

**A review of
Coverage with Evidence Development (CED)
in different countries: What works and what doesn't**

Urs Brügger 2014

(Final Version)

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List of abbreviations

CCG	Clinical commissioning group
CE	Conformité Européenne
CED	Coverage with evidence development
CG	Clinical Guidelines
CMS	Centers for Medicare & Medicaid Services
CVZ	College voor zorgverzekeringen
DH	Department of Health
FDA	Food and Drug Administration
G-BA	Gemeinsamer Bundesausschuss
GC	Clinical guideline
GCP	Good clinical practice
HAS	Haute Autorité de Santé
HTA	Health Technology Assessment
IDE	Investigational Device Exemption
MEA	Managed entry agreement
MTA	Multiple technology appraisal
MTAC	Medical Technologies Advisory Committee
MTEP	Medical Technologies Evaluation Programme
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
OIR	Only in reserach
OWR	Only with research
PAS	Patient access scheme
PASLU	Patient access scheme liaison unit
PPP	Purchasing power parity
RCT	Randomized controlled trial
STA	Single technology appraisal
TA	Technology appraisal
TAVI	Transcatheter Aortic Valve Implantation

Chapter 1 Introduction

- 1.1 Whether or not to make a specific health technology available to patients in a solidarity based health system is a critical policy decision to be made. Such coverage decisions¹ in health care are decisions made under uncertainty. Decision makers are typically faced with limited and imperfect evidence when making such decisions, especially for novel and innovative medical technologies. Their mandate is to balance the goals of enabling timely access for patients to medical innovations and of guaranteeing value for money under these difficult circumstances.
- 1.2 In many countries, such decisions follow recommendations of appraisal committees that base these recommendations on health technology assessments (HTA) that summarise the best available scientific evidence from a multidisciplinary perspective. Ideally HTA could perfectly distinguish between ‘good value’ and ‘poor value’ technologies (where ‘value’ is determined by the decision-making body, that is, whether it is effectiveness, cost-effectiveness or other criteria). However, in reality the uncertainty associated with HTA, for example due to a poor evidence base, means there is a risk that incorrect decisions could be made. This could be compared to a diagnostic test; in that decision makers are faced with the problem of possible errors (see Figure 1).

		Conclusion of HTA for health technology	
		‘Good value’	‘Poor value’
Coverage Decision	Yes		Type I error
	No	Type II error	

Figure 1: Decision uncertainty in health care

- 1.3 Type I errors (or false positives) are cases in which a technology is reimbursed that might not be safe, effective or cost-effective. Therefore the system runs the risk of potentially harming its patients or wasting resources. Type II errors (or false negatives) are cases in which a technology is not reimbursed and yet it could be safe, effective and cost-effective. In this case patients might suffer for not getting the best available treatment and furthermore innovation could be hampered because suppliers of medical

¹ The terminology used for paying for health care varies across health care system. In Canada it is called ‘funding’, in England ‘commissioning’, in Australia ‘subsidizing’ and in countries with a health insurance system ‘reimbursement’. In this review the US terminology ‘coverage’ is used because it refers to the topic ‘coverage with evidence development’ which is also a US terminology.

technologies might be discouraged from further investments into research and development.

- 1.4 A decision-making body may feel comfortable to recommend or not recommend a technology where there is little risk of error (type I or II). However, where there is risk of an error in the decision, a decision making body may simply wait for more research, to have a better basis for decision making. However, there are situations where waiting for further research might not be the right approach because further evidence may not be generated timely or at all. A possible solution for the decision maker in such circumstances is to say 'yes, but' and enter into one of many different types of so called managed entry agreements.[1-3]
- 1.5 'Coverage with Evidence Development' (CED) is one such approach for early adoption of pharmaceuticals, medical devices, diagnostics or medical procedures for a limited period of time and under the explicit requirement of further evidence generation. The name CED was coined in the United States in 2005 by the Centers for Medicare and Medicaid Services (CMS).[4] The concept as such, however, existed before and can vary across countries or reimbursement systems. It carries different names in other jurisdictions such as 'interim funding' (Australia), 'conditionally funded field evaluation' (Ontario), 'conditional reimbursement' (Netherlands), 'still in research' (France) or 'monitored use' (Spain).[5] One common theme of all these programmes is the ongoing data collection while the medical technology is already being funded by the health care system. The widespread adoption of similar approaches is a reflection of the importance of the competing social objectives that lead to the same general approach – persistent demand for early access to technologies, particularly those that appear to have significant promise to address important health needs, yet important uncertainties about benefits, risks and/or costs make policymakers reluctant to fund them broadly.
- 1.6 Despite its great intuitive appeal the experience with CED has been mixed. Costs and complexities of data collection (particularly project management and co-ordination) seem to be one obvious obstacle.[6, 7] Some countries such as Australia or Belgium more or less stopped the use of CED after initial enthusiasm. However, there are also success stories and learnings from the first attempts. Although the first experiences were associated with disappointments and setbacks, the CED approach still seems to be a promising option. In 2011, the Centers for Medicare and Medicaid Services (CMS) in the US withdrew its 2006 guideline on CED and issued a new draft guidance in

2012.[8] The Netherlands and Germany only very recently introduced new CED programmes for non-drug interventions.[9, 10]

- 1.7 In the meantime some countries have 10 and more years of experience with CED. Therefore the published literature and interviews with experts from different jurisdictions could provide an understanding of the initial high expectations of CED and a certain disillusionment thereafter. Literature and interviews also gave a good insight into the lessons learned of these countries and a shift of some of them to a more modest and more focused CED approach coupled with more realistic expectations regarding its scope.

Objectives of study

- 1.8 The objectives of this study are to produce a summery overview of different CED approaches around the world and to generate in-depth knowledge of such approaches for a number of selected countries in order to better understand what works and what doesn't with CED.

Chapter 2 Methods

- 2.1 A mixed methods approach was used for data generation. Firstly, a literature search in different data bases was performed. The electronic data bases 'Medline' and 'ABI inform' were searched with the following search terms ('coverage with evidence development'; 'access with evidence development'; 'conditional coverage'; 'managed entry'). A google search for grey literature was performed using the same search terms. Further documents were received by experts and included if they fulfilled the criteria.
- 2.2 Secondly, telephone interviews with experts in different countries were performed. The selected countries were: Australia, Belgium, Canada/Ontario, UK/England, France, Germany, Italy, Netherlands, Sweden, Switzerland, and USA/CMS (see Appendix A). The experts were contacted by e-mail for consent and scheduling. In case of consent an interview guide (see Appendix B) was sent to the interviewee together with a taxonomy (see Figure 5) of different managed entry agreements (MEA). The taxonomy was used to discuss CED as a type of MEA. After gaining informed consent, the interviews were tape recorded so they could be listened to again. Notes were taken alongside the interviews.
- 2.3 Thirdly, various conversations with experts from NICE and other organisations in England generated further knowledge and helped to improve the understanding of CED in general and both in England and other jurisdictions.
- 2.4 The project was started with the intention to focus on CED for non-drug technologies. In some countries there is a clear difference in the HTA process for drugs and non-drug technologies whereas in others there is none. The main difference between the two categories is the market authorisation process. This is particularly true for Europe, where there are no strict requirements for efficacy/effectiveness data for the CE mark necessary for devices compared to the regulatory authority for drugs (EMA). The main objective of the study was to find principles for a successful implementation of CED in general. To what extent there might be a difference between a successful CED process for non-drug technologies and pharmaceuticals is not within the scope of this study.
- 2.5 In order to understand CED, the wider context of HTA, coverage decisions, and how these domains are integrated in different health care systems had to be studied and conceptualized. Country data was ordered in a tabulated form and analysed. Learnings and recommendations were derived from the literature and interviews, and discussed with experts from NICE and other organisations.

Chapter 3 Overview over the literature

- 3.1 A literature search was performed in March 2014. 1880 references were retrieved. After assessment of the abstracts 124 references were included. References were selected when they contained information about CED that was more than just a mentioning of the term. In case of doubt documents were rather included than excluded.
- 3.2 The number of publications per year increased rapidly after the year 2005 and reached a peak of 25 publications in the year 2010 as shown in Figure 2. Since 2011 the annual number of publications is stable at around 20 per year.

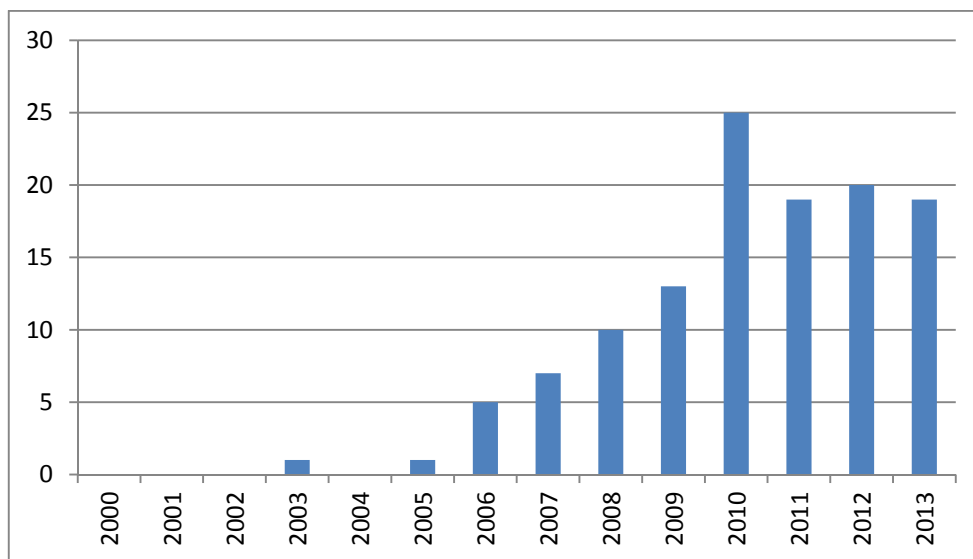


Figure 2: Number of publications per year

- 3.3 Different types of studies were identified but it was difficult to unambiguously categorise them. There were studies that have a clear focus on the concept of CED and some general principles.[3, 4, 11-14] There were studies that discuss CED as one part of managed entry agreements or risk-sharing arrangements between payers and manufacturers.[1, 2, 15] There were studies that describe and discuss CED in different countries. [5, 16-18] A clearly distinct category is documents explaining the functioning of CED regimes issued by HTA bodies or decision makers. Only three examples of this type were retrieved.[8-10]
- 3.4 Many studies contained descriptions and evaluations of CED arrangements from specific countries. Figure 3 shows the total number of studies per country in the included references. Of note, many studies do not refer to a specific country and that some stud-

ies cover more than one country. There is a clear majority of studies about Anglo-Saxon countries (USA, UK, Canada and Australia) followed by the Netherlands and Sweden.

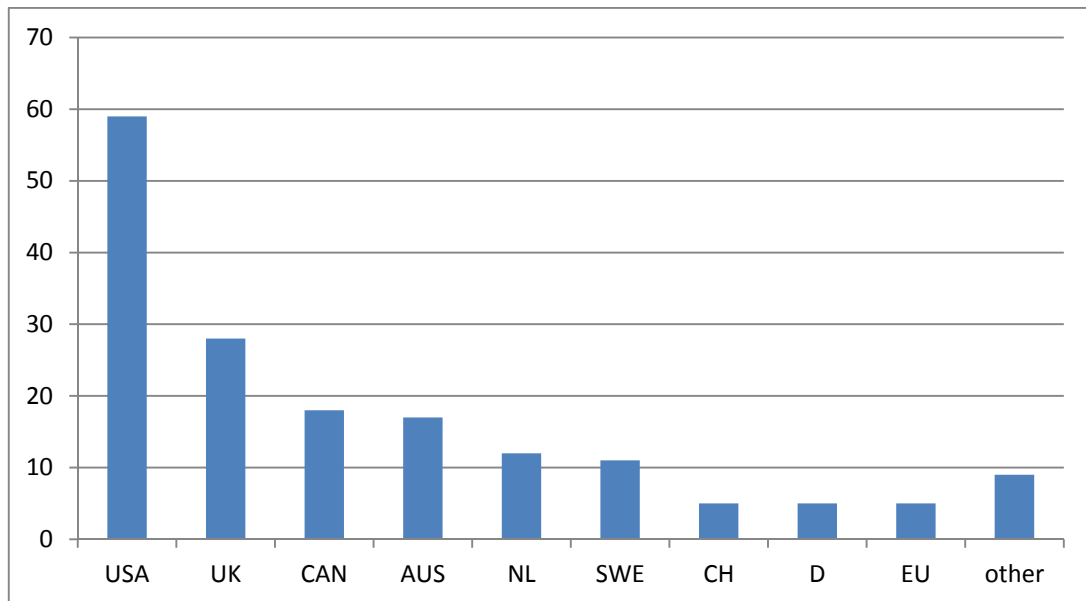


Figure 3: CED-Studies by Country

3.5 Finally, the references to CED were classified according to drug and non-drug health technologies. This was not always possible and often both types of health technologies were mentioned in one article. 25 articles made a clear reference to pharmaceuticals whereas 33 articles made a reference to non-drug health technologies such as devices, diagnostics or interventional procedures (mostly containing implants).

