This is the published version:

Mortimer, Duncan, Li, Jing Jing, Watts, Jennifer and Harris, Anthony 2011, Breaking up is hard to do: the economic impact of provisional funding contingent upon evidence development, *Health economics, policy and law*, vol. 2011, no. 6, pp. 509-527.

Available from Deakin Research Online:

http://hdl.handle.net/10536/DRO/DU:30054605

Reproduced with the kind permission of the copyright owner.

Copyright: 2011, Cambridge University Press
Breaking up is hard to do: the economic impact of provisional funding contingent upon evidence development

Duncan Mortimer, Jing Jing Li, Jennifer Watts and Anthony Harris

Health Economics, Policy and Law / Volume 6 / Issue 04 / September 2011, pp 509 - 527
DOI: 10.1017/S1744133111000144, Published online: 08 August 2011

Link to this article: http://journals.cambridge.org/abstract_S1744133111000144

How to cite this article:

Request Permissions : Click here
Abstract: Funding contingent upon evidence development (FED) has recently been the subject of some considerable debate in the literature but relatively little has been made of its economic impact. We argue that FED has the potential to shorten the lag between innovation and access but may also (i) crowd-out more valuable interventions in situations in which there is a fixed dedicated budget; or (ii) lead to a de facto increase in the funding threshold and increased expenditure growth in situations in which the programme budget is open-ended. Although FED would typically entail periodic review of provisional or interim listings, it may prove difficult to withdraw funding even at cost/QALY ratios well in excess of current listing thresholds. Further consideration of the design and implementation of FED processes is therefore required to ensure that its introduction yields net benefits over existing processes.

1. Introduction

Funding contingent upon evidence development (FED) has recently been the subject of some considerable debate in the literature (Carino et al., 2006; Tunis and Pearson, 2006; Lindsay et al., 2007; Tunis and Chalkidou, 2007; Miller and Pearson, 2008). FED has been characterized as a pathway to ‘provisional’ funding for promising new drugs or devices that are likely to face difficulties in meeting the usual standard of proof for funding approval (Tunis and Pearson, 2006; Tunis and Chalkidou, 2007; Miller and Pearson, 2008). For interventions that fall short of the usual standard of proof with regard to safety, effectiveness or cost-effectiveness, further phase II/III data may be required to permit funding
agencies to make an informed decision regarding permanent listing. FED for drugs/devices that lack adequate phase II/III evidence and therefore fall short of the usual standard of proof for funding approval is denoted in the discussion that follows as FED-L (Funding contingent upon Evidence Development - Low). According to a decision-making framework proposed by Chalkidou et al. (2008), FED-L may be appropriate where (i) expected net benefits are positive but uncertain; (ii) the value of information exceeds the cost of evidence development; and (iii) the net costs of delaying listing (saying ‘no’ to applications for listing until sufficient evidence is available to meet the usual standard of proof) exceed the net costs of bringing forward (potentially limited) access to an intervention that may prove to be inferior to current practice.

Others have argued that the phase III data that usually support ‘yes’/‘no’ listing decisions do not always permit decision-makers to clearly identify an intervention as either cost-effective or cost-ineffective. There might, for example, remain considerable uncertainty as to whether the treatment effects identified in phase III trials can be replicated in routine practice (Hutton et al., 2007). Permitting provisional funding under FED based on phase III data would then allow ‘yes’ decisions to be replaced with ‘maybe’ contingent upon the collection of post-marketing surveillance data as to effectiveness in routine practice. In this case, a higher standard of proof (phase III data plus FED data) would presumably be required to move from provisional funding to permanent listing than is currently required for ‘yes’ listing decisions (phase III data only). We denote this second type of conditional funding as FED-H (Funding contingent upon Evidence Development - High). Applying the Chalkidou et al.’s (2008) framework once again, interventions eligible for FED-H listing and that are able to meet existing standards of proof for ‘yes’ listing decisions should have no trouble demonstrating expected benefits in excess of expected costs. Nonetheless, there will be little point in replacing a ‘yes’ with a ‘maybe’ contingent upon evidence development unless the value of this evidence exceeds the cost of development. Funding agencies should further consider whether the net costs of replacing a ‘yes’ with a ‘maybe’ exceed the net costs of opting for the immediate and unconditional listing of an intervention that may turn out to be inferior to current practice.

In the United States, both FED-L and FED-H mechanisms are now available to the Centres for Medicare and Medicaid Services (CMS) when making national coverage determinations (NCDs). The CMS may authorize coverage to patients enrolled in a clinical trial where ‘evidence is not adequate to support coverage and where additional data gathered in the context of a clinical trial would further clarify the impact of these items and services on the health of Medicare beneficiaries’ (CMS, 2006: 4). This coverage with study participation (CSP) authority is available to interventions that would previously have fallen short of the usual ‘reasonable and necessary’ standard for unconditional coverage under Medicare. The CMS may also authorize coverage with appropriateness determination (CAD) in situations in which “there is adequate evidence to determine that
an item or service is reasonable and necessary... but that additional clinical data is needed... to ensure that the item or service is being provided to appropriate patients in the manner described in the NCD” (CMS, 2006: 3). CMS use of CAD and CSP authority has been described in detail elsewhere (Carino et al., 2006; Tunis and Pearson, 2006; Lindsay et al., 2007).

