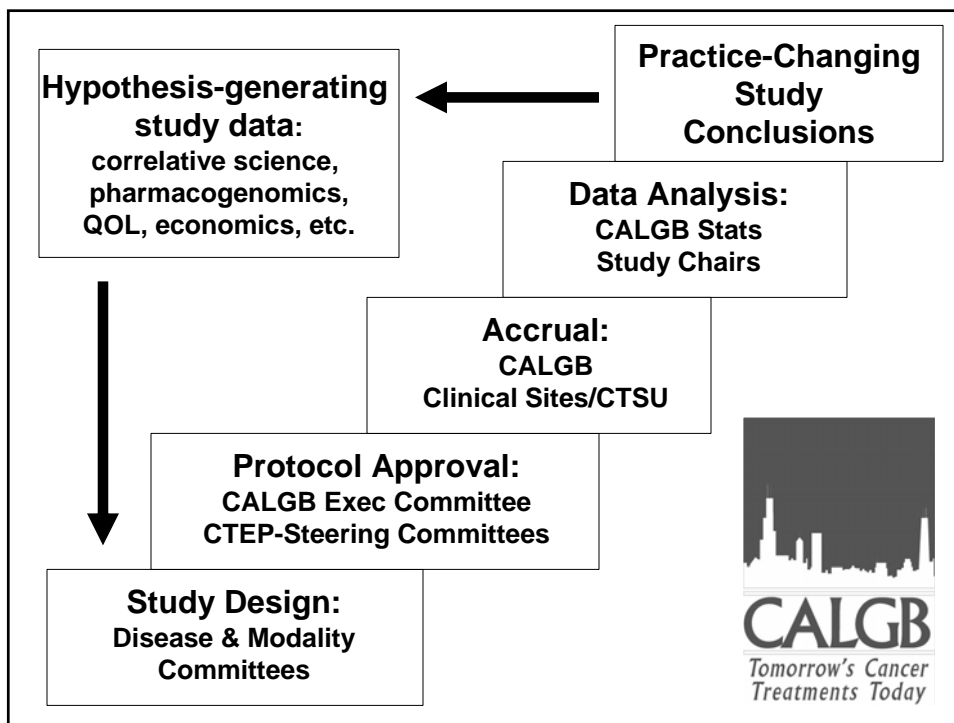


Protocols From Concept to Publication (12 easy steps)

Gini Fleming, M.D.
University of Chicago



STEP 1: Generate Hypothesis



- New drug available (paclitaxel)
- New technology (recurrence score)
- New trial results available

The Path



The Path



Process Map at CALGB



- Steps to activate a study

A screenshot of a complex process map or flowchart. It consists of numerous rectangular boxes connected by arrows, representing a multi-step process. The text within the boxes is small and difficult to read, but the overall structure is a dense network of steps.

30ft



STEP 2: Convince someone else that you have a Great Idea

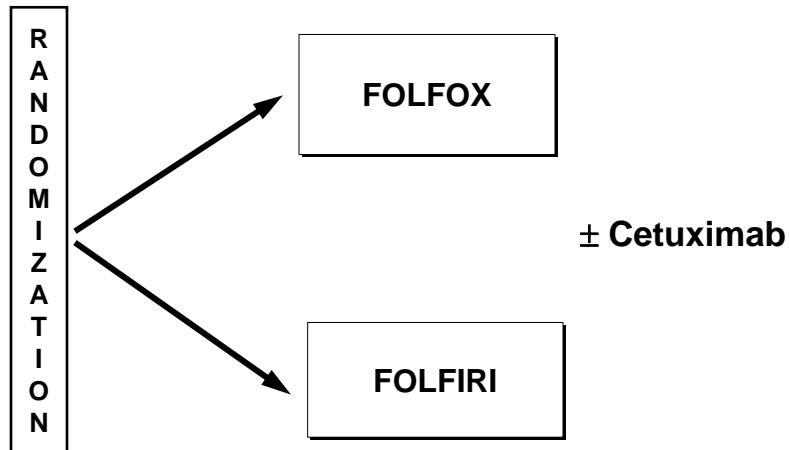
- Get committee chair to allow presentation to committee
- ↓ ↑
- Get suggestions, represent to committee

STEP 3: Convince even more people your Idea is Great *and* feasible

- Statistician
- Other committees
 - CCHO for QOL/Economic Components
 - PET for PK/Pharmacogenomics
 - Advocates
- Industry
- Other Funding Sources

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n=2200



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.