Chapter 4 The concept of CED and its wider context

- 4.1 CED contains the term ‘coverage’, which is a step in a larger process following regulatory approval and a health technology assessment (HTA) as shown in Figure 4. Coverage refers to processes determining which interventions will be provided, paid for or reimbursed in a health system. Regulatory approval refers to market authorization for a health technology. HTA aims to collect and analyse information relevant to health decision makers using scientifically sound and transparent methods.[19] Figure 4 shows that these three steps are part of a large translational process from research into clinical use.[20]

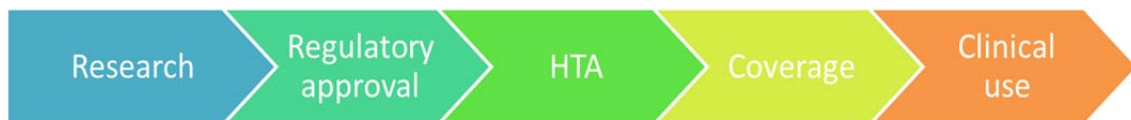


Figure 4: Pathway for translation of research into clinical use (ad. from Cooksey 2006)

- 4.2 The concept of CED can best be clarified with help of a taxonomy that shows the larger context. In the literature review about half a dozen of such taxonomies were found.[1, 2, 15, 17, 21, 22] The Taxonomy by Morel et al as shown in Figure 5 was chosen for this study as an aid as it appeared to be the clearest and most comprehensive of them all. In telephone interviews it was used as a starting point and basis for discussion. All interviewees found it understandable and useful, though not perfect in all respects. They could typically assign their own system to the different components of the taxonomy.
- 4.3 Figure 5 shows the taxonomy where CED is one part of the larger entity called managed entry agreements (MEA).[22] MEAs all mean conditional coverage and they could be described as the type of decision ‘yes, but’. However, there are other forms of conditional coverage decisions that would not fall under the term MEA and that simply set limitations to the use of a health technology.² In contrast to that, MEAs are basically agreements between manufacturers or service providers and health care payers that stipulate that access and funding to a health technology can be provided to patients on-

² Such limitations could be the use for a particular patient group only, the limitation to specialized centres or specialized service providers or the requirement of a quality management programme for the use of a technology.

ly under specific requirements. The taxonomy distinguishes on a first level between financial-based arrangement and performance-based arrangements. It further mentions the reasons why a MEA might be set up. The financial-based arrangement serve ‘to manage budget impact’ for the health care system whereas the performance-based arrangements can either have the purpose ‘to manage utilisation in the real world’ or ‘to provide evidence regarding decision uncertainty’.

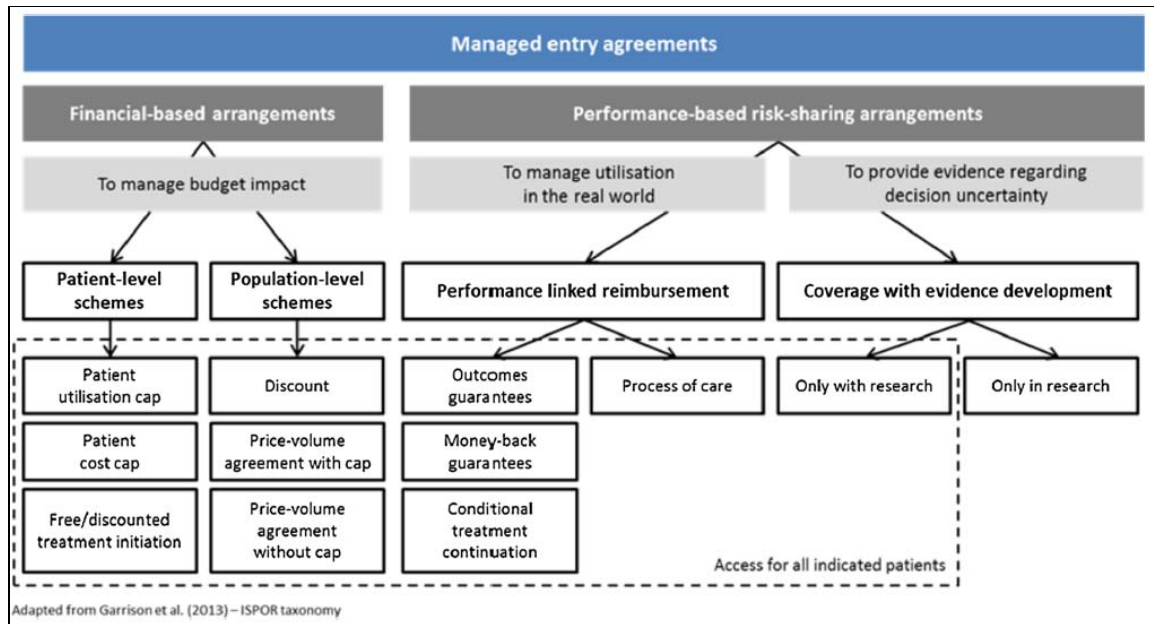


Figure 5: Taxonomy of managed entry agreements (Morel et al. 2013)

4.4 The financial-based arrangements can mean simple discounts or more complex schemes such as price-volume agreements, patient utilization caps, patient cost caps or free/discounted treatment initiation. The arrangements to manage utilisation in the real world can be outcome or money back guarantees conditional treatment continuation or monitoring of process of care. According to this taxonomy, coverage with evidence development is the type of agreement that is made in order to produce further evidence to reduce decision uncertainty while the medical technology is already being funded.

4.5 As Figure 5 shows CED can theoretically be one of two types. The following definitions are taken from Walker et al. [23] There is more information on the subject also in other publications.[1, 2]

- *Only in research (OIR): Coverage of a technology is available only to patients involved in research. This option may involve the purchaser paying for the research, which would require the purchaser to have some influence over research decisions (i.e., being able to contract for the research to be conducted). Alternatively, it may involve the purchaser rejecting the technology and simply recommending research, with the research being paid for by another party (e.g. the manufacturer or another stakeholder), which would not require the purchaser to be able to ensure the research was conducted.*
- *Only with research (OWR): A positive coverage decision is conditioned upon the collection of additional evidence to support continued, expanded or withdrawal of coverage.[1] So the technology is paid for all but further research is also required. This research may be funded by the purchaser, the manufacturer or another stakeholder, but such a decision would require that the purchaser was able to enforce that the research is actually conducted, so will be treated here as an available option only when the purchaser can ensure the research is conducted.*

4.6 These definitions mean that the OIR option is much more restrictive than the OWR option because not all patients who fall within the indication will have access or exposure to the new technology. This option therefore has the characteristics of a decision that means 'no, unless' rather than 'yes, but'. [24] If a randomised controlled trial is chosen as the appropriate research to be carried out, it further means that patients who chose to take part in the study cannot be certain they will get the new technology because of randomisation. This might cause problems if there are strong patients' preferences for the new technology or the comparator.³ Consequently, there may be concerns about coercing patients to enrol in research studies. In all cases where no research is set up, the OIR option becomes a straight 'no' from a patients' perspective.

4.7 The OWR option is less restrictive and such a decision is clearly of the type 'yes, but' because all indicated patients have access to a technology. There are several version of this option. It can mean that data from all patients who receive the new technologies is collected in a register. It can also mean that a randomised controlled trial (RCT) is conducted but not all patients receiving the treatment must take part in the study. And it

³ There are innovative trial designs where patients' preferences can be taken into account.

can finally mean that results of an ongoing study is awaited which is carried out in the respective country or elsewhere.

4.8 Several articles examine conceptual ideas and discuss when and how to set up and run a CED scheme.[3, 11, 13-15, 18]. A prominent one is the so-called 'Consensus statement from the Banff Summit'. Experts from around the world gathered in Banff, Canada in February 2009 and discussed principles for CED. They came up with five essential principles of good practice of CED approaches. These principles are⁴:

Principle 1: The decision problem that the CED is designed to address should be clearly specified;

Principle 2: The objective(s) of the CED should be stated;

Principle 3: The objective(s) of the CED should inform the design of the study;

Principle 4: The design of the CED should reflect the organizational characteristics and objectives of the healthcare system in which it operates;

Principle 5: The CED governance should ensure the independence of the scheme from any parties with a vested interest in its outcomes.

Despite the fact that these principles are to be applauded, they do not appear to have been widely implemented as yet in many jurisdictions.[25]

⁴ In this paper the term 'access with evidence development' (AED) was used. For consistency, it was changed in this report to the synonymous term 'coverage with evidence development' (CED).

Chapter 5 CED in different countries

- 5.1 CED is used in many jurisdictions around the world. [1, 5, 16, 18, 26-28] Table 1 shows an overview over a selection of countries that have used CED and that were included in this study. It clearly shows that not only the terms that are used for CED in different jurisdictions vary but also the approaches and the experiences.
- 5.2 CED has been used both in tax financed national health care systems ('Beveridge-type' such as Canada, England, Italy or Sweden) and in health insurance financed systems ('Bismarck-type' such as Germany, Holland or Switzerland). One finding of this study was that coverage decisions for non-drug technologies in general seem to be more centralized in health insurance based health care systems than in tax financed systems where such coverage decisions are frequently made at the regional level. In insurance based systems there is typically a centrally defined claims code for reimbursement which does not exist in tax financed systems.
- 5.3 Experiences with CED for non-drug technologies in different countries have been mixed. In some countries the use of CED has been more successful than in others. Success in this context means that (1) appropriate and scientifically sound research is carried out, (2) that the technology is only funded according to the conditions during the CED phase, (3) that the results of the research are fed back to the decision making and (4) that the funding and use of the health technology can be adjusted according to the new evidence.
- 5.4 Most countries can be assigned to two categories: (1) there are countries where CED was used for some time but where the use has been reduced or practically stopped because the approach was not satisfactorily working such as Australia, Belgium, and Switzerland. Problems were that data collection did not happen, that research did not answer the initial questions or the research did not feed back into the decision making. All these countries are currently thinking about redesigning and restarting the process. (2) There are countries where CED was started or restarted recently with a clear focus and process, or where the first experiences were positive such as Germany, the Netherlands and the USA/CMS. The Netherlands and the US restarted CED after partially unsuccessful experiences. Two countries do not fit into this pattern just described. Ontario, in Canada, a particular CED approach seems to be working quite well, potentially because of having a champion who is driving the programme. Finally, in England there are several different approaches to CED.

