Health Technology Appraisal and Access to Cancer Drugs in the UK

A report on four workstreams of the CASMI CRUK Fellowship project.

Initial report: March 2018

REFERENCE

Please cite this report as:

Morrell, L; Wordsworth, S; Rees, S; Barker, R. (2018). Health Technology Appraisal and access to cancer drugs in the UK. CASMI, Radcliffe Department of Medicine, University of Oxford, UK.

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ACKNOWLEDGEMENTS

The authors thank the Policy team at CRUK for constructive and helpful discussions throughout the project, particularly Kirsty Henderson, Emlyn Samuel, and Emma Greenwood.

We also thank the members of the project's Advisory Panel for valuable input and interesting discussions: Adrian Towse (OHE), Charlotte Chamberlain (University of Bristol), Louise Longworth (Brunel University), David Taylor (UCL), Roger Wilson (National Cancer Research Institute Consumer Forum), Maggie Wilcox (Independent Cancer Patient Voice), Nick Hicks (Cobic Commissioning), Paul Catchpole (ABPI), Anna Schuh (Department of Oncology, University of Oxford), Mark Middleton (Department of Oncology, University of Oxford).

FOREWORD

I am pleased to introduce this report exploring the role of Health Technology Appraisal in patient access to cancer drugs, on behalf of our partner Cancer Research UK. The topic of the value of medicines, particularly in the area of cancer, is a vital one for health care and wider society, and we are glad this has been the subject of our first joint fellowship with CRUK.

Our work explored the perceptions and attitudes towards cancer that has led it to be termed "The Emperor of all Maladies" [3]. In our qualitative work, people describe the life cut short, the tantalising hope for a miracle of cure or remission, the tragedy of late diagnosis, and the disease's long reach into the future with a lingering fear that it may, one day, come back. In parallel with completing this report, we are designing further research to evaluate how such features might be factored into the value of a new technology when it is evaluated for use in routine care.

We also investigated elements of current HTA processes in the UK and elsewhere, as they were being applied to cancer medicines. We worked with CRUK to prioritise targets for improvement and opportunities to transfer aspects of models from other countries to the UK. The accelerated access increasingly being offered (or discussed) for highly promising cancer medicines via "adaptive pathways" poses new challenges. We will need adaptive pricing mechanisms, not only to manage cost-effectiveness, but to adjust pricing as an initially uncertain evidence base evolves. Greater definition in this area will be vital if such adaptive pathways (one of CASMI's principal areas of research) are to succeed in practice. The government's recent acceptance of the recommendations of the Accelerated Access Review (in which CASMI played a key role) will require rapid progress in this area.

By working closely with CRUK Policy Advisers during the project, we are gratified to see our findings reflected in CRUK policy positions, including a policy paper on drug access, and responses to a broad range of consultations from NICE, NHS England, and the Department of Health. We see this as a promising synergy between academic research and the evolution of policy by patient organisations wishing to base their own submissions on rigorous and independent research.

CASMI is also delighted to support CRUK's recently launched research programme on outcomes-based pricing, bringing together the two strands of our joint work – adaptive pricing, and broadening the definition of 'value' in cancer care.

We look forward to future opportunities to collaborate.

Richard Barker
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This work was carried out by the Centre for the Advancement of Sustainable Medical Innovation, a partnership between Oxford University and UCL, created to develop new models for medical innovation.

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1 INTRODUCTION

PROJECT HISTORY

Cancer Research UK (CRUK) believes cancer patients should have access to evidence-based, innovative cancer drugs. In particular, as a leading funder of cancer research, CRUK has an interest in seeing the fruits of its investment being made available to the public who are the only source of the research funds.

Against the complex and changing policy environment described below, CRUK funded independent academic research, intended to stand back from the day-to-day policy flux and take a longer-term view. The Centre for the Advancement of Sustainable Medical innovation (CASMI), University of Oxford, supported by the Department of Population Health and the Department of Primary Healthcare Sciences, was funded to do the work.

AIM

The aim of the project was to inform CRUK policy positions on cancer drug access related to Health Technology Appraisal (HTA). Specifically, we aimed to identify the rationale for special approaches to HTA in cancer, and key elements of a process that would support increased sustainable access to cancer drugs.

APPROACH

Initial work explored the justification for special HTA approaches for cancer, based on a literature review of social preferences for prioritisation in health care. This work did not find consistent support for prioritising cancer *per se*, but did indicate that there may be aspects of cancer care that society does value highly [4]; these might include, for example, the value of hope, or reducing anxiety about recurrence.

The work therefore progressed as two threads: identifying aspects of value in treatment of cancer beyond what is captured in the current Quality-Adjusted Life Year (QALY) metric, and analyses of elements of existing HTA processes elsewhere in the world to evaluate potential alternatives and improvements for the UK.

As the project progressed, the relationship between CASMI and CRUK developed to include collaboration on immediate pressing issues, such as responding to consultations, forming views on government policy changes, and joint working on current projects; these collaborations included work to inform a proposed thought-leader summit on HTA reform, and discussions of CRUK policy priorities. Findings from the research were thereby integrated into CRUK policy thinking throughout the life of the project.

REPORT FOCUS

This report describes findings from four workstreams of the project, that focus on specific elements of the HTA process. These report topics were selected by the CRUK policy group as the parts of the work with the greatest immediate policy impact.

- Evaluation of **reforms to the HTA process in Scotland**, implemented in June 2014, which aimed to improve access to new drugs
- Analysis of **uncertainty in NICE appraisals of cancer drugs**, to identify the main sources of uncertainty and whether they would be resolved through data collection via a managed access agreement within the reformed Cancer Drugs Fund.
- A review of the **role of pricing mechanisms in managing uncertainty**, considering case studies from across Europe

- Is it **nicer in NICE?** An exploration of current cancer drug access decisions for England, and how that has changed over the duration of this project.

Results from the first three of these have been published in peer-reviewed journals [5-7], and this report provides a summary of the papers, along with policy implications specifically for CRUK. All four workstreams were presented to CRUK at the time the work was done, so that findings could directly inform policy.

A shorter Summary Report has also been produced alongside this Full Report. The Summary Report takes an overview of the project as a whole; it therefore incorporates findings from other work not covered in detail in this report, which nonetheless was essential to our thinking overall. This includes the literature review into social preferences in health care outlined above[4], and qualitative research on public perceptions of cancer in comparison to other serious health conditions [8]. The published papers are accessible via CASMI's website, and links are provided in the Appendix to this Full Report.

1.1 BACKGROUND

AN INTRODUCTION TO HEALTH TECHNOLOGY APPRAISAL IN THE UK

Health Technology Appraisal (HTA) refers to the process of making decisions about whether a particular technology will be funded by the health service. Manufacturers of drugs are required to demonstrate the drug's safety, efficacy, and quality (their ability to manufacture it consistently to pharmaceutical-grade standards) in order to receive the licence (marketing authorisation) required to sell a pharmaceutical product. The additional arose in response to escalating health care costs, with formal regulations developing from the 1990's. Currently, in England, 60-75 drug appraisals in total are carried out each year, with 30-40 being cancer drugs[9].

In the UK – in common with other countries in Europe as well as Canada, Australia, and New Zealand – this decision is based on cost-effectiveness: how much health is created for the population for each pound spent. The costs and effects of a new test or treatment are compared against standard care, which could be an existing test or treatment, or no treatment if one is not currently available. The comparison of costs and effects are calculated as the cost-effectiveness ratio: additional cost for the new treatment, divided by the additional health benefit. The health benefit is often measured using Quality-Adjusted Life Years (QALYs): a measure that takes account of both the duration of life, and the quality in which that life is lived. Hence, the calculated cost-effectiveness ratio is often referred to as the cost-per-QALY.

The cost-per-QALY is compared to a threshold value to determine whether the technology is considered cost-effective. The threshold value reflects the concept of opportunity cost, where introducing a new treatment at higher cost than the current one necessarily means that funds must be diverted from elsewhere in the health system, resulting in foregone health for other patients. If a technology exceeds the cost-per-QALY threshold, that indicates the health loss by diverting funding exceeds the health gained from the new technology, thus resulting in net health loss for the population as a whole; this would normally not be considered a good use of health care resources, and the technology would not be funded.

VARIATION IN DECISION MAKING

HTA is a devolved responsibility in the UK. The National Institute for Health and Care Excellence (NICE) makes these funding recommendations for the NHS in England, and works with an explicit threshold range of £20 000 to £30 000 per QALY. In Scotland, this role is fulfilled by the Scottish Medicines Consortium (SMC), and similarly for Wales by the All Wales Medicines Strategy Group (AWMSG). All three agencies take the same cost-effectiveness approach based on the cost-per-QALY. However, it is possible for them to make different decisions about a given drug.

The public both fund our health care systems through their taxes, and benefit from that care, so it important that public preferences are reflected in decision–making. These preferences could differ between the UK nations – in terms of priorities both within health care, and between health and other areas of public spending – leading to differences in policy and hence funding choices. The devolved health services could also come to different commercial arrangements with the pharmaceutical industry, resulting in different cost-per-QALY numbers and potentially, divergent decisions.

HTA AND CANCER DRUGS

Cancer drug appraisals have historically been challenging for HTA across the UK. Acceptance rates have typically been lower than for drugs overall (65% overall during 2000-2014, compared to 82%), and specific funding decisions have been highly contentious. At the time this project was funded (late 2014), HTA in the UK was considered to be a significant barrier to patient access. There was also considerable policy uncertainty at the time, with funding mechanisms such as the Cancer Drugs Fund (CDF) under challenge, and calls for radical changes to the UK's approach to HTA; much of the pressure was focused on NICE as the agency responsible for decisions affecting England. This history is outlined below.

Early high-profile examples included trastuzumab (Herceptin) in breast cancer (2002, 2006), and imatinib (Glivec) in chronic myeloid leukaemia (2002); initially rejected by NICE, these decisions were overturned following legal challenges and political campaigns by patients, clinicians, and the pharmaceutical industry, despite exceeding NICE's usual £30K/QALY. In a further significant case, a draft decision in August 2008 not to recommend four drugs for advanced renal cell carcinoma led to further pressure from patients. This led to the introduction of NICE's "end-of-life criteria", which define situations in which evaluation committees can place greater weighting on health gain for patients with short life expectancy[1], and enabled the recommendation of one of the disputed drugs (sunitinib, Sutent) for funding.

Cancer drug access in the UK has to be seen against the backdrop of two other sets of findings. Firstly, Sir Mike Richards was commissioned in 2010 to investigate access to drugs in the UK compared to other European countries. Both the Richards report [10], and a more recent update [11], found that access to drugs in the UK was typically slower than in other countries. Secondly, international comparisons of cancer survival showed that the UK, despite having improved survival rates in several cancers, lagged behind comparator countries [12]. Whilst neither of these observations necessarily trace directly to NICE's decisions, they do contribute to the intensity of the debate.

The continued public pressure led to the introduction of the CDF in autumn 2010. The CDF was a ring-fenced fund independent of NICE, and was created by the coalition government to fund cancer drugs not routinely available on the NHS; this included drugs rejected by NICE, pending a decision, or not scheduled to be reviewed by NICE. The CDF was intended as a temporary solution, to allow development and implementation of an alternative approach known as "Value-Based Pricing" (VBP), intended to increase access to new drugs by broadening the scope of the NICE appraisal.