In Australia, the Medical Services Advisory Committee (MSAC) may recommend interim funding through temporary listing on the Medical Benefits Schedule (MBS) “to enable data collection to be undertaken on new and promising interventions for which conclusive evidence on safety, effectiveness and cost-effectiveness is lacking” (MSAC, 2005a: 49). Recommendations for temporary listing require various primary and secondary criteria to be met, including: clinical need, ‘some’ evidence of effectiveness, ‘adequate’ evidence of safety, a likelihood of cost-effectiveness and the potential for further studies to reduce uncertainty. “The objective of the interim funding arrangements is to raise the level of evidence above the existing level for the interventions under review” (MSAC, 2005a: 52); for example, to obtain level II evidence where only level III evidence was previously available, or to obtain level III-2 evidence where only level IV evidence was previously available. For example, in MSAC Assessment 1031 – Deep brain stimulation for the symptoms of Parkinson’s disease, interim funding was recommended “subject to patients’ participation in an appropriate controlled trial to obtain information on adverse events, longer-term patient outcomes and costs in the Australian setting” (MSAC, 2001a: 37). For Assessment 1014 – Transurethral needle ablation for benign prostatic hyperplasia, interim funding was “linked to the acquisition of data on the type of patients treated and safety data to monitor use under interim arrangements” (MSAC, 2002a: ix). For Assessment 1065 – Sentinel lymph node biopsy in breast cancer, interim funding was provided “pending the outcome of trials already in progress” (MSAC, 2005b: ix). In other cases, interim funding was recommended without any specific reference to trials in progress and without any requirement to collect additional funding but contingent upon review within a specified period (MSAC, 2002b). For MBS items that do not undergo assessment through MSAC, the standard listing is now time limited (normally for a period of between three to four years) and contingent upon monitoring/evaluation [Medicare Benefits Reviews Task Group (MBRTG), 2010]. At the end of the time-limited period, the relevant MBS advisory committee may recommend: discontinuation of listing, extension of the time-limited listing, amendment before conversion to ongoing listing or conversion to ongoing listing without amendment (MBRTG, 2010).

Also in Australia, the Pharmaceutical Benefits Advisory Committee (PBAC) used an FED-L mechanism as early as December 2003. Specifically, the PBAC entered into an agreement with the industry sponsor to list bosentan for idiopathic pulmonary artery hypertension despite the fact that the sponsor’s claims regarding cost-effectiveness were reliant on an assumed survival benefit that was
not then supported by the available evidence (Wlodarczyk et al., 2006). Listing was contingent upon the collection of registry data and pricing was to be contingent upon observed survival in registry enrolled patients wherein price reductions would compensate for any departure from the assumed survival benefit (Owen et al., 2006; Wlodarczyk et al., 2006).

In the United Kingdom, the National Institute for Health and Clinical Excellence (NICE) may issue ‘only in research’ (OIR) guidance where the available evidence for health technologies, public health programmes or clinical practice is not yet sufficiently strong to support a positive or negative recommendation (Chalkidou et al., 2007). Approximately 4% of NICE technology appraisals published between 1999 and early 2007 recommended use only in the context of research. NICE use of OIR provisions has been described in detail elsewhere (Chalkidou et al., 2007).

Despite a recent proliferation of papers discussing issues of implementation and design (Carino et al., 2006; Tunis and Pearson, 2006; Chalkidou et al., 2007; Lindsay et al., 2007; Tunis and Chalkidou, 2007; Miller and Pearson, 2008; Briggs et al., 2010; Dhalla et al., 2010; Menon et al., 2010), relatively little has been made of the economic impact of permitting provisional funding under FED-type mechanisms. The present paper characterizes the economic impact of permitting FED-L or FED-H under (i) a fixed dedicated budget and (ii) an open-ended budget with one or more exogenously determined funding threshold(s).

2. Breaking up is hard to do

Much of the argument that follows relies on the premise that breaking up is hard to do. Or, put another way, on the “general consensus that it is politically more difficult for decision-makers to withdraw coverage – even if formally temporary – than to refuse coverage in the first place” (Hutton et al., 2007: 427). For the most part, explicit delisting of drugs/devices from formularies has previously been carefully avoided by bodies with direct control of coverage such as the PBAC and MSAC; perhaps because of the anticipated political resistance. Instead such bodies have adopted a largely passive role and have relied upon clinicians to modify their prescribing practice to replace inferior interventions with more effective or better-tolerated alternatives as and when they become available. This passive approach has the potential to achieve a sharp curtailment of use where interventions are revealed to have a poor risk/benefit trade-off and where physicians face strong financial incentives and clear ethical imperatives to ‘do no harm’ (Tunis and Chalkidou, 2007). Where the required change in prescribing practice entails reversion to an older and possibly less-effective (but more cost-effective) intervention, the passive approach is unlikely to curtail the natural diffusion of an FED-listed technology.