	Australia	Belgium	Canada / Ontario	England	Germany	Netherlands	Sweden	Switzerland	USA / CMS
Terminology	Interim funding	Conditional reimbursement	Conditionally funded field evaluations	No clear CED policy. Only in research (OIR)/Approval with reserach (AWR); Commissioning through eval. (CTE)	Testing of methods (Erprobung von Methoden)	Conditional reimbursement of health care (Voorwaardelijke toelating)	Recommended only for research	Yes, in Evaluation'; and 'No, in eval' but no coverage	Coverage with evidence development
Type of CED (according to taxonomy by Morel)	OWR	OWR	OIR; and to manage utilisation	1) OIR in England is not really CED. 2) CTE is OIR	OIR for out-patient care; OWR for in-patient care	OIR	OIR	OIR; and to manage utilisation	OIR; earlier also CAD (coverage with appropriateness determination)
Purpose / reason for programme	unclear at the beginning	limit the speed of innovation ('waiting room')	(1) pre-market: bend diffusion curve; (2) post-market: help promising technologies entering the system	uncertainty about effectiveness or cost-effectiveness	1) improve decision making; 2) help MedTech industry to innovate	Speed up process; better access for patients	uncertainty about effectiveness	promote innovation; fast access for patients; manage utilisation	1) political pressure 2) evidence generation
Mandate	no clear mandate	law	Policy decision by ministry	NHS policy decision	Law (SGB V §137 e)	law	policy decision by regional authority	law	CMS
Intruded	1998	~2008	2003	OIR (2000); CTE (2013)	2013 (but some precursors)	2012	2009	1996	2005 (but precursors)
Drugs	no	no	no	yes	No	yes	yes	no	no
non-drug techn.	yes	yes	yes	yes	Yes	yes	yes	yes	yes
further specification		only devices (not diagnostics and interv. Procedures)		CTE limited to interventional procedures so far	Different process for in-patient and out-patient care	only for hospital care	effectiveness, cost-effectiveness, severity of disease		
Decision criteria	Comparative safety, effectiveness, and cost-effectiveness	Therapeutic value; price; therapeutic and societal needs; Budget impact; cost-effectiveness	effectiveness, cost-effectiveness, sometimes safety	effectiveness, cost-effectiveness	Patient benefit in comparison to standard therapy (patient relevant endpoint)	1) Effectiveness (law); 2) C/E 'inofficial' ICER EUR 80K but not reinforced yet	Effectiveness, cost-effectiveness and other (e.g. human dignity, need and solidarity)	effectiveness, cost-effectiveness (CE and BI and price comparison); appropriateness	reasonable and necessary; (but not clearly defined)
Criteria for CED	no clear criteria	no clear criteria	magnitude of effect; relevance to health system; residual uncertainty	no clear criteria	Potential ('Potenzial')	EUnethTA Criteria	Low evidence (GRADE)	no clear criteria; promising	no clear criteria; promising
Patients access	All indicated patients	All indicated	Only patients in study, study	Only patients in study	In-patient: all patients if DRG; out-patient: only patients in study	Only patients in study	Only in study but not strictly followed by health care providers	only reimbursed of part of study but not strictly enforced; randomization not possible	only reimbursed if part of data collection
Funding of research	unclear	unclear	Government (CAD 600,000 p. field evaluation)	OIR: unclear; CTE: NHS	manufacturer pays overhead of study (if no manufacturer G-BA could finance)	ZonMw: research (Co financing of manufacturer possible but not done yet)	Through research bodies	manufacturer, research funding body; health ministry (exception)	different payers for reserach (manufact.; user fee for registries; reserach funding body)
Experience	rather unsatisfactory, stopped in 2009	rather unsatisfactory, stopped	overall positive	OIR unsatisfactory; CTE too new to say	New programme but 4 precursors; two successfully completed, two ongoing	New programm; 5 ongoing; some difficulties but overall working well so far; 5 planned	mixed, feedback to decision making not systematic	Over 40 technologies in CED since 1996 mixed experience; unstructured approach	15-20 cases so far; mixed experience

Table 1: Characteristics of CED in different countries

UK/England

Population ¹	63.7m (2014)
GDP per capita ¹	37,307 USD (PPP, 2013)
Health Expenditures ¹	9.4% of GDP (2011)
Type of health care system ¹	National Health Service divided into semi-autonomous regional health service organizations
Criteria for coverage ²	Effectiveness, cost-effectiveness, other criteria also relevant
HTA body ²	NICE (National Institute of Health and Care Excellence)
Decision making body for coverage decision ²	NHS England, mostly decentralized (e.g. CCGs), partly centralized (positive recommendation in NICE TAs mean compulsory coverage)

¹ UK ² England

- 5.5 Although funding for the NHS comes directly from taxes levied by the central government, decision making for most coverage decisions has remained mostly decentralized in regional entities of the NHS. One reason why NICE was set up in 1999 was to help to reduce significant local variations in health care delivery that were identified in the UK.[29] Currently NICE produces different forms of guidance: Technology appraisals (since 2000), clinical guidelines (2001), guidance on interventional procedures (2003), public health guidance (2006) and guidance on diagnostics and on medical technologies (2010).
- 5.6 Guidance produced by technology appraisals (TA) has a special status. The NHS is legally obliged to fund and resource medicines and treatments recommended by the NICE's TAs. However, there are two caveats: (1) A regional authority could still pay for a drug despite the fact that it is not recommended by NICE. Therefore, strictly speaking only a 'yes' is binding for the NHS but not a 'no'. (2) However, even NICE's other guidance may still have some legal implications for funding. There has been a recent court ruling that said that Clinical Commissioning Groups (CCGs) cannot simply choose not to follow NICE guidance because they disagree with it even if there is no statutory duty to follow it. In that particular case a patient demanded oocyte preservation due to a severe disease and the relevant guidance in the form of a clinical guideline (CG) recommended it.[30] Despite these two debatable points, one could still argue that TA recommendations are virtually coverage decisions and other NICE guidance is not.
- 5.7 In principle, England knows free pricing on manufacturer's side but the Department of Health (DH) does have to agree the price. This means that the DH does not actively negotiate the price of pharmaceuticals, as is the case in other countries. Since 2009,

however, so-called patient access schemes (PAS) have been available. A PAS is a managed entry agreement typically between the Department of Health and a pharmaceutical company with input from an independent expert panel administered within a dedicated unit at NICE (PAS liaison unit).[31, 32] A PAS must be initiated by the manufacturer, which typically takes place after a negative recommendation by NICE due to an unfavourable cost-effectiveness of a product. The process initiated thereafter is different from the standard appraisal process and it also involves a different committee. Figure 6 shows that PASs cover the left hand side of the taxonomy on managed entry agreements introduced before. Under this scheme different types of agreements are possible. PAS deal with budget impact or price sometimes linked to performance measures. A requirement for further evidence generation is seldom made, although it is possible. There is an interesting example that will be discussed further later.

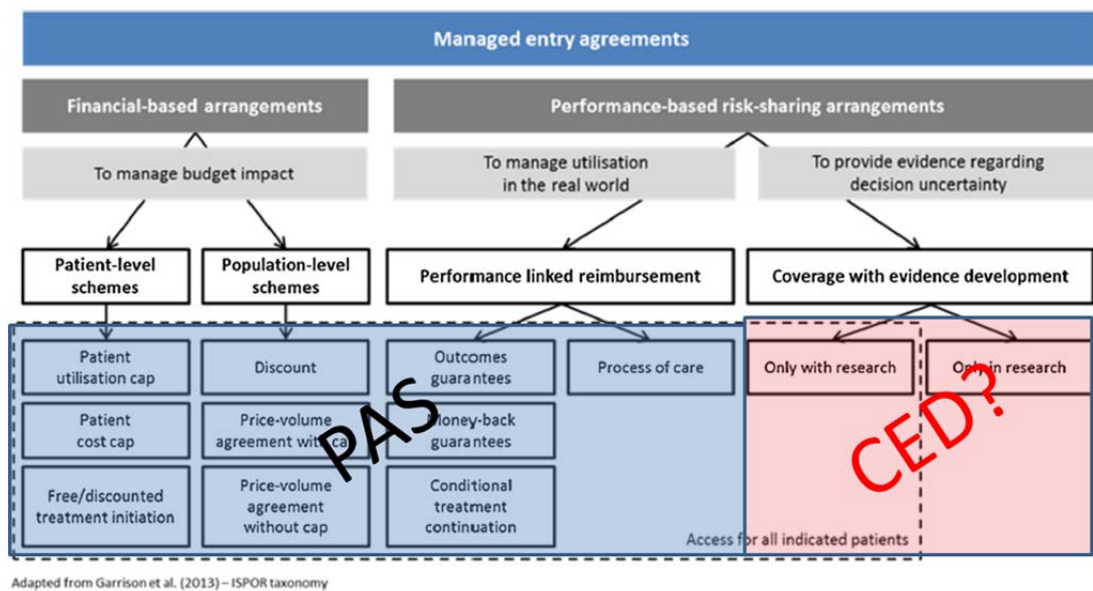


Figure 6: Taxonomy of managed entry agreements and NICE decisions (Morel et al. 2013)

5.8 In order to maintain the principle of free pricing, the PAS is proposed by the manufacturer and it is then evaluated by NICE PAS liaison unit. A PAS is not a negotiation on price but rather a mechanism for a proposal from the manufacturer that aims to reflect NHS judgements on value. Most PAS comprise of simple discounts on the list price. Because the publicly available price (that is, the list price) is used in many other countries as the reference prices, the manufacturer usually requests that the level of discount is kept confidential. A recent press statement of NICE’s CEO Sir Andrew Dillon showed that NICE has moved away from an exclusively passive role. He openly asked

a pharmaceutical company for a better deal: "We had hoped that Roche would have recognised the challenge the NHS faces in managing the adoption of expensive new treatments by reducing the cost of Kadcyra to the NHS." [33]. This point is important here because a PAS requires dialogue and collaboration between a manufacturer, the NICE PAS liaison unit, the DH, and possibly other players involved such as clinicians. The same seems to be true for a successful CED scheme that cannot simply be imposed on a sponsor of a technology or the NHS, in order to be successful.

OIR/OWR

- 5.9 The question is now whether some NICE guidance can also recommend CED as indicated in Figure 6. Since 1999 NICE can use four statutory options in decision making. (1) It can recommend the unconditional routine use of an intervention in the NHS within the limits of its market authorization, (2) it can recommend the use with limitations to smaller subsets of patients which is called 'optimized' recommendation, (3) it can recommend that the intervention is not used in the NHS or (4) it can recommend the use only in the context of appropriate research.
- 5.10 In the updated guide to the TA methods published in 2013, two clearly distinct options for a recommendation in the context of research were mentioned for the first time. *'When the evidence of clinical effectiveness or impact of a technology on other health outcomes is either absent, weak or uncertain, the Appraisal Committee may recommend that the technology is used only in the context of research or while the technology is recommended as an option, research is also conducted.'* [34] In addition a series of criteria are mentioned in the methods guide for the appraisal committee to be considered when recommending either of the two options. These criteria are:
- *the need for and potential value to the NHS of additional evidence that can inform the development of NICE guidance and clinical practice on the use of the technology*
 - *the uncertainty in the analysis and what could be gained by reconsidering the decision in the light of research findings*
 - *whether the research is feasible in circumstances when the Appraisal Committee recommends the intervention for NHS use outside the context of research*
 - *irrecoverable costs incurred from introducing the technology*
 - *the likely net benefits for all NHS patients of use only in a research setting during the time that the recommended research is being conducted.*

The methods guide states explicitly that the appraisal committee will not consider who is financing or conducting the research. A final criterion is whether the study itself is likely to be worthwhile. There is published research and an elaborated methodology

about this topic under the term value of information analysis. [35]. However, the NICE methods guide does not specify how this criterion should be applied and whether formal value of information analysis should be used.

- 5.11 These two research based decision options correspond to the two CED sub categories in the taxonomy in Figure 6. The first one is explicitly stated as only in research (OIR) in the methods guide and the second one is a description of only with research (OWR). However, NICE states that these two options do not have the status of CED, due to issues with implementation due to the organisational responsibilities. NICE does not have a mandate to commission research, let alone to enforce it. OIR has mostly not worked as CED in the past and OWR is new and so far (May 2014) there has not been such a decision yet.⁵ NICE has in the past recommended technologies and in addition the guidance included some research recommendations. These were referred to in a publication as ‘approved with research’ but in these circumstances the research recommendations did not form part of the formal guidance, whereas the OWR option means that the research recommended is part of the formal guidance.[25]
- 5.12 OIR decisions have been made in a number of published appraisals. According to the summary statistics of NICE decisions, OIR was decided in 26 out of 518 decisions (5%) from 1 March 2000 to 31 March 2014. These decisions were more frequent in multiple technology appraisals (MTA) with 22 out of 377 (6%) OIR decisions in comparison to single technology appraisals (STA) with 4 out of 177 (3%) such decisions. Figure 7 depicts the number of OIR decisions in TAs by year and it suggests that the number of OIR decisions has been less frequent in recent years than earlier. One plausible explanation is the introduction of the STA process the year 2006 but it could also be related to other factors. Proportionally more OIR recommendations were issued for TAs of procedures on devices than on pharmaceuticals.[25]

⁵ At the time of writing (May 2014) there is an internal discussion at NICE in one ongoing TA whether this decision option should be taken into consideration. If the appraisal committee made that the decision it would be the first such decision (OWR).