VBP, and its later derivative Value-Based Assessment (VBA), aimed to broaden the definition of the value derived from technologies under assessment, by including parameters such as severity of disease, productivity, reliance on carers, and the innovative nature of the technology. However, despite significant research, and development of proposals, an implementation plan acceptable to all stakeholders could not be reached, and plans were shelved in 2014.

Meanwhile, NICE's decisions on cancer drugs continued to cause debate, reaching a significant point at the end of 2013 when no cancer drug had been recommended for funding during the year. The CDF was also under continued challenge, with questions raised about its sustainability, and introduction of a "prioritisation" process used to manage its (overspent) budget, including periodic rounds of delisting that also made the headlines [13]; whilst no specific plans for changes to the CDF had been made public at that

time, there was an expectation of reform.

CONTINUED POLICY EVOLUTION

The policy context has continued to evolve. NICE and NHS England implemented significant reform to the CDF in April 2016 [14], returning all cancer drug funding decisions to NICE, and transforming the CDF into a managed access fund. Drugs are granted conditional market access, with data collection during clinical use to resolve uncertainties in the evidence base. Further process evolution (April 2017) saw NICE's introduction of a Fast Track process for drugs with a cost-per-QALY below £10 000, and a Budget Impact Test, which allows NHS England increased flexibility in the timescale for introduction of drugs with an annual budget impact of over £20 million. This latter change has been controversial, raising concerns that access to cost-effective drugs for common cancers (such as breast, colon, and prostate) could be delayed.

Concerns about the UK's lag in adopting new treatments was investigated by the Accelerated Access Review in 2015 [15], leading to recommendations for a process to accelerate adoption of promising therapies in the NHS, which was accepted by government in November 2017. The 2015 Cancer Strategy for England called for continued access to cancer drugs ahead of full NICE recommendation, and additional flexibility in NICE's process to support sustainable access to new cancer drugs.

THE THERAPEUTIC PIPELINE

Advances in drug development have also continued, with two important emerging trends: "precision medicine" which actively targets the specific genetic defect(s) causing cancerous growth; and the promise of immunotherapies, which engage the patient's own immune system in the destruction of cancer cells. These developments bring their own challenges for HTA. Precision medicines are likely to be expensive given the smaller market. Both are likely to be used in succession or combination as the cancer evolves, and both biomarker-targeted and immunotherapy drugs are likely to be used across a range of cancer sites, disrupting current definitions of the site-specific "indication".

2 IMPACT OF HTA REFORMS IN SCOTLAND

2.1 INTRODUCTION

HISTORY

The Scottish Medicines Consortium (SMC) evaluates the cost-effectiveness of new drugs for use in the National Health Service in Scotland, analogous to NICE's appraisal for England. Both agencies have faced public, clinical and industry pressure as a result of negative funding decisions, amid concerns that the UK's access to new drugs lags behind that of other countries [11].

In response, both agencies have made changes to their processes to increase flexibility in approvals for particular classes of drugs. These began with NICE's 2009 introduction of the "end-of-life criteria", which define situations in which evaluation committees can place greater weighting on health gain for drugs to treat patients with short life expectancy [1] – in effect, raising the cost-effectiveness threshold from £20,000-£30,000 per QALY to £50,000 per QALY, for drugs that meet the criteria. Scotland followed by introducing "modifiers", which defined circumstances under which they could accept a higher cost-per-QALY figure, or greater uncertainty, in the cost-effectiveness of a drug under appraisal [16].

However even with these in place, the Scottish Government faced continued pressure to increase access to new drugs. As a result, a set of changes to SMC processes were introduced in May 2014, for two classes of drugs where access was a particular concern: drugs to treat patients in the last months of life (known as "end-of-life" drugs), and drugs to treat rare conditions (known as orphan and ultra-orphan conditions). These changes are outlined below.

SCOTLAND'S 2014 REFORMS

Scotland's 2014 reforms had the explicit aim of increasing access to new drugs for rare diseases and end-of-life situations, and take the form of an add-on process that is triggered if the initial decision by SMC's New Drugs Committee (NDC) is not to recommend funding for a drug of this type [2]. The reforms include:

- Definitions of end-of-life (EoL), orphan, and ultra-orphan conditions. A drug may qualify under rarity, end-of-life, or both (for example a rare cancer). Drugs that meet these definitions are entitled to make use of the add-on process described below. Box 2.1 compares SMC and NICE definitions; note that NICE's criteria are more restrictive than SMC's (i.e. fewer drugs will qualify as EoL for NICE).
- Introduction of a Patient and Clinician Engagement (PACE) meeting. The purpose is to clarify aspects of value perceived by patients and clinicians that are not fully captured in the QALY, implicitly supporting acceptance of medicines with a cost-per-QALY above the normally accepted level.
- Option for the submitting company to propose or modify a Patient Access Scheme (PAS) at the PACE stage. Patient Access Schemes are commercial arrangements that provide a confidential reduction in price such that the drug can be considered cost-effective (see Chapter 4: Pricing mechanisms).
- An additional framework of non-scored criteria for evaluating ultra-orphan drugs.

Box 2.1: comparison of NICE[1] and SMC[2] criteria for consideration as an EoL or rare condition. Note that the rarity requirement was removed from the NICE criteria in April 2016.

NICE EoL criteria	SMC EoL and Rarity criteria
the treatment is indicated for patients with a short life expectancy, normally less than 24 months;	EoL: medicine to treat a condition at a stage that usually leads to death within 3 years.
and	
the treatment offers an extension to life, normally of at least an additional 3 months;	
and	or
for small patient populations normally not exceeding a cumulative total of 7000 for all licensed indications in England *(ie 1 in 7700*)	Orphan: medicine to treat a condition affecting fewer than 2,500 people in a population of 5 million) *(ie 1 in 2000).*
	or
	Ultra-orphan: medicine to treat a condition with a prevalence of 1 in 50,000 or less.

Following the PACE meeting and/or submission of a PAS, the complete submission is reviewed as any other submission at an SMC meeting, and is given one of three decisions: Accepted, Restricted to a specific sub-group of the patient population, or Not Recommended.

Although these are not cancer-specific reforms, they are of particular interest in cancer, which is expected to benefit from the end-of-life element. Further, cancer uniquely has different access arrangements across the UK nations, due to the presence of the CDF in England; the CDF at the time of the introduction of these SMC reforms paid for cancer drugs not routinely available on the NHS, creating disparities in access between the countries, and confusion and a sense of unfairness for patients. We were therefore interested to explore whether the reforms had increased cancer drug access in Scotland, and any impact on cross-border equity.

AIMS

This chapter of the study aimed to learn from Scotland's experience as the basis for recommendations for the rest of the UK. Specifically, we were interested in which drugs were making use of the new process, and whether it changed funding decisions. Further, we particularly wanted to understand the impact of the PACE meeting, which is a novel approach to incorporating added aspects of value into the cost-effectiveness analysis.

We evaluated the impact of the changes on access to new cancer drugs in Scotland, in the first two years post-reform. Subsequent to our work, the Scottish government also commissioned a review of the reforms, led by Dr. Brian Montgomery, published in December 2016. The Montgomery report considered whether the changes had increased access to these drugs, and made recommendations for further improvements to the process [17].

2.2 METHODS

Information on decisions made by SMC in the first two years since the reforms (10/2014 to 9/2016) was taken from the 'Detailed Advice' published on SMC's website. Data for the two years pre-reform were used as a comparison.

Published summaries of the PACE meetings were used for thematic analysis, to identify common issues discussed in the PACE meetings, and whether they could be related to the decision. Themes were identified by review of the text, to discover and link related ideas across the PACE meetings.

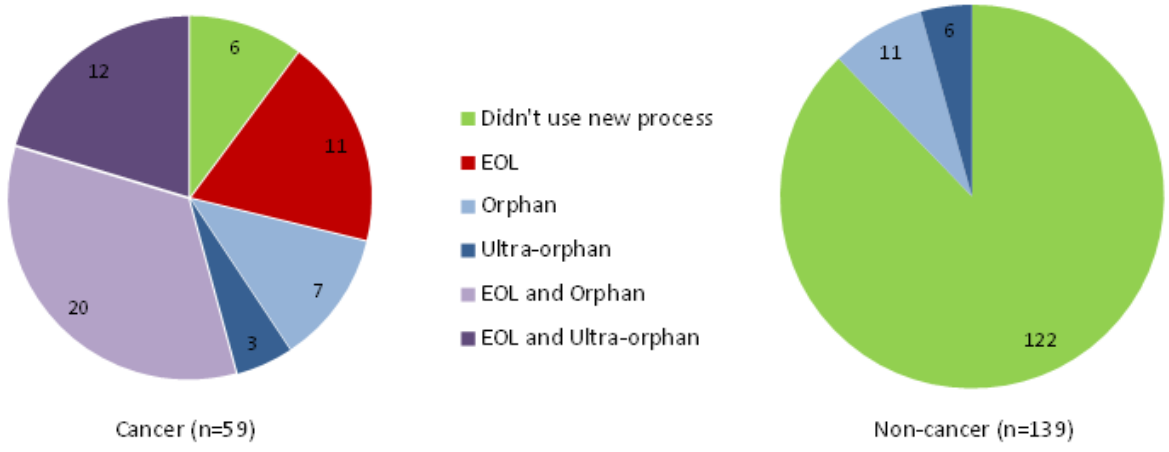
To compare cancer drug access between Scotland and England, NICE's decision for the same drugs was accessed from NICE's website. Information on drugs being funded by the CDF was accessed from the CDF pages of NHS England's website. Because funding decisions can undergo revision, the access comparisons presented are snapshots, based on funding decisions in force in September 2016 (the end of our study period), with an update for the same drugs in September 2017. Further details can be found in Appendix 8.1.1.

2.3 FINDINGS

USE OF THE NEW PROCESS

The new process was used predominantly in cancer submissions, and most cancer submissions were made under at least one of the new definitions (rarity or EoL). All EoL submissions were cancer drugs (Figure 2.1). Among the cancer drugs triggering the new process, 51 out of 53 took advantage of the PACE process; the other two presented only a revised Patient Access Scheme.

Figure 2.1: use of the new process, and the definition used to qualify – cancer drugs vs. all other submissions



Data: SMC evaluations published Oct 2014 to Sept 2016

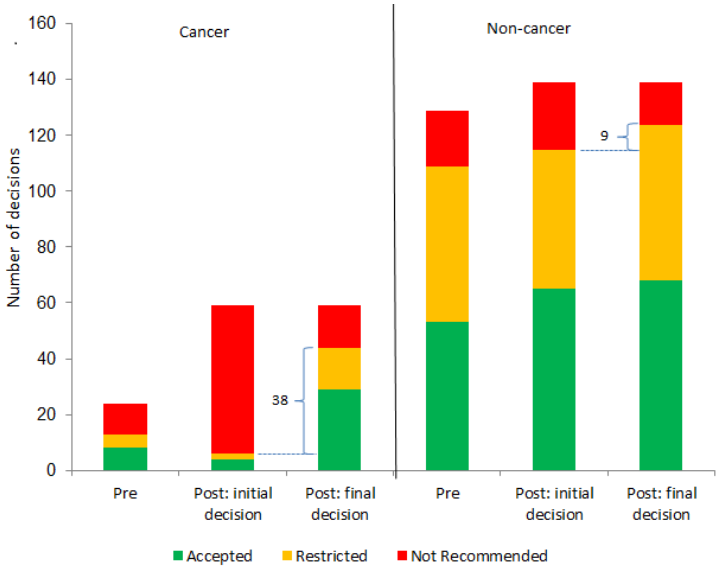
IMPACT ON ACCEPTANCE OF CANCER DRUGS

The new process allowed funding of up to 38 drug/indication combinations that might not have been funded pre-reform; this compares to up to 9 non-cancer drugs (Figure 2.2).