Hutton et al. argue that “where coverage with evidence development is managed by a body with direct control of coverage … the removal of coverage
is usually a sufficient incentive mechanism to contain any further use” (2007: 430). While we agree that control of coverage provides an obvious mechanism for curtailing use and diffusion, additional enforcement action may sometimes be required to obtain the required change in practice. Even where funding agencies are successful in delisting FED drugs or devices for a specific indication, there may be considerable inertia in practice if the FED drug/device or procedure remains listed for closely related indications or by other funding agencies. For example, lung volume reduction surgery (LVRS) for advanced emphysema was included in the Australian MBS under services that do not attract Medicare benefits; reflecting February 2001 recommendation of the MSAC that public funding should not be supported (MSAC, 2001b). Previously, Medicare benefits for LVRS were claimed under item numbers 38,456 (intrathoracic operation), 38,424 (thoracotomy) and 38,440 (wedge resection of the lung) (MSAC, 2001b). In addition to withdrawal of coverage, MSAC also recommended that surgeons should obtain approval from their hospital’s ethics committee before performing LVRS, that patients should be informed of the risks of LVRS and that Australian state and federal health ministers should be informed of the decision to discontinue public funding (MSAC, 2001b). In effect, MSAC recognized that withdrawal of MBS coverage might not be sufficient to curtail utilization (even for an intervention with a poor risk/benefit trade-off) and therefore took steps to directly influence hospital policy, patients’ treatment decisions and decision-making by other fund holders.

Although there is general consensus that ‘breaking up is hard to do’ even where coverage is explicitly time limited, there are as yet few examples where an explicit and concerted attempt has been made to delist or restrict coverage of a FED-listed intervention. In many cases, the decision to award provisional funding under an FED-type mechanism has yet to be formally reviewed. For example, the UK Multiple Sclerosis Risk Sharing Scheme (MSRSS) – a collaborative agreement under which manufacturers supplied their drugs at a discounted price – and the UK Department of Health approved provisional funding for multiple sclerosis (MS) drugs under an FED-type mechanism. In this case, it is simply not possible to evaluate the difficulty (or otherwise) of withdrawing provisional funding based on FED data because the MSRSS Monitoring Study “has yet to publish any analysis of the data and there has been no price review, some seven years after it was established” (McCabe et al., 2010).

Where review has been undertaken, very often the recommendations of the review are yet to be released into the public domain such that it is not possible to observe whether an attempt to restrict or withdraw coverage has been made. In a recent review describing the operation of FED schemes, Stafinski et al. (2010) were unable to access information regarding interim or final listing decisions based on FED data for 25 of 26 ‘pay for performance’ or ‘outcomes guarantee’ schemes. Stafinski et al. (2010) were also unable to access information regarding interim or final listing decisions based on FED data for 15 of the 32 ‘funding with
study participation’ schemes; although in many cases this was because FED data collection was ongoing at the time of their review. In such situations, provisional funding is often simply extended until adequate supplementary data are available to support a formal review; suggesting that an absence of further evidence may be enough to avoid delisting or restriction. In the context of ‘yes’/‘no’ decisions for permanent listing, Chalkidou et al. noted that “with reimbursement secured, sponsors of the technology may be less inclined to fund research that could narrow the indications for their technology” (2008: 1643). Depending upon the extent of any restrictions on patient access during the FED period, a similar incentive may operate to delay evidence development if the default position is simply to extend funding until the data become available. Note, for example, that “CMS continues to provide coverage for implantable cardiac defibrillators as part of a registry study” despite the fact that the evidence compiled by “the registry was deemed unable to answer CMS questions” (Stafinski et al., 2010: 126 and 128).

For several of the ‘funding with study participation’ schemes in which information on funding decisions and findings from FED data were both available, Stafinski et al. (2010) characterized interim or final decisions to extend or confirm funding as being inconsistent with FED data. In the case of LVRS for emphysema, the CMS extended coverage for many non-high-risk patients. This was despite the fact that the FED data suggested that the technology had ‘significant risks and limited benefits’ (Chalkidou et al., 2008); even in the subgroup of non-high-risk patients who were most likely to obtain a survival benefit from LVRS (Carino et al., 2006; Chang et al., 2007).

