ENGELBERG CENTER for
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at BROOKINGS

FRIENDS of CANCER RESEARCH

Conference on Clinical Cancer Research

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SUSAN G. KOMEN FOR THE CURE

September 14, 2009 • Washington, DC

Panel 1: Data Submission Standards

Richard L. Schilsky, M.D.
Professor of Medicine
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Past President, American Society of Clinical Oncology

Panel Members

- Richard L. Schilsky, M.D. (Chair)

  University of Chicago
- Gwen Fyfe, MD

  Consultant
- Jeffrey Abrams, MD

  National Cancer Institute
- Robert Erwin

  Marti Nelson Cancer Foundation
- Robert Temple, MD

  Food and Drug Administration

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  - Allen Melemed, MD
  - Jackie Gough
  - Jonathan Denne, PhD
- Friends of Cancer Research
  - Jeff Allen, PhD
  - Rasika Kalamegham, PhD
- Genentech
  - Lee Kaiser, PhD
  - Chin-Yu Lin, PhD
  - Carol Brannan
- GlaxoSmithKline
  - Will Bushnell
  - Alaknanda Preston
  - Melissa Stutts
  - Susan Bertino
- Novartis
  - Hilary Chaudri-Ross
  - Lynne McGrath, MPH, PhD
  - Antonella Maniero
  - David Carr

History

- **NCPF Meeting** (July '08) - Panel discussed discordance between data collection standards in NCI Cooperative Group and industry-sponsored clinical trials.
- **Brookings Conference on Clinical Cancer Research** (Sept. '08) - Panel discussed data collection necessary to support claims of safety and effectiveness for NDAs (BLAs) and sNDAs (sBLAs).
- ASCO organized Data Optimization Project to address issues raised with focus on AE reporting.

Why is this important?

- Protect patient safety by improving the overall quality of data submitted in supplemental applications
- Increase efficiency—more drugs developed with similar resources
- Standard data sets permit more rapid initiation and completion of studies
- Reduce data collection burden on clinical trials system - align resources to focus on key data elements
- Enhance physician participation in clinical trials
- Reverse the trend to study new agents in the ROW and increase access to clinical trials for U.S. patients

Conclusions of Brookings 2008

- The amount of data collected in Phase III trials for supplemental approvals is excessive
- Cooperative groups and industry should collect similar data to support a marketing application
- Random subsampling of Genentech clinical trials used to support sBLA applications suggested no valuable data would be lost
  - A critical area for study: toxicity data collection

Toxicity Data Re-Analysis

- ASCO formed the **Data Optimization Working Group** in October 2008:
  - as an outgrowth of the Brookings meeting to provide a forum for FDA, NCI, and industry to discuss data collection standards.
  - to re-analyze multiple clinical trial toxicity databases and examine various sampling methods to determine if 'optimal' data collection would provide sufficient safety data for supplemental applications.

FDA's Questions

- Based on prior experience with a drug, is there a more effective approach for data collection for supplemental indications?
- Considerations regarding re-analysis of data from oncology supplemental applications:
  - What safety signals would be missed if certain data (such as Grade 1/2 toxicities or a modified collection of con meds) were not collected in every patient?
  - Is there a way to improve collection of SAEs and dose modifications/discontinuations so that this information appears in the label in a useful and consistent manner?
  - What prior experience is required to implement an optimized data collection set (how much data, what types of applications, etc.)?
  - Other considerations for implementation of an optimized data set (similar population, same dose/schedule, etc.)?

Principles

- Safety data collection for new drug applications should remain comprehensive
- DO would apply only for agents with a well-defined safety profile that had received regulatory full approval
- Collect necessary safety data to inform regulatory review, labeling and clinical decisions:
  - Perform symmetric data collection across study arms
  - Detailed information on study deaths and SAEs
  - Information on AEs leading to discontinuation or dose modification
  - Targeted AEs and concomitant meds as needed based on a drug's known safety and pharmacologic profile

Principles (cont.)

- Data collection requirements for supplemental applications will vary based on:
  - safety database/known pharmacology and drug interactions
  - similarity of study population/intended use
  - similarity of regimen to that already approved

Project Logistics

- Assess the extent of safety data collection sufficient to inform regulatory and clinical decisions in a supplement.
- Assess concomitant medication data collection efforts
- Four companies and one cooperative group agreed to participate:
  - CALGB, GSK, Eli Lilly, Novartis and Genentech
- Statistical Analysis Plan for AE subsampling was developed, reviewed by FDA, used by all parties.

