

Rising to the Challenge of Rapid Protocol Activation

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Chairman, Cancer and Leukemia Group B

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)

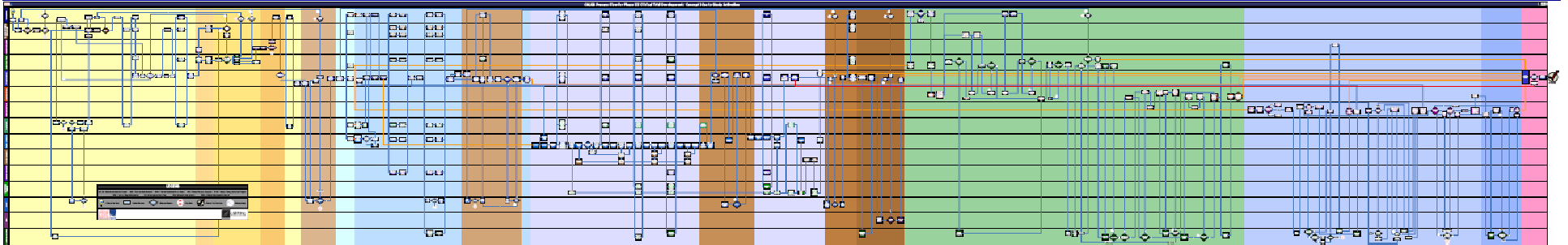
CALGB and Pharma

- 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



30ft



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.

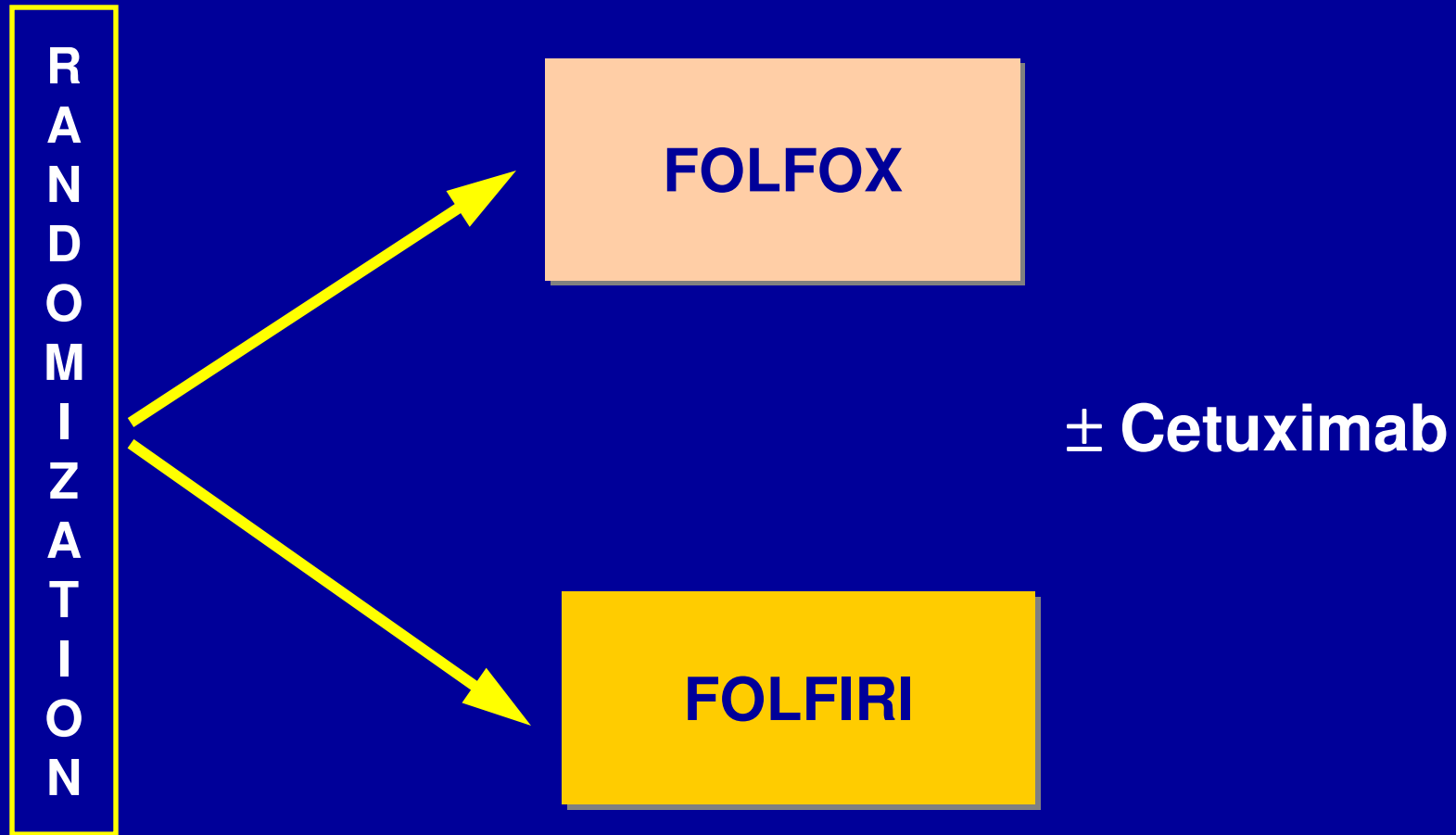
CALGB 80203

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.

