization: Therapeutic Approach			15%
+/- Adj Chemotx (Neoadj, Hormonal, vs Adj and/or vs an IV placebo)	8	Bladder, Germ Cell, Gyne, Glioma, Prostate (3), Rectal, Renal	
Investigational to Commercial Agents Available - Competing Trials w/Potential Data Soon (*) or Change to Alternative Surgical/Technical Approach	9	Brain, CRC, Diffuse Large B-Cell Lymphoma (2), Myeloma (2), Rectal, Lung, Peds Retinoblastoma	17%
Site Interest in Treatment Approach Not Sufficiently High	8	Breast, CRC (3), GIST, H&N (2), Prostate	15%
Competing Studies (Group or Other)	5	Breast, Gyne (3), Peds ALL	9%
Other	4	MDS (restrictive selection tx regimen); Amyloidosis (rare cancer); Lung and Peds BMT (regulatory)	8%

(*) AGENTS: Temozolomide (Brain), Bevacizumab (CRC and Rectal); Pemetrexed (Lung) Bortezomib, Lenalidomide, Rituximab, Thalidomide (Lymphoma, Myeloma)

Assessment of CTEP Slow Accrual Guidelines for NCI Cooperative Group Phase 3 Treatment Trials (4/1/2004 to 6/30/2011)

Guidelines developed in 2005.

Applied to phase 3 trials activated after April 1, 2004.

If the accrual in Quarter 5-6 is:

$\leq 20\%$ of projected \rightarrow STOP trial

$< 50\%$ and $> 20\%$ of projected \rightarrow Study Team given 6 months to improve accrual

If the accrual in $20\% < Q5-6 < 50\%$ and the accrual in Quarter 8 is:

$< 50\%$ of projected \rightarrow Amend trial to reflect actual accrual with approval of amendment based on implications of this new rate on study relevance and feasibility

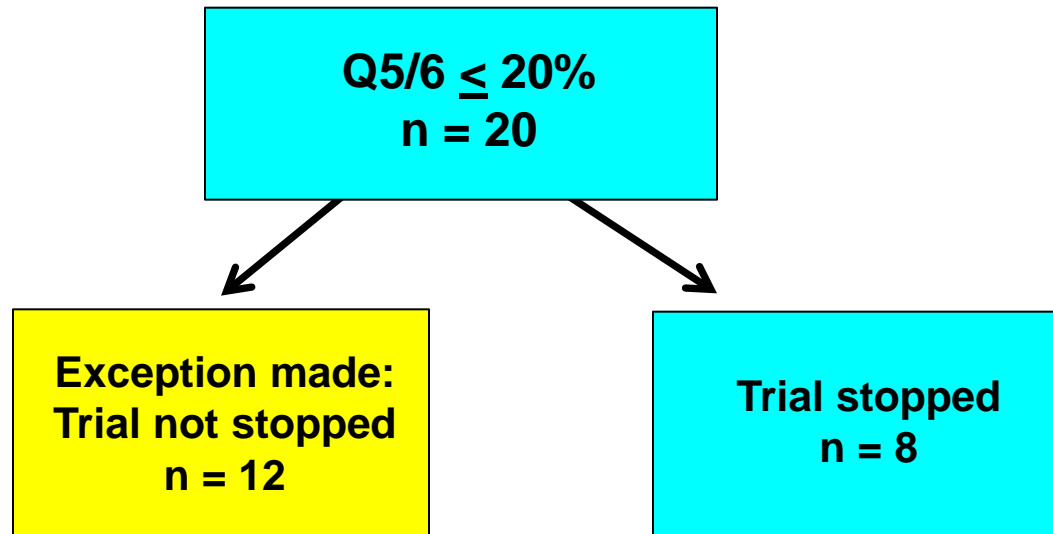
Development of Slow Accrual Guidelines

Quarter 5-6 results	Trials activated 1988-2001
≤20% of projected	15 (6%)
20-50% of projected	52 (22%)
≥50% of projected	172 (72%)
Total	239 (100%)

Assessment of Slow Accrual Guidelines (in progress)

Quarter 5-6 results	Trials activated 1988-2001	Trials activated 4/1/2004 - 6/30/2011
Stopped before the end of Q6	N. A.	<8>
≤20% of projected	15 (6%)	20 (14%)
20-50% of projected	52 (22%)	34 (23%)
≥50% of projected	172 (72%)	91 (63%)
Total	239 (100%)	145 (100%)

