Triangulating Developers, Regulators and Payers to Reap Rewards and Address Challenges with Curative Therapies

MARK SCULPHER, Professor of Health Economics, University of York, York, UK
ANIRBAN BASU, Stergachis Family Endowed Professor, University of Washington, Seattle, WA, USA
ADRIAN TOWSE, Director of the Office of Health Economics, London, UK
SHELBY REED, Professor in Population Health Sciences, Duke University, Durham, NC, USA

Motivation

• Pipeline of potentially-curative therapies has (only just) begun production
  • Significant health gains
  • Large up-front costs and potential long-term savings
• Value frameworks may or may not be up to the task
  • Limited data
  • Methodological challenges
• New financing mechanisms may be needed
Themed Section in *Value in Health*

Value of Curative Therapies
- Health technology assessment
- Methodological issues
- Regulatory issues
- Financing mechanisms

Co-edited by Don Husereau and Shelby Reed

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Speakers

Mark Sculpher MSc, PhD, Professor of Health Economics, University of York, York, UK
- HTA perspective

Anirban Basu, PhD, Stergachis Family Endowed Professor, University of Washington, Seattle, WA, USA
- Heterogeneity in assessing value

Adrian Towse, MA, MPhil, Director of the Office of Health Economics, London, UK
- Payment mechanisms
TRIANGULATING DEVELOPERS, REGULATORS AND PAYERS TO REAP REWARDS AND ADDRESS CHALLENGES WITH CURATIVE THERAPIES

MARK SCULPHER, PHD

PROFESSOR OF HEALTH ECONOMICS
CENTRE FOR HEALTH ECONOMICS
UNIVERSITY OF YORK, UK

Complexity in evaluation

- System disruption
- Few patients
- Non-health effects
- Fragile intellectual property
- Claims for high social value
- Affordability & upfront costs
- Evidential uncertainty
Complexity in evaluation

- System disruption
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- Fragile intellectual property
- Affordability & upfront costs

Cost-effectiveness and affordability

Price = $40,000 per QALY

Cost $20,000 per QALY

QALYs gained

2
Cost-effectiveness and affordability

Health opportunity cost: 1 QALY per £20,000 (Budget impact 1)

Price = P* £40,000

£20,000 per QALY

2 QALYs gained

2 QALYs opportunity cost

Cost

QALYs gained

Cost-effectiveness and affordability

Health opportunity cost: 1 QALY per £20,000 (Budget impact 1)

Price = P* £40,000

£20,000 per QALY

£6

2 QALYs gained

2 QALYs opportunity cost

Cost

QALYs gained
Cost-effectiveness and affordability

Health opportunity cost: 1 QALY per £20,000 (Budget impact 1)

Price = P* £40,000

QALYs gained

Cost

Net Health Benefit

1 QALY

Health opportunity cost: 1 QALY per £13,333 (Budget impact 2)

QALYs gained

Cost

Net Health Benefit

1 QALY
Estimating opportunity cost by budget impact

Evidential uncertainty – example of oncology

- Mortality risk in delayed event
- Plateau in OS
- Long-term OS treatment effect
- Long-term OS
- Separation in OS curves
- PFS as a surrogate for OS

Quality-adjusted survival
Example in oncology

Decision uncertainty and its implications

- **Cost-effective**
  - Adopt: True positive: gains in health
  - Reject: False negative: loss in health

- **Not cost-effective**
  - Adopt: False positive: loss in health
  - Reject: True negative: no change
Dealing with uncertainty

Analysis
• Magnitude and cost of uncertainty
• Key uncertainties
• Feasibility & timing of research
• Irrecoverable costs
• Impact of price changes

Policy responses
• Fund
• Reject
• Price reduction
• Risk-sharing
• Fund only in research
• Fund with research

Should we value putative cures differently?

• **Product A**
  • 2 life-years gained
  • Good QoL
  • Die of disease

Versus

• **Product B**
  • 2 life-years gained
  • Good QoL
  • Die of other causes
Sharing value over time

Conclusions

Evaluation challenges not unique to ‘cures’

The toolkit exists, needs to be used

Always need for further development

- Survival modelling
- Policy responses to uncertainty
- Policy responses to high upfront costs

Principles of value-based pricing remain
Thank you!
mark.sculpher@york.ac.uk

https://www.york.ac.uk/che/

@MJSculpher

Incorporating evidence on
effect-heterogeneity in CEA

ANIRBAN BASU
basua@uw.edu
@basucally

THE CHOICE INSTITUTE
School of Pharmacy
Background

Cost-effectiveness analysis is beginning to play a major role in decision-making for private and some public plans in the US.