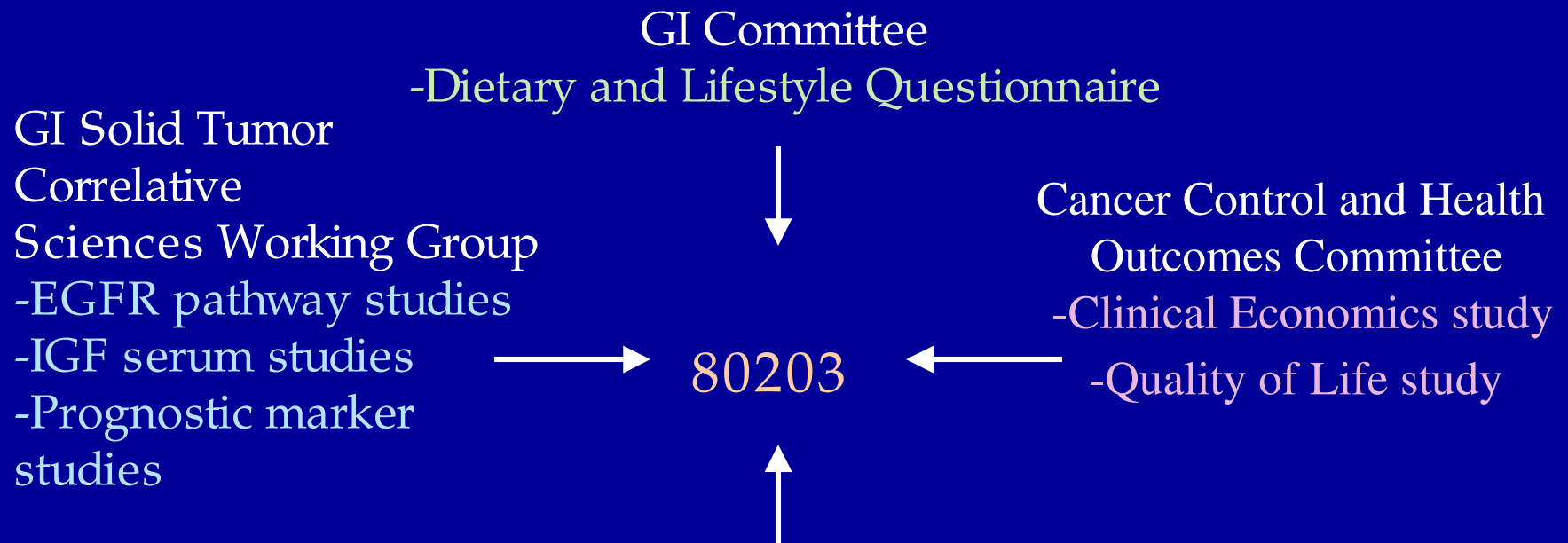
CALGB 80203

n=2200



CALGB 80203

Embedded companions



Specimens required: Tumor block, serum, blood for DNA

CALGB 80203

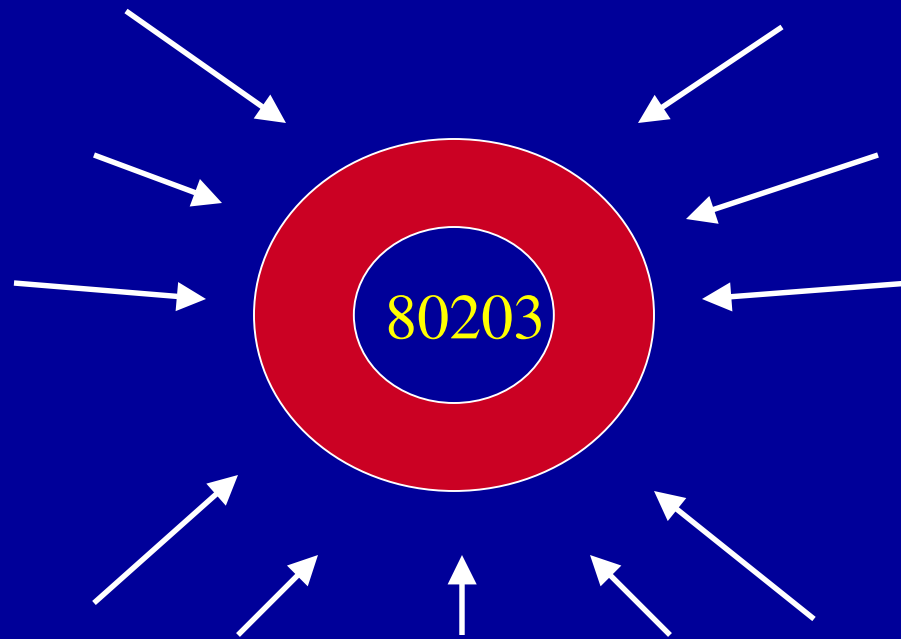
