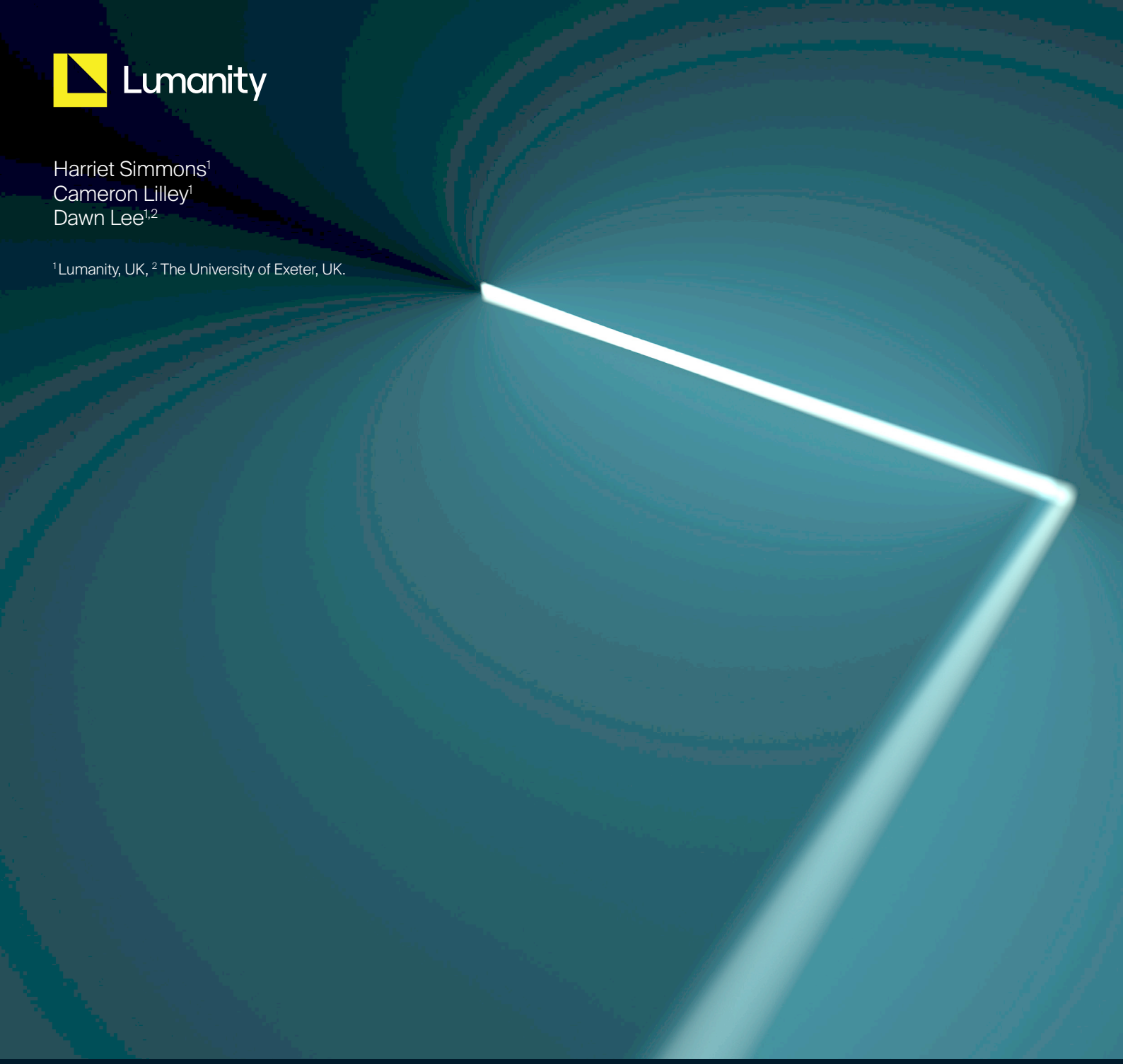

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Comparing Outcomes Pre- and Post-Cancer Drugs Fund

What Can We Learn?

What can we learn from the Cancer Drugs Fund about predicting survival?

