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**Considerations for Summary Review of
Supplemental NDA/BLA Submissions
in Oncology**

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Considerations for Summary Review of Supplemental NDA/BLA
Submissions in Oncology

Rachel Sherman, MD
Greenleaf Health LLC

Speakers

- **Rachel Sherman, MD, Greenleaf Health LLC**
- **Paul Kluetz, MD, FDA**
- **Tatiana Prowell, MD, FDA**
- **Katherine Sugarman, MD, Eli Lilly**
- **Laurie Strawn, PhD, Pfizer**
- **Kannan Natarajan, PhD, Novartis**
- **Raji Sridhara, PhD, FDA**
- **Robyn Lim, PhD, Health Canada**
- **Andrew Thomson, PhD, EMA**

Contributors: Lisa LaVange, PhD, Bob O'Neill, PhD, Rick Pazdur, MD

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Paul Kluetz, MD
FDA

The Issue

- OHOP receives many efficacy supplements for new indications
- Regardless of the quantity of existing clinical and post-marketing data, clinical reviewers often spend time verifying analyses submitted in the CSR from raw and derived datasets
- Time spent analyzing primary datasets for select efficacy supplements with well known safety and efficacy in other heme/onc indications could be better spent

Proposal

- Review clinical study reports rather than primary datasets for carefully selected efficacy supplements
 - Initially for narrow subset of supplements
 - Eligibility determined by OHOP at the pre-NDA meeting

Eligible Supplements for Summary Review:

- Approved drug with large existing clinical trial and post-marketing safety database:
- Established, objective primary endpoint
 - Overall Survival
 - Very Large PFS Result
- Robust efficacy result, internal consistency and clear risk:benefit
- No new significant safety signal noted by sponsor

NOT Eligible for Summary Review

- Prevention, adjuvant or neo-adjuvant trials
- Accelerated approvals or their confirmatory trials
- Unestablished or novel endpoints for the indication
- Unclear risk:benefit: advisory committee may be required
- Novel Combinations Depending on Additive Toxicities or significant Drug-Drug Interactions

Opportunities / Challenges

- Opportunities

- Optimize use of limited FDA review staff
- May decrease review times for supplemental applications
- May increase the incentive for sponsors to submit supplements (rather than off-label use)

- Challenges

- Requires a major culture shift from OHOP clinical reviewers
- Will need way to screen for data integrity
- Will need to develop SOP for FDA and sponsors
 - Devil is in the details

Refocus OHOP Medical Officers:

- More efficient FDA review of supplemental applications can directly and indirectly benefit all stakeholders
- Focus FDA reviewers
 - NME reviews
 - Improved safety surveillance of existing products
 - FDA collaboration and oncology patient engagement
 - Regulatory science initiatives fostering patient-focused drug development and innovation.

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Tatiana Prowell, MD
FDA

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Katherine Sugarman, MD
Eli Lilly

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Laurie Strawn, PhD
Pfizer

Pros from the Industry Perspective

- Potential reduced resources for preparation of submission-ready datasets, programming, patient narratives, case report forms
- Fewer queries on these items
- Shortened sNDA preparation and review times
 - Drug to patients sooner
- A new indication, as opposed to a compendial listing:
 - Ensures that physicians have the information in the labeling they need to treat patients appropriately
 - Allows promotion
- FDA resources could shift to review other applications and collaborative policy work

Cons from the Industry Perspective

- May trigger significantly more information requests during the review
- If the FDA reviewer(s) determine once the review has started that they need additional data,
 - The Sponsor must have all data ready to submit, thereby not saving resources, or
 - The Sponsor must prepare the data quickly, which may impact quality and possibly delay the review
- Other Health Authorities that rely on FDA review may change their requirements

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Kannan Natarajan, PhD
Novartis

Further Enhancements – Industry Perspective (1)

- Following pilot phase, sNDAs limited to summary documents and study reports.
 - Data to be provided only if issues identified during review
- Shorter review timeline with transparent review process.
- Optimize data collection to pertinent efficacy and safety data
 - Adverse events restricted to CTCAE Grade 3/4
 - Laboratory parameters, as appropriate
- Collaboration with CDRH on accelerated companion diagnostics review, when appropriate.