These 38 are submissions that were initially Not Recommended by the New Drugs Committee (NDC), and were therefore offered the new process options. We make the

assumption that had the new process options not been available, these drugs would have actually become Not Recommended had the new process options not been available – that is, we assume they would not have been funded pre-reform, but were 'rescued' by the new process.

Figure 2.2: Funding decisions pre- and post-reform



Pre:	*pre-reform, advice published October 2012 – September 2014*
Post:	*post-reform, advice published October 2014 – September 2016*
Initial decision:	*the initial recommendation of SMC New Drug Committee; we assume that all drugs given an initial 'Not Recommended' decision would actually have become 'Not Recommended' under the pre-reform process*
Final decision:	*the actual published decision of SMC*

2017 UPDATE

A recent update of the 2016 findings in September 2017, adding the third year post-reforms, found similar results. The number of funded drug/indication combinations that might not have been funded pre-reform (as described above), had risen to 57 in cancer. Only one cancer submission in Year 3 did not use the reformed process; that is, it was initially Accepted by the NDC, and subsequently by the SMC committee, without needing to use PACE.

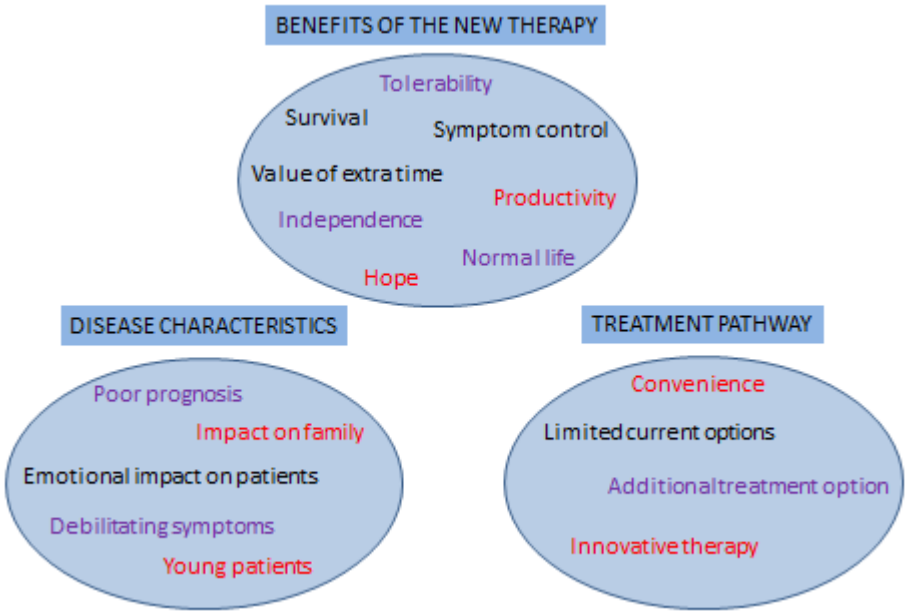
PACE MEETING THEMES

All PACE meeting summaries covered themes that fell into 3 broad areas: specific aspects of the disease; the benefits of the new drug to patients; and its effect on the treatment pathways and drug choices (Figure 2.3).

The PACE meetings provide additional insight into the value patients attach to the clinical benefits of the drugs: for example, improved progression-free survival means that patients remain out of treatment, and can continue with some level of normal life and activities; having future treatment options available provides hope for patients and families, and reduces anxiety about the future. However, there was no obvious

relationship between the points covered in the PACE meeting, and the final funding decision, and the Detailed Advice documents do not comment on how the PACE input influenced the decision.

Figure 2.3 Themes from the PACE meeting summaries



Colour of text indicates the extent that this feature is incorporated in typical UK health technology appraisal.
Black: explicitly included
Purple: partially or implicitly included
Red: not included or explicitly excluded

Some of the features are already captured explicitly in the quantitative cost-effectiveness as assessed by SMC; for example, survival and symptom reduction. However, others are not (for example: convenience, hope, impact on the family), or are indirectly covered. For example, severity is not weighted specifically, but elements of severity such as symptoms and survival are explicitly captured. Similarly, independence is reflected to the extent that the ability to be independent is symptom-related, particularly the capability to carry out usual activities and self-care, but is not explicitly evaluated.

ACCESS COMPARISON WITH ENGLAND

Comparing NICE and SMC's decisions in force in September 2016 regarding drugs which triggered the new SMC process, we find 25 cases of differential funding, with 3 drugs funded in England only, and 22 in Scotland only. However, to fully describe drug access from a patient perspective, we need to include funding via the CDF in England, which funded some of the drugs rejected by NICE. This reduces the number of differently funded drugs to 15, with a more equal spread between the countries (Figure 2.4a).

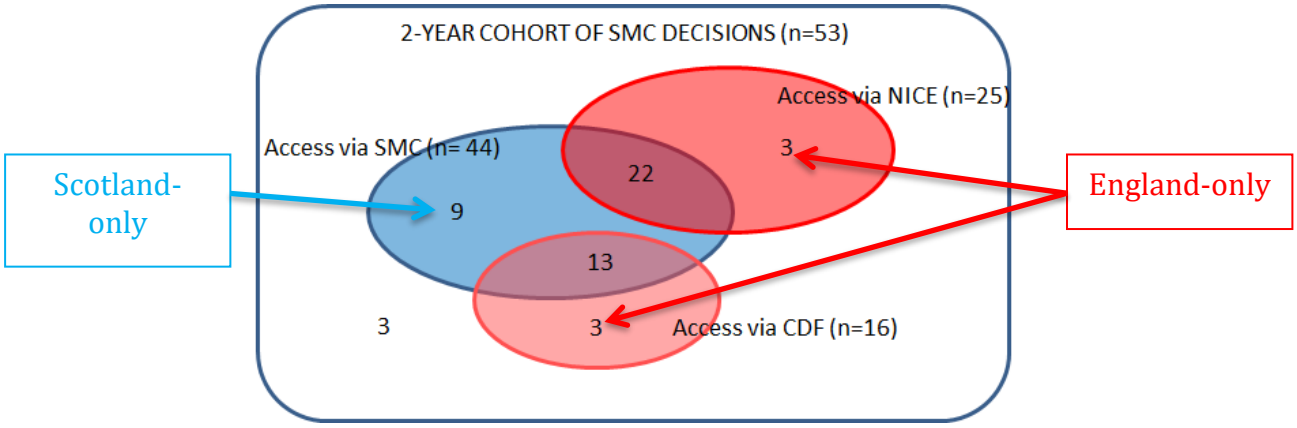
The access landscape has continued to evolve; by September 2017, access is more similar between the two countries. Importantly, not only has the number of drugs with differences in availability of funding decreased, but the mechanism of funding is more

consistent: following CDF reform in 2016 (see Chapter 3), access in England is increasingly provided through routine commissioning via a NICE recommendation, with drugs transitioning from the original, standalone CDF (Figure 2.4b).

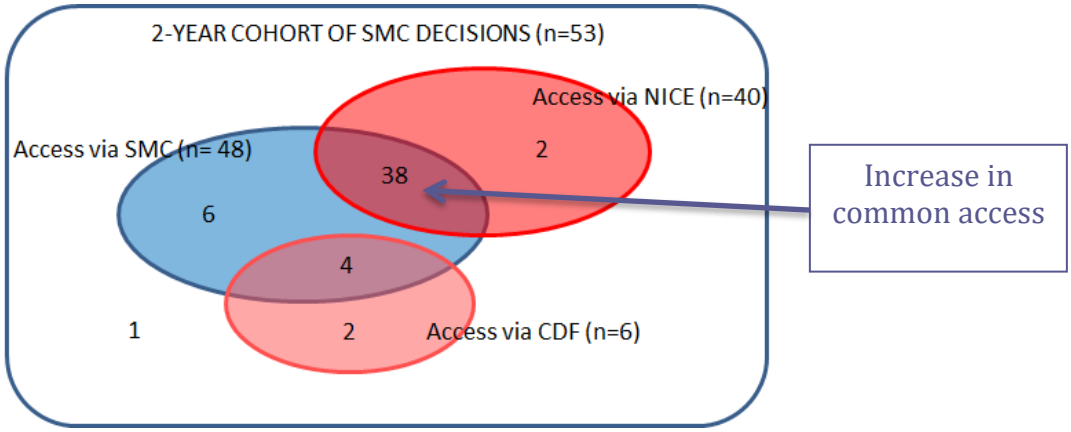
Hence, although in the September 2016 snapshot the SMC appeared to be more permissive than NICE in funding for this batch of drugs, over time the access picture has become more similar between the two countries.

Figure 2.4 Comparison of patient access to cancer drugs in Scotland and England

2.4a Access in September 2016



2.4b Access in September 2017



'Access' indicates the decision was either Recommended, or Restricted for a specific sub-group of the patient population (termed Optimised by NICE)
'Access via CDF' refers to drugs funded under the terms of the original CDF; drugs funded through the reformed CDF are included within 'Access via NICE'

To examine the reasons for the discrepancies in access, we looked in more detail at why the drugs concerned were not funded in England (in 2016), and the role of the differences in definitions of EoL and rarity. We found that over half of the 2016 SMC-only drugs are because no decision had been made by NICE: the appraisal was pending or suspended, no submission had been made by the company, or the drug had not been referred to NICE for appraisal.

Differences in funding decisions are not fully explained by the more restrictive EoL criteria used by NICE. In this cohort of drugs, 25 drugs were assessed for EoL status by both agencies, and only 7 were designated EoL in Scotland and not in England. Of these, only one might have been approved for funding if NICE had adopted SMCs definition of EoL; others would have still been outside the acceptable cost-per-QALY range based on the numbers submitted to NICE.

Hence differences in decision timelines, and in which drugs are submitted for appraisal, had a greater effect on access than the differences in definition (at least in this cohort of drugs).

2.4 DISCUSSION

In summary, our findings suggest that the reforms are enabling SMC to approve drugs they could not have accepted before, with the "add-on" process, including PACE, becoming the norm for cancer drugs. In terms of access, we find Scotland had more generous access than England by September 2016, although the situation in England was rescued somewhat by the CDF. However, the contributions of the various elements of the reforms are unclear; in particular, it is not obvious how the issues covered in the PACE meeting are reflected in the final decision. Our findings are consistent with those in the Montgomery report, which also noted increased access to these classes of drugs, and suggested a need to broaden evaluations to include a "basket of measures" such as patient-reported outcomes and wider social benefits [17].

