Balancing the risks of harms and chances of benefits

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Stakeholders request benefit-risk analysis

Patients seek shared decision making\(^1\)

Physicians & FDA Advis. Comm\(^2\) request quantified benefit-risks

Payors (NICE-UK, etc) “weigh up the cost & benefits of treatments”\(^3\)

\(^1\) Kon AA. JAMA 2010;304:903-904.
\(^3\) http://guidance.nice.org.uk/
Current state of benefit-risk

- Benefit-Risk Action Team has worked to quantify benefit-risk for 6 years, with >10 companies
  - efforts now in Centre for Innovation in Regulatory Science

- Few benefit-risk analyses actually presented; limited published data is available.
Benefit-Risks are quantified and complex \(^1\)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Study drug risk(^a)</th>
<th>Placebo risk(^a)</th>
<th>Risk difference per 10,000 person-years</th>
<th>Risk difference forest plot(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac-vascular issues</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Angina requiring CABG</td>
<td>3.7</td>
<td>6.4</td>
<td>-2.6 (−6.4, 1.2)</td>
<td></td>
</tr>
<tr>
<td>Coronary heart disease death</td>
<td>31.0</td>
<td>33.6</td>
<td>-2.7 (−16.9, 11.6)</td>
<td></td>
</tr>
<tr>
<td>Lipid levels meet target</td>
<td>6700</td>
<td>2900</td>
<td>3800 (2,691, 4,909)</td>
<td></td>
</tr>
<tr>
<td>Nonfatal myocardial infarction</td>
<td>22.1</td>
<td>43.3</td>
<td>-21.2 (−95.2, 52.8)</td>
<td></td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Fatal ischemic stroke</td>
<td>18.6</td>
<td>35.4</td>
<td>-16.8 (−29.9, −3.6)</td>
<td></td>
</tr>
<tr>
<td>Nonfatal ischemic stroke</td>
<td>97.5</td>
<td>119.8</td>
<td>-22.3 (−39.8, −4.8)</td>
<td></td>
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<tr>
<td>Liver damage</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liver failure</td>
<td>0.6</td>
<td>0.6</td>
<td>0.0 (−1.6, 1.6)</td>
<td></td>
</tr>
<tr>
<td>Persistently elevated transaminases</td>
<td>13.6</td>
<td>10.1</td>
<td>13.5 (−3.8, 10.9)</td>
<td></td>
</tr>
<tr>
<td>Muscle damage</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myopathy</td>
<td>5.9</td>
<td>5.3</td>
<td>0.6 (−4.5, 5.6)</td>
<td></td>
</tr>
<tr>
<td>Rhabdomyolysis</td>
<td>0.6</td>
<td>0.5</td>
<td>0.1 (−1.5, 1.6)</td>
<td></td>
</tr>
<tr>
<td>Severe rhabdomyolysis → kidney failure</td>
<td>0.029</td>
<td>0.026</td>
<td>0.003 (−0.07, 0.08)</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\)Risk per 10,000 person-years

\(^1\)Coplan PM et al. Clin Pharm & Ther 2010; 89: 312-315.
and even more complex….¹

Figure 9. Most frequent on-therapy adverse events sorted by relative risk.

Metrics are needed **throughout** development.

- Required metrics at each development phase will foster:
  - reasoned discussions of benefit-risk
  - aggressive pursuit of safety issues early in development

**Metrics create pressure for improvement**
Drug X

- Novel mechanism, first to market, & efficacy in early studies!
- MW 450 and highly lipophilic
- CYP3A4 metabolized, quinone forms and covalent binding ≥200 pmol eq/mg protein
- Centrilobular necrosis in high dose rat studies and mild biliary hyperplasia in cynomolgous monkeys
- 400mg dose by PK/PD and inhibits BSEP
Complex info is hard to analyze…

- Most complex decisions are made **intuitively**; not analytically\(^1,2\)
- Statistical understanding’s limited, even among physicians\(^3\)
- Employees find it hard to share negative info, as per interviews
  - 85% unable to raise important concerns (and 74% of peers aware of concern also didn’t wish to speak up)\(^4\)