Further Enhancements – Industry Perspective (2)

- Patient narratives, if required, provided as patient profile summary without clinical interpretation
- Minimal but effective data monitoring:
 - Remote monitoring
 - SDV only key efficacy and safety data
- Sponsor audit
 - Steps that could be put in place to enhance data reliability and acceptance by the FDA.
- Further streamline clinical, clinical pharmacology and statistical review process across all NDAs.

Review of Supplemental Submissions

Rajeshwari Sridhara, Ph.D.
Director, Division of Biometrics V
CDER, FDA

Improve Efficiency

- Summary Review
- Less data collection – specifically less safety data collection

Review of Supplemental Applications: Statistician's Role

- Thorough review of the study report, protocol and its amendments, pre-specified analysis plan, and independent review committee charters including DMC charter, to understand the study conduct, impact of protocol violations and amendments, impact of deviations from pre-specified analyses and role of independent committees. Many exploratory analyses are necessary to evaluate these
- Review of data (efficacy and safety) to ensure absence of systematic bias or any other potential bias in the conduct and analyses of the study; verify applicant's claims
 - Audit check of raw or CRF extracted data
 - Analyses using derived or analysis data
- Product label reflects FDA verified results/claims

Data Integrity QC for Summary reviews without submitted data:

- FDA statistical reviewers will look for data patterns (enrollment, exposure, efficacy, safety, etc.) by site, treatment, calendar time, etc. in study reports/summary data submitted to FDA
- QA/QC plan developed and agreed upon with sponsor
- May involve requesting a sample (random or purposive) of data (from CRF data and analysis files) to be submitted for checking
- Created variables and analysis file structures examined in the random sample
- Program code may also be requested
- FDA reviewers may request many analyses to be submitted during the review to assess impact of amendments and deviations from protocol on the outcome (both safety and efficacy)
- QA/QC edits will be used to draw conclusions about data quality

Optimal Oncology Safety Data Collection Project

PROJECT TEAM:

Drs. Jade Chen, Sean Khozin, Ellen Maher,
Sirisha Mushti, Rajeshwari Sridhara, Yun Wang

Motivation

- Brookings 2009 meeting and subsequent 2010 publication
- Safety data collection in supplemental NDA/BLA applications with established extensively studied safety profiles from the initial approval based on randomized controlled trials (RCT)
- The retrospective analysis conducted by ASCO included eight previously completed prospective Phase III trials. These were both industry sponsored and publicly funded randomized control trials. A total of 107,884 AEs were reviewed in the analysis

Kaiser et al Proposal

1. Collect all study deaths, serious adverse events (SAEs), adverse events (AEs) leading to drug discontinuation or dose modifications (“serious+” AEs) ✓
2. Collect NCI CTCAE Grade 3 or 4 toxicities in a subgroup of patients in all treated groups ?
3. Collect targeted AEs and concomitant meds as needed based on drug’s knowledge of safety and pharmacologic profile ✓
4. No collection of NCI CTCAE Grade 1 or 2 toxicities not listed in (1) or (3) above. ✓

FDA Project

- **Objective:** Examine the above proposal for sample-based safety data (Grade 3/4) collection in supplemental NDA/BLA applications with prior approval based on RCT by conducting a retrospective analysis of the data submitted to FDA
- **Goal:** To evaluate if the benefit-risk assessment is compromised by sample-based safety data collection approach
- **Focus:** Limit to products approved for supplemental indications in non-hematologic malignancies

Data

- Drugs@FDA , www.pharmapendium.com, and other publicly available resources
- 57 studies were initially identified where the supplemental indication was considered after the product was approved based on results from a RCT.
- In 12 studies data could not be retrieved for the purpose of this project
- Of the remaining 45 studies:
 - 35 with 1:1, 4 with 2:1, and 6 with 1:1:1 randomization
 - 13 with $N < 500$, 15 with $500 < N < 800$ and 17 with $N > 800$
 - Included 965, 819 AEs and 70,748 Grade 3/4 AEs