Overall, the reforms appear to have achieved their aim of improving access – at least in cancer, where the EoL designation appears to be acting as a proxy for prioritising cancer. However, is it premature to recommend that NICE should adopt a PACE-like process; we find limited evidence for the impact it specifically has had on decisions, hence cannot justify the additional resource and time taken in the appraisal process. Tracing that impact would be helped by, for example, a section in the Detailed Advice describing how the PACE input influenced the decision. This was also suggested in the Montgomery report [17] based on feedback from PACE participants, and our findings support that recommendation.

Our PACE analysis, however, does have implications for technology appraisal methodology. The PACE content highlights aspects of cancer treatments that have value to patients, some of which are not reflected in the appraisal, or are indirectly or implicitly covered. These may point to benefits valued by patients that could be considered for formal inclusion in the appraisal process.

The most recent attempt at such a broader definition of value was the Value-Based Pricing (VBP) initiative, starting in 2010 [18]. This was ultimately shelved due to implementation difficulties, but the key value parameters identified in that work included severity of disease, unmet need, and reliance on care. Seeing the same themes occurring here – and in other qualitative work by CASMI [4] – suggests that these issues remain important to patients, and that until these concerns are addressed, they will continue to be reflected in patient and public frustration when much-supported drugs are not recommended for funding. Hence, we expect to see a reconsideration of VBP (perhaps under a different name), and recommend that CRUK continues to actively support discussions on this topic.

Our access comparison found that disparity in access was caused not only by different

decisions between the agencies, but also by which drugs were presented for appraisal, and decision timings. Proposals for CDF reform (April 2016), which brought the CDF within NICE's remit, also made process changes for cancer drugs within NICE [19]: removal of the rarity requirement in NICE's end-of-life criteria; the expectation that NICE will publish a decision within 90 days of the marketing authorisation; and a requirement that *all* new cancer drugs will now be referred to NICE. These bring NICE and SMC's processes into closer alignment, and we recommended at the time that CRUK support these changes at NICE.

The differences between NICE and SMCs definitions of EoL do not appear to have a strong empirical basis. Whilst the difference is difficult to explain, it does not appear from this analysis to have contributed extensively to cross-border differences in access, so we do not recommend that CRUK gives high priority to advocating for rationalising the criteria.

The additional PAS step in Scotland may be providing a mechanism for companies to test the water with an aggressive pricing strategy, but then re-negotiate if the initial assessment suggests it is unlikely to be accepted. It may be that this is encouraging flexibility on the part of the submitting companies, and is contributing to the higher levels of positive recommendation. We are seeing a similar pattern in England, with renegotiation of Patient Access Schemes and commercial access agreements during NICE's appraisal consultation process (see Chapter 5, Is It Nicer in NICE?). Processes that enable such negotiation can only be positive for drug access, and CRUK would welcome future process adjustments that provide additional explicit opportunities for companies to present alternative commercial arrangements.

This work informed CRUK's response to the Montgomery report, and thinking on broader outcomes beyond the QALY.

LIMITATIONS

A potential limitation of our analysis is our assumption that all the submissions that triggered the new process, would have been rejected had the reforms not been in place. Some of them might in fact have been granted some level of access following further deliberation and negotiation, leading us to over-estimate the impact of the reforms. For this reason we have specified "up to" 38 drugs gained approval that would have been at risk of rejection pre-reform.

A second limitation is our use of information available in the public domain, which includes PACE meeting summaries by SMC staff and excludes commercially confidential information, leading to risk of bias due to missing and secondary information. Note, though, that the PACE summary does reflect the information seen by the SMC committee at the point of decision.

SUMMARY OF RECOMMENDATIONS

- We recommended that CRUK support proposals in the CDF reform to accelerate NICE approvals, and to have all cancer drugs evaluated by NICE*
- CRUK should continue to engage with discussions on additional benefits 'beyond the QALY' over the longer term*
- We do not at this stage recommend that CRUK advocate for addition of a PACE-like step to the NICE process.
- We do not recommend that CRUK prioritises advocating for alignment of NICE and SMC's EoL criteria

* recommendations that have been reflected in CRUK policy positions

Our evaluation was presented to CRUK during 2015 and 2016, and has been published following peer review [5]; this chapter presents a summary of the published paper, with discussion of implications for CRUK.

3 UNCERTAINTY IN NICE'S APPRAISALS OF CANCER DRUGS

3.1 INTRODUCTION

The Cancer Drugs Fund (CDF) in England aimed to improve access to new cancer drugs, by providing funding for drugs not routinely available on the NHS. The Fund was intended to be an interim measure whilst proposals for alternative pricing mechanisms were developed; however, these plans were shelved, and the fund continued, with annual expenditure rising from £200 million at its inception in 2011/12, to over £400 million in 2014/15 [20].

Following extensive debate about the CDF's sustainability, justification, and decision processes [21, 22], the CDF underwent major reform in April 2016. The reforms consolidated responsibility for funding decisions with NICE (replacing the separate CDF process), and established the CDF as a managed access fund. Where there is too much uncertainty in the clinical evidence and cost-effectiveness estimates to recommend the drug for routine use, the drug can be funded through the CDF, with data collection from this clinical use (known as "real-world data", RWD) to resolve the uncertainty [23]. The funding decision would then be reviewed – including the new data – at a pre-agreed point, expected to be within 2 years.

The issue of uncertainty is central to the operation of the reformed CDF. Some degree of uncertainty is inevitable, as society does not want to wait until we have fully mature datasets before making promising drugs available to patients. With current pressures for earlier access (as evidenced by initiatives like the Accelerated Access Review and the UK's Early Access to Medicines Scheme), the challenges of dealing with uncertainty are likely to increase.

Further, continued focus on both "precision" medicine, and treatments for rare diseases, also has the potential to increase uncertainty, due to the smaller population sizes available for clinical study. The reformed CDF is therefore a key element in evolving our evaluation processes away from a point-in-time decision, to a situation where access can develop alongside the data.

AIMS

At the point in time when the CDF was undergoing these reforms, it was not clear what might be funded via this new route: specifically, what uncertainties there might be in the economic case for candidate drugs, and what data collection during NHS use would be required to resolve that uncertainty. This chapter of the study aimed to identify the likely sources of uncertainty in future cancer drug submissions to NICE, and consider how these could be resolved via data collection within the reformed CDF.

3.2 METHODS

Information on the uncertainties in a ~2-year cohort of NICE cancer drug appraisals (January 2014 – March 2016) was taken from NICE's appraisal decision documents (Final Appraisal Documents, or FADs), accessed on NICE's website. Comments on uncertainty were classified into categories. We report the frequency of occurrence of each category of uncertainty, as the number of FADs in which it occurs.

The FAD includes a headline summary, which reflects key features of the appraisal overall, and this headline summary mentions uncertainty in some cases. To explore the strength of concern with uncertainty in the decision, we assumed that the FADs with

comments on uncertainty in the headline are those where uncertainty was a highly salient feature of the decision, and designated these FADs as "high uncertainty". Further details can be found in Appendix 8.1.2.

3.3 FINDINGS

33 appraisals were published in the specified timeframe, of which 4 were terminated by NICE following non-submission of data by the manufacturer, leaving 29 cases for analysis (21 solid tumours, 8 haematological malignancies). Of these, 18 were recommended for funding, 5 optimised (that is, recommended with restrictions) and the remaining 6 not recommended for funding.

EFFECT OF UNCERTAINTY ON ACCEPTANCE

Funding decisions were not driven by the level or type of uncertainty *per se*, but by where the resulting cost-per-QALY estimate fell in comparison with the cost-effectiveness threshold. A drug with a highly uncertain evidence base, for example, could be Recommended if the spread of cost-effectiveness estimates fell within the acceptable range; the evidence base may be uncertain, but the cost-effectiveness decision is this case, is not. Conversely, a drug with a very high, although relatively certain, cost-per-QALY is likely to be Not Recommended.

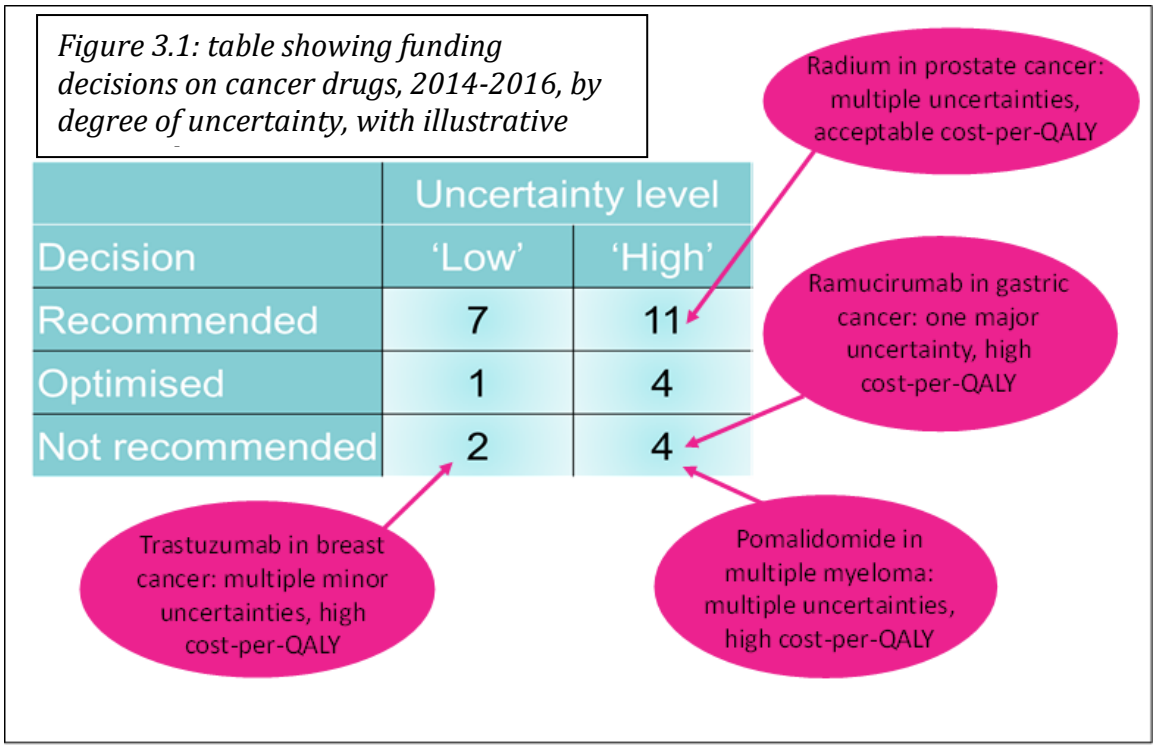
Figure 3.1 shows the funding decisions broken down by the level of uncertainty, and finds no statistical relationship between the decision and the level of uncertainty (chi-square test). The case studies shown in Figure 3.1 further illustrate that there is no clear relationship between the decision, and the level or number of types of uncertainty in the evidence base.

SOURCES OF UNCERTAINTY

The most common sources of uncertainty are shown in Table 3.1.

