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

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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

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Study	Treatment n/N	No treatment n/N	Relative risk (95% CI)
Epoetin therapy v. no therapy			
Rose et al.,[19] 1994	11/142	4/79	1.53 (0.50–4.65)
Cazzola et al.,[20] 1995	4/117	3/29	0.33 (0.08–1.40)
Osterborg et al.,[21] 1996 X	15/47	7/25	1.14 (0.54–2.42)
Osterborg et al.,[21] 1996 Y	11/48	7/24	0.79 (0.35–1.77)
Dammacco et al.,[24] 1998	9/40	5/31	1.40 (0.52–3.74)
Johnson Pharm,[23] 1998	8/136	3/65	1.27 (0.35–4.65)
Kettelhack et al.,[26] 1998	2/52	0/57	5.47 (0.27–111.39)
Oberhoff et al.,[27] 1998	8/114	14/104	0.52 (0.23–1.19)
ten Bokkel Huinink et al.,[28] 1998 X	1/45	1/17	0.38 (0.03–5.71)
ten Bokkel Huinink et al.,[28] 1998 Y	5/42	1/16	1.90 (0.24–15.07)
Dammacco et al.,[30] 2001	1/69	7/76	0.16 (0.02–1.25)
Littlewood et al.,[31] 2001	35/251	22/124	0.79 (0.48–1.28)
Osterborg et al.,[33] 2002	28/170	22/173	1.30 (0.77–2.17)
Bamias et al.,[36] 2003	7/72	4/72	1.75 (0.54–5.72)
Henke et al.,[38] 2003	109/180	89/171	1.16 (0.97–1.40)
Christodoulakis et al.,[44] 2005 X	2/69	0/34	2.50 (0.12–50.67)
Christodoulakis et al.,[44] 2005 Y	3/67	0/34	3.60 (0.19–67.81)
Mystakidou et al.,[45] 2005	3/50	3/50	1.00 (0.21–4.72)
O'Shaughnessy et al.,[46] 2005	1/47	0/47	3.00 (0.13–71.82)
Witzig et al.,[47] 2005	12/166	10/164	1.19 (0.53–2.67)
Shanghai Roche Pharm,[49] 2006	1/30	0/30	3.00 (0.13–70.83)
Shanghqi Roche Pharm,[48] 2006	4/61	0/60	8.85 (0.49–160.97)
Wilkinson et al.,[50] 2006	3/114	0/59	3.65 (0.19–69.55)
Strauss et al.,[54] 2008	8/34	5/40	1.88 (0.68–5.22)
Overall	291/2163	207/1581	1.12 (0.97–1.29)
Darbepoetin therapy v. no therapy			
Vansteenkiste et al.,[56] 2002	22/156	19/158	1.17 (0.66–2.08)
Hedenus et al.,[57] 2003	10/174	4/170	2.44 (0.78–7.64)
Kotasek et al.,[58] 2003	7/198	3/51	0.60 (0.16–2.24)
Taylor et al.,[59] 2005	20/193	23/193	0.87 (0.49–1.53)
Charu et al,[61] 2007	16/226	3/59	1.39 (0.42–4.62)
Gordon et al.,[64] 2008	11/164	5/54	0.72 (0.26–1.99)
Smith et al.,[65] 2008	138/515	96/470	1.31 (1.04–1.65)
Overall	224/1626	153/1155	1.22 (1.01–1.47)
Overall	515/3789	360/2736	1.15 (1.03–1.29)

