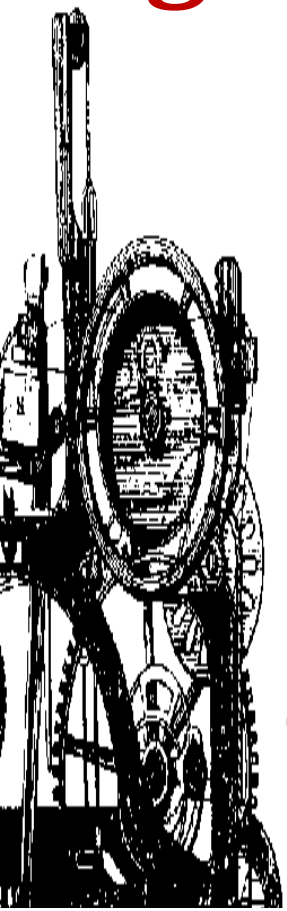
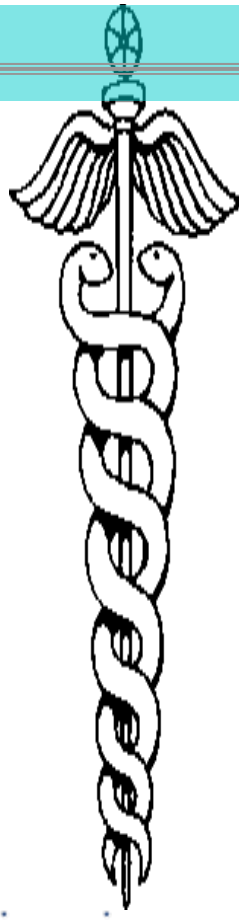
CTEP/CIRB Process Flow and Timing Study

David M. Dilts, PhD, MBA
Co-Director, Center for Management Research in Healthcare
cMRHc.org

Are oncology clinical trials going the way of Oldsmobile?



Activating and Opening Oncology Clinical Trials



David Dilts PhD, MBA

Professor & Director, Engineering Management Program, School of Engineering
Professor & Director, Center for Management Research in Healthcare (www.cmrhc.org)
Owen Graduate School of Management
Vanderbilt University

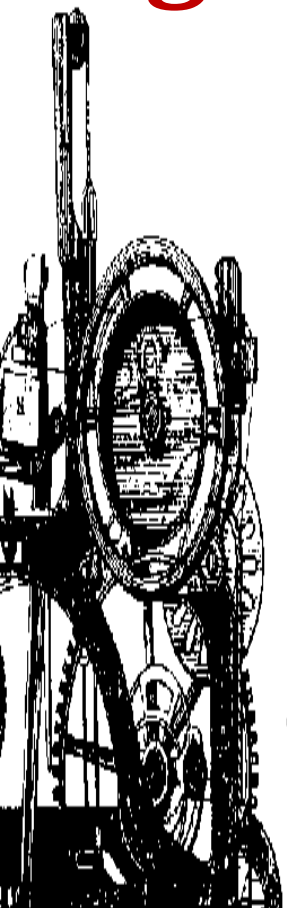
David.dilts@vanderbilt.edu

VANDERBILT UNIVERSITY
OWEN GRADUATE SCHOOL OF MANAGEMENT

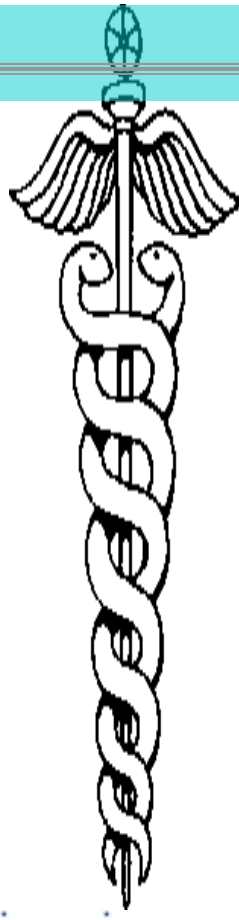
Center for Management Research in Healthcare

School of Engineering
Vanderbilt University

Are oncology clinical trials going the way of CHRYSLER Ford GM?



Activating and Opening Oncology Clinical Trials



David Dilts PhD, MBA

Professor & Director, Engineering Management Program, School of Engineering
Professor & Director, Center for Management Research in Healthcare (www.cmrhc.org)
Owen Graduate School of Management
Vanderbilt University

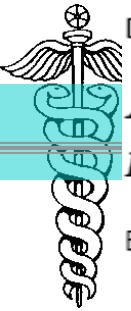
David.dilts@vanderbilt.edu

VANDERBILT UNIVERSITY
OWEN GRADUATE SCHOOL OF MANAGEMENT

Center for Management Research in Healthcare

School of Engineering
Vanderbilt University

THE WALL STREET JOURNAL.
WSJ.com



DECEMBER 2, 2008, 6:11 P.M. ET

Auto Makers Detail Restructuring Plans

Ford Seeks $9 Billion in Bridge Financing, Chrysler Asks for $7 Billion, While GM Needs Injection of $18 Billion

By JOHN D. STOLL and MATTHEW DOLAN

DETROIT -- General Motors Corp., Chrysler LLC and Ford Motor Co. on Tuesday presented turnaround plans to Congress that suggest GM is in a more dire situation than previously thought.

As part of a renewed bid to win backing for a government bail out, GM requested a total of $18 billion in federal loans -- $6 billion more than it said it would a few weeks ago -- and added it needs an immediate injection of $4 billion to stay afloat until the end of the year.

In testimony before Congress last month, GM Chief Executive Rick Wagoner said the company could run short of cash by the time President-elect Barack Obama takes office in January if it doesn't get federal loans. At the time he said GM needed $10 billion to $12 billion.

WSJ.com THE WALL STREET JOURNAL. ONLINE

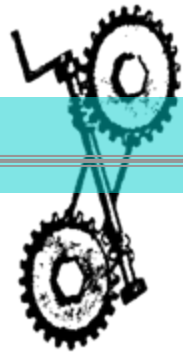
August 6, 2008

COMMON SENSE

Detroit Finally Gets It. Is It Too Late?

By JAMES B. STEWART
August 6, 2008; Page D1

During the past two weeks, **General Motors** reported a $15.5 billion quarterly loss (including special items), following **Ford Motor**'s $8.7 billion loss the week before. I shudder to think how bad it is at Chrysler, now in the hands of private-equity investor Cerberus Capital, but note that Chrysler Financial couldn't renew all of its $30 billion in short-term debt.



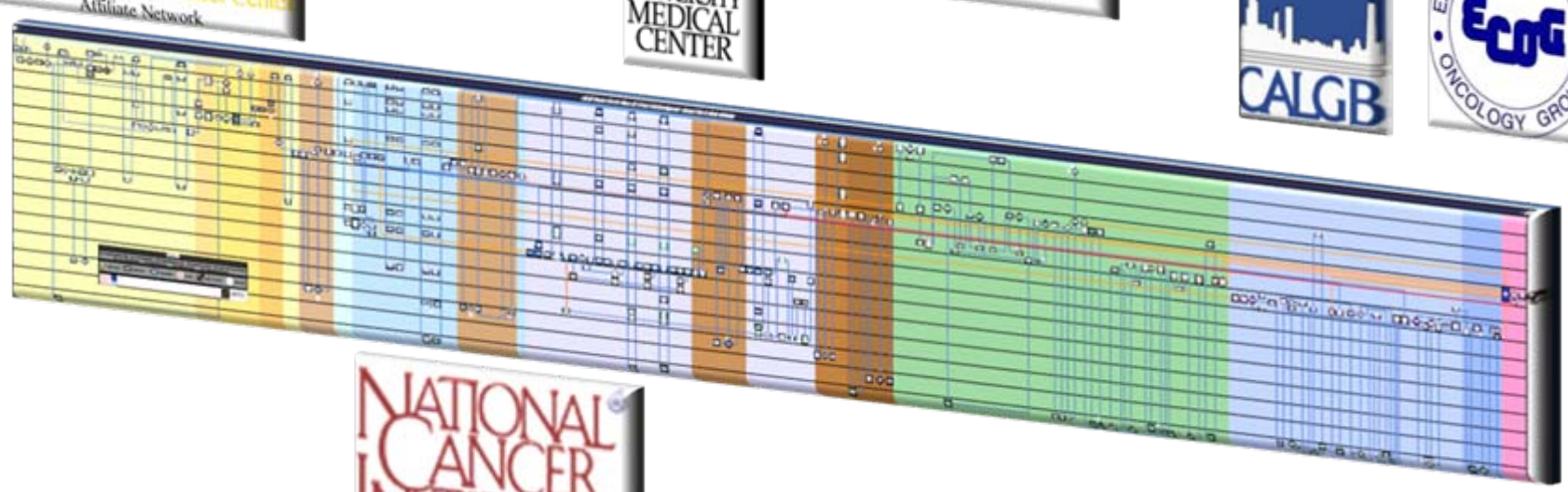
But Mr. Wagoner has struggled to show results on the bottom line. GM reported cumulative losses of roughly $50 billion for 2005, 2006 and 2007. GM has lost more than $18 billion so far this year.

Or, $53.3 million lost / day;
$2.2 million lost / hour

<u>Lessons to Learn</u>:

- **What was good yesterday, might not be good today**
- **What was bad yesterday is even worse today**

Thank you to the study sites



Vanderbilt-Ingram Cancer Center
Affiliate Network

UNC
LINEBERGER COMPREHENSIVE CANCER CENTER

THE OHIO STATE UNIVERSITY
UNIVERSITY MEDICAL CENTER

FOX CHASE
CANCER CENTER
Partners

CALGB

EASTERN COOPERATIVE ONCOLOGY GROUP
ECOG

NATIONAL CANCER INSTITUTE

CTEP
Cancer Therapy Evaluation Program

CIRB

CENTER FOR CANCER RESEARCH

Pharma Companies

cMRHc

The cMRHc Team

- Current Team
  - *David M. Dilts*, PhD – OGSM & VUSE
  - *Alan B. Sandler*, MD – VICC
  - *Josh Crites*, PhD Post-Doc
  - *Steven Cheng*, PhD
  - *Lori Ferranti*, MBA, MSN, PhD cand.

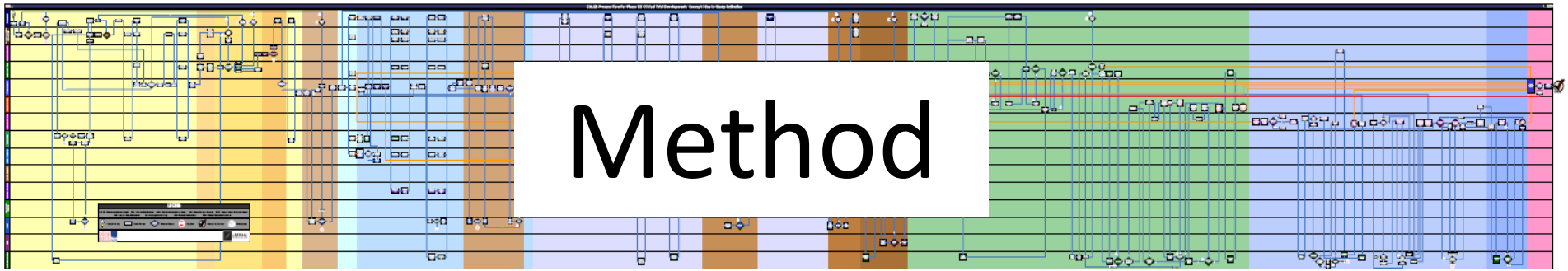
- Former Team Members
  - Travis Ansel, MBA - OGSM
  - Mathew Baker, MBA - OGSM
  - David Browning, BS –VICC
  - Jillian Danker, MBA - OGSM
  - Krista Fakoory, MBA – OGSM
  - Steven McGuire, MS -VUSE
  - Gourija Menon, MS -VUSE
  - Sitora Muzafarova, MBA – OGSM
  - Dindi Rouch, MD – VICC
  - Jason Reusch, MBA - OGSM
  - Maren Scoggins, MBA – OGSM
  - Amy Wu, BMus
  - Bin Xie, PhD –VUSE
  - Kai Zhou, MBA – OGSM

OGSM - Owen Graduate School of Management
VICC – Vanderbilt-Ingram Cancer Center
VUSE - Vanderbilt University School of Engineering (VUSE)

cMRHc

Agenda

- Methodology & Process Flow Map Overview
- Process Step Counts
- Timing
- Accrual
- Impact of
  - Timing on achievement of accrual goals
  - First patient on study on achievement of accrual goals



Method

Part I: Process Mapping

- Extensive visits at each site to document processes, loops and decisions:
  - *Say*…..: What participants say is done
  - *Should*: What policies and procedures say should be done
  - *Do*……: What trial chart reviews shows was done
- Creation of process map

Part II: Process Timing

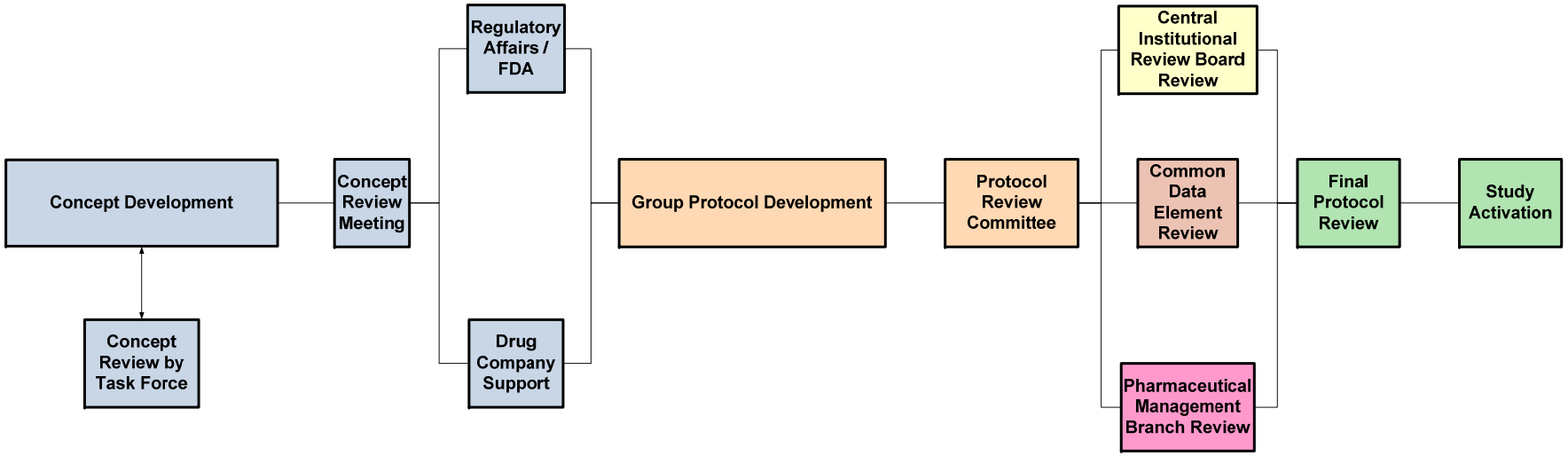
- Identify calendar time for total process and major steps, and potential influencers of the time

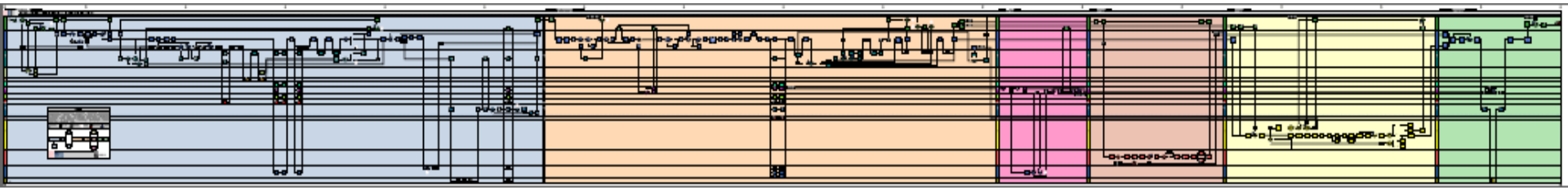
Part III: Accrual Data

- Investigate actual accrual results of trials

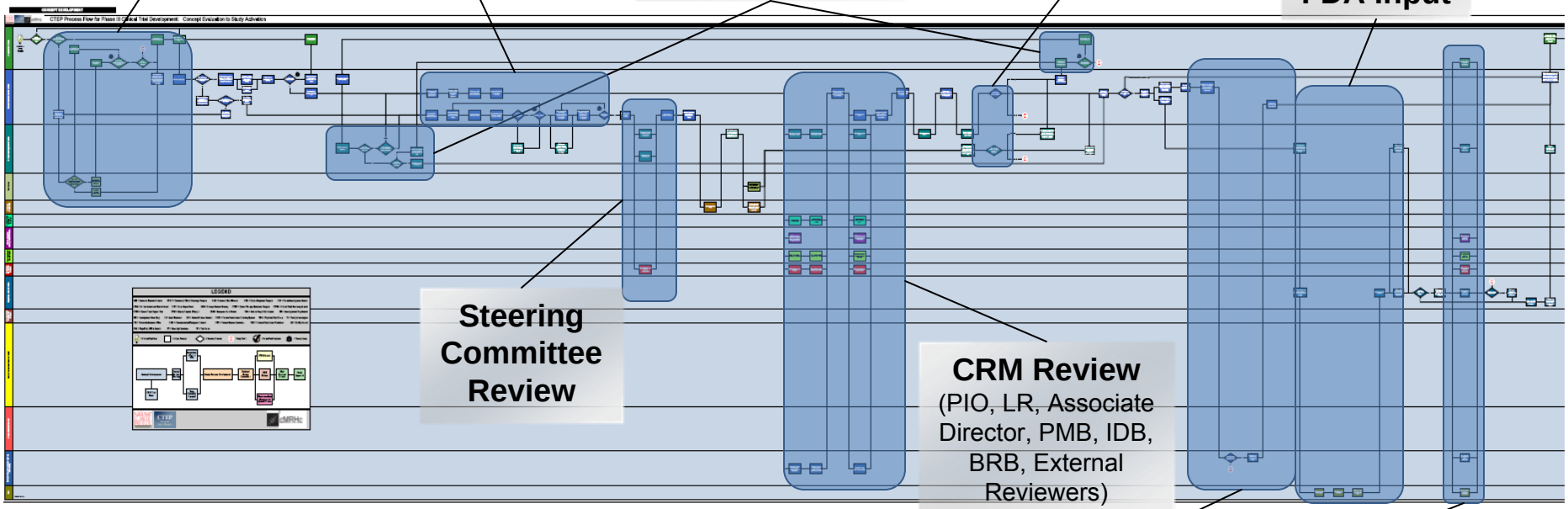
- Dilts DM and Sandler AB (2006) "The Invisible Barriers to Opening Clinical Trials, *J Clinical Oncology,* 24(28): 4545-52
- Dilts DM et. al (2006) "Processes to Activate Phase III Clinical Trials in a Cooperative Oncology Group: The Case of Cancer and Leukemia Group B," *J Clinical Oncology,* 24(28): 4553-57.
- Dilts DM et. al (2008) "Development of Clinical Trials in a Cooperative Group Setting: The Eastern Cooperative Group," *Clinical Cancer Research*, 14(11):3427-33
- Dilts, et al. (2008) "Accrual to Clinical Trials at Selected Comprehensive Cancer Centers," *ASCO* (Abstract #6543)
- Dilts et al. (forthcoming) "The Steps and Time to Process Phase III Clinical Trials at CTEP*", J Clin Onc*