Immature survival data and comparator relevance are common regardless of the level of uncertainty considered. Uncertainties due to patient population and quality of life data are frequently discussed, but are not as prevalent in the "highly uncertain" appraisals. Cost estimates and uncertainties stemming from trial design are less commonly discussed, but around half of the instances are found in the more uncertain appraisals.

Figure 3.1: table showing funding decisions on cancer drugs, 2014-2016, by degree of uncertainty, with illustrative



SURVIVAL DATA AND COMPARATOR UNCERTAINTY

Two key sources of uncertainty were immature survival data, and comparators that did not reflect current practice in the UK.

For survival data, uncertainty arises because cost-effectiveness modelling used for decision-making takes a "lifetime" time horizon: we model the complete lifetime of the patients in the model, to capture all the health and cost consequences of the intervention[1]. If the duration of the trial is shorter than this, the survival data has to be extrapolated, using statistical methods, and that extrapolation introduces uncertainty. The choice of statistical model that provides the "best fit" to the data – particularly with early data – is often a matter of extensive debate, as different models will give rise to different projections for survival, and several approaches may be equally plausible.

In the case of comparator uncertainty, the drugs had not been tested directly against the treatment(s) considered to be the relevant comparator(s) in England – for example, a trial against a treatment no longer in routine use, due to practice improvements since the trial was done. The effectiveness of the drug compared to current practice in the NHS then has to be estimated: a simple example would be using data on each of drugs A and B versus placebo, to estimate the relative effectiveness of drug A versus B, although more complex approaches may be needed [24]. Again, using estimation rather than data introduced uncertainty.

Table 3.1: uncertainty themes in NICE appraisals of cancer drugs, 2014-2016

Category	Number of FADs where theme is mentioned	Number of FADs with uncertainty in headline summary ("high uncertainty") where theme is mentioned
	(n=29)	(n=19)
Immature survival data	27	16
Comparator not relevant to UK	16	10
Trial design	15	8
Quality of Life data	19	4
Patient population in trial	18	4
Cost estimates	8	4
Downstream pathway	5	2
Optimum duration of use	2	2

Neither of these classes of uncertainty are likely to be resolved by generating 2 years' real-world data in the CDF. For comparator uncertainty, the key issue for CDF data is that patients in clinical practice are prescribed a given therapy based on clinical characteristics; they are therefore systematically different from patients on any other treatment, so we cannot show that a difference in outcome is due purely to the drug used.

For survival uncertainty, we also need to consider the timeframe: in our examples, the submitted trials already have 2+ years' data, and yet there remains substantial uncertainty in survival. Two years' *de novo* in-use data will provide no new information on long-term survival. In this situation, the role of CDF funding would be to allow clinical use whilst the original survival data matures in ongoing trials. There may however be specific situations where 2 years' RWD could contribute to reducing survival uncertainty, such as demonstrating a relationship between actual survival and an indirect measure of outcome that is expected to predict survival (known as a 'surrogate': for example, tumour shrinkage, or a change in the level of a biological marker).

OTHER SOURCES OF UNCERTAINTY

Key sources identified relate to trial design, quality of life data, trial patient population, and costs.

Under trial design, the most common examples were divergence from licenced or current practice, such as use of a different dose, dose regimen, or dose form. Use of crossover in trials also created uncertainty, as it creates difficulties in estimating the ultimate survival benefit due to the trial drug.

Uncertainties in quality of life data are typically where data are missing: data not

collected in the trial, or not collected using NICE's preferred method. In these situations, values from the literature or alternative methods are used, and these have varying levels of validity.

The trial population category includes cases where the patient sample in the trials does not precisely match the licenced indication. The evaluation is therefore being performed using a *post hoc* secondary analysis of the trial data, which the trial may not have been designed for. There were further cases where the trial locations did not include the UK leading to concerns with generalisability to a British population if there is reasonable expectation of racial or geographic differences.

Cost uncertainties included uncertainties in how long the patient would survive on the drug, and optimal duration of treatment. This uncertainty is not mitigated by Patient Access Schemes based on dose capping (for example lenalidomide in multiple myeloma, where the NHS only pays for the first 26 cycles of treatment), because the average cost of the drug then becomes uncertain – even though the budget impact is capped. Other cost uncertainties were costs of treating adverse events, and the impact of wastage and vial sharing.

These sources of uncertainty are more readily addressed by RWD collection in the CDF: for example, measuring duration of use or dosage patterns, where a comparison is not required, or where the aim is to verify consistency with predictions from another population.

3.4 DISCUSSION

Overall, we find common sources of uncertainty in technology appraisals of cancer drugs during 2014-16 are the overall survival estimates, and availability of relevant comparator data. Neither of the two main types of uncertainty is likely to be readily resolved by generating two years of RWD within the CDF. Other sources of uncertainty are quality of life data, trial design, patient population, and costs, and these are more amenable to resolution through RWD. Funding decisions do not appear to be driven by the level or types of uncertainty in the evidence *per se*, but by the uncertainty of the decision relative to the cost-effectiveness threshold.

The reformed CDF provides a mechanism for funding promising cancer drugs that could be cost-effective, but where the evidence available at the point of evaluation, is too uncertain to be confident that funding the drug would be an effective use of NHS resources. As these drugs would not have been funded under the usual Yes/No binary decision, CASMI welcomed the provision of an alternative 'Maybe' decision option for NICE, and concurred with CRUK's support for the reforms. We also recommended that, as CDF reform represents a significant policy initiative on uncertainty, CRUK monitors its effectiveness, but prioritises other areas for advocacy and future research (for example, Chapter 4, Pricing Mechanisms).

Based on our findings, we predicted that the types of uncertainty we would see being resolved through CDF data collection would be related to quality of life data, dosing and usage patterns, and population comparisons, rather than survival. This has been borne out in experience to date with CDF data collection plans: we have tracked 8 CDF recommendations to October 2017, 7 of which rely on continued follow-up and analysis of ongoing clinical trials for further survival data, with CDF data collection focusing on treatment patterns, duration of use, and verifying how similar the NHS patients are to

those in a key trial. We expect this pattern to continue, with survival data coming from ongoing trials and CDF RWD being used to resolve other uncertainties.

The remaining challenge for CDF data collection is where uncertainty arises because the drug has been evaluated against a comparator that does not reflect current practice in the NHS. Options for establishing a comparator dataset include using historical data, trial data, or in-use data from other countries; these need careful consideration for their generalisability to the current, UK, clinical population. Alternatively, NICE's 'only in research' status could be used to allow data gathering as part of a pragmatic randomised trial within the NHS [25].

We observed significant levels of commercial renegotiation for some drugs when NICE suggests using the CDF route; we identified 2 examples where such negotiations allowed drugs to enter routine commissioning. It may be that the manufacturer was not confident of generating data that would support the higher price, so preferred to reduce the price for the stability of routine commissioning. Hence the promise of future data may be supporting price discussions based on realistic expectations of what a drug can deliver, which is welcome.

CHALLENGES AND RISKS

Challenges will arise in the future when NICE re-appraises the CDF drugs to determine whether funding is continued. Both NICE and pharma will be under pressure to continue funding drugs that may have become routine treatment. However, patients treated in real-world clinics are different from those in clinical trials, and will typically be less 'well', with comorbidities or low fitness levels that were excluded from the trials; their outcomes may well be worse [26].

Cost-effectiveness estimates incorporating such data are therefore not strictly comparable with estimates based only on trial data, and we do not as yet have any agreed principles on how this will be considered in the re-appraisals. As there is little positive experience published to serve as a model for such re-appraisals (see Chapter 4), this is an opportunity for the UK to take a lead; we believe this will require early engagement with a broad range of stakeholders to ensure a balanced evaluation and acceptance of the decision.

It is important to acknowledge that there are risks with early access to drugs with uncertainty in the evidence base. From the perspective of the marketing authorisation, the key issue is the balance of benefit to risk; regulators may consider patients' willingness to take personal risk, and decide to grant early access alongside pharmacovigilance (safety data collection). In contrast, from an HTA perspective, the risk is that the drug under-delivers, having been funded at the expense of other patients in the health service, who have therefore foregone health gain. This issue of who bears the consequence of a 'wrong' decision can lead to regulators and HTA coming to different decisions on a given technology.

This work informed CRUK's position on the Cancer Drug Fund reforms, expectations for the CDF, and priorities for HTA reform.

LIMITATIONS

This study is limited by the relatively small number of appraisals included, and the secondary nature of the source, which is a summary of the discussion, so has already

undergone some filtering to produce the FAD. Using primary transcripts would avoid this risk, but require a higher level of interpretation by the researchers. Secondly, most of the data extraction and classification was done by a single analyst. However, we were focusing on explicit content expressed in specific technical terms, rather than requiring high levels of interpretation as in, for example, thematic analysis of focus groups, where more than one researcher would code and interpret themes to minimise bias. Our work could be supplemented by formal interviews with committee members and NICE staff to verify our conclusions.

RECOMMENDATIONS AND IMPLICATIONS

- These findings encouraged CRUK to support the 2016 reforms to the Cancer Drugs Fund, as a mechanism to reduce important uncertainties whilst gaining access at a cost-effective price*
- We expect drugs with uncertainties in quality of life data, dosing, costs (including duration of use), and relevance to the UK population, to enter the CDF with requirement to collect real-world data
- We predict that uncertainties in survival data will not be resolved through data collection in the CDF, but by later analyses of ongoing trials
- With the reformed CDF as a substantial policy initiative on uncertainty, we recommend CRUK prioritises other areas for advocacy or funding, in parallel with ongoing evaluation of the reformed CDF*

* recommendations that have been reflected in CRUK policy positions

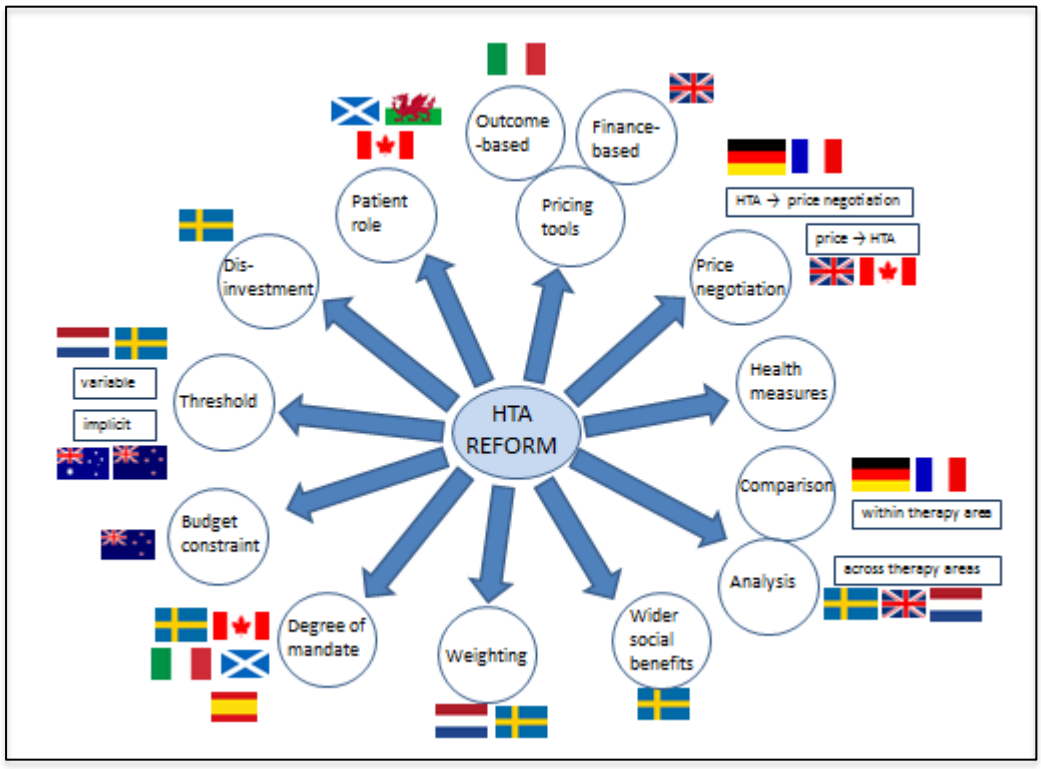
Our evaluation has been submitted for peer reviewed publication [6]; this chapter presents a summary of the published paper, with discussion of implications for CRUK. The work was presented to CRUK in June 2016.

