Evidence and Values: Requirements for public reimbursement of drugs for rare diseases. A case study in oncology

Stuart MacLeod · Michael Drummond · Pierre Karakiewicz
Bill Evans · Jacques LeLorier · Douglas Martin · Peter Tugwell

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What is a rare disease?

- consensus: 1 in 2,000
- USA: 1 in 1,500
- Australia: 1 in 10,000

- orphan diseases
- orphan drugs
- orphan patients
Applied health research & evaluation for decision makers

- Does it work in real life?
- For whom?
- Is it safe?
- Compared to what?
- At which cost?

public health decision makers
physicians
patients

Reimburse drug?
Recommend treatments?
Healthcare direction

Treat my patients?

What to choose?

« The best for my population »
« The best for my patients »
« The best for me »

revised from Jean-Paul Collet, 2008
Challenges in studying treatment of rare diseases

- interests of those who suffer from a rare disease may conflict with interests of policymakers and payors
- logistical and geographic limitations on data accrual for rare diseases
- extraordinary expense of clinical investigation
- necessary reliance on surrogate markers
- scientists with greatest level of expertise in rare disease likely to be engaged in studies
- RCTs vs evaluation of real world safety and effectiveness
- health economic and outcomes review not feasible at early stage
Three questions...

- What are the limitations of the current approach to reimbursement decisions, especially for rare diseases?
- How can priority setting for expensive drugs for rare diseases be improved?
- What can be done to improve the evidence-base that contributes to these decisions?
Case study: Sorafenib for renal cell carcinoma

- S is a multikinase inhibitor for treatment of local advanced, metastatic renal cell carcinoma in patients who have failed prior cytokine therapy or are unsuitable for such therapy.

- Efficacy data from TARGET study (n = 903): randomized patients received S 400mg bid + BSC or BSC alone

- S doubled PFS compared to BSC alone (24 weeks vs 12 weeks: HR = 0.44; 95% CI = 0.3 - 0.55, p < 0.000001)

- On basis of interim findings, FDA requested that all TARGET subjects be unblinded and offered treatment with S.
Case study: Sorafenib for renal cell carcinoma

Survival analysis

- At first overall survival analysis prior to crossover, S patients showed 39% improvement compared with BSC
  HR = 0.72; 95%CI = 0.55 - 0.95; p = 0.018

- No estimate of median survival since median had not been reached for S patients at time of stopping trial.

- Second analysis 6 months post crossover showed overall median survival advantage for S of 3.4 months (19.3 vs 15.9 months) HR = 0.77; 95% CI = 0.63 - 0.95; p = 0.015

- It is likely that observed survival advantage was diluted due to the crossover.
Case study: Sorafenib for renal cell carcinoma

Secondary analysis

- Secondary analysis was performed censoring patients who had crossed over.

- Secondary analysis showed median overall survival advantage of 5 months:
  19.3 vs 14.3 months; HR = 0.74; 95% CI = 0.58 - 0.93; p = 0.10

- Overall median survival likely to increase with further trial followup but subsequent analyses will also reflect dilution of effect.
Case study: Sorafenib for renal cell carcinoma

Markov model

• Submission to CDR used a Markov model….key parameter estimates based on TARGET trial.

• Estimate of transition probabilities based on trial data (transitions from PFS to progressive disease or death up to crossover point)

• Markov model estimated overall (lifetime) survival difference of 1.21 years and incremental cost per life-year gained of $36,046.
Case study: Sorafenib for renal cell carcinoma

CDR analysis

- CDR concluded, given early termination of trial, that overall survival advantage and hence true C-E of S was uncertain.

- Conducted independent analysis based on assumption that S would have no survival impact once patients entered a progressive disease state.

- CDR analysis estimated overall survival gain of 4.5 months.

- Incremental cost per life-year gained rose to $78,227.

As a result, CEDAC recommended that S not be listed for reimbursement.
Sorafenib in ethical ‘no man’s land’

- manufacturer has lost the opportunity to continue trial in original form to a clear outcome
- no longer possible to prove/disprove statistically significant benefit of study drug on overall survival
- not ethically acceptable to conduct another RCT
- above reasons are used as rationale to deny reimbursement listing
Limitations of current approaches

- Adjudicating amongst clusters of relevant values is the core of priority setting re drugs.

- There is no overarching principle for resolving the cluster of value conflicts when, for example,
  - incremental cost effectiveness is high,
  - evidence is weak,
  - benefit is small,
  - cost is high, and
  - patients have no feasible alternative therapy.

- Culyer has suggested that decisions about drug reimbursement from a publically funded program require a process blending algorithmic and deliberative approaches. (Healthcare Papers 2007)

- Must also be unbiased and ethically acceptable.
4 conditions:

- stakeholder engagement
- publicity beyond transparency (active dissemination)
- revisions (openness to challenge)
- leadership (Daniels and Sabin 2002)
Drugs in advanced disease

• What can we reasonably expect to learn from RCTs?

• What other studies might permit better interpretation of RCT evidence?

• How to reconcile the clinical imperatives of quick approval vs methodological needs for high quality data?
The paradox

The more effective the drug…

the shorter the time to crossover…

the lower the chance of conclusively proving advantage in overall survival.
New analytic approaches

- disease specific methods, eg, for cancer
- critical analysis of arguments for collecting more data
- coverage with evidence development
- incorporate concepts of fairness/social value; address value conflicts embodied in economic approaches
The relationship between social value and incremental cost per quality-adjusted life-year (QALY)
Needs

- multi-stakeholder debate
- commitment to ‘fairness’ for rare diseases
- more stakeholder involvement
- validation of surrogate markers
- balancing equity with efficient resource use
An improved decision basis:
A deliberative process that considers context

- central focus on comparative effectiveness
- reduced reliance on RCTs
- examine observational studies that go beyond RCT’s composite outcomes
- acceptance of colloquial evidence (Lomas et al)
Questions?