Method

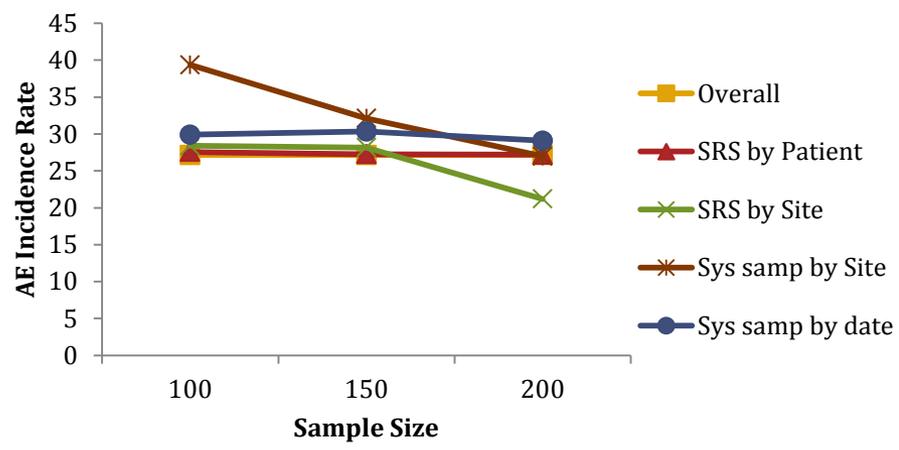
- Random sample of
 - Patients
 - Sites
- Systematic sample by
 - Largest site
 - Randomization date
- Sample sizes, n ranging from 100 – 300 per arm
- Safety signal: Difference in AE rates of 2% or 5% between arms

Questions:

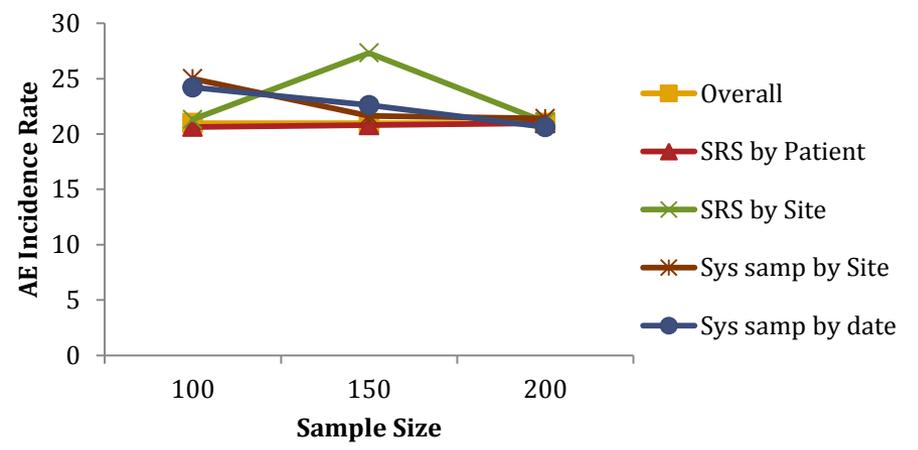
1. Can we get reasonable estimates of the toxicity from the sample
2. Did the sample miss a safety signal
3. Did the sample identify a spurious safety signal

Results from a study with N < 500

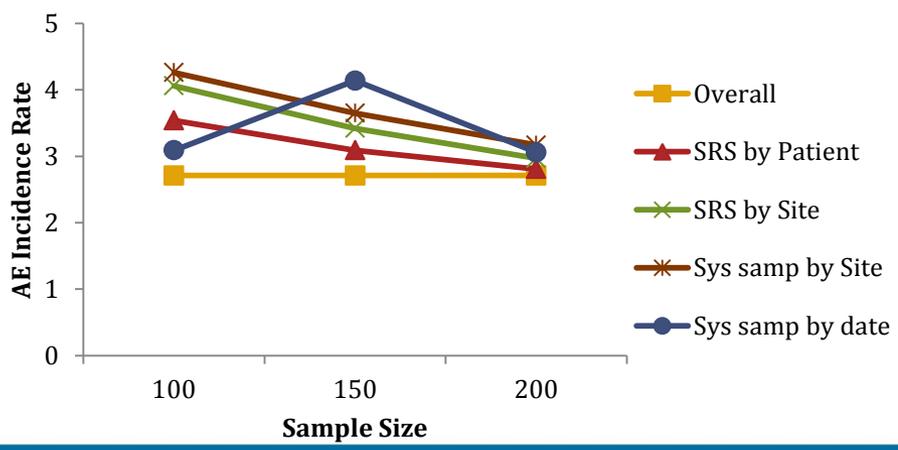
Serious+ and Grade 3,4 Asthenia in treatment group(N=221)



