Strengths and limitations of industry vs. academic randomised controlled trials

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Conflicts of interests

• Advisory board or associated:
  - Ferring
  - Aridis
  - Medimmune
  - Eumedica
  - Tigenix
Industry sponsored trials benefits

- New drugs and compounds
- Excellent basic science and preclinical data
- Provide important « logistics »
- Well structured organisation and work
- Regulatory authorities experience
- Monitoring complete
- And use of CRO
Academic research

- Basic science to understand mechanisms of disease
- Clinical expertise and access to patients
- Better defines the target population in clinical studies
- Endpoint not driven by marketing issues
- Agenda not tight
- Single center, or network of known colleagues supporting a concept
Academic research

But ..

- Limited resources
- Data collection often less complete
- Monitoring more restricted
- Regulatory: often limited knowledge
- Prolonged study duration, slowing recruitment over time and study termination not always reaching the predefined sample size
# Working with Industry: What Is the Conflict?

Peter W. Marcello, MD


<table>
<thead>
<tr>
<th>Mission of academic health center</th>
<th>Mission of drug, medical device, or biotech company</th>
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<tbody>
<tr>
<td>Conduct basic research to understand the mechanisms of disease and human functioning</td>
<td>Develop new products that will generate profits for the company</td>
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<td>Train graduate students and fellows to become independent investigators who can compete effectively for funding from the National Institutes of Health</td>
<td>Encourage graduate students and fellows to carry out research on the company’s promising products for development</td>
</tr>
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<td>Promote evidence-based medicine and independent critical judgment by physicians</td>
<td>Develop marketing strategies to improve sales and profits</td>
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<td>Provide cost-effective care to patients and achieve a profit margin from clinical care that can be used to subsidize other activities</td>
<td>Increase profits through increased sales of products</td>
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<td>Improve public health, global health, and care for orphan diseases for which patients seek care at the hospital</td>
<td>Work on issues of public health and global health and on treatments for orphan diseases if it fits the company’s business model or plan for charitable giving or enhances its reputation</td>
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Source: From Lo. Reprinted with permission of the Massachusetts Medical Society.
Educational investigator benefits?

Table 1: Missions of academic health centers and medical companies

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Mistakes from industry?

- Phase II signals generating Phase III are underpowered. Patient’s model based on phase II leads to unrealistic scenario.

- Population selection of non-existing population.
- Review and adjust endpoints according to market.
- Rush! Agenda and timelines are not realistic.
- Pushing recruitment to meet targets.
- Non-inferiority to access to market.
- Selected populations with low or moderate risk of dying, low associate comorbidities to prevent from poor outcome: the more severe population or with a potential bigger benefit often excluded.

- Less likely to publish negative trials. Access to databank?
Anti-Inflammatory Sepsis Trials
Apparent Benefit and Confidence Intervals

Natanson et al.
Crit Care Med
26:1927-1931, 1998
E. coli Lipid A Versus Eritoran (E5564) as a Lipid A Antagonist

E. coli lipid A

TLR4 binding site

β hydroxyl myristic acid (3)

Hexa-acyl format

C-length (2)

Tetra-acyl format (1)

E. coli Lipid A

Eritoran Phase II Clinical Trial

High-Risk Patients: APACHE II >50%

- Low-dose eritoran: 45 mg/6 days (n=58)
- High-dose eritoran: 105 mg/6 days (n=51)
- Placebo (n=53)

**Graph:**
- Probability of Survival (%) vs. Study Day
- Key:
  - Placebo (n=53)
  - Low-dose eritoran: 45 mg/6 days (n=58)
  - High-dose eritoran: 105 mg/6 days (n=51)

Statistical Significance:
- P=0.07

References:
- Tidwell et al. *Crit Care Med* 2010;38:72-83
Eritoran Phase II Clinical Trial

Prospectively Defined Subgroups

Mortality by APACHE II Quartile

- Placebo
- 105 mg eritoran

Mortality by Presence of Shock

- Presence of Shock at Baseline

P=0.598
P=0.434
P=0.105
P=0.083
P=0.503
P=0.913

Tidwell et al. Crit Care Med 2010;38:72-83
Quality and completeness of data documentation in an investigator-initiated trial versus an industry-sponsored trial.