3. Endowment effects and gain/loss asymmetry

Why then should withdrawal of coverage (or ‘breaking up’) be any more difficult than refusal of coverage in the first place, even where coverage is explicitly time limited and contingent on the development of evidence? Breaking up might be particularly hard to do if individuals must be paid more in compensation for the loss of an entitlement or ownership than they would willingly pay to gain the same entitlement or ownership. The available evidence suggests that this type of ‘gain/loss asymmetry’ may be a pervasive characteristic of preferences (Knetsch and Wong, 2009), with ratios of willingness to accept (WTA) to willingness to pay (WTP) well in excess of unity for both private goods such as mugs, chocolate or hockey tickets and public goods such as environmental amenity or public infrastructure (Bischoff, 2008). In the health sector, gain/loss asymmetry would most obviously arise in patients’ valuations of health gains/losses (and, because health care is instrumental to health gains/losses, in the value that patients place on access to health-care interventions). Gain/loss asymmetry may also arise in the value that clinicians and industry/shareholders place on profits/losses associated with delivery of health care and the sale of drugs and devices.
The phenomenon of gain/loss asymmetry has been attributed to an ‘endowment effect’ wherein “individuals asked for their WTA for a certain good will consider this good part of their endowment while individuals asked for their WTP do not” (Bischoff, 2008: 284). Gain/loss asymmetry would then arise if individuals’ valuations of a good or service depend upon whether or not they have an entitlement to, or ownership of, that good or service either because of general loss aversion or disutility associated with the mere act of parting (Bischoff, 2008). Contrary to this view, it has been suggested that gain/loss asymmetry arises not as a consequence of an endowment effect but from framing biases, learning effects, imprecision and/or strategic thinking (see Smith et al., 1999 for a review). For example, an upward bias in WTA valuations might arise as a consequence of respondents’ relative lack of familiarity with expressing WTA (O’Brien and Gafni, 1996), or because WTA is not constrained by ability to pay (Gafni and Ravid, 1989; Whynes and Sach, 2007). Where gain/loss asymmetry arises due to one or more of these alternative explanations, an argument can be made for disregarding empirical evidence of a divergence and ignoring what amounts to a bias or framing effect. In this context, it is worth noting that there is evidence for the persistence of gain/loss asymmetry even after controlling for many such alternative explanations including learning effects (Morrison, 1998, 2000), strategic thinking (Kahneman et al., 1990), substitution effects (Morrison, 1998), imprecision (Dubourg et al., 1994; Morrison, 1998) and incentives induced by experimental design (Knetsch and Wong, 2009).

A recent review of the literature concluded that the magnitude of gain/loss asymmetry can be substantial, with WTA/WTP ratios ranging from 1.9 to 6.4 for health studies (n = 2), 1.1 to 3.6 for safety studies (n = 4) and up to 89.4 in one environmental study (O’Brien et al., 2002). Whynes and Sach (2007) reported a WTA/WTP ratio of 4.0 (£497.80/£124.10) for paediatric cochlear implant in the one-third of respondents who provided both WTA and WTP valuations. Grutters et al. (2008) confirmed a quantitatively important divergence between WTA and WTP valuations in the context of a discrete choice experiment. WTA/WTP ratios from the study by Grutters et al. (2008) ranged from 1.7 to 3.2 when WTA and WTP were calculated for several different modes of hearing aid provision (defined by provider/accuracy of assessment, follow-up, duration of treatment and payment/discount).

For interventions that are more effective than their comparators, gain/loss asymmetry would equate to a higher threshold for delisting than for listing. With a listing threshold of between 42,000 and 76,000 AUD/QALY in 1989–1990 values (George et al., 2001) and a WTA/WTP ratio of 2.0, the delisting threshold for an intervention in the north-east quadrant of the cost-effectiveness plane would be between 84,000 and 152,000 AUD/QALY. In a recent review of the Australian cost-effectiveness literature, 218 of the 245 interventions (89%) included in the review had a reported incremental cost-effectiveness ratio (ICER)
below $152,000/LY or QALY or DALY in June 2005 values (Dalziel et al., 2008). For a WTA/WTP ratio of 4.0, the delisting threshold would increase to between 168,000 and 304,000 AUD/QALY.

Even higher delisting thresholds than those postulated above may arise in the event that WTA/WTP ratios are found, for example, to be systematically higher in the case of life-threatening conditions for which there is no alternative treatment. As yet, too few studies have been conducted to provide empirical evidence for systematic variation in WTA/WTP ratios by disease or severity (Whynes and Sach, 2007). Empirical evidence from revealed and stated-preference studies does, however, suggest that WTP for a unit of health gain varies with characteristics of the intervention or patient population (e.g. Mortimer and Segal, 2008; Segal et al., 2010). NICE Appraisals Committees have – when certain specified conditions are met – recently been granted license to recommend life-extending medicines for terminal illnesses affecting small numbers of patients; even in situations in which such medicines deliver incremental cost/QALY ratios well in excess of the standard £30,000 listing threshold (NICE, 2005, 2010). A higher listing threshold for life-extending medicines for terminal illnesses would then imply a higher delisting threshold for this type of intervention such that delisting might remain difficult even at incremental cost-effectiveness ratios in excess of $500,000/QALY.

4. An impolitic policy?

O’Brien et al. (2002) argued from a welfarist perspective that any gain/loss asymmetry evident in patient and provider preferences should be reflected in funding thresholds for coverage decisions. Dowie (2004, 2005), on the other hand, argues that “within an extra-welfarist framework, decision-makers committed to cost-effectiveness as the ethical basis for resource allocation in public health care can remain coherent only by ignoring irrelevant private preferences such as those embodied in a kinked ICER” (Dowie, 2005: 1204). We suggest here that remaining coherent and ignoring private preferences may be easier said than done when faced with political pressure for the protection of existing entitlements (amplified in comparison to appeals for access to new drugs/devices due to gain/loss asymmetry). Put another way, political pressure is suggested as a possible mechanism through which gain/loss asymmetry acts to make delisting much more difficult than denying listing.