Partners

Pharmaceutical

- BMS
- Imclone
- Sanofi

Regulatory

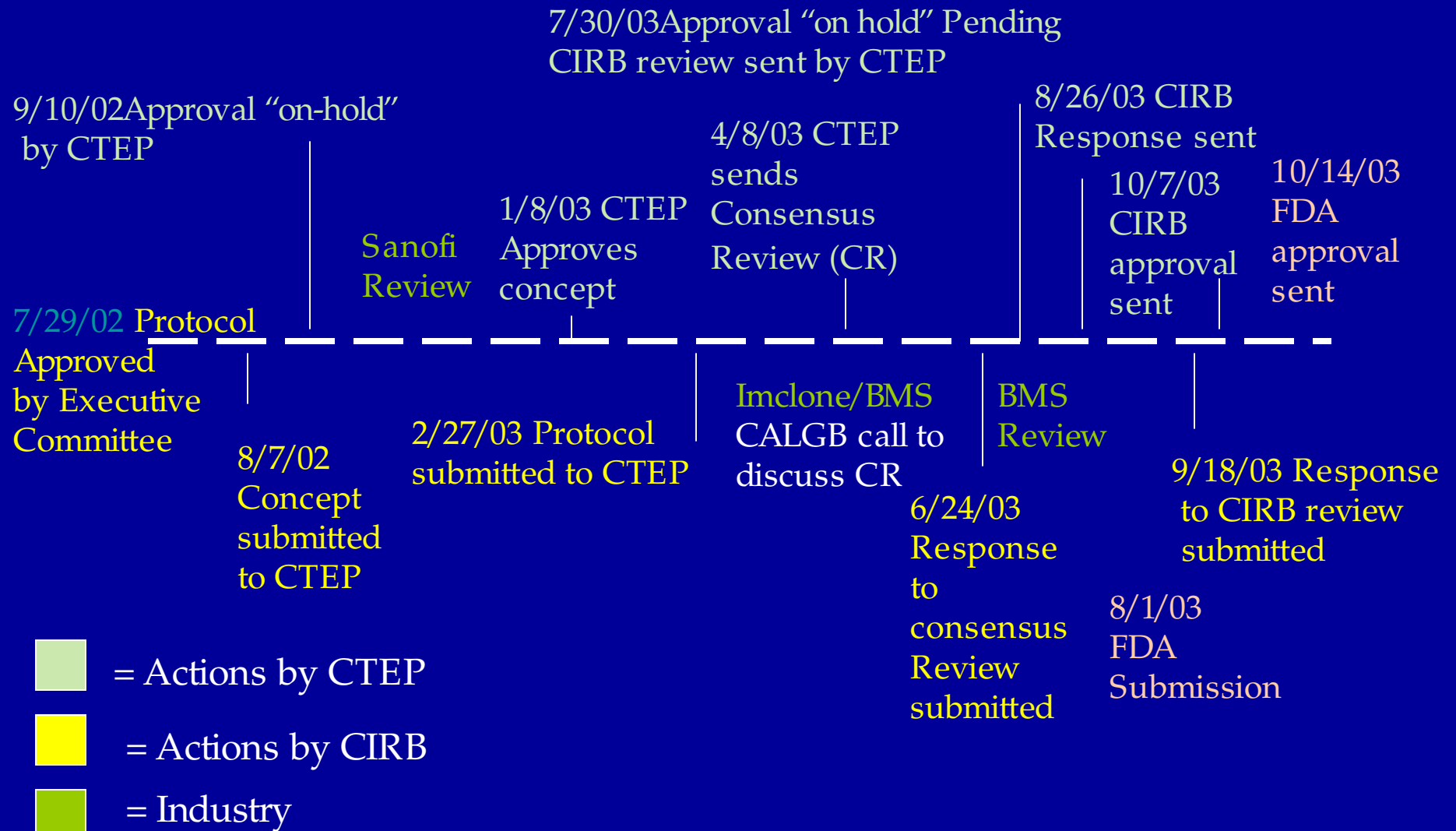
- NCI/CTEP
- CIRB
- FDA



CALGB Disease and Modality Committees
PET ** GI ** Clinical Economics**QOL **STCS

