Rising to the Challenge of Rapid Protocol Activation

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Stakeholders

- Cooperative group (owner of the study)
- NCI (funding agency)
- CIRB/Local IRB (human subjects protection)
- Collaborating company (ies) (NDA submission, funding)
- FDA (approval for marketing)
- Patients (participants/beneficiaries)

Issues Faced by Cooperative Groups

- All volunteer army
- Staffing
- Many cooks in the stew
- Control vs. Enable
- Tinkering
- Revolving doors
- Ownership
- Communication/Synchronization
- Who pays?
- U10 terms of award

Protocol Development

- Input from multiple investigators, statisticians
- Internal review by investigators, relevant modalities, scientists, nursing, CRA, pharmacy, repositories, regulatory
- None of the investigators employed by CALGB
- Protocol coordinators work on average of 4-6 protocols at a time, plus amendments

Statistician Workload

- Last 5 years:
  - 181 new concepts
  - 74 protocols activated
  - 126 protocols closed
  - 122 DSMB reports
  - 49 protocols in development
  - >550 abstracts/manuscripts published

NCI Funding

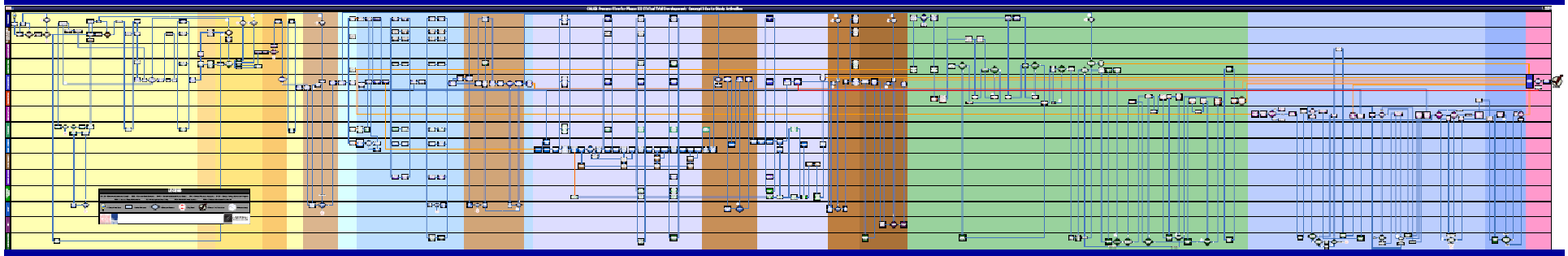
- NCI Budget: $150M/year
- CTSU phase III protocols: 70
- Annual accrual: 26,000
- NCI investment
  - $5800/patient including infrastructure
  - <$2.0M/protocol
- CALGB Funding
  - Peer review recommended: $33.8M/year
  - Awarded: $14.4M/year (43% of recommended)

CALGB and Pharma

- 32 CALGB held INDs since 2003
- 64 contracts in place to support CALGB protocols (35 since 2004)
- Companies don’t understand cooperative groups
- Company attorneys charged to protect company interests
- Company staff change frequently

Process Map at CALGB

- Steps to activate a study



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CALGB 80203

A Phase III Trial of Irinotecan /5-FU/Leucovorin or Oxaliplatin /5-FU/ Leucovorin with and without Cetuximab for Patients with Untreated Metastatic Adenocarcinoma of the Colon or Rectum

CALGB 80203

Objectives

Primary Objective:

- To determine if the addition of C225 to FOLFIRI or FOLFOX chemotherapy prolongs survival of patients with untreated, advanced or metastatic colorectal cancer.

Secondary Objective:

- To determine if the FOLFIRI and FOLFOX regimens are equivalent for survival as front-line therapy.

CALGB 80203

Secondary Objectives

- To assess whether tumor expression of EGFR is an independent predictor of treatment outcome
- To assess whether markers of EGFR pathway activity are independent predictors of treatment outcome
- To determine whether serum levels of IGF-1, C-peptide, and IGFBP-3 are independent predictors of treatment outcome
- To assess whether specific germline polymorphisms related to chemotherapy metabolism and resistance correlate with treatment-related toxicity and treatment outcome
- To assess the influence of diet, obesity, physical activity, and other lifestyle habits on treatment-related toxicity, progression-free survival and overall survival.