4 PRICING MECHANISMS TO MANAGE UNCERTAINTY

4.1 INTRODUCTION

HTA is a multi-faceted process, so in advocating for reforms, it is essential for CRUK to focus on the aspects expected to have the greatest impact on patient access to drugs. During the summer of 2016, CASMI worked with CRUK to identify a wide range of potential targets for reform (Figure 4.1), and provided literature reviews and international comparisons that were used to prioritise focus areas for future work.

Figure 4.1: elements of HTA considered as targets for reform, with relevant international examples of alternative approaches



Following an initial overview, the topic of pricing mechanisms was selected for further exploration; this reflected CRUK and CASMI's interest in the issue of uncertainty, and the potential for flexible pricing mechanisms to move away from a single point-in-time evaluation of cost-effectiveness, to pricing that adapts in response to an evolving evidence base.

Other topics explored (cost-effectiveness threshold, role of patients in HTA) are not reported here but our working papers are listed in Appendix 8.3 and can be found on CASMI's website.

AIM

Our aim here was to identify key principles for successful pricing schemes that could be applied more broadly in the UK.

4.2 METHODS

We reviewed case studies illustrating a range of pricing mechanisms in the UK and

Europe, to identify common issues and factors for successful implementation. Our examples included:

- conditional reimbursement (funding granted for a fixed period, during which time additional data would be collected for re-evaluation – as exemplified by the reformed CDF)
- outcome-based schemes (payments adjusted on a per-patient basis depending on pre-agreed outcomes)
- finance-based schemes (limits to budget impact, such as discounts, caps, free stock, and cost sharing)

Further details can be found in Appendix 8.1.3.

4.3 FINDINGS

This chapter summarises the common themes that emerged from the case studies. The details of the case studies are described in a CRUK/CASMI working paper (listed in the Appendix to this report, and available CASMI's website) and are also described in a paper co-authored by CASMI, Strategy& (PWC) and AIFA, on flexible pricing approaches in adaptive pathways [7], which incorporates work reported through the Accelerated Access Review (AAR) by Strategy& [27].

CASE STUDIES

The findings reported here are based on a review of 5 case studies:

UK: the Multiple Sclerosis Risk Sharing Scheme: one of the earliest conditional reimbursement schemes (2002), providing patient access alongside data collection to measure long-term cost-effectiveness. Although a 2-year analysis suggested the drugs were less effective than expected, no cost reduction was enacted; the validity of the comparator, and the modelling approach were then re-examined, and a 6-year analysis using new methods found the drugs to be cost-effective. The scheme was criticised for failure to adjust prices in response to the evolving data, and for conflicts of interest in governance.

More recently, the UK (England) has given conditional reimbursement to drugs for very rare metabolic conditions, and to cancer drugs via the reformed CDF. These specify precise details of data collection and ownership, analyses, and timeframes for re-evaluation.

Netherlands: conditional reimbursement. Conditional reimbursement was introduced in 2006 to facilitate access to orphan drugs following public pressure; drugs were temporarily approved, with additional data collection and re-evaluation in 4 years. As of May 2013, 14 orphan drugs had received conditional reimbursement. Of these only 4 had been re-evaluated, with 3 receiving negative advice on cost-effectiveness, but none have been delisted following significant public pressure [28]. Observers have also commented on the varying governance models between the schemes [28], missing data relating to effectiveness and safety, and difficulties in agreeing methods to measure key endpoints [29].

Italy: registries and managed-entry agreements. Italy is actively using a wide range of managed entry approaches, both financed-based (budget caps, free product) and outcome-based schemes (rebates for non-responders, payment only for responders). These operate alongside an established system of monitoring registries; data from the registries can be used for re-evaluation of cost-effectiveness. The schemes are

acknowledged to create administrative complexity [27, 30], and rebate payments have been extensively disputed (and delayed) due to debates over endpoints [31 32].

UK: patient access schemes. PAS's are confidential commercial arrangements that reduce the effective price of a drug such that it becomes cost-effective, and include both financial and performance-based schemes. Although the first scheme was purely outcome-based, the increasing majority are simple discounts. The early outcome-based schemes were criticised for administrative load, difficulties handling rebates and credits to the provider, and strict procedural requirements leading to failed claims [33].

UK: the former Cancer Drugs Fund. Although clearly not set up as a managed access scheme, the former CDF provides an example of dynamic price negotiation: following periodic rounds of delisting, drugs identified for removal from the CDF remained available, and as the supporting data did not change, this appears to have been via price renegotiation. Further, the CDF was a single central budget, so credits and rebates were straightforward, in contrast to the complexities of linking credits back to specific providers across the NHS [7].

FINANCE VS OUTCOME-BASED APPROACHES

Whilst financial schemes such as simple discounts provide budget control, they do not make any contribution to reducing uncertainty, and typically have no link to the value provided by the technology. In particular, capping schemes as seen in the UK (that is, setting a maximum duration, number of doses, or cost per-patient) work counter to value; the longest-surviving patients represent high value for the NHS, but end up being funded by industry. Schemes based on free initial product provide at least a weak link to value, if non-responders can be identified during the free period and switched to an alternative therapy.

Outcome-based approaches fall into two types: individual-based, where the payment is determined for a given patient based on their response (e.g. Italy's performance-based schemes), or population-based, where all patients' data are collected and analysed for a subsequent review of pricing and reimbursement status (as in both the Netherlands' and UK's conditional reimbursement schemes, and Italy's registries). Some schemes combine both: for example, the UK's managed access agreement for ataluren in Duchenne muscular dystrophy has stopping rules for patients who do not benefit, whilst collecting population-level data for future evaluation. Both provide routes to link the payment to the value delivered.

DATA COLLECTION AND ADMINISTRATIVE LOAD

Administrative load is a common criticism of previous outcome-based schemes (UK, Italy), and has led to providers preferring simple discount schemes (UK). The most efficient schemes would avoid data-based rebate claims, not require additional data beyond what would be needed for routine clinical decision-making, and would credit or rebate directly to the relevant budget-holder.

Similarly, high-quality data collection is more likely to be achieved when data collection is mandated (as in the Italian registries, and UK SACT database); the data collected are in line with what is needed for routine clinical use (as in the Italian registries); and where there is established capability for collecting such data (such as the UK SACT database).

PRICING RENEGOTIATION IN OUTCOME-BASED SCHEMES

All three case studies of conditional reimbursement with data collection have been criticised for not making effective decisions at the end of the coverage period, particularly where that decision would have been to delist or reduce prices. However, the reinstatement of drugs delisted from the former CDF provides a recent example of willingness to negotiate – and return to negotiations as circumstances change - from both NHS England and industry.

4.4 DISCUSSION

Overall, the case studies confirm that pricing mechanisms can be used to enable access, manage uncertainty, and in some cases link to the value provided by the technology. Key challenges in delivering a successful scheme are: minimising the administrative load; unambiguous definition of data requirements; allocating rebates or credits to the specific provider; and ensuring any deferred decisions can be upheld once data are available.

We recommended that CRUK prioritises support for development of a range of flexible pricing mechanisms – not only as a mechanism to provide more access out of the fixed NHS budget, but also as a route to enable the price to change with an evolving evidence base, providing a way of managing uncertainty. Further, we believe that whilst finance-based mechanisms can help manage budget impact, prices that truly reflect the value provided by the technology are a sound approach to achieving cost-effectiveness whilst continuing to incentivise the pharmaceutical industry to develop and introduce innovative and effective products. We therefore also recommend that CRUK advocates for pricing mechanisms that are outcome-based.

This position is consistent with the recommendations of the AAR [15], which recommends that NHS England should be able to consider a range of flexible pricing models, and suggests examples of mechanisms used internationally. It is also consistent with the trend towards managed access arrangements in the UK, as evidenced by the reforms to the Cancer Drugs Fund, the development of adaptive pathways such as the UK's Early Access to Medicines Scheme (EAMS), and examples of managed access agreements in very rare conditions, such as Duchenne's muscular dystrophy. There have also been calls from advocacy groups (e.g. Breast Cancer Now and Prostate Cancer UK, [34]) and the pharmaceutical industry (e.g. ABPI [35]) for increased flexibility in pricing negotiations and commercial arrangements to enable patient access to drugs.

The reformed Cancer Drugs Fund has embedded the concept of conditional approval in the NICE process. Whilst the approach has been effective in getting drugs funded that could not be recommended for routine commissioning, we have no experience of the review process: how the observational data from the CDF will be integrated with clinical trial data, and whether the decision-making process will be effective. CASMI and CRUK will continue to monitor the operation of the CDF, and the decisions made at the end of the data collection periods. As a respected advocate, CRUK may have the opportunity to engage with other stakeholders in ensuring a credible decision-making process.

Although not directly focused on uncertainty, we also recommend that CRUK considers multiple indication pricing (MIP). Cancer drugs increasingly are being developed to treat more than one type of cancer: for example, nivolumab, an immunotherapy drug, currently is licensed to treat 7 cancer indications, with 15 more in the pipeline. The degree of benefit provided in each of those indications will be different; however, the drug has a single list price across all the indications. This means the price does not reflect the true

value provided by the drug in each of its indications, and may provide a counter-incentive for the manufacturing company, as it risks having to drop the price to accommodate the lower value indications [36, 37]. Multiple indication pricing would mean the price reflects the value provided in that indication, and can also respond to an evolving evidence base in the less mature indications.

Resistance to MIP is largely practical: managing multiple prices for the same drug, and avoiding arbitrage (using the drug for one indication but billing it as a cheaper one). The small number of examples take advantage of existing systems (the Italian registries), use a weighted average price (France) or use different brand names for the same drug in different therapeutic categories (for example aflibercept is branded as Zaltrap in cancer, and Eylea in ophthalmology) [37].

SUMMARY OF RECOMMENDATIONS

- Prioritise flexible pricing mechanisms in advocacy and future research*
- Continue to monitor the new CDF for effective operation, and the decision-making when drugs are reviewed
- Develop a position on multiple indication pricing

* recommendations that have been reflected in CRUK policy positions

This work has informed CRUK's position paper on access to cancer drugs (August 2017), and development of an outcome-based pricing research programme [38].