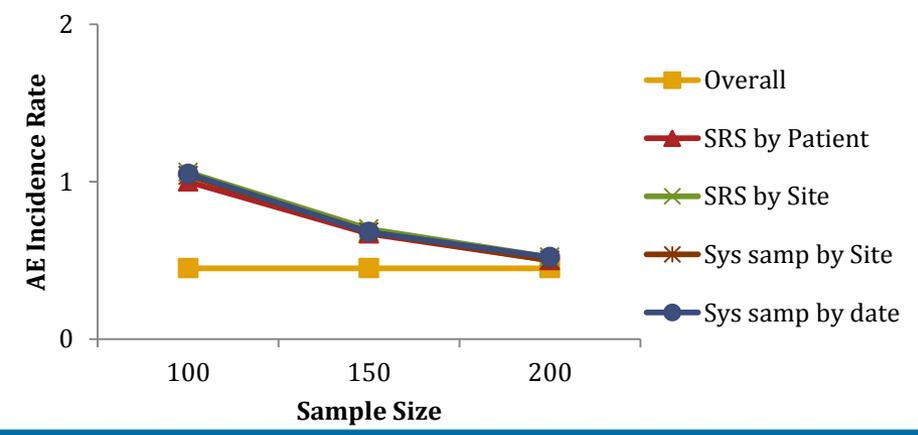
Serious+ and Grade 3,4 Asthenia in Control group(N=224)



Serious+ and Grade 3,4 Depression in treatment group(N=221)

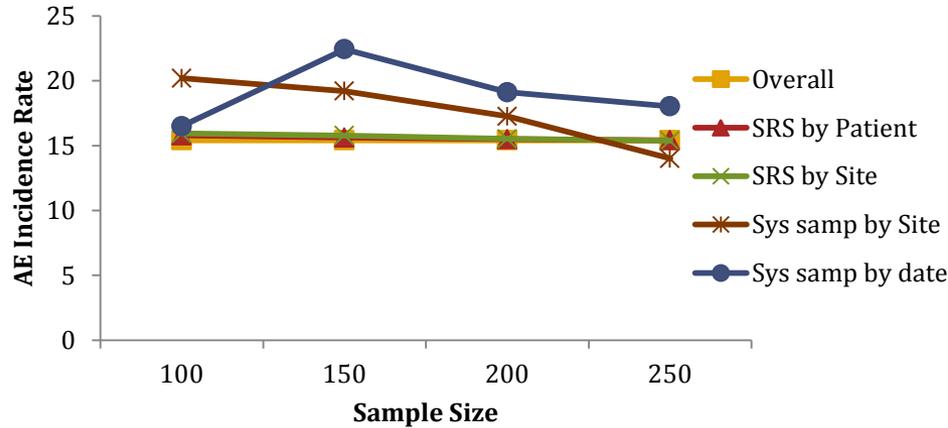


Serious+ and Grade 3,4 Depression in treatment group(N=221)