CALGB 80203

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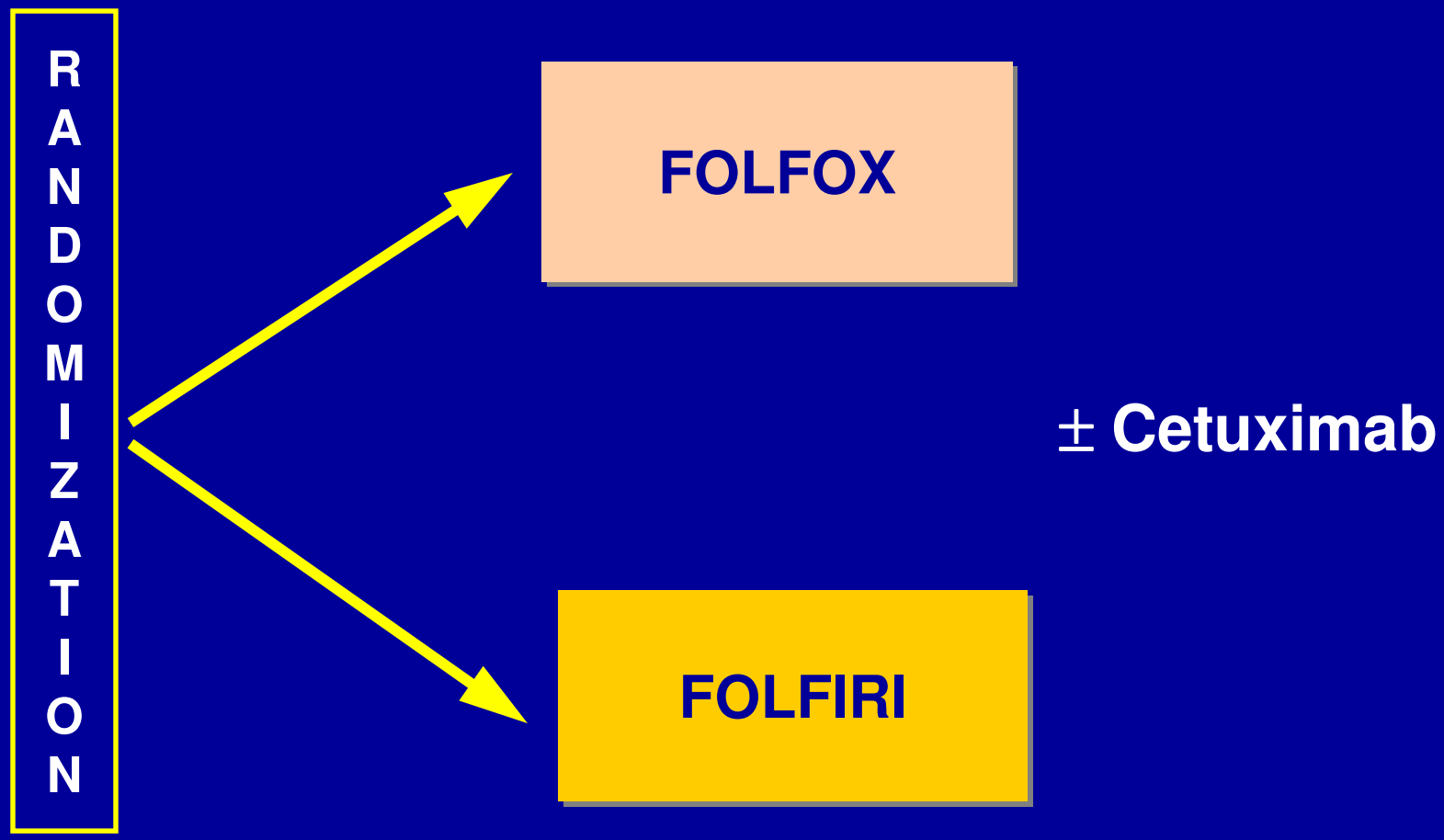


CALGB 80203

Embedded companions

GI Committee
-Dietary and Lifestyle Questionnaire

GI Solid Tumor Correlative Sciences Working Group
-EGFR pathway studies
-IGF serum studies
-Prognostic marker studies

80203

Cancer Control and Health Outcomes Committee
-Clinical Economics study
-Quality of Life study

Phamacology and Experimental Therapeutics Committee
-Study of pharmacogenomic predictors of toxicity and outcome