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\(^1\) Kahneman D. Am Econ Rev 2003; 93:1449-1475
Key info understood about Drug X

Novel mechanism, first to market & efficacy in early studies!
Drug X

**BENEFITS**
- Novel mechanism, first to market, & efficacy in early studies!

**RISKS**
- MW 450 and highly lipophilic
- CYP3A4 metabolized, quinone forms and covalent binding >200 pmol eq/mg protein
- 400mg dose by PK/PD and inhibits BSEP
- Centrilobular necrosis in high dose rat studies and mild biliary hyperplasia in cynomolgous monkeys
Clinical hepatotoxicity universally observed in 8/8 of 223 marketed drugs with these features\(^1\)

**Drug X**

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Let’s develop a **simple** common language


Lightbulb1.com at: [digitalsherpa.com](http://digitalsherpa.com)
Let’s use an easy way to highlight key information...

- Clear preference to maintain routines and follow default options$^{1,2}$

- So, new system must use current analyses & improve evaluation$^3$

- Successful information systems align with existing processes, are supported by leaders and reinforced.$^4$

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Traffic light labels are easily understood

- UK proposes traffic light food labels¹

- Consumers five times more likely to identify healthy food using traffic light labels² than using simple black & white info. on g/mg & % daily value for: total fat, saturated fat, sugar & sodium

- Traffic light labels understood across all socioeconomic groups²

Traffic light labels enhance understanding of both efficacy & safety data

Danger

Caution

Good / Safe

Nearly 80% of drug withdrawals (1990-2006) due to liver and cardiac safety.¹

¹Shah RR Pharmacogenomics 2006;7:889-908.
Benefit-Risk analyses **throughout development**

Enhanced Preclinical screens decrease hepatotoxicity by 65%\(^1\)

- Phase I
- Phase II
- Phase III

**Postmarketing**: Elec med records; Large natural history studies; Epidemiology studies; Medwatch

Traffic light examples for drug- and dose-related safety

CV: QT prolongation/tdp\(^1\)
- Effects on heart rate, blood pressure
- Effects on cardiac function/congestive heart failure

Liver: Graded liver chemistries\(^2\) in treated vs. placebo
- Hy’s Rule\(^3\) (e.g. ALT\(>3\times\text{ULN}\) & bilirubin\(>2\times\text{ULN}\))

Renal: creatinine 1.5x, 2xULN, \(\geq 0.5\text{mg/dl from baseline}\)^4

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\(^4\)Hoste EAJ et al. Critical Care 2006, 10:R73 (doi:10.1186/cc4915) at: [http://ccforum.com/content/10/3/R73](http://ccforum.com/content/10/3/R73)
Use “traffic light” safety metrics linked with clear clinical outcomes

- CV,¹ liver,²,³ and renal⁴ safety metrics available now

- Agree metrics for: muscle, hematol., skin, neuropsych.

Develop “traffic light” safety metrics linked with clear clinical outcomes

- Completed and discontinued projects can be analyzed
  - identify the earliest point that safety issues are detected
  - develop evidence-based “traffic light” safety metrics
  - examine nonclinical tests for safety predictors &
    to identify mechanisms of injury
Drug X “traffic light” metrics highlight heart failure & liver injury

- QT prolong
- Heart Rate/Incr. BP
- Heart Failure
- Liver Injury
- Hy’s Law
- Renal Injury
At each phase, analyze efficacy & safety:

- Are efficacy or safety issues associated with:
  - PK exposure, drug /transporter interactions, concom. meds?
  - age, gender, biomarkers?
  - time to key event(s)?
  - nonclinical findings?

- Evaluate current screening/safety measures
  - Are additional safety measures, epidemiologic or nonclinical studies needed?

- Examine key efficacy & safety, relative to marketed drugs
Benefits and risks clear with:

**Simple “traffic light” metrics, linked to clinical outcomes & applied to:**
- each phase of clinical development
- nonclinical data
- postmarketing

**Traffic light labels are easily understood & communicated by stakeholders & patients; can use in:**
- product label
- drug comparisons
Thank you