5 IS IT NICER IN NICE?

5.1 INTRODUCTION

The Cancer Drugs Fund (CDF) in England aimed to improve access to new cancer drugs, by providing funding for drugs not routinely available on the NHS [39]. The CDF developed its own process for selecting drugs to be funded. This was independent of NICE's evaluation, and aimed to "*put clinicians and cancer specialists at the heart of decision-making*" [40]. The evaluation tool scored each drug per indication under 5 clinical domains, alongside a confidential score for cost, and a budget-dependent cut-off was used to determine which drugs were funded. Of note, the evaluation was based directly on trial data, and required statistically significant differences and that the results had been published in peer-reviewed journals in order to contribute to the score. [40]

Reforms to the CDF in April 2016 removed the function of the CDF as an additional funding mechanism, and consolidated all cancer drug funding decisions in NICE [14]. As the CDF had funded drugs that had been rejected by NICE, there were concerns among some stakeholders that reverting all decisions to NICE would damage patient access, in the absence of a significant reform to NICE and its processes [41 42].

Given this view of the former CDF as a more permissive route to access, it was perhaps surprising to find examples of drugs that had been rejected by the CDF, but subsequently recommended by NICE. Having picked up examples of this unexpected approval pattern by chance during our work on uncertainty (Chapter 3), we examined these cases further to help understand the differences between the NICE and former CDF appraisal processes.

The former CDF had become a major part of cancer drug provision, accounting for a quarter of total cancer drug spending and a fifth of new patients starting treatment [20]. This provision could not be simply removed with the reform of the CDF, and so these drugs continued to be funded pending review by NICE. One particularly interesting group is the eleven drugs that were in the CDF as a result of previously being rejected by NICE; for these drugs, a "Rapid Reconsideration" process was devised, focusing on any changes to the evidence base since the previous NICE decision. We monitored these drugs through the re-evaluation, as an early indicator of the access landscape in a post-CDF era.

AIM

The aim of this work was to inform CRUK's position on the new CDF, and priorities for advocacy for NICE reform. To investigate the impact of CDF reforms on access to drugs, we used two complementary approaches:

- Characterising the unexpected group of CDF-rejected drugs later approved by NICE
- Monitoring NICE's reconsideration of previously NICE-rejected, CDF-funded drugs

The work on CDF-rejected drugs was presented to CRUK in June 2016, and at the annual symposium of the Radcliffe Department of Medicine, University of Oxford, in March 2017 [43].

5.2 METHODS

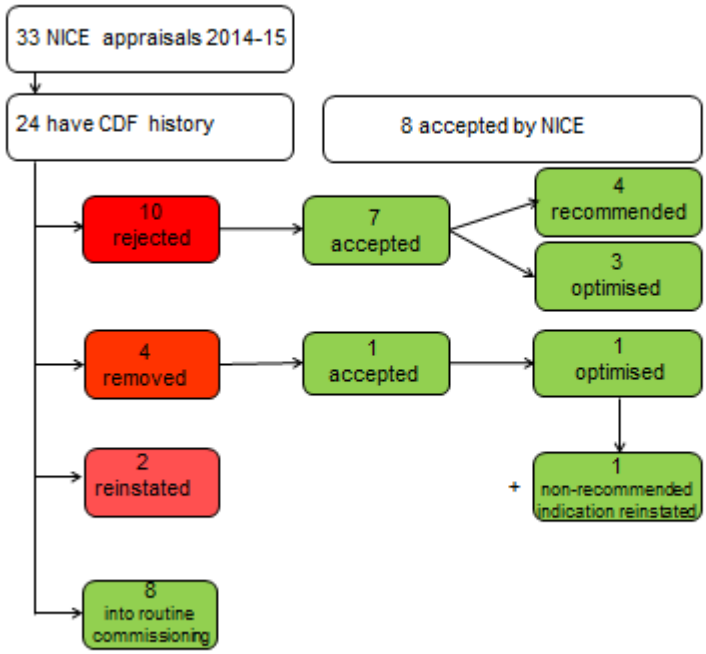
All data are public domain. Data on NICE's decisions on a 2-year cohort of cancer drugs (2014-2016) were extracted from published decisions on NICE's website (as described in Chapter 3). Information on these drugs' history with the CDF was extracted from the CDF's pages on NHS England's website. Decision on the Rapid Reconsideration drugs were monitored on NICE's website. Data on NICE's decision rates overall was taken from NICE's published table of all decisions, accessed on NICE's website (ta-decision-summary-sep-17.doc). Further details can be found in Appendix 8.1.4.

5.3 FINDINGS

CDF NO, NICE YES

Eight drugs were identified that were Recommended or Optimised by NICE, having previously been rejected or removed from the former CDF (Figure 5.1).

Figure 5.1 CDF history of a 2-year cohort of NICE appraised drugs, 2014-2015



The reasons for rejection or removal by the CDF included survival data: no survival data presented, immature data, or survival data that did not show a significant difference relative to the comparator. Other reasons were uncertainties, similar to those noted by NICE (Chapter 3). These included the use of a comparator that was not relevant to the UK, and data not generalisable to a UK population. In two cases, the CDF Decision Summary noted that the evidence base was "too uncertain" to support funding.

The evidence base seen by the CDF and NICE was essentially the same, with some examples of additional subgroup analyses (3 cases), additional supporting trials (2 cases) or a more recent data cut of the same trial (1 case), being provided to NICE, typically at NICE's request.

RAPID RECONSIDERATION: NICE NO, THEN NICE YES

All eleven drug/indication pairs went through Rapid Reconsideration between May 2016 and August 2017. **All** were recommended for funding (3 with Optimised recommendations for a sub-group of the patient population).

A feature of the reconsiderations is the high degree of redaction in the public documents, indicating significant commercial renegotiation. In some cases, where the appraisal required multiple Appraisal Committee meetings, three or four prices were evaluated between the original price and the final agreement.

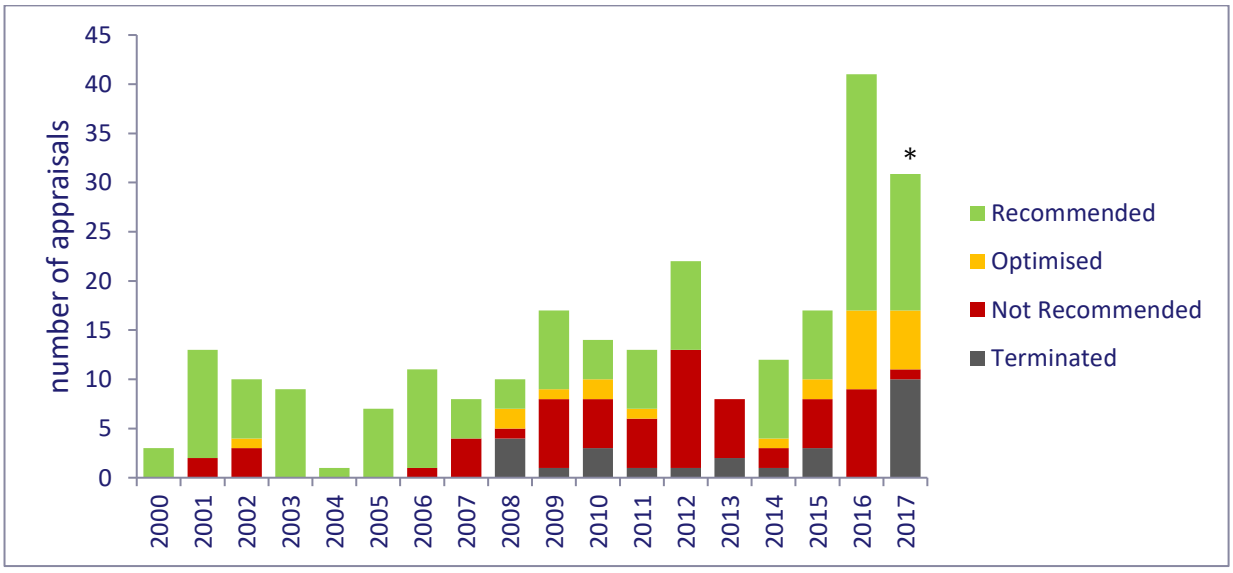
There is limited submission of updated datasets as part of the reconsiderations. In particular, there is a notable absence of use of real-world data gathered during the period of original CDF funding, with only one example found among the 11 reconsiderations (sorafenib in hepatocellular carcinoma: the submission cited an independent audit of CDF data, in support of the manufacturer's survival modelling).

OVERALL RECOMMENDATION RATES

NICE acceptance rates of all cancer drugs (Recommended and Optimised acceptances) have increased since 2013, with the proportion of Recommended and Optimised for 2014 to 2017 consistently above that seen in from 2007 to 2013 (see Figure 5.2).

2016 and 2017 saw an increase in the number of cancer drug appraisals completed by NICE, and a noticeable increase in the proportion of Optimised appraisals. The implications of this trend are explored below.

Figure 5.2 NICE decisions on cancer drugs, 2000-2017



** 2017 data are January to September*

5.4 DISCUSSION

Overall, we conclude that the consolidation of cancer drug funding decisions with NICE has not to date had a negative effect on access. Our findings suggest that the NICE appraisal is not necessarily a tougher hurdle than the former CDF, particularly for promising new drugs seeking access at an early stage of development – a trend illustrated by the development of the UK's Early Access to Medicines Scheme (EAMS), and with the government's recent acceptance of the proposals of the Accelerated Access Review (AAR) [15, 44].

An important driver of acceptance of former CDF drugs for routine commissioning is active price renegotiation between the pharmaceutical company and NHS England. Experience and relationships developed during the former CDF may be facilitating discussions; in addition, the reformed CDF requires commercial arrangements to make new CDF drugs be cost-effectiveness on entering the fund, thus creating an expectation of negotiation which appears to be extending to drugs entering routine commissioning.

In reviewing NICE appraisals, we have noticed increasingly common references to a 'commercial access arrangement with NHS England', rather than to a Patient Access Scheme, suggesting an accepted (although not formally defined) direct negotiation even for non-CDF drugs. Additionally, we recently saw the transfer of the Department of Health's Commercial Medicines Unit into NHS England [45], which may have facilitated increased negotiation during 2017.

Such evidence of willingness of NHS England and the pharmaceutical industry to work together to support access, is welcome, and fits with CRUK's focus on pricing flexibility as a means to maximise cost-effective access. We expect to see further expansion in NHS England's commercial role, with the government's acceptance of the AAR's recommendation for a Strategic Commercial Unit with capacity to negotiate innovative pricing mechanisms, and the proposed transfer of responsibility for Patient Access Schemes from NICE to NHS England [44].

Cancer decisions by NICE show an increased use of Optimised recommendations – recommendations only for a patient subgroup where the treatment is most cost-effective. This approach has enabled some drugs to gain access for a limited patient population, where treatment across the whole of the indicated population would not have been cost-effective. This is expected to increase, given increased focus on developing stratified, 'personalised' therapies.

Where the non-targeted patient group got very little benefit from the drug, then exclusion from that treatment option will have enabled that group to avoid toxicities from low-benefit treatment. However, in other cases the non-targeted group would have obtained some benefit, which is being denied, along with the hope raised of having a further treatment option. Although each case would need to be considered on its own merits, we suggest CRUK might develop a policy position on the use of Optimised recommendations and their equity implications.