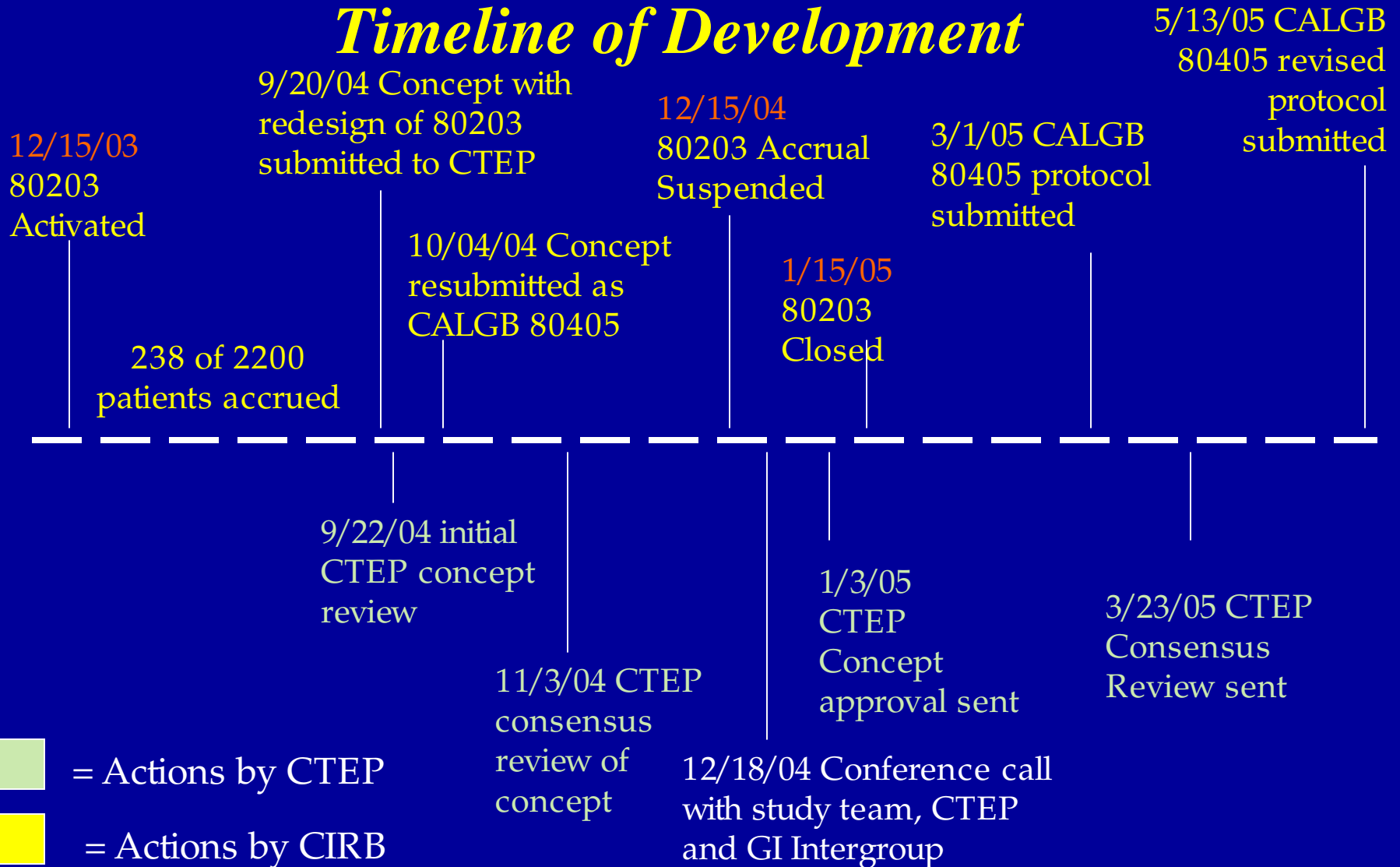
CALGB 80203




Timeline of Development



CALGB 80203/80405

Timeline of Development



-  = Actions by CTEP
-  = Actions by CIRB
-  = Industry

CALGB/SWOG C80405

Timeline of Development

5/13/05 80405
revised protocol
submitted

6/28/05 CIRB
first protocol
review

9/06/05 Final
CIRB approval

5/27/05
Third
protocol
submission

7/12/05 CIRB
response and
revised protocol
submitted

9/15/05 80405
Activated

6/6/08
CALGB/SWOG
80405
Suspended

1417 of 2289 accrued

5/31/05 CTEP Approval on
hold with recommendations

9/08/05 Final CTEP
Approval

5/24/05 CTEP
2nd Consensus
Review sent

8/04/05 Final CTEP
Approval on Hold

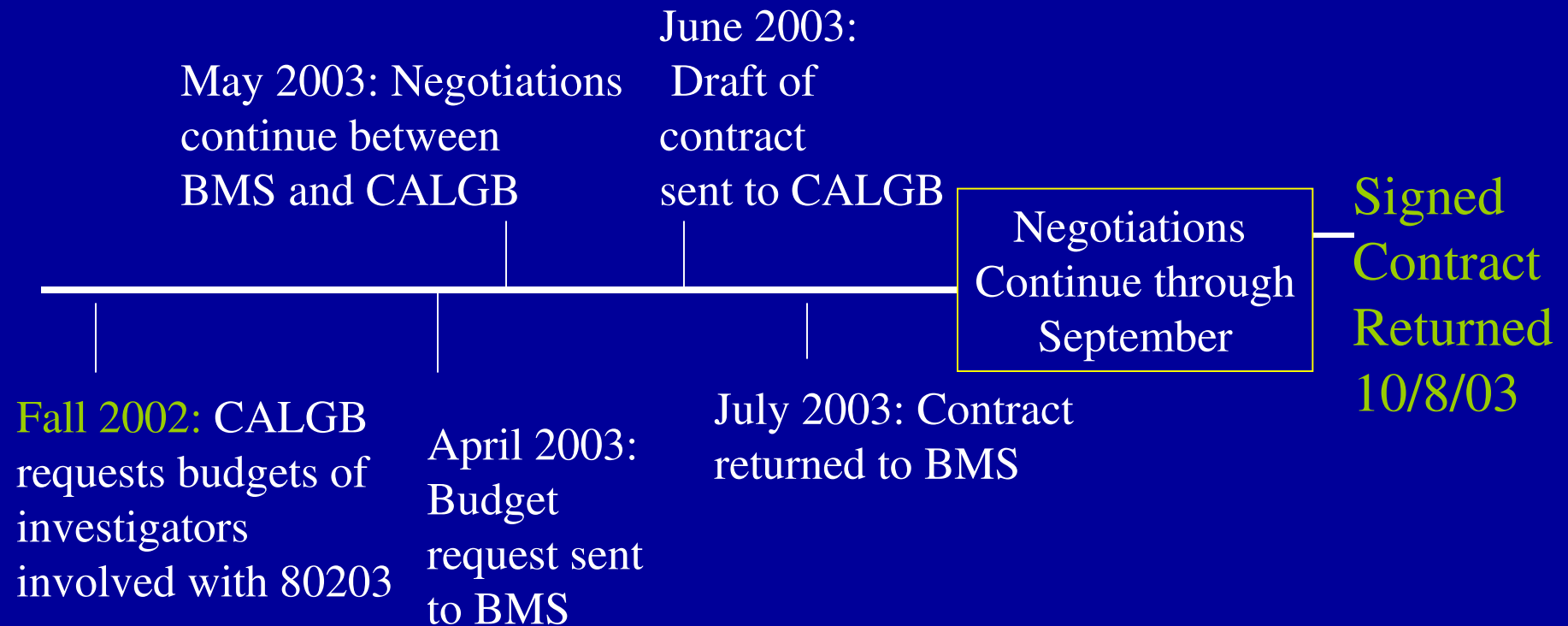
5/31/08 Release of
KRAS status results
at ASCO