High success rate

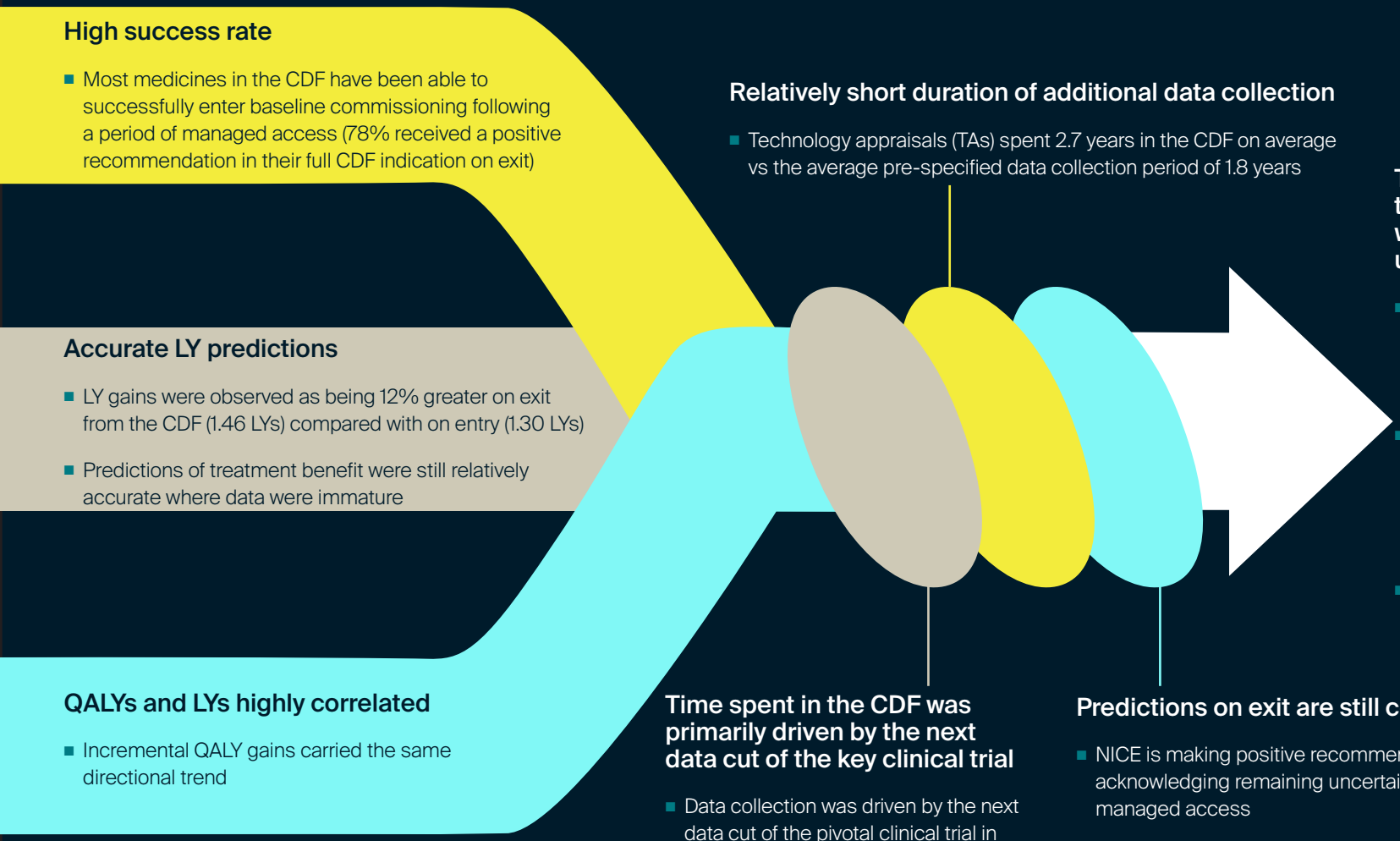
- Most medicines in the CDF have been able to successfully enter baseline commissioning following a period of managed access (78% received a positive recommendation in their full CDF indication on exit)