Specimens required: Tumor block, serum, blood for DNA

CALGB 80203

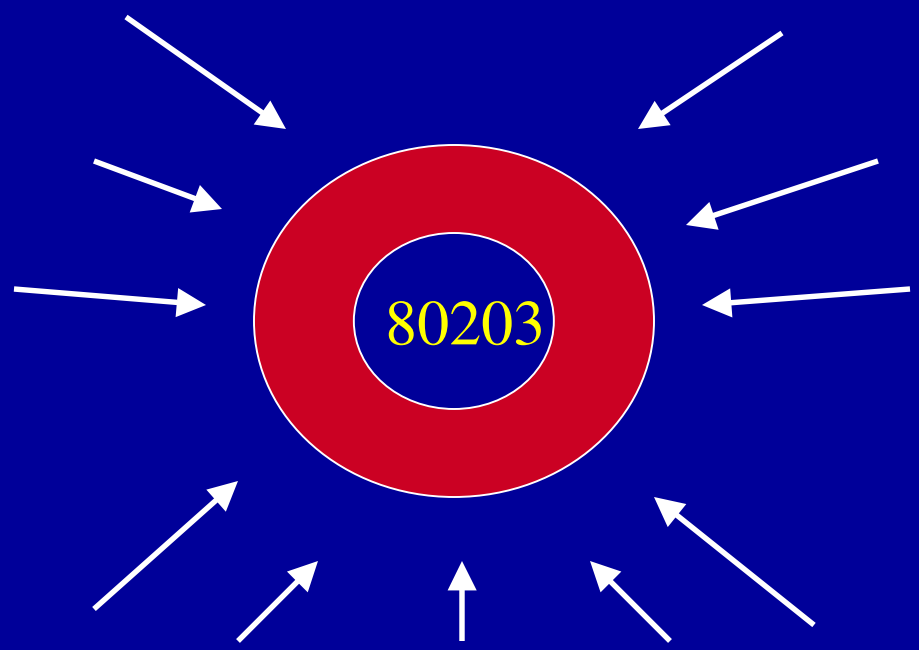
Partners

<u>Pharmaceutical</u>

- BMS
- Imclone
- Sanofi

<u>Regulatory</u>

- NCI/CTEP
- CIRB
- FDA



CALGB Disease and Modality Committees

PET ** GI ** Clinical Economics**QOL **STCS

CALGB 80203

Timeline of Development

7/30/03Approval "on hold" Pending CIRB review sent by CTEP

9/10/02Approval "on-hold" by CTEP

8/26/03 CIRB Response sent

4/8/03 CTEP sends Consensus Review (CR)