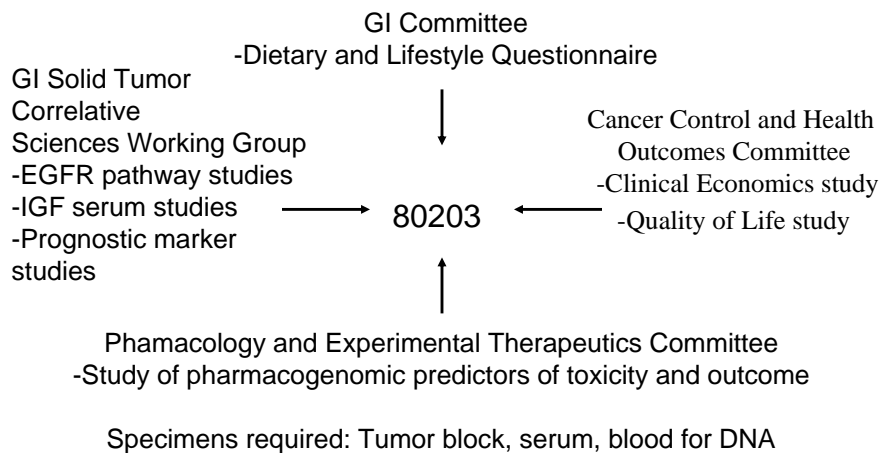
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Secondary Objectives

- 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.

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Embedded companions



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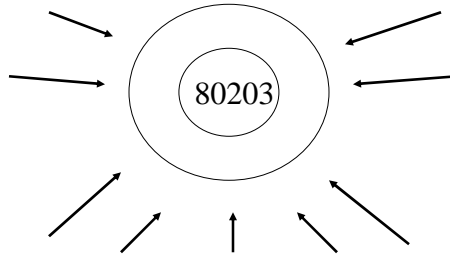
Partners

Pharmaceutical

- BMS
- Imclone
- Sanofi

Regulatory

- NCI/CTEP
- CIRB
- FDA



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

Where Do Protocol Drugs Come From?

- Commercially purchased
- NCI supplied (and distributed)
- Industry supplied (and distributed)
- Home grown

Some drugs are commercially available yet supplied by study. Investigational drug supply must be used where appropriate!!

IF Drugs Are

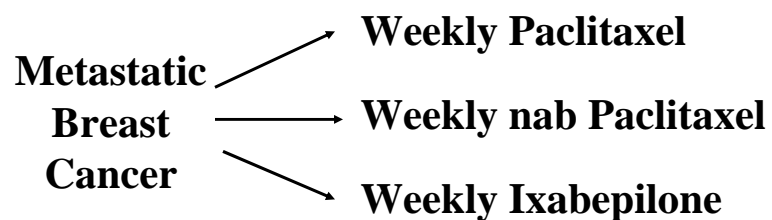
- Not FDA Approved

and

- Made by different companies

The protocol hardly ever happens

CALGB



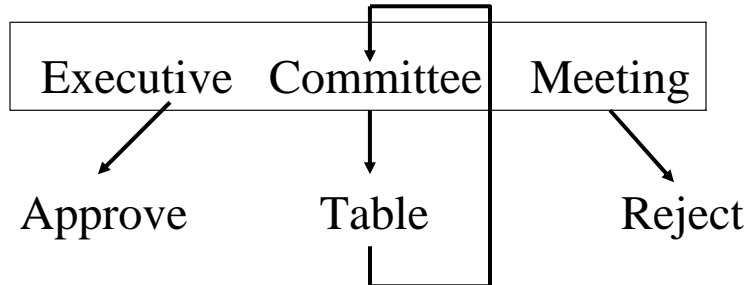
STEP 4: Test Idea in Wider World

- Committee chair holds casual conversations with CTEP representatives
- Committee chair calls in favors from other cooperative groups

STEP 5: Submit Concept to Executive Committee

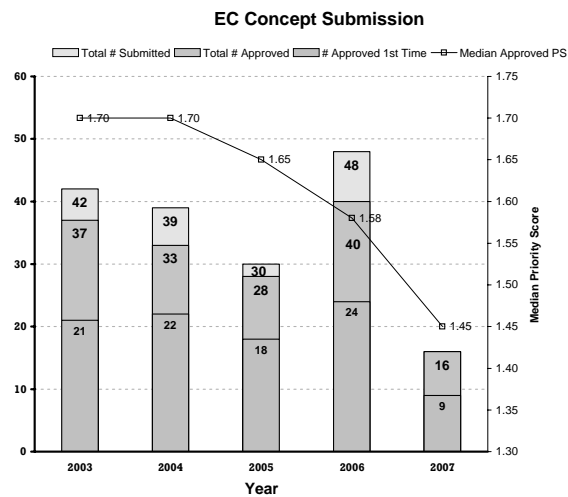
- Use concept submission form A007 from website
- Obtain sign-off from statistician, and all of relevant committee chairs, forward to protocol editor
- Committee Chair writes cover letter and sends to central office (EC review deadlines are on website)