CTEP/CIRB Process Map





Concept Development and Review



Informal Task Force/Concept Development

PIO Pre-meeting Preparation

Concept Revision and Re-review

CRM/SC Outcome

FDA Input

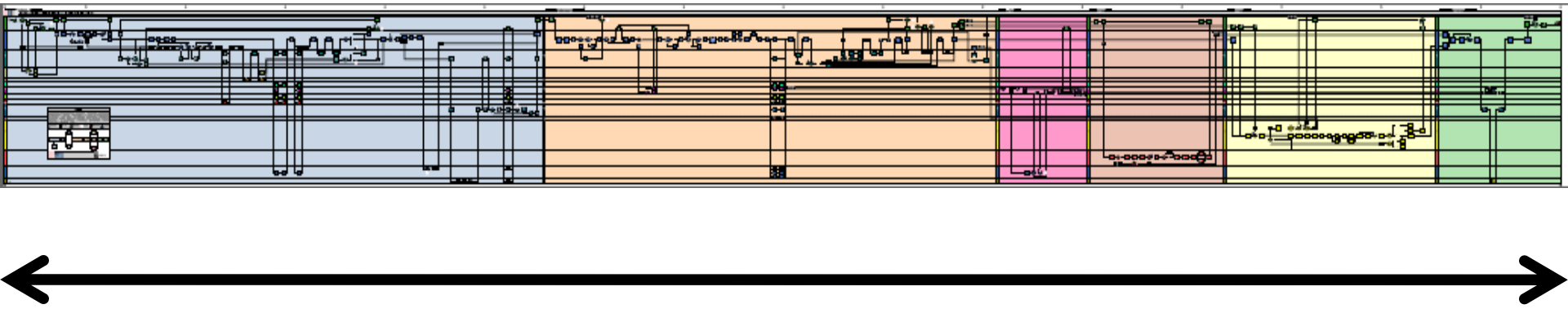
Steering Committee Review

CRM Review
(PIO, LR, Associate Director, PMB, IDB, BRB, External Reviewers)

Drug Company Commitment

Telecon to resolve FDA Issues

CTEP/CIRB Process Map



45’ x 5’

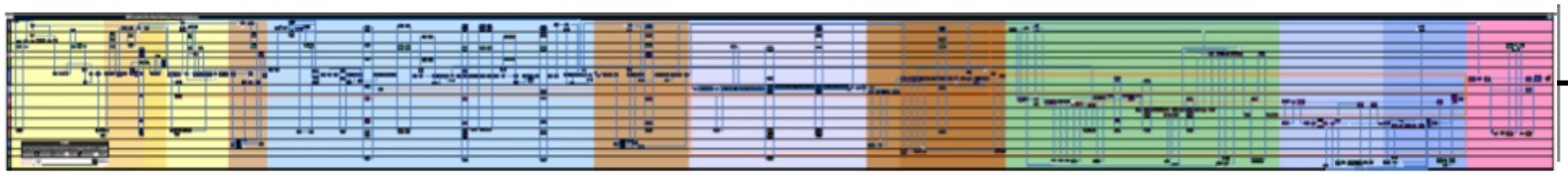
CTEP/CIRB Process Counts

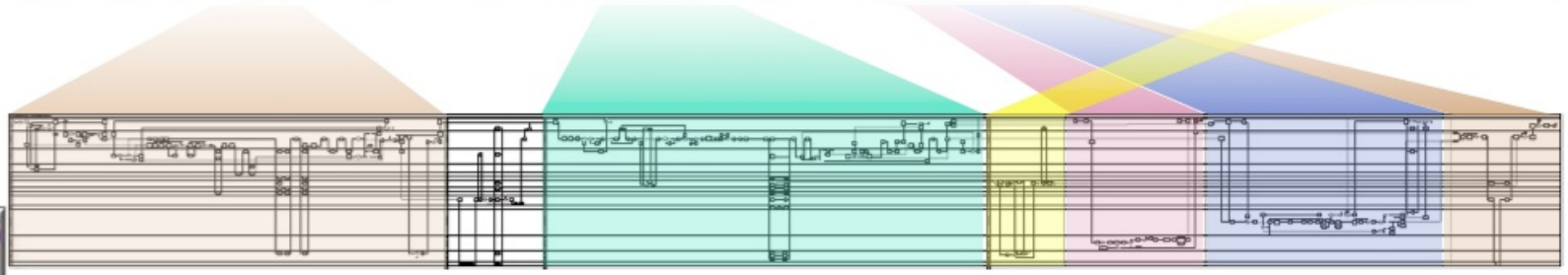
Area	Processing Step	Decision Point	Loop	Stopping Point
				
Concept (total)*	106	21	5	6
CRM	76	13	2	4
Task Force	71	19	4	5
Protocol	88	17	7	4
PMB	10	6	2	1
CDE	20	4	1	0
CIRB	34	9	5	2
Final Review	16	3	3	0
Total CRM	*244*	*52*	*20*	*11*
Total Task Force	*239*	*58*	*22*	*12*

* Overlapping steps account for total difference

Opening a Phase III Cooperative Group Trial at a CCC

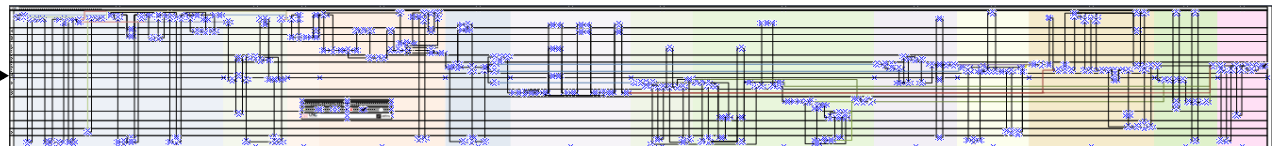
50 ft x 5 ft in 8pt font





45 ft x 5 ft in 8pt font

37’1’ x 3’6” ft in 8pt font



Process Steps for Opening a Phase III Cooperative Group Trial

	Cooperative Group	CTEP /CIRB	CCC	Total
Process Steps	>458	>216	>136	>810
…Working Steps	>399	>179	>74	>652
…Decision Points	59	37	62	158
Potential Loops[2]	26	15	27	68
No. of Groups Involved	11	14	13	38

1. Representative cooperative group and Comprehensive Cancer Center
2. Process steps reported only show one loop in the process. Actual development frequently includes multiple loops

Reviews Required to Develop a Cooperative Group Phase III Trial

Table 2. Types of Reviews Required to Develop a CTCG Trial: Categorized by Stakeholders

	CTCG	CTEP	CCC	CCOP/Affiliates	Others
Scientific Review	Disease Site Committee Executive Committee Protocol Reviews (2-4)	Steering / CRM PRC CTEP Final	Protocol Review	Feasibility Review Site Surveys	Industry Sponsor
Data Management	CRF Reviews (2-4) Database Review	CDE Review			
Saftey / Ethics	Informed Consent		Local IRB	Informed Consent	CIRB
Regulatory	Regulatory Review	PMB Review RAB Review			FDA
Contracts / Grants	Budget Language				Industry Sponsor
Study Start-up	Start-up Review		Start-up Review	Start-up Review	

Abbreviations: CCC, Comprehensive Cancer Centers; CCOP, Community Clinical Oncology Program; CDE, Common Data E CIRB, Central Institutional Board Review, CRF, Case Report Form; CRM, Concept Review Meeting; CTCG, Clinical Trials Coc Group; CTEP, Cancer Therapy Evaluation Program; FDA, Food and Drug Administration; PMB, Pharmaceutical Management PRC, Protocol Review Committee; RAB, Regulatory Affairs Branch

The Problem in a Microcosm

- Forms required to be completed to do Grand Rounds at one cancer center

W-9 (Rev. October 2007)
Department of the Treasury
Internal Revenue Service

Request for Taxpayer Identification Number and Certification

Give form to the requester. Do not send to the IRS.

Print or type
See Specific Instructions on page 2.

Name (as shown on your income tax return)
David M. Dilts

Business name, if different from above

Check appropriate box: ☑ Individual/Sole proprietor ☐ Corporation ☐ Partnership
☐ Limited liability company. Enter the tax classification (D=disregarded entity, C=corporation, P=partnership) ▶ _____
☐ Other (see instructions) ▶

Address (number, street, and apt. or suite no.)
670 Church St #817

Requester's name and address (optional)

City, state, and ZIP code
Brentwood, TN 37027

List account number(s) here (optional)

Part I Taxpayer Identification Number (TIN)

Enter your TIN in the appropriate box. The TIN provided must match the name given on Line 1 to avoid backup withholding. For individuals, this is your social security number (SSN). However, for a resident alien, sole proprietor, or disregarded entity, see the Part I instructions on page 3. For other entities, it is your employer identification number (EIN). If you do not have a number, see How to get a TIN on page 3.

Note. If the account is in more than one name, see the chart on page 4 for guidelines on whose number to enter.

Social security number
___ ___ ___

or

Employer identification number
___ ___

Part II Certification

Under penalties of perjury, I certify that:

1. The number shown on this form is my correct taxpayer identification number (or I am waiting for a number to be issued to me), and
2. I am not subject to backup withholding because: (a) I am exempt from backup withholding, or (b) I have not been notified by the Internal Revenue Service (IRS) that I am subject to backup withholding as a result of a failure to report all interest or dividends, or (c) the IRS has notified me that I am no longer subject to backup withholding, and
3. I am a U.S. citizen or other U.S. person (defined below).

Certification instructions. You must cross out item 2 above if you have been notified by the IRS that you are currently subject to backup withholding because you have failed to report all interest and dividends on your tax return. For real estate transactions, item 2 does not apply. For mortgage interest paid, acquisition or abandonment of secured property, cancellation of debt, contributions to an individual retirement arrangement (IRA), and generally, payments other than interest and dividends, you are not required to sign the Certification, but you must provide your correct TIN. See the instructions on page 4.

Sign Here | Signature of U.S. person ▶ | Date ▶ October 29, 2008

General Instructions

Section references are to the Internal Revenue Code unless otherwise noted.

Purpose of Form

A person who is required to file an information return with the IRS must obtain your correct taxpayer identification number (TIN) to report, for example, income paid to you, real estate transactions, mortgage interest you paid, acquisition or abandonment of secured property, cancellation of debt, or contributions you made to an IRA.

Use Form W-9 only if you are a U.S. person (including a resident alien), to provide your correct TIN to the person requesting it (the requester) and, when applicable, to:

1. Certify that the TIN you are giving is correct (or you are waiting for a number to be issued),
2. Certify that you are not subject to backup withholding, or
3. Claim exemption from backup withholding if you are a U.S. exempt payee. If applicable, you are also certifying that as a U.S. person, your allocable share of any partnership income from a U.S. trade or business is not subject to the withholding tax on foreign partners' share of effectively connected income.

Note. If a requester gives you a form other than Form W-9 to request your TIN, you must use the requester's form if it is substantially similar to this Form W-9.

Definition of a U.S. person. For federal tax purposes, you are considered a U.S. person if you are:

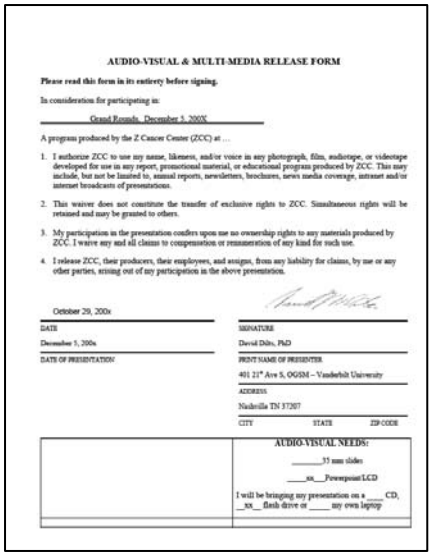
- An individual who is a U.S. citizen or U.S. resident alien,
- A partnership, corporation, company, or association created or organized in the United States or under the laws of the United States,
- An estate (other than a foreign estate), or
- A domestic trust (as defined in Regulations section 301.7701-7).

Special rules for partnerships. Partnerships that conduct a trade or business in the United States are generally required to pay a withholding tax on any foreign partners' share of income from such business. Further, in certain cases where a Form W-9 has not been received, a partnership is required to presume that a partner is a foreign person, and pay the withholding tax. Therefore, if you are a U.S. person that is a partner in a partnership conducting a trade or business in the United States, provide Form W-9 to the partnership to establish your U.S. status and avoid withholding on your share of partnership income.

The person who gives Form W-9 to the partnership for purposes of establishing its U.S. status and avoiding withholding on its allocable share of net income from the partnership conducting a trade or business in the United States is in the following cases:

- The U.S. owner of a disregarded entity and not the entity,

Cat. No. 10231X Form **W-9** (Rev. 10-2007)



AUDIO-VISUAL & MULTI-MEDIA RELEASE FORM

Please read this form in its entirety before signing.

In consideration for participating in:

Grand Rounds, December 5, 2008

A program produced by the Z Cancer Center (ZCC) at …

1. I authorize ZCC to use my name, likeness, and/or voice in any photograph, film, audiotape, or videotape developed for use in any report, promotional material, or educational program produced by ZCC. This may include, but not be limited to, annual reports, newsletters, brochures, news media coverage, intranet and/or internet broadcasts of presentations.
2. This waiver does not constitute the transfer of exclusive rights to ZCC. Simultaneous rights will be retained and may be granted to others.
3. My participation in the presentation confers upon me no ownership rights to any materials produced by ZCC. I waive any and all claims to compensation or remuneration of any kind for such use.
4. I release ZCC, their producers, their employees, and assigns, from any liability for claims, by me or any other parties, arising out of my participation in the above presentation.

October 29, 200x
DATE

December 5, 200x
DATE OF PRESENTATION

SIGNATURE

David Dilts, PhD
PRINT NAME OF PRESENTER

401 21st Ave S, OGSM – Vanderbilt University
ADDRESS

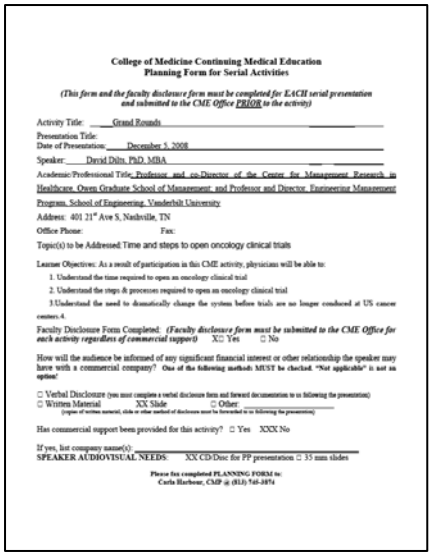
Nashville TN 37207
CITY STATE ZIP CODE

AUDIO-VISUAL NEEDS:

_____35 mm slides

____xx___Powerpoint/LCD

I will be bringing my presentation on a ____ CD, _xx_ flash drive or _____ my own laptop



College of Medicine Continuing Medical Education
Planning Form for Serial Activities

(This form and the faculty disclosure form must be completed for EACH serial presentation and submitted to the CME Office PRIOR to the activity)

Activity Title: ____Grand Rounds_____

Presentation Title:
Date of Presentation: ____December 5, 2008_____

Speaker: ____David Dilts, PhD, MBA_____

Academic/Professional Title: Professor and co-Director of the Center for Management Research in Healthcare, Owen Graduate School of Management; and Professor and Director, Engineering Management Program, School of Engineering, Vanderbilt University

Address: 401 21st Ave S, Nashville, TN

Office Phone: Fax:

Topic(s) to be Addressed: Time and steps to open oncology clinical trials

Learner Objectives: As a result of participation in this CME activity, physicians will be able to:

1. Understand the time required to open an oncology clinical trial
2. Understand the steps & processes required to open an oncology clinical trial
3. Understand the need to dramatically change the system before trials are no longer conducted at US cancer centers. 4.

Faculty Disclosure Form Completed: ***(Faculty disclosure form must be submitted to the CME Office for each activity regardless of commercial support)*** X☐ Yes ☐ No

How will the audience be informed of any significant financial interest or other relationship the speaker may have with a commercial company? **One of the following methods MUST be checked. "Not applicable" is not an option!**

☐ Verbal Disclosure (you must complete a verbal disclosure form and forward documentation to us following the presentation)
☐ Written Material XX Slide ☐ Other: _____
(copies of written material, slide or other method of disclosure must be forwarded to us following the presentation)

Has commercial support been provided for this activity? ☐ Yes XXX No

If yes, list company name(s): _____
SPEAKER AUDIOVISUAL NEEDS: XX CD/Disc for PP presentation ☐ 35 mm slides

Please fax completed PLANNING FORM to:
Carla Harbour, CMP @ (813) 745-3874

Travel and AV Information Form
ZCC Grand Rounds

Name: David M. Dilts E-mail Address: david.dilts@vanderbilt.edu

Emergency Contact

Name: _____ Phone #: _____

Airline Transportation

In order for your airfare to be billed to our Z Conference account, please call *American Express Travel* at 800-872-9954 or E-mail cellardiamlich@amex.com. Mention you are a Speaker for Z Grand Rounds. Airlines Reservations must be made no later than 30 days prior to the program and will cover coach fare only.

For our records, please advise us of your flight details:

Arrival Date/Time:_____ Airline/Flight #_____

Departure Date/Time:_____ Airline/Flight #_____

Ground Transportation

Round/trip transportation from The International Airport to the Embassy Suites Hotel will be arranged for you and billed to the conference. A driver will meet you outside the baggage claim area of the airline you traveled on.

Your cell number: _____.

Hotel Accommodations:

Embassy Suites Hotel, 3705 cs Blvd,
Phone: (, **Website:** www.embassysuites.com

☐ King ☐ 2 Doubles ☐ Special Requests _____

A confirmation number will be E-mailed to you.

Notes - up to one night is provided by Moffitt (additional nights are self-pay).

I will be traveling: XX Alone ☐ With: _____

Audio/Visual Needs: (PowerPoint will be used in all sessions.) Please bring your presentation on flash drive or CD. ☐VCR (VHS ___ or DVD ___) ☐Study/Internet Connection ☐Other _____

NOTE! Please arrive one hour prior to the start of the conference to set up your presentation. Bring a back-up copy of your presentation.

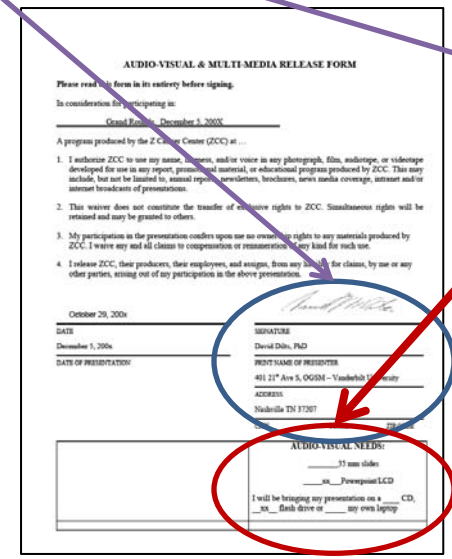
PLEASE FAX THIS FORM TO: xxx, No Later Than November 7, 2008

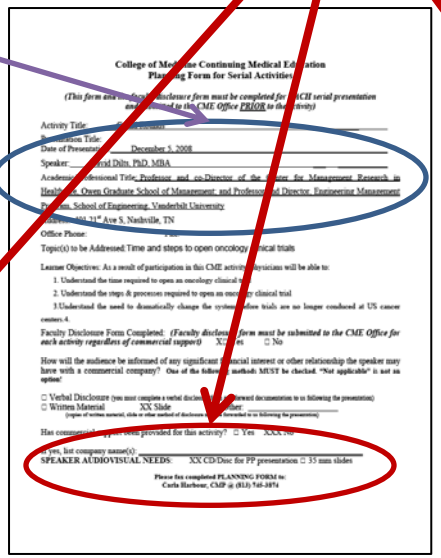
For Questions, Please Call: yyy

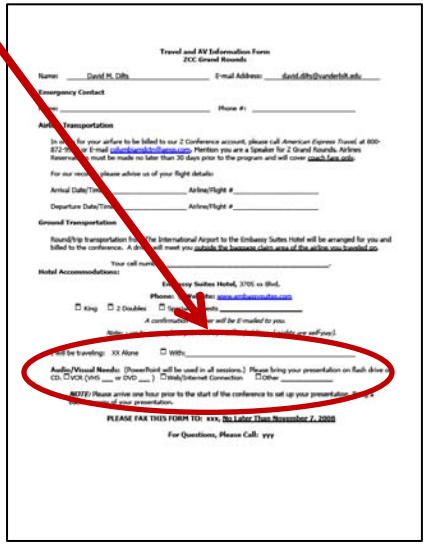
The Problem in a Microcosm

Name and Address

AV Requirements







In filling out <u>exactly</u> the same thing 3 times, only in slightly different ways,

1. **How much effort is wasted?**
2. **What are the chances of making a mistake?**

