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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

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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?

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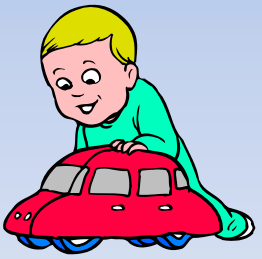
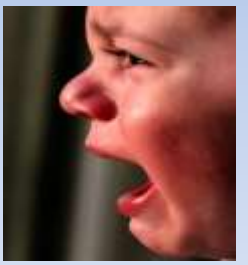
The risk to be managed

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

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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?

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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*

Hutton et al. *Coverage with evidence development: an examination of conceptual and policy issues.* IJTAHC 2007; 23(4):425-35

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

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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.

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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

Confidence "discount"

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.

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Confidence "discount"

- 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?

Henshall et al. *Using health technology assessment to support optimal use of technologies in current practice: the challenge of "disinvestment".* IJTAHC 2012; 28(3):203-10

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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

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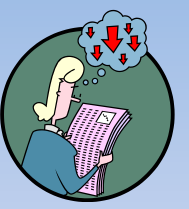
Common feature: Take mitigating action



- 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

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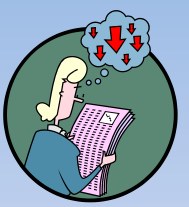
Mitigating options



- 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

Henshall et al. *Using health technology assessment to support optimal use of technologies in current practice: the challenge of "disinvestment".* IJTAHC 2012; 28(3):203-10

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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

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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

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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

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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

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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

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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

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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