NCI Cooperative Group Phase 3 Treatment Trials

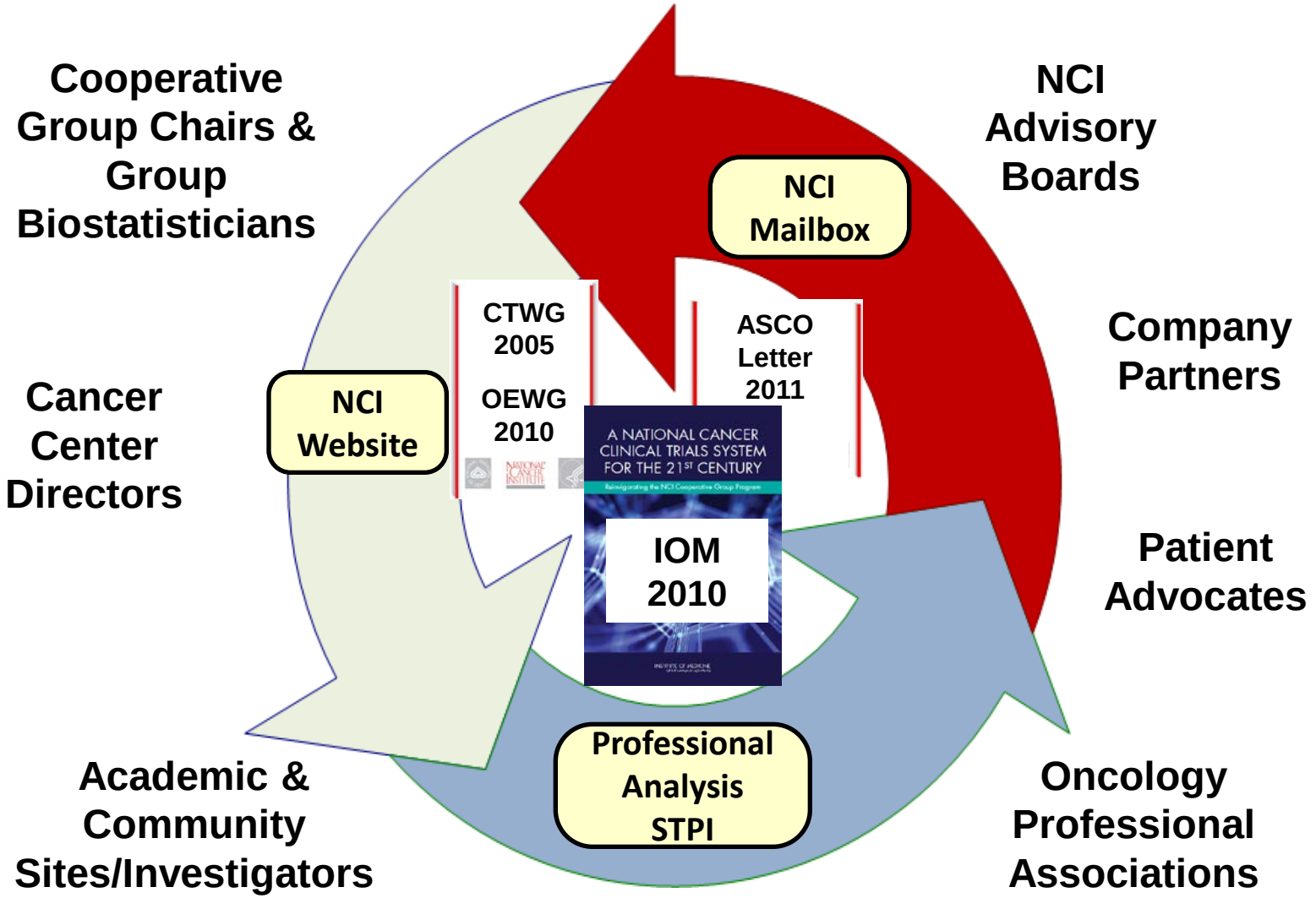
Historical Accrual Experience of Trials Activated 2000-2010

and

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

Ed Korn, PhD, DCTD Biometric Research Branch, NCI
Meg Mooney, MD, DCTD, CTEP, Clinical Investigations Branch, NCI

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
≥ 90% accrued so far	41
<90% accrued so far	10
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

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
<u>All trials</u>		
# of trials	254	191
Trials <90% accrued	21.1%	22.0%
Patients on these trials	1.6%	1.7%
<u>Non-pediatric trials</u>		
# 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 Lymhoma (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:

≤ 20% of projected → STOP trial

< 50% and > 20% of projected → 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 →Amend trial to reflect actual accrual with approval of amendment based on implications of this new rate on study relevance and feasibility