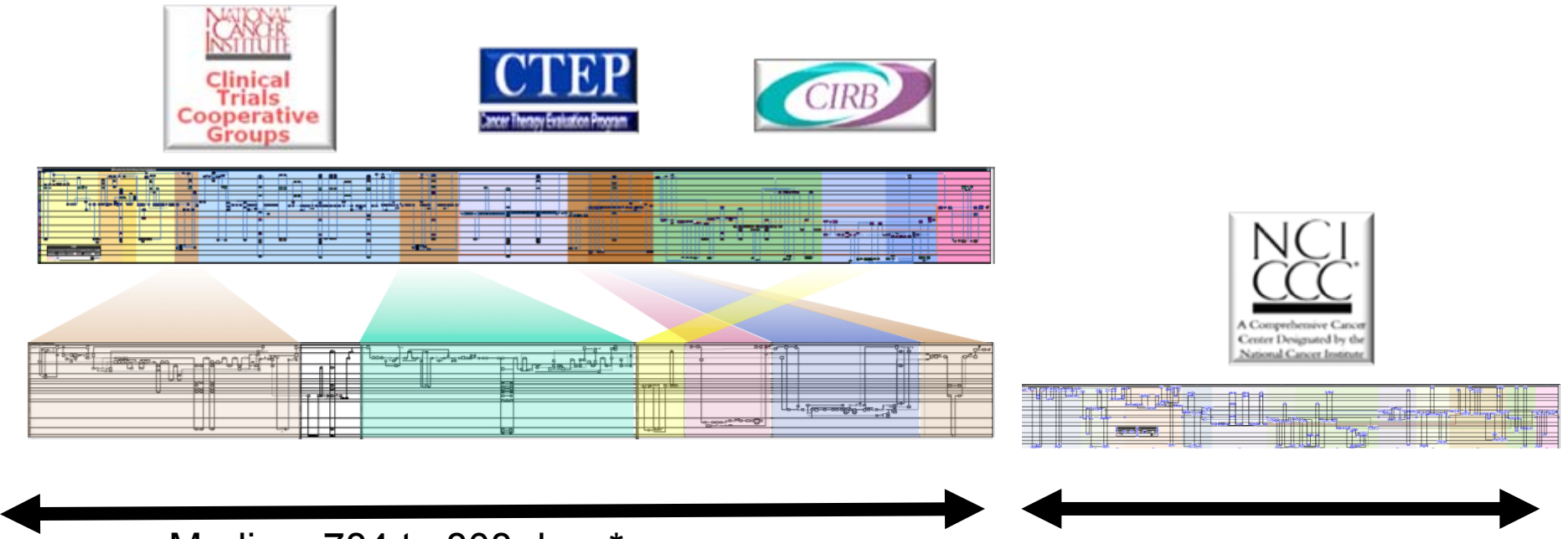
Need for Standards

"Say what you mean & mean what you say"

- Use standard and consistent terminology
  - *Approval* versus *Final-Approval* versus *Final-Final Approval*
- Use schedules that are schedules, priorities that are priorities and "no's" that are "no's"
  - If 50% of studies are "Priority 1", then all studies are "Priority 1"
  - If the only penalty for being late is getting more time, then why do something on time?
    - **CORRECTION: the complete CTEP Phase III data shows that expediting a study does reduce its development time**
  - If a study can be rejected at concept review, at protocol review , and at group but still be opened, does "no" mean "no"?
    - 14 disapproved concepts had protocols created, 11 resulted in active protocols
    - 17 of withdrawn concepts had protocols created, 8 of which resulted in active protocols

cMRHc

Total Time to Open a Phase III Cooperative Group Study



Median: 784 to 808 days*
Range: 435-1604 days

Median: 116 to 252 days*
Range: 21-836 days

Total Median Time from idea to opening~920 days (2.5 years)
Range: 456 – 2440 days (1.25 - 6.7 yrs)

* Depending upon site, based on the Phase III trials studied

cMRHc

Some Comparisons

- Disneyland was created, from breaking ground to first paying customer in 366 days in 1955
- John Kennedy was in office for 1036 days

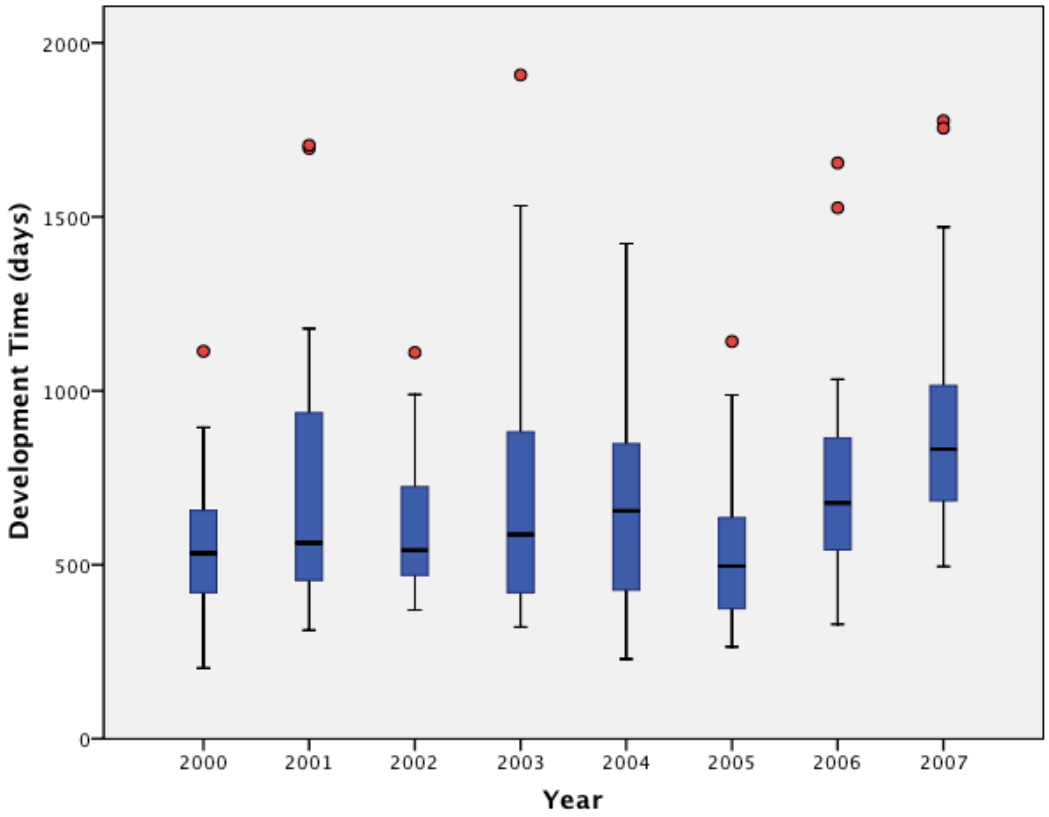


Figure 4. Development time for a phase III trial, CTEP Concept Receipt to Activation. Box ranges (H-Spread) indicate lower 25th and upper 75th percentile of the sample. T-bars indicate the 95.0% confidence intervals by year. Dots indicate trial development time outside the bounds of the CI. Year indicates the year that the trial was activated.

Actual Accrual Per Trial Ranges

Comprehensive Cancer Centers[1]

Accrual Per Trial	CCC 1	CCC 2	CCC 3	CCC 4	Total
N	*148*	*323*	*104*	*323*	*898*
0	20.9%	26.9%	26.9%	34.4%	28.6%
1-4	33.0%	32.3%	30.3%	31.3%	30.8%
5-10	19.3%	16.1%	22.7%	18.0%	18.6%
11-15	11.0%	7.3%	8.4%	4.3%	7.7%
16-20	3.7%	3.7%	3.4%	5.3%	4.1%
>20	12.4%	15.0%	7.6%	6.8%	10.1%

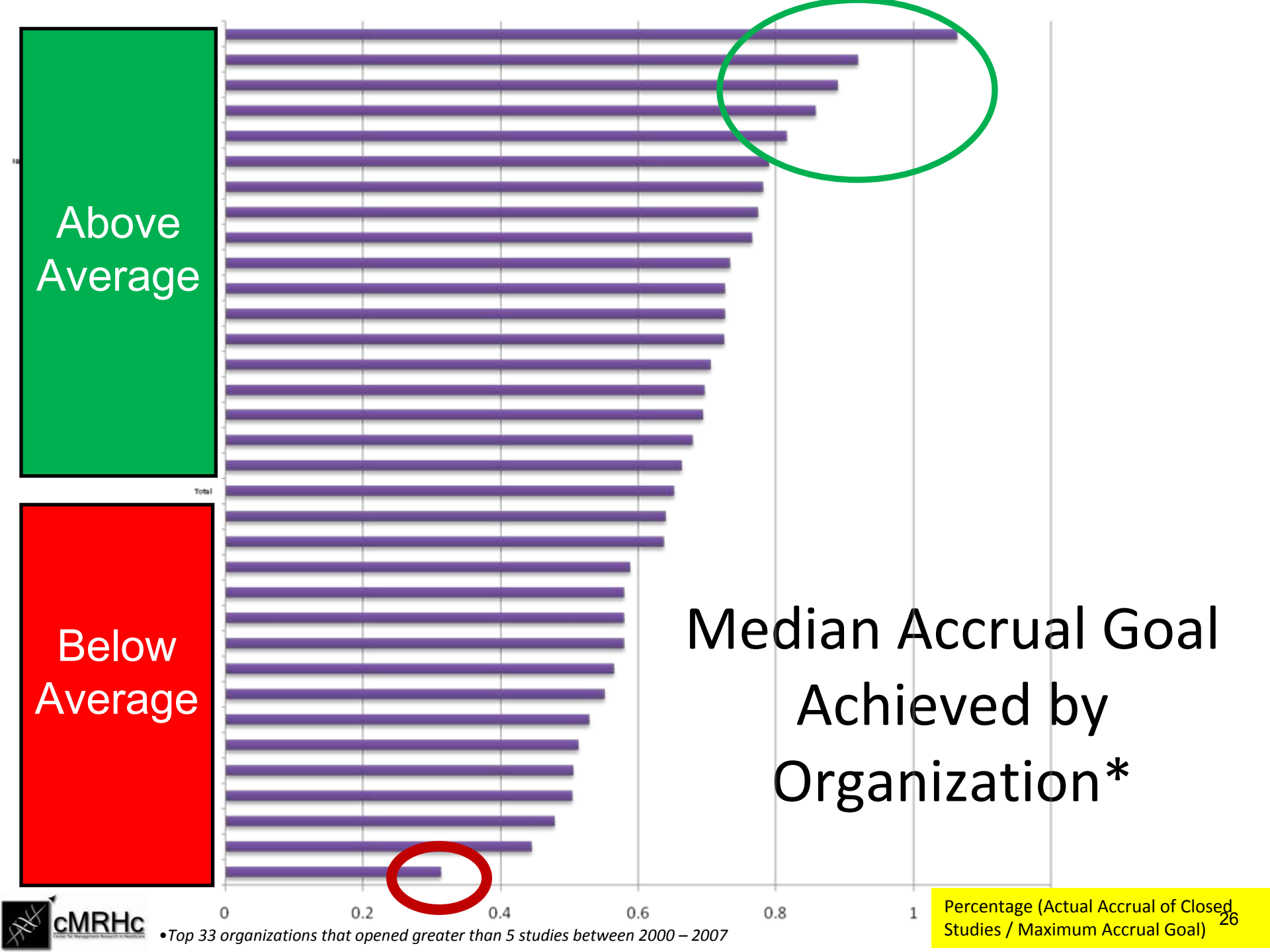
cMRHc

[1]Excludes pediatric studies

Accrual at CCCs:

Cooperative v. non-Cooperative Group Trials

Cooperative Group Trials	**CCC 1**	**CCC 2**	**CCC 3**	**CCC 4**	**Total/ Average**
N	*37*	*166*	*61*	*130*	*394*
0	27.0%	38.6%	29.5%	46.9%	38.8%
1 to 4	37.8%	38.6%	39.3%	38.5%	38.6%
5 or more	35.1%	22.9%	31.1%	14.6%	22.6%
Non-Cooperative Group Trials	**CCC 1**	**CCC 2**	**CCC 3**	**CCC 4**	**Total/ Average**
N	*111*	*157*	*43*	*193*	*504*
0	18.9%	14.6%	23.3%	25.9%	20.6%
1 to 4	30.6%	22.9%	9.3%	26.4%	24.8%
5 or more	50.5%	62.4%	67.4%	47.7%	54.6%



Median Accrual Goal Achieved by Organization*

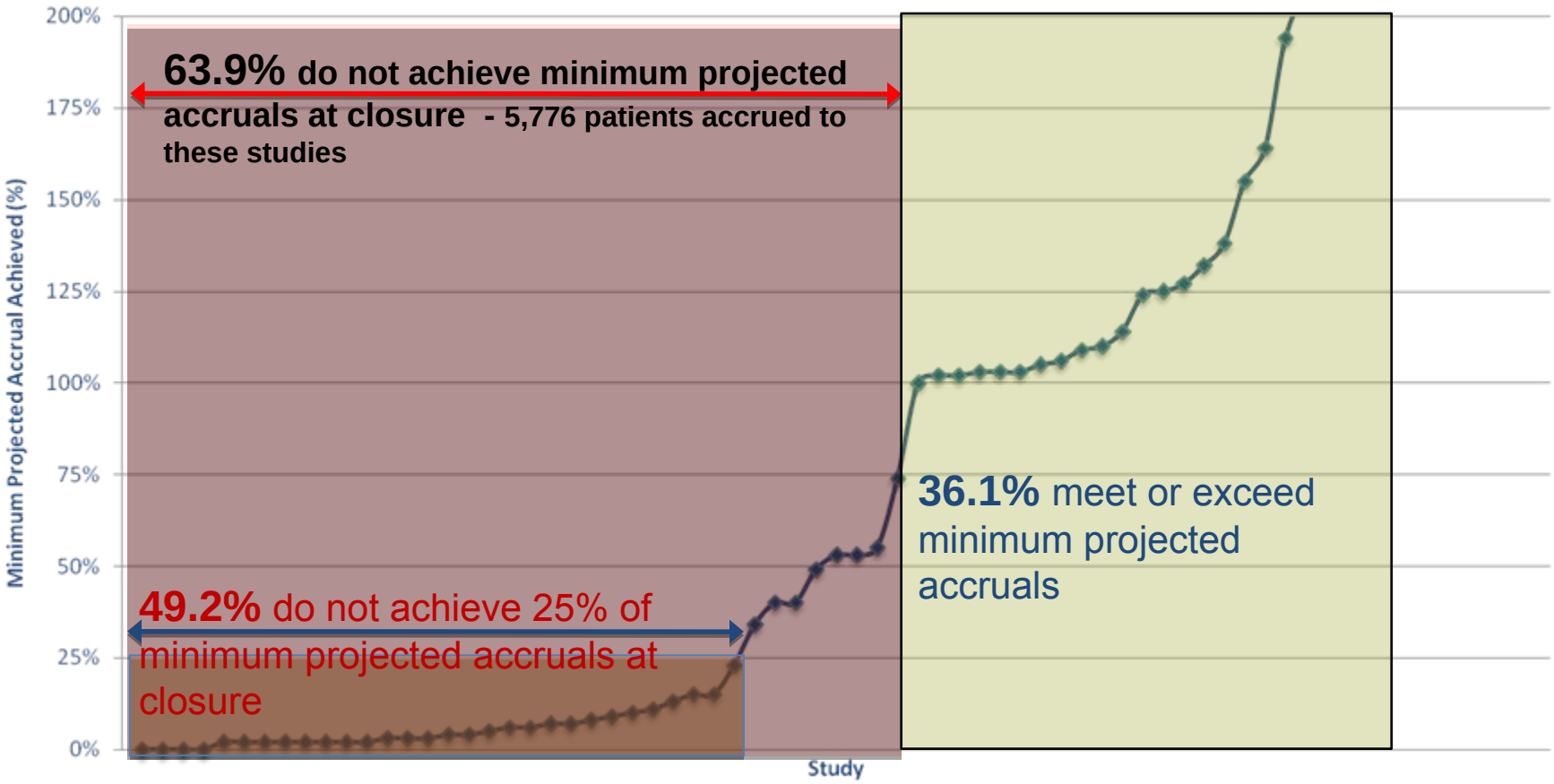
Percentage (Actual Accrual of Closed Studies / Maximum Accrual Goal)

*Top 33 organizations that opened greater than 5 studies between 2000 – 2007

cMRHc

Final Accrual* of CTEP-Sponsored P-III Trials

Opened and Closed between 2000 – 2007 (n=61)

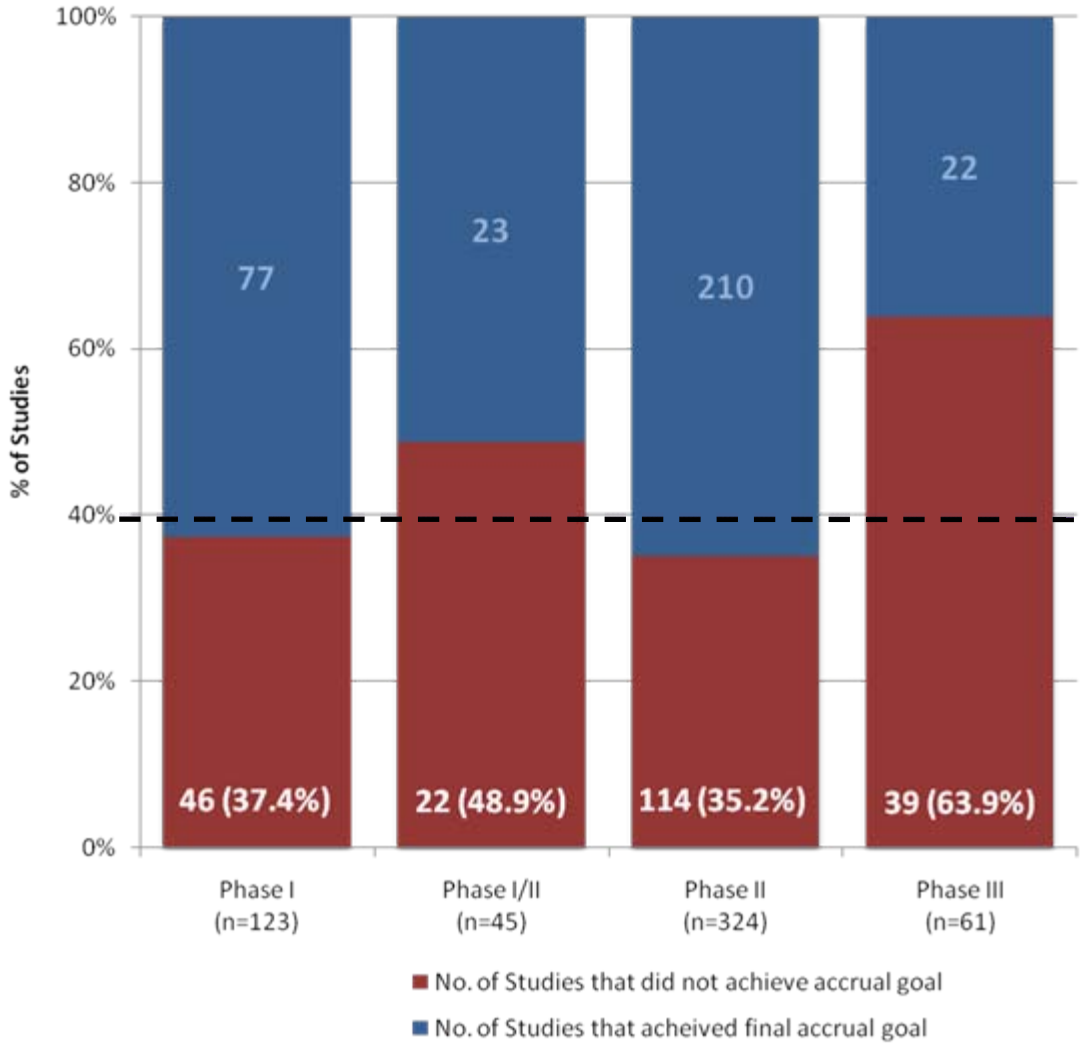


Accrual Performance is calculated based on the percentage of final accruals of studies completely closed to accrual compared to the projected minimum accrual goals as stated at the time of activation

Pediatric studies are excluded from the sample

cMRHc

Accrual Success Rate (by Phase)



◆Dotted line indicates the median number of studies that do not achieve accrual success across the total sample

Overall, **two out of every five** trials did not meet their minimum accrual goal

More than **three out of every five** Phase III trials did not meet the minimum accrual

"Phase III trials are the priciest part of clinical development, making up an estimated 70% of a compound's clinical development cost. Improving their success rate would be the single biggest factor in bringing down the cost of drug development"

(Pearson, Nature 2006)

Data: CTEP recorded therapeutic, non-pediatric, Phase I-III opened and closed w/ complete development time between January 1, 2000 and December 31, 2007 (n=553)

