Data collection and optimization in cancer clinical trials seeking sNDA/sBLA

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What are we talking about?

- Establishing data collection standards that meet clinical needs, regulatory standards and the goals of cooperative groups and industry
- Defining the minimum data set necessary to support a claim of safety for an sNDA or sBLA
- Specifying the data required to permit appropriate labeling and to inform clinical use
- Clarifying the nature, extent, frequency, format of clinical data reporting
- Determining % of study population necessary for informative data capture

Why is this important?

- Insure adequate data collection to inform regulatory and clinical decisions
- Protect patient safety by improving the overall quality of data submitted in supplemental drug applications
- Increase efficiency—more drugs developed with similar resources
- 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

General Principles

- Collect necessary data to inform regulatory review, labeling and clinical use
- Use the data collected; don't collect data not used
- Data collection for new drug applications should remain comprehensive
- Data collection requirements for supplemental applications could vary based on:

  -safety database/known pharmacology and drug interactions

  -similarity of study population/intended use to original

  -similarity of regimen to that already approved

  -whether supplemental application follows initial full or accelerated approval

Principles of Data Collection

- Reduced data collection 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
  - Collect detailed information on study deaths and SAEs
  - Collect information on AEs leading to discontinuation or dose modification
  - Collect targeted AEs and concomitant meds as needed based on a drug's known safety and pharmacologic profile

Toxicity Data Re-Analysis Project

- ASCO formed the **Data Optimization Working Group** in October 2008:
  - to re-analyze multiple clinical trial toxicity databases and examine various sampling methods to determine if ‘optimized’ data collection would provide sufficient safety data to support supplemental applications.

Objectives of the Analysis

- Determine what adverse events might be missed through sampling a subset of trial participants
- Determine a target subset size that minimizes the chance of missing clinically important adverse events
- Determine a subset size in which noise events are acceptably low
- Determine the preferred method of subsampling patients
- Assess the extent of data collection and cleaning effort saved by limited sampling
- Evaluate what concomitant medication data is collected and what is used in regulatory and clinical decisions

Project Logistics

- Four companies and one cooperative group participated:
  - CALGB, GSK, Eli Lilly, Novartis and Genentech
- Statistical Analysis Plan for AE subsampling was developed, reviewed by FDA, used by all parties.
- Subsampling simulations of each candidate trial included 1000 independent replications targeting sample sizes of 200, 300, 400, 500, 600 patients.

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 adverse events in these studies
  - Evaluated potential subsampling methods
    - Random methods
    - Site selection
    - Recruitment order

Methods

- Collected detailed information on all study deaths and SAEs
- Collected information on all AEs leading to drug discontinuation or dose modification
- Focused on subsampling of grade 3 and higher AEs with $\geq$ 2% difference in frequency between treatment and control and grade 1-2 AEs with $\geq$ 5% difference in frequency
- Known safety profile determined from NDA filing, drug label, safety database, literature

Metastatic Disease Trials

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
GNE	AVF2107g	1st Line mCRC	813	Overall Survival	N	Y	Y	Y
GNE	ECOG 4599	1st Line non-squamous NSCLC	878	Overall Survival	N	Y	N	N
GNE	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

Adjuvant Trials

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
GNE	HERA	HER2+ adj breast cancer	3386	DFS	Y	Y	Y	Y

Findings

AEs Potentially Missed

- Toxicity records available for 17,184 patients from the 8 trials
- 43 grade 3+ events observed in at least 2% excess although 34 already known (Δ=9)
- 24 grade 1-2 events observed in at least 5% excess although 20 previously known (Δ=4)

Probability of Detecting Grade 3+AEs in Trial Subsets

Table 3. Probability of Detecting AEs Under Random Subsampling Methods for Metastatic Disease Studies

