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# Articles



# Population-health impact of new drugs recommended by the National Institute for Health and Care Excellence in England during 2000–20: a retrospective analysis

Huseyin Naci, Peter Murphy, Beth Woods, James Lomas, Jinru Wei, Irene Papanicolas

### **Summary**

Background Health systems experience difficult trade-offs when paying for new drugs. In England, funding recommendations by the National Institute for Health and Care Excellence (NICE) for new drugs might generate health gains, but inevitably result in forgone health as the funds cannot be used for alternative treatments and services. We aimed to evaluate the population-health impact of NICE recommendations for new drugs during 2000–20.

Methods For this retrospective analysis, we identified technology appraisals for new drugs in England published in NICE's publicly available database of appraisals between 2000 and 2020. We excluded products with terminated appraisals, not recommended, or subsequently withdrawn from the market and excluded appraisals in programmes focusing on medical devices, diagnostics, or interventional procedures. We included drugs that