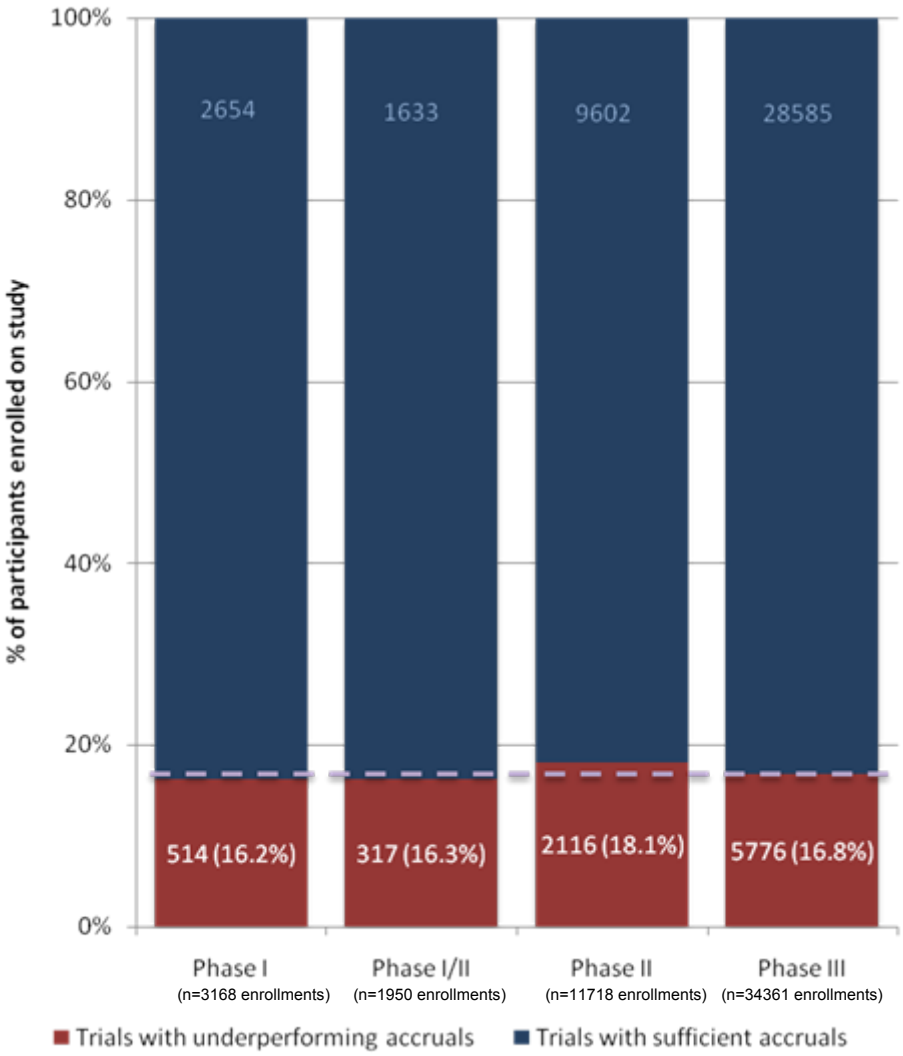
cMRHc

Source: Cheng, SK "The Impact of Delay", PhD Dissertation, Vanderbilt University,

Clinical Trial Participation

51,197 total participants enrolled on trials in the sample

8,723 (17.0%) of the participants enrolled on trials that had under-performing accrual

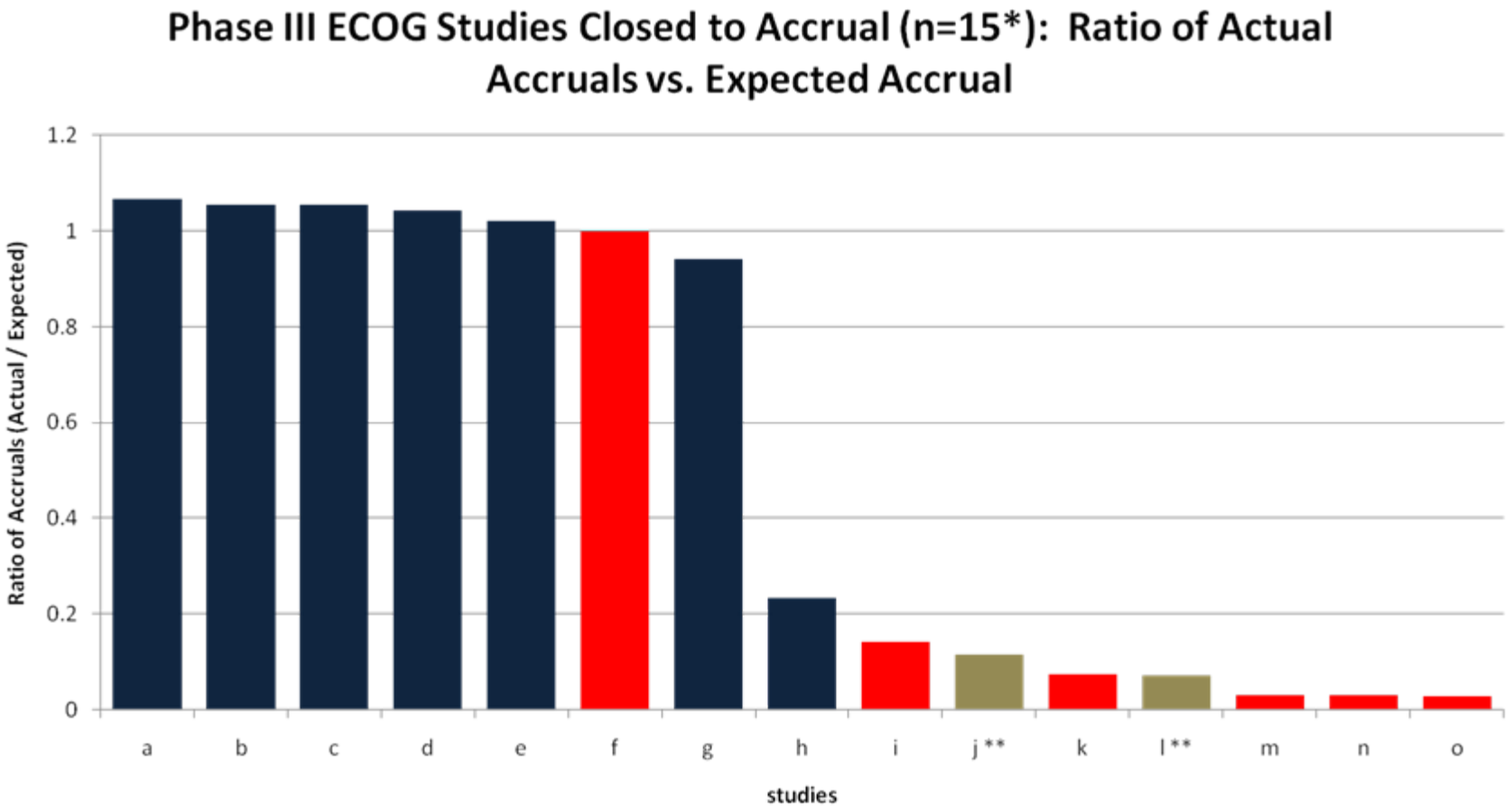


- Underperforming Accruals = Closed trials achieving < 100% of the minimum projected accrual
- Sufficient Accruals = Closed trials achieving ≥100% of the minimum projected accrual

Data: CTEP recorded therapeutic, non-pediatric, Phase I-III opened and closed w/ complete development time between January 1, 2000 and December 31, 2007 (n=553)

Source: Cheng, SK "The Impact of Delay", PhD Dissertation, Vanderbilt University, 2008

Phase III Accrual Performance



•All phase III studies activated and closed to accrual between 1/2000 – 7/2006

•red : > median time to open; blue: <median time to open

• gray: studies closed due to reasons other than poor accrual

cMRHc

TABLE 1. Summary Statistics for CTEP-sponsored Oncology Clinical Trials by Development Time and Accruals

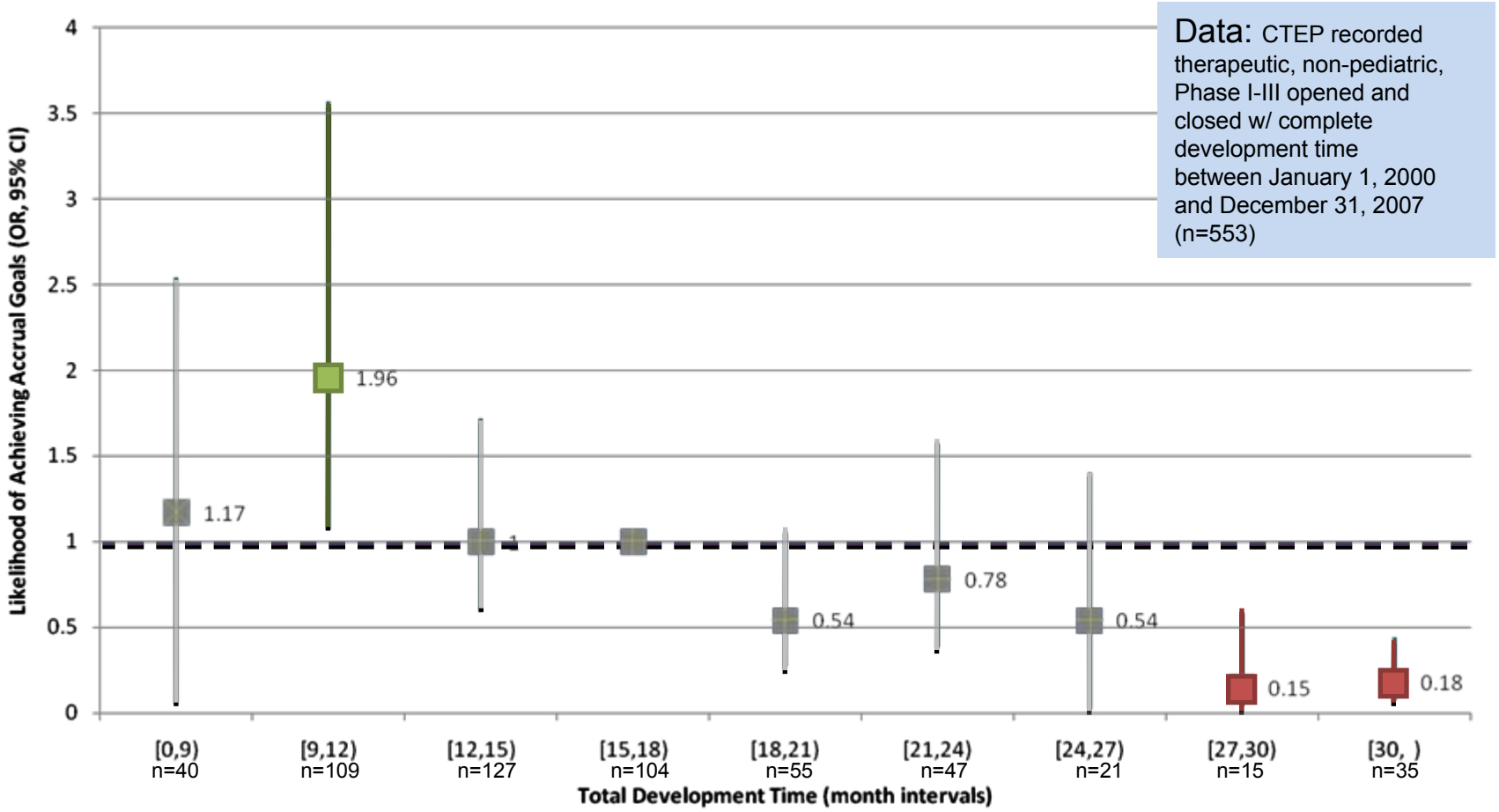
Percent of Project Minimum Accrual Met		Type of Trial				
		Phase I (n=123)	Phase I/II (n=45)	Phase II (n=324)	Phase III (n=61)	Overall (n=553)
0%						
	No. (% by Type of Trial)	8 (6.5)	1 (2.2)	13 (4.0)	2 (3.3)	24 (4.3)
	Development Time, months (Median, IQR)	20.3 (16.4 - 34.4)	31.6 (N/A)	16.4 (12.0 - 22.7)	12.7 (11.3 - 14.1)	18.7 (12.5 - 26.9)
	Minimum Projected Accrual (Median, IQR)	14 (12 - 25)	90 (N/A)	20 (12 - 34)	396 (292 - 500)	20 (12 - 33)
	Subjects Accrued	0	0	0	0	0
	Total Proposed	132	90	331	792	1,345
.1% - 24.9%						
	No. (%)	7 (5.7)	7 (15.6)	20 (6.2)	28 (45.9)	62 (11.2)
	Development Time, months (Median, IQR)	17.9 (12.1 - 41.3)	13.9 (12.7 - 16.4)	19.4 (14.4 - 24.7)	19.4 (15.8 - 31.0)	18.5 (14.1 - 29.2)
	Minimum Projected Accrual (Median, IQR)	18 (12 - 40)	22 (20 - 66)	26 (16 -43)	545 (371 - 1,013)	67 (22 - 480)
	Subjects Accrued	15	28	82	1,546	1,671
	Total Proposed	167	243	634	26,147	27,191
25% - 49.9%						
	No. (%)	3 (2.4)	3 (6.7)	24 (7.4)	4 (6.6)	34 (6.1)
	Development Time, months (Median, IQR)	16.0 (14.9 - 20.7)	14.6 (14.1 - 19.1)	16.8 (14.1 - 21.0)	22.8 (17.3 - 48.7)	16.8 (14.6 - 20.9)
	Minimum Projected Accrual (Median, IQR)	25 (19 - 42)	12 (8 - 18)	33 (21 - 48)	779 (406 - 1,196)	33 (20 - 50)
	Subjects Accrued	26	14	342	1,241	1,623
	Total Proposed	86	38	894	3,175	4,193
50% - 74.9%						
	No. (%)	13 (10.6)	8 (17.8)	33 (10.2)	4 (6.6)	58 (10.5)
	Development Time, months (Median, IQR)	14.3 (11.9 - 17.9)	18.1 (13.5 - 22.2)	17.1 (12.5 - 22.6)	19.7 (12.9 - 24.2)	17.1 (12.6 - 21.7)
	Minimum Projected Accrual (Median, IQR)	25 (6 - 33)	30 (19 - 45)	36 (24 - 42)	586 (278 - 2,460)	34 (21 - 44)
	Subjects Accrued	207	201	877	2,540	3,825
	Total Proposed	324	313	1,403	4,432	6,472
75% - 99.9%						
	No. (%)	15 (12.2)	3 (6.7)	24 (7.4)	1 (1.6)	43 (7.8)
	Development Time, months (Median, IQR)	16.8 (11.5 - 24.2)	16.8 (12.0 - 20.0)	13.9 (11.7 - 19.9)	36.6 (N/A)	15.6 (11.9 - 22.6)
	Minimum Projected Accrual (Median, IQR)	18 (12 - 25)	25 (24 - 36)	30 (20 - 58)	450 (N/A)	25 (18 - 37)
	Subjects Accrued	266	74	815	449	1,604
	Total Proposed	320	85	941	450	1,796
≥100.0%						
	No. (%)	77 (62.6)	23 (51.1)	210 (64.8)	22 (36.1)	332 (60.0)
	Development Time, months (Median, IQR)	13.7 (10.6 - 17.9)	13.5 (10.4 - 19.3)	13.6 (11.3 - 17.0)	17.4 (11.4 - 19.5)	13.8 (11.0 - 17.6)
	Minimum Projected Accrual (Median, IQR)	12 (6 - 21)	18 (9 - 30)	20 (16 - 32)	535 (346 - 1,138)	20 (14 - 35)
	Subjects Accrued	2,654	1,633	9,602	28,585	42,474
	Total Proposed	1,262	577	6,104	22,600	30,543
Total						
	No.	123	45	324	61	553
	Development Time, months (Median, IQR)	14.9 (11.0 - 19.6)	14.6 (11.5 - 18.7)	14.4 (11.6 - 19.0)	18.3 (14.2 - 26.0)*	15.0 (11.6 - 19.4)
	Minimum Projected Accrual (Median, IQR)	15 (9 -25)	21 (15 - 36)	22 (17-39)	500 (360 - 975)**	22 (15 - 42)
	Subjects Accrued	3,168	1,950	11,718	34,361	51,197
	Total Proposed	2,291	1,346	10,307	57,596	71,540

* Phase III > Phase I, I/II, II; P=.001,adjusted alpha <.008)
** Phase I <Phase I/II, II, III; P<.001, adjusted alpha <.008)
Phase III> Phase I,I/II,III; P<.001, adjusted alpha <.008)

All therapeutic, non-pediatric, Phase I, I/II, II, and III oncology trials evaluated by CTEP that with submitted protocol opened to patient accrual, and subsequently closed to accruals between January 1, 2000 and December 31, 2007 in the United States. Starting date is initial LOI/concept receipt to CTEP, end date is trial open for accrual.

cMRHc

Development Time and the Likelihood of Achieving Accrual Goal at Study Closure



Data: CTEP recorded therapeutic, non-pediatric, Phase I-III opened and closed w/ complete development time between January 1, 2000 and December 31, 2007 (n=553)

- Odds Ratios calculated using binary logistic regression adjusting for study size
- Dotted line indicates the referent as defined as the median development time of the sample
- Squares represent the odds ratio; vertical lines represent 95% CI

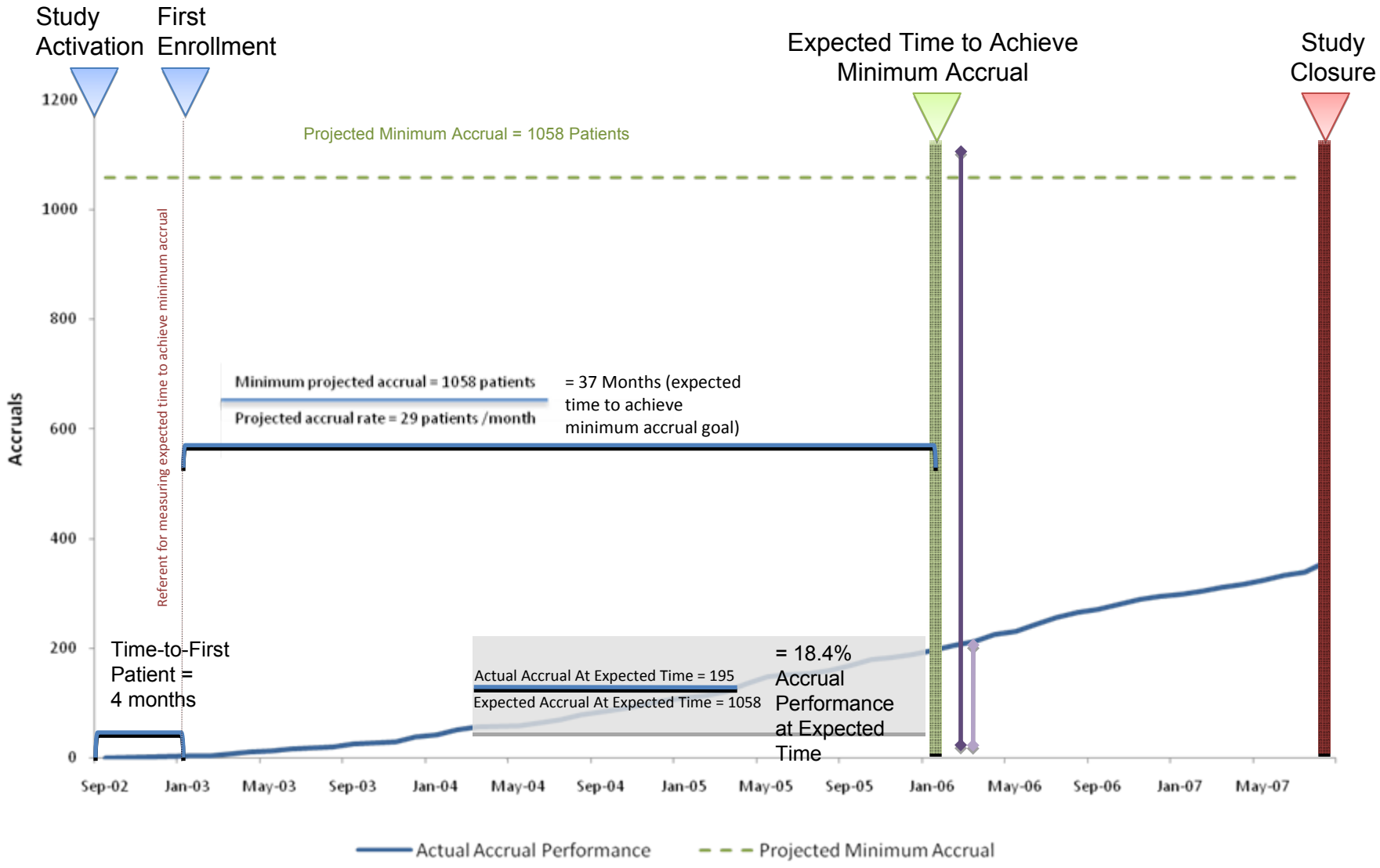
Source: Cheng, SK "The Impact of Delay", PhD Dissertation, Vanderbilt University, 2008

cMRHc

"A 'No' uttered from deepest conviction is better and greater than a 'Yes' merely uttered to please, or what is worse, to avoid trouble."