Study, AE, Active Arm Rate Excess in Full Study	Sampling Method	Subsample Size (total No. of patients)				
		200 (%)	300 (%)	400 (%)	500 (%)	600 (%)
Grade 3+ events						
JMDB, anorexia*†, 2.1%	Random by patient	62.4	61	63.3	60.4	61
	Random by center‡	50.6	49.9	52.7	56.7	56.4
AVAiL, *weight decreased*, 2.1%	Random by patient	63	65	66	68	**79**
	Random by center‡	51	54	52	59	65
ECOG 4599, *infection without neutropenia*, 2.4%	Random by patient	63	67	68	72	**75**
	Random by center‡	57	60	63	68	70
EGF30001, *leukopenia*, 2.4%	Random by patient	68	70	**79**	**86**	NA
	Random by center‡	58	61	66	**79**	NA
EGF30001, *nausea*, 2.4%	Random by patient	66	68	73	**84**	NA
	Random by center‡	54	57	64	71	NA
ECOG 4599, proteinuria,* 3.0%	Random by patient	**87**	**91**	**94**	**96**	**98**
	Random by center‡	**78**	**85**	**90**	**93**	**98**
AVF2107g, *abdominal pain*, 3.4%	Random by patient	72	**77**	**80**	**85**	**92**
	Random by center‡	65	72	**75**	**80**	**90**
JMDB, nausea,*† 3.5%	Random by patient	72.9	74.5	**78.1**	**79.7**	**82**
	Random by center‡	68.7	69.6	**75.5**	**77.2**	**80.5**
AVAiL, epistaxis,† 4.3%	Random by patient	**94**	**98**	**99.4**	**100**	**100**
	Random by center‡	**91**	**97**	**99.6**	**100**	**100**
AVF2107g, *leukopenia*, 6.7%	Random by patient	**79**	**88**	**92**	**97**	**99.4**
	Random by center‡	**77**	**85**	**90**	**96**	**98**
Grade 1 to 2 events						
AVAiL, stomatitis,* 6.4%	Random by patient	**76**	**76**	**88**	**92**	**99.5**
	Random by center‡	67	70	**78**	**87**	**97**
AVAiL, headache,* 15.4%	Random by patient	**99.5**	**100**	**100**	**100**	**100**
	Random by center‡	**98**	**99.9**	**100**	**100**	**100**

Probability of Detecting Grade 3+AEs in Trial Subsets

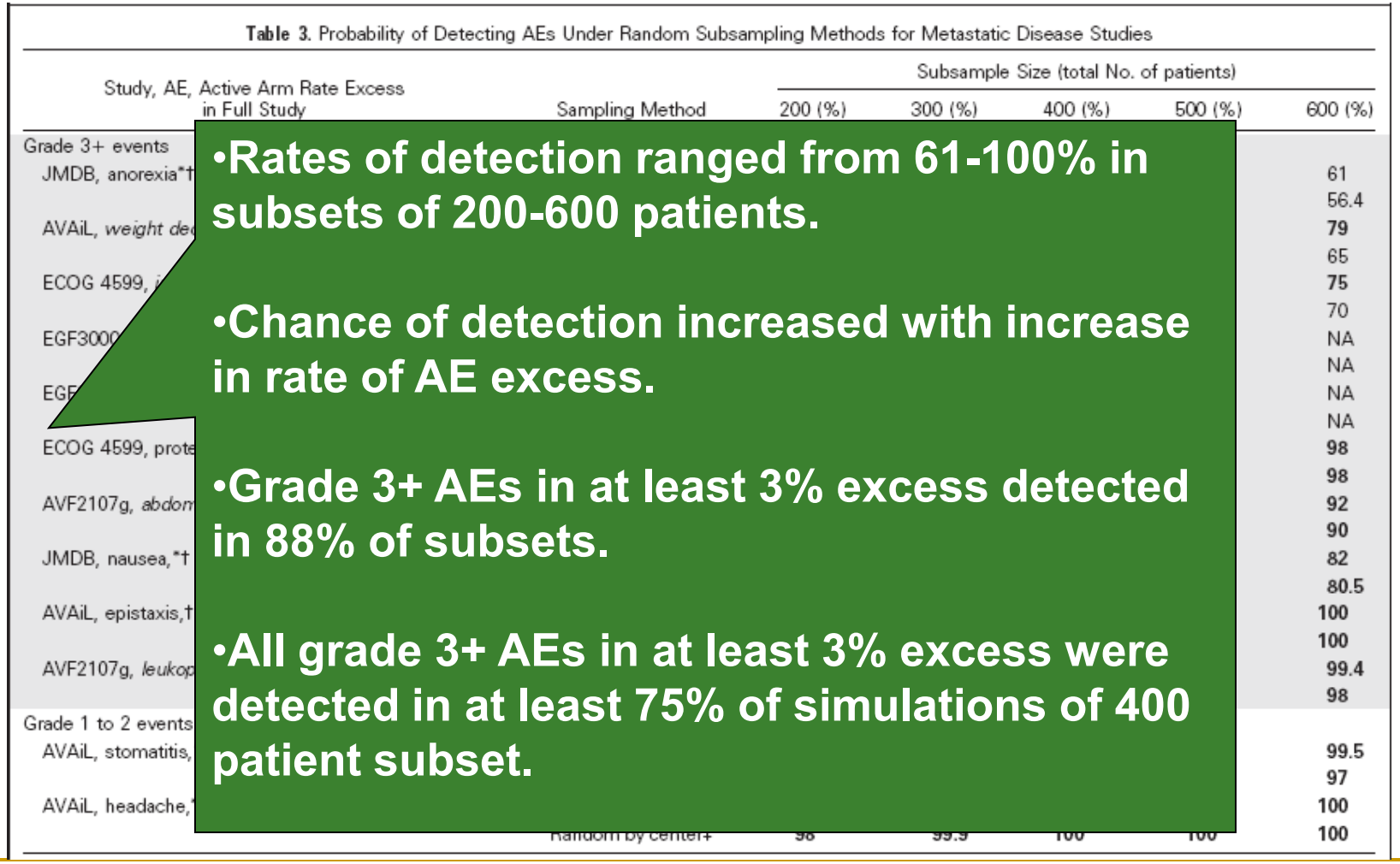

Table 3. Probability of Detecting AEs Under Random Subsampling Methods for Metastatic Disease Studies

