Surrogates Endpoints: Challenges Created for Post-Licensing Advisory Bodies

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Outline

- Mandates of Regulatory agencies vs Advisory Bodies
- Impact of Surrogate Endpoints for Advisory Bodies
- Impact of Surrogate Endpoints on Assessment of Cost effectiveness
- Examples from CDR
- Potential solutions
Mandate: Health Canada (TPD)

- “speeding up the regulatory process for drug approvals to ensure Canadians have faster access to the safe drugs they need…”

- “a manufacturer must present substantive scientific evidence of a product's safety, efficacy and quality”
Health Canada – with regards surrogates...

- NOC/C: given when *promising* evidence of clinical effectiveness is present based on the drug having the potential to provide: a) effective treatment ..., of a disease or condition for which no drug is presently marketed in Canada, or b) offers a significant increase in efficacy ... over existing therapies

- PROMISING CLINICAL EVIDENCE: evidence based on well-controlled clinical trials establishing that the drug product has an effect on a surrogate or clinical endpoint that is reasonably likely to predict clinical benefit.

- Does the potential benefit outweigh any safety concerns?
Mandate: Advisory Bodies (CEDAC)

- “provide formulary listing recommendations to the participating drug plans, based on an assessment of the medication’s effectiveness, safety and cost-effectiveness compared to existing therapies”.
  - Is it safe and effective (compared to other treatments)?
  - Does it provide good value for money?
Why use surrogates?

- In the initial investigation of new drugs for use in human disease, biomarkers can assess whether a potential drug candidate is likely to be therapeutically active.
- May provide important information for designing phase III randomized clinical trials
- “an efficient method of screening among potential drug candidates”
- Regulatory agencies, including Health Canada and the FDA, have permitted the use of biomarkers (“potential surrogates”) to establish therapeutic efficacy in registration trials
How to determine if a surrogate is really a surrogate!

- “a response variable for which a test of the null hypothesis of no relationship to the treatment groups under comparison is also a valid test of the corresponding null hypothesis based on the true endpoint” (Prentice).
- requires the surrogate to wholly account for the effect of an intervention on a clinical endpoint
- “[a] surrogate endpoint is expected to predict clinical benefit (or harm or lack of benefit or harm) based on epidemiologic, therapeutic, pathophysiologic, or other scientific evidence” (NIH working group / FDA)
Statistically Speaking…

- According to Prentice’s criteria the treatment (Z) must be prognostic of the surrogate endpoint (S) (Equation 1); Z must be prognostic of clinical endpoint (T) (Equation 2); and S must be prognostic of T (Equation 3).

\[
S_{ij} \mid Z_{ij} = \mu S + \alpha Z_{ij} + \varepsilon S_{ij} \quad \text{(Equation 1)}
\]
\[
T_{ij} \mid Z_{ij} = \mu T + \beta Z_{ij} + \varepsilon T_{ij} \quad \text{(Equation 2)}
\]
\[
T_{ij} \mid S_{ij} = \mu + \gamma S_{ij} + \varepsilon_{ij} \quad \text{(Equation 3)}
\]

- Prentice’s criteria thus specify that \(\alpha \neq 0\) (there is an effect of treatment on the surrogate), \(\beta \neq 0\) (there is an effect of treatment on the clinical endpoint) and \(\gamma \neq 0\) (the surrogate must have an effect on the clinical endpoint). As such:

\[
T_{ij} = \mu' + \beta S Z_{ij} + \gamma Z S_{ij} + \varepsilon_{ij} \quad \text{(Equation 4)}
\]

- Mathematically, \(\beta S\) must equal 0 to fulfill Prentice’s criteria that the surrogate fully captures the effect of the treatment on the clinical endpoint.
Scientific discovery of drug A

Early drug development

Evidence of efficacy based on appropriate biomarkers

Pivotal RCT using clinical and surrogate endpoints

- Evidence of efficacy based on clinical endpoints?
- Validation of surrogate endpoints

Further RCTs which might consider validated surrogate endpoints only

Drug B might be approved for use based solely on evidence of its effect on the validated surrogate marker

Scientific discovery of a similar drug B

Change in clinical practice
Efficacy based on surrogate endpoint

- Subsequent RCT with clinical endpoint
  - Surrogate Validated
  - NOT VALID
- Subsequent RCT never completed
Potential additional problems of using surrogates in resource allocation decisions

- Does a drug provide good value for money?
  - How to assess?
    - Economic evaluation
      - “Comparative analysis of alternative courses of action in terms of both their costs and health benefits”
    - “life years gained” or impact on quality of life (QALYs)

- When the clinical effect is based on an (unvalidated) surrogate endpoint, how do you estimate the true “clinical effect”
  - Modeling
Efficacy based on surrogate endpoint

