Session Outline

• First ~ 60 min
  – Each fellow will provide ‘highlights’ of their career focusing on lessons learned

• Last ~ 30 min
  – Panel discussion from fellows on 2 questions facing current clinical trialists
Fellows Line-up

• Simon Day
• Wendy Parulekar
• Ivan Chan
• Eleanor Mcfadden
• Daniel Sargent
Reflections and Discussion of Current Controversies in Clinical Trials
Perspectives from SCT Fellows

Boston 20th – 22nd May 2013

Dr Simon Day
Me?

• Elected a Fellow in 2012
• Citation:

“For having influenced the practice and evaluation of clinical trials as an industry leader and expert in clinical trials; for education through publications, lectures, and courses, notably on the Science of Small Clinical Trials; and as a regulator having positively impacted the practice of clinical trial design and analysis.”

• Very flattering!
This year’s session (like previous years)

• “...each Fellow will provide insight into a clinical trial of special relevance to their career with specific emphasis to their involvement in the clinical trial and lessons learned.”
Where does the torrent start?
The torrent grows...
And eventually...
So what are those rain drops I helped create?


≈800
Orphan drugs; orphan indications; orphan products
Orphan drugs; orphan indications; orphan products

Institute of Medicine, 2001
Orphan drugs; orphan indications; orphan products

Getting Reliable Evidence

Dr Simon Day

International Conference on Rare Diseases & Orphan Drugs
The Science of Small Clinical Trials Course

FDA White Oak Campus, Silver Spring, Maryland, November 27–28, 2012

On Wednesday and Thursday, November 27 and 28, 2012, the Food and Drug Administration (FDA) Office of Orphan Products Development along with the National Institutes of Health (NIH), Office of Rare Diseases Research (ORDR), National Center for Advancing Translational Sciences (NCATS), held the Science of Small Clinical Trials Course at the FDA White Oak Campus in Silver Spring, MD. The course covered techniques for clinical studies with limited sample sizes including a focus on the study of rare diseases, and provided examples of how such methods have been implemented. There were over 80 attendees from government, academia, industry, and patient advocacy groups and more than 200 additional participants who joined the event via live webcast.
Orphan indications

• In the US, “fewer than 200,000 persons affected” (≈1 in 3,500)
• In Japan, “fewer than 50,000 patients” (≈1 in 2,500)
• In the EU, “fewer than 1 in 2,000 people affected” (≈250,000)

• Generally between $\frac{1}{200,000}$ to $\frac{1}{1,000}$

• Many orphan diseases are “ultra-orphan”
  • 100s of cases
  • 10s of cases
My contribution

• I think(!) has been to
  • Be practical
  • Be objective
  • Be flexible
  • Be compassionate
  • Be really passionate!

• Convince others (by example) that there are ways to study treatments for rare diseases, that can be
  • better than just doing nothing, and
  • better than just doing bad science
**Orphan indications**

- In the US, fewer than 200,000 persons affected (≈1 in 3,500)
- In Japan, fewer than 50,000 patients (≈1 in 2,500)
- In the EU, fewer than 1 in 2,000 people affected (≈250,000)
- Generally between $\frac{1}{200,000}$ to $\frac{1}{1,000}$
- BUT, between 7000 and 8000 recognised orphan diseases
- Burden on US is about 30 million patients
Many small contributions
Many rare disease
Perspectives From a SCT Fellow

Ivan S. F. Chan, Ph.D.
Merck Research Laboratories

Society For Clinical Trials Annual Meeting
Boston, MA

May 19-23, 2013
A Few Words About Me

- Born in China, grew up in Hong Kong, live in US
- Studied Statistics (MS) and Biostatistics (PhD)
  - The Chinese University of Hong Kong
  - University of Minnesota
- Work at Merck Research Laboratories
  - Executive Director, Late Development Statistics
- SCT participation since 1997, key activities include
  - Program Committee Chair (2008)
  - Industry/FDA Affinity Group Chair (2009-2011)
  - Development Committee Chair (2011 to present)
  - Board of Directors (2011 to 2015)
SCT Fellow, class of 2011

Citation reads

For significant contributions to the advancement of the science and practice of clinical trials

Very honored…
Contributions to Clinical Research

- Trial design and analysis for vaccine studies
  - Exact statistical inference for large efficacy studies of rare diseases
  - Noninferiority trials
  - Adaptive designs
    - Seamless phase II/III design
    - Dose selection using biomarker
    - Population enrichment
    - 2-stage design with sample size re-estimation
Contributions to Clinical Research

Evaluation of correlates of protection (biomarkers) for vaccines

- Statistical modeling for predicting efficacy of chickenpox vaccine (Varicella) based on antibody responses
- Causal inference approach to evaluate antibody response as a correlate of protection for herpes zoster vaccine
Contributions to Clinical Research