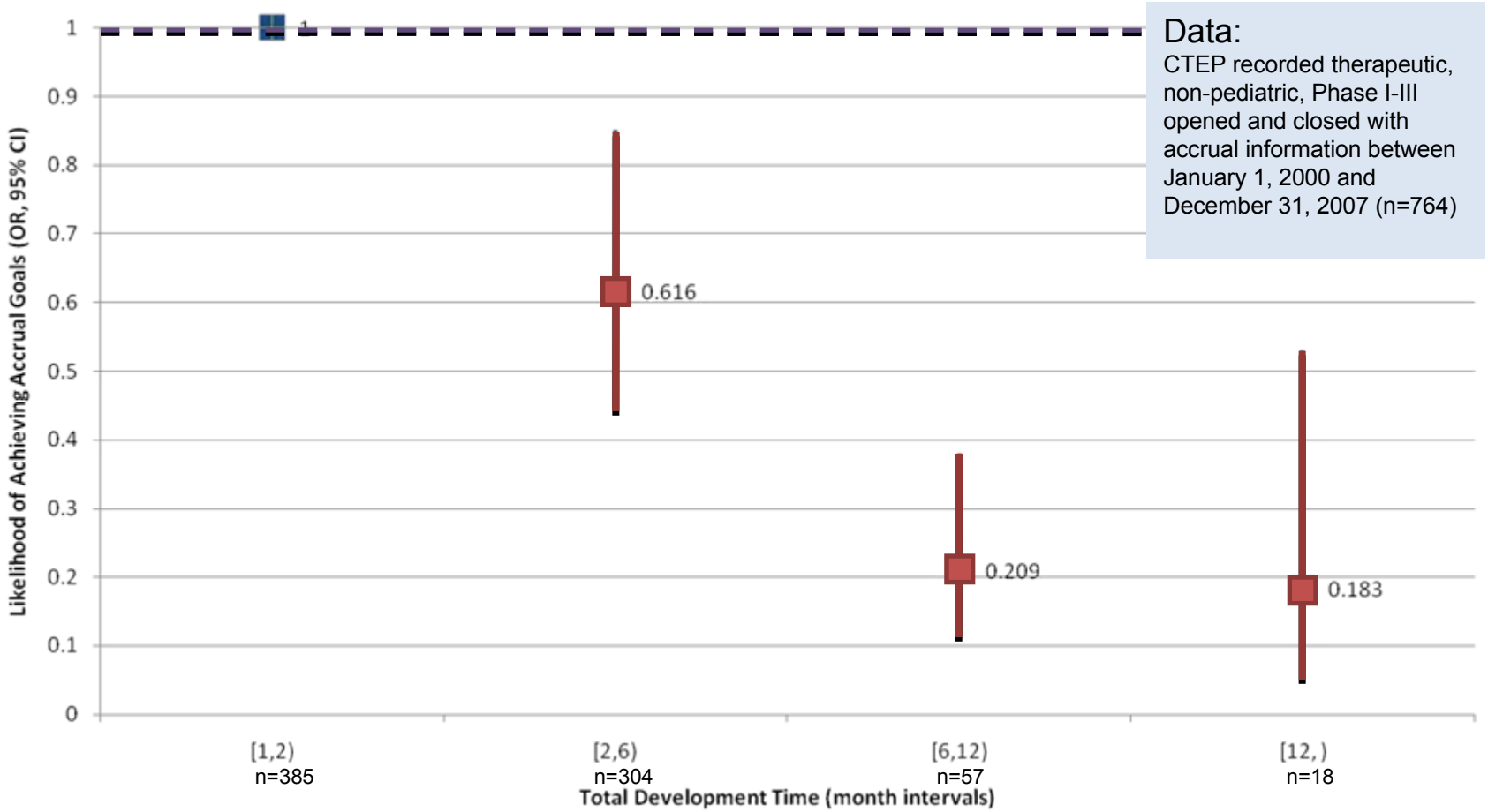
--- Mahatma Gandhi

Example: Phase III Cooperative Study



Source: Cheng, SK "The Impact of Delay", PhD Dissertation, Vanderbilt University, 2008

Impact of Time-to-First Patient on Accrual Success

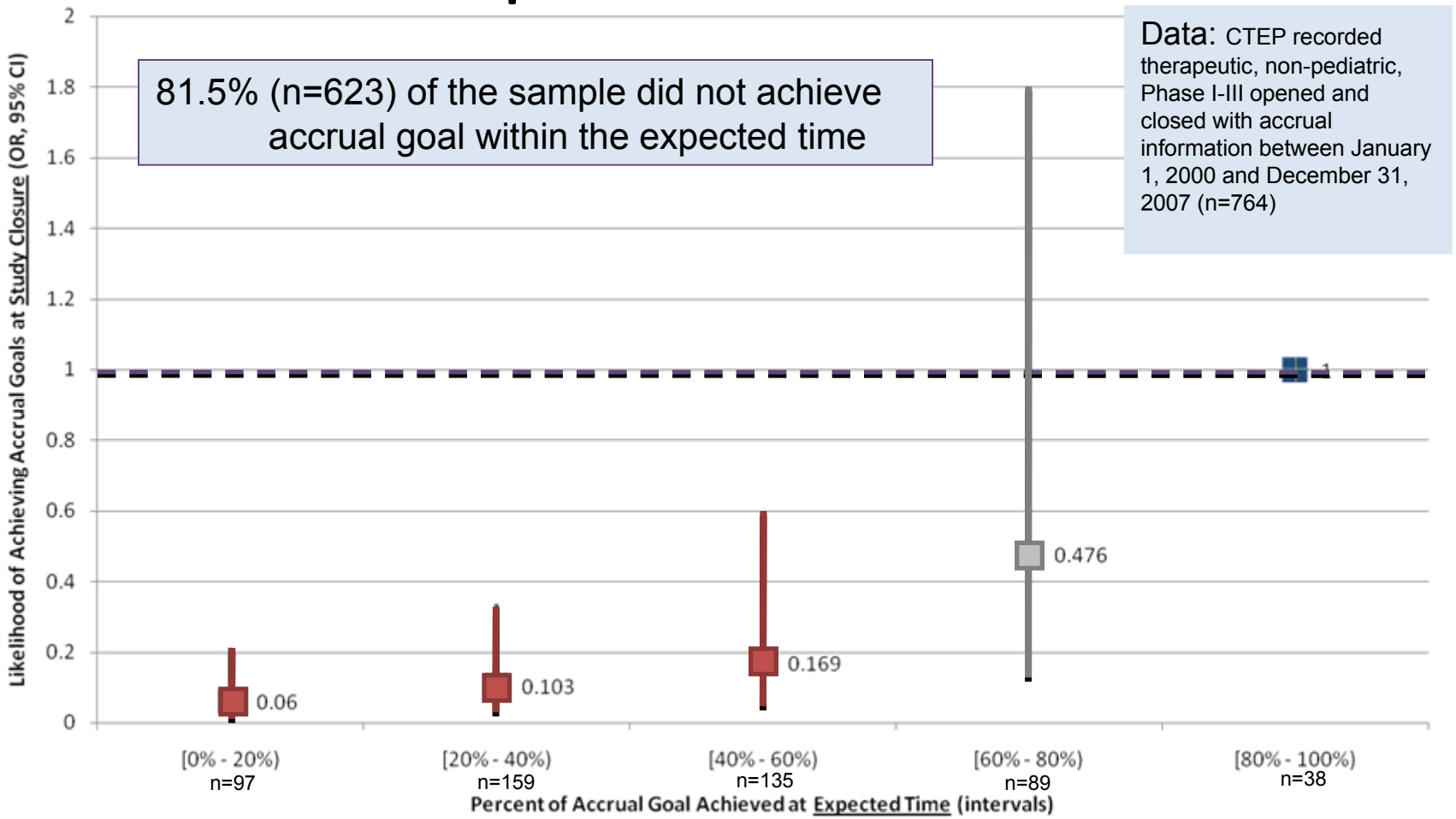


Data:
CTEP recorded therapeutic, non-pediatric, Phase I-III opened and closed with accrual information between January 1, 2000 and December 31, 2007 (n=764)

- Odds Ratios calculated from binary logistic regression adjusting for study size, phase, cancer incidence rate, and cancer mortality rate
- Dotted line indicates the referent as defined as by trials that enroll the first patient within 2 months
- Squares represent the odds ratio; vertical lines represent 95% CI

Source: Cheng, SK "The Impact of Delay", PhD Dissertation, Vanderbilt University, 2008

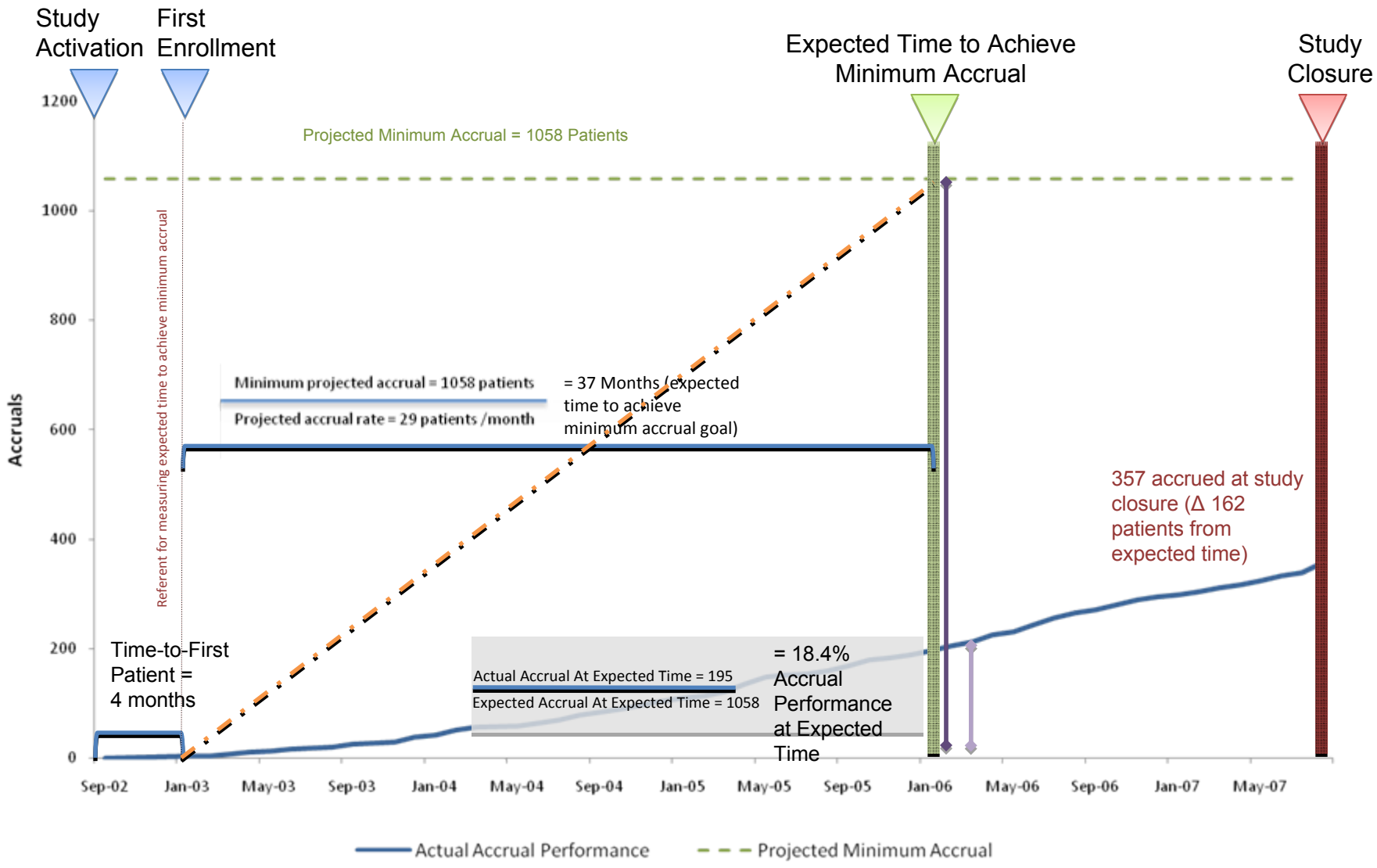
Actual Accrual Performance at Expected Time



- Odds Ratios calculated from binary logistic regression adjusting for study size, phase, cancer incidence rate, and cancer mortality rate
- Dotted line indicates the referent as defined as by trials that enroll the first patient within 2 months
- Squares represent the odds ratio; vertical lines represent 95% CI
- Sample size includes studies that have not achieve minimum accrual goals at expected time

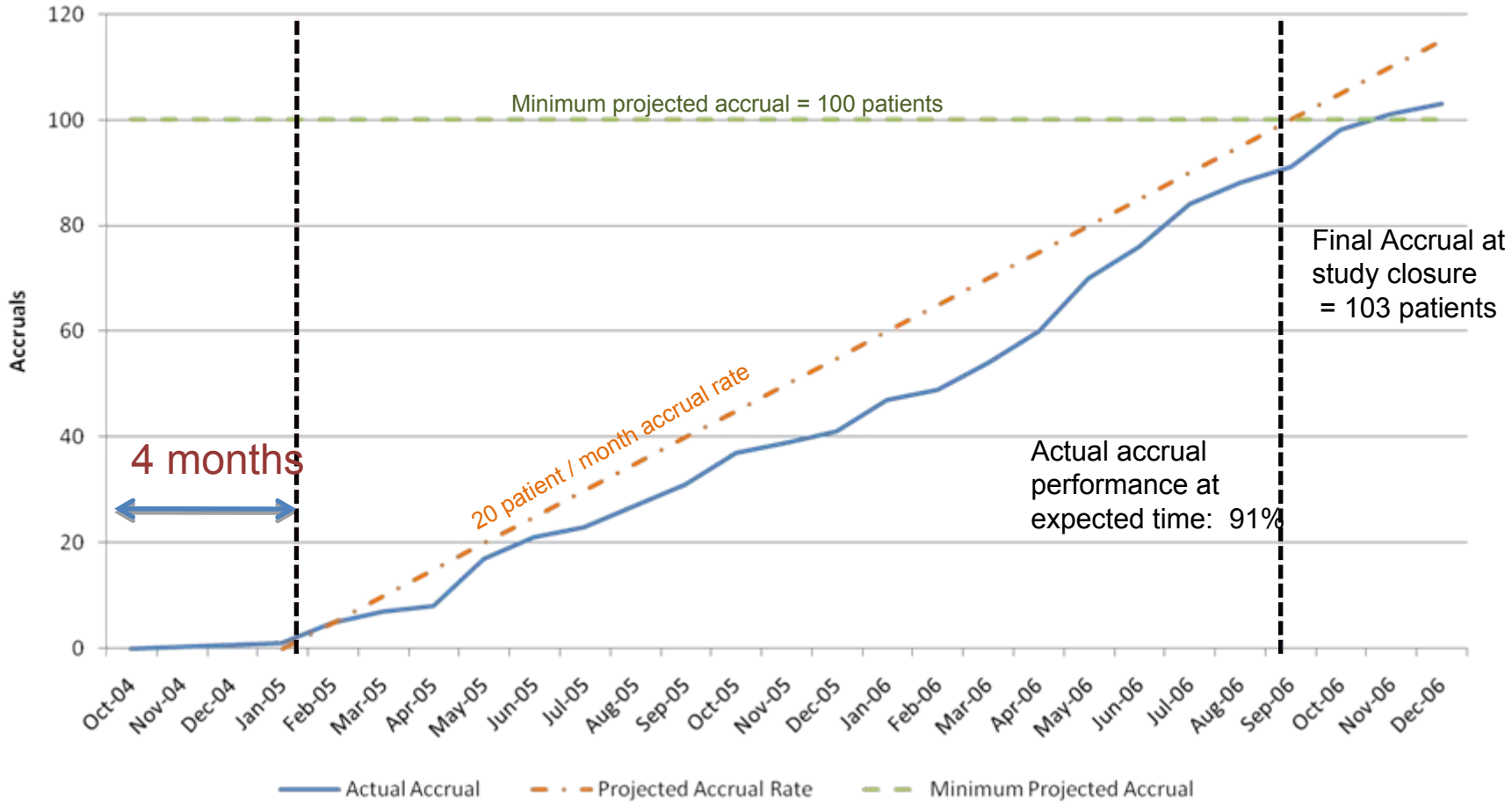
Source: Cheng, SK "The Impact of Delay", PhD Dissertation, Vanderbilt University, 2008

Example: Phase III Cooperative Study



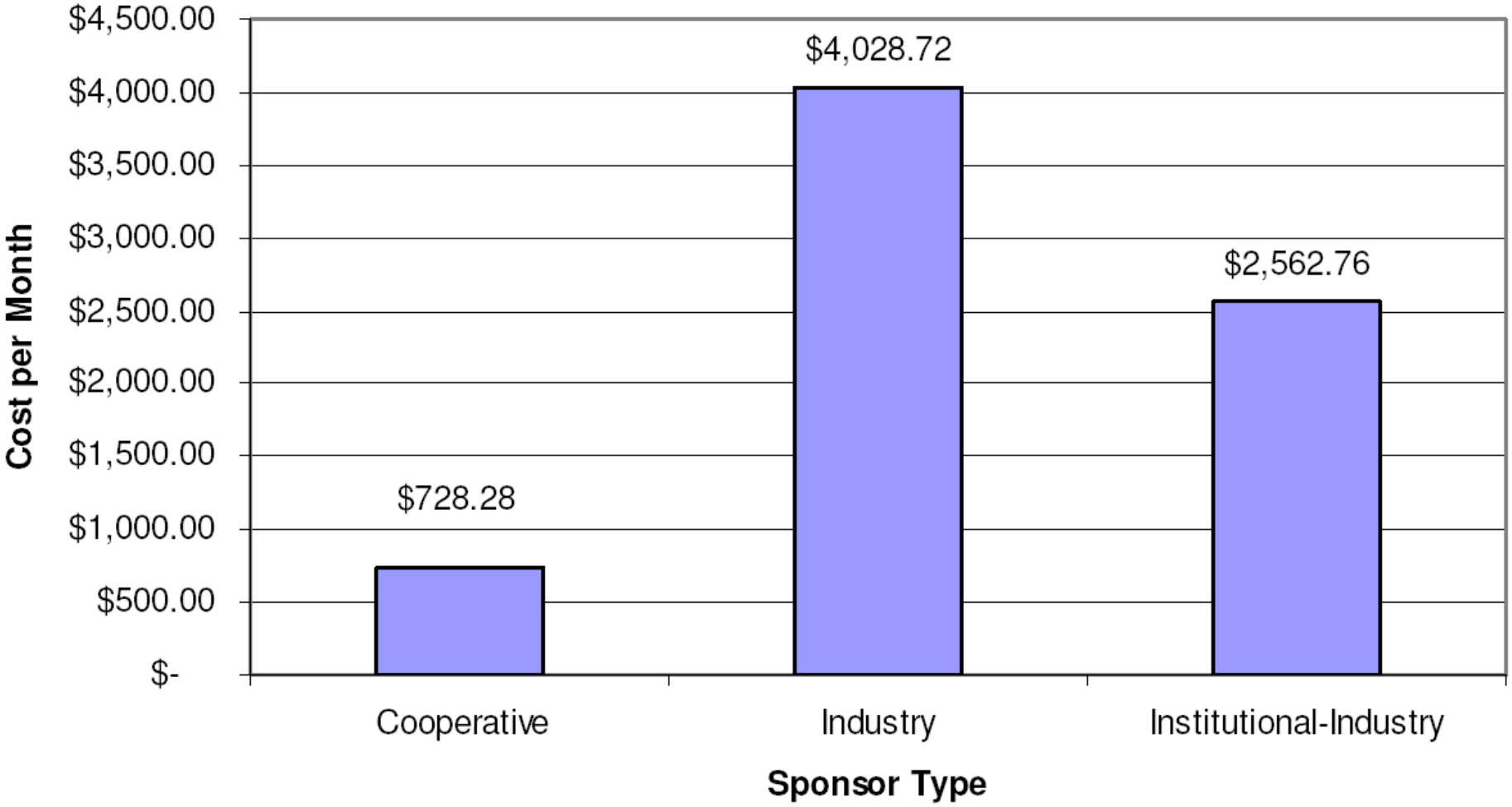
Source: Cheng, SK "The Impact of Delay", PhD Dissertation, Vanderbilt University, 2008