Booth et al. (2007) suggest that there are interdependent relationships between media, politics, industry and patient interest groups, which together may influence funding decisions. Ferner and McDowell (2006) observe that patient interest groups often share a common interest with industry in promoting/protecting access to drugs/devices through public coverage. With industry funding of patient lobby groups being the rule rather than the exception (Marshall and Aldhous, 2006; Mintzes, 2007), patient interest groups provide
an arms-length vehicle for companies to influence public perception of their
drugs (Herxheimer, 2003). Patient interest groups along such lines have exer-
cised both direct (through, for example, representations to funding committees)
and indirect (through, for example, the press or political representatives) pres-
ture to promote the shared interests of their members and of industry. In the
context of FED-listed interventions, such tactics proved effective in pressuring
the Ontario Ministry of Health and Long-Term Care to end FED requirements
for positron emission tomography (PET) several years before the forecast
completion of evidence development (Stafinski et al., 2010).

The role of political pressure will likely vary depending on the characteristics of
the disease (e.g. prevalence, severity), patients (e.g. age group, education) and
intervention (e.g. availability of substitutes, expected cost and effectiveness).
Certainly patients may be more motivated to exert political pressure to secure or
maintain coverage of last-line treatment for life-threatening illnesses than for
preventative or ‘me-too’ interventions (MacKenzie et al., 2008). All else equal, the
role of political pressure will also depend upon the extent to which the relevant
technology has diffused across eligible patients and providers. Where FED status
limits diffusion of a technology, the size of the eligible population with a perceived
entitlement will be similarly limited. Limitations on access may also have the
effect of restricting the number of providers afforded an opportunity to become
familiar with the new technology and with a perceived entitlement to revenues
or cost savings arising from application of that technology. FED with access
limitations can therefore be expected to limit political pressure simply because
fewer patients and providers experience the endowment effect. While access under
FED will typically imply limited access in comparison with permanent listing
(and, all else equal, weaker political resistance to attempts to restrict or withdraw
coverage), political pressure should be weaker still if access can be withheld until
sufficient evidence is available to support permanent listing.

Conversely, attempts to restrict access or withdraw coverage of rapidly
diffusing technologies will likely be met with a more widespread resistance if they
have already achieved widespread use. In late 2007, the CMS and Congress
proposed ‘sharp limits on coverage’ for computed tomographic (CT) angiography,
then a new and rapidly diffusing technology that had hitherto avoided restriction
under the NCD process (Appleby, 2008). In the absence of an NCD, ‘rapid
adoption’ had occurred supported by local coverage. This relatively unrestricted
local coverage had created a “financial incentive to order and perform all manner
of CT scans” and had strengthened the impetus for “an increasing number of
physicians own or lease their own CT machines” (Appleby, 2008: 2). In an
attempt “…to address the overall growth in CT angiography despite a paucity
of evidence” (Appleby, 2008: 4), the CMS proposed limitations on access
that would have restricted coverage by both indication and study participation
status. However, faced with a concerted and coordinated campaign against their
proposal, the CMS decided not to pursue a NCD; effectively preserving the
status quo of unrestricted coverage through local medicare contractors (CMS, 2008). Although it is not possible in this case to examine the counter factual of CMS limitations on access and coverage prior to widespread diffusion across medicare providers, many private sector fund holders who restricted coverage relatively early in the piece (e.g. AETNA, 2007) have maintained restrictions despite continued lobbying by industry and professional associations [e.g. Society of Cardiovascular Computer Tomography (SCCT), 2010].

We have argued above that political pressure is one mechanism through which gain/loss asymmetry acts to make delisting much more difficult than denying listing in the first place and which – all else equal – renders disinvestment of fully diffused technologies more difficult than disinvestment of provisionally funded interventions that are subject to ‘OIR’-type restrictions. It should, however, be emphasized that several other of the now well-known barriers to disinvestment (Elshaug et al., 2007) also vary by reimbursement status and/or the ‘complete-ness’ of technology diffusion. For example, there may be considerable inertia in clinical practice; particularly for interventions with a long-standing place in both formularies and clinical practice. For patients with chronic illness who have already commenced treatment, physicians facing an ethical imperative to ‘do no harm’ may find themselves faced with the unpalatable prospect of having to discontinue or modify an apparently effective and well-tolerated treatment regimen (Tunis and Chalkidou, 2007). For new patients not yet commenced on treatment, clinicians may be resistant to modifying their practice if they have incurred sunk costs in self-education and become familiar with the risks and benefits of the FED-listed intervention.

