Predicting future evidence in drug reimbursement
a government policy and decision-making perspective

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The context
• High, urgent, unmet clinical need
• Accelerated regulatory approval
• Clinical evidence not strong for the most patient-relevant health outcomes
  – trial powered to less important outcomes
  – trial immature or contaminated for more important health outcomes
  – single-arm studies showing promise, but without an estimate of comparative treatment effect
Possible solutions

• Risk share agreements
  – mostly used to address budgetary risk
  – can therefore also address acceptable VFM
• Managed entry schemes/coverage with evidence development
  – likely to be more applicable here

• What are the issues to consider?

The risk to be managed
Having something nice taken away is perceived as worse than not being given it at all

Managed entry schemes “give” early: they move all players from a neutral position
Sources of problems

- Unexpected harms -- rare, delayed, severe
- Alternative therapies emerge
- Inadequate extent of health gain
- Expansion of treated population

Take preventive action

- Use only if confident that later evidence will be more convincing
- Adopt as a last resort
- Agree a “confidence discount”
Later evidence must be more convincing

Why?

Later evidence must be more convincing

- Focussed and limited research questions
- Answerable in a reasonable, defined time
- Agreed funding source
- Independent and transparent data collection, analysis and reporting
- Unequivocal for all stakeholders
- Fit for purpose scientific methods

Fit for purpose scientific methods

• Often need to detect smaller and/or later comparative treatment effects
  – which are more meaningful outcomes to patients
• These usually require randomised comparative trials to minimise selection bias
  – but may no longer be at equipoise, so should be
    • on-going
    • recruitment completed
    • few later treatment departures

Some examples

• Surrogate to final outcomes
  – beyond biomarkers, so include progression events in cancer
• Inadequate follow-up
• Treatment departures
  – post-progression use of alternative therapies especially in comparator arm
  – crizotinib
A greater risk of managed entry schemes

- That a core research question is identified, especially in relation to comparative effectiveness for patients, but is never answered.
  - It tells current patients and prescribers that we were not confident.
  - It perpetuates the lack of confidence for all future patients and prescribers.
  - No-one ever knows whether the potential gains are realised.

Potential solution:
MES with confidence “discount”

- Memorandum of Understanding between Commonwealth of Australia and Medicines Australia (2010-2014)
- Clauses 26 and 27 = “Managed Entry Scheme”
  - MES arrangements still in effect
  - currently being revisited by AMWG
26. From 1 January 2011, the Commonwealth undertakes to introduce a mechanism whereby the PBAC may recommend PBS coverage at a price justified by the existing evidence, pending submission of more conclusive evidence of cost-effectiveness to support listing of the drug at a higher price. The PBAC will provide advice in relation to sources of uncertainty and specific evidence required to support a subsequent application.

- Agreement that:
  - there is a clinical need, but
  - insufficient evidence to justify preferred price, and
  - later evidence will be more convincing

- Lower price now; if later evidence confirms potential => request for higher price

- Explicitly valuing reduced confidence

- Avoiding perverse incentive signals

- Hard to reconcile with existing industry incentive models
Managing stakeholders

• Requires full transparency from the outset
  – fact of the arrangements
  – details of arrangements (except pricing)
  – results
• No “partial” transparency based on “commercial interests”
  – payer is investing in the data collection via the supplier
• Aim for buy-in across all stakeholders
• Independence?


Early experience

• MES may not be the right solution
  – everolimus (Afinitor®, Novartis) for SEGA
  – rifaximin (Xifaxan®, Norgine) for hepatic encephalopathy
• MES initially proposed as a way forward with additional data collection
  – registry (everolimus), retrospective cohort analysis (rifaximin)
  – in each case, a working group provided advice about whether data would be “fit for purpose”
  – in each case, the sponsor’s response to the working group advice also included a reduced price offer
• Both subsequently listed without the need for an MES
Example of this MES type

Pembrolizumab (Keytruda®, Merck Sharp & Dohme)

• formal Deed of Agreement involved both MES and RSA
  – initial cost per patient set with reference to ipilimumab
  – explicit specification of how emerging trial data should be modelled for PBAC reconsideration

Common feature:
Take mitigating action

• If later evidence does not support expected potential
  – OK, if lower price still justified as being acceptably cost-effective
    • prevention worked
  – harder if even the lower price is not justified
    • need mitigation
Mitigating options

• Partial disinvestment
  – decrease price
    • eg cinacalcet
  – decrease eligible population by removing patients with ↓ benefit and/or ↑ harm
    • eg KRAS => RAS for anti-EGFR antibodies

• Full disinvestment
  – remove entirely

• Importance of clinical groups and patient population knowledge of this

Confidence “discount” variation

• November 2014 PBAC

• Higher price now
  – if later evidence confirms potential => retain price
  – if later evidence exceeds potential => retain price
    • gain is earlier access
  – if later evidence does not confirm potential
    • reduce price
    • calculate rebate based on extent of previously subsidised use multiplied by the price differential
    • also pay interest on the rebate
  – avoid perverse incentives to dispute later evidence or not supply it
Examples of this MES variation

• crizotinib (Xalkori®, Pfizer) for ALK+ NSCLC
  – data on first 50 patients to be provided
  – explicit consideration of possibility of how new competing treatments would impact
• trametinib (Mekinist®, Novartis) for BRAF+ melanoma
  – data from ongoing trial to be provided to revise model

The challenge

• Additional data can usually resolve uncertainty, but
  – it usually resolves in one direction
  – the new treatment is usually shown to be not as cost-effective as the early data and model predicted
  – a consistent pattern is emerging that interim analyses suggest a greater relative treatment effect than final data
  – also that the extent of PFS gain (shown early) does not translate to the same extent of OS gain (shown later)
  – adverse events tend to emerge with more data
  – and early subsidised access cannot be reversed easily
• Finding a way to share these risks between funders, the community, patients and sponsors
  – financial risks, resource allocation risks, health risks
Carry through

1. Harmful
   – harms shown to exceed benefits
   – hard for regulators/industry
   – easy for HTA/payers

2. Wasteful
   – comparative benefits balance comparative harms, so any price advantage is unjustified
   – disinvestment exposes inter-individual variation against the population-based assessment of balance

Carry through?

3. Beneficial, but not cost-effective
   – hard for all
   – not aware of any examples of full disinvestment on these grounds
   – back to the essential issue

4. Flow-on to subsequent comparators
   – expect that subject medicine will become the comparator for a subsequent medicine
   – so expect that consequences will apply to both affected medicines
What are the benefits of early access?

– earlier subsidised access to medicines for patients
  • providing hope in areas of urgent high unmet clinical need
  • reducing the prospect of potentially catastrophic financial burden
– providing treatment options to current patients

What are the risks of early access?

• Balance of benefits to harms is overly optimistic
• Setting a new benchmark for an acceptable ICER
• Changing landscape and treatment options mean the data to resolve uncertainty will never become available
• The opportunity costs to patients and the community if the initial data were optimistic
Key issues for managed entry

• The agreed initial price and associated modelled ICER
• Clearly identified areas of uncertainty
  – that can be resolved with additional data, that will be forthcoming, within a reasonable timeframe
  – and can be used to revise the initial model
• Identified and agreed options following review
• Transparent communication of this plan to patients and clinicians

Conclusions

• Taking the toy from the toddler is difficult
• Knowing the difficulties of disinvestment should guide how arrangements are set up
• The methods used to generate later evidence should give greater confidence, not their results
• Beware the “dead end” of never knowing
• Beware perverse incentives
• Use only when appropriate