Project Logistics (cont.)

- Re-analyzed eight studies:
  - Metastatic and Adjuvant settings
  - Assessed what was learned in the analysis of Grade 3/4 AEs and Grade 1/2 AEs relative to
    - what was known from prior studies and
    - what was learned in the analysis of serious events in these candidate studies.
  - Evaluated potential subsampling methods
    - Random methods
    - Site selection
    - Recruitment order
- Discussed data results and implementation feasibility

Objectives of the Analysis

- What adverse events might be missed through subsampling?
- Is there a target subset size that appropriately minimizes the chance of missing an adverse event?
  - Does this target number of subsampled patients depend on the size of the candidate trial?
- Is there a subset size in which noise events are appropriately low?
- Is there a preferred method of subsampling patients?
- What is the extent of data collection and cleaning effort saved by subsampling?
- What concomitant medication data is collected and what is used in regulatory and clinical decisions?

Candidate Trials - Metastatic

Company	Candidate Study	Patient Population	Trial Size	Primary Endpoint	AE Characteristics			
					Gr 1/2 All Pts	Gr 3/4 All Pts	All SAEs: All Pts and All Study Arms	All Discon/ Dose Change r/t Inv Agent
Genentech	AVF2107g	1st Line mCRC	813	Overall Survival	N	Y	Y	Y
Genentech	ECOG 4599	1st Line non-squamous NSCLC	878	Overall Survival	N	Y	N	N
Genentech	AVAIL	1st Line non-squamous NSCLC	656	PFS	Y	Y	Y	Y
GSK	EGF 30001	Metastatic breast	580	TTP	Y	Y	Y	Y
Lilly	JMDB	1st Line NSCLC	1669	Overall Survival	Y	Y	Y	Y

Candidate Trials - Adjuvant

Company	Candidate Study	Patient Population	Trial Size	Primary Endpoint	AE Characteristics			
					Gr 1/2 All Pts	Gr 3/4 All Pts	All SAEs: All Pts and All Study Arms	All Discon/ Dose Change r/t Inv Agent
Novartis	BIG 1-98	PMP women with HR+ EBC	8028	DFS	N Gr 1/2 target AEs Y in DK	Y	Y	Y
CALGB	89803	Patients with resected adenocarcinoma of the colon	1264	Overall Survival	Y	Y	N	Y Discon N Dose Change
Genentech	HERA	HER2+ adj breast cancer	3386	DFS	Y	Y	Y	Y

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AE Analysis Plan and Results

Gwen Fyfe, MD
Consultant

Methodology

- Define the safety profile based on (1) previous knowledge (2) "Serious +" AEs (candidate trial)
- Determine what additional safety signals are discovered through the collection of Grade 3/4 events in all patients. These are the events that could be missed with subsampling
  - In many cases, there aren't any events to miss and/or knowledge of these events will not change medical practice with the drug
  - With subsampling simulations we assess whether we might miss one or more of these additional safety signals or we might identify events that we would not have identified with full Grade 3/4 collection (noise).
- Determine if site or patient recruitment order is a better systematic approach.