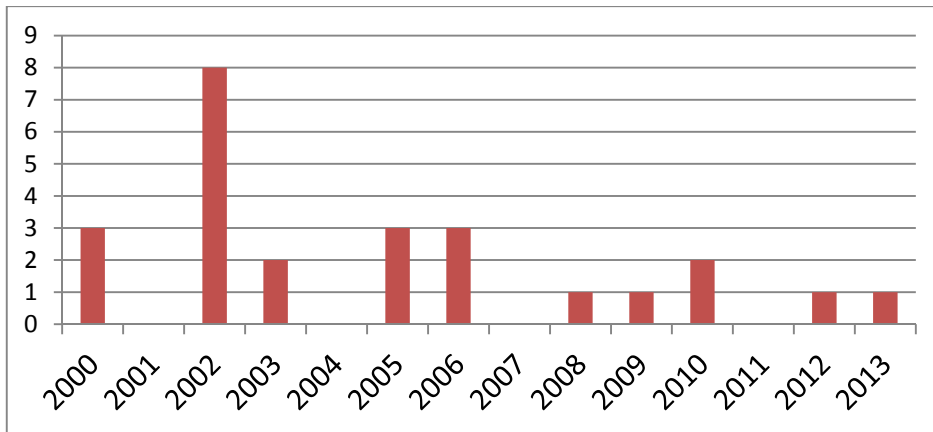


Figure 7: Number of OIR decisions in TA by year

- 5.13 Notwithstanding its appearance as CED, OIR decisions in England have often been viewed as ‘no’ decisions or they were paraphrased as a means of saying no politely.[24, 36] One reason is that many OIR decisions have not been followed by the research required to reduce uncertainty. As stated above, the challenge is that NICE has no mandate to enforce the research and the regional NHS authorities can still fund a technology despite a NICE recommendation for OIR even if no research is carried out.
- 5.14 The interviewed experts could not say whether an OIR decision meant that the NHS has a statutory obligation to fund the intervention (not the research) as part of a study if the required research is undertaken or not.

Two case studies of CED:

Beta interferon for MS and Pazopanib for renal cell carcinoma

- 5.15 One of the often cited examples of CED in England is the UK Multiple Sclerosis Risk-Sharing Scheme (MSRSS).[12] This scheme was set up by the Department of Health after negative NICE guidance for the drugs (interferon beta and glatiramer acetate). The idea behind the scheme was to develop more evidence and to improve cost-effectiveness. Data of a cohort of approximately 10’000 patients was collected and the manufacturing companies reduced the price to reach a target ICER of GBP 35’000 per QALY gained or less. However, the scheme is not being seen as a successful example of CED. It took too long, independence of evidence generation was not established and feedback of information to decision making was not guaranteed.[36] Despite the flaws which the scheme had for policy making the data collection was still useful for scientific

purposes. It allowed the collection of effectiveness data from a large number of MS patients over a long period of time.[37]

- 5.16 A positive example for CED in the NICE context was pazopanib for the first-line treatment of advanced renal cell carcinoma (TA 215). Interestingly it was not framed as an OIR decision but given a positive recommendation based on a PAS with a research requirement. It stated:

'Part B of the patient access scheme, the details of which are 'commercial in confidence', offers a future rebate linked to the outcome of the head-to-head COMPARZ trial. The Department of Health considered that this patient access scheme does not constitute an excessive administrative burden on the NHS.'

- 5.17 This PAS linked a research requirement to a future rebate in case the outcome of a specific trial that was required by the EMA was negative. In other words it meant that the manufacturer would have to pay back part of its revenues if the trial did not show the expected results. The trial was completed and it showed successful results and as a consequence the NICE guidance was adapted accordingly. Part B of the PAS became obsolete thereafter. This is a good example that illustrates some of the success criteria necessary for effective CED. One important aspect was that the EMA required the trial and therefore it was inevitable for the manufacturer to conduct it because its marketing authorisation was at stake. The study questions and the necessary quality standards of the study were also clear. This example shows that a PAS has further important features for the success of a CED scheme. It allowed dialogue between different stakeholders (meaning the company, regulators and NICE) and it linked the research recommendation to the coverage decision.

Research recommendations in MTEP Guidance

- 5.18 A further interesting option for a research decision exists as part of the Medical Technologies Evaluation Programme (MTEP) process. One of the possible decisions there is a recommendation for more research in case the medical technology is promising but has not yet shown its effectiveness sufficiently in appropriate scientific research. This situation arises in Medical Technologies because there is no requirement to submit data on effectiveness as part of the regulatory route in Europe, unlike pharmaceuticals. The Medical Technologies Advisory Committee (MTAC) has the possibility to make both an OIR and an OWR decision.[38]

- 5.19 The term ‘promise’ plays an important role. The committee chair expressed the meaning in a published article as follows: *“In addition, the committee seems to make a qualitative judgment, which will be familiar to all professionals who, when using a new tool, judge that it looks and feels right and does the job well. (...) A Technology’s promise seems to comprise the nature of the benefits it is claimed to have, the size of these benefits, and their plausibility”*[39] The term ‘promise’ is comparable to ‘Potenzial’ (engl. potential) that is used in Germany.
- 5.20 Unlike in other programmes, NICE has established a specific function to help the sponsor of the technology to conduct independent research that can be used for a new and better informed recommendation by the committee. However, the recommendations of the medical technology evaluation process lack the clear status of leading to formal coverage decisions. Therefore these research activities, although clearly linked to guidance recommendations, do not qualify as CED. Nevertheless, they contain some highly relevant aspects regarding successful CED implementation, such as dialogue and cooperation between stakeholders, supervision of research by an independent organisation (in this case NICE), using professional research groups to conduct the study, and integrating the generation of primary research data directly into the HTA process.

Commissioning through evaluation (NHS England)

- 5.21 Recently NHS England started a new programme called commissioning through evaluation. Their website states: *‘The programme is aimed at improving access to services which are not currently routinely funded by the NHS as the existing evidence base does not yet demonstrate sufficient clinical and cost-effectiveness for its routine use’*. [40]. Under this programme, medical technologies are provided in selected specialized centres to patients that are clinically suitable. NHS England chose a first batch of six technologies for the programme. They are:
- *Selective Internal Radiotherapy (SIRT) for liver cancer*
 - *Selective dorsal rhizotomy for reducing spasticity in children with cerebral palsy.*
 - *Left atrial appendage occlusion to prevent stroke in patients with atrial fibrillation*
 - *Patient foramen ovale occlusion to prevent stroke*
 - *Mitraclip*
- As of May 2014, more technologies are being evaluated to be included in the programme.

5.22 Such a programme was possible because NHS England has a centralized budget over GBP 13.5bn for specialised services, such as cancer, cardiac, or specialized children's services. This means that there is one payer that makes centralized coverage decisions and links them to the outcome of research (that has been designed by the payer). This programme shows the characteristics of CED.

5.23 There are still a lot of methodological and practical issues under this programme.[41] One problem is that only observational data (mainly through registers) are collected so far. It remains to be seen what will be done in cases where an experimental trial design as in a RCT would be the appropriate method to answer a specific question. As yet, all evaluated technologies under this programme have been interventional procedures, for which the scientific evidence is typically weak and there is no equivalent for a thorough market approval process. Unlike in the US where the FDA can demand solid scientific evidence for market approval of high risk devices⁶, the CE mark that is required in Europe is a far lower hurdle to take.

⁶ There are many devices that go through the 510(k) process for which the evidence requirement is very weak.

Australia

Population	23.8m (2014)
GDP per capita	43,073 USD (PPP, 2013)
Health Expenditures	9.5% of GDP (2011)
Type of health care system	Medicare (publicly funded universal health care scheme) that coexists with a private health system.
Criteria for coverage	Comparative safety, effectiveness, and cost-effectiveness
HTA body	MSAC (medical technologies, procedures and services), PBAC (drugs)
Decision making body for coverage decision	Ministry for Health

5.24 CED in Australia is called ‘interim funding’ and it was started in the early 2000s shortly after MSAC (Medical Services Advisory Committee) was established in 1998. There is no legal mandate and no guidance for interim funding arrangements. According to an interviewed expert the recommendation for interim funding has not usually been accompanied by the prospective documentation of a research plan and agreements for cessation or continuation of funding. Interim funding means that all indicated patients have access to the technology but research has to be collected while the technology is reimbursed temporarily. In the taxonomy in Figure 5 it would be only with research (OWR).

5.25 The first attempts of CED in Australia were of limited success. The experience showed that either the research did not happen and the technology was funded anyway or the research did not deliver the evidence but the funding could not be stopped. Due to its ad hoc nature, many crucial points were unclear at the beginning such as the criteria for CED, the funding and the outcome criteria. The disappointment with interim funding can be seen in this statement:

‘In our experience interim funding is effectively full approval, because the evidence typically doesn’t come back, and even when the item is subsequently reviewed it’s almost impossible to withdraw funding because at least one patient will be disadvantaged by its removal. So it seems like a fairly futile exercise (..) in its current format it is unconvincing because we have no way of getting into a legal agreement with the applicant to collect the data and hence we can’t mandate that the applicant collect the data.’

5.26 In most cases of CED in Australia the funding just continued. There were only two examples where the committee decided to withdraw funding after the result of the study carried out after a CED decision were not as expected. The first was for kyphoplasty/vertebroplasty following publication of a randomised controlled study published by an

academic group. The second was for hyperbaric oxygen treatment (HBOT) for non-diabetic ulcers. That decisions caused a heated discussion with doctors, patients and politicians and a public debate in the media took place.

- 5.27 Since 2009 there were no new cases of interim funding recommended by MSAC. If in doubt the committee would either accept a promising health technology even if the evidence base is weak or reject the application, particularly in case of doubts about safety. Particularly for patient groups with high clinical need or rare patient groups, the committee may accept a new health technology on the basis of a lesser level of evidence than typically required for more common conditions. This principle may not apply in countries which are less able to afford expensive technologies than Australia.
- 5.28 It is likely that CED (interim funding) will be reinvented in a better form in the future in Australia. The interviewed expert names the following factors needed for success: a clear mandate, a binding agreement with the applicant, clear measures of success and failure, and an explicit communication strategy that explains the logic of CED and its possible outcomes. This last point was expressed as follows:

(...) there must be an effective communication strategy. So that the communication is provided at the very outset to the public, to the applicants, to the people who would receive the device or the test or whatever it is and the possible outcomes when that's reviewed. So it needs a lot of energy and emphasis on the communication around what CED means for that particular technology and in general.

Belgium

Population	11.1m (2014)
GDP per capita	37,881 USD (PPP; 2013)
Health Expenditures	10.6% of GDP (2011)
Type of health care system	Universal coverage through mandatory health insurance, competition between health insurers
Criteria for coverage	Medical necessity, activity, cost-effectiveness, safety
HTA body	KCE
Decision making body	Health ministry

5.29 Belgium has the possibility to initiate a so-called 'conditional reimbursement'. What is meant by the term is not precisely defined according to the interviewed expert but it allows the government to link a reimbursement decision to additional data collection. The legal text of the regulation for conditional reimbursement of implants is in article 35, catégorie 5 of the nomenclature of reimbursed procedures and products and is rather vague:

'Pour les implants de la catégorie 5 (...) le Conseil technique des implants propose les modalités d'évaluation, les critères de remboursement et le montant de l'intervention de l'assurance....'. (In English: 'For implants category 5 (...) the Technical Council of implants proposes an evaluation procedure, the criteria for reimbursement and the amount for reimbursement by the insurance...')

5.30 According to the interviewed expert, the first attempts of CED have not been successful. The problems were that compliance with data collection by doctors was weak, the monitoring of the study was poor because of lack of staff and there was no uptake of the research in the decision making process later on.

5.31 It is planned to restart CED after initial unsuccessful attempts. The appraisal committee (recommending body) can propose the reimbursement of a medical device that is part of a technological innovation in the context of a restricted clinical application. This applies if the committee, when considering the request made for an innovative technology, determines there is uncertainty whether the technology offers an added value compared to existing alternatives. At this point in time, it is too early to say how effective the improvements will be.

Canada / Ontario

Population	35.3m (2011) Canada
GDP per capita	43,472 USD (PPP, 2013)
Health Expenditures	11.2% of GDP (2011)
Type of health care system	Publicly funded universal health care scheme, organized by each province
Criteria for coverage	Effectiveness, cost-effectiveness
HTA body in Ontario	Health Quality Ontario
Decision making body for coverage decision	Ontario government, ministry of health

- 5.32 CED in Ontario Canada is called 'field evaluation studies' and it was started in the year 2003. According to the interviewed expert the purpose is to have '*real time evaluation of health technologies where there is residual uncertainty following systematic review and/or economic analysis.*' It started with PET scanning where the Ontario HTA agency decided that they would only recommend funding if clinical utility could be demonstrated based on more research. The uncertainty in that case was around effectiveness and cost-effectiveness. Since then, 6 studies for PET scanning have been completed and according to the interviewed expert better informed decisions have been made based on them.
- 5.33 A set of informal criteria appear to be in place that are not explicitly written down in a kind of process guide. Such criteria are magnitude of effect, relevance to health care system and existing residual uncertainty. Each field evaluation is estimated to cost CAD 600,000, which includes protocol development and implementation and costs attributed to data collections, analysis and reporting.[42] An available infrastructure for rapidly and efficiently conducting CED studies was described as an important success factor by the interviewee.
- 5.34 Field evaluation studies are also used for purposes other than CED. In some cases such studies have been set up in order to explore how the use of a technology should be organized in the health care system. For example, a study was completed for HPV screening, however this was not linked to a coverage decision and so does not qualify as CED.
- 5.35 Ontario distinguishes between two types of CED: (1) pre-market and (2) post-market (see Figure 8). In the pre-market situation Ontario has a programme that is called 'excellence in clinical innovation and technology evaluation' (EXCITE) in which govern-

ment, academia, industry and the health system are collaborating to evaluate new technologies. The evaluation studies are paid by industry to a neutral research body which then commissions the research with the money so that industry is arms-length removed.