 = Actions by CTEP

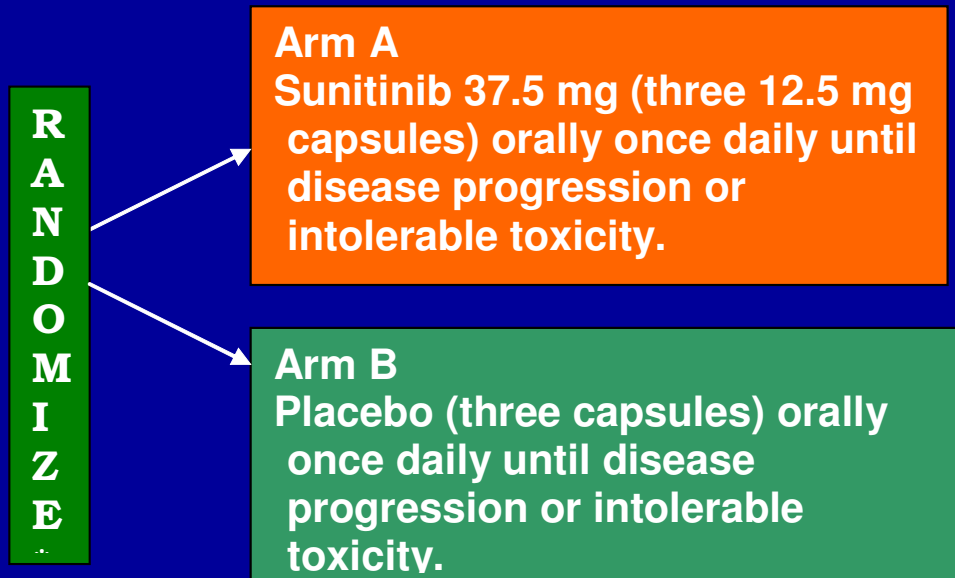
 = Actions by CIRB

CALGB 80203

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



CALGB 30607



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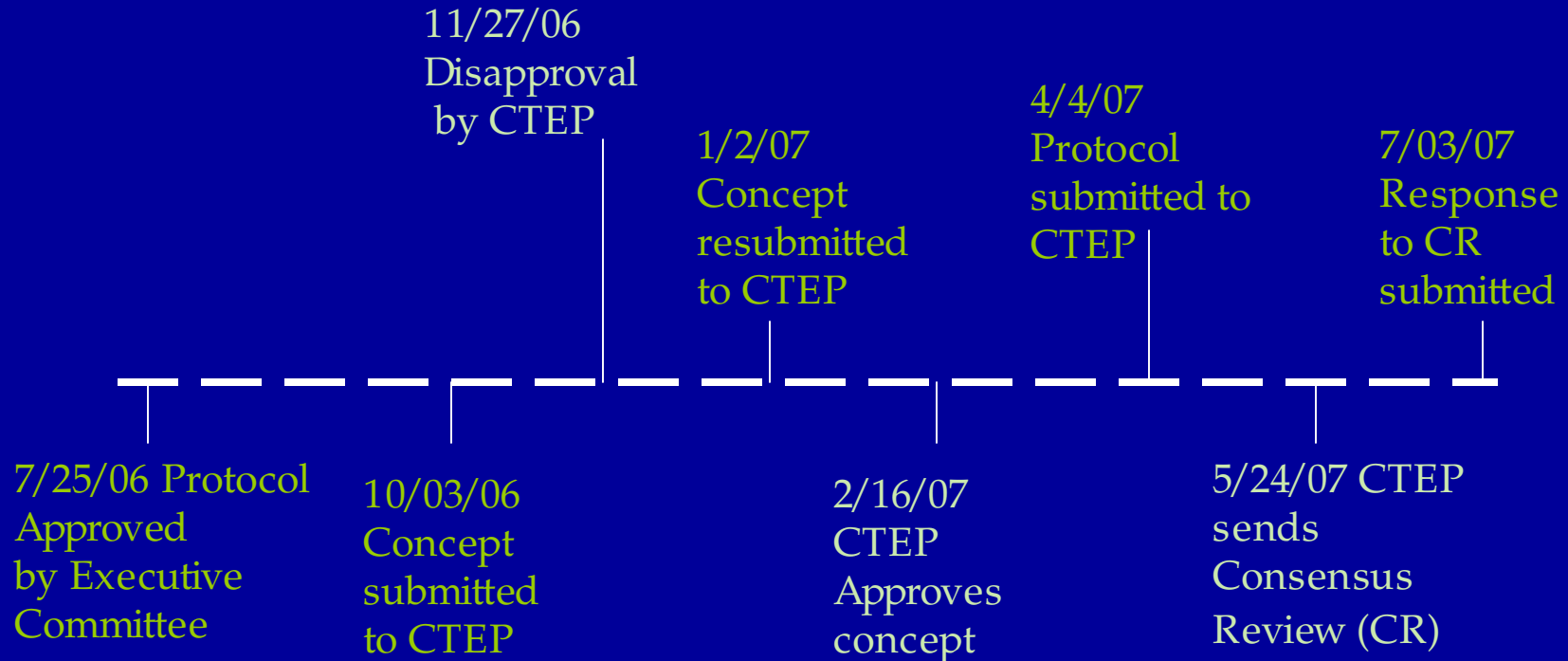
Patients will be randomized 3-5 weeks after the completion of the fourth cycle of first-line therapy. Only those patients with stable or responding disease will be randomized to CALGB 30607.