Many of these additional barriers to disinvestment may be more amenable to modification than is the political pressure arising from gain/loss asymmetry. For example, it may be possible to improve the quality and completeness of the evidence-based supporting disinvestment by modifying incentives or increasing funding. Although the analysis that follows does not in any way rely on barriers to disinvestment beyond the amplified political resistance arising from gain/loss asymmetry, the continued operation of one or more additional barriers to disinvestment (due, for example, to a failure of evidence development or approval of provisional funding without specifying processes for review) can be expected to further complicate attempts to withdraw or restrict provisionally listed interventions at the end of the FED period.

5. Economic impact of FED

Given the existence of asymmetry in the value of health gains/losses, the difficulties in withdrawing coverage, and the political economy of coverage decisions, what then is the likely economic impact of permitting provisional funding under FED? In the analysis that follows, we characterize the economic impact of FED-L or FED-H under (i) a fixed dedicated budget and (ii) an open-ended
budget with one or more exogenously determined funding threshold(s). Recall that FED-L entails the collection of phase II/III data during the evidence development period for interventions that fall short of the usual phase II/III data requirements for ‘yes’/’no’ listing decisions. In contrast, FED-H requires interventions to meet the usual phase II/III data requirements before provisional funding and to then clear an additional hurdle before permanent listing (based on post-marketing surveillance or registry data collected during the evidence development period). To facilitate clear exposition, we define $\lambda$ as the threshold for permanent listing under current provisions; $\gamma$ as the threshold for post-FED delisting; $Y_t$ is the set of interventions able to demonstrate ICER $< \lambda$ at time $t$ based on phase II/III data; $M_t$ is the set of ‘promising’ but unproven interventions without phase II/III data supporting ICER $< \lambda$ at time $t$; and $K_t$ is the subset of $M_t$ with ICER $< \lambda$ based on FED data at the end of the evidence development period.

### 5.1 Economic impact of FED-L

For FED-L, a higher proportion of interventions will meet the criteria for permanent listing and/or provisional funding under FED-L than would meet the criteria for permanent listing under current provisions. This follows directly from the definition of FED-L as provisional FED for drugs/devices that fall short of the usual standard of proof for funding approval. The set of interventions eligible for permanent listing and/or provisional funding under FED-L: $M_0 + Y_0$, includes all interventions that would meet the usual standard of proof for permanent listing, that is, $Y_0$, plus a further set of interventions, that is, $M_0$, that might be considered ‘promising’ but unproven at the current threshold for listing, that is, $\lambda$.

Consider first the economic impact of FED-L with an open-ended budget constrained only by an implicit or explicit and exogenously determined funding threshold that approximates the marginal value of health gains. In the absence of gain/loss asymmetry, the set of permanently listed interventions, that is, $K_0 + Y_0$, should be the $Y_0$ plus the subset of $M_0$ that are eventually shown to satisfy ICER $< \lambda$ based on FED data, that is, $K_0$. Access to the $K_0$ is effectively brought forward, with $M_0 - K_0$ delisted based on FED data, no change in the funding threshold, and relatively minor impact on expenditure growth (associated with accelerated provisional funding for $M_0$ during the FED period). However, two complications can be expected to multiply the magnitude of this expenditure growth many times over.

First, the share of interventions seeking accelerated access to provisional funding through the FED-L pathway, that is, $M_0$, can be expected to increase over time; producing a corresponding decrease in the share of interventions obtaining funding through traditional pathways, that is, $Y_t$. Hutton et al. argue that “the level of evidence available on a technology at the time of launch is …, to a large extent, determined by the regulatory requirements that apply to the
technology” (2007: 425). If, for example, phase IIB trials were sufficient to meet the standard of proof for provisional funding under FED-L, the incentive for sponsors to engage in costly and time-consuming phase III trials would presumably be very much reduced. If the sponsor decides to conduct phase III trials, there is a risk that the FED-L pathway will subsequently be closed to the intervention (because additional phase III data that could be obtained under FED provisions will be less valuable once data from the sponsor’s phase III trial become available). There is also a risk that uncertainty will be sufficiently reduced to warrant an outright ‘no’ at $\lambda$. This raises the very real possibility that FED-L will reduce rather than increase the evidentiary basis for funding decisions.

Where sponsors forgo traditional funding pathways and opt instead for accelerated access to provisional funding under FED-L, expenditure growth associated with FED funding for $M_i$ can be expected to increase over time. It is also possible that – in the absence of mechanisms for recovering costs from manufacturers such as profit sharing during the FED period or the introduction of ‘early access fees’ – FED-L will shift regulatory compliance costs from sponsors to tax payers and transfer responsibility for development of phase III evidence on to public funding agencies. Although it is unlikely that public funding agencies would accept responsibility for development of phase III data in the long term, there is currently provision for public funding agencies in Spain (Catalan Agency for Health Technology Assessment in Spain) and Australia (MSAC) to cover costs associated with FED data collection (Hutton et al., 2007). In a recent review describing the operation of FED mechanisms, Stafinski et al. noted that “access with evidence development schemes in Italy, the Netherlands and Ontario were entirely payer financed” (2010: 127). In other cases, “the payer provided funding for the technology/service, while the costs of data collection were covered by other parties” (Stafinski et al., 2010: 127).