Patwardhan S¹, Gogtay N¹, Thatte U¹, Pramesh CS².


Study to compare the quality of data and documentation in an investigator-initiated trial (IIT) with those in an industry-sponsored study.

Investigator-initiated studies carried out by independent researchers in high-volume academic centres, even without active data monitoring and formal audits, appear to adhere to the high standards.
Study monitoring

- Pro  Industry driven studies
  - Properly organized and defined
  - GCP followed
  - SAE definitions strict
  - All events recorded
  - Dedicated personnel
  - Structured reporting during studies
Study monitoring

- **Con**
  - Use of dedicated CRO
  - Experience in the field?
  - Concentrate on less relevant data (metrics)
  - Missing the big picture?
  - Change in personnel
  - Repeated irrelevant queries
  - Associated cost
Industry sponsored research:

Influence of industry on trial findings?

More likely to favour the product developed by the company?
Industry sponsorship bias in research findings: a network meta-analysis of LDL cholesterol reduction in randomised trials of statins

Huseyn Naci research fellow; fellow in pharmaceutical policy research, Sofia Dias research fellow, A E Ades professor

BMJ 2014;349:g5741 doi: 10.1136/bmj.g5741 (Published 3 October 2014)

**Fig 5** Dose comparative effects of statins on serum low density lipoprotein (LDL) cholesterol concentration in industry sponsored clinical trials versus non-industry sponsored trials. Findings from industry sponsored trials are shown in white and findings from non-industry sponsored trials are shown in blue. Estimates shown are mean (95% credible interval) change from baseline serum LDL cholesterol concentration compared with control
Industry sponsorship bias in research findings: a network meta-analysis of LDL cholesterol reduction in randomised trials of statins

Huseyin Naci research fellow; fellow in pharmaceutical policy research\textsuperscript{1,2}, Sofia Dias research fellow\textsuperscript{3}, A E Ades professor\textsuperscript{3}

*BMJ* 2014;349:g5741 doi: 10.1136/bmj.g5741 (Published 3 October 2014)

**Conclusions** Our analysis shows that the findings obtained from industry sponsored statin trials seem similar in magnitude as those in non-industry sources. There are actual differences in the effectiveness of individual statins at various doses that explain previously observed discrepancies between industry and non-industry sponsored trials.
Treatment Success in Cancer: Industry Compared to Publicly Sponsored Randomized Controlled Trials

Benjamin Djulbegovic$^{1,2,3}$, Ambuj Kumar$^{1,2,3}$, Branko Miladinovic$^{1,2}$, Tea Reljic$^{1,2}$, Sanja Galeb$^{3}$, Asmita Mhaskar$^{1,2}$, Rahul Mhaskar$^{1,2}$, Iztok Hozo$^{4}$, Dongsheng Tu$^{5,6}$, Heather A. Stanton$^{5}$, Christopher M. Booth$^{5,6,7}$, Ralph M. Meyer$^{5,6,7}$

Industry sponsored studies associated with more success?

Figure 2. Success rate of GlaxoSmithKline (GSK) compared with National Cancer Institute Canada Clinical Trials Group (CTG) cohort of studies. (A) Distribution of success rate according to statistical significance of the results for the primary outcome; (B) Distribution of success rate according to investigators’ judgments. *Data for one comparison in the GSK cohort were not available to make a decision on investigators’ judgments. For ten comparison in the GSK cohort and two comparisons in the CTG cohort data were not available to make a judgment on whether investigators considered the experimental treatment to be a breakthrough (= fit for adoption as standard of care). **The results were available in the summary format (unpublished). Therefore, investigator judgments were not possible to assess for 10 comparisons. (C) Forest plot showing quantitative pooling of data on primary outcome for studies conducted by CTG and GSK. The summary pooled estimate (odds/hazard ratio) is indicated by rectangles, with the lines representing 99% confidence intervals (CIs).