Current and New Approaches to Making Drugs More Affordable

Managed Healthcare Executive

Background

Criticisms

September 12, 2018

Mr. Larry J. Merlo
President and Chief Executive Officer
CVS Health
One CVS Drive
Woonsocket, Rhode Island 02895

Dear Mr. Merlo:

Therefore, we request that you reconsider this decision. CVS Health’s stated purpose is “helping people on their path to better health.” Reliance on cost-effectiveness thresholds like ICER’s falls short of this purpose, replacing deeply personal, individual health care decisions with an opaque algorithm based on average study results that do not address the needs of different patients and special populations.
Premise

> Relying on average cost-effectiveness of a new technology has been criticized in the presence of heterogeneity.

> Consider three issues in this talk:
  - Stochastic (first-order) uncertainty vs variability
  - Implication for learning by doing
  - Demand-weighted cost-effectiveness analysis
    > Its relationship to indication-based pricing

Stochastic (first-order) uncertainty vs variability

> Stochastic (first-order) uncertainty
  - Represents uncertainty in subject-level outcomes that is entirely due to chance.
  - E.g. even if you specify that subjects have a 5% chance of death, for any single individual at any point in time, either he dies and stay alive.

> This uncertainty is due to pure randomness (e.g. flipping a coin) – UNPREDICTABLE

> Cannot be used as a basis to allocate resources.
Stochastic (first-order) uncertainty vs variability

> Variability
  - PREDICTABLE differences in outcomes and costs for subgroups determined by subject characteristics

> Important for resource allocation
  - Heterogeneity may also arise due to system characteristics and also individual preferences

> Efficient allocation of resources should try to directly incorporate variability in decision-making

Fig. 2 – Effect of improvements in health-related quality of life on the cost-effectiveness of omalizumab. The subgroups with three or more exacerbations are not shown because the curves overlap the other subgroups and the overall population. EQ-5D, EuroQol five-dimensional questionnaire; ICER, incremental cost-effectiveness ratio; OCS, oral corticosteroid; QALY, quality-adjusted life-year.
Omalizumab for treating severe persistent allergic asthma

Technology appraisal guidance
Published: 24 April 2013
nice.org.uk/guidance/ta278

1 Guidance

1.1 Omalizumab is recommended as an option for treating severe persistent confirmed allergic IgE-mediated asthma as an add-on to optimised standard therapy in people aged 6 years and older:

- who need continuous or frequent treatment with oral corticosteroids (defined as 4 or more courses in the previous year), and
- only if the manufacturer makes omalizumab available with the discount agreed in the patient access scheme.

https://www.nice.org.uk/guidance/ta278/

Learning-by-Doing

THE CHOICE INSTITUTE
School of Pharmacy
Learning-by-Doing: Transition of Stochastic Uncertainty to Variability

> Physician and patients learn from the random variation in outcomes

> Develop algorithms to identify subgroups with higher/lowered than average outcome

> Should resource allocation be generous up-front to allow for learning?
  - Fundamentally a trade-off between current health & costs and future health
  - Depends on expected quality-of-learning and the rate of learning
  - Empirical evidence suggest that learning exists but far from perfect.
Structured learning-by doing

> Centralized learning from doing
  – Learning during the outcomes-based agreement
  – Tuesday Poster 3:00 – 7:00 pm

> Needs structure
  – Determine time for learning
  – Select methods to learn faster
  – Have explicit decision-making tied to the end of learning period

Demand-weighted CEA
Demand-weighted cost-effectiveness

> Evidence on variability is important even if

- there is no learning-by-doing
- there is no opportunity to implement sub-group-based coverage


David D. Kim, PhD; Anirban Basu, PhD
Medical Decision Making 2017

ICER for Alternative Treatments

Typical ICER compares Treatment A vs B

\[
\text{ICER} = \frac{E(C_A) - E(C_B)}{E(Q_A) - E(Q_B)} = \frac{E(\Delta C_{AB})}{E(\Delta Q_{AB})}
\]

\[
= \frac{\sum (P_j E(\Delta C_{AB,j}))}{\sum (P_j E(\Delta Q_{AB,j}))} = 1, 2, 3
\]