Strategic planning and interactions with regulatory agencies and government bodies (e.g. FDA, CDC) on vaccine approval and national immunization practice recommendation

– Varicella vaccine (VARIVAX®)
– Herpes zoster vaccine (ZOSTAVAX®)
– HPV vaccine (GARDASIL®)
– Measles-mumps-rubella-varicella combination vaccine (ProQuad®)
Trial Involvement:
Herpes Zoster Vaccine (ZOSTAVAX®)

- Lead statistician from phase I to phase III and approval process
- Herpes zoster (HZ)
  - A viral disease characterized by a painful skin rash with blisters
  - Caused by reactivation of varicella-zoster virus (VZV)
- Two large phase III efficacy trials:
  - Protocol 004: ~38,000 subjects 60+ years of age
  - Protocol 022: ~22,000 subjects 50-59 years of age
Shingles Prevention Study (SPS)  
(Protocol 004/403, Oxman et al., NEJM 2005)

- Double-blind, placebo-controlled, multicenter trial
- N = 38,546 subjects ≥60 years of age randomized 1:1 to receive ZOSTAVAX® or placebo
- Conducted by Dept. of Veteran Affairs Cooperative Studies Program (VA CSP) in collaboration with the National Institutes of Health (NIH) and Merck & Co., Inc.
- Close collaboration with VA CSP at West Haven, CT  
  (Peter Peduzzi, Gary Johnson, Jane Zhang)
Key Efficacy Endpoints of SPS

- **HZ incidence**

- **Postherpetic neuralgia (PHN)**
  - Clinically significant pain persisting for or present after 90 days of HZ rash onset

- **HZ pain burden of illness (BOI)**
  - Composite of incidence, severity, and duration of pain
    (Chang, Guess and Heyse 1994)
  - Novel endpoint
ZOSTAVAX® Efficacy: HZ Incidence
Estimate of the Cumulative Incidence of HZ Over Time by Vaccination Group

VE_{HZ}=51%  
\ p<0.001

Number of subjects at risk

<table>
<thead>
<tr>
<th></th>
<th>ZOSTAVAX™</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>19254</td>
<td>19247</td>
</tr>
<tr>
<td>1</td>
<td>18994</td>
<td>18915</td>
</tr>
<tr>
<td>2</td>
<td>18626</td>
<td>18422</td>
</tr>
<tr>
<td>3</td>
<td>9942</td>
<td>9806</td>
</tr>
<tr>
<td>4</td>
<td>1906</td>
<td>1856</td>
</tr>
</tbody>
</table>
ZOSTAVAX® Efficacy

25% = prespecified lower bound success criterion

HZ

PHN

BOI

25% = prespecified lower bound success criterion

Vaccine Efficacy (%)
Correlate of Protection Analysis From Two Phase III Trials of ZOSTAVAX® (Antibody Responses by gpELISA)

<table>
<thead>
<tr>
<th>Study Protocol</th>
<th>Population</th>
<th>Vaccine Effect on incidence of HZ</th>
<th>Vaccine effect on antibody response</th>
<th>Correlation between antibody and risk of HZ</th>
</tr>
</thead>
<tbody>
<tr>
<td>004 sub-study (N=38546,n=1328)</td>
<td>60+ years</td>
<td>51% (p &lt;.0001)</td>
<td>1.7 fold (p &lt;.0001)</td>
<td>38% risk reduction per one-log-unit increase (p &lt;.0001)</td>
</tr>
<tr>
<td>022 case-cohort (N=22439,n=2269)</td>
<td>50-59 years</td>
<td>70% (p &lt;.0001)</td>
<td>2.3 fold (p &lt;.0001)</td>
<td>31% risk reduction per one-log-unit increase (p &lt;.0001)</td>
</tr>
</tbody>
</table>

VZV antibody response measures (natural log scale):
(1) gpELISA titer at 6 weeks
(2) gpELISA fold rise at 6 weeks (6-week titer/baseline titer)
Correlate of Protection Analysis

Antibody responses by gpELISA: Titer + \[\text{foldrise}>\text{cutoff}\]

- Prentice’s Criteria

<table>
<thead>
<tr>
<th>Study</th>
<th>Proportion of Treatment Effect Explained (PTE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>004</td>
<td>0.783</td>
</tr>
<tr>
<td>022</td>
<td>0.645</td>
</tr>
</tbody>
</table>

- Causal inference analysis also shows the antibody response predicts vaccine efficacy
- Antibody responses accepted as primary endpoint for subsequent bridging trials
Vaccine Efficacy Curve
Lessons Learned

- Like the industry-government partnership
- Enjoyed the close collaboration with VA CSP at West Haven, CT (Peter Peduzzi, Gary Johnson, Jane Zhang)
  - Design, analysis, and reporting (publication, CSR, filing)
  - Interaction with PIs and DSMB
- Statistical innovation can improve clinical development process
- Overall, feel good to see public health benefit from a great vaccine
WHAT HAVE I DONE?