Stratification Factors:

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

CALGB 30607

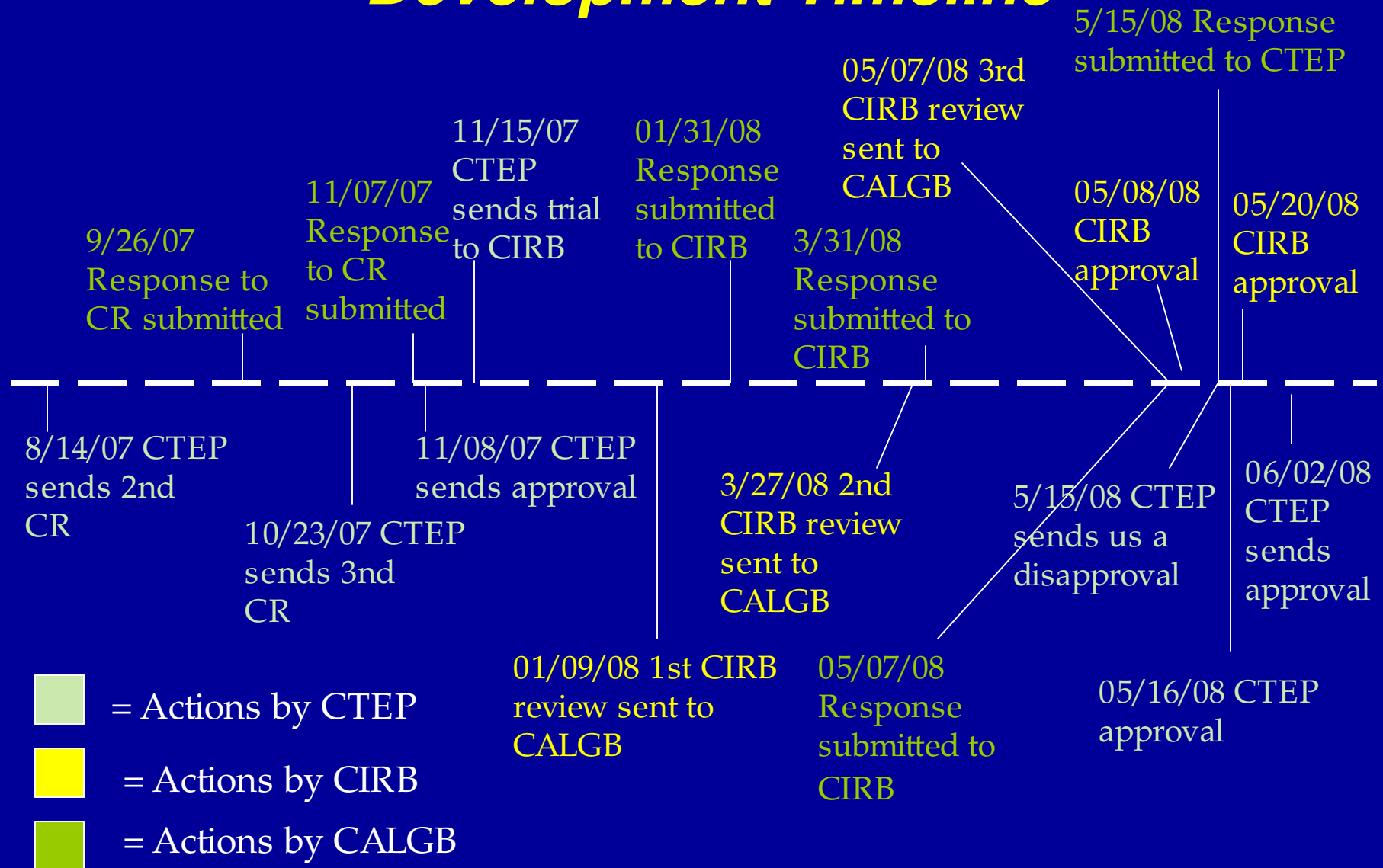
Development Timeline



-  = Actions by CTEP
-  = Actions by CIRB
-  = Actions by CALGB

CALGB 30607

Development Timeline



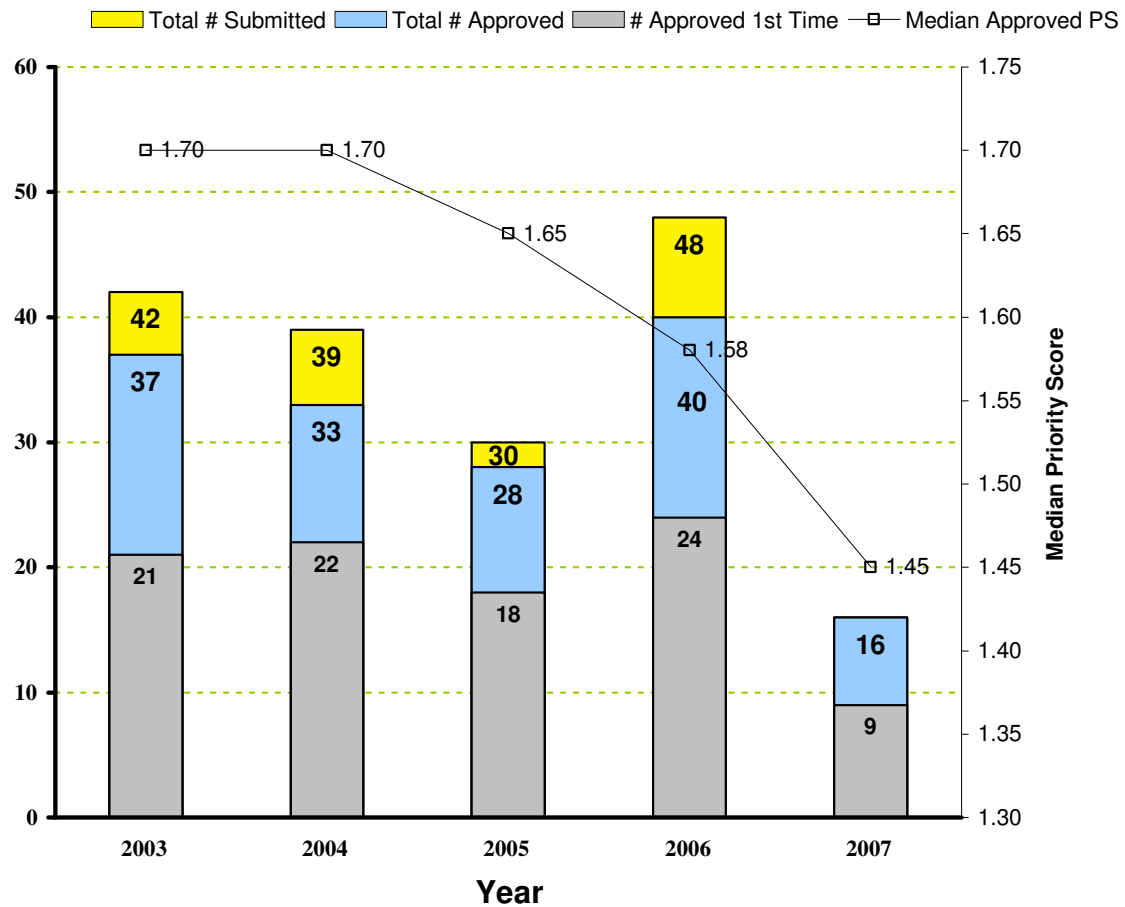
- = Actions by CTEP
- = Actions by CIRB
- = Actions by CALGB