Subsequent RCT with clinical endpoint

Surrogate Validated

Cost per QALY gained Based on Clinical Endpoint

Subsequent RCT never completed

NOT VALID

Estimated cost per QALY

Based on Clinical Endpoint

Estimated cost per QALY

Cost per QALY gained

Based on Clinical Endpoint

Estimated cost per QALY

Cost per QALY gained

Based on Clinical Endpoint

Estimated cost per QALY

Cost per QALY gained

Based on Clinical Endpoint
Sevelamer for End Stage Renal Disease (ESRD)

- Patients with ESRD have high mortality rates and abnormal mineral metabolism, including high phosphate and low calcium.
- Observational data have linked abnormal mineral metabolism, such as high phosphate, to higher mortality.
- Treatment of high phosphate is with oral binders, either calcium ($85) or sevelamer ($4211).
- Association between the cumulative total dose of oral calcium and vascular calcification, which in turn may be associated with mortality in ESRD.
110 HD patients; calcification score (measured by ultrasonography) ranges from 0 (no calcification in any arterial segment) to 4 (calcification in all sites examined).
Surrogate vs Clinical Endpoint: Impact on the results of an Economic Evaluation

Sevelamer for End Stage Renal Disease (ESRD)

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- Treatment of high phosphate is with oral binders, either calcium ($85) or sevelamer ($4211).
- Association between the cumulative total dose of oral calcium and vascular calcification, which in turn may be associated with mortality in ESRD.
- Sevelamer reduces vascular calcification.
Fig. 1. Median percentage change in coronary artery calcification (A) and aortic calcification (B) scores from baseline to week 26 and week 52 in patients with calcification (scores ≥30) at baseline.

Comparisons between calcium-treated (Hatched) and sevelamer-treated (BLACK) groups.
Health and Economic Consequences of Sevelamer Use for Hyperphosphatemia in Patients on Hemodialysis

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### Table 7  Results of the cost-effectiveness analysis (base case)

<table>
<thead>
<tr>
<th></th>
<th>Sevelamer</th>
<th>Calcium acetate</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>One-year EBT</td>
<td>1,362</td>
<td>1,557</td>
<td>-195</td>
</tr>
<tr>
<td>CVD events (per 100 patients):</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peripheral arterial disease</td>
<td>65 (21 F)</td>
<td>74 (24 F)</td>
<td>-9</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>17 (1 F)</td>
<td>20 (1 F)</td>
<td>-2</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>7 (3 F)</td>
<td>8 (3 F)</td>
<td>-1</td>
</tr>
<tr>
<td>Aortic disease</td>
<td>32 (12 F)</td>
<td>36 (14 F)</td>
<td>-4</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>3 (1 F)</td>
<td>4 (1 F)</td>
<td>0</td>
</tr>
<tr>
<td>Total costs ($)</td>
<td>18,113</td>
<td>17,734</td>
<td>379</td>
</tr>
<tr>
<td>CVD costs ($)</td>
<td>15,045</td>
<td>17,101</td>
<td>-2,056</td>
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<tr>
<td>Hospitalization costs ($)</td>
<td>13,323</td>
<td>15,166</td>
<td>-1,843</td>
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<tr>
<td>Subsequent care costs ($)</td>
<td>1,722</td>
<td>1,935</td>
<td>-213</td>
</tr>
<tr>
<td>Statin costs ($)</td>
<td>364</td>
<td>363</td>
<td>0.36</td>
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<tr>
<td>Treatment costs ($)</td>
<td>2,704</td>
<td>270</td>
<td>2,431</td>
</tr>
<tr>
<td>Life expectancy (year)</td>
<td>9.19</td>
<td>8.95</td>
<td>0.241</td>
</tr>
<tr>
<td>Life expectancy discounted (year)</td>
<td>7.61</td>
<td>7.43</td>
<td>0.178</td>
</tr>
<tr>
<td>Incremental cost-effectiveness, $/life-year gained</td>
<td>7.61</td>
<td>7.43</td>
<td>1,641</td>
</tr>
<tr>
<td>Incremental cost-effectiveness, $/discounted life-year gained</td>
<td>2,219</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incremental cost-effectiveness, $/CVD event prevented</td>
<td></td>
<td>4,448</td>
<td></td>
</tr>
</tbody>
</table>

CVD, cardiovascular disease; F, fatal.
Dialysis Clinical Outcomes Revisited (DCOR) trial

- Multi-center, **open-label** parallel design trial
- Patients randomized to receive sevelamer or a calcium-based phosphate binder in a 1:1 fashion
- A total of 2103 hemodialysis patients from 75 US sites were randomized
DCOR - Results

All-Cause Mortality

Cumulative Incidence of All-Cause Mortality

- Calcium
- Sevelamer

Time on Study (Years)

No. at Risk
Calcium  1007
Sevelamer  1033

640  430  161
656  449  195
DCOR - Results

All-Cause Mortality in Patients ≥ 65 Years of Age

Cumulative Incidence of All-Cause Mortality

Time on Study (Years)