\(P_j = \text{Size of Subgroup} j\)

• Suppose, clear evidence on variability in ICER across subgroups.
ICER for Alternative Treatments

- ICER comparing potential realized value of Treatment A vs B

\[
ICER = \frac{\sum_j [P_j \cdot D_j \cdot E(\Delta C_{AB,j})]}{\sum_j [P_j \cdot D_j \cdot E(\Delta Q_{AB,j})]}
\]  (4)

- \(D_j\): the rate of adoption of treatment A in the population subgroup j

- Similar to “Volume weighted price” across indications

ICER for Alternative Policies

- The Rate of the uptake is endogenous to the policy
- So ICER should be comparing two coverage policies – Policy \(k\) vs Status quo

\[
ICER = \frac{\sum_j [P_j \cdot D_{jk}(f_k) \cdot E(\Delta C_{AB,j}) \cdot f_k]}{\sum_j [P_j \cdot D_{jk}(f_k) \cdot E(\Delta Q_{AB,j})]}
\]

\(f_k\): a fraction of the incremental costs under a policy \(k\) borne by a payer
Table 1  Illustration of Traditional and Modified ICERs and INMBs under a Health-Care Sect

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\(^a\) NMB calculated as the difference between the costs and QALYs of the intervention and comparison groups.

\(^b\) NMB calculated using the traditional ICER.

\(^c\) NMB calculated using the modified ICER.

\(^d\) NMB calculated using the hypothetical scenario.
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Future Work in CEA

- To use demand weighted CEA at launch
  - Can we develop reliable estimates for evidence elastic of demand?
    - Discrete choice experiments
    - Retrospective analysis
    - Validated prediction model for technology diffusion

- CEA at 5 year assessment
  - Direct estimate from real-world use.

Crossroads

Decision makers focus of population averages because of the lack of reliable evidence on heterogeneity

Manufacturers argue that there is no incentive to generate evidence on heterogeneity
Conclusions

- Are we failing to produce the necessary evidence of heterogeneity of effects, which can improve value in the society, by not providing sufficient reward incentive for such information.

- Importantly to create an environment that respects and rewards evidence on heterogeneity.

- Laying a clear path of incorporating reliable evidence on heterogeneity in third-party assessor’s base analysis. This includes
  - not reporting population average cost-effectiveness results when there are distinct differences in subgroup-specific results,
  - experimenting with demand weighted cost-effectiveness approaches.

F4: Triangulating Developers, Regulators, and Payors to Reap Rewards and Address Challenges with Curative Therapies Payment Mechanisms and Handling Uncertainty

Adrian Towse\textsuperscript{1} and Elisabeth Fenwick\textsuperscript{2}

\textsuperscript{1}Director of the Office of Health Economics
\textsuperscript{2}Senior Director, Modelling and Meta-Analysis, Pharmerit International

ISPOR Barcelona 2018
Agenda

What do we know about payer willingness to embrace new payment models for curative therapies?

Handling uncertainty – avoiding a bias against curative therapies

Fitting both parts together – a recipe for progress?
Payer willingness to embrace new payment models for curative therapies? Remarks based on three papers


Discussions with payers

- None of the US payers saw extraordinary measures as needed to pay for “cures”
- Costs dealt with via policy and competition
- Do not want to legitimise increased funding for drugs
- Likewise European payers – we got through....
  - Discounts, revenue caps limiting returns on R&D to “reasonable” or “affordable” levels

Payers are reluctant to adopt amortisation, although may sign up to outcomes-based agreements
Trade off is the signal payers want to send about R&D

Higher the share of social return going to the innovator in the patent period, the stronger are the incentives to find additional “cures” but greater affordability pressures.

Having similar maximum revenue caps across different diseases where the social value of a cure may be very different sends the signal that payers are indifferent between them. Is this an acceptable consequence?

In the Hep C “cures” market, competition was a key driver of discounts. Evidence of a competitive R&D supply side. But will this happen in the subsequent areas of curative therapies?

Affordability (non-marginal budget impact) matters. But pragmatic approaches are needed. Need to avoid bias against cures.

Agenda

What do we know about payer willingness to embrace new payment models for curative therapies?

**Handling uncertainty – avoiding a bias against curative therapies**

Fitting both parts together – a recipe for progress?
Handling uncertainty – avoiding a bias against curative therapies

For simplicity we focus on one aspect of uncertainty – duration of treatment effect.

