Reliance on 'real world' observational data poses threat to patient outcomes: further reform to the Cancer Drugs Fund is required

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The Cancer Drugs Fund (CDF) reforms were an excellent opportunity to generate evidence on the effectiveness of new cancer drugs: unlike the previous arrangements, they require data collection on patients' outcomes. However, the reforms' reliance on 'real world' (observational) data, will not generate reliable evidence of effectiveness. We propose an alternative model for the CDF that would establish which drugs are relatively effective, by conducting timely Randomised Controlled Trials (RCTs) within routinely collected data sources. The current CDF encourages early access to drugs, with high prices but uncertain benefits, whereas our proposal will provide high quality evidence for future NICE decisions, and therefore larger gains in population health.

The original CDF was introduced in England in 2010/11 with a £50m budget which grew to £340m in 2015/16 without evidence of patient benefits.[1] Following the reforms, NICE is responsible for appraising all new cancer drugs which will be funded if there is a chance they will be shown to be cost-effective after two years of 'real world' data collection. However, once a drug is recommended, precedent suggests it is very difficult to stop use. For example, NHS funding for Beta Interferon for patients with Multiple Sclerosis continued after an independent evaluation that used 'real world' data found it did not improve patient outcomes.[2]

The CDF reforms will not encourage manufacturers to conduct RCTs, and NICE will have to make decisions without trial evidence. The central role given to 'real world' data is a major cause for concern. For such observational data to provide accurate estimates of relative effectiveness, requires that outcomes are compared for patients who do, and do not, take the new drug, but who have similar prognostic characteristics.[3] However, key characteristics will be unmeasured, and so the effectiveness estimates will be biased due to residual confounding. The conduct of observational studies must also avoid manipulation by those with vested interests. The presumption that, without addressing these profound difficulties, 'real world' data can provide unbiased evidence, ignores all we know about good research design for identifying causal effects, and the reasons why well-designed RCTs are the cornerstone of evidence-based medicine.[4]

Instead, we propose that NICE makes 'only in research' recommendations, whereby these drugs are only available within pragmatic, low-cost RCTs. These studies should be designed to provide timely, unbiased estimates of effectiveness, by routinely randomising patients to the new drug versus current practice, at the point-of-care within the NHS.[5] While routine randomisation can provide timely results, this can only be achieved with strong support from funders, ethics committees, regulators and central government, and if a research culture is embedded within the NHS.[6] These trials require clinician time to recruit patients, and investment in informatics,[5] but the costs will be low compared to the CDF budget. Furthermore, follow-up data can be collected from the UK's high-

quality routinely collected clinical datasets, including the world's largest cancer registry, linked to existing radiotherapy and chemotherapy datasets such as Anti-Cancer Therapy (SACT) data set (see [7] for details, including limitations), and to sources of electronic health records such as the Clinical Practice Research Datalink (CPRD). Future trials could be linked to cohorts with genetic information.

These RCT designs can be flexible, and provide a platform for new drugs as they emerge. Multi-Arm Multi-Stage trials, in particular, allow more treatments to be assessed than traditional 2-arm trials, and enable the range of patient subgroups and treatments to 'adapt' as the data provide insights about which patients respond best to which drugs.[8] These trials can recruit patients from within observational databases, and include international centres to improve statistical power and generalisability.

For some new cancer drugs, an NHS-funded RCT may provide insufficient additional value to justify the costs.[9] If there is an ongoing trial for regulatory purposes it may be more efficient to delay a NICE decision, pending availability of evidence on long-term outcomes from the regulatory trial. For drugs where any RCT is judged unethical or impractical, then careful non-randomised studies should be conducted to minimise confounding, by collecting longitudinal data on all relevant prognostic characteristics and outcomes for patients receiving and not receiving the new drug. To reduce residual confounding, studies should collect data on characteristics that predict treatment selection, but are unrelated to outcomes.[10]

The CDF reforms, related initiatives such as the Accelerated Access Review,[11] and comparative effectiveness research such as from using Surveillance, Epidemiology and End Results (SEER)-Medicare–linked data,[12] all rely on 'real world' data. These initiatives will undermine the evidence base for clinical practice; once these products are in widespread use, randomisation will be impossible. Instead, we propose a CDF that permits initial use only within rapid, flexible and efficient RCTs. Building NHS capacity for this programme would capitalise on the UK's strength in trials, generate long-term evidence of value worldwide, and yield large benefits to patients.

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