Specific Questions Addressed in the SAP

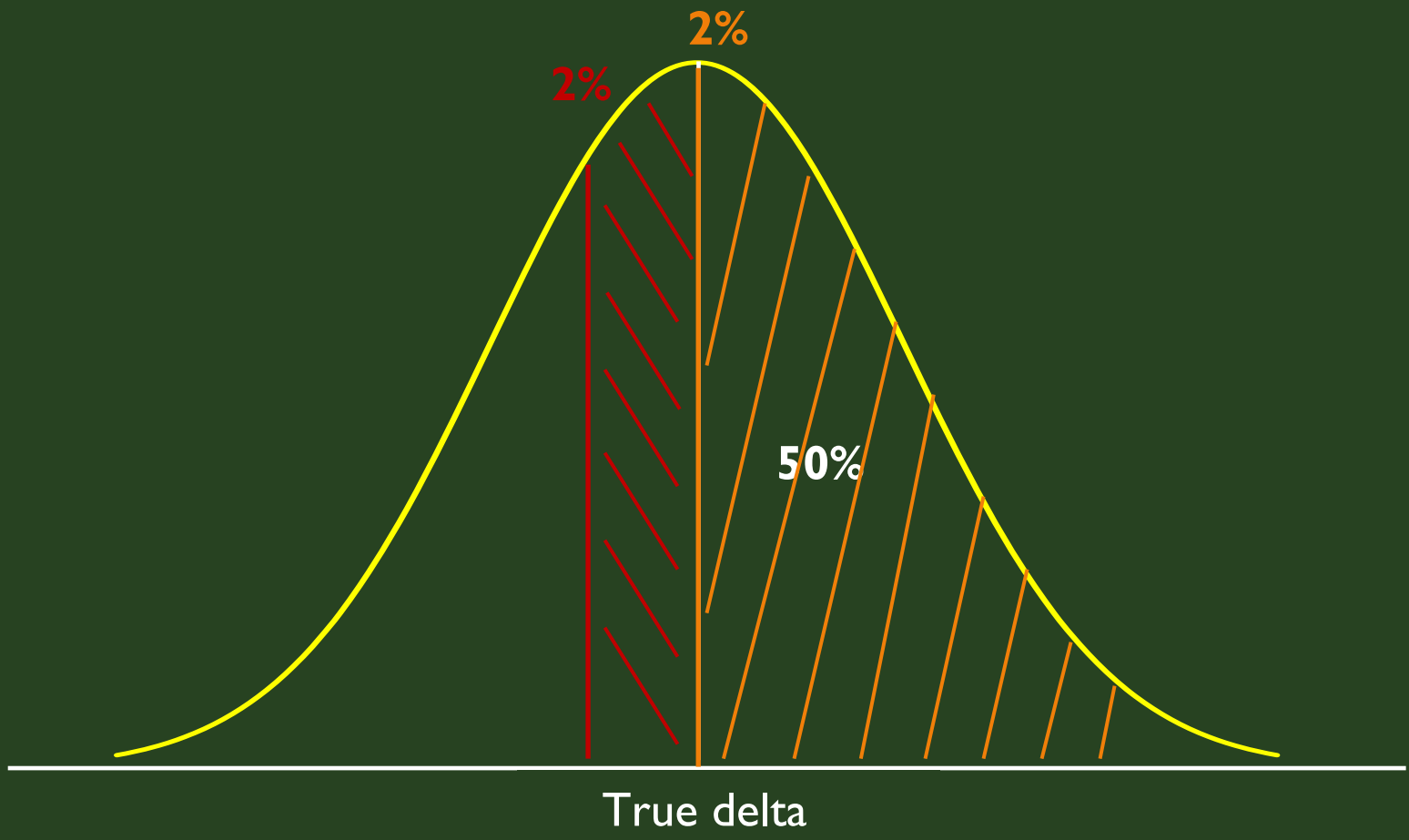
- Looked at the impact of subset size on our ability to see a 2% difference in rates of Grade 3/4 AEs or a 5% difference in Grade 1/2 AEs
  - Are these the right numbers? Will they inform HCPs?
- Important caveat: regardless of sample size, observed differences close to the 2% or 5% cut-offs have a high probability of being missed or, conversely, inappropriately identified as signals when they are noise.

Observed Difference in AE incidence

The distribution of the observed delta is symmetric around the true delta.
With a fixed sample (regardless of size),

If true delta=2%, there is a 50% chance of observing a delta ≥ 2%.