Accurate LY predictions

- LY gains were observed as being 12% greater on exit from the CDF (1.46 LYs) compared with on entry (1.30 LYs)
- Predictions of treatment benefit were still relatively accurate where data were immature

QALYs and LYs highly correlated

- Incremental QALY gains carried the same directional trend



Relatively short duration of additional data collection

- Technology appraisals (TAs) spent 2.7 years in the CDF on average vs the average pre-specified data collection period of 1.8 years

Time spent in the CDF was primarily driven by the next data cut of the key clinical trial

- Data collection was driven by the next data cut of the pivotal clinical trial in the majority of submissions, rather than by the collection of additional real-world data

Predictions on exit are still considered uncertain

- NICE is making positive recommendations at CDF exit despite acknowledging remaining uncertainty following the period of managed access

There is potential for less reliance on the CDF, reserving it for appraisals with genuinely high clinical data uncertainty

- There is an opportunity to identify medicines that could be suitable for rapid entry into managed access using the clinical trial program maturity as an indicator
- The majority of treatments approved by the CDF are of a common drug class (immunotherapy), where methods of extrapolation are well understood, providing further certainty on extrapolations
- NICE should have more confidence in making recommendations for routine commissioning in the first instance

Key: CDF, Cancer Drugs Fund; LY, life year; NICE, National Institute for Health and Care Excellence; QALY, quality-adjusted life years; TA, technology appraisal.

Introduction

In this paper we look at the 18 appraisals that had entered and exited the CDF between June 2016 and April 2022 to provide insights on what manufacturers can expect from the CDF and to understand whether the CDF is operating optimally to resolve genuine uncertainty in submissions.

The Cancer Drugs Fund (CDF) was established in England to provide patients with faster access to innovative cancer treatments that show promising early results but have significant remaining clinical uncertainty. The CDF was reformed in 2016 to include clear entry and exit criteria and to better define the process of data collection and reassessment.[1]

The funding for medicines entering the CDF is temporary and based on receiving approval to enter the CDF by the National Institute for Health and Care Excellence (NICE). Entry is conditional on having a Managed Access Agreement (MAA) in place that consists of a Data Collection Agreement (DCA) and Commercial Access Agreement (CAA). Managed access allows manufacturers additional time (generally a maximum of 5 years) to collect additional evidence to address uncertainties identified during the Technology Appraisal (TA) and to demonstrate the clinical and cost-effectiveness of the treatment for routine use in the NHS.[2] In addition to the data collection component, entry into the CDF requires negotiation of a CAA with NHS England and Improvement (NHSE&I) with additional price discounting to offset the uncertainty associated with the available data. At the end of the managed access period, medicines must exit the CDF, with re-evaluation following the NICE TA process. The resubmissions receive either a positive, optimised (recommended in a narrower population than the licensed indication) or negative recommendation based on the extent to which the new evidence has addressed the uncertainties identified in the original appraisal.

For manufacturers considering the CDF route, understanding and being able to demonstrate how initial projections are likely to be accurate for predicting future outcomes is crucial both to internal planning and to negotiations around the size of discount required for CDF entry.

To offer some insight into the ability of manufacturers to estimate clinical outcomes entering the CDF and what manufacturers should anticipate from CDF-based data collection, the 18 appraisals that had entered and exited the CDF between June 2016 and April 2022 were reviewed (see Appendix for a full list of the reviewed TAs). We identified the following key areas of interest:

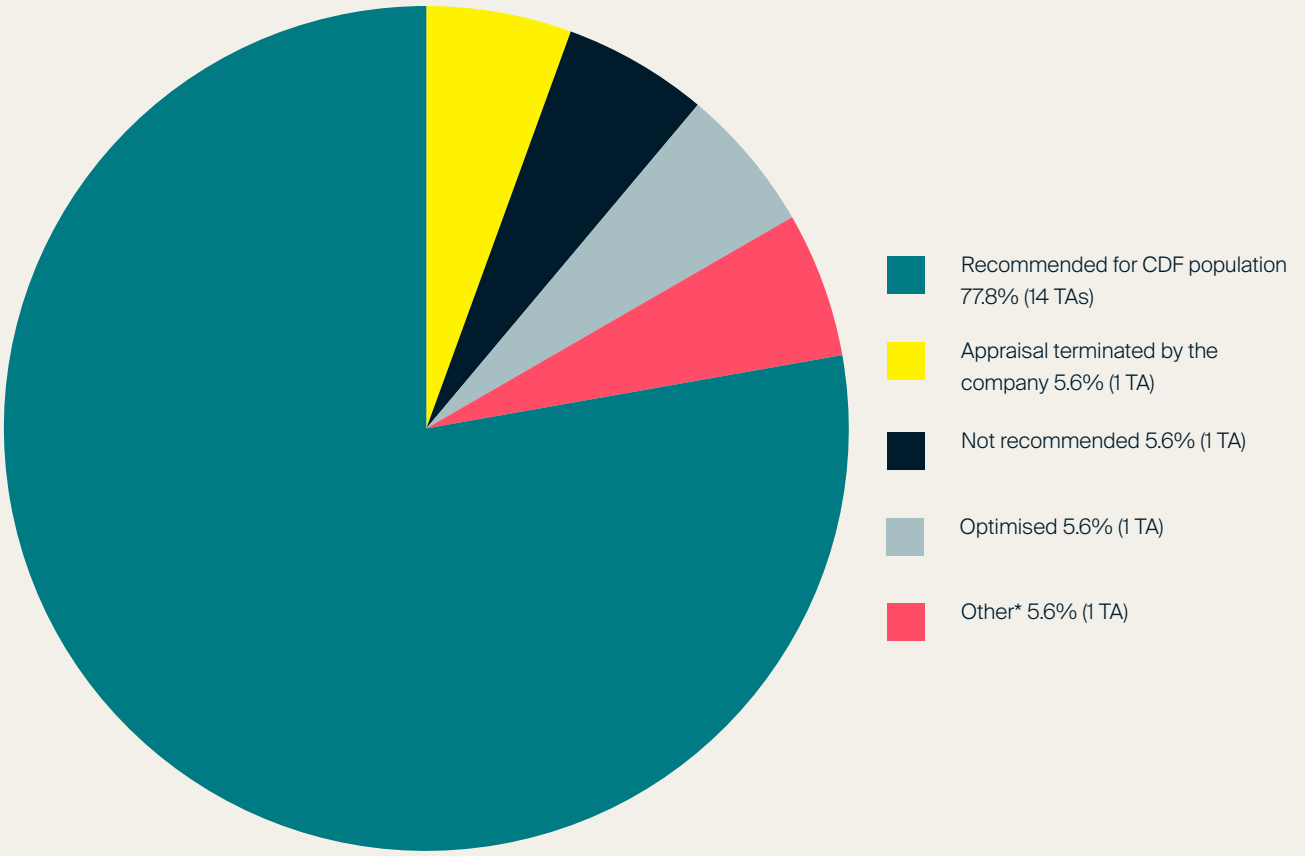
- Overall success of CDF resubmissions: The proportion of submissions that received a positive recommendation
- Predictive ability: Changes in life years (LYs) and quality-adjusted life years (QALYs) between the initial submission and subsequent resubmission
- Time taken to resolve uncertainties: The time spent by treatments in the CDF and any remaining data uncertainties identified by NICE at CDF exit.

How successful were CDF resubmissions?

Most TAs that entered the CDF (78%) went on to receive a positive recommendation for their full CDF indication (see Figure 1).

There was some commonality in both the disease and treatment areas for exit submissions that did not receive a positive recommendation, with two of these TAs (terminated and not recommended) being in urothelial cancer. An appraisal in non-small-cell lung cancer (NSCLC) also received an optimised recommendation for a smaller subgroup than the CDF population. Additionally, olaratumab was approved for use for treating advanced soft-tissue sarcoma on the CDF but later had its license withdrawn (and therefore MAA terminated). Given that 78% of appraisals were associated with a successful resubmission following CDF exit, it could be concluded that in most cases the data collection efforts (and any subsequent price changes) were successful in sufficiently reducing uncertainty for the NICE Committees to make a positive recommendation.