doi:10.1371/journal.pone.0058711.g002
Figure 12. Meta-regression of effect of time (year of publication), choice of active control and sample size on the magnitude effect in National Cancer Institute Canada Clinical Trials Group (CTG) cohort of trials (A) and GlaxoSmithKline (GSK) cohort (B). None of the variables were statistically significant in NCIC CTG cohort of trials ($R^2 = -0.68\%$). In GSK cohort sample size showed no statistical significant association with the results ($p = 0.08$) while year ($p = 0.048$) and the choice of comparator ($p < 0.000$) were statistically associated with the observed results in GSK cohort. These two variable accounted for about 72% of the observed variation in the results ($R^2 = 71.69\%$). In general, the effect size was closer to 1 (ln HR = 0) when the active comparator was employed.

doi:10.1371/journal.pone.0058711.g012
Association between funding source, methodological quality and research outcomes in randomized controlled trials of synbiotics, probiotics and prebiotics added to infant formula: A Systematic Review

Conclusion
This study assessed the impact of funding by the food industry on trial outcomes and methodological quality of synbiotics, probiotics and prebiotics research in infants. There was no significant association between source of funding and methodological quality of study in the domains of sequence generation, allocation concealment and blinding. Industry funded trials had less missing data and were free of other bias than non-industry funded trials.
PROWESS (Study EVAD): Cumulative Mortality Rates Over Time

First patient enrolled - amended protocol
Last patient enrolled - original protocol

Number of Sites = 164
Number of Patients = 1690

Placebo

Drotrecogin Alfa (activated)

Over Time (by Covance Randomization Date)
PROWESS (Study EVAD): Cumulative Mortality Sites
Enrolling at least 20 Patients

Number of Sites = 20
Number of Patients = 655

Placebo
Drotrecogin Alfa
(activated)

Over Time (by Covance Randomization Date)
Type of Violation by Sequence of Enrollment

Percentage of Patients

- Informed Consent
- Safety
- Inclusion/Exclusion
- Study Drug

Sequence of Patients within a Site

- 2
- 3-4
- 5-8
- 9-12
- >12

ESCMID Online Lecture Library
Survival curves of patients with ARF & MODS: CVVHDF vs HDI (60-day survival).

CVVHDF: 32.6% (25.6-39.5)

IHD: 31.5% (24.8-38.2)

C. Vinsonneau, JF Dhainaut et al.)
Cumulative Survival during the study period: CVVHDF vs IHD

Time Survival improvement (Cox model, p: 0.003)

CVVHDF: p: 0.62

IHD p < 0.0001

Dec. 2000 to March 2003

C. Vinsonneau, JF Dhainaut et al)
PAFASE Study (PAF-AH)

- **Severe Sepsis**
  - 1 or > OD (Sepsis-ind)

- **Time Window**:
  - < 12 h after 1st OD

- **Exclusion**:
  - ARDS
  - Steroids
  - Unsustained OD
  - Moribund, DNR, < 6 months
  - Child C
  - ....

CCM 2004
Excluded Population in PAF-AH: Severity and 28-day all cause mortality?

- Follow-up of excluded population
- Cause of exclusion, Severity score and 28-day all-cause mortality
- 3 centers (2 academic)
- N = 199
- APACHE II: 24 +/- 10 (study: 21.4 +/- 7)
- Mortality: 32.6% (study: 24.5%)
## Cause of Exclusion, severity and mortality