Second, asymmetry in the value of health gains/losses can be expected to raise the threshold for delisting, that is, $\gamma$, above the threshold for listing, that is, $\lambda$. Increased expenditure growth will then result simply because a significant number of interventions that would previously have received an outright ‘no’ at $\lambda$ will meet the lower standard of proof for provisional listing through the FED-L backdoor and might then prove very difficult to delist even at a cost/QALY ratio well in excess of $\lambda$ (but below $\gamma$). Taken together, these two complications can be expected to produce a *de facto* increase in the ‘yes’/’no’ funding threshold; with a larger and larger share of interventions seeking funding through the FED pathway and achieving permanent listing (or, at least, avoiding delisting) whenever $\text{ICER} < \gamma$ based on FED data.

Next, we consider the economic impact of FED-L on a fixed budget with $\lambda$ endogenously determined as the shadow price of health outcomes. In this situation, we argue that interventions funded through FED-L will crowd out interventions that would have received an outright ‘yes’ under existing funding pathways. Consider the set of interventions that would previously have received
an outright ‘no’ at \( \lambda \) but that is now eligible for provisional funding under FED-L. At the conclusion of the FED period and cessation of provisional funding, some such interventions may be confirmed based on FED data to have lower cost/QALY ratios (when health losses and gains are weighted equally) than interventions for other patient populations or other diseases that would previously have received an outright ‘yes’ at \( \lambda \). Here, allowing more cost-effective interventions that would previously have received an outright ‘no’ to displace less cost-effective interventions that would previously have received an outright ‘yes’ is desirable and – subject to certain caveats – perfectly consistent with health maximization. There may, however, be many cases in which FED data confirm that provisionally listed interventions are relatively cost ineffective (when health losses and gains are weighted equally) such that ICER \( > \lambda \). Unless these apparently cost-ineffective interventions are delisted at the end of the FED period, they too will displace interventions that would previously have received an outright ‘yes’ at \( \lambda \). Note, however, that endowment effects and gain/loss asymmetry can be expected to amplify the usual political costs associated with withholding coverage and it may prove very difficult indeed to subsequently withdraw these cost-ineffective interventions even at cost/QALY ratios well in excess of \( \lambda \).

While allowing promising but ultimately cost-ineffective interventions in \( M_t \) to displace marginal interventions in \( Y_t \) necessitates a departure from the health maximizing solution, the net impact of FED-L on aggregate health may nonetheless be positive if total health gains derived from the \( M_t \) exceed total health gains from displaced interventions in \( Y_t \). FED-L may offer a substantial increment in aggregate health if \( M_t = K_t \) and if delay to listing is significant under current provisions. However, FED-L will likely entail a reduction in aggregate health if, for example, \( K_t \) is a null set. More generally, welfare analysis of FED-L for \( M_t = K_t \) would require further information regarding (i) the distribution of true population ICERs for interventions in \( M_t \), (ii) the relative costs of data collection and regulatory compliance under FED-L and under current provisions, (iii) the expected value of FED-L data, (iv) the distribution of true population ICERs for any displaced interventions in \( Y_t \), (v) the duration of the FED-L period and the relative timing of funding decisions under FED-L as compared with current provisions and (iv) the probability of delisting for interventions with ICER \( > \lambda \) at the conclusion of the FED period.

### 5.2 Economic impact of FED-H

For FED-H, interventions that would previously have received an outright ‘yes’ at \( \lambda \) are now approved instead for provisional funding subject to collection of FED data. Therefore, by definition, the same proportion of interventions \( (Y_0) \) would meet the criteria for provisional funding under FED-H as meet the criteria for permanent listing under current provisions (it is just that
FED-listed interventions would be required to clear an additional hurdle to achieve permanent listing. Under FED-H, there is no mechanism by which sponsors can shift the cost of phase III trials onto funding agencies and the lag between innovation and access remains as for traditional funding pathways.

For an open-ended budget, FED-H may entail additional costs associated with FED data collection but is unlikely to lead to any significant increase or reallocation of health-care funding. Although FED-H provides a formal mechanism for periodic review and removal of interventions that are revealed to be cost-ineffective by FED data, gain/loss asymmetry can be expected to hamper attempts at delisting even with cost/QALY ratios well in excess of current listing thresholds. Because each of the interventions approved for provisional funding under FED-H would have received an outright ‘yes’ under current provisions, the introduction of FED-H is likely to leave us with much the same formulary (or, if delisting of some cost-ineffective interventions can be achieved, a slightly smaller formulary) but with additional data describing the cost-effectiveness of funded interventions in routine practice.

The impact of FED-H under a fixed budget (with \( \lambda \) endogenously determined as the shadow price of health outcomes) will be almost identical to the impact of FED-H under an open-ended budget. At the conclusion of provisional funding under FED-H, some interventions that would previously have received an outright ‘yes’ at \( \lambda \) may turn out (based on FED data) to have higher cost/QALY ratios in routine practice than interventions that would previously have received an outright ‘no’ at \( \lambda \). Here, there may be some scope to allow more cost-effective interventions that would previously have received an outright ‘no’ to displace less cost-effective interventions that would previously have received an outright ‘yes’ (but that are now required to clear an additional hurdle under FED-H).