- 5.36 In the post-market situation, field evaluations are used to avoid diffusion of a technology where there are still considerable uncertainties regarding effectiveness or cost-effectiveness. Safety is typically not included because safety in Canada is a federal jurisdiction. However, even if there is an approval of Health Canada (regulatory authority in Canada) and a safety concerns is identified through systematic review it can and will be included in the field evaluation. An example is endovascular abdominal aortic aneurysm repair where a safety assessment of endoleak was done.[42]

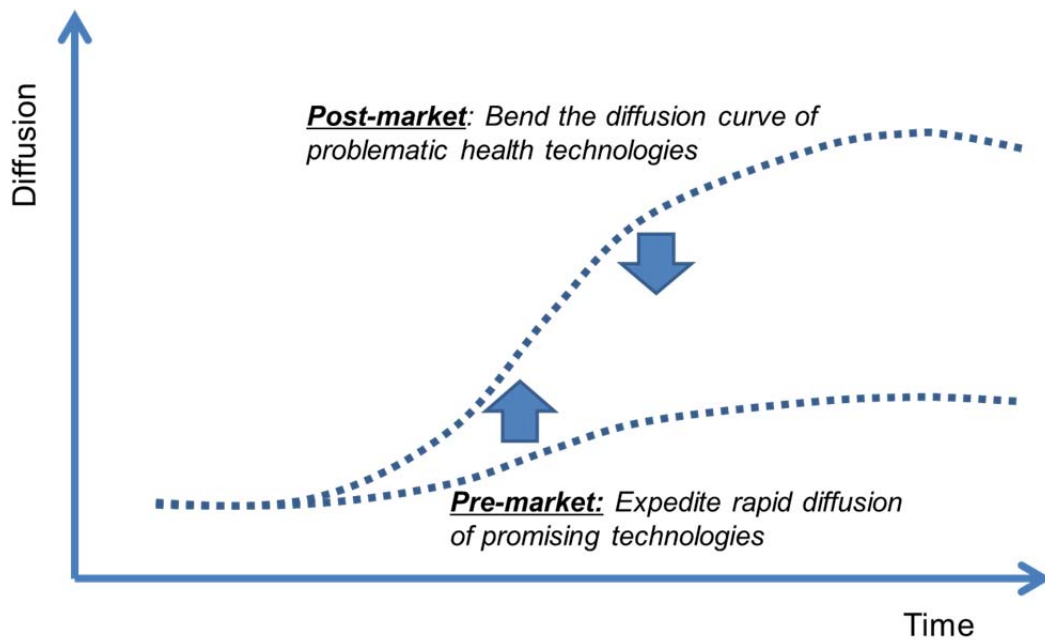


Figure 8: CED in pre-market and post-market situations

- 5.37 In the post-market situation the evaluations are paid by the government. According to the interviewed expert the studies would 'pay for themselves'. The reason is that the diffusion of contested technologies is slower and its use more targeted with a field evaluation than it would be without it. In the case of drug eluting stents and PET scanning, Ontario has potentially saved millions of dollars, particularly if the diffusion process is compared with the one in the US.

- 5.38 The interviewed expert summed up the two situations where field evaluations are used for coverage decisions: *‘There is one track where we are trying to facilitate the quality agenda in the pre-market space but in the post-market space wherever we are coming across uncertainty for potentially clinically important technologies, we are using field evaluation studies to help us. So we have these two different tracks going on at the same time. Pre-market kind of pushes you to drive excellence and quality into the system and post-market is to stop poor quality entering it. On one side you are policing technology (post-market) on the other side you are pushing good quality research to help meaningful technologies (pre-market).’*
- 5.39 Timing is important. The time frame during which the research is carried out should be kept to a minimum in order to keep it relevant to the policy decision makers. In Ontario they try to keep the evaluation period down to two years but it varies. There were instances where the period was as long as five years.
- 5.40 In Ontario there is no legal basis for CED but it is done to inform policy by the ministry of health and the broader health system. The interviewed expert sees CED as a meaningful form of *‘evidence based policy development’* because the evidence generation is built into the policy making.

France

Population	65.9m (2014)
GDP per capita	35,784 USD (PPP, 2013)
Health Expenditures	11.6% of GDP (2011)
Type of health care system	Universal coverage through mandatory national health insurance
Criteria for coverage	Benefit in comparison to standard therapy for patient relevant end-points (such as mortality, morbidity, quality of life)
HTA body	HAS (Haute Autorité de Santé)
Decision making body for coverage decision	CEPS (Comité Economique des Produits de Santé)

- 5.41 France uses both options of CED as depicted in Figure 5. The only with research option is called ‘post-listing studies’ (in French: ‘études post-inscription’) and has been used since around the year 2000. The only with research option is called ‘forfait innovation’ and it was introduced in 2009.
- 5.42 The post-listing studies are used to supervise real life use of drugs and medical devices or procedures. They are set up if there is a concern regarding medical, economic or organisational questions. If the authorities are concerned with a potential overuse of new technologies such studies are initiated to monitor volume. These post-listing studies are often linked to regulatory measures (such as a limitation to specialised centres or minimum volume regulations) or to managed entry agreements (particularly price-volume-agreements). In the latter case the post-listing studies are used to monitor the agreed quantities and to use the information for enforcing the contracts with industry. If post-listing studies are purely used to monitor volume they are strictly speaking not CED in the narrow sense as defined in this study.
- 5.43 There are some challenges with the post-listing studies. The main problem is that the doctors are reluctant to provide the data that are requested. There is the possibility of sanctions for the health authorities such as a decrease in price or a refund. However, in practice according to the French expert this does not seem easy to do.
- 5.44 ‘Forfait innovation’, the OIR option, was introduced in France to help innovative new medical devices entering the market. According to the French expert it was to bridge the time between market authorisation (CE mark) and approval of the Haute Autorité de Santé (HAS), the French HTA body. Typically the goal is to do an RCT after first successful smaller studies have been completed.

- 5.45 In 2011 three technologies were initially selected for forfait innovation, two were medical devices that were submitted by manufacturers and one was an interventional procedure submitted by health care professionals. However, there were difficulties in all of them. In the case of one medical device another study was already going on and in the case of the other medical device there was no agreement between the authorities and the manufacturer regarding the type of study. The required study by the authorities was seen as too expensive by the manufacturer.
- 5.46 Because of these initial practical problems with forfait innovation a revised law was introduced in 2013 to clarify three points that were seen as the major obstacles in the beginning: (1) clearly stated selection criteria, (2) clear relationship between all actors and (3) limitation of the duration of the study under forfait innovation. In April 2014 a first technology was selected for forfait innovation. It is a retinal prosthesis system called Argus II.

Germany

Population	80.7m (2014)
GDP per capita	40,007 USD (PPP, 2013)
Health Expenditures	11.3% of GDP (2011)
Type of health care system	Universal coverage through mandatory health insurance, competition between health insurers
Criteria for coverage	Benefit in comparison to standard therapy for patient relevant end-points (such as mortality, morbidity, quality of life)
HTA body	IQWiG (Institute for Quality and Efficiency in Health Care)
Decision making body for coverage decision	The Federal Joint Committee (Gemeinsamer Bundesausschuss G-BA; joint self-government of physicians, dentists, hospitals and health insurance funds)

- 5.47 In Germany there is an important difference in reimbursement between in-patient care and out-patient care. In in-patient care, a health technology is reimbursed if it is part of a DRG-category. In case of controversies about safety or effectiveness, the stakeholders represented in the Federal Joint Committee (G-BA) or specific associations of sickness funds can request a review of a health technology. This means it goes to the decision making body which is the Federal Joint Committee (G-BA). Then the German HTA-agency (IQWiG) carries out an assessment of the health technology but most often in such cases the evidence remains weak. Until recently the G-BA could then only decide either to suspend the process and to wait until new research was published or to exclude the health technology from the system if the evidence showed that the health technology was not effective. In the first case the controversial health technology could still be provided by the hospitals and be reimbursed by the health insurance. This was an unsatisfactory situation.
- 5.48 In out-patient care the situation is different. Only health technologies that have demonstrated patient benefit and were assessed by the G-BA are put on a positive list and get reimbursed. The hurdle for the medical technology industry to get reimbursement is comparatively higher in out-patient care than in in-patient care. Therefore the German government wanted to find a way to help the medical technology industry, which contributes significantly to the creation of wealth in the country, to get an easier access to the health care system for its innovations.
- 5.49 For two reasons (1) better decision making and (2) helping industry to innovate, CED was set up in Germany. In 2013 a new legal regulation was introduced with the new paragraph §137e in the social code five (Sozialgesetzbuch V) that allowed CED.[43] In

addition to the already quite precise legal text there is a very detailed rule of procedure (Verfahrensordnung) that regulates the process details. The relevant part that deals with CED is 20 pages long.

- 5.50 For in-patient care, the new paragraph gives a mandate to the G-BA to initiate a study if three conditions are fulfilled: (1) the approval process is suspended; (2) no new studies are to be expected in the near future and (3) the health technology has a 'potential'. A first study that is about to be initiated is PET scanning for colorectal cancer. For in-patient care CED has the status of 'only with research' meaning that the technology is funded for all eligible patients if research is conducted.
- 5.51 The new regulation gives companies with a promising technology the right to apply for CED. In this case a study is set up and the technology is reimbursed by the health insurance fund but only for the patients who take part in the study. The administrative costs of the study have to be paid by the manufacturer. For out-patient care CED has the status of 'only in research' meaning that the technology is only reimbursed if a patient takes part in a study. For in-patient care, CED has the status 'only with research' because the technology is available to patients also outside the study. That means it would be very difficult to recruit patients for the study. Therefore such a CED application does not make much sense for a company in the in-patient setting and it has not happened yet.
- 5.52 The notion of 'potential' ('Potenzial') was introduced and it is important in this context. It means that a health technology appears to be more effective, less harmful or less resource intensive, more efficient or that it has other advantages. The intention of the lawmaker was to set a low threshold for overcoming this hurdle. There is a submission template that has to be filled in by the manufacturer where he has to demonstrate the potential of the new technology. This could include weak scientific evidence, such as case series or small controlled or uncontrolled studies. The manufacturer also has to agree that they will guarantee to fund the administrative cost of a study, if the technology is accepted for CED. The costs of the health technology would then be covered by the health insurance fund.
- 5.53 In a first step the G-BA assesses the completeness of the submission, and then it is handed over to IQWiG for an assessment of the potential of the intervention. Optionally, the manufacturer can suggest a study design and some key elements (e.g. comparator, endpoints). If the manufacturer does so, IQWiG comments on the evidence; if not, IQWiG develops a proposal for a study design if the assessment of the potential is positive. IQWiG has 6 weeks until the manufacturer's submission with IQWiG's comments

goes to a separate working group of the G-BA for a decision on the technology's potential. This working group meets every 2 weeks. The decision must be made three months after submission at the latest. The G-BA communicates its reasons to the manufacturer for whether it sees a potential or not. Until this point the process is confidential. Only if a positive decision for CED is made does the G-BA publish it. The manufacturer can appeal a negative decision. In this case the manufacturer also has the right to generate and collect new evidence within a year and to submit again. The G-BA also offers scientific advice for these submissions for a fee. Such advice could be regarding the formalities of the application process, methodological requirements for the assessment, suitability of a new method for consideration under section 137eSGB V, and funding specifics.[43]

5.54 If a number of technologies has been categorised as 'having potential', the G-BA can prioritise the different technologies if the resources do not allow conducting a study for all of them. Apart from the potential of a health technology the committee also considers the feasibility of a scientific study for its decision-making. As the expert admitted, this is a difficult task and the technologies might be in totally different disease areas which would make prioritisation difficult. So far, no clear criteria have been developed how to prioritize and therefore this is left to the judgement of the G-BA. Most likely there will not be operationalized criteria in the future. The G-BA has also the option also make a positive decision for CED, but defer the study for a year. The G-BA currently has no fixed budget for this mandate.