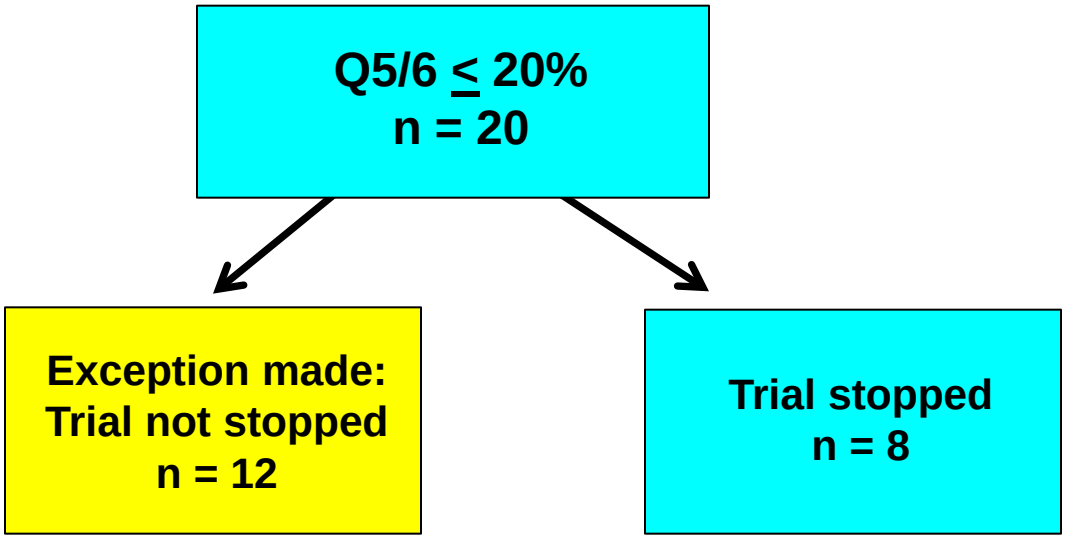
Development of Slow Accrual Guidelines

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 ≤ 20% of projected



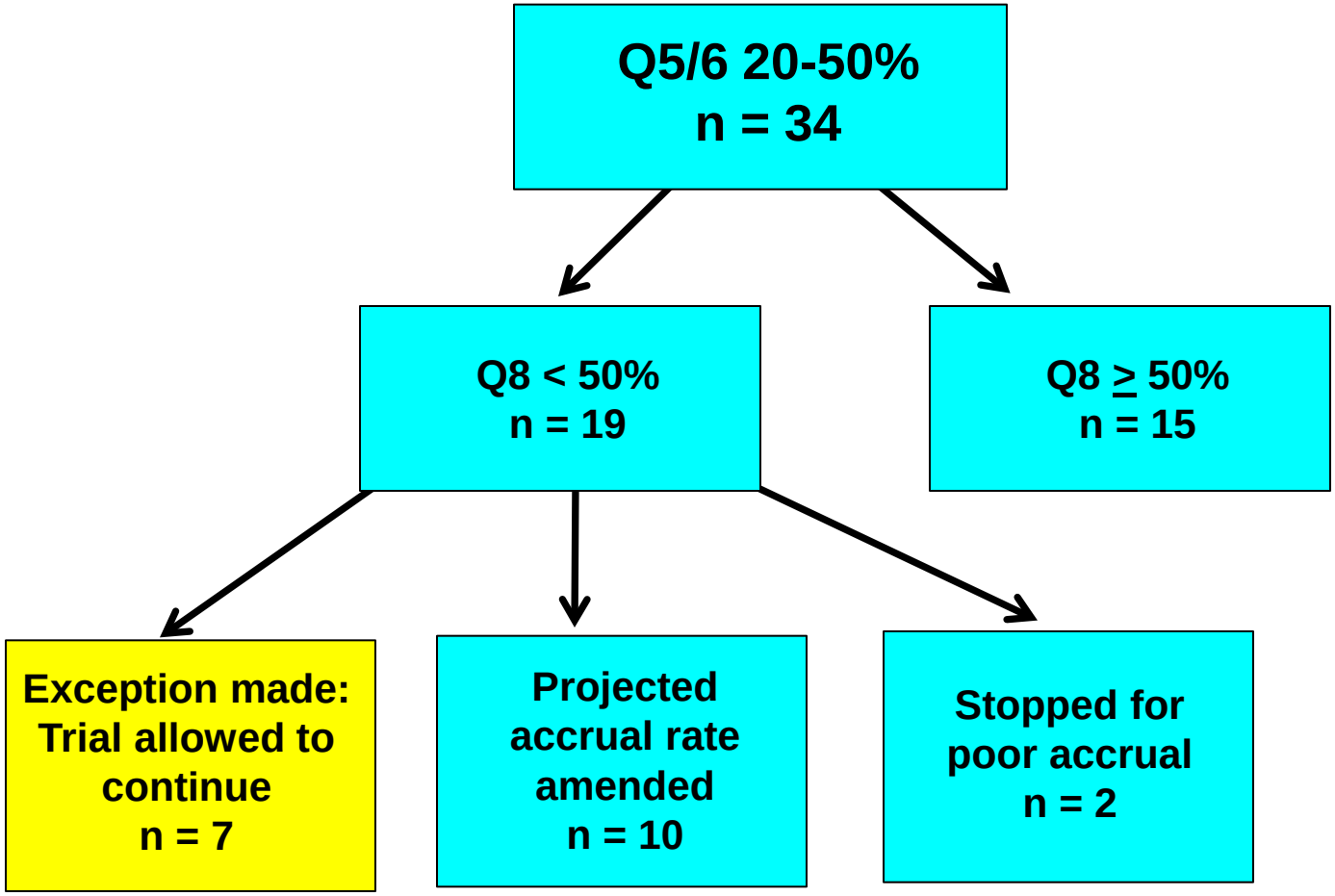
Disposition of 12 trials whose Quarter 5/6 accrual was ≤ 20% of projected, and which were given exceptions

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