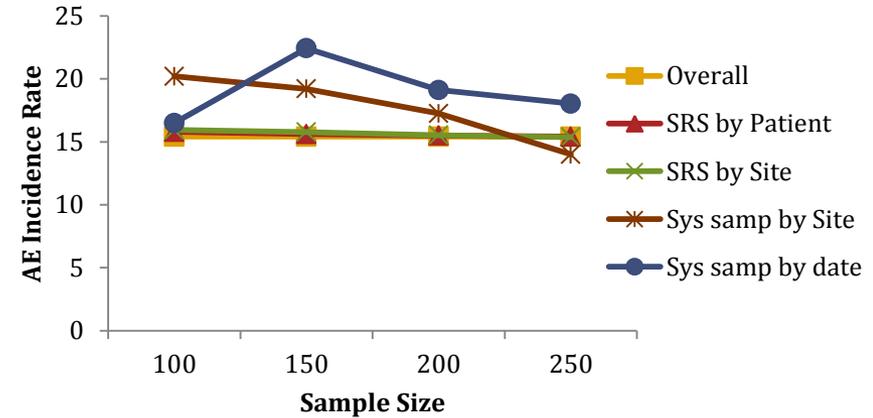


Results from a Study with $500 < N < 800$

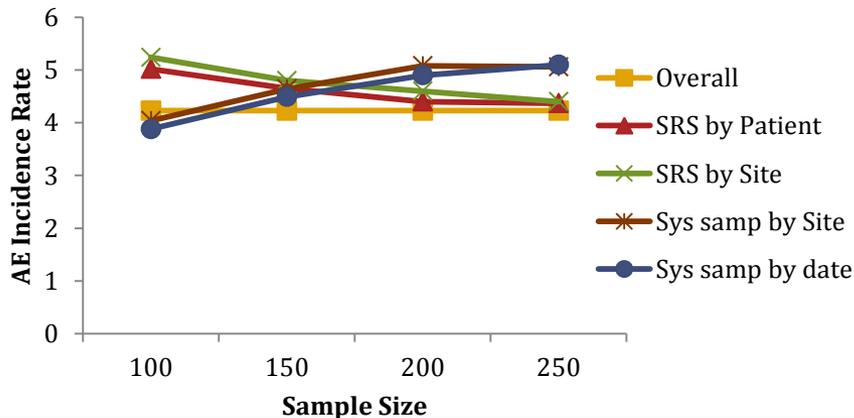
Serious+ and Grade 3,4 Asthenia in treatment group(N=331)



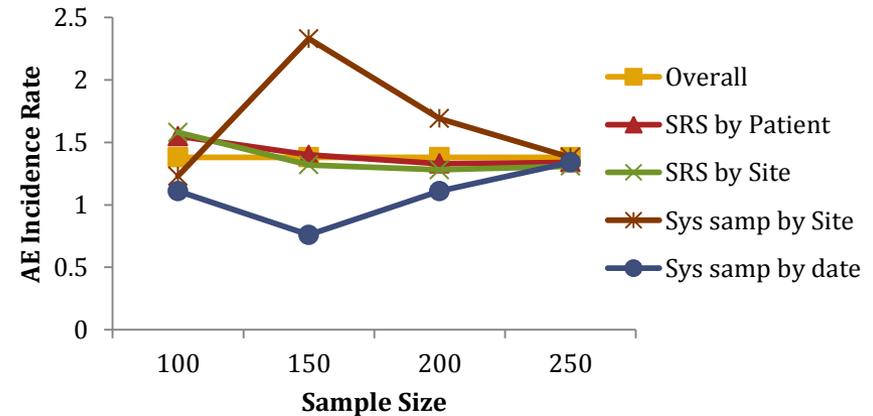
Serious+ and Grade 3,4 Asthenia in Control group(N=289)



Serious+ and Grade 3,4 Thrombocytopenia in treatment group(N=331)

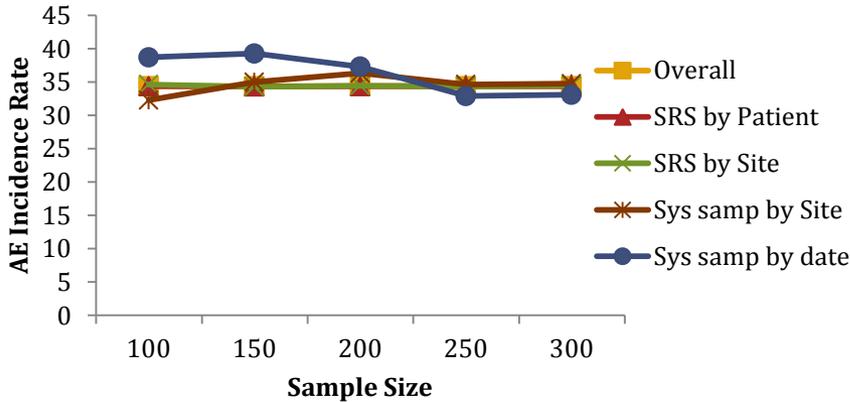


Serious+ and Grade 3,4 Thrombocytopenia in Control group(N=289)