Eleanor McFadden
Managing Director, Frontier Science (Scotland) Ltd
Brief History

- Started work as a Data Manager for the Eastern Cooperative Oncology Group in 1977. Frontier Science was grantee organisation.
- Became head of the data management team in 1978 and eventually Director of the ECOG Coordinating Centre in the late 1980’s.
History (ctd)

- Worked with ECOG for more than 20 years
- Moved back to Scotland in 2000 and established a branch of Frontier Science
- Since then, working primarily on industry sponsored studies via a not-for-profit organisation in Belgium
Areas of Experience

- Data Management
- IT systems for clinical trials
- Site monitoring/ audits
- Project Management
Contributions

- Recognition of Data Management as a profession which makes key contribution to the overall success of clinical trials
- Development of Intergroup Guidelines for the US Cancer Cooperative Groups, working together when relevant
- Development of on-site audit program for cancer cooperative groups in late 70’s/ early 80’s
Contributions (2)
Clinical Trial Highlight

- HERA Trial – first project after I moved back to Scotland from Boston
- Involved in data management, project management and statistics
- Allowed me to establish Frontier Science (Scotland) as a viable entity
Office in Scotland
HERA

- Most overwhelmingly statistically significant trial that I remember working on
- Data released at time of first interim analysis
- Used in submissions around the world to get approval for use of Herceptin in women with HER2 +ve early stage breast cancer
- Helped to give hundreds of women access to this treatment
Disease-free survival

Median follow-up: 1 year
HR, hazard ratio; CI, confidence interval

SABCS 2005
Lessons Learned

- Too many to talk about!
Daniel Sargent: About me

- Graduate of U of MN – 1996
- Immediately to Mayo Clinic, started working on colon cancer clinical trials
- 2000: NCCTG Group Statistician
- 2001: Director, Biostatistics, Mayo Clinic Cancer Center
- 2010: CALGB Group Statistician
- 2011: Alliance for Clinical Trials in Oncology Group Stat
- Professor of Biostatics and Oncology, Mayo Clinic
Research Focus Areas

• Very large pooled analyses of endpoints and subsets

• Prospective validation of biomarkers in stage II and III colon cancer
NOW > 33,000 Patients

~ dozen high profile publications

- Very young
- Elderly
- Race

Similar Database (> 22,000 patients) in metastatic CRC

Overall survival

Disease-free survival
IDEA: International Duration Evaluation in Adjuvant colon cancer

- Worldwide effort to address duration of chemotherapy (3 vs 6 mos)

**Common question**

- 3 mos
- 6 mos

**Group-specific question**

- e.g.
  - +/- BEV
  - +/- Celecoxib
  - +/- Agents X/Y/Z

- Participating groups
  - CALGB/SWOG (US); GISCAD (Italy – TOSCA)
  - SCOT (UK, Australia); HORG (Greece)
  - GERCOR (France); ACHIEVE (Japan)

- Stage III colon cancer, ≥ 10,500 total patients
- Non-inferiority margin of 2.5%
Other database activities

• RECIST database mining (S Mandrekar, M An)

• Follicular Lymphoma – FLASH (Q Shi)

• Pancreas (forming)
Biomarker Validation through pooled analyses

GCC as a molecular Marker for Recurrence in Low Risk Stage II Patients

LN > 12, T3, and negative margins (n=181)

Overall Survival by Treatment, stage II dMMR patients

<table>
<thead>
<tr>
<th>Risk Group Classifications</th>
<th>Group Stratification</th>
<th>N (%</th>
<th>Recurrence-Free Survival at 5 yrs (K-M Estimates)</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>&gt; 0.10</td>
<td>64 (35.4%)</td>
<td>73.1%</td>
</tr>
<tr>
<td>Low</td>
<td>0–0.10</td>
<td>117 (94.6%)</td>
<td>96.0%</td>
</tr>
</tbody>
</table>

HR 5.06 (1.61-15.91) p-value: 0.003

Ongoing 500 patient trial
Mayo Coordinating and Statistical Center

Sargent et al, Annals Surg Onc, 2011

P-value = 0.014 for treatment by MMR status interaction

Untreated 5 yr OS

N = 55

Treated

N = 47

Untreated 93%

Treated 75%

HR: 3.15 (1.07-9.29) p=0.03

Sargent et al, JCO 2010
Lessons learned

• If you can, intensely focus within a disease area

• Non MDs can lead large projects with (extensive clinician collaboration)

• Data is precious, and highly underused – tremendous opportunities for new discovery

• Respect your collaborators – then they will trust you
Panel Discussion
Question #1

• What is the greatest challenge facing the clinical trials community in 2013?
Question #2

• What should we as clinical trialists, and the SCT more broadly, be doing to ensure that public policy is based on sound, evidenced based data?