10/7/03 CIRB approval sent

10/14/03 FDA approval sent

Sanofi Review

1/8/03 CTEP Approves concept

7/29/02 Protocol Approved by Executive Committee

8/7/02 Concept submitted to CTEP

2/27/03 Protocol submitted to CTEP

Imclone/BMS CALGB call to discuss CR

BMS Review

6/24/03 Response to consensus Review submitted

9/18/03 Response to CIRB review submitted

8/1/03 FDA Submission

= Actions by CTEP

= Actions by CIRB

= Industry

CALGB 80203/80405

Timeline of Development

12/15/03
80203
Activated

238 of 2200
patients accrued

9/20/04 Concept with
redesign of 80203
submitted to CTEP

10/04/04 Concept
resubmitted as
CALGB 80405

9/22/04 initial
CTEP concept
review

11/3/04 CTEP
consensus
review of
concept

12/15/04
80203 Accrual
Suspended

12/18/04 Conference call
with study team, CTEP
and GI Intergroup

1/15/05
80203
Closed

1/3/05
CTEP
Concept
approval sent

3/1/05 CALGB
80405 protocol
submitted

3/23/05 CTEP
Consensus
Review sent

5/13/05 CALGB
80405 revised
protocol
submitted

= Actions by CTEP

= Actions by CIRB

= Industry

CALGB/SWOG C80405

Timeline of Development

5/13/05 80405 revised protocol submitted

5/27/05 Third protocol submission

6/28/05 CIRB first protocol review

7/12/05 CIRB response and revised protocol submitted

9/06/05 Final CIRB approval

9/15/05 80405 Activated

1417 of 2289 accrued

6/6/08 CALGB/SWOG 80405 Suspended

5/24/05 CTEP 2nd Consensus Review sent

5/31/05 CTEP Approval on hold with recommendations

8/04/05 Final CTEP Approval on Hold

9/08/05 Final CTEP Approval

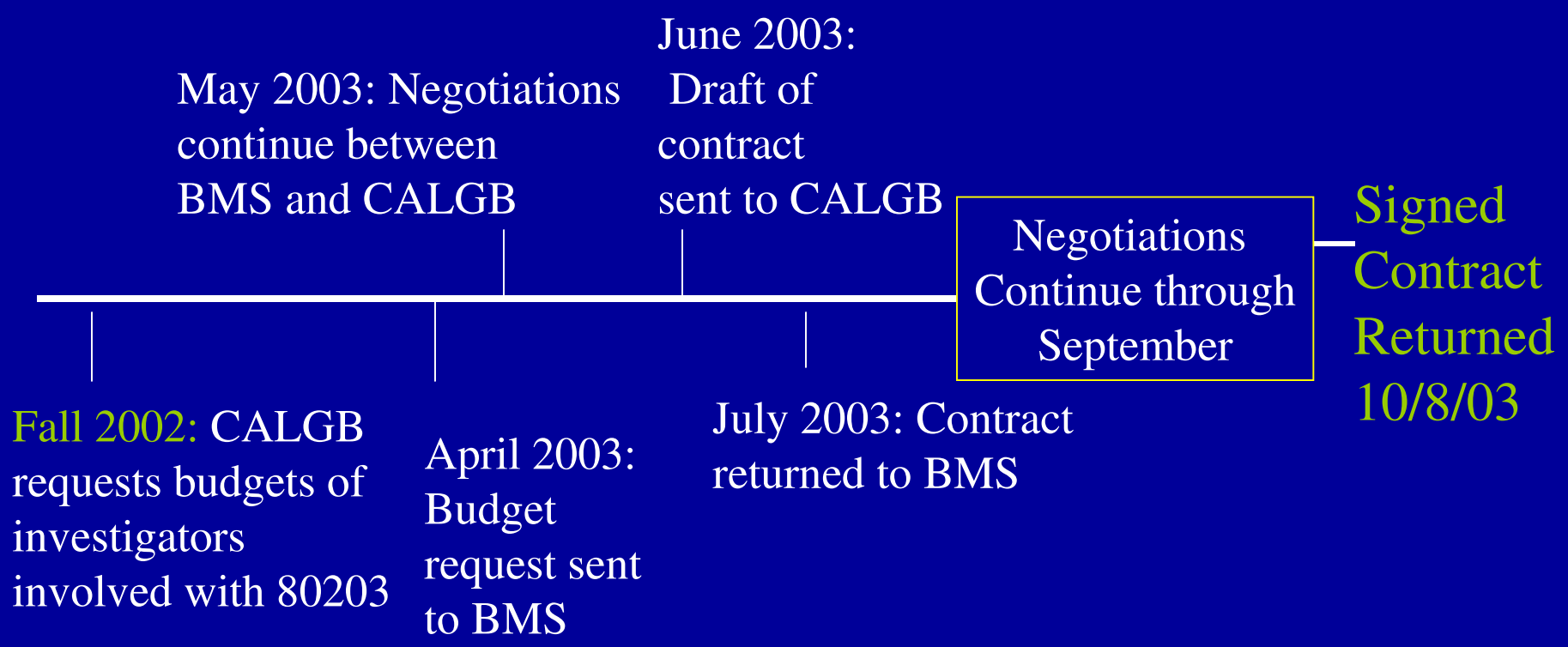
5/31/08 Release of KRAS status results at ASCO