Figure 1
TAs by CDF exit recommendation



Key: CDF, Cancer Drugs Fund; TA, technology appraisal.
Note: * TA465: Olaratumab had licence withdrawn whilst in the CDF.

How did LYs and QALYs change between submissions?

LY estimates in the original submission were predictive of LYs at CDF exit, even where the data were immature.

We investigated whether outcomes estimated during the initial TA were predictive of outcomes that further evidence generation would confirm at CDF exit. We used LYs as the primary outcome measure, where possible, and confirmed these conclusions using QALYs. LYs were the primary outcome for comparison given that uncertainty in long-term survival is often cited as the largest area of data uncertainty for oncology medicines, often driven by data immaturity and the necessity of making assumptions regarding extrapolations. As such, within oncology, outside of drug price, the difference in predicted LYs is usually the key driver of the incremental cost-effectiveness ratio (ICER). LYs were more frequently reported than QALYs by manufacturers in publicly available Committee documents, allowing for a larger evidence base for investigation of changes between initial appraisal and reappraisal.

LYs for the interventions and comparators were extracted from publicly available Committee documents, where available. In each case, LYs were extracted for the scenario(s) that aligned most closely with the Committee's preferred assumptions, where this information was available. Where the Committee considered multiple scenarios in its decision making, the average LY across scenarios was calculated for the intervention and comparator arms, respectively. Where LY data for the Committee's preferred assumptions were not publicly available, this was sought directly from the manufacturers for eight submissions. In two further cases where LYs were not reported for the Committee's preferred assumptions, LYs were extracted for the company's base case on entry into and exit from the CDF. In both cases the Committee considered the company's base case relevant, alongside other scenarios for which LYs were not reported. Where LY data could not be obtained through any of the above methods, for four submissions LYs on exit were estimated using available information on overall survival (OS) from the Committee documents. LYs were generated for the intervention and comparator arms by digitising Kaplan–Meier curves from the pivotal trial and generating pseudo patient-level data (PLD) using the Guyot algorithm.[3] OS was then extrapolated over the specified time horizon using the Committee's preferred distribution(s) and assumptions. As a result, LY data were obtained for the intervention and the key comparator in 13 of the 16 TAs that had both an initial appraisal and CDF resubmission. Given the additional layer of uncertainty associated with digitising and then extrapolating Kaplan–Meier data, scenario analysis was also conducted excluding the four TAs that used digitised LYs.

Table 1 presents the results of the LY analysis. We found that the overall size and direction of results in the scenario that excluded TAs based on digitisations were comparable to the results in Table 1.

Table 1
Summary of LYs between CDF entry and exit submissions

	Intervention	Comparator	Incremental
N of appraisals	**13**	**13**	**13**
Instances where LYs increased	**8**	**9**	**7****
%	**62%**	**69%**	**54%**
Mean LYs			
On entry into the CDF	**4.62**	**3.32**	**1.30**
On exit from the CDF	**5.07**	**3.62**	**1.46**
Absolute change in LYs			
Mean	**0.454**	**0.300**	**0.154**
Min	-0.670	-0.560	-0.450
Max	2.426	2.603	1.194
SD	**0.446**	**0.350**	**0.274**
Proportional change in LYs			
Mean	**9.83%**	**9.05%**	**11.79%**
Min	-23.84%	-34.57%	-30.61%
Max	46.13%	85.90%	535.00%*

Key: CDF, Cancer Drugs Fund; LYs, life years; min, minimum; max, maximum; n, number; SD, standard deviation.

Notes: * Due to very small increment on CDF entry in one case. However, when removing this TA the overall direction of results remained the same, and the size remained similar.

**There were no instances where the increment remained the same between submissions; therefore, in six (46%) instances the increment decreased.

In the original appraisal, observed LYs were routinely underestimated compared with the resubmission for both the intervention and comparator arms

An increase in LYs was observed in most TAs, with eight TAs (62%) experiencing an increase in intervention LYs and nine TAs (69%) experiencing an increase in comparator LYs. Additionally, on average, LYs increased by nearly 10% between submissions for the intervention (9.83%) and comparator (9.05%) arms, respectively.