Example: Phase II Cooperative Study



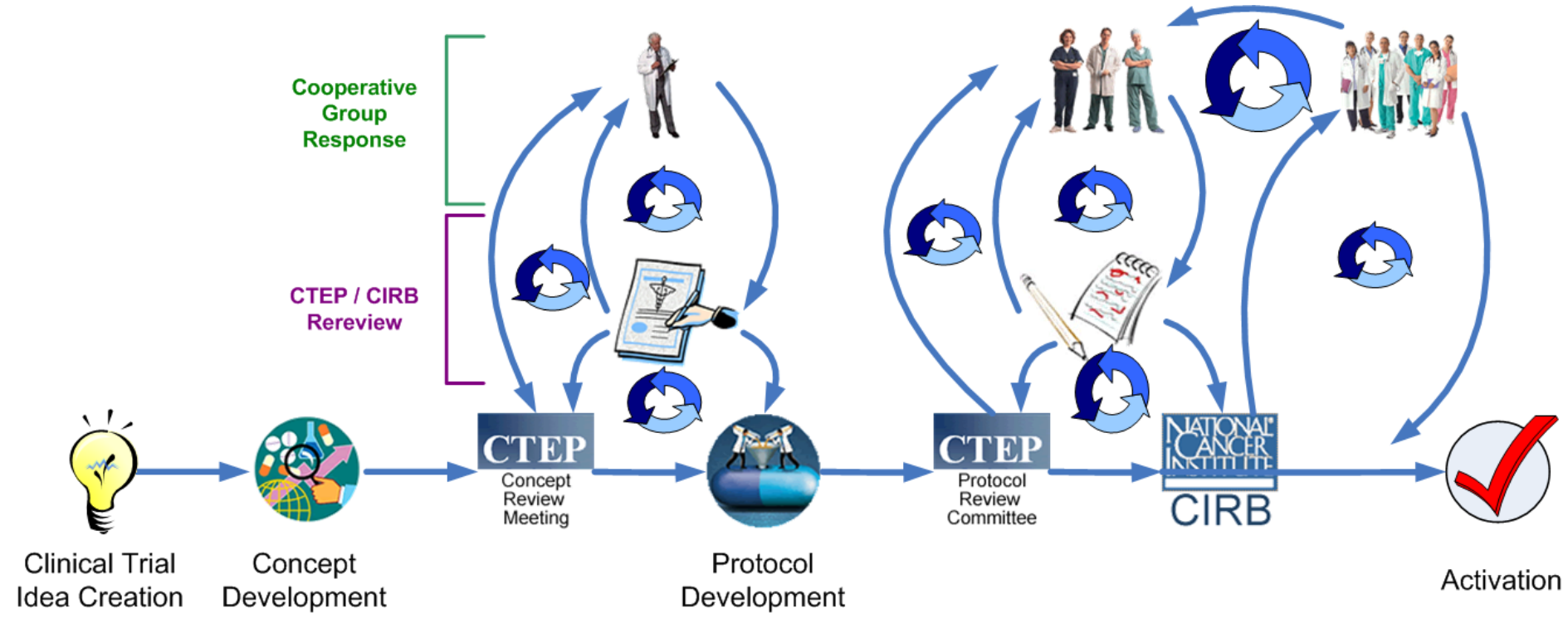
Source: Cheng, SK "The Impact of Delay", PhD Dissertation, Vanderbilt University, 2008

For Low Accruing (0-2) Studies
Average Cost per Active Year

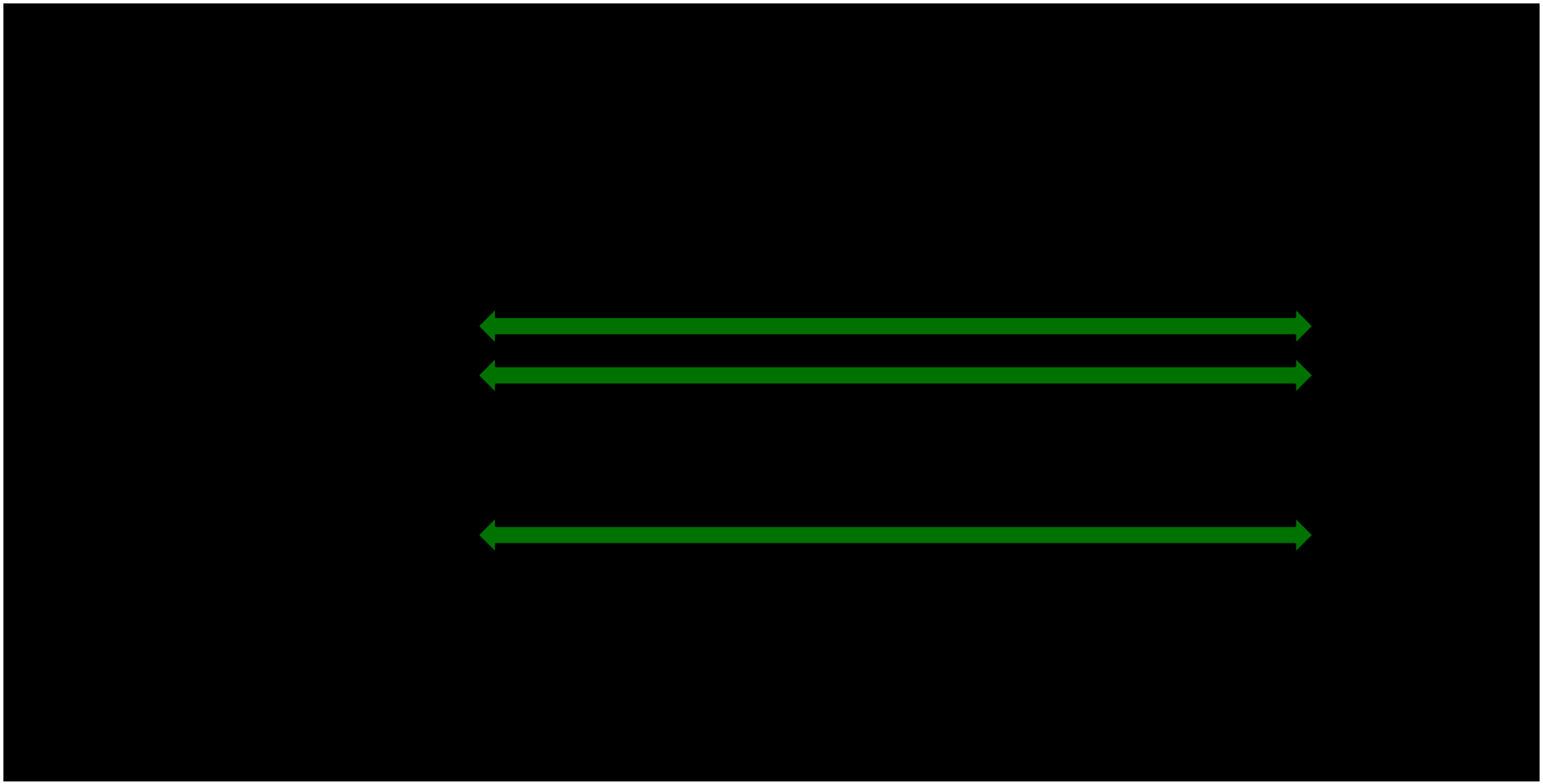


Source: UMCCC Clinical Trials Office

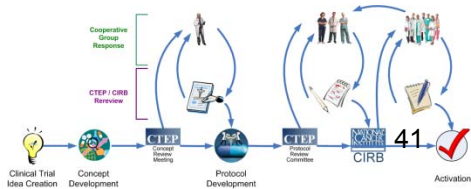
High Level Process Flow for Phase III Studies



Simulation Results of Working Together



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



On-Going Manuscript Progress

- **Opening an Oncology Phase III Clinical Trial**: *a process of chutes and ladders*
- **Unethical delay:** *The Ethical Ramifications of Delay in Clinical Trial Opening*
- **Oncology Clinical Trials at Four Major Comprehensive Cancer Centers**: *time to open and accrual comparison*

"An analysis of executive contributions comes up with an embarrassing richness of important tasks; any analysis of executives' time discloses an embarrassing scarcity of time available for work that really contributes."

--Peter Drucker *"The Effective Executive"*, p. 100

"Unless a decision has 'degenerated into work' it is not a decision; it is at best a good intention."

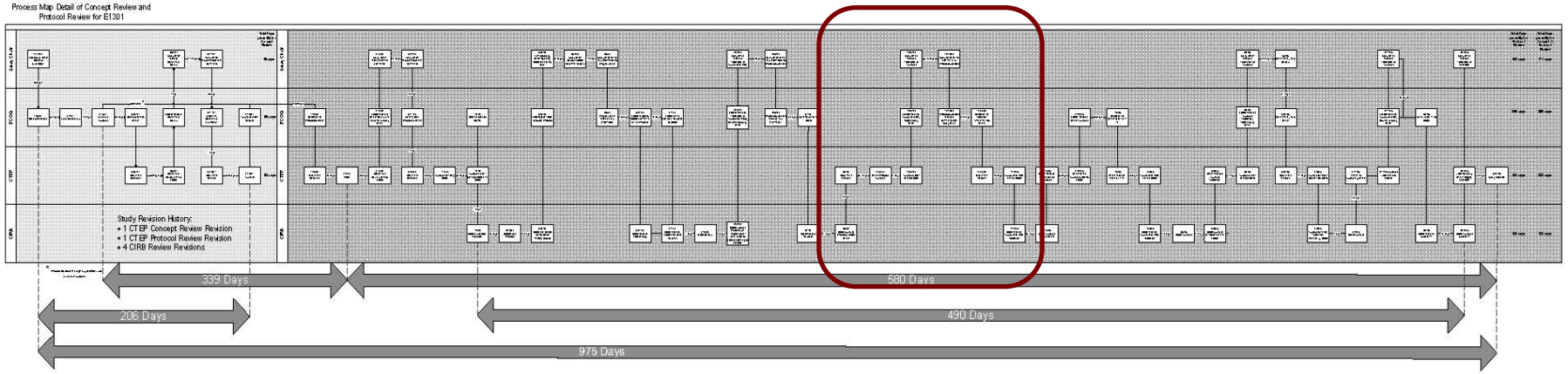
-- Peter Drucker *"The Effective Executive"*, p. 114

cMRHc

Thank you

www.cMRHc.org

Example Of The Flow: *E1301*



	Concept Review Days	Protocol Review Days	Total Days
Study Chair	49	122	171
Co-Operative Group	59	340	399
CTEP	98	184	282
CIRB	n/a	123	123
Total	206	769	975

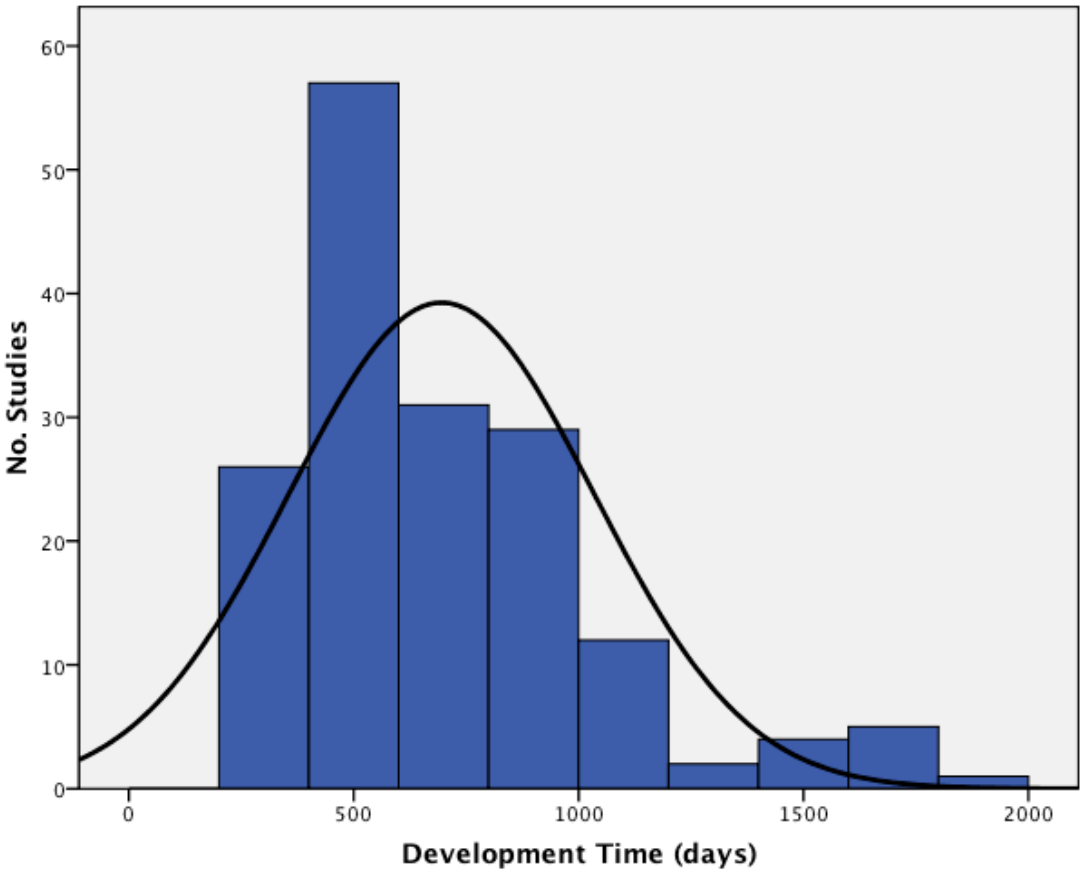


Figure 3: Number of CTEP-sponsored phase III Therapeutic Oncology Clinical Trials activated from January 2000 to December 2007 organized by Development Time. Development time is calculated from the initial receipt of the concept by CTEP to the time the trial is activated by the CTCG.

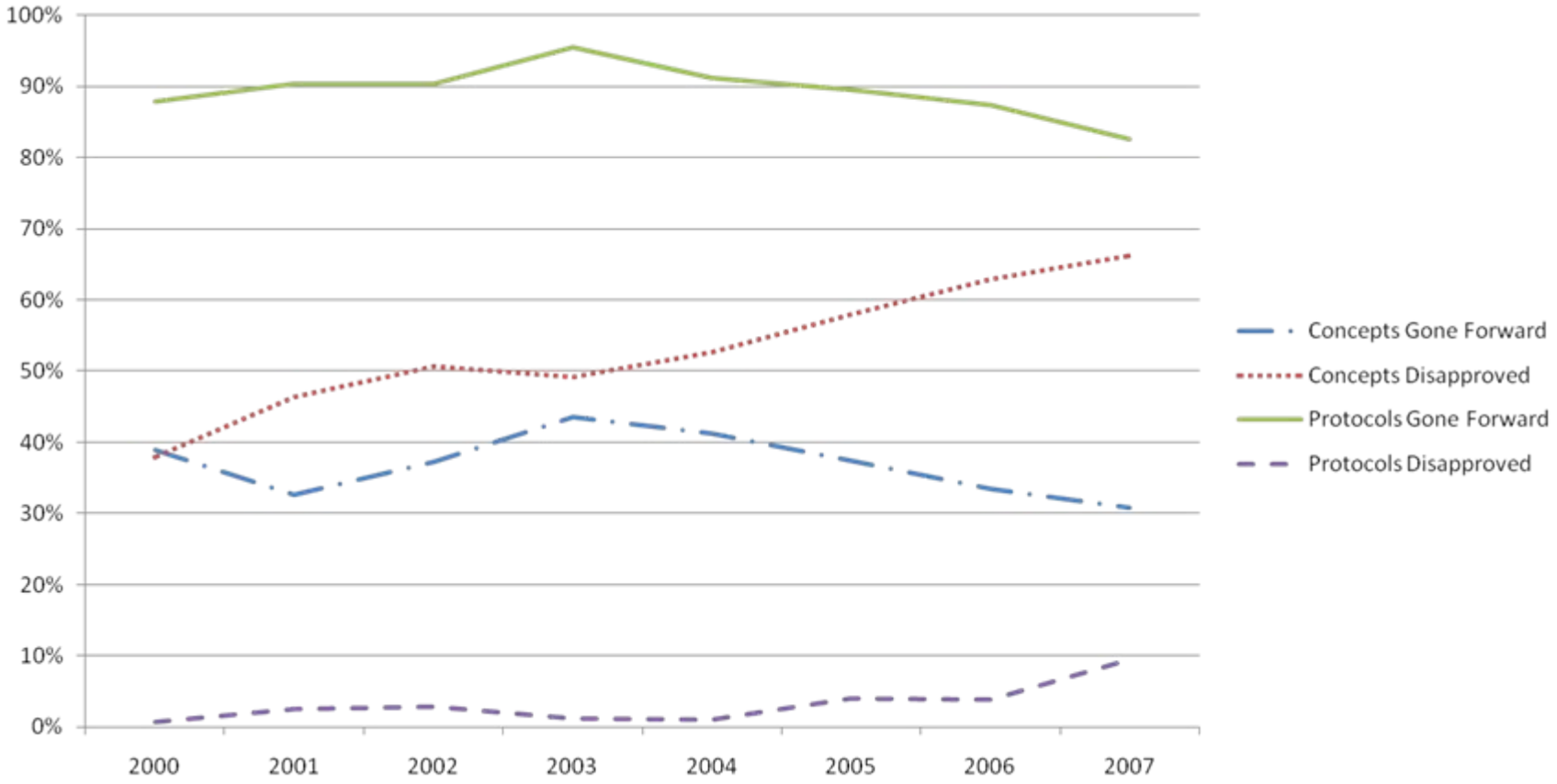
Concept and Protocol Acceptance Success Rates by Phase

	Phase	I	I/II	II	III	Other	Pilot	Total
Concepts	*n*	*1421*	*490*	*2649*	*513*	*25*	*52*	*5150*
	Gone Forward	33.4%	29.8%	35.3%	55.0%	28.0%	48.1%	36.3%
	In Review	2.4%	3.5%	1.4%	1.9%	8.0%	3.8%	2.0%
	Withdrawn / Replaced	13.7%	6.3%	13.6%	21.2%	24.0%	11.5%	13.7%
	Disapproved	50.5%	60.4%	49.6%	21.6%	40.0%	36.5%	47.9%
Protocols	*n*	*388*	*166*	*1,031*	*192*	*150*	*72*	*1,999*
	Gone Forward	88.9%	80.7%	86.9%	83.3%	74.7%	81.9%	85.3%
	In Review	4.6%	6.0%	4.3%	8.3%	8.7%	6.9%	5.3%
	Withdrawn / Replaced	5.9%	9.6%	6.8%	6.3%	10.0%	6.9%	7.1%
	Disapproved	0.5%	3.6%	2.0%	2.1%	6.7%	4.2%	2.3%

For all protocols received by CTEP, 1/2000 to 12/2007

cMRHc

Concept and Protocol Acceptance Success Rates by Year*



* Excludes concepts or protocols "in review"

• total n = 6,713

For all protocols received by CTEP, 1/2000 to 12/2007

Reviews Requiring Response

Calendar Days of Reviews and Group response by review type* for Phase III Cooperative Group Studies (n=28 studies) activated from 2000 - 2005

			Review Time			Group Response Time			Total Time		
	Reviewer	n	median	min	max	median	min	max	median	min	max
Concept											
CRM	CTEP	14	60.0	15	104	71.5	1	368	126	16	411
CEP	CTEP	4	48.0	19	66	35.5	22	84	83.5	41	150
Concept Re-review	CTEP	3	6.0	1	6	17.0	1	56	23	7	57
Industry **	Industry	14	32.5	1	168						
Protocol											
PRC	CTEP	33	32.0	5	69	32.0	1	188	63	8	230
Protocol Re-review	CTEP	22	7.5	1	84	8.5	1	266	17	2	315
CIRB											
CIRB	CIRB	43	29.0	5	55	21.0	2	83	51	10	112
Re-review after CIRB	CTEP	19	12.0	1	32	17.0	1	140	34	2	144
Amendment * **											
Protocol Re-Review	CTEP	2	9.0	1	17	5.5	5	6	14.5	6	23
CIRB	CIRB	10	12.0	2	34	29.5	3	67	40.5	11	101
Re-review after CIRB	CTEP	1	1.0	1	1	22.0	22	22	1	23	23

* Reviews listed are only are partial list of required reviews. Other reviews including RAB, PMB, and CTSU are required but were not available at the time of data collection.