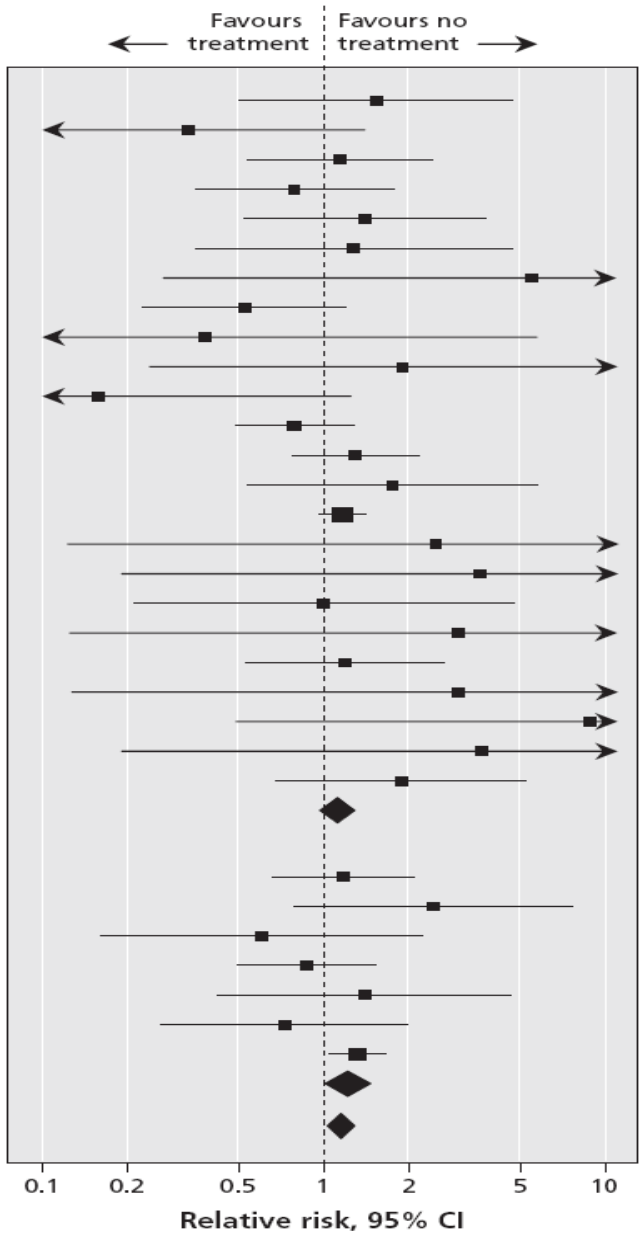


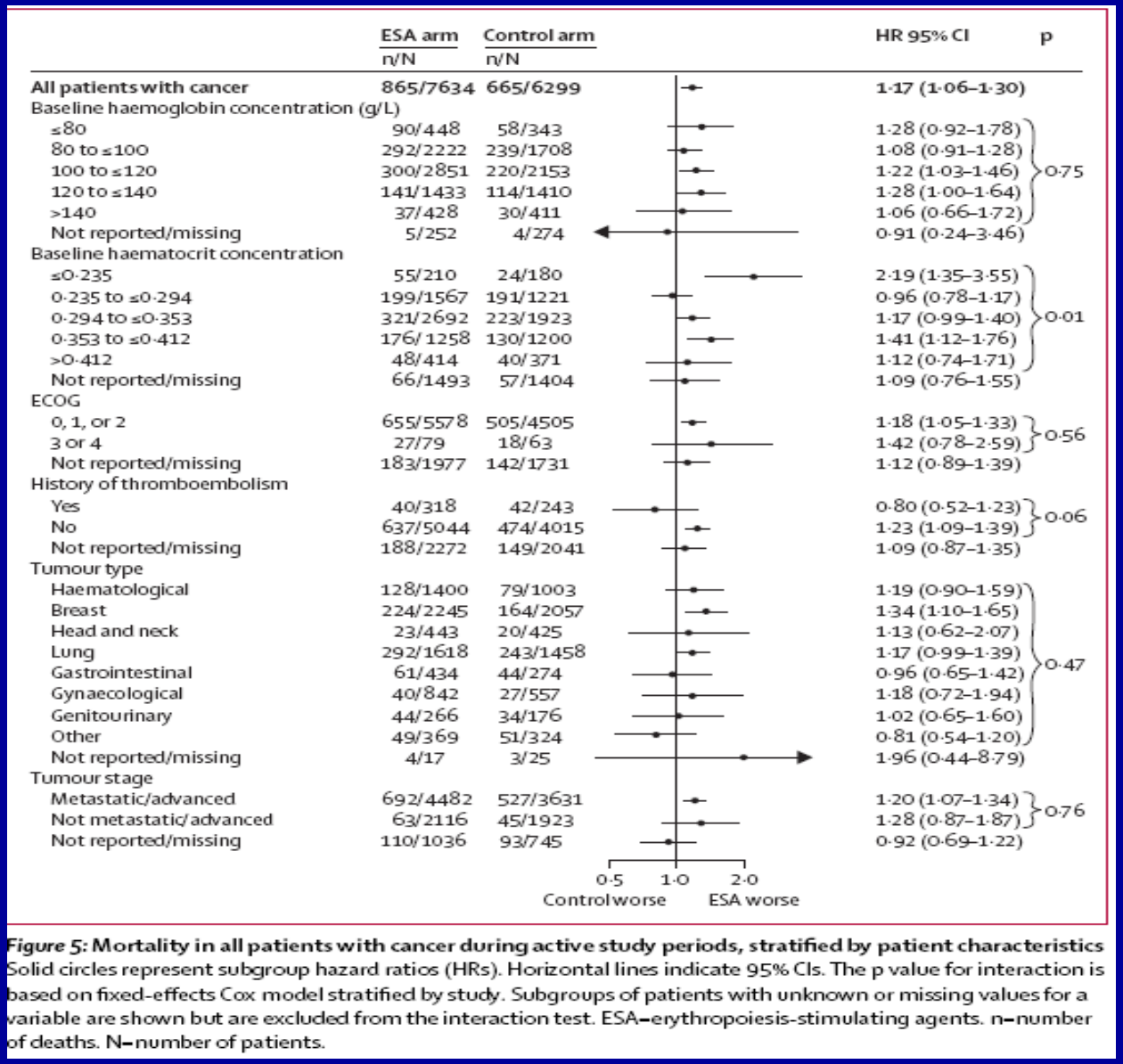
Figure 2: Effect of treatment with erythropoiesis-stimulating agents versus no treatment on all-cause mortality. CI = confidence interval. The letters X and Y following study names are indicated for studies with more than one treatment arm.