5.55 There were precursor projects that were not initiated by the G-BA but by the health insurance funds. Those were also cases where the G-BA had suspended the process because the evidence was not sufficient to make a decision, but it did not have the right to initiate a study at the time. A lot of the knowledge that was used to set up the new CED programme was derived from these earlier test cases. Table 2 shows the list of the precursor projects in Germany.

Intervention under CED	Method	Status	Result
Balneo-phototherapy for patients with psoriasis	Multi-centre study	completed	Accepted
Acupuncture for four indications (knee osteoarthritis, low back pain, migraine, tension headaches)	RCT	completed	2 accepted (knee, low back pain) other 2 rejected
Vacuum assisted closure therapy (VAC) for chronic wounds	RCT	ongoing	
Brachytherapy for localized prostate cancer	RCT (preference based)	ongoing	

Table 2: Precursor projects in Germany

5.56 The experience in Germany is limited. The two precursor projects completed were described as a success by the interviewed expert. There were some learnings as follows:

- Doctors play a crucial role. Incentives for doctors have to be set. Doctors have to be reimbursed for their contribution to the study. Professional societies and associations should be included. Sometimes idealism of doctors can be triggered. The G-BA has the right to set quality standards in the in-patient setting which could make study participation a requirement. Otherwise CED decisions in the in-patient setting in Germany are only with research (OWR) decisions (see paragraph 5.46). However, this possibility has not been used yet.
- A big problem is recruiting the patients. If possible financial incentives for patients should be set, for example reduction of obligatory deductibles for doctor visits. This is more important in the in-patient setting where participation in the study is not mandatory for reimbursement. In the out-patient setting it is much easier to recruit patients since the medical technology is only reimbursed if the patient participates in the study.
- A professional research organization has to run the study that guarantees compliance with GCP (Good clinical practice) principles and research governance, which also includes ethical aspects.

Netherlands

Population	16.8m (2014)
GDP per capita	41,711 USD (PPP, 2013)
Health Expenditures	11.9% of GDP (2011)
Type of health care system	Universal coverage through mandatory health insurance, competition between health insurers (managed competition)
Criteria for coverage	Primarily effectiveness ('evidence-based health care'); additionally cost-effectiveness (unofficial threshold of EUR 80'000 per QALY)
HTA body	Zorginstituut Nederland (former CVZ)
Decision making body	Ministry of Health

5.57 The Netherlands had an early version of a CED programme in place that started in 1993. In the end the programme deteriorated because of a lack of guidance. Some studies were slow in enrolling subjects and had to be extended in time. According to the interviewed expert the programme was difficult to manage and not always successful. The minister of health stopped that programme in 2002 and a research fund with public money was set up instead. Cost-effectiveness studies could be funded with it but the health intervention itself was not funded. This proved to be unsatisfactory.

5.58 In 2012 the minister of health decided to start a new and clearly regulated CED programme. The programme was designed by the Dutch HTA agency named Zorginstituut Nederland (former CVZ) and it is also run by it. The mandate for CED is stated in the law and each health technology is listed. For every new intervention that falls under CED, the law has to be altered each year. This means that the CED decision in each case is taken by the minister of health following a request by the Zorginstituut Nederland. Under the CED programme the health care intervention is funded through the health care system (health insurance) and the research is funded through a public research body. In principle it is possible that a manufacturer would have to contribute to the costs of the research but this has not happened yet.

5.59 In order to decide which technologies are suitable for CED, the Dutch adopted the approach that was developed by the EUnetHTA Joint Action working package 7. A CED programme can be set up for a maximum of 4 years. RCTs or registers are used depending on the question and the feasibility. Before a study is started, a signed letter of both the relevant medical association and the relevant patient association has to be received that says that they agree with the study design.

5.60 In the Netherlands CED is done to generate effectiveness data. The intervention is then only funded within a research context (OIR). Patients participating in an RCT have to be willing to be randomized to qualify for reimbursement. According to the expert this has caused some discussions among doctors but, the expert explained that this was in line with the medical principle of 'primum non nocere' (first, do no harm) and it would be unethical to provide a medical service where the risk-benefit profile compared to current standard of care is not known outside the context of research.

5.61 The Zorginstituut Nederland monitors the research and can advise the minister to end it earlier than planned. Twice a year there is a large meeting involving the HTA body (Zorginstituut Nederland), the research funding body, the researchers and the funders or the health technology itself (health insurers), to discuss the research.

5.62 The programme is currently small, and an interviewed expert explained that it is important to keep it small in order to be successful. The first five interventions that came under CED are seen in Table 3. Five more interventions are currently being planned.

Intervention under CED	Method	Start
Radiofrequency denervation (an anesthetic pain management technique) in patients with chronic non-specific low back pain	RCT	2012
Intra-arterial thrombolysis / thrombectomy in a stroke unit	RCT	2013
Renal denervation in treatment-resistant hypertension	RCT	2013
Autologous stem cell transplantation in refractory patients with Crohn's disease	Register	2014
Transluminal endoscopic step-up approach in patients with infected pancreatic necrosis	RCT	2014

Table 3: interventions in the Dutch CED program

5.63 So far there have been difficulties in two cases that had to be overcome.

- Radiofrequency denervation for low back pain: After the start of the study it became clear that the comparator which was optimal conservative treatment was not really used in practice although it was in the Dutch guidelines. So, optimal conservative treatment had to be established first, in order to have a comparator for the study. There was a lot of discussion about what was current usual care. The study was nearly stopped.
- Renal denervation for hypertension: Several different devices came to the market during the study. Clinicians were asked to define the criteria for the devices to be included in the study. This had the advantage that it led to acceptance by the clinicians which is seen a crucial point for a successful CED.

One case was reported as particularly successful one:

- Intra-arterial thrombolysis/thrombectomy: A study had started before but did not go well because hospitals had to pay themselves for the interventions. Since the technology has been subjected under a CED scheme the recruiting is going very well.

5.64 The interviewed experts noted that they gradually learned the relevance of study-design, statistics, follow-up and clinical relevance as important parts of a successful CED process.

Sweden

Population	9.7m (2014)
GDP per capita	41,188 USD (PPP, 2013)
Health Expenditures	9.5% of GDP (2011)
Type of health care system	National health care system divided into 21 regional county councils that are responsible for health care delivery
Criteria for coverage	Effectiveness, cost-effectiveness (no clear ICER threshold), other criteria such as severity of disease and number of patients
HTA body	SBU (non-drug technologies), TLV (drugs), regional HTA organisations
Decision making body for coverage decision	Regional health authorities (21 county councils)

5.65 There are two national HTA organisations in Sweden. One is SBU which was founded in 1987 and is the oldest HTA organisation in Europe that publishes guidance for non-drug technologies. The other one is TLV that looks at pharmaceuticals and dental care. Coverage decisions are made at a regional level in Sweden in the so-called 21 county councils. The following information is from an interview with a representative from the region Västra Götaland.

5.66 Västra Götaland region has its own regional HTA organisation that produces short HTAs particularly new and costly health technologies both for drugs and non-drugs. The organisation was founded in 2011. Its reports consist of about 10 pages with a one page summary and encompass information on effectiveness, cost-effectiveness as well as on ethical and other issues if relevant. They are produced in a short time frame typically 3-4 month. The effectiveness evidence is classified with the GRADE system. Then a so-called priority board that consists of doctors, hospital directors and administrators makes a coverage recommendation. In most cases the recommendations are followed by the decision maker which is the regional health authority at a political level.

5.67 The recommendations can be 'recommended', 'not recommended' and 'recommended only in research'. If the decision is for 'only in research' then research has to be conducted. The research must be funded through normal research budgets. There is no funding from the health care budget. The health care system pays only the amount necessary for the standard of care. The type of research conducted depends on the study question.

5.68 The problem with the Swedish system is that there is no systematic feedback of the research results to the decision making process. Completed research is published and influences practice of care but it remains at the level of the professionals. There is no

authority responsible for oversight of the research. The interviewed expert mentioned that it would not be desirable for the regional HTA unit to take on that role. According to the interviewee HTA needs to keep the image of being a helper for a better quality health care system. Supervision of the research may create conflicts of interest for such a HTA body.

Switzerland

Population	8.1m (2014)
GDP per capita	46,430 USD (PPP, 2013)
Health Expenditures	11.0% of GDP (2011)
Type of health care system	Universal coverage through mandatory health insurance
Criteria for coverage	Effectiveness, appropriateness, cost-effectiveness
HTA body	No HTA agency; submission process with 3 Federal commissions (for drugs, medical services, analyses & medical items) that make recommendations (appraisal function)
Decision making body	Federal Department of Home Affairs / Federal Office of Public Health (for drugs)

5.69 In Switzerland there has been obligatory health insurance for all residents since 1996.

The law stipulates that all health care (pharmaceuticals, procedures, diagnostics etc.) is reimbursed if it is ‘effective, appropriate and cost-effective’. There is a positive list for pharmaceuticals, in vitro diagnostics and non-implantable medical products. In contrast, all medical services and procedures are covered by social health insurance in Switzerland by default. This means that Swiss physicians and hospitals enjoy the so-called “principle of trust”.

5.70 There is, however, a health technology assessment process to identify medical services that do not fulfil the criteria for coverage. It is used in two cases: (1) post-market, meaning that a medical service is controversial and it is challenged by someone with a legitimate interest, e.g. a health insurance provider or (2) pre-market, meaning that a manufacturer of an innovative medical technology wants an authoritative decision that can be used in reimbursement negotiations with health insurers. A submission has to be handed in by the sponsor of the technology to the Federal Office of Public Health, which is responsible for the supervision of the benefits basket. A rudimentary and not very transparent HTA process is then triggered that leads to a recommendation by an appraisal committee and finally to a coverage decision.

5.71 For promising and innovative non-drug technologies, the legal possibility has existed since 1996 that they are temporarily reimbursed under the heading ‘yes, in evaluation’ even if their effectiveness, appropriateness and cost-effectiveness have not been sufficiently demonstrated. In that case further evidence has to be generated in order to reduce existing uncertainty. The intention is that a final decision ‘yes’ or ‘no’ can be made

at a later point in time. This is the Swiss version of CED and it has been used for over 40 health technologies.

5.72 The purpose of the system was to help industry to get innovative products faster into the system and to get quick and early access to patients for innovative technologies.

5.73 The CED system in Switzerland is not very transparent and until recently it has never been evaluated by external research. An independent research group (of which the author of this report is part of) was set up a research project two years ago. The following results are from that research.[44]

5.74 The study found that the duration of the CED phase (called ‘in evaluation’ in Switzerland) ranged from 1.5 years to 11 years. The CED decision is made for an initial time period. If the results from the research are not sufficient for decision making at the end of that period, the CED phase can be extended. Mean evaluation time for the initial CED period without extension was 4.5 years (median 5 years) and 5.8 years (median 6 years) for the total evaluation period including extension. Figure 9 shows a longitudinal sequence of the 45 medical technologies in the category ‘yes, in evaluation’ between 1996 and 2012.