<table>
<thead>
<tr>
<th>Cause</th>
<th>n</th>
<th>death</th>
<th>mortality</th>
<th>APACHE</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARDS</td>
<td>11</td>
<td>5</td>
<td>45 %</td>
<td>28 (13-40)</td>
</tr>
<tr>
<td>Child C</td>
<td>7</td>
<td>5</td>
<td>71.4 %</td>
<td>27.3 (20-36)</td>
</tr>
<tr>
<td>CPR</td>
<td>10</td>
<td>7</td>
<td>70 %</td>
<td>35.5 (25-52)</td>
</tr>
<tr>
<td>DNR/limitat</td>
<td>14</td>
<td>11</td>
<td>78 %</td>
<td>27.2 (14-45)</td>
</tr>
<tr>
<td>Moribund</td>
<td>9</td>
<td>7</td>
<td>77.7 %</td>
<td>26.1 (15-33)</td>
</tr>
<tr>
<td>Surv &lt; 6m</td>
<td>24</td>
<td>11</td>
<td>45.8 %</td>
<td>27 (16-42)</td>
</tr>
<tr>
<td>Wind 12 h</td>
<td>15</td>
<td>3</td>
<td>20 %</td>
<td>22.4 (14-36)</td>
</tr>
<tr>
<td>Wind 24 h</td>
<td>18</td>
<td>5</td>
<td>27.7 %</td>
<td>23 (8-32)</td>
</tr>
<tr>
<td>OD unsustain</td>
<td>36</td>
<td>0</td>
<td>0 %</td>
<td>20.1(5-36)</td>
</tr>
</tbody>
</table>
Cost-effectiveness:
- Large population and recruitment potential
- Lower cost
- Potential market for industry

Limitations:
- GCP
- Investigators fee higher than salary with potential bias in recruitment
- Standard of care?
- Follow-up?
- Access to care for patients otherwise not accessible?
Discrepancy in SAE reporting?

Discrepancies in SAE from articles and registered summaries

Need for complete access from clinical trials
### Experience with the Open-Access Clinical Trial System, May 7, 2013, through May 31, 2014.*

<table>
<thead>
<tr>
<th>Part of the Process</th>
<th>No. of Proposals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Submission</td>
<td>58</td>
</tr>
<tr>
<td>Requirements check</td>
<td></td>
</tr>
<tr>
<td>In process</td>
<td>4</td>
</tr>
<tr>
<td>Withdrawn by the requestor</td>
<td>2</td>
</tr>
<tr>
<td>Did not meet requirements or further details were required</td>
<td>7</td>
</tr>
<tr>
<td>Met requirements</td>
<td>45</td>
</tr>
<tr>
<td>Review by independent review panel</td>
<td></td>
</tr>
<tr>
<td>In process</td>
<td>6</td>
</tr>
<tr>
<td>Rejected or advised to resubmit</td>
<td>3</td>
</tr>
<tr>
<td>Approved or approved with conditions</td>
<td>36</td>
</tr>
<tr>
<td>Data-sharing agreement</td>
<td></td>
</tr>
<tr>
<td>In process</td>
<td>12</td>
</tr>
<tr>
<td>Withdrawn by the requestor</td>
<td>1</td>
</tr>
<tr>
<td>Agreed and signed</td>
<td>23</td>
</tr>
<tr>
<td>Data preparation</td>
<td></td>
</tr>
<tr>
<td>In process</td>
<td>10</td>
</tr>
<tr>
<td>Complete, with data available</td>
<td>13</td>
</tr>
<tr>
<td>Research project in process</td>
<td>13</td>
</tr>
</tbody>
</table>

* A total of 4 of the 37 proposals submitted since January 2014 have included requests for data from multiple sponsors. The requirements check is the check done by the sponsor of the study whose data are being requested to make sure the information is complete and that the proposal meets the requirements of this initiative and the sponsor’s requirements for informed consent. Proposals are then sent to the independent review panel.
Sharing resources

IMI

Combacte and WP
Conclusions

• Industry sponsored risks and benefits are well balanced compared to investigators driven research.

• Industry should better design their study and objectives with the advises from academics.

• Academics should learn from the industry how to better organize and monitor their studies.

• Both should share the databanks to better explore the optimal populations and generate new hypothesis.
Conclusions and Future studies?

• Sites experience seems to be an important variable
• « Learning curve »? Each site acts as his own control?
• Less variability in centers with higher enrollment
• Less protocol violation over time
• Monitor protocol violation during study
• Sites failing to enroll at an acceptable rate or violations should be discontinued
• Need for a CC, CEC, and close monitoring of investigative sites.