= Actions by CTEP

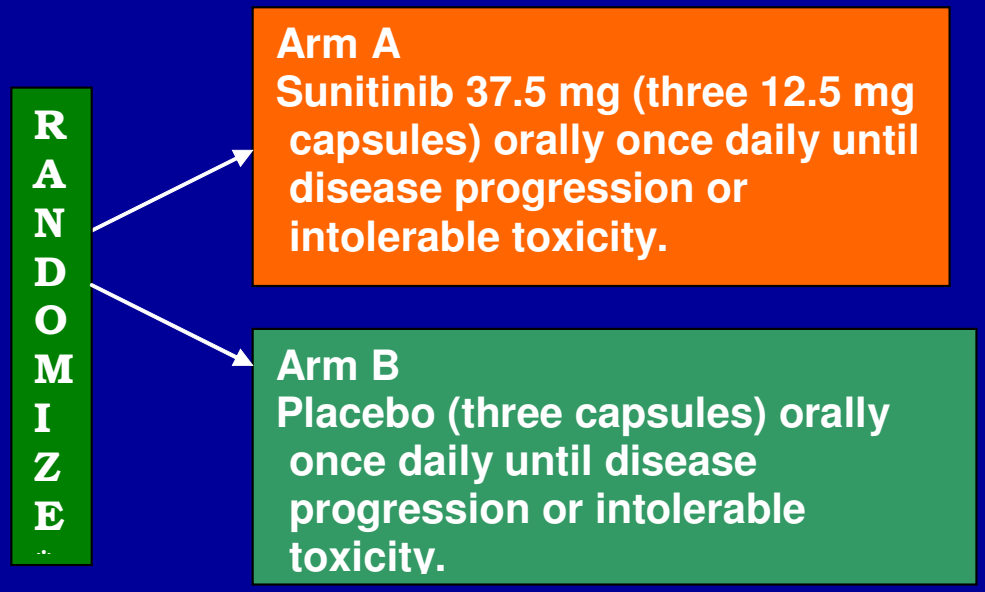
= Actions by CIRB

CALGB 80203

Timeline of Contract Negotiations with Bristol Myers Squibb (BMS) /ImClone



CALGB 30607



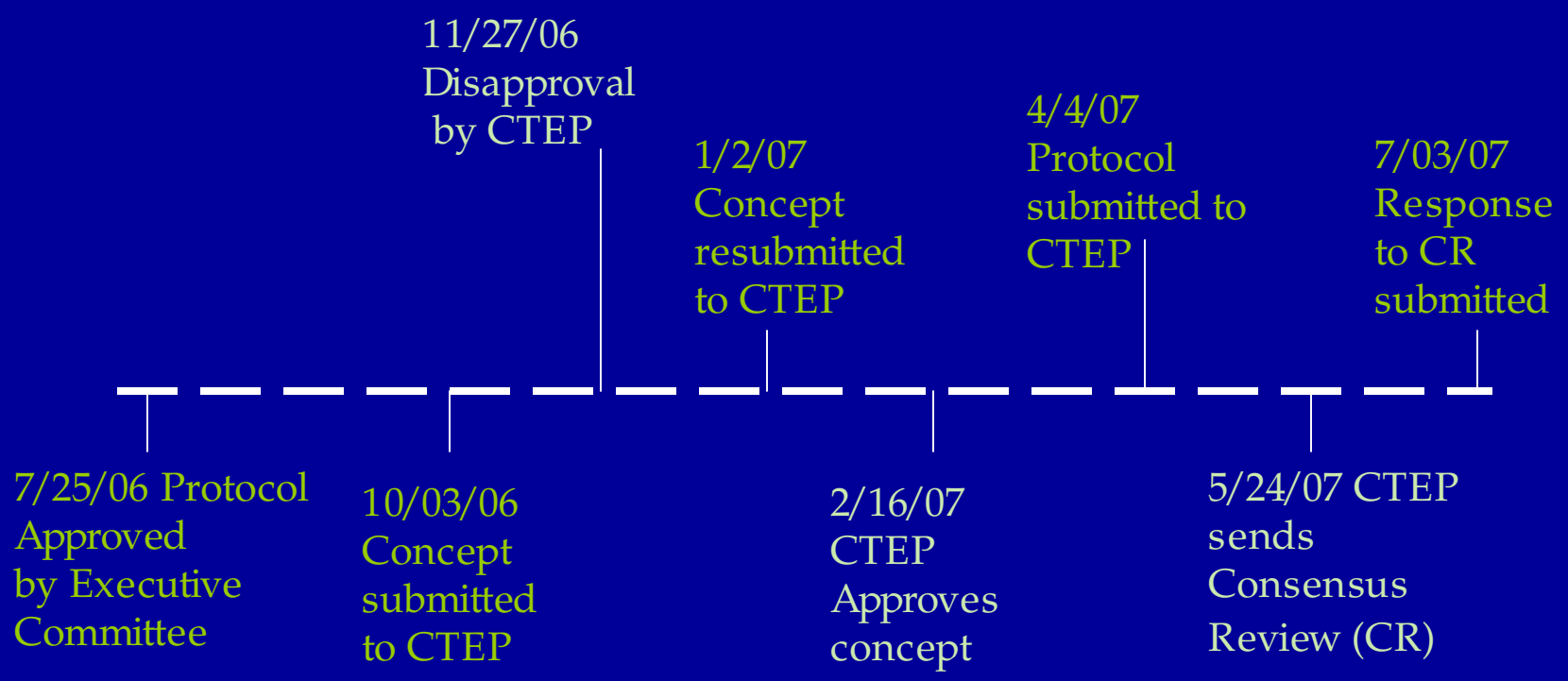
*

Patients will be randomized 3-5 weeks after the completion of the fourth cycle of first-line therapy. Only those patients with stable or responding disease will be randomized to CALGB 30607.