CALGB Approach

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

CALGB Concept Review

EC Concept Submission



Operational Review

Operational
Complexity

Scientific
Merit

High



Low



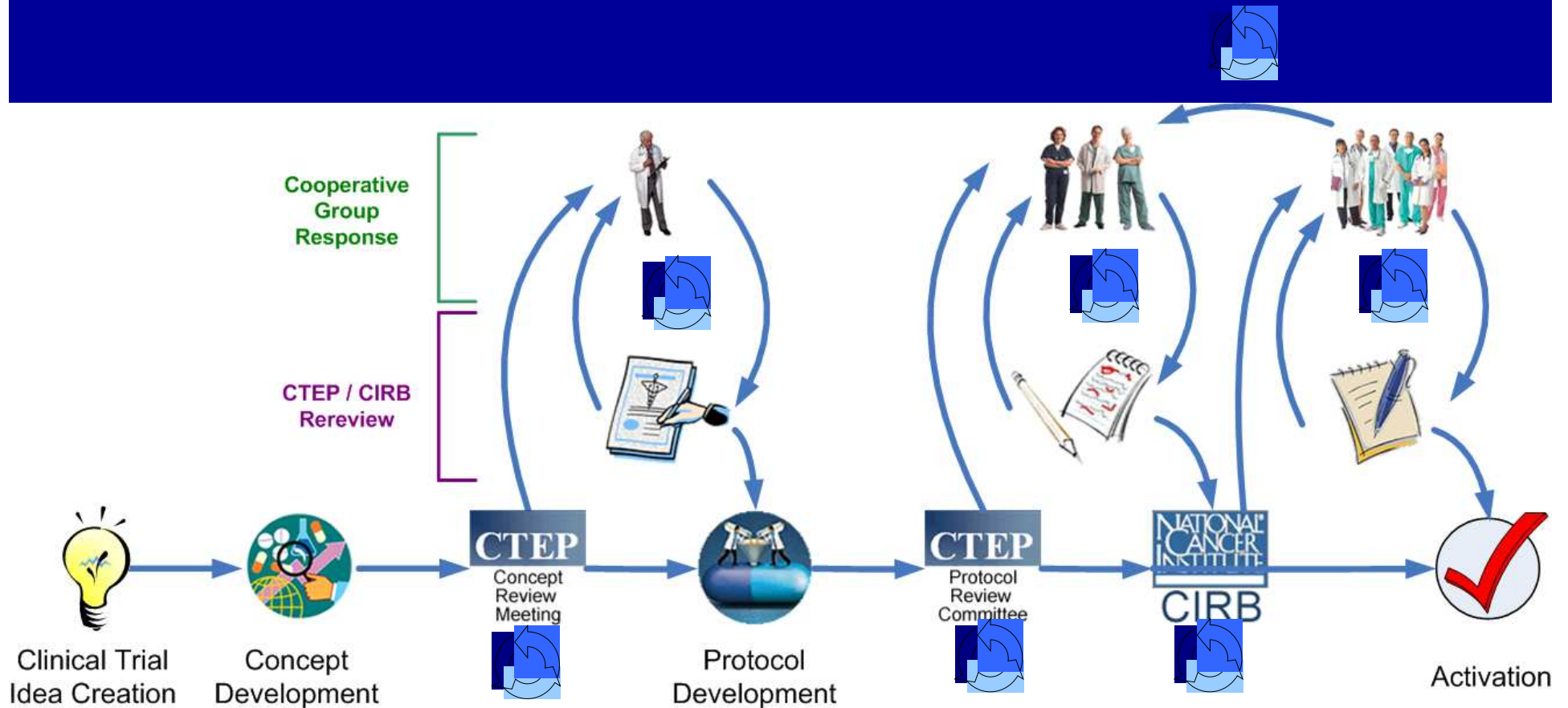
Fill

High