** Group response time to industry cooperation not available

*** Recorded time for amendments only include study amendments prior to study activation

cMRHc

Significance of Cancer Incidence or Mortality Rate on Time-to-First Patient

Disease Site	Number of Trials	Incidences (per 100,000)	Mortality (per 100,000 cases)	Time to First Patient, months	IQR	Min - Max
Gastrointestinal (including colon and pancreas)	119	84.4	43.5	2	1 - 4	1 - 12
Lung, Mediastinal and Pleural	86	63.9	54.1	3	2 - 4	1 - 8
Miscellaneous Neoplasm	75	19.7	13.4	2	1 - 4	1 - 19
Leukemia	64	12.3	7.4	2	2 - 2	1 - 13
Breast	58	126.1	25	2	1 - 3.25	1 - 22
Female Reproductive	57	47.3	15.9	3	1 - 4	1 - 16
Skin	46	21.1	3.5	2	1 -3	1 - 10
Lymphoma	44	22.2	7.8	4	2.25 - 5.75	1 - 18
Central Nervous System	41	6.5	4.4	3	1.5 - 4	1 - 14
Male Reproductive (including prostate)	36	168.4	27	3.5	1.25 - 6	1 - 16
Kidney	36	13.2	4.2	2	1 - 3	1 -22
Head and Neck	35	14	3.9	3	2 - 5	1 - 14
Urothelial Tract	18	21.2	4.3	4	2 - 5.25	1 - 11
Soft Tissue	17	3.1	1.3	3	2 - 5.5	1 - 12
Myeloma	13	5.6	3.7	3	1.5 - 3.5	1 - 7
Endocrine	7	9.8	0.8	2	1 - 2	1 - 2
AIDS-related	5	1.2	n/a	5	1 - 10.5	1 - 12
Immune Disorder	2	0.7	0.8	4.5	4 - 5	4 - 5
Germ Cell	2	0.4	0.2	1.5	1 -2	1 - 2
Hematopoietic (excluding Leukemia, lymphoma, and myeloma)	1	0.5	0.4	2	n/a	n/a
Bone	2	0.9	0.9	2.5	2 -3	2 - 3

Cancer Incidence Rate vs. Time-to-First Patient: Mann-Whitney, p=0.749

Cancer Mortality Rate vs. Time-to-First Patient: Mann-Whitney, p=0.152

◆ Cancer Incidence and Cancer Mortality Rate Statistics gathered from the Surveillance Epidemiology and End Result (SEER) program (1975 – 2005) based on 2007 Data Submission, posted to the web 2008

Source: Cheng, SK "The Impact of Delay", PhD Dissertation, Vanderbilt University, 200

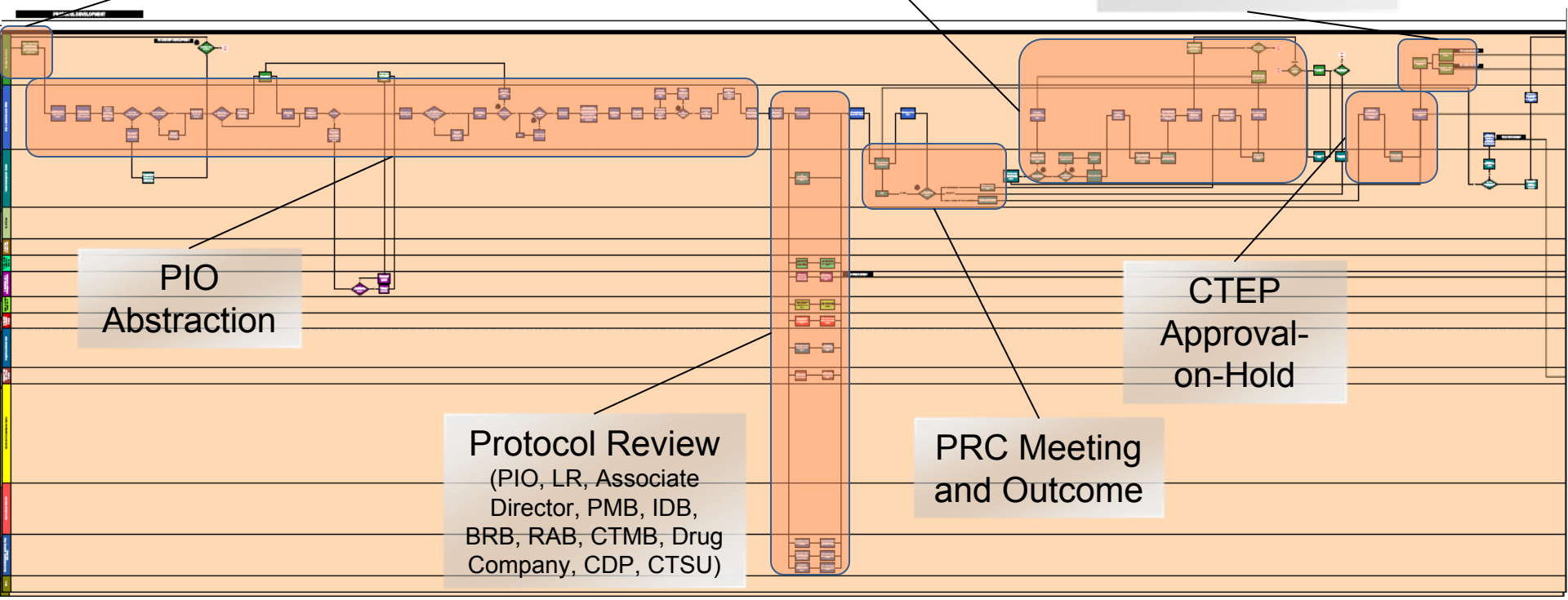
Percent of Goal Achieved by Phase for CTEP Reviewed Studies*

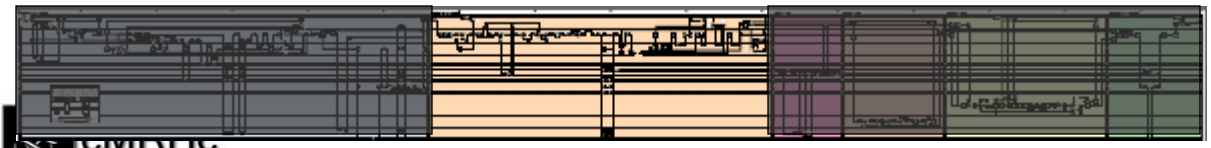
Phase	I	I/II	II	III	Other	Pilot	Total
n	*194*	*79*	*573*	*69*	*36*	*30*	*981*
Of Maximum Goal							
Zero	6%	8%	4%	6%	28%	10%	6%
.1% to 25%	16%	28%	14%	41%	28%	10%	18%
26 to 50%	18%	16%	19%	9%	11%	7%	17%
51 to 75%	21%	11%	20%	7%	3%	10%	18%
76 to 100%	20%	19%	13%	6%	6%	17%	14%
>100%	20%	18%	29%	32%	25%	47%	27%
% achieving >75%	***40%***	***37%***	***42%***	***38%***	***31%***	***64%***	***41%***
Of Minimum Goal							
zero	6%	8%	4%	6%	28%	10%	6%
.1% to 25%	6%	15%	8%	39%	19%	7%	11%
26 to 50%	10%	6%	9%	7%	14%	3%	9%
51 to 75%	10%	11%	8%	7%	3%	7%	8%
76 to 100%	10%	8%	12%	1%	6%	13%	10%
>100%	58%	52%	59%	39%	31%	60%	56%
% achieving >75%	***68%***	***60%***	***71%***	***40%***	***37%***	***73%***	***66%***

cMRHc

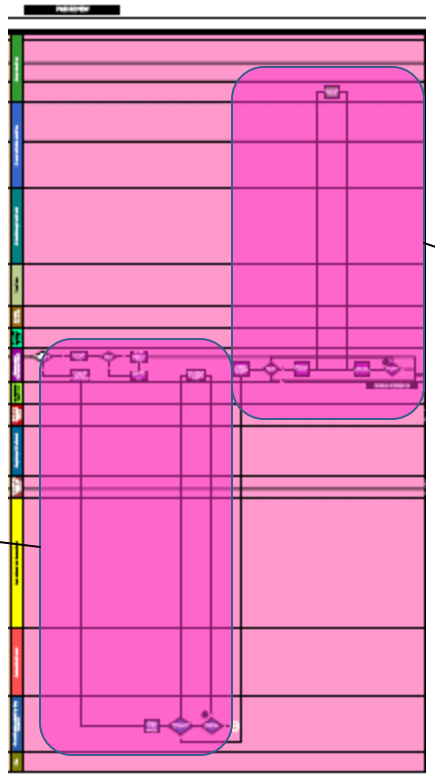
* Excludes active studies

Protocol Development and Review





PMB Review

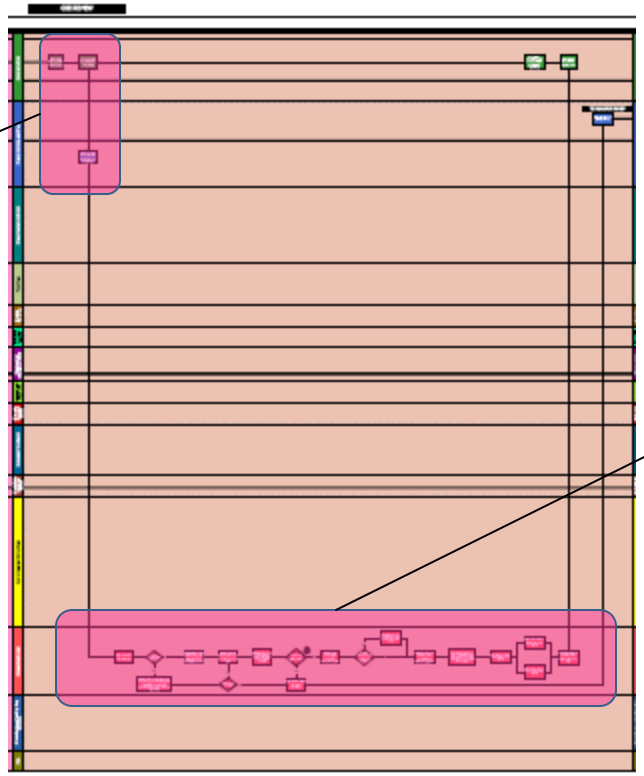


PMB and Group set up database

Drug Company Negotiations for new drug

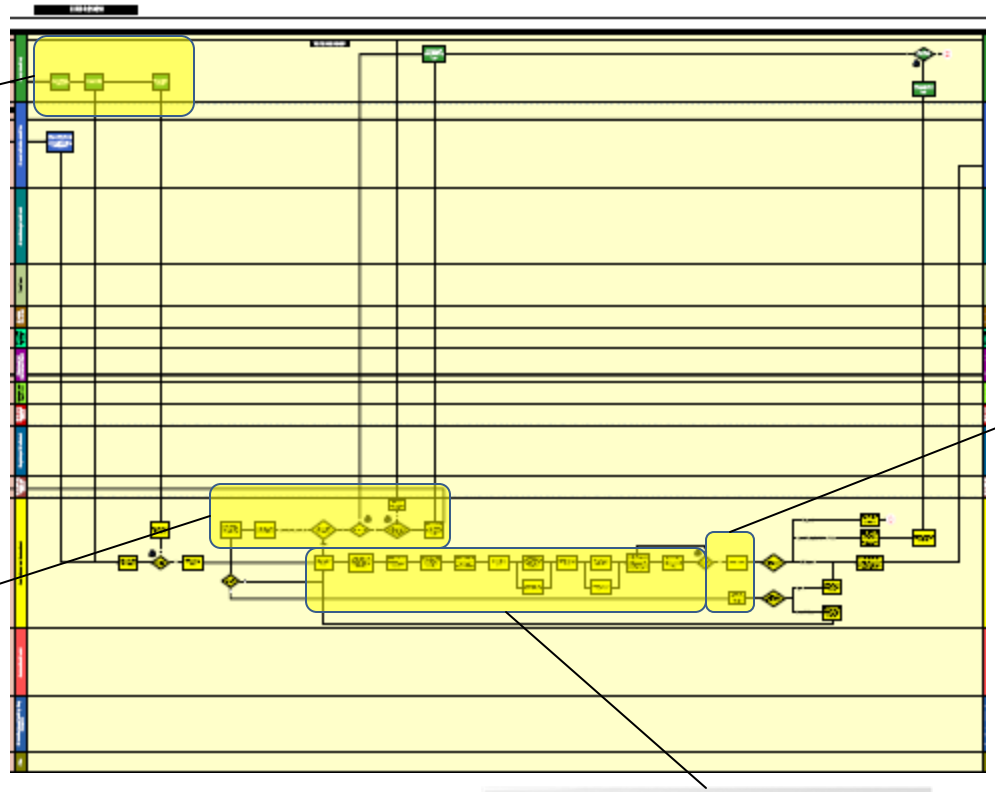
CDE Review

CRF Completion and Submission



CDE Compliance Review

CIRB Review



CIRB Application Completion and Submission

CIRB Board Meeting

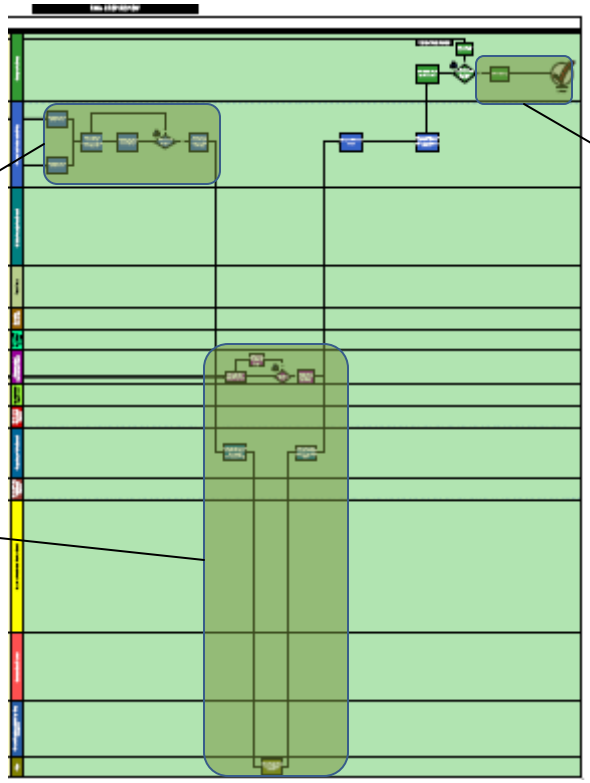
CIRB receives Revised Protocol

CIRB Board Meeting Preparation

Final CTEP Review

PIO Compiles Final Approval Packet

PMB and RAB receive Final Approval Packet

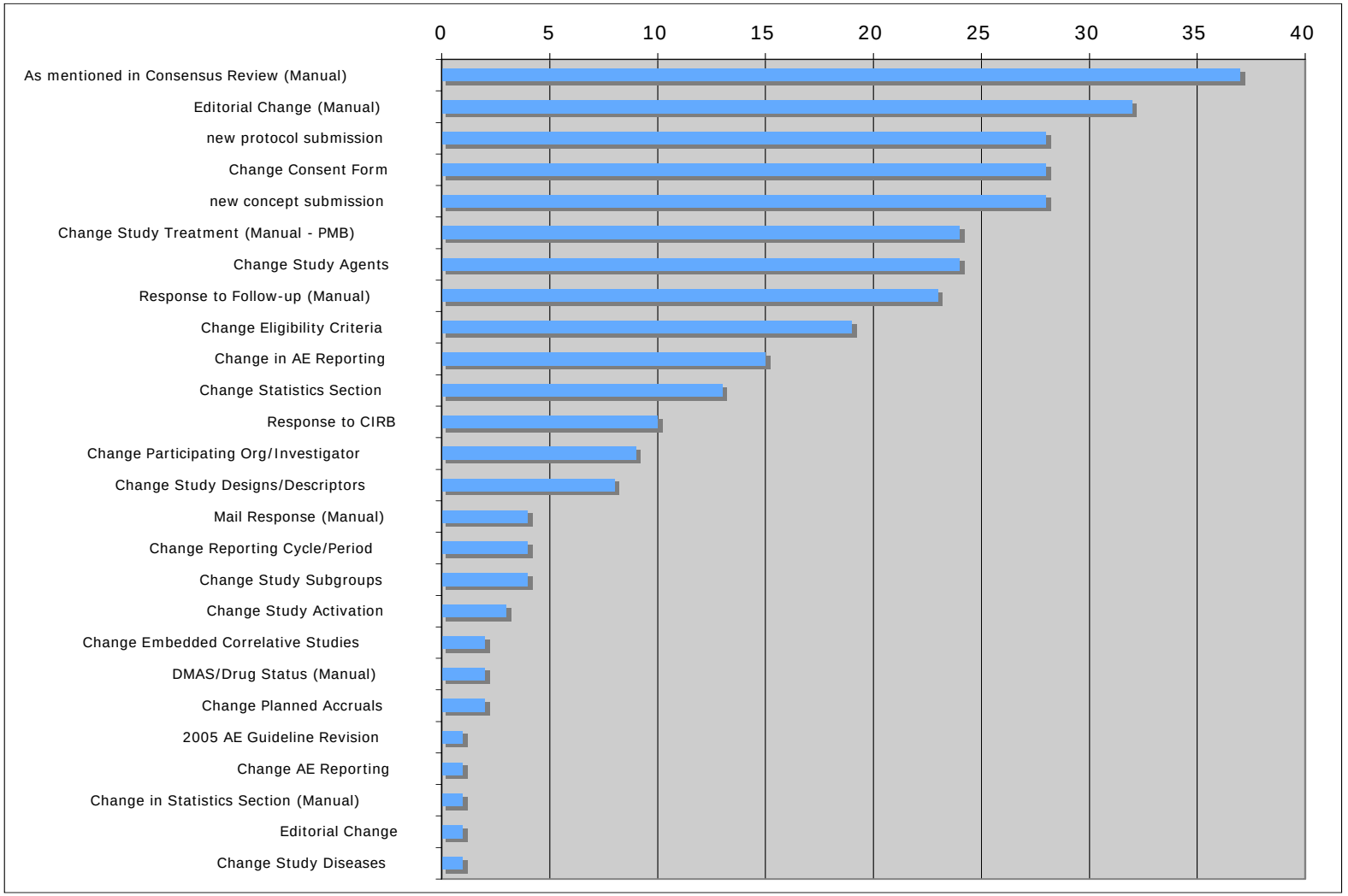


Study Activated

Top 5 reasons for Document Changes

	Concept		Protocol		Amendment	
	Reason	Percentage	Reason	Percentage	Reason	Percentage
1	New Concept Submissions	65%	New Protocol Submission	13%	Editorial Change	16%
2	Consensus Review	30%	Consensus Review	12%	Change in Study Agents	14%
3	Follow-up Response	5%	Change Consent Form	11%	Change Study Treatment	12%
4			Follow-up Response	10%	Change Eligibility Criteria	12%
5			Editorial Change	10%	Change in Consent Form	8%