The NICE data show a sharp increase in the number of cancer drug appraisals being considered by NICE over the past 2 years, only part of which is explained by the CDF Rapid Reconsiderations. In October 2017, NICE consulted on proposals for increased capacity in the Technology Appraisals programme [46], to help accommodate this increased workload. The proposals aim to reduce the number of repeat Appraisal Committee meetings on a given drug, and include a 'technical engagement' step to allow technical issues to be debated and resolved ahead of the Appraisal Committee meeting.

In principle we recommend that CRUK supports these proposals, as they should accelerate decisions by reducing the number of meetings and consultations needed to arrive at a decision; in addition, the approach may reduce the tension created by the somewhat adversarial set-up of the technical debate in the public forum of the Appraisal Committee meeting, and enable open scientific dialogue. However, the risk of these discussions happening outside the public forum is loss of transparency, and we recommend CRUK takes a strong position on the need for full documentation of these discussions.

This work has influenced CRUK's position on the CDF reforms and approaches for accelerated access.

SUMMARY OF RECOMMENDATIONS

- We recommend that the NICE appraisal and the reformed CDF continue to be the mechanism for evaluating cancer drugs with significant uncertainty, including those seeking early access*
- We recommend CRUK supports NICE's current proposals for increasing capacity, with the proviso that transparency is maintained as technical discussions move outside the public forum
- We suggest CRUK develops a position on the increased use of Optimised recommendations in HTA decisions

* recommendations that have been reflected in CRUK policy positions

6 ACRONYMS

AAR	Accelerated Access Review
ABPI	Association of the British Pharmaceutical Industry
AIFA	Agenzia Italiana del Farmaco (Italian medicines agency)
AWMSG	All-Wales Medicines Strategy Group
BIT	Budget Impact Test
CASMI	Centre for the Advancement of Sustainable Medical Innovation
CDF	Cancer Drugs Fund
CRUK	Cancer Research UK
EAMS	Early Access to Medicines Scheme
EoL	End-of-life
FAD	Final Appraisal Document
HTA	Health Technology Appraisal
MIP	Multiple Indication Pricing
NHS	National Health Service
NDC	New Drugs Committee
NICE	National Institute for Health and Care Excellence
PACE	Patient and Clinical Engagement
PAS	Patient Access Scheme
QALY	Quality-Adjusted Life Year
PWC	PriceWaterhouse Coopers (rebranded Strategy&)
RWD	Real-World Data
SACT	Systemic Anti-Cancer Therapy database
SMC	Scottish Medicines Consortium
VBA	Value-Based Assessment
VBP	Value-Based Pricing

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8 APPENDICES

8.1 METHODS

This section provides details on the methods and approaches used, and complements the summary Methods sections within Chapters 2-5

8.1.1 CHAPTER 2: IMPACT OF HTA REFORMS IN SCOTLAND

Both NICE and SMC publish their funding decisions on each drug/indication they assess, and the evidence and rationale behind their decision, on their respective websites. Information on decisions made by SMC in the first two years since the reforms (10/2014 to 9/2016) was taken from the 'Detailed Advice' published on the SMC's website (www.scottishmedicines.org.uk), including: whether the new process was used, under which of the criteria, and the final funding decision. We then counted numbers of decisions that used the new process, under which element of the definition each one qualified, and of each type of outcome (Accepted, Restricted, Not Recommended). Data for the two years pre-reform were used as a comparison.

A simple before/after analysis does not cleanly isolate the effect of the changes. However, for our analysis we were able to take advantage of the structure of the reform: it provides an *additional* process that is triggered if the initial decision by SMC's New Drugs Committee (NDC) is not to recommend funding for a drug used at the end-of-life or for a rare condition [2 47]. We therefore made the assumption that all drug candidates using the new process were initially Not Recommended, and that a change in that initial decision was due to use of the new process. Drugs using the new process were identified by the statement in the Advice headline that the submission was assessed "under the end-of-life/orphan/ultra-orphan process".

The Detailed Advice includes a summary of the PACE meeting, and these were used for thematic analysis, to identify issues discussed in the PACE meetings, and whether they could be related to the decision. Themes are developed by determining the core idea of each segment of text, and linking together related ideas to form themes that arise as common threads across the PACE meetings. Thematic analysis was performed inductively – that is, themes are identified from the review of the text, rather than by imposing a pre-determined framework.

The comparison of access between Scotland and England focused on the cancer drugs. NICE's funding decision for the same drugs for England, was accessed from NICE's website (www.nice.org.uk). Further, some of these drugs were being funded by the Cancer Drugs Fund (CDF) outside the NICE process during the period of this study; information on which of these drugs were funded through the CDF was accessed from the CDF pages of NHS England's website. (Note that the CDF pages from NHS England's website have now been archived and are not easy to find. CASMI has downloaded and saved these pages for future reference if needed.)

Because funding decisions can be revised over time, the access comparisons presented here are snapshots, based on funding decisions in force in September 2016 (the end of our study period), with an update for the same drugs in September 2017.

9.1.2 CHAPTER 3: UNCERTAINTY IN NICE'S APPRAISALS OF CANCER DRUGS

Our approach assumed that the uncertainties seen in previous cancer drug submissions might help predict uncertainties in future submissions. We therefore used NICE's Technology Appraisal output, the Final Appraisal Document (FAD), as our source to examine types of uncertainty. The FADs publish the Committee's decision, deliberations and the evidence on which these were based, for each appraisal. We chose a period of two complete calendar years prior to the date of analysis (Jan 2014 – March 2016) to have enough appraisals to analyse, but for them also to be recent enough to reflect the 'state of the art' in the data submitted.

The Committee's deliberations are discussed in Chapter 4 of the FAD, which contains a table summarising the Committee's key discussions and conclusions; these tables were used as our primary source of data, with the rest of the appraisal referred to when clarifications or further information were needed. We reviewed the summary tables, extracted text relating to uncertainty, and classified the texts into categories of related content using an inductive process – that is, the categories were suggested by the text rather than an imposed framework. We report the frequency of occurrence of each category of uncertainty, as the number of FADs in which it occurs (ie irrespective of the number of mentions within any FAD).

The summary table includes a headline summary, which reflects key features of the appraisal overall. From an initial review of the FAD's, we observed that this headline summary mentions uncertainty in some cases. To explore the strength of concern with uncertainty in the decision, we assumed that the FADs with comments on uncertainty in the headline are those where uncertainty was a highly salient feature of the decision, and designated these FADs as 'High uncertainty'.

9.1.3 CHAPTER 4: PRICING MECHANISMS TO MANAGE UNCERTAINTY

We reviewed case studies from experience with a range of pricing mechanisms in the UK and Europe, to identify common issues and factors for successful implementation. Relevant examples are covered by the general term 'managed access agreement', which have been defined as:

"*an agreement between a pharmaceutical company and payer that enables access to a health technology subject to specified conditions. These arrangements can use a variety of mechanisms to address uncertainty about the performance of technologies, or to manage the adoption of technologies in order to maximize effective use, or limit their budget impact*" [7].

Our examples included:

- conditional reimbursement (funding granted for a fixed period, during which time additional data would be collected for re-evaluation – as exemplified by the reformed CDF)
- outcome-based schemes (payments adjusted on a per-patient basis depending on pre-agreed outcomes)

- finance-based schemes (limits to budget impact, such as discounts, caps, free stock, and cost sharing)

The information on the case studies described was synthesised from a range of sources, including literature searching (PubMed, Medline), and information taken directly from regulatory and HTA authorities' websites, supplemented by informal discussions, and CASMI's knowledge from involvement with adaptive licencing projects.

This chapter summarises the common themes that emerged from the case studies. The details of the case studies are described in a CRUK/CASMI working paper (provided as an Appendix to this report, and on CASMI's website) and are also described in a paper co-authored by CASMI, Strategy& (PWC) and AIFA, on flexible pricing approaches in adaptive pathways [7], which incorporates work reported through the AAR by Strategy& [27].

9.1.4 CHAPTER 5: IS IT NICER IN NICE?

Data on NICE's decisions on a 2-year cohort of cancer drugs (2014-2016) was extracted from NICE's published decisions accessed via NICE's website (as described above for Chapter 3.).

Information on these drugs' history with the CDF was extracted from the CDF's pages on NHS England's website, using two document sets. The CDF Lists of funded drugs was used to identify whether each drug had been funded through the CDF. The details of the CDFs funding decisions on each drug were traced by searching the CDF Decision Summaries; these are published outcomes of the deliberations of the CDF committee, which decided whether each drug would be available through the CDF, using the CDF's own evaluation tool [40]. The Decision Summaries record the drug's score on the evaluation tool, the data supporting that score, and the funding decision; this information was extracted and tabulated.

Information on the decisions made for each drug by NICE and the CDF was tabulated to enable comparison. Drugs of interest for our study were identified as: Recommended by NICE following rejection or removal from the CDF. For these drugs, CDF Decision Summaries and the NICE Final Appraisal Documents (FADs) were reviewed in detail to identify reasons for the differences in decision.

Decision on the Rapid Reconsideration drugs were monitored via the FADs published on NICE's website.

Data on NICE's decision rates overall was taken from NICE's published table of all decisions, accessed on NICE's website (ta-decision-summary-sep-17.doc) [9]

9.2 PUBLISHED PAPERS

INTRODUCTION

Does the public prefer health gain for cancer patients? A systematic review of public views on cancer and its characteristics.

L Morrell, S Wordsworth, S Rees, R Barker. Pharmacoeconomics 2017: 35 (8) 793-804. DOI: 10.1007/s40273-017-0511-7

Cancer as 'the perfect storm'? A qualitative study of public attitudes to health conditions.

L Morrell, SS Ii, S Wordsworth, R Wilson, S Rees, R Barker. Health Science Reports 2017. e216. DOI: 10.1002/hsr2.16 (epub ahead of print)

CHAPTER 2

Cancer drug funding decisions in Scotland: impact of new End-of-Life, Orphan and Ultra-orphan processes.

L Morrell, S Wordsworth, H Fu, S Rees, R Barker. 2017. BMC Health Services Research 17: 613 DOI: 10.1186/s12913-017-2561-0

CHAPTER 3

Will the reformed Cancer Drugs Fund address the most common types of uncertainty? An analysis of NICE cancer drug appraisals.

L Morrell, S Wordsworth, A Schuh, M Middleton, S Rees, R Barker. 2018. BMC Health Services Research 18, 393. DOI: 10.1186/s12913-018-3162-2

CHAPTER 4

Pricing and reimbursement experiences and insights in the European Union and the United States: Lessons learned to approach adaptive payer pathways.

SD Faulkner, M Lee, D Qin, L Morrell, E Xoxi, A Sammarco, S Cammarata, P Russo, L Pani, R Barker. 2016. Clin Pharmacol Ther. 100, 730-742. DOI: 10.1002/cpt.508.

8.2 CASMI INTERNAL PAPERS

CASMI working paper 1: cost-effectiveness thresholds

CASMI working paper 2: patient involvement

CASMI working paper 3: uncertainty and pricing mechanisms