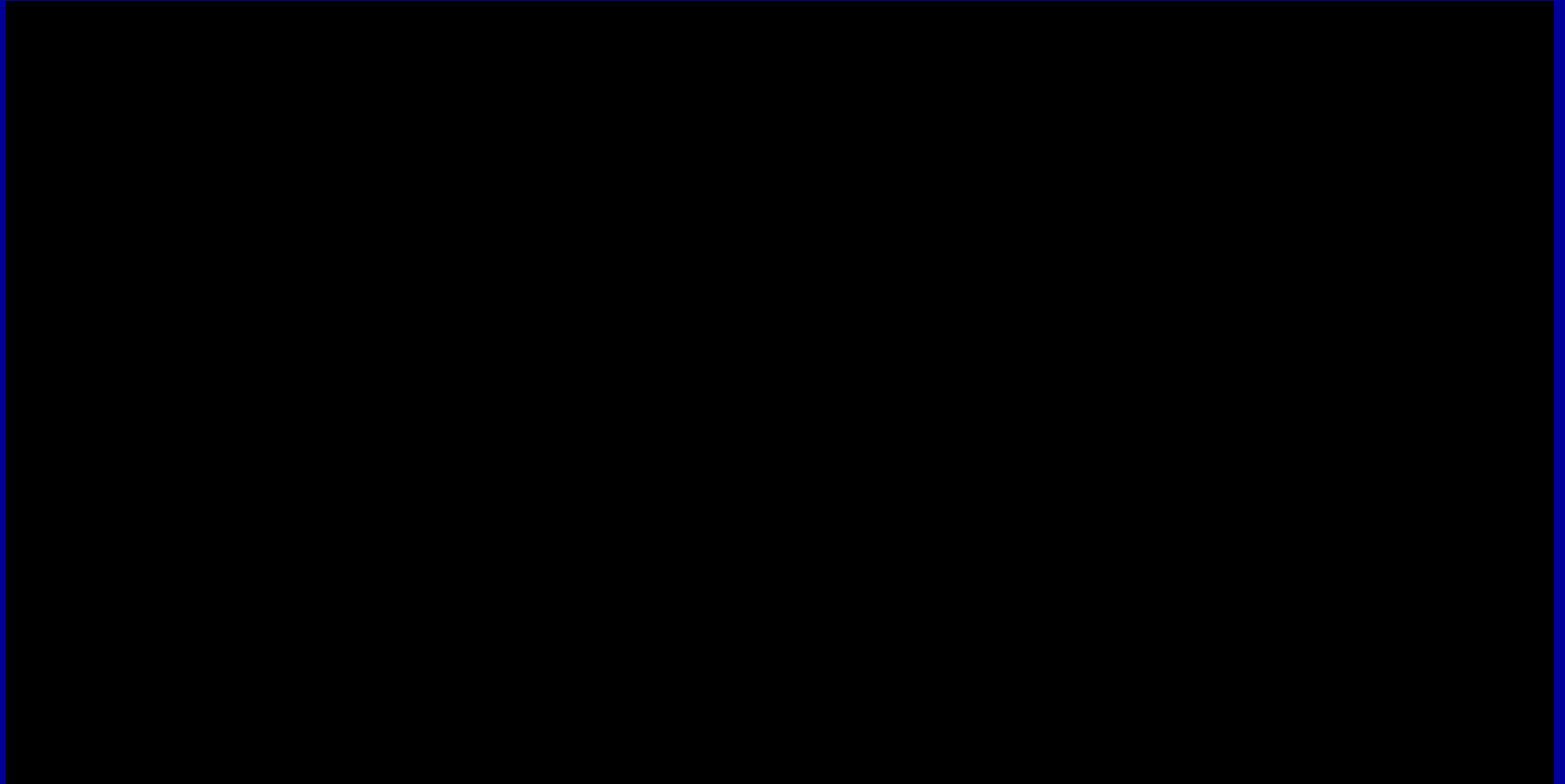
Low

Simulating the System:

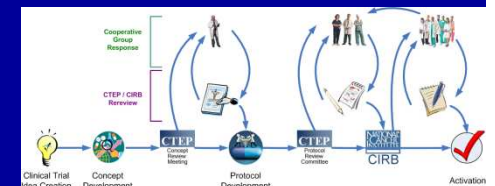
High Level Process Simulation of Phase III Study Processes



Simulating Simultaneous Solutions



- * 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?