As 11 of the 13 TAs we analysed were for immuno-oncology (IO) therapies, our findings are consistent with literature that has previously analysed OS predictions over time.[4-6] In particular, a review of OS extrapolation in immune-checkpoint inhibitor (ICI) NICE TAs concluded that 'OS extrapolations employed by manufacturers and External Assessment Groups (EAGs) generally predicted OS reasonably well when compared to more mature data (when available), although on average they appeared to underestimate OS'.[4]

There is clearly a precedent for LY underestimation between CDF entry and exit. This, along with the findings of the wider literature noted above, may help to inform the expectations of manufacturers and decision makers who are anticipating longer follow up of OS data on the CDF.

There was an increase in the treatment benefit between CDF entry and exit submissions; however, this should be interpreted with caution

The mean LY increment (intervention LYs minus comparator LYs) increased by 11.79% from the original submission, suggesting an overall increase in the treatment benefit between submissions. The increase was slightly larger when looking exclusively at submissions for which LY data corresponded to the Committee's preferred assumptions. However, the standard deviation of the increment is high, highlighting uncertainty in the overall direction, magnitude and statistical significance of any changes over time. Despite this, we conclude that there is no evidence to suggest that NICE should anticipate routinely worse clinical outcomes at CDF exit based on more mature data, and that data collection in the form of longer follow up is often confirmatory of prior assumptions around the expected treatment benefit.

The ability to predict outcomes was greater with more mature data

Unsurprisingly, there were smaller changes in LYs between submissions where data were more mature at the time of CDF entry. However, even in submissions where the data were less mature on entry, and there were reasonably large changes in survival per arm between entry and exit, changes to the incremental LYs were much more modest. This could in part be due to either equivalent improvements in both intervention and comparator survival over time, or standardisation of assumptions for both the intervention and comparator in light of persistently immature data (such as assuming the same distribution in both treatment arms for extrapolation of survival outcomes). Alternatively, this may indicate that the data presented in the original submissions were able to accurately predict long-term incremental difference leading to very small changes in incremental LYs over time. As such, even when data are immature on initial submission, because the overall treatment benefit still does not appear to be subject to a high degree of change over time, decision makers should have more confidence that what they are observing through extrapolations is likely to be reflective of long-term patient outcomes; therefore, in some cases a baseline commissioning recommendation should be considered.

The change in QALYs between submissions was consistent with the change in LYs

Evidence suggests that similar results to the above can also be expected when looking at the change in QALYs between submissions. Based on seven TAs where full LY and QALY data were available, there was a strong correlation between changes in LYs and QALYs between submissions for the intervention, comparator and increment, respectively, i.e. the Pearson's correlation coefficient was very close to 1 in each case (Table 2).

As a result, NICE and manufacturers should be able to confidently predict that QALY outcomes will follow the same patterns observed in LYs, which helps to give a better indication of overall changes to cost-effectiveness. This may, at least in part, be due to there often being very little additional data on health-related quality of life presented between initial submission and CDF-exit.

Table 2
Correlation between QALYs and LYs

	Intervention	Comparator	Incremental
N of appraisals	7	7	7
Mean change in LYs	0.308	0.338	-0.029
Mean change in QALYs	0.120	0.135	-0.015
Correlation coefficient	0.985	0.988	0.975

Key: LY, life year; QALY, quality-adjusted life year.