Disposition of 20 trials whose Quarter 5/6 accrual was $\leq 20\%$ of projected



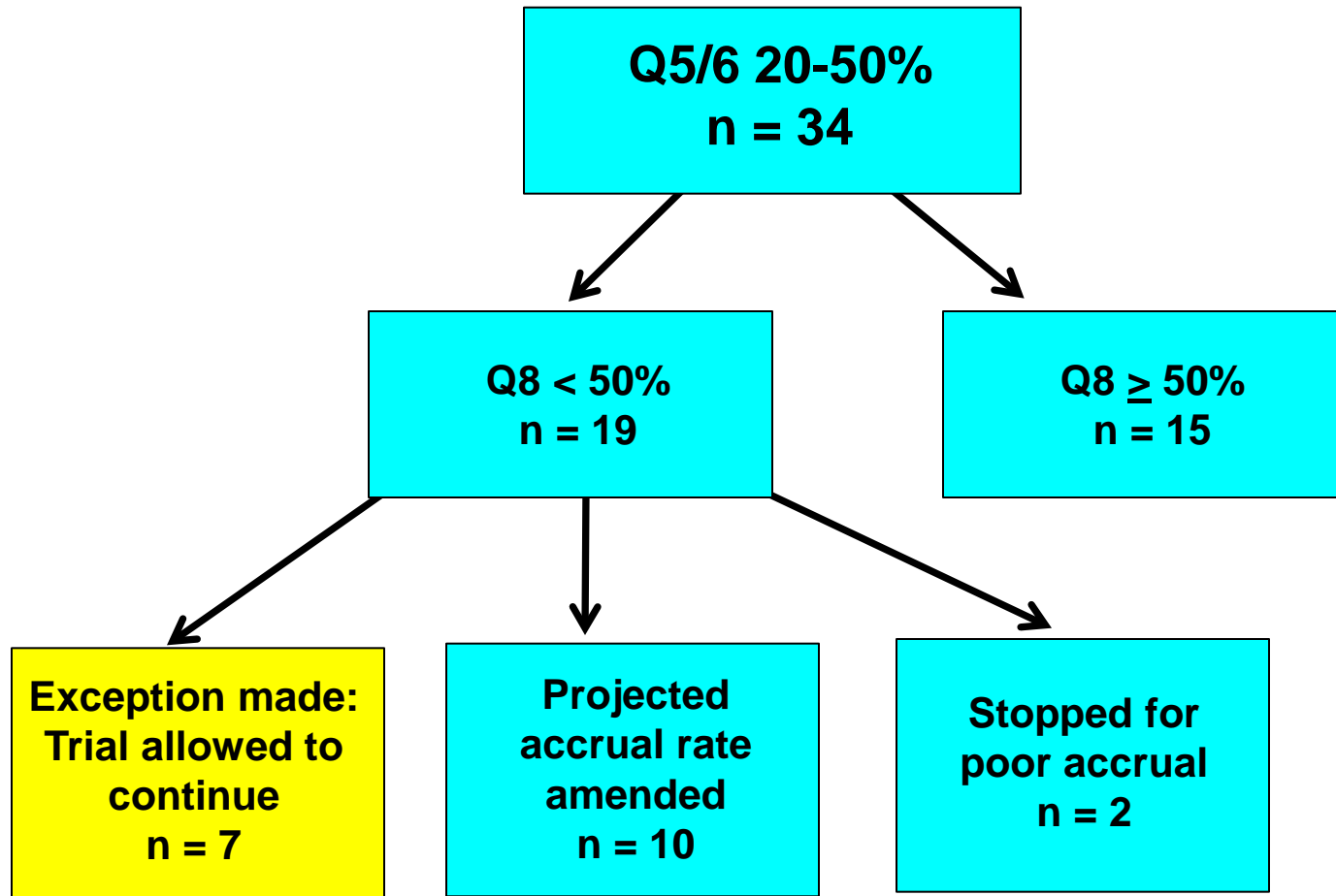
Disposition of 12 trials whose Quarter 5/6
accrual was $\leq 20\%$ of projected, and which
were given exceptions

7 failed to achieve their accrual goals

2 succeeded

3 too early to tell (still accruing)

Disposition of 34 trials whose Quarter 5/6 accrual was $> 20\%$ and $< 50\%$ of projected



Disposition of 7 trials whose Quarter 5/6
accrual was $> 20\%$ and $< 50\%$ of projected,
and which were given exceptions

- 1 closed early with drug supply issues
- 3 succeeded
- 3 too early to tell

On-Going & Future Analyses & Activities

- ❑ Analysis on-going for reasons some trials succeeded and others did not with similar attributes
- ❑ Analysis of trial attributes for those trials that accrued well and/or better than expected
- ❑ Accrual Intervention projects for trials identified as potentially challenging with respect to accrual
- ❑ Enhancement of “feasibility” assessment for trials at concept development and during concept evaluation & improved monitoring of trials in new NCTN as well as improved projections for trials

Major Questions to CTAC

- Should exceptions be given at Qtr 5/ Qtr 6 if accrual is $< 20\%$ of projected accrual?
- What is a reasonable percentage for trials that do not accrue well given that risk is inherent in launching any robust clinical trial program?
- Other Concerns / Questions from CTAC