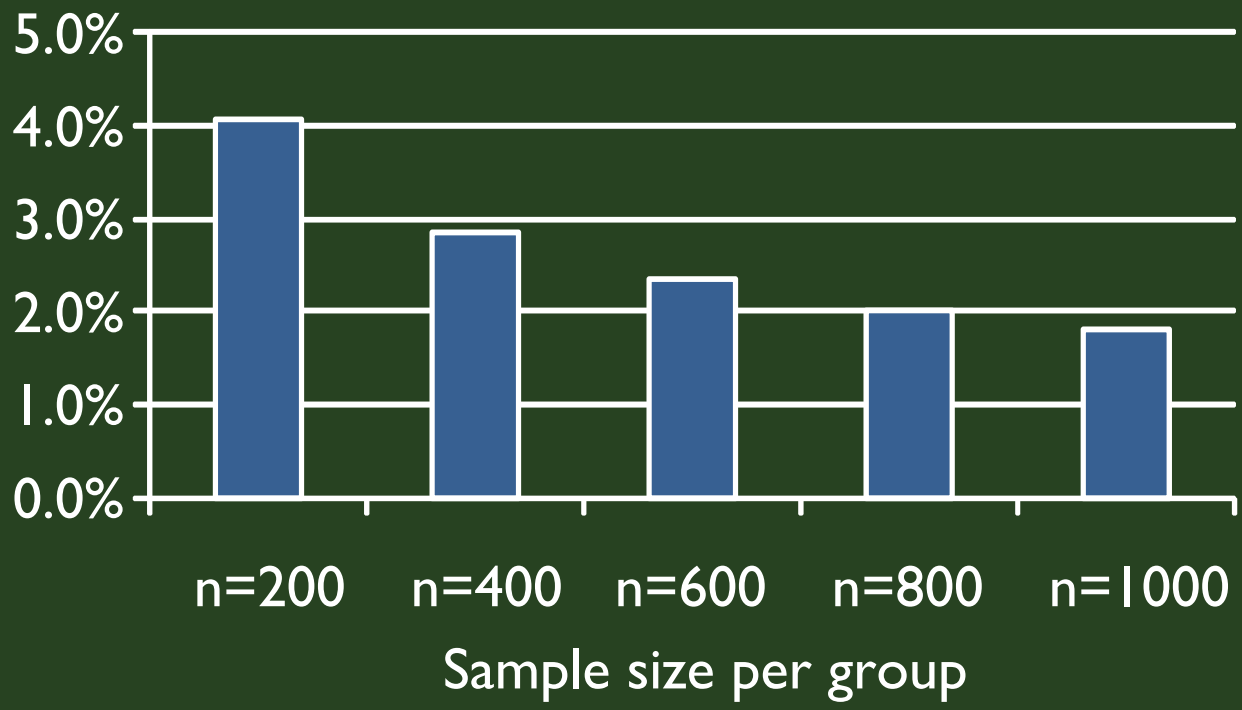
The larger the true delta, the higher the chance to detect it.



Difference in AE Incidence: Half-Width of 95% CI

The estimation precision increases slowly with increased sample size.

AE incidence in the control arm: 3%, delta=3%



Description of Initial Trials
Genentech Metastatic Cancer Studies

Study	AVF2119g	AVF2107g	E3200
Indication	mBC	FL mCRC	2nd-line mCRC
Treatment	• Capecitabine • Capecitabine +BEV	• bolus IFL + placebo • bolus IFL + BEV	• FOLFOX4 • FOLFOX4 + BEV
Sample Size	462	813	585 (arms 1 & 2)
Study Duration	Nov 00 – Sep 02	Sep 00 – Apr 03	Nov 01 - Aug05

Description of Candidate Trials
Genentech Metastatic Cancer Studies

Study	AVF2107g	E4599	AVAIL
Indication	FL mCRC	FL mNSCLC	FL mNSCLC
Treatment	• Bolus IFL + placebo • Bolus IFL + BEV	• Paclitaxel/Carboplatin • Paclitaxel/Carboplatin + BEV	• Cisplatin/Gemcitabine • Cisplatin/Gemcitabine + BEV
Sample Size	813	878	656 (arms 1 & 2)
Study Duration	Sep 00 – Apr 03	Jul 01 – Dec 05	Jan 05 –Nov 06
Initial Trial	AVF2119g (mBC, n=462)	AVF2107 (FL mCRC, n=813) E3200 (SL mCRC, n=585)	

Grade 3/4 AEs and SAEs, Drug D/C in 2% Excess from All Patients in the Candidate Trials

AVF2107g (Genentech)	**E4599^** (ECOG)	**AVAIL** (Roche)
• **Abdominal pain**	• **Febrile neutropenia**	• **Weight decreased**
• **Leukopenia**	• **Infection w/o neutropenia**	• Asthenia*
• Constipation+	• **Hyponatremia**	• Epistaxis+
• Deep thrombophlebitis*+	• Fatigue*	• Hypertension*+
• Diarrhea+	• Headache*	• Nausea*
• Hypertension*	• Hypertension*	• Neutropenia*+
• Pain+	• Neutrophils*	• Proteinuria*
	• Proteinuria*	• Vomiting*