From Table 1 of CMAJ

Patient subgroup	Mortality		
	n/N	RR (95% CI)	I^2, %
Any hemoglobin level at baseline			
All patients	31/6525	1.15 (1.03–1.29)	0
No chemotherapy-induced anemia	8/2252	1.22 (1.06–1.40)	0
Chemotherapy-induced anemia	23/4273	1.04 (0.86–1.26)	0
Target hemoglobin < 120 g/L	9/2436	1.15 (0.94–1.40)	2
Baseline hemoglobin < 100 g/L			
All patients	14/3631	1.04 (0.81–1.32)	28
Chemotherapy-induced anemia	13/2646	0.96 (0.73–1.26)	18
Chemotherapy-induced anemia, target hemoglobin < 120 g/L	3/289	0.77 (0.36–1.66)	41
Baseline hemoglobin 100–120 g/L	14/2478	1.16 (0.99–1.36)	0
Baseline hemoglobin > 120 g/L	1/94	3.00 (0.13–71.82)	NA
Baseline hemoglobin unclear	2/322	2.20 (0.38–12.79)	34

Note: RR = relative risk, CI = confidence interval, NA = not applicable.

Figure 5: Lancet (using IPD)



	ESA arm n/N	Control arm n/N	HR 95% CI	p
All patients with cancer	865/7634	665/6299	1·17 (1·06–1·30)	
Baseline haemoglobin concentration (g/L)				
≤80	90/448	58/343	1·28 (0·92–1·78)	
80 to ≤100	292/2222	239/1708	1·08 (0·91–1·28)	
100 to ≤120	300/2851	220/2153	1·22 (1·03–1·46)	0·75
120 to ≤140	141/1433	114/1410	1·28 (1·00–1·64)	
>140	37/428	30/411	1·06 (0·66–1·72)	
Not reported/missing	5/252	4/274	0·91 (0·24–3·46)	
Baseline haematocrit concentration				
≤0·235	55/210	24/180	2·19 (1·35–3·55)	
0·235 to ≤0·294	199/1567	191/1221	0·96 (0·78–1·17)	
0·294 to ≤0·353	321/2692	223/1923	1·17 (0·99–1·40)	0·01
0·353 to ≤0·412	176/1258	130/1200	1·41 (1·12–1·76)	
>0·412	48/414	40/371	1·12 (0·74–1·71)	
Not reported/missing	66/1493	57/1404	1·09 (0·76–1·55)	
ECOG				
0, 1, or 2	655/5578	505/4505	1·18 (1·05–1·33)	0·56
3 or 4	27/79	18/63	1·42 (0·78–2·59)	
Not reported/missing	183/1977	142/1731	1·12 (0·89–1·39)	
History of thromboembolism				
Yes	40/318	42/243	0·80 (0·52–1·23)	0·06
No	637/5044	474/4015	1·23 (1·09–1·39)	
Not reported/missing	188/2272	149/2041	1·09 (0·87–1·35)	
Tumour type				
Haematological	128/1400	79/1003	1·19 (0·90–1·59)	0·47
Breast	224/2245	164/2057	1·34 (1·10–1·65)	
Head and neck	23/443	20/425	1·13 (0·62–2·07)	
Lung	292/1618	243/1458	1·17 (0·99–1·39)	
Gastrointestinal	61/434	44/274	0·96 (0·65–1·42)	
Gynaecological	40/842	27/557	1·18 (0·72–1·94)	
Genitourinary	44/266	34/176	1·02 (0·65–1·60)	
Other	49/369	51/324	0·81 (0·54–1·20)	
Not reported/missing	4/17	3/25	1·96 (0·44–8·79)	
Tumour stage				
Metastatic/advanced	692/4482	527/3631	1·20 (1·07–1·34)	0·76
Not metastatic/advanced	63/2116	45/1923	1·28 (0·87–1·87)	
Not reported/missing	110/1036	93/745	0·92 (0·69–1·22)	

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!

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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

21st 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

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