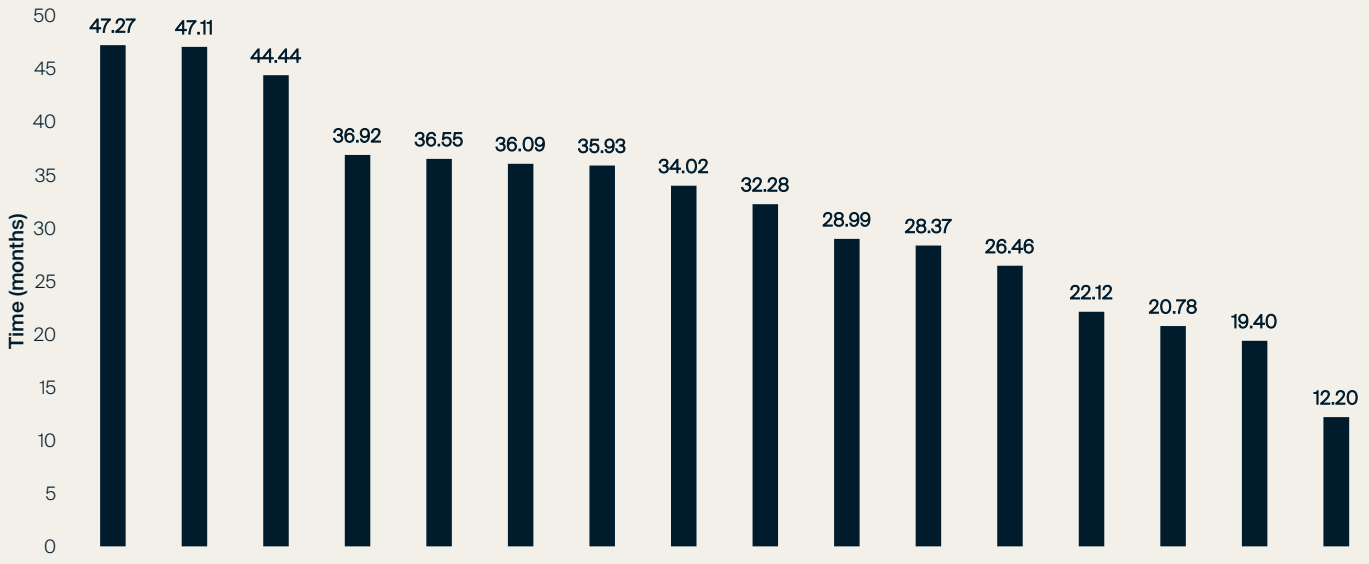
Time spent to resolve uncertainty in the CDF

Time spent in the CDF was primarily driven by data availability within the pivotal trial rather than additional real-world data collection.

In 94% of TAs, long-term survival outcomes were cited as a key source of uncertainty in the MAA, all of which aimed to resolve this through additional data collection from the pivotal trial. As a result, it is evident that for the vast majority of TAs, time actually spent in the CDF was driven by timing of subsequent trial data cuts, with very few TAs noting primary evidence collection during the managed access period from alternative sources.[7] The data show that often manufacturers are resubmitting to NICE with relatively short additional follow up (i.e. the next trial analysis), and in doing so, resubmissions are producing outcomes that are similar to the original submission as shown by minimal changes in LY outcomes. Consequently, this raises questions about the extent to which uncertainty is genuinely being resolved during the CDF period and whether in some cases a baseline commissioning recommendation could have been made instead.

Treatments spent on average 2.7 years on the CDF, just over half of the maximum allowed time of 5 years (see Figure 2). On average, treatments spent nearly a year longer on the CDF than the specified data collection period of 1.8 years, as per the MAA. In part, the additional time spent by treatments in the CDF may be attributed to the time taken to conduct the reappraisal process. In most cases CDF data collection adds relatively little additional follow up, which may potentially be driving the relatively small changes in incremental LYs between submissions.

Figure 2
*Time spent in the CDF by TA**



Key: CDF, Cancer Drugs Fund; NICE, National Institute for Health and Care Excellence; TA, technology appraisal.
Note: *Excludes TAs that did not resubmit to NICE i.e. TA465 (olaratumab had license withdrawn whilst in the CDF) and TA674 (CDF review of TA522) (appraisal was terminated).

Was uncertainty resolved on exit from the CDF?

