Uncertainty in NICE appraisals of cancer drugs: implications for the Cancer Drugs Fund

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Background

The Cancer Drugs Fund (CDF) in England has recently been transformed into a Managed Access Fund (MAF). The MAF will provide conditional funding for cancer drugs where there is uncertainty in the economic case. A requirement for funding is that the uncertainty will be be addressed by generating "real world" data (RWD) during two years' use in-practice, to inform a subsequent review and decision.

Aim

Explore the types of uncertainty encountered in recent cancer submissions to NICE, identify illustrative examples, and consider the extent to which these can be resolved through RWD

Methods

Technology Appraisals for cancer drugs for the period January 2014-March 2016 were accessed via the NICE website. The summary tables from Section 4 of the Appraisal documents were reviewed, details of uncertainty in the evaluation extracted, and analysed for common themes. Comments on uncertainty were classified by where they occurred in the document, as a proxy for the degree of concern to the Appraisal Committee.

Results

29 appraisals of the 33 published in the study period were included in the analysis. 4 non-submissions were excluded.

18 were recommended by NICE for funding, with a further 5 optimised recommendations restricted to specified patient groups. 6 were not recommended.

Uncertainty itself did not drive funding decisions

	Uncertainty level	
Decision	'Low'	'High'
Recommended	7	11
Optimised	1	4
Not recommended	2	4

Radium in prostate cancer: multiple uncertainties, acceptable cost per QALY*

Ramucirumab in gastric cancer: one major uncertainty, high cost per QALY*

Trastuzumab in breast cancer: minor uncertainties, high cost per QALY*

Pomalidomide in multiple myeloma: multiple uncertainties, high cost per QALY *

*QALY: unit of health (quality-adjusted life year)

Thematic analysis of comments on uncertainty identified **survival data** and **comparators** as the main sources of uncertainty

Theme	All Technology Appraisals (n=29)	Uncertain Technology Appraisals (n=19)
Immature survival data	27	16
Appropriateness of comparators	16	10
Trial issues	15	8
Cost estimates	8	4
Quality of Life data	19	4
Relevant patient population	18	4

Common themes

Less common, but tend to contribute to the most uncertain appraisals

Frequent, but less in the most uncertain appraisals

Trial uncertainty: crossover, and differences in drug regimens or dosages compared to UK practice.

Cost: impact of Patient Access Schemes, adverse event management, dosing, and vial sharing.

Patient population: trial patients may not perfectly reflect intended UK usage, such as subgroups defined by mutations, or prior lines of treatment.

Quality of Life data: capture effects on morbidity, and are estimated if they have not been directly measured in the trials.

Resolution by RWD? Feasible

Survival data uncertainty occurs when trial follow-up is short, relative to the lifetime horizon used in the cost-effectiveness analysis. Extrapolation introduces uncertainty in the choice of statistical model used.

- afatinib in non-small cell lung cancer: less than 30% of patients in the trial had died, so median survival could not be presented
- aflibercept in metastatic colorectal cancer: 15 year model horizon, extrapolated from a trial with 2 years' median follow-up

Resolution by RWD? Unlikely over 2 years, unless survival is very short, or the original trial continues

Comparators: no direct data against the relevant UK comparator

- enzalutamide in prostate cancer: data vs. placebo
- bortezomib in multiple myeloma: data vs. a regimen not used in the UK
- pomalidomide in late stage multiple myeloma: no defined current best practice

Resolution by RWD? Challenging: patients assigned to treatment alternatives are clinically different, so outcome differences cannot be attributed to the treatments

Discussion

The main types of uncertainty relate to overall survival estimates and availability of valid UK comparator data. These are described as structural uncertainty, where the uncertainty is due to assumptions that need to be made for modelling, rather than parameter uncertainty which are the data put into the model. Neither survival nor comparator uncertainty can readily be resolved by 2 years' conditional funding with real-world data collection within the reformed structure of the CDF.
The other sources of uncertainty are more amenable to resolution through RWD, and it is cases with these sources of uncertainty we might expect to see receiving conditional funding through the reformed CDF.

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