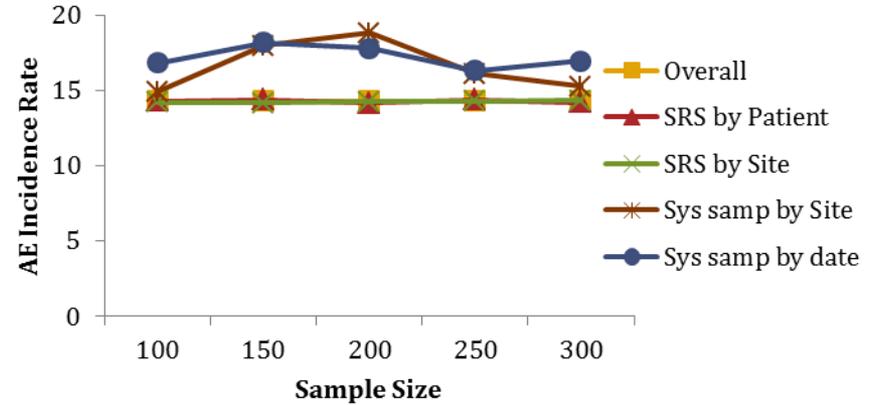


Results from a Study with N > 800

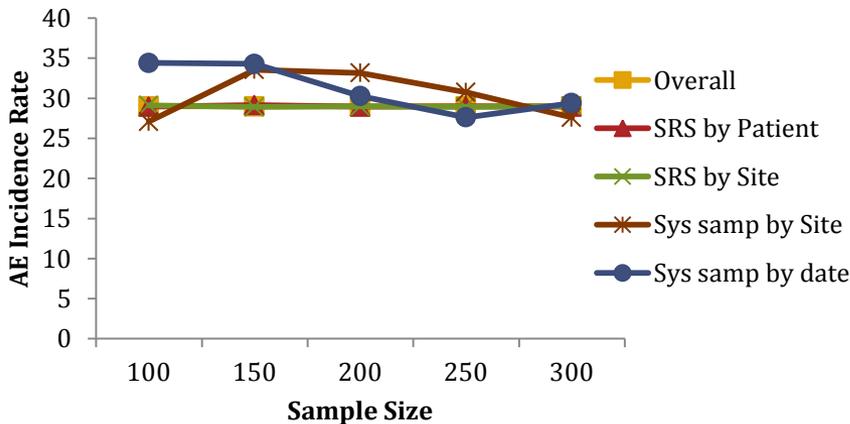
Serious+ and Grade 3,4 Thrombocytopenia in treatment group(N=483)



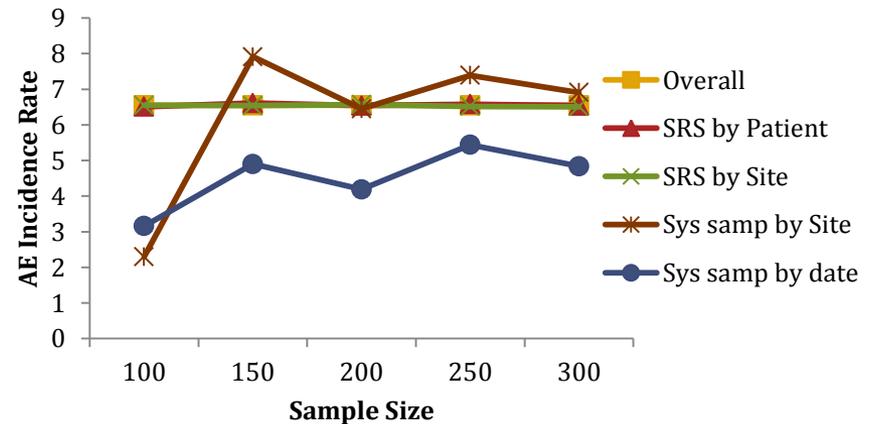
Serious+ and Grade 3,4 Thrombocytopenia in treatment group(N=504)