NICE Committees make positive recommendations despite recognising remaining uncertainty at CDF exit

Despite the primary purpose of the CDF to allow time for companies to resolve data uncertainties, in the majority of resubmissions (63%) NICE still cited substantial remaining uncertainty in the data or that data collected within the CDF were limited. For example, in TA684, which received a positive recommendation in the full CDF indication, NICE highlighted that 'there are still not enough data from the Cancer Drugs Fund and the trial to be certain by how much nivolumab increases the length of time people live'.[8]

There may always be circumstances where CDF-mandated data collection is unable to fully resolve clinical uncertainty. This is a reality that will be further exacerbated by scope changes upon resubmission as part of the new managed access exit criteria set out in NICE's new manual for health technology evaluations.

If a more pragmatic view was taken as to whether managed access was likely to resolve the clinical uncertainty rather than simply delaying the same questions by several years, it may be possible for more medicines to be recommended for use in routine commissioning at the time of the initial appraisal.

What does the future hold for the CDF?

Recent related research has already highlighted that there is currently a high success rate for submissions exiting the CDF.[9] Additionally, we found that there are positive signs for manufacturers regarding sustained treatment benefits in LYs and QALYs at resubmission, based on relatively accurate initial predictions at CDF entry.

However, the extent to which the trend will continue in light of changes to NICE's methods and processes for TA implemented this year is uncertain. The introduction of the severity modifier will be key given that we know achieving end-of-life (EOL) eligibility has been critical for many entrants onto the CDF. A rescope following CDF exit means manufacturers may be asked to address an alternative Decision Problem on resubmission, adding an additional layer of planning and unpredictability.

The evidence from existing CDF appraisals demonstrates that, on average, incremental LY and QALY estimates, and by extension cost-effectiveness, were quite accurate, particularly where data were more mature in the original submission. This analysis raises some thoughts as to the extent of the value added through spending time on the CDF. This may be because many treatments spend a relatively short amount of time (2-3 years) in the CDF. This suggests that a new balance may need to be struck between NICE and manufacturers in considering which treatments should enter the CDF to resolve genuine uncertainty surrounding long-term clinical outcomes and for how long. Some treatments should be considered more seriously for routine commissioning based on commonly observed levels of uncertainty, for which outcomes may be generally predictable within the original submission.

Moreover, the requirement for a full TA on entry to and exit from the CDF places a significant amount of resource burden on NICE, manufacturers, and other stakeholders involved in TAs. A pilot is planned via the HTA Lab to introduce a process for rapid entry into managed access. This may help address the current resource burden of the process, if a sufficiently pragmatic approach can be found to make early decisions about medicines which are suitable for managed access.[10]

Acknowledgments

This research was supported by The Association of the British Pharmaceutical Industry (ABPI)

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Appendix

CDF exit submissions (CDF entry submission)	Drug	Indication
TA524 (CDF review of TA446)	Brentuximab vedotin	Lymphoma
TA531 (CDF review of TA447)	Pembrolizumab	NSCLC
TA629 (CDF review of TA472)	Obinutuzumab with bendamustine	Lymphoma
TA653 (CDF review of TA416)	Osimertinib	NSCLC
TA655 (CDF review of TA483)	Nivolumab	NSCLC
TA674 (CDF review of TA522)	Pembrolizumab	Urothelial cancer
TA683 (CDF review of TA557)	Pembrolizumab	NSCLC
TA684 (CDF review of TA558)	Nivolumab	Melanoma
TA687 (CDF review of TA593)	Ribociclib	Breast cancer
TA691 (CDF review of TA517)	Avelumab	Metastatic Merkel cell carcinoma
TA692 (CDF review of TA519)	Pembrolizumab	Urothelial cancer
TA713 (CDF review of TA484)	Nivolumab	NSCLC
TA725 (CDF review of TA579)	Abemaciclib	Breast cancer
TA736 (CDF review of TA490)	Nivolumab	Squamous cell carcinoma of the head and neck
TA770 (CDF review of TA600)	Pembrolizumab	NSCLC
TA766 (CDF review of TA553)	Pembrolizumab	Melanoma
TA780 (CDF review of TA581)	Nivolumab	Renal cell carcinoma
TA465*	Olaratumab	Soft tissue sarcoma

Key: LY, life year; QALY, quality-adjusted life year; NSCLC, non-small-cell lung cancer; TA, technology appraisal.

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