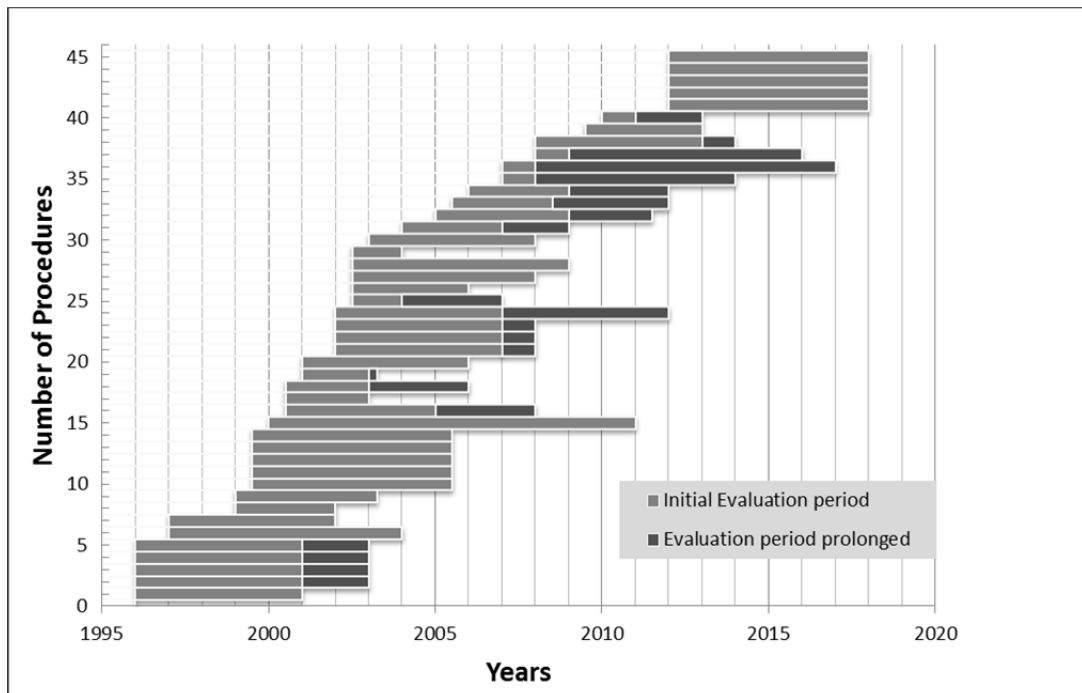


Figure 9 Longitudinal Sequence of decisions “yes, in evaluation” (1996- 2012)

5.75 Figure 9 shows that CED was used more frequently before 2004 than thereafter. In addition, the proportion of negative final decisions after the evaluation period de-

creased to zero after 2006, as can be seen from Figure 10. In practice therefore the state 'yes, in evaluation' could be viewed as a 'delayed yes'.

5.76 Figure 10 shows some of the institutional context of the decision making (names above the box). There was a change of the organisational unit that is responsible for health insurance in the Department of Home Affairs from one federal office (BSV) to another one (BAG). There were four different federal ministers (shown in the second line of names). Finally, there were six different chairs of the appraisal commission (shown in the third line of names). The majority of negative decisions were made in the era of one commission chair (Fritz Britt), the only other negative decision was made by Brunner. While the last three chairs and the last two federal councillors were in office there was not a single negative decision. The patterns that were observed imply that the decision making could be influenced by the institutional context, however, it is not clear how, or how much.

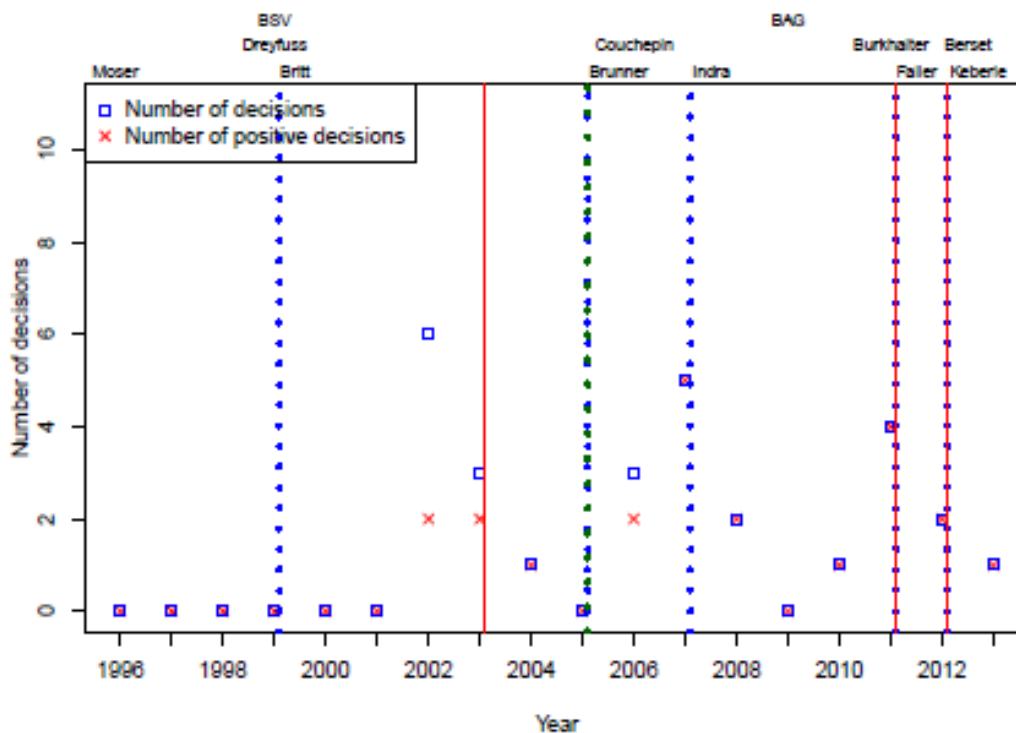


Figure 10: Share of positive decisions in total decisions and institutional context

5.77 'Yes, in evaluation' is broader than CED. It can be used if there are concerns about the overuse of the product, excessive costs to the system, or issues in the quality of implementation. Data is then collected to monitor relevant parameters of usage.

- 5.78 From 1996 to 2004 a fourth category 'no, in evaluation' was used. This meant that the medical technology was not reimbursed but that the decision maker wanted to indicate that there was good hope for the sponsor of the technology to get reimbursement at a later time, provided sufficient evidence could be presented. This was seen by the decision maker as more than a 'polite no' but rather an 'encouraging no' to motivate further research. Nevertheless, the category was discontinued in 2004 because there was no possibility of enforcing the research because the technology was not reimbursed; it did not work.
- 5.79 The analysis of 17 years of experience with CED in Switzerland showed that the CED process evolved over time but lacks uniform standards. CED criteria have just been formulated and are currently being tested (they have not been published yet). CED is still seen as a valuable policy tool in Switzerland by the relevant stakeholders, which include medical doctors, hospitals, industry, and health insurers.

United States / CMS

Population	317.9m (2014)
GDP per capita	53,101 USD (PPP; 2013)
Health Expenditures	17.7% of GDP (2011)
Type of health care system	Private insurance and tax financed public systems (Medicare, Medicaid, Veterans administration)
Criteria for coverage	Reasonable and necessary
HTA body	CMS
Decision making body	CMS

- 5.80 The USA has a highly fragmented health care system that consists of a mix of public and private financing. The discussion below focuses on CMS (Centers for Medicare & Medicaid Services), which are the administrators and the payers for the large public health care programmes Medicare, Medicaid and CHIP (Children's Health Insurance Program). The budget of CMS was USD 526 billion for the fiscal year 2013.
- 5.81 The reason for setting up CED for Medicare in the CMS was twofold: (1) There was political pressure to pay for innovative medical technologies by CMS and (2) CMS needed evidence generation. Before CED was set up under its current terminology in 2005 there were some precursor studies, however, at the time they were not called CED. One was lung volume reduction surgery for which a trial was financed by Medicare.
- 5.82 In 2005 CMS started with two types of CED. One was called Coverage with Study Participation (CSP) and the other one was called Coverage with Appropriateness Determination (CAD). According to the taxonomy in Figure 5 only the first one would fall under CED in the strict sense. CAD was more a form of monitoring utilization in the real world. Mostly registers were set up for this purpose. One example of CAD was on cardiac defibrillators. In 2012 Medicare revised its CED policy and proposed to exclude CAD. Since then the term CED is only used for the type that was formerly called CSP where study participation is mandatory.[7, 8]
- 5.83 Under CED the health technology is financed only for the people participating in the study, which corresponds to an 'only in research' (OIR) regime. There are no clear criteria as to when CED has to be initiated. However, according to the interviewed expert, evidence that the technology is promising has to exist if the evidence base is still too vague for a clear decision.

- 5.84 An important point to mention is that in the US the FDA is the regulatory body not only for drugs but also for devices. For devices, the requirements for market authorization are a lot stricter than they are for getting the CE mark used in Europe. Therefore the FDA may require further studies, sometimes under so called Investigational Device Exemption (IDE). This allows the investigational device to be used in a clinical study in order to collect safety and effectiveness data while it is reimbursed for the patients participating in the study.
- 5.85 An interesting case is the evaluation of Transcatheter Aortic Valve Implantation (TAVI) where CMS and the FDA collaborated for the first time to evaluate the technology. TAVI is only reimbursed if patients take part in the study that is required by the FDA. TAVI is therefore under IDE and CED at the same time.
- 5.86 Up to May 2014 there have been 16 technologies under CED at CMS. These are all non-drug technologies. CED is typically used for expensive high-tech technologies, as for example PET scanning, artificial hearts, stem cell transplantation or TAVI.
- 5.87 Under CED the technology is paid by Medicare/Medicaid whilst the studies are financed either by the manufacturer or by a research funding body. Registers are often funded through user fees. The interviewed expert explained that a close collaboration with industry and physician specialist societies is crucial for success of CED.
- 5.88 The experience is mixed. There have been some successful cases such as PET scanning for oncology where the study was terminated and final decisions were made. So far there has been only one final 'no' decision after CED which was PET scanning for prostate cancer. The decision was well accepted by the medical professionals since the relevant medical society was involved in the decision making.
- 5.89 However, there have also been unsuccessful cases where the study was not been completed over ten years and a final decision has yet to be made, e.g. cochlear implants or positron emission tomography (FDG) for suspected dementia. The expert explained that generally a maximum of four years until study completion and final decision seems to distinguish successful from unsuccessful cases.

Chapter 6 CED: What works and what doesn't

6.1 The experience from different jurisdictions has demonstrated that CED has potential but that it does not work in many circumstances in practice. The following principles are derived from that experience, from interviews and the literature. If any one of the principles is violated, CED has been shown not to work satisfactorily.

Principle 1: There must be a clear mandate for CED and a clear process

6.2 It must be clear what the objectives of CED are within a certain jurisdiction, how the process works and who is responsible for what. Both the HTA agency and the health care payer must be involved and their roles and activities must be coordinated. There must be a clear set of criteria for CED to be used in a meaningful way. However, the regulation should not be too rigid regarding details, in order to allow for some 'deal-making' between a sponsor and the health care system about the concrete implementation of a specific CED decision (see also principle 6).

Principle 2: Research must be clearly linked to coverage

6.3 This principle sounds like stating the obvious but it is not. It means that the public health care payer pays for the intervention as part of the research. Vice versa, it means that the public health care payer should not pay for the intervention if the research is not conducted.

6.4 Another question is who pays for the research (meaning the costs for the administration and the data collection and not the costs of the health technology). This could be the manufacturer, the health care funder, a research funding body or a patient foundation. All these options are used in the different countries examined, sometimes in combination. There are pros and cons for all options. It seems to be important that there are clear rules for funding in a CED regime that lead to the provision of sufficient funding for the necessary research.

6.5 Both the OIR scheme and the OWR scheme as presented in Figure 5 seem to have some advantages and some disadvantages. Under an OIR scheme it is easier to enforce the research than under an OWR, because taking part in the study is the only way for a patient to access to the technology (if it is properly enforced). However, there is the risk that eligible patients do not get access if the study is not conducted and there

is a risk that the health service gets somehow delivered or funded without research. This could be the case if service providers decide to deliver the health technology to patients as a 'loss leader' or the funder just pays regardless of whether research is carried out or not. In an OWR scheme there is the risk that patients get access without the research being carried out.

Principle 3: The CED recommendation should be carefully made and with a clear indication of the evidence gap

- 6.6 This principle means that each individual CED scheme has to be set up for a clear reason and a goal and not because the recommending body could not decide between 'yes' and 'no'. It should always remain an exception in decision-making and not the rule. A series of considerations have to be made. It may be appropriate to develop a checklist for making a CED recommendation.
- 6.7 Clear criteria should be developed for a CED recommendation. The recommending body (e.g. an appraisal committee) should check if there is a fair chance that a study is feasible and that it can be generated within a reasonable time period. The recommending body should not be required to define the exact parameters of a study but the decision question should be clear. Most likely, the recommending body will need scientific advice on the study design and the feasibility of a study. One possibility is that there is collaboration with the HTA organisation that advises the committee in this respect.
- 6.8 Experience in different countries has shown that CED has the best chance to work if there is a promising technology but there is insufficient evidence, mainly regarding effectiveness but sometimes also safety or use in practice. A technology may be especially suitable for CED if it targets a severe disease and there are no existing alternative treatments, or if it has a potential for a significantly higher reduction in the burden of disease than with existing technologies. A recommendation for CED is also more likely to be appropriate if there is expected to be a considerable economic impact of a new technology.
- 6.9 Before making a recommendation for CED, it should be clarified whether there are any ongoing research projects that might address the research question. In such a case it may be appropriate to wait for those results rather than making a CED recommendation.
- 6.10 The recommending body should make a judgment between the value of the additional information and the costs of generating this information. Whether formal value of infor-

mation analysis can and should be used requires further testing and simplification of these approaches, e.g. with calculation tools. None of countries included in this report using this approach.