Note: AEs highlighted in yellow were identified as events that could potentially be missed in subsampling

* Known from previous trial information

+Identified from Serious+ AEs in candidate trial

^ SAEs and Drug D/C not collected in E4599

Grade 3/4 AEs that Could Potentially be Missed in the Subsampling:

Event	Study	Delta (%)	Incidence (%)	
			Control	Treatment
Weight Decreased	AVAIL	2.1	1.5	3.6
Hyponatremia	E4599	2.4	1.1	3.5
Infection w/o Neutropenia	E4599	2.4	2.7	5.2
Febrile Neutropenia	E4599	2.6	1.8	4.4
Abdominal Pain	AVF2107g	3.4	6.3	9.7
Leukopenia	AVF2107g	6.7	31.3	38.0

Summary of Grade 3/4 Subsampling Findings: Random Sampling Methods

Chance of finding the events with ≥ 2% higher incidence in the subsamples						
Targeted # of Patients Sampled	Sample Centers at Random					
	AVAIL	E4599	E4599	AVF2107g	AVAIL	AVF2107g
	Weight Decreased 2.1%	Infection w/o Neutropenia 2.4%	Proteinuria* 3%	Abdominal Pain 3.4%	Epistaxis+ 4.3%	Leukopenia 6.7%
200	51	57	78	65	91	77
300	54	60	85	72	97	85
400	52	63	90	75	99.6	90
500	59	68	93	80	100	96
600	65	70	98	90	100	98

Note: Proteinuria and Epistaxis were identified as 'known' events and therefore cannot be missed. They are being used for illustrative purposes.

Summary of Grade 3/4 Subsampling Findings: Noise Events

Number of Noise Events			
Targeted # of Patients Sampled	Sample Centers at Random		
	AVF2107g	E4599	AVAIL
200	8.8	6.7	5.4
300	5.1	4.3	2.8
400	3.6	2.8	1.5
500	2.5	2.0	0.7
600	2.0	1.2	0.2

Summary of Grade 1/2 Subsampling Findings: Random Sampling Methods

Chance of finding the events (of any grade) with ≥ 5% higher incidence in the subsamples		
Targeted # of Patients Sampled (% of all pts)	Sample **Centers** at Random	
	AVAIL	
	Stomatitis* 6.4%	Headache* 15.4%
200 (30%)	67	98
300 (46%)	70	99.9
400 (61%)	78	100
500 (76%)	87	100
600 (91%)	97	100

Note: Stomatitis and Headache were identified as "known" events and therefore cannot be missed. They are being used for illustrative purposes.

Efforts Saved from Toxicity Data Subsampling

Number of Distinct Adverse Events (average # events per patient)			
Study	**Grade 1/2 (not serious+)**	**Grade 3/4 (not serious+)**	**SAEs and AEs leading to dose discon/change (serious+)**
Metastatic Studies			
AVF2107g (n=788)	*not collected*	1,297 (1.6)	1,187 (1.5)
AVAIL (n=656)	6,245 (9.5)	1,030 (1.6)	849 (1.3)
EGF3001 (n=580)	6,943 (11.97)	377 (0.65)	725 (1.25)
JMDB (n=1669)	10,514 (6.3)	835 (0.5)	2,504 (1.5)
Adjuvant Studies			
BIG 1-98 (n=8028)	28,098 (3.5)	9,634 (1.2)	12,845 (1.6)
89803 (n=1264)	13,904 (11.0)	4,171 (3.3)	10,870 (8.6)
HERA (n=3386)	7,701 (2.3)	161 (0.05)	535 (0.2)

- Grade 1/2 events greatly outnumber SAEs and AEs leading to DC and dose changes; Grade 3/4 AEs are approximately equal in number.
- Considerable efficiency in focusing on SAEs and AEs leading to DC or dose changes.