Serious+ and Grade 3,4 Anemia in treatment group(N=483)



Serious+ and Grade 3,4 Anemia in treatment group(N=504)



Initial Results

- Estimates of toxicity from random sample are close to the estimates from all available data.
- Estimates from systematic sample by randomization date generally overestimates
- Smaller the sample size more uncertainty – although depends on the proportion sampled
- Missed AEs decrease with sample size when using random sample but no specific pattern with systematic samples
- Spurious AEs similar to missed AEs
- Project is ongoing – evaluating other sampling methods

References

- Kaiser LD, et al JCO 28: 5046-5053, 2010
- Guidance for Industry: Cancer Drug and Biological Products — Clinical Data in Marketing Applications, 2001
- Draft Guidance for Industry: Determining the Extent of Safety Data Collection Needed in Late Stage Premarket and Postapproval Clinical Investigations, 2012

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Robyn Lim, PhD
Health Canada



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Re-analysing Clinical Trial Data – A European Perspective

Presented by: Andrew Thomson

An agency of the European Union





Disclaimer

The views expressed in this talk are the personal views of the author and may not be understood or quoted as being made on behalf of or reflecting the position of the EMA or one of its committees or working parties.



Trust

Regulatory System is based on trust

1. Patients Trust Doctors
2. Doctors Trust Regulators
3. Regulators Trust Industry
4. Industry Trust Doctors / Patients

This is circular, not always unconditional, and relies on safeguards to ensure trust is maintained



Actions and factors that can facilitate trust

1. Doctors are trained and revalidated – personal relationship
2. What do Regulators need to do to gain and keep trust?
3. GCP Inspections, requesting reanalysis during review
4. Site monitoring for fraud, errors. Choosing appropriate sites. Making sure patients report AEs, and take medication in line with protocol.



What factors might influence whether we trust the data?

- Marginal results in terms of statistical significance
- High influence of outliers
- Sensitivity Analyses giving contradictory results
- GCP Issues – either identified by inspectors or highlighted by the Company themselves.
- Lack of basic scientific knowledge about how the drug works e.g. Clinical Pharmacology, Mechanism of Action
- Benefit risk balance is borderline:
 - safety concern that would overturn the balance if benefit is not robust
 - Method for assessing efficacy is not robust – soft endpoints



Towards a risk-based approach

- Situations can be envisaged where the risk-based approach leads to a request for data to be re-analysed
- Tolerance of risk may depend on where you start from, with respect to historical acceptability of summary review
- Risk accepted by different Agencies need not be the same

A close-up photograph of a hand holding a grey marker, writing the words "Thank you" in a cursive script on a white surface. The marker is positioned at the end of the word "you".

Any questions?



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Backup Slides

Current FDA Guidance – Oncology Specific

- Data on National Cancer Institute (NCI) grade 4-5 hematologic toxicity and grade 3-5 nonhematologic toxicity should always be collected.
- 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. Data on serious adverse events associated with the use of a drug, or adverse events leading to discontinuation or dose reduction of treatment should always be collected.

FDA Guidance - General

- If there is generally a well established safety profile for a marketed drug being used in a postmarket clinical trial, it may not be necessary to collect certain types of safety data in such a trial
- In such cases, more selective safety data collection may (1) improve the quality and utility of the safety database and safety assessment without compromising the integrity and validity of the trial results or losing important information, (2) ease the burden on investigators conducting and patients participating in a study, and (3) lower costs, thereby facilitating increased use of large, simple trials and better use of clinical trial resources generally.

FDA Guidance - General

In general, selective or specifically targeted safety data collection is appropriate when the following conditions are present:

- The number of subjects exposed to the drug in previous studies is sufficient to characterize the safety profile for all but rare events
- The occurrence of adverse events has been generally similar across multiple studies
- There is a reasonable basis to conclude that occurrence of adverse events in the population to be studied will be similar to previously observed rates

If Targeted Safety Data Collection:

- Important to pre-identification of data that need not be collected
- Identify data in which subset of study population should be collected
- May also consider decreased frequency of data collection