We consider whether the way in which uncertainty is handled should, or does, differ as between a one-off curative therapy and a repeat dose curative therapy which requires regular administration, but achieves the same expected health gain.

If mechanisms for handling uncertainty in economic evaluations and in payer / HTA decision making processes create a bias against a one-off curative therapy (for example by accepting a lower price for a cure as compared to a repeat treatment for an equivalent health effect) this would send inefficient incentives.

If, however, the consequences of, and nature of the uncertainty associated with a one-off curative therapy is different to that of a repeat dose curative therapy then we need to send appropriate differential incentives for R&D.

Our main assumptions

We have a prevalence of 8000 patients,

General (background) mortality rate of 0.05% per month

Curative therapy with either the one-off or regular dose gives an expected discounted gain of 5.51 QALYs, and stops disease mortality

Current ineffective treatment generates 0.2 QALYs and costs $740 per month but has no impact on the disease mortality rate of 0.5% per month

Both curative treatments have an ICER of $40,000 per QALY, within the payer threshold ICER of $50,000 per QALY, i.e. they are cost-effective

The one-off therapy costs $296K and the regular dose therapy costs $4.5K per annum, with the same discounted cost of $296K

Time horizon is 50 years and we discount costs and outcomes at 5%

Annual monitoring costs are $120 per patient

The effectiveness of the curative therapy falls from 100% in year 1 to 92% in year 30.
What we are exploring

We compare the uncertainty associated with the one-off and repeat dose curative therapies, if evidence emerges that the treatment has stopped working
• With both we can stop treating new patients
• With repeat dose we can also discontinue treatment for existing patients

We look at the impact of introducing for the one-off treatment
• Outcomes based payments
• Annuity payments

Uncertainty on the (incremental) cost-effectiveness plane
Observations

With the one-off, it is the iterations where the treatment is least effective (i.e. the duration of effect is shortest) which are not cost-effective.

With the repeat dose, it is the complete opposite.

The introduction of an outcomes based payment or annuity payment changes the profile of the one-off to resemble repeat dose.

In a VoI calculation we can:
- treat the outcomes-based approach as equivalent to coverage with evidence development or OWR;
- expect that the alternative of delay is not preferred and adopt with no new evidence is only preferred if no outcomes-based arrangement is possible.

CEAC and EVPI for one-off curative therapy
Outcomes versus annuity payment

Annuity payment is £26,276 per annum, pay each year patient is alive.
Outcomes based payment is £57,499 per annum, for each year patient remains cured.

Why the difference? The cure rate is not 100%. So manufacturer “needs” more per annum in an outcomes-based payment in order to receive the same revenue as when paid upfront for the one-off.

A subject for negotiation?
Net Health Effect per patient

Illustrates the initial investment by the payer if a one-off cure is used

But not clear it adds anything to the ICER and the CEAC and EVPI illustrations...other than to look scary

But the key issue is expected value (for a risk neutral payer) and the costs and benefits of investing in uncertainty reduction

The profile of repeat dose indicates (as above) that an outcomes based scheme is likely to be a good investment
Introducing an expensive comparator

Steve Pearson and ICER have highlighted the challenge of an expensive cost-ineffective comparator

If our comparator cost $7,400 instead of $740 per month, the price for one-off (at an ICER of $40K) would rise to $1.06m, an increase of more than $750K

One option would be to only reward based on a cost-effective comparator. This would reduce the price of the comparator to roughly $8 per month and so reduce the value of the curative therapy from $296K to $218K.

But what are we trying to achieve?

◦ Incentivising saving costs of ineffective comparators
◦ Some sort of share of cost-savings but the health gain goes to the innovator in the patent period?

Agenda

What do we know about payer willingness to embrace new payment models for curative therapies?

Handling uncertainty – avoiding a bias against curative therapies

Fitting both parts together – a recipe for progress?
Fitting both parts together – a recipe for progress?

Payers don’t want new payment mechanisms other than outcomes-based agreements

One-off treatments, paid for as one-off, present affordability issues

There is high uncertainty for the payer with one-off treatments and genuine issues around discontinuation with one-off versus repeat dose

Outcomes-based agreements overcome bias against one-off curative treatments by:

◦ addressing the large amount of uncertainty and
◦ reducing the affordability challenge

THANK YOU FOR YOUR ATTENTION

To enquire about additional information and analyses, please contact Professor Adrian Towse at atowse@ohe.org

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It’s time for you to ask questions.