Frequency of Reasons for Document Versions

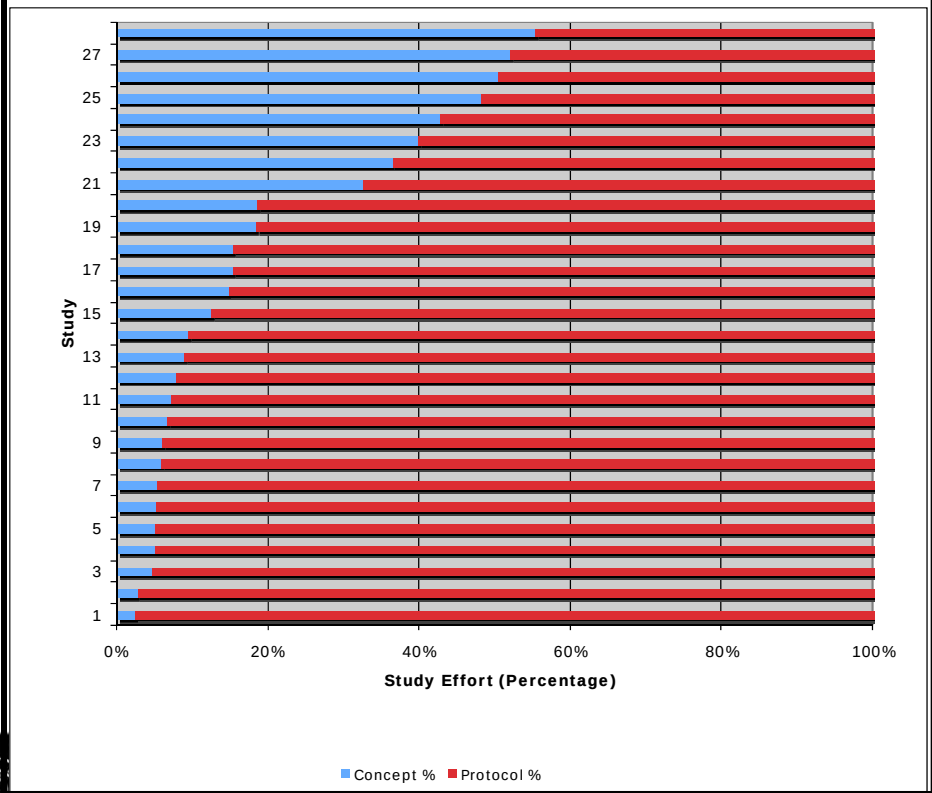


Reasons listed for document version change from Concept, Protocol, and Amendments* (n= 324 reasons for changes to document versions in 186 document versions) for Phase III Cooperative Group Studies activated between 2000 - 2005

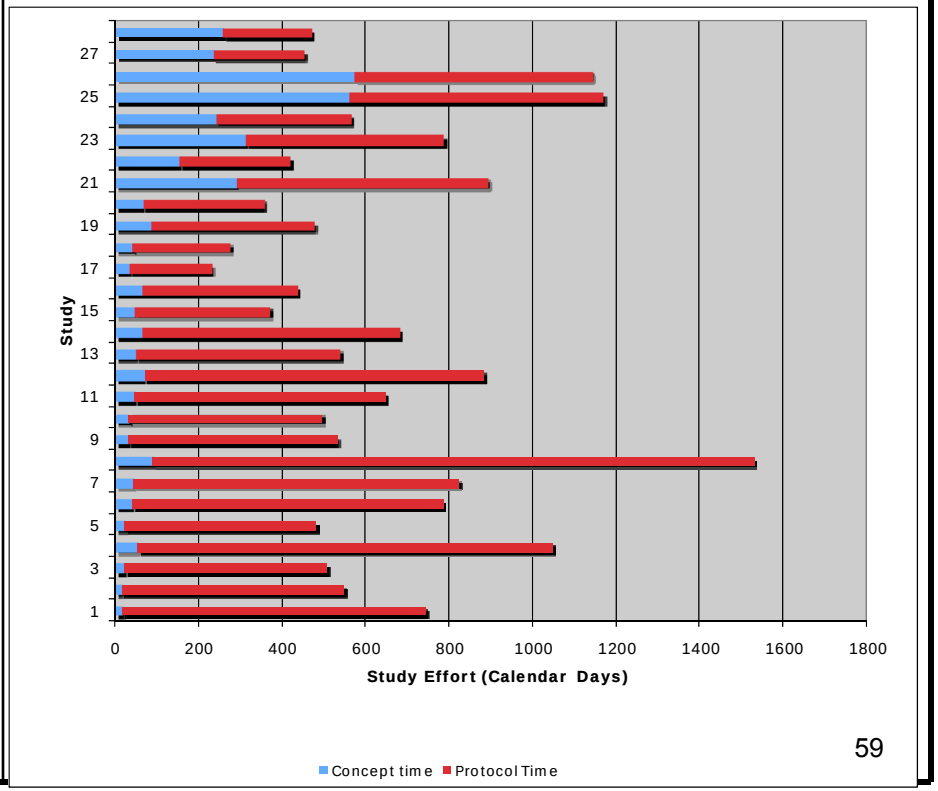
Concept vs. Protocol Development Effort

Phase III Cooperative Group Study Effort (n=28) ordered by concept development time represented by percentage and days of total CTEP development time

By Percentage



By Calendar Days



Number of Reviews per Study

Number of reviews per study by review type for Phase III Cooperative Group (n=28 studies) activated from 2000 - 2005*

				Occurance per study		
		Reviewer	n *studies*	median *reviews*	min *reviews*	max *reviews*
Concept	CRM	CTEP	27	1	1	3
	CEP	CTEP	2	2	1	3
	Routing (CRM)	CTEP	8	1	1	2
	Industry	Industry	11	1	1	2
Protocol	PRC	CTEP	28	1	1	3
	Routing (PRC)	CTEP	25	2	1	5
CIRB	CIRB	CIRB	26	2	2	6
	Routing (CIRB)	CTEP	22	1	1	5
Amendment	Routing (PRC)	CTEP	9	1	1	3
	CIRB	CIRB	9	1	1	3
	Routing (CIRB)	CTEP	2	1	1	1

- Reviews per study were counted from the Concept Complete Sheets, Protocol Complete Sheets, and CIRB data

** Reviews for amendments are only counted for those amendments initiated prior to activations

***Reviews listed are only are partial list of required reviews. Other reviews including RAB, PMB, and CTSU are required but were not available at the time of data collection.

Reviews Per Study

Number of reviews per study by development stage for Phase III Cooperative Group (n=28 studies) activated from 2000 – 2005*

		Reviews per Study		
	n *studies*	median *reviews*	min *reviews*	max *reviews*
Concept	28	2	1	6
Protocol	28	9	5	20
Amendment **	4	5	2	6
Total	28	12	6	26

* Reviews per study were counted from the Concept Complete Sheets, Protocol Complete Sheets, and CIRB data

** Reviews for amendments are only counted for those amendments initiated prior to activations

Number of Document Versions (pre-activation)

	Concept *		Protocol **		Amendments ***		Total	
n	28		28		9		28	
	Number of Versions	Time to Complete (Calendar Days)	Number of Versions	Time to Complete (Calendar Days)	Number of Versions	Time to Complete (Calendar Days)	Number of Versions	Time to Complete (Calendar Days)
median	1	194.5	3	216	1	88	6	481.5
min	1	83	2	14	1	26	3	204
max	3	637	10	758	3	324	13	1395

* concept days = date of first concept submission to date of 1st protocol submission

** protocol days = date of first protocol submission to date of last protocol submission

*** amendment days = date of last protocol submission to date of last amendment (if any)

CTEP_doc_versions_rational_rev2.xls::Pivot - doc versions

Initial Recommendations

- Immediate (Quick-Fix)
- Mid-range
- Long term

Initial Quick-Fix Recommendations

- Immediately start collecting & analyzing data
- "Just Say No"
  - Eliminate "entitlement culture"
- Stop tweaking
  - "Two strikes and you're out"
- Say what you mean & mean what you say

Initial Medium Term Recommendations

- Triage concepts using scientific merit and operational complexity
- Eliminate redundant, non-value added steps in the entire process
  - Cooperative Groups, CTEP, CIRB, & Comprehensive Cancer Centers
- Benchmark other NIH Institutes & Pharmaceutical firms
- Create processes that build quality in “automatically”

Triaging Concepts:

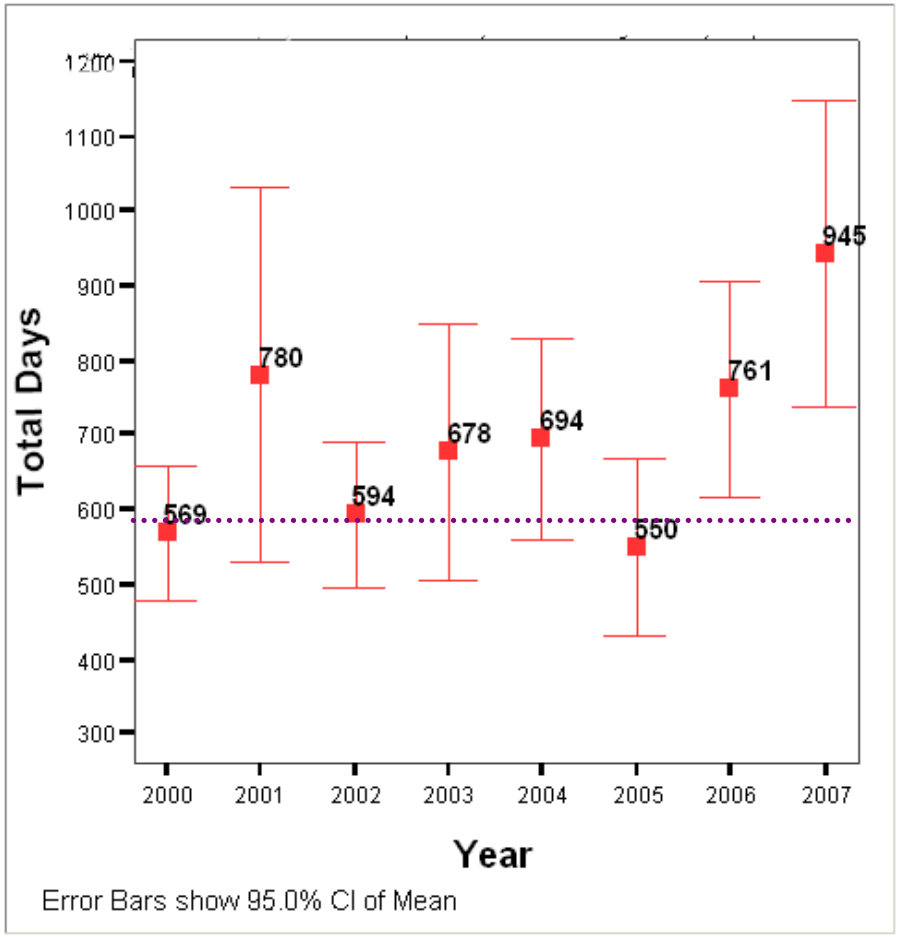
One Technique for Determine Entrance

Scientific Merit \ Operational Complexity	High	Low
High		
Low		***FILL***

66

Time From Concept Receipt to Activation

Phase III Therapeutic Studies activated Through CTEP 1/2000 – 6/2007†
by Activation Year



Year	Number	Median Days**	Min Days	Max Days
2000	29	542	203	1114
2001	15	563	312	1706
2002	19	528	370	1110
2003	23	539	321	1908
2004	24	655	229	1423
2005	18	496	264	1142
2006	22	678	329	1655
2007*	15	866	519	1776
Total/ Overall	165	594	203	1908

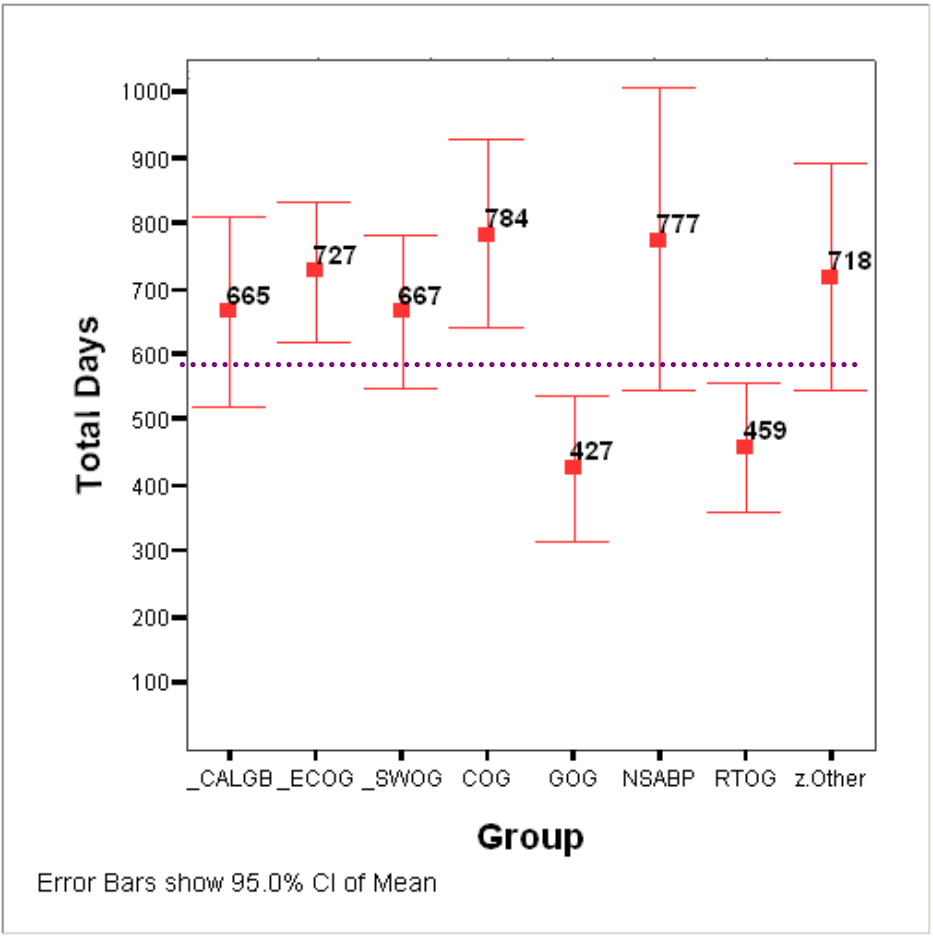
† these dates do not include the days for concept development & approval at the cooperative group
*** Concept approval time represented 8% to 39% of the days, depending upon Group*

cMRHc

Time From Concept Receipt to Activation

Phase III Therapeutic Studies activated Through CTEP 1/2000 – 6/2007†

by Co-Operative Group



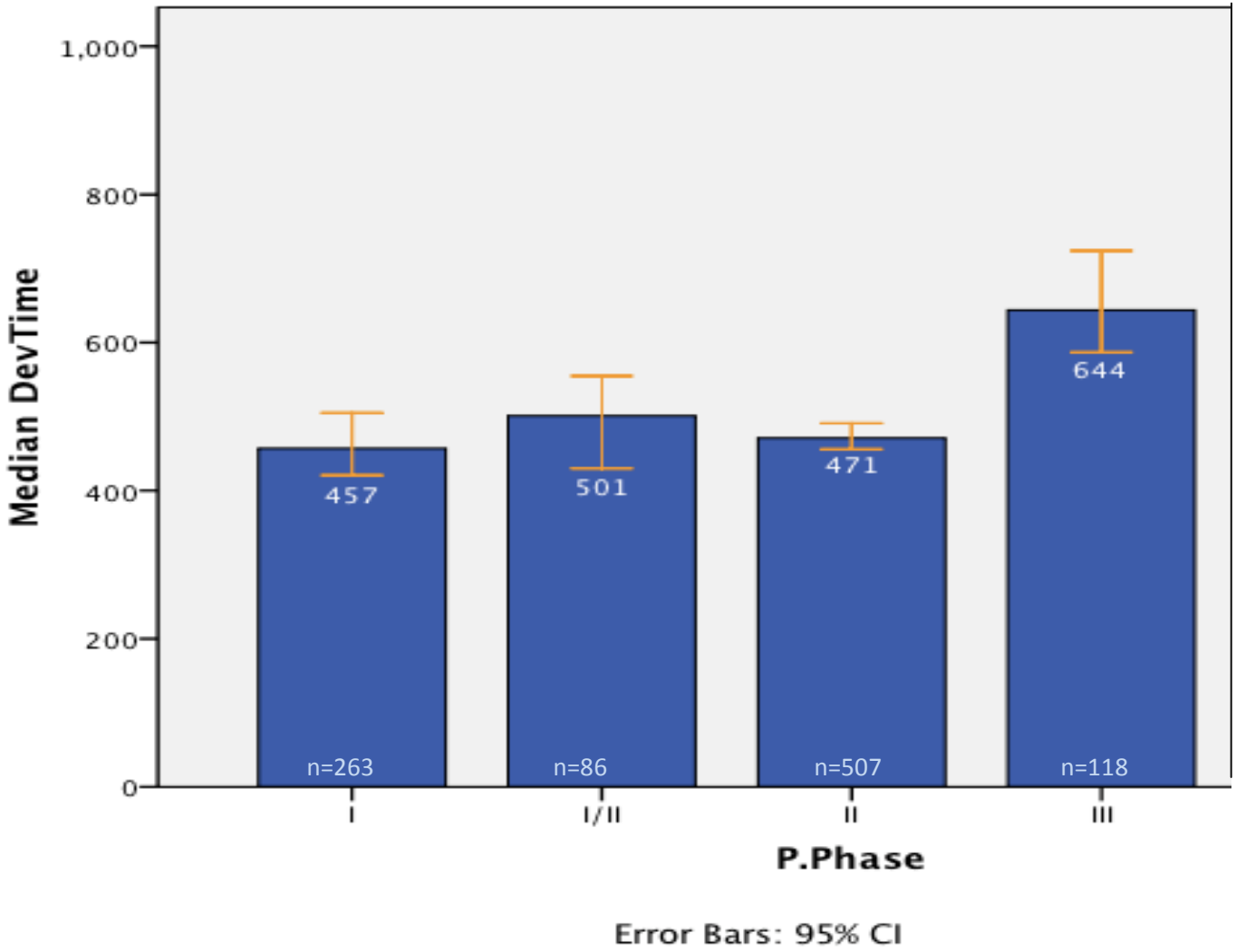
Group	Number	Median Days**	Min Days	Max Days
CALGB	21	532	229	1526
ECOG	27	635	274	1532
SWOG	27	597	342	1706
COG	34	719	203	1908
GOG	9	402	298	665
NSABP	13	691	317	1655
RTOG	16	432	264	989
Other*	18	583	372	1697
Total/ Overall	165	594	203	1908

*Other: ACOSOG, IBCSG, NCCTG, NCIC, NCIMB, TX035

† these dates do not include the days for concept development & approval at the cooperative group

*** Concept approval time represented 8% to 39% of the days, depending upon Group*

Median Development Time*: CTEP sponsored studies activated from 2000 -2007



* From Concept Receipt to Study Activation

Development Time and the Likelihood of Achieving Accrual Goal at Study Closure

Development Time Intervals (months)	Unadjusted Analysis		Adjusted Analysis Controlling for Projected Minimum Accrual		Adjusted Analysis Controlling for Phase of Trial	
	Odds Ratio (95% CI)	*P Value*	Odds Ratio (95% CI)	*P Value*	Odds Ratio (95% CI)	*P Value*
[0,9)	1.20 (0.55 - 2.59)	0.650	1.17 (0.54 - 2.54)	0.686	1.13 (0.52 - 2.46)	0.758
[9,12)	1.94 (1.06 - 3.52)	0.010	1.96 (1.07 - 3.57)	0.029	1.86 (1.02 - 3.40)	0.044
[12,15)	1.01 (0.59 - 1.74)	0.960	1.00 (0.59 -1.72)	0.987	0.97 (0.56 - 1.67)	0.906
[15,18) (referent)	1.0		1.0		1.0	
[18,21)	0.52 (0.27 - 1.00)	0.051	0.54 (0.27 - 1.05)	0.068	0.55 (0.28 - 1.07)	0.078
[21,24)	0.78 (0.39 - 1.57)	0.482	0.78 (0.38 - 1.57)	0.478	0.75 (0.37 - 1.53)	0.435
[24,27)	0.52 (0.20 - 1.35)	0.179	0.54 (0.21 - 1.40)	0.205	0.53 (0.20 - 1.37)	0.191
[27,30)	0.14 (0.04 - 0.54)	0.004	0.15 (0.04 - 0.58)	0.006	0.16 (0.04 - 0.59)	0.006
[30,)	0.17 (0.07 - 0.41)	<0.001	0.18 (0.07 - 0.44)	<0.001	0.19 (0.08 - 0.46)	<0.001

* Referent indicates the median development time of all clinical trials in the sample

Data: CTEP recorded therapeutic, non-pediatric, Phase I-III opened and closed w/ complete development time between January 1, 2000 and December 31, 2007 (n=553)

- Odds Ratios calculated using binary logistic regression adjusting for study size, and type of trial (phase)

cMRHc

Source: Cheng, SK "The Impact of Delay", PhD Dissertation, Vanderbilt University, 2008