Study, AE, Active Arm Rate Excess in Full Study	Sampling Method	Subsample Size (total No. of patients) 200 (%)	300 (%)	400 (%)	500 (%)	600 (%)
Grade 3+ events						
JMDB, anorexia*†						61
AVAiL, *weight de*						56.4
ECOG 4599, *i*						**79**
EGF3000						65
EGF						**75**
ECOG 4599, prote						70
AVF2107g, *abdon*						NA
JMDB, nausea,*†						NA
AVAiL, epistaxis,†						NA
AVF2107g, *leukop*						NA
Grade 1 to 2 events						**98**
AVAiL, stomatitis,						**98**
AVAiL, headache,*						**92**
						90
						82
						80.5
						100
						100
						99.4
						98
						99.5
						97
						100
	Random by center+	98	99.9	100	100	**100**

- **Rates of detection ranged from 61-100% in subsets of 200-600 patients.**
- **Chance of detection increased with increase in rate of AE excess.**
- **Grade 3+ AEs in at least 3% excess detected in 88% of subsets.**
- **All grade 3+ AEs in at least 3% excess were detected in at least 75% of simulations of 400 patient subset.**

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.

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)
Adjuvant Studies		
Big 1-98 (n=878)	*not collected*	
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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Efforts Saved from Concomitant Medication Reporting*

Number of Con	patient)
Study	on Med Data Fields
Metastatic Studies	
AVF2107g (n=788)	3,992 (106.6)
E4599 (n=878)	
AVAIL (n=656)	47,828 (72.9)
EGF30001 (n=578)	,270 (16.04) / 94,245(163.05)
JMDB (n=1669)	24,168 (14.5) / 120,840 (72.4)
Adjuvant Studies	
Big 1-98 (n=878)	*not collected*
89803 (n=878)	*not collected*
HERA (n=3386)	13,249 (3.9) / 52,996 (15.7)

136,608 Con Med records in these trials

* Exclude concomitant medications for the primary cancer.

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Conclusions

Conclusions Regarding Safety Data

Re-analysis of data from eight clinical trials of varying type, duration, and size demonstrated:

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

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

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 except in 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) (e.g., tamoxifen study and CYP 2D6 inhibitors)
- Collect specific con meds when agent has known anti-cancer properties (e.g., 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)

Recommendations

- For future supplemental trials that fit the appropriate qualifications, researchers need not collect:
  - Grade 1/2 adverse events (already known)
  - Grade 3/4 events in all patients
    - Subsample of ~ 400 pts provides adequate probability of detecting events with at least a 3% excess toxicity
  - 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.

FDA Actions

- Feb. 2012: Draft guidance “Determining the Extent of Safety Data Collection Needed in Late Stage Premarket and Postapproval Clinical Investigations”
- Dec. 2012: Guidance “Safety Reporting Requirements for INDs and BA/BE Studies”

February 2012 Draft Guidance

- Acknowledges that in some settings it may not be necessary to collect certain types of safety data.
- Recognizes that excessive data collection may have negative consequences.
- Proposes collection of all SAEs, collection of AEs that lead to drug discontinuation or dose modification, targeted laboratory tests.
- Discusses circumstances when comprehensive safety data collection needed and types of data that should always be collected.

February 2012 Draft Guidance

- Targeted safety data collection may be appropriate when:
- safety profile already well characterized from prior studies;
- AE type and frequency similar across multiple studies;
- expected AE rates in study population likely to be similar to previous studies.
- Targeted safety data collection may be appropriate for post-marketing studies for new indications; studies required to meet post-marketing requirements; large outcome studies.

February 2012 Draft Guidance

- Types of data appropriate for selective collection:
- non serious AEs not requiring drug discon.;
- routine lab monitoring;
- con meds;
- history and PE.
- Mentions collecting data from a sample of the study population and possibility of decreased frequency of data collection
- Pre-specified plan for selective safety data collection should be included in protocol and discussed with FDA.

February 2012 Draft Guidance

- Concludes: “In an oncology setting, Gr 3 and 4 AEs as well as Gr 2 events that affect vital organs should always be collected”.
- Request harmonization with 2001 guidance “Cancer Drug and Biological Products - Clinical Data in Marketing Applications” that states, “In supplemental efficacy applications that propose a new use for an already marketed drug in a similar population, additional data on grade 1-2 nonhematologic toxicity and grade 1-3 hematologic toxicity may not be important and may not need to be collected.”