Having said that, the sponsors of interventions revealed to be disappointingly cost-ineffective by FED data may feel relatively confident of their product’s place on the formulary. Decision-makers may face significant political resistance to formal delisting as patient interest groups and industry exploit public opinion to protect their shared vested interests. Therefore, again, the introduction of FED-H is likely to leave us with additional data describing cost-effectiveness in routine practice but is unlikely to substantially alter the composition of the formulary.

It should be emphasized that the influence (or otherwise) of FED data in updating the formulary will be highly dependent on the ease with which political barriers to delisting or restriction can be negotiated at the end of the FED period. However, this need not imply that investment in evidence generation under FED is not worthwhile in situations in which ‘breaking up is hard to do’. Even where FED data exerts little or no influence over the composition of the formulary, it may still have considerable value by informing evidence-based practice and for fund holders who have opted to delay provisional and permanent listing until further evidence becomes available (Hutton et al., 2007).
To date, provisional funding under FED has typically been granted to interventions that fall short of the standard of proof for funding through existing pathways (Hutton et al., 2007; Lindsay et al., 2007). That is to say, implementation has taken the FED-L path rather than the FED-H path. This is particularly worrying given the relatively adverse consequences of FED-L in comparison with FED-H. Although FED-L does have the advantage of decreasing the lag between innovation and access, it may also have the unintended effects of lowering industry investment in evidence development and shifting research costs to public fund holders. Of greater concern is the potential for FED-L to (i) crowd-out interventions funded through existing mechanisms in situations in which there is a fixed dedicated budget or (ii) lead to a de facto increase in the funding threshold and increased expenditure growth in situations in which the programme budget is open-ended.

The potential benefits of FED should not, however, be understated. First, FED has the potential to shorten the lag between innovation and access; increasing (or, at very least, bringing forward) net benefits derived from safe, effective and cost-effective interventions. For many orphan drugs that offer limited opportunities to recoup research and regulatory compliance costs and for many non-drug interventions that have no natural commercial sponsor, traditional funding pathways offer only weak incentives for private investment in evidence development (Hughes et al., 2005; Tunis and Chalkidou, 2007: 433). For these interventions, the lag between innovation and access may be substantial (or even interminable). Second, FED data may have considerable value outside of its role in updating listing decisions at the end of the FED period. Irrespective of the influence of FED data in decisions to convert FED funding to permanent listing at the end of the FED period, the evidence gathered under FED processes will inform evidence-based practice and may prove decisive in the (delayed) provisional or permanent listing decisions of other fund holders (Hutton et al., 2007).

Finally, it should be emphasized that much can be done to avoid the potentially undesirable consequences of FED if policymakers are cognisant of the difficulties that are likely to be faced when delisting provisionally funded interventions. Careful consideration of the design and implementation of FED processes – particularly with regard to delisting at the end of the FED period – can do much to ensure that the addition of an FED pathway yields net benefits rather than net costs. In Australia, PBAC risk-sharing agreements have specified pricing schedules that link departures from anticipated health gains to price reductions (Owen et al., 2006; Wlodarczyk et al., 2006). Towse and Garrison note that this type of agreement can be structured to ensure “that the technology remains cost effective or to reimburse the payer for some or all of the costs of reversing a decision” (2010: 96). Although such agreements would ideally be structured to ensure that price schedules are enforceable, even informal agreements may act to focus public
opinion on the question of ‘value’ and ameliorate political resistance to delisting (in the event that the sponsor opts to withdraw supply in the wake of scheduled price reductions). In the United Kingdom, the NICE OIR provisions restrict access to patients enrolled in clinical trials and this has the effect of restricting numbers with a perceived entitlement to anticipated health gains. The use of OIR-type provisions, perhaps modified along the lines suggested by Dhalla et al. (2010), in preference to FED mechanisms with relatively unrestricted access might therefore limit the political significance of asymmetries in the value of health gains/losses. Although it is likely that the design and implementation of FED-type mechanisms will involve a complex trade-off between competing objectives, it also seems clear that fund holders should prepare for the worst in the knowledge that breaking up is often very hard to do.

Acknowledgements

We thank our colleagues who participated in the November 2008 and March 2009 sessions of the Evaluation Discussion Group held at Monash University’s Centre for Health Economics for their assistance in testing and developing the arguments presented herein. The comments and advice of two anonymous referees during the peer-review process greatly improved the paper. The views expressed are those of the named authors and may not reflect the views of either referees or of the Evaluation Discussion Group.

References

AETNA (2007), Clinical Policy Bulletin: Cardiac CT, Coronary CT Angiography and Calcium Scoring. Update to Provide Medical Necessity Indications for Cardiac CT Angiography, Hartford, CT: AETNA.


National Institute for Health and Clinical Excellence (NICE) (2005), *Appraising Orphan Drugs*, London: NICE.