STEP 5: (Continued)

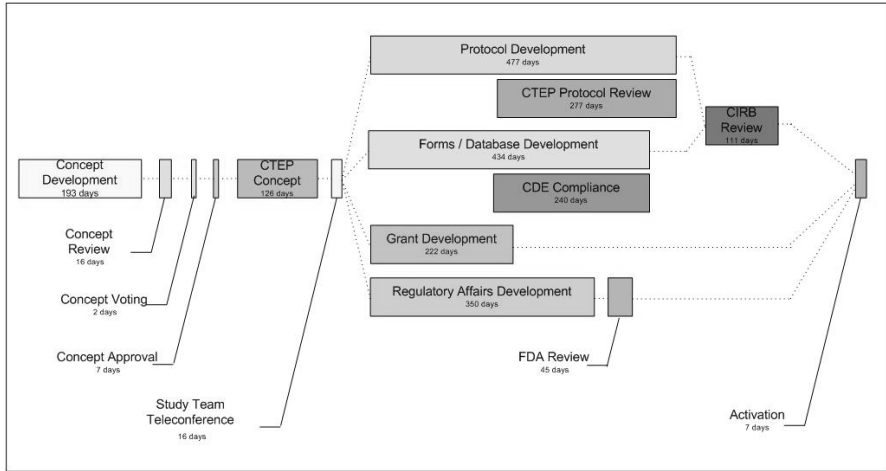


If concept approved, study chair signs first of many Conflict of Interest disclosure forms

CALGB Concept Review



Process Map for CALGB



Dilts, D. M. et al. J Clin Oncol; 24:4553-4557
2006

580 days

STEP 6: NCI LOI Approval

Does A Relevant NCI Steering Committee Exist?

Yes

Is protocol phase III
or >100 subjects

Yes

Submit LOI form to
Steering Committee
Disease Task Force

Submit to Steering
Committee

No

Does protocol involve
CTEP – supplied drug

Yes

Submit LOI to CTEP

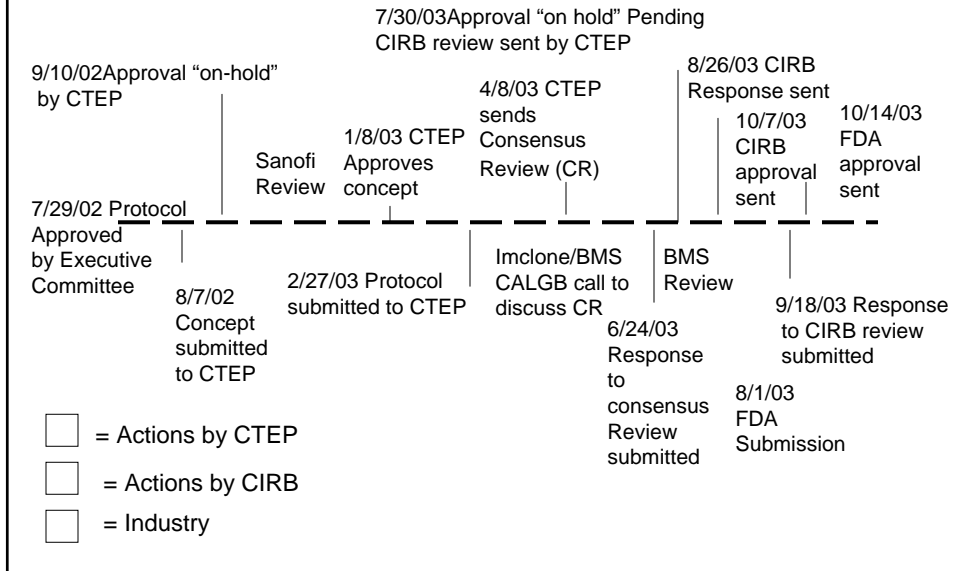
“Consensus Review”
Write revised LOI with CR
response - LOI approval!!
(30% Approval Rate)

No

Submit LOI to CTEP

CALGB 80203

Timeline of Development



STEP 7a: Write Protocol

Use standard template

Initial review (Co-chair, stats, disease, chairs, data coordinators, executive officers)



Fix



Expanded review



Fix



NCI Fix → Approval!