- 6.11 Finally it is important to consider the impact of the new evidence after the CED period on the final coverage decision. What would the impact of a final 'yes' or a final 'no' be? Mainly the latter outcome is critical because it raises the question whether funding should be stopped.

Principle 4: Research must be carried out in a scientific robust way

- 6.12 The research should be carried out in professional way. It should be carried out by an independent research group and follow standards of good clinical practice (GCP) and research governance. This includes ethical standards and approval of the study by an ethics committee. There must be a clear time plan, and professional data management.
- 6.13 The research should be designed to address the uncertainty identified. Experience in different countries has shown that registers are often set up for practical reasons (access for patients to technology, low costs) but that they are then not able to answer the questions. As a consequence many CED schemes were unsuccessful because of inadequate data collection.
- 6.14 Funding of the study (which can be independent to the funding of the intervention itself) must be guaranteed. There are several possibilities of funding that have been shown to work: government, sponsor of the technology, research body or a mix the different sources. It is very important that the funding is uncoupled from the research and that the funding body does not have influence over the study. This includes the decision about who conducts the study.
- 6.15 Furthermore the study should be supervised by an independent body. The appropriate group would depend on the local situation. It could be the HTA agency although not every such organisation might be comfortable taking on that role. It could also be a research funding body. What is more appropriate depends on the local circumstances of the health care system

Principle 5: There must be feedback of the study results to the decision making

- 6.16 There must be a clear feedback from the study results back to the decision making bodies. The decision making body should receive (annual) reports from the body ap-

pointed accountable to supervise the study. It would be informed on the progress of the study and should be notified if there are any deviations as planned.

- 6.17 It should be clear that if the research is not carried out properly, or negative results come out of the research, the funding body must stop coverage for the health technology. This will not be easy, as was experienced in some countries, as this resembles the challenge of disinvestment. [45]

Principle 6: There must be dialogue between stakeholders and agreement

- 6.18 Cooperation and dialogue is needed between the relevant stakeholders. These are typically doctors, manufacturers, policy makers/health care funders, HTA agencies, research organisations and patient organisations. If such dialogue and agreement does not take place before the start of the study, an unsuccessful outcome is very likely. It was noted that doctors should not be excluded from the process. If these important stakeholders are not willing to comply with the rules of the CED scheme, it would be very difficult to run it successfully.
- 6.19 Where there was coordination or alignment of CED with the activities of regulatory authorities, CED recommendations have been particularly successful (eg. TAVI in the US; pazopanib in England). Therefore, where possible, it is ideal to include the regulatory authority in the CED process.
- 6.20 Dialogue should be organised so that conflicts of interest in the study design or the decision making can be prevented.
- 6.21 Dialogue alone is not sufficient. There should be agreement on important issues such as for example the relevant questions to be addressed with the research, the conditions of study participation, the financing of the research as well as the health technology, the prices paid and the consequences if the research does not show the expected results. If there is considerable disagreement about such issues then there is a high likelihood that CED will not be successful. As explained earlier CED is a form of managed entry agreement and the term 'agreement' expresses this point.

Chapter 7 Discussion

- 7.1 Experience across different countries has shown that although CED can work, very often it does not. Typically, for the unsuccessful cases one of the six principles outlined in section 6 was violated. Many unsuccessful CED schemes were initiated because the recommending body was not confident to say 'yes' or 'no'. Common problems seem to have been: inappropriate study design, inadequate funding, incompliance of doctors with data collection and/or the use of the technology, lack of feedback of results to decision makers, there was no link between funding and the evidence generation, or the research was not completed.
- 7.2 Both the OIR scheme and the OWR schemes have strengths and weaknesses. The OIR scheme is more restrictive and can mean that there may be limited access for patients or none in cases where the research is not done. On the other hand the OWR scheme means easier access but at the risk of the research not being done. In such cases OIR becomes more or less a 'no' whereas OWR becomes practically an unrestricted 'yes'.
- 7.3 From a policy making perspective, CED schemes tend to be used for three purposes: (1) to generate evidence for a promising technology, (2) to monitor use or control volume and (3) to help innovations enter the market.
- 7.4 The 'classic' purpose of CED is to generate evidence that is missing but a 'no' decision does not seem to be appropriate.
- 7.5 In some countries CED is used to control the use or to control volume of health technologies. This can be linked to a serious concern about effectiveness, safety or cost-effectiveness of a technology. It can also be because there are concerns about budget impact or overuse of a technology by doctors.
- 7.6 Some countries, such as Canada, Germany, Switzerland and the US, have clearly stated that CED can help promising innovations to enter the market. This is particularly true for non-drug technologies where new products are often developed by small companies that do not have the knowhow and the financial means of conducting a high quality clinical study.
- 7.7 There is a risk of CED being perceived as a tool for monitoring or controlling doctors particularly with registers on interventional procedures with or without devices. This is a critical point and for that reason one of the interviewed experts said that the HTA body should not be involved in the monitoring of the studies conducted as part of a CED scheme.

- 7.8 Despite these possible difficulties, CED is seen as a tool to counter several risks in the decision making process that might otherwise occur. One is that passive diffusion of a ‘bad’ technology happens (Type I error) or no diffusion of a ‘good’ technology is possible (Type II error).
- 7.9 There are some other practical issues around CED that have not been mentioned so far. One is whether patient preferences should be taken into account or not.[46] According to several interviewed experts this should not be the case where there is clear uncertainty about effectiveness and safety. If an RCT can be conducted ethically it should not be unethical to randomize patients to either the new intervention or the comparator.

Wider significance of CED

7.10 Although CED is not used very often and its potential is limited, it has a larger significance for understanding the modern and possibly future health care systems. The linear and consecutive stepwise process shown in Figure 4 does not correspond perfectly to current reality, nor is it likely to in the future. Research does not finish with a phase III study, or at the point of market authorisation; there is a shift to a more complicated picture and more parallel processes as shown in Figure 11.

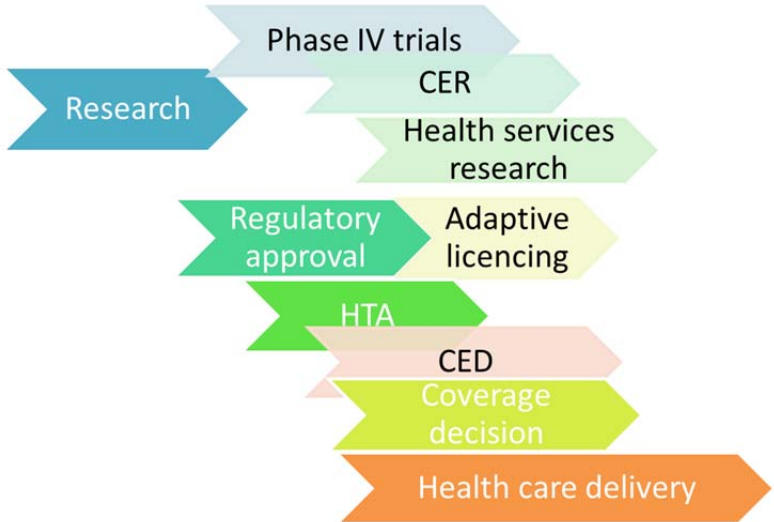


Figure 11: Future Pathway for translation of research into clinical use

7.11 The importance of studies in the ‘real world’ such as phase IV trials and health services research has become more accepted over recent years. There is still a clear bias in fa-

vour of basic research but there appears to be a shift. [20] Regulatory approval has become a more refined process adaptive licencing where research and market approval are linked is now discussed as a possible option for the future. CED fits into this new world, where research, HTA and coverage decisions are integrated.

- 7.12 One could even speak of a paradigm shift. In this new world one cannot simply wait until the research is finished before the decision is made. There are parallel processes and overlap. Therefore more communication, dialogue and coordination are necessary. The successful examples of TAVI in the US and pazopanib in the UK are good examples for this new paradigm. In both examples there was alignment of interests between the regulatory authority and the HTA process with the coverage decision. There have been other occasions where a closer coordination of the two processes were suggested.[47]

Limitations of the study

- 7.13 There are some limitations in this study. The literature search was limited to English and German language documents and therefore documents, particularly in the grey literature, written in other languages could not be identified and included. Documents were likely to have been missed because they mentioned CED using different terminology. The selection of countries was also limited. There are countries that could not be included in the study because they were excluded at the beginning, or no interview could be conducted.
- 7.14 The taxonomy used was useful, although not perfect. For instance the purpose to control volume because of concerns of overuse and negative budgetary impacts is not depicted. Furthermore, real live situations are blurred and do consist elements of several managed entry agreements in combination.
- 7.15 Only a selection of countries was examined. The selection of countries did not follow strict criteria but was made by judgement. Variations of CED in countries that were not included could have been overlooked. Unfortunately a contact with Italy could not be established and the information gathered about France was sparse. In France only an expert that was familiar with MEAs for medicines could be contacted. The post-listing studies done in France are strictly speaking not CED because their purpose seems to be mainly to monitor usage and volume in many cases in order to manage price-volume-agreements.
- 7.16 The perspectives included in this study are comprehensive. Only one expert per country was interviewed. These were all high-level experts with an in-depth understanding

of the situation in their countries, however, there could exist divergent opinions and overlooked aspects. Important stakeholder groups were not included in the gathering of information for the study. For example the perspectives from industry and service providers were not included in the study.

Conclusion

7.17 CED can be a useful policy option in situations where there is a critical evidence gap for a novel and promising health technology. However, there are major institutional and organisational challenges that have to be overcome in order to make CED a successful decision-making tool. CED should therefore only be used in carefully selected circumstances where the 6 principles discussed in section 6 in this report can be followed. CED is a learning case and a representation of a new paradigm in health care where processes are more parallelized and scientific research is interwoven with decision-making.

Chapter 8 Recommendations

The recommendation is to follow the 6 principles laid out in chapter 6. They can be used as a checklist. If one of the principles is violated there is a high likely that CED in an individual application is not successful:

- Principle 1: There must be a clear mandate for CED and a clear process**
- Principle 2: Research must be clearly linked to coverage**
- Principle 3: The CED recommendation should be carefully made and with a clear indication of the evidence gap**
- Principle 4: Research must be carried out in a scientific robust way**
- Principle 5: There must be feedback of the study results to the decision making**
- Principle 6: There must be dialogue between stakeholders**

Annex A Interviewed experts

Nr	Country	Expert	Organisation	Name for CED
1	Australia	Robyn Ward	Chair MSAC	Interim funding
2	Belgium	Raf Mertens	Director KCE	Conditional reimbursement
3	Canada / Ontario	Les Levin (HQO)	Vice president Health Quality Ontario	Conditionally funded field evaluations
4	England	Chris Henshall *)	HTA expert	?
5	France	Gerard de Pouvourville, Cédric Carbonneil	Essec Business School Ministère des Affaires Sociales et de la Santé	Forfait innovation / Post-listing studies
6	Germany	Mattias Perleth	Gemeinsamer Bundesausschuss	Testing of methods
7	Netherlands	Gerry Ligtenberg	Zorginstituut Nederland (former CVZ)	Conditional reimbursement
8	Sweden	Christina Bergh	HTA agency county Västra Götaland	Recommended only for research
9	Switzerland	10 insider-experts	Committee members, health ministry	Yes, in evaluation
10	USA / CMS	Louis Jacques	ex CMS	Coverage with evidence development
		*) plus a lot of input from NICE employees		

Annex B Interview guide

1. How would you define CED?
(Discuss taxonomy of Morel at al. 2013)
2. Do you have CED in your country and what is its purpose?
3. What is the mandate for CED in your country? (ask for documents of legal texts, processes, structures, guidelines etc.)
4. Do you know when CED for non-drug technologies was used for the first time in your country?
5. For which categories of non-drug technologies (devices, diagnostics, interventional procedures, programs, others) has CED been used in the past? (ask for list of technologies under CED or examples)
6. What are the current decision criteria for coverage of health technologies in your country?
7. Are there any criteria for selecting the CED option and what are they?
8. What are the methods used to close the existing evidence gap?
9. How are the evaluations financed?
10. What is the past experience with CED in your country? Where has the strategy worked and where has it not?
11. Can you give an example of a successful / unsuccessful case?
12. What else do you find relevant in this context?

Thank you very much!

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