Efforts Saved from Concomitant Medication Reporting*

Number of Con Med Records (average # per patient)		
Study	# Con Med Records	# Con Med Data Fields
Metastatic Studies		
AVF2107g (n=788)	20,998 (26.6)	83,992 (106.6)
E4599 (n=878)	*not collected*	
AVAIL (n=656)	11,957 (18.2)	47,828 (72.9)
EGF30001 (n=578)	9,270 (16.04)	94,245(163.05)
JMDB (n=1669)	24,168 (14.5)	120,840 (72.4)
Big 1-98 (n=878)	56,966 (7.1)	1,841,572 (230)
89803 (n=878)	*not collected*	
HERA (n=3386)	13,249 (3.9)	52,996 (15.7)

* Exclude concomitant medications for the primary cancer.

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Conclusions

Jeffrey Abrams, MD
Associate Director, CTEP, DCTD
National Cancer Institute

Baseline Assumptions

- Toxicity data collection for new drug applications should remain comprehensive.
- Not applicable to first supplemental post-accelerated approval.
- Collect symmetric SAEs, deaths, dose discontinuations/modifications (and reasons for) in all patients when collecting an optimized supplemental data set.
- Concomitant medications should continue to be recorded in narrative SAE forms for all patients and as targeted collections in CRFs as appropriate.

Conclusions Regarding Safety Data

Re-analysis of data from eight supplemental applications of varying type, duration, and size demonstrated under the data collection method specified in the SAP:

- excess Grade 1/2 events did not appear to add to the known safety profile;
- the probability of missing a clinically significant Grade 3/4 AE was considered low;
- the probability of adding a noise event was considered low; and

Similar conclusions regarding the safety profile would have been reached as with full data collection.

How might subset size[+] be determined?

- In the metastatic setting, ~ 400* patients should be subsampled, regardless of trial size.
- In the adjuvant setting, with a study size of 800 - 6000 patients, a total subsample size of ~ 400 – 900* patients should be adequate.
- Cost-effectiveness may become an issue for trials with populations under 600 patients.

+ Assuming 2% excess; 2-arm trial

* Statistical rationale: equal standard error and equal power methodologies

What is an appropriate subsampling method?

Sampling by Centers at Random:

of the methods we evaluated, it provides the best balance of statistical legitimacy and practicality of implementation:

- Specific random selection of sites should be representative to ensure lack of bias
  - stratify sample of small, medium and large centers based on size of site vs. projected accrual
- Site projected accrual varies from actual accrual. To ensure minimum subsample size requirement is met:
  - overestimate number of sites selected to ensure enough patients per arm
  - actively monitor site accrual

Concomitant Medications

Review of concomitant medication databases from six trials demonstrated that no new information was learned from the summary tabulations listed in the sNDA/sBLAs.

- Useful information is typically learned from
  - initial clinical trials
  - SAE narratives
  - targeted con med collection
  - known pharmacologic and safety profile of the drug

How should con meds be addressed?

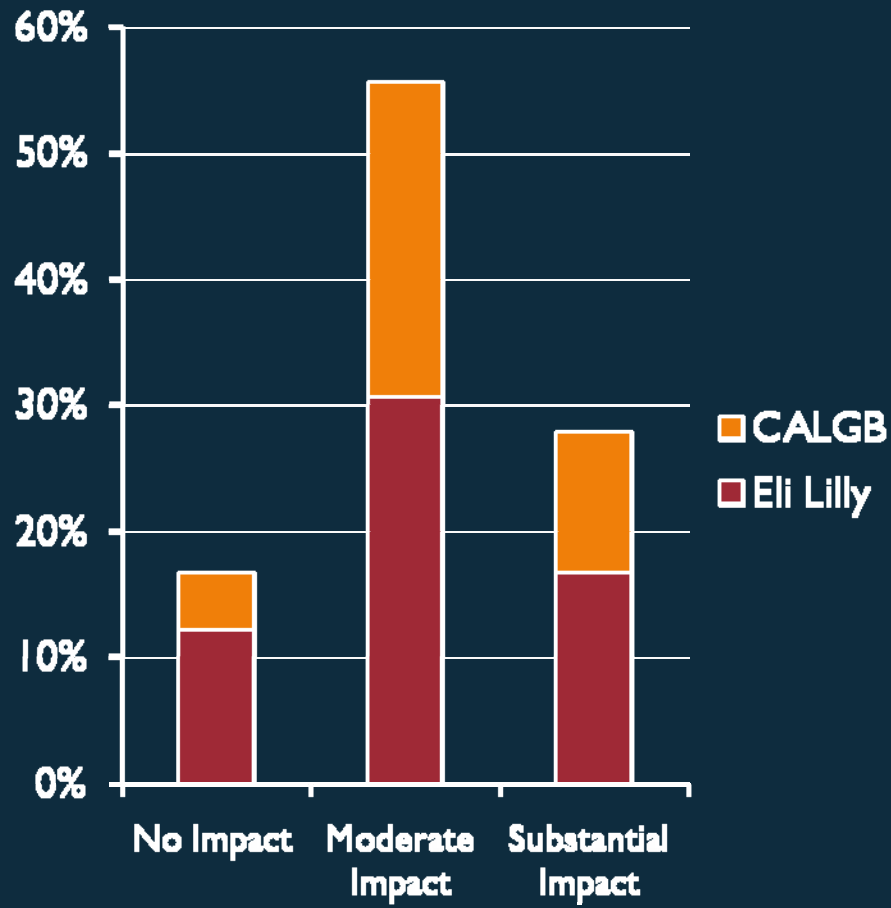
Con meds should not be collected in supplemental applications outside of the following instances:

- Continue to report associated con meds in the narrative section of SAE forms
- Identify and collect targeted con meds based on known safety and pharmacologic profiles of the investigational agent(s) (i.e., tamoxifen study and CYP 2D6 inhibitors)
- Collect specific con meds when agent has known anti-cancer properties (i.e., bisphosphonates in adjuvant breast cancer trial) and post-study therapy in the case of treatment trials with survival endpoint
- Collect con meds that meet a specific objective of the trial (e.g. , health economics/costing)

Data Optimization Impact on Resources

Regarding toxicity data collection on a Phase III trial– instead of full data set collection, suppose you were asked to collect a limited data set.*

Please indicate the level of impact such data collection would have on your site's resources.

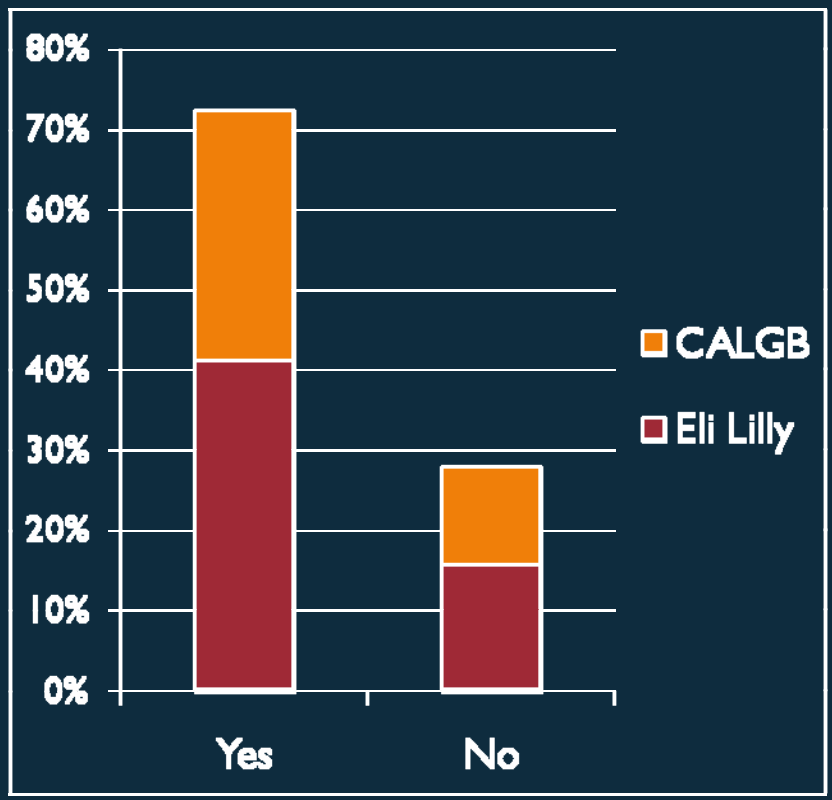


* Limited data collection defined according to SAP

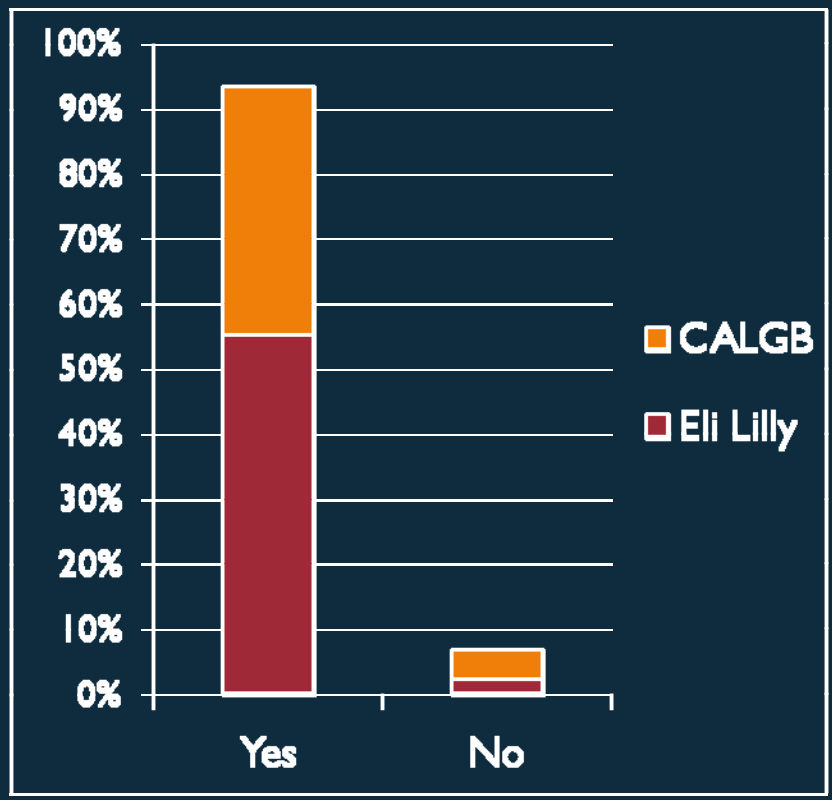
Data Optimization Impact on Resources (cont.)

Would freeing these additional resources allow you to do the following:

Expand participation by increasing accrual to the clinical trial with reduced data collection and/or to participation in additional protocols?



Improve quality of data collection resulting in fewer queries?



Considerations for Data Optimization

- Collect necessary data to inform regulatory review, labeling and clinical use
- Data collection for new drug applications should remain comprehensive
- Data collection requirements for supplemental applications will vary based on:
  - safety database/known pharmacology and drug interactions
  - similarity of study population/intended use
  - similarity of regimen to that already approved
  - whether supplemental application follows initial full or accelerated approval