No. at Risk
Calcium 556
Sevelamer 585

Calcium
Sevelamer

No. at Risk
Calcium 366 245 98
Sevelamer 381 253 99
<table>
<thead>
<tr>
<th>Model</th>
<th>Strategy</th>
<th>Cost</th>
<th>Effectiveness (QALYs)</th>
<th>Incremental cost per QALY gained</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1 (Overall)</td>
<td>Calcium</td>
<td>$374,000</td>
<td>4.33</td>
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</tr>
<tr>
<td></td>
<td>Sevelamer</td>
<td>$407,000</td>
<td>4.54</td>
<td>$157,500</td>
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<tr>
<td>Model 2 (No effect)</td>
<td>Calcium</td>
<td>$374,000</td>
<td>4.33</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sevelamer</td>
<td>$391,000</td>
<td>4.33</td>
<td>Sevelamer dominated</td>
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<tr>
<td>Model 3 (By duration)</td>
<td>Calcium</td>
<td>$374,000</td>
<td>4.33</td>
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<tr>
<td></td>
<td>Sevelamer</td>
<td>$437,000</td>
<td>4.83</td>
<td>$127,000</td>
</tr>
<tr>
<td>Model 4 (By age)</td>
<td>Calcium</td>
<td>$374,000</td>
<td>4.33</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sevelamer</td>
<td>$401,000</td>
<td>4.43</td>
<td>$278,100</td>
</tr>
</tbody>
</table>
**Cost effectiveness of sevelamer**

<table>
<thead>
<tr>
<th>Efficacy based on surrogate endpoint</th>
<th>$59,000 per life year gained</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efficacy based on clinical endpoint</td>
<td>$102,600 per life year gained ($83,000 – 180,000)</td>
</tr>
</tbody>
</table>
CDR’s experience with Surrogate endpoints (2004-2005)

- 14 innovative drugs ("first in class")
- 9 were based exclusively on "non-clinical endpoints"
- Of those, only 2 were recommended for restricted listing
Examples from CDR

- Cinacalcet for Secondary Hyperparathyroidism in ESRD
- Pegvisomant for Acromegaly
- Sildenafil for Pulmonary Hypertension
Cinacalcet for ESRD

- In RCTs, “cinacalcet significantly reduces PTH and serum calcium levels”
- Insufficient evidence that it reduces clinically important outcomes
- Cost between $4,000 and $23,000 per year
- Economic analyses based on surrogate endpoint
Pegvisomant for Acromegaly

- In 2 RCTs (6 and 12 weeks), “pegvisomant resulted in a greater proportion of patients with normalized IGF-1 levels”
- “While pegvisomant has been shown to reduce IGF-1 levels, it is uncertain whether a reduction in IGF-1 levels is a valid surrogate endpoint for improvement in clinical outcomes”
- Cost between $60,000 and $80,000 per year
- Economic analyses based on surrogate endpoint
Sildenafil for pulmonary hypertension

- In RCTs, sildenafil improves six minute walk time
- It is unclear if six minute walk times are valid surrogate endpoints for improvement in survival
- In addition to 6mwt, sildenafil was shown to improve quality of life
- Cost $31 per day, compared with $128 per day for a relevant funded comparator with similar data issues
Potential additional problems of using surrogates in resource allocation decisions

- In the setting of unvalidated surrogate endpoints, the opportunity cost associated with a new drug cannot be determined (since its true clinical benefit is unknown).
- When evaluating novel therapies, reliance on surrogates rather than clinically relevant outcomes could result in incorrect resource allocation.

- How to proceed?
What CEDAC is currently doing?

- Continuing to have a hard line on drugs where efficacy is only based on surrogate endpoints
- Changes to the submission requirements for the economic analyses done by manufacturer
  - Not necessarily evidence based
  - Based on (often) unsubstantiated assumptions
  - Problems with limited/poor quality data
  - (e.g., efficacy extrapolated from surrogate endpoints, lack of head-to-head trials, data from other disease areas)
- Often, CDR clinical findings do not concur with the clinical data used in economic analyses
- Manufacturers are no longer asked to submit full economic evaluations when the efficacy of their drug is based only on (unvalidated) surrogate endpoints
Mid-range Approaches:

- Regulatory agencies develop a separate category of approval for all drugs that are approved on the basis of “non-clinical” endpoints.
- Full approval unlikely at this stage, but limited approval might be considered for some drugs; price “would” be lower to acknowledge that information on effectiveness is uncertain.
  - Coverage with evidence development...
- Companies perform further RCTs using clinical endpoints as “suggested” by regulatory agency.
- Drug reassessed by regulatory and advisory bodies.
Long term solutions:

- Medications are becoming so expensive that without coverage through a public formulary, patients cannot "access" a drug (even if it has been approved by a regulatory agency)
- Companies need to plan RCTs within a subsidy, rather than a regulatory framework
  - Appropriate comparator
  - Appropriate study length
  - Use of clinical endpoints