The Current Regulatory Environment and its Impact on the Analysis of Safety Data AND Some Comments on the Role of Statisticians in Safety Assessment During Development

Presented by
Jesse Berlin
Epidemiology, Johnson & Johnson Pharmaceutical R&D

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S ..... Safety
P ..... Planning
E ..... Evaluation
R ..... Reporting
T ..... Team
Introduction

• SPERT
  – formed in 2006 by PhRMA*
  – Industry biostatisticians, epidemiologists, and safety physicians + representative(s) from FDA

• Goal: recommend an industry standard for safety planning, data collection, evaluation and reporting

• Scope: new product development programs
  – First-in-human through planning of post-approval period

* Pharmaceutical Research and Manufacturers of America
The environment

• You may have noticed the increased focus on drug safety by FDA and other health authorities
  – Many well-publicized recent examples of drug withdrawals, restrictions on use, etc.
  – Clinical program for a new pain drug (with a novel mechanism: anti-NGF) is on clinical hold

• SPERT developed as a “proactive response” to this concern about safety
Key SPERT Ideas

• Planning for safety assessment not always well-defined or coordinated program-wide

• Focus on individual trials

• Often wait for Summary of Clinical Safety just prior to submission of the application

• Concept: Opportunity to respond to evolving safety/tolerability profile may be missed by waiting

• **Could** result in an avoidable gap in knowledge of the safety profile at time of submission.
Key SPERT Ideas (cont)

• Proactive approach with the goal of providing a more complete safety profile at the time of new product approval
  – to meet the expected demands by health authorities

• Establishment of Safety Management Teams (SMTs) as recommended in CIOMS* VI.
  – Review of safety data from all available sources at regular intervals during clinical development and marketed use of a product
  – Earlier planning with appropriate level of detail documented in a Program Safety Analysis Plan (PSAP) or equivalent

* CIOMS = Council for International Organizations of Medical Sciences
Proactive Approach

• Look early, look at regular intervals.

• Consider data standardization issues early, to facilitate ongoing integration and interpretation.

• Adjust objectives as new safety information emerges.
Program Safety Analysis Plan (PSAP)

• Program-wide analytical plan
  – Potential and identified risks
  – Identification of safety signals

• A ‘living’ document, amended as needed

• Discussed with FDA and other regulatory agencies (e.g., end-of-phase II meeting)

• POINT: Make safety analysis plans look more like efficacy analysis plans than they have in the past
Other things going on: changes to the environment

• FDA guidance on safety assessment during drug development (PSAP)
  – Coming sometime (soon?)

• FDA guidance on meta-analysis in drug safety assessment
  – Pre- and post-approval (definitely coming soon)

• CIOMS X Working Group: Considerations for applying good meta-analysis practices to clinical data within the biopharmaceutical regulatory process
How to get involved

- Let your manager(s) know of your interest in particular subjects
  - Talk to him / her directly
  - Speak up at meetings
  - Look for announcements

- Volunteer to participate, e.g., to contribute to responses to requests for public comments

- Be smart and articulate
EXAMPLES

To illustrate challenges that arise in practice
(not to generate controversy)
Benefits and harms of erythropoiesis-stimulating agents for anemia related to cancer: a meta-analysis

Marcello Tonelli MD SM, Brenda Hemmelgarn PhD MD, Tony Reiman MD SM, Braden Manns MD MSc, M. Neil Reaume MD MSc, Anita Lloyd MSc, Natasha Wiebe MMath PStat, Scott Klarenbach MD MSc