Recommendations

- Optimization of toxicity data for supplemental trials as specified in the SAP is a viable option.
- For future supplemental trials that fit the appropriate qualifications, researchers need not collect:
  - Grade 1/2 adverse events
  - Grade 3/4 events in all patients
    - Subsample of ~ 400 pts provides adequate probability of detecting events with at least a 3% excess toxicity
    - Even Phase IVs not powered for rare safety events
  - Stop/start dates for AEs except by cycle
  - All concomitant medications
- FDA should put forth a detailed guidance document with clear directives on data collection requirements.

NCI Considerations

- Collaboration with FDA, industry and other stakeholders to develop common data collection standards for industry and cooperative group trials.
- Promotion of symmetric SAE collection.
- Differentiate between collecting con meds on SAE reports but not on CRFs routinely for supplemental indications unless a specific rationale exists

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Data Optimization from the Patient's Perspective

Robert Erwin

Marti Nelson Cancer Center

The Patient Perspective

- Collect necessary data to inform regulatory review, labeling and clinical use
- Data collection for new drug applications should remain comprehensive
- Data collect should remain comprehensive for symmetric SAEs, deaths, dose discontinuations/modifications (and reasons for) in all patients when collecting an optimized supplemental data set.
- Contribute to a reduction in data collection burden improving the likelihood of
  - critical data collected is complete/accurate
  - physician participation in clinical trials
  - more rapid completion of studies
  - prompt delivery of results to patients
  - retaining studies in the U.S. vs. overseas