(Forms get CDE Review)

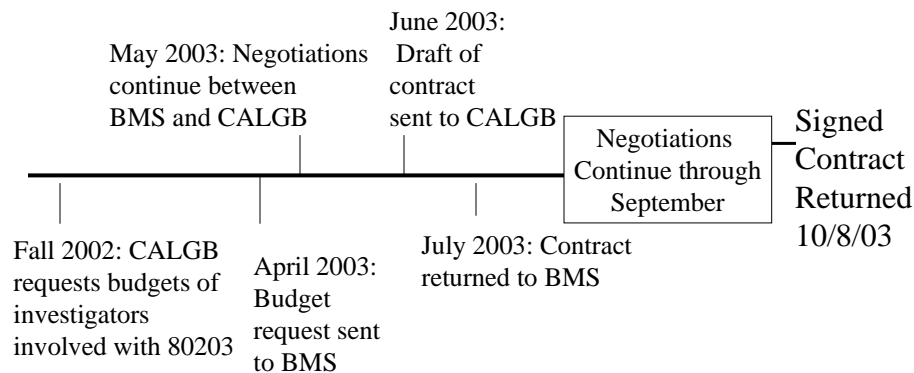
STEP 7b: While Study Chair is Writing Protocol

- IND/drug distribution issues are addressed
- Budget issues are addressed
- Forms are developed (new forms field tested by nursing and CRA designees)
- Educational materials developed (advocates)
- Correlative issues worked out

IND = Investigational New Drug

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



STEP 8: CIRB Review

- New Change: Protocol can go to institutional IRBs without CIRB approval

STEP 9: Institutional Activation

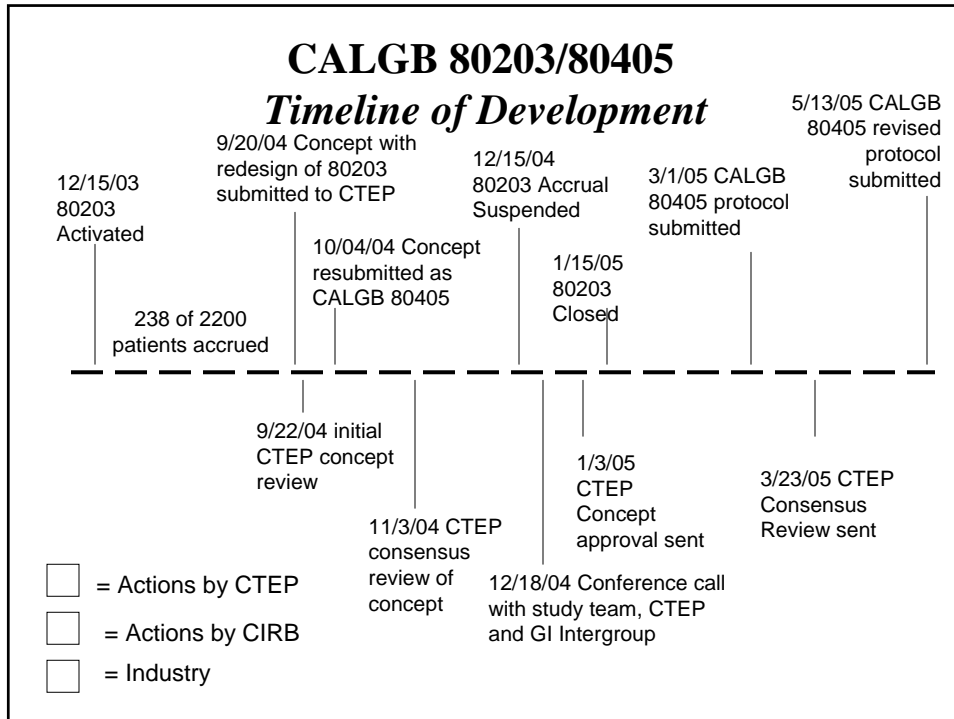
- Institution decides to activate
- Institutional IRB approval
(no risk elements to be omitted from consent!)

STEP 10a: Conduct Protocol

- Accrual (NCI accrual monitoring)
- Monitor → DSMB 2x/year
 - CDUS reporting
 - (Clinical data update system)
 - SAE reporting
- Study chair answer queries and reviews eligibility issues (CO93 form)
- CRA sends in forms!!!

STEP 10b: Conduct Protocol

- Amendments – may require re-consent!
- Protocol generally goes on hold to accrual for amendments that require re-consent until new consent approved
- Don't use old consent versions!!



STEP 11: Data Analysis

- Data must mature
- Study Chair does case evaluations
 - \geq gr 2-3 AEs
 - Stratification factors
 - Adherence
 - Primary Endpoint
(full review for trials of \leq 250 pts, if larger 250 + 5-10%)
- Statistician generates report

STEP 12: Write Manuscript