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<table>
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<th>No treatment n/N</th>
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<td>1.27 (0.35–4.65)</td>
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<td>3/114</td>
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<td>5/40</td>
<td>1.88 (0.68–5.22)</td>
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<td><strong>Overall</strong></td>
<td>291/2163</td>
<td>207/1581</td>
<td>1.12 (0.97–1.29)</td>
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<td><strong>Darbepoetin therapy v. no therapy</strong></td>
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<td>Vansteenkiste et al., 2002</td>
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<td>19/158</td>
<td>1.17 (0.66–2.08)</td>
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<td>4/170</td>
<td>2.44 (0.78–7.64)</td>
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<td>Smith et al., 2008</td>
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<tr>
<td><strong>Overall</strong></td>
<td>224/1626</td>
<td>153/1155</td>
<td>1.22 (1.01–1.47)</td>
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<tr>
<td><strong>Overall</strong></td>
<td>515/3789</td>
<td>360/2736</td>
<td>1.15 (1.03–1.29)</td>
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**Figure 2:** Effect of treatment with erythropoiesis-stimulating agents versus no treatment on all-cause mortality. CI = confidence interval. The letters X and Y following study names are indicated for studies with more than one treatment arm.
<table>
<thead>
<tr>
<th>Patient subgroup</th>
<th>Mortality</th>
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<tr>
<td></td>
<td>n/N</td>
<td>RR (95% CI)</td>
<td>I², %</td>
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<tr>
<td>Any hemoglobin level at baseline</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>All patients</td>
<td>31/6525</td>
<td>1.15 (1.03–1.29)</td>
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<tr>
<td>No chemotherapy-induced anemia</td>
<td>8/2252</td>
<td>1.22 (1.06–1.40)</td>
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<tr>
<td>Chemotherapy-induced anemia</td>
<td>23/4273</td>
<td>1.04 (0.86–1.26)</td>
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<td>Target hemoglobin &lt; 120 g/L</td>
<td>9/2436</td>
<td>1.15 (0.94–1.40)</td>
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<td>Baseline hemoglobin &lt; 100 g/L</td>
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<tr>
<td>All patients</td>
<td>14/3631</td>
<td>1.04 (0.81–1.32)</td>
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<td>Chemotherapy-induced anemia</td>
<td>13/2646</td>
<td>0.96 (0.73–1.26)</td>
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<td>Chemotherapy-induced anemia, target hemoglobin &lt; 120 g/L</td>
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<td>0.77 (0.36–1.66)</td>
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<td>Baseline hemoglobin 100–120 g/L</td>
<td>14/2478</td>
<td>1.16 (0.99–1.36)</td>
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<td>Baseline hemoglobin &gt; 120 g/L</td>
<td>1/94</td>
<td>3.00 (0.13–71.82)</td>
<td>NA</td>
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<tr>
<td>Baseline hemoglobin unclear</td>
<td>2/322</td>
<td>2.20 (0.38–12.79)</td>
<td>34</td>
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</tr>
</tbody>
</table>

Note: RR = relative risk, CI = confidence interval, NA = not applicable.
Figure 5: Mortality in all patients with cancer during active study periods, stratified by patient characteristics. Solid circles represent subgroup hazard ratios (HRs). Horizontal lines indicate 95% CIs. The p value for interaction is based on fixed-effects Cox model stratified by study. Subgroups of patients with unknown or missing values for a variable are shown but are excluded from the interaction test. ESA—erythropoiesis-stimulating agents. n—number of deaths. N—number of patients.
Issues Raised by ESA Analyses

• Were study designs “appropriate” for understanding mortality?
  – Length of follow-up? (why discard any data?)
  – Study size? (why discard any data?)
  – Predefining subgroups of interest (e.g., anemia correction vs. beyond anemia correction)
  – Standardizing definitions of thrombotic events
Implications for Development

• We can’t always anticipate what the future “issues” are likely to be, but...

• When we can anticipate, we should standardize data collection and definitions across the program (and into the post-approval setting)

• Think about study designs and how they fit together (“meta-design”)
What’s a statistician to do?

• Play a central role in all of this!
Acknowledgements


• Chrissie Fletcher, Greg Campbell and Ivan Chan for borrowing a couple of their past presentation slides.
Evolving Role of Statisticians

Little use of Statistics =>

“Required” use of Clin Statistics =>

Tactical use of Statistics =>

Strategic use of Statistics & “Statistical Thinking”
Industry Perspective: “Then”

- Statisticians were hired to get things through the regulatory agency (mostly in the US)
- Statisticians blessed clinical trial designs with minimal intellectual participation except sample size
- Statisticians focused on trials and manufacturing
- There was very little statistical input outside of “the necessary”, low involvement in non-clinical areas
- Statisticians played a secondary role
Statistician’s Role: Now and the Future

- Full and equal partner with basic, clinical & regulatory scientists as articulated in the ICH-E9 document
- Focus on experimental design and development strategy
- Application of statistical thinking throughout the life cycle of a pharmaceutical product
- Parallel development in other disciplines such as epidemiology, genomics, data mining, biomarker development, portfolio evaluation and risk management has expanded statistician’s contributions
Scientific Opportunities for Statisticians

• Methods to support all aspects of personalized medicine including biomarkers and subgroup strategy (the payer environment)
• Adaptive strategies at the program level
• Standards for accessing and analyzing electronic health records for effectiveness and safety
• A common framework for risk/benefit assessment
Personal Strategy

• Learn the power of networking as our work environment becomes increasingly more virtual
• Continue to broaden our knowledge base and keep our minds open – we don’t know as much as we think we do
• Allow flexibility in our career paths – consider a secondment and learn non-statistical skills
• Volunteer and take advantage of opportunities, big and small, to build leadership qualities
Leadership Qualities

• Ability to let go of the small stuff and focus on the big picture
• **Effective communication** – the power of open, frequent, candid (and ARTICULATE) communication
• Leadership by actions – People watch what we do
• Willingness to see things as they are, not as what we wish them to be!!!!!! (The power of “group think”)
• Wisdom to know when to step in and when to get out of the way
21\textsuperscript{st} Century Pharma Statisticians

- Being technically smart is not enough:
  - Understand the broad clinical, regulatory and public-health context
  - Communicate statistical strengths and weaknesses
  - Know when to “dig your heels in” and when it’s OK to compromise
Authors/Acknowledgements*

Authors (alphabetical order):

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