Stratification Factors:

- Performance Status (0 vs. 1)
- Stage (IIIB vs. IV)
- Prior use of bevacizumab (yes or no)
- Gender (male vs. female)

CALGB 30607
Development Timeline

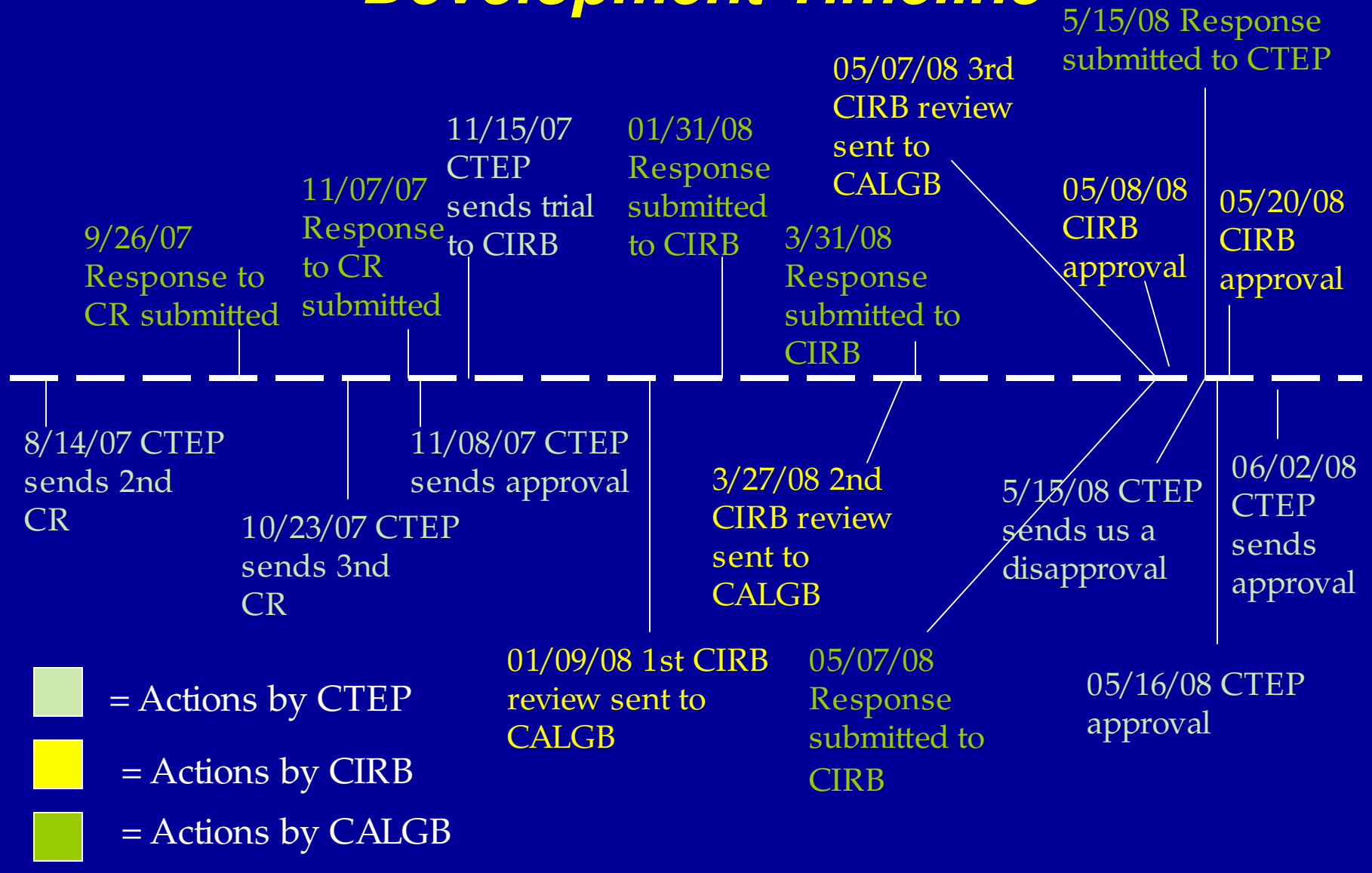


= Actions by CTEP

= Actions by CIRB

= Actions by CALGB

CALGB 30607
Development Timeline



= Actions by CTEP

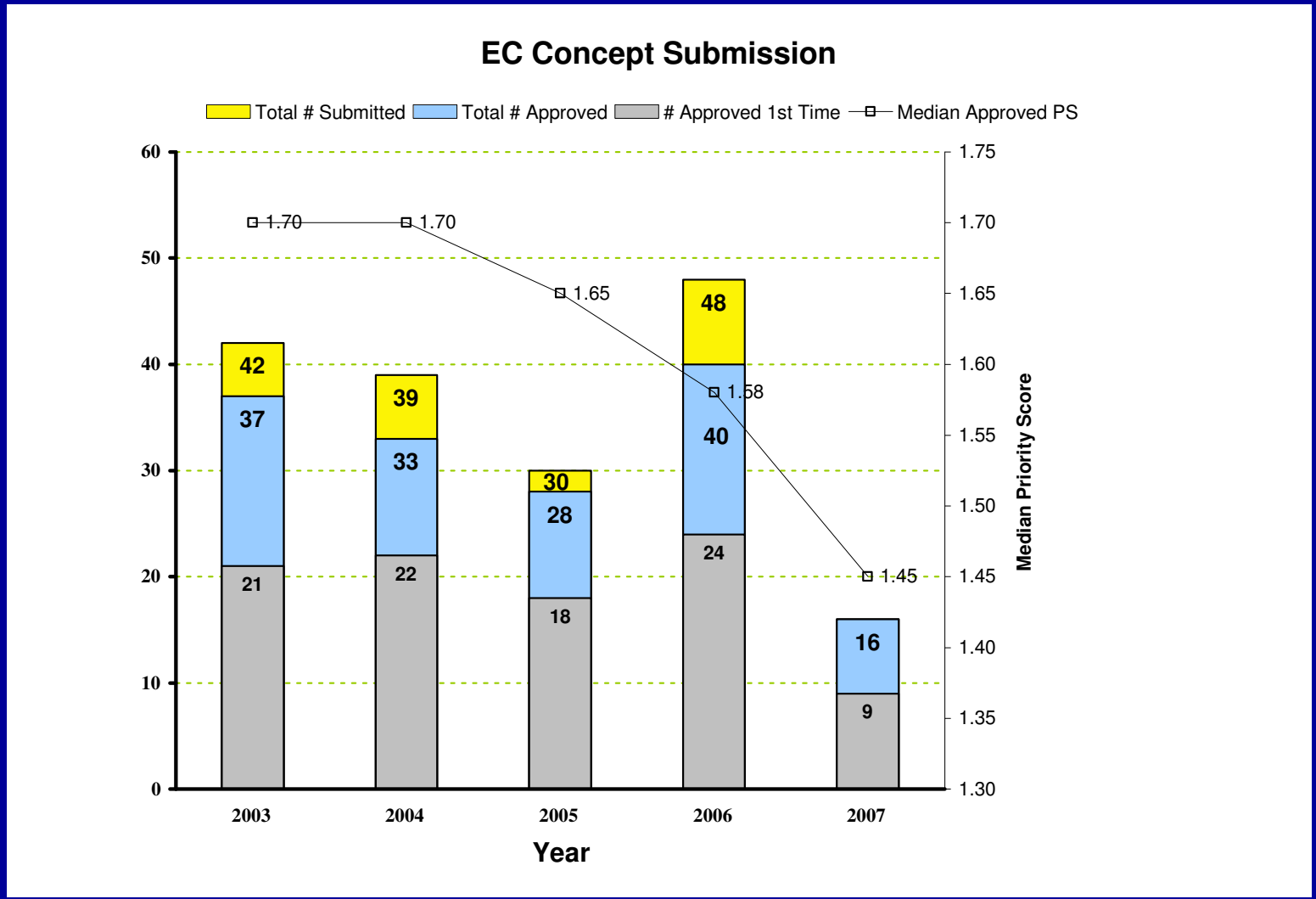
= Actions by CIRB

= Actions by CALGB

CALGB Approach

- Two strikes and you're out
- No tinkering
- Master priority list
- Protocol tracking
- Operational review

CALGB Concept Review

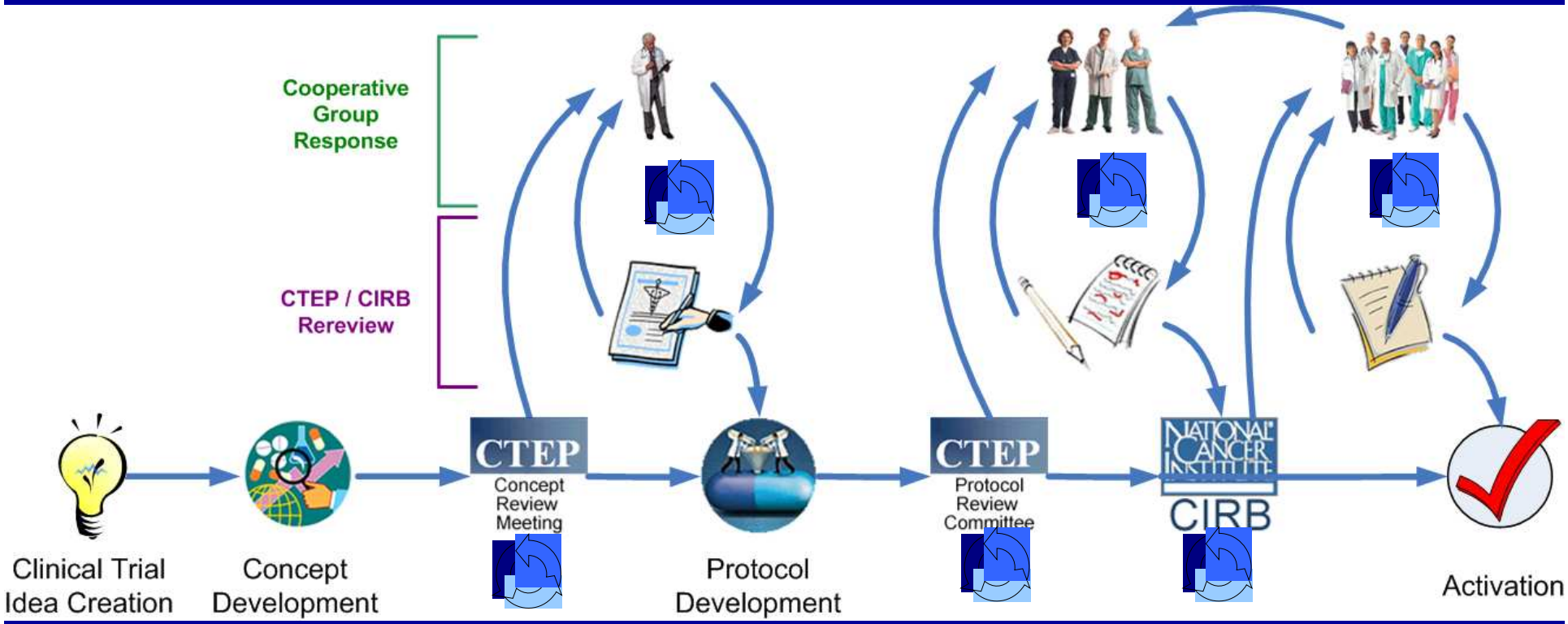


Operational Review

Scientific Merit	Operational Complexity: High	Operational Complexity: Low
High		
Low		***Fill***

Simulating the System:

High Level Process Simulation of Phase III Study Processes



Simulating Simultaneous Solutions

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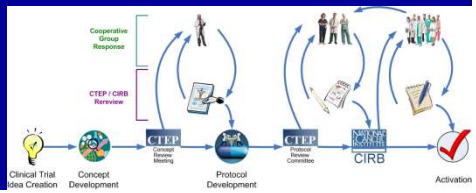
* Simulation period defined over a period of 5 years (1825 Calendar Days)
* Note: Axes on the Timing Distribution Graphs are different



All Hands On Deck!

- For NCI IND studies, combined NCI and FDA review within 30 days
- For Group IND studies, FDA review only
- For non IND studies, Group review only
- Modify terms of U10 to provide more flexibility (why does NCI provide 50% of the funding but retain 100% of the control?)
- FDA to specify a “minimum data set” necessary for NDA submission
- FDA to assess value-added of SPA
- Re-consider value of CIRB
- CMS to cover all clinical care costs for patients on trials and modify MD billing codes

Should We Downsize?

- By industry standards, NCI budget sufficient for a handful of phase III trials.
- Yet, 70 phase III trials on the CTSU menu, others not on the menu and hundreds of phase I-II studies ongoing.
- This is not sustainable.
- If no increase in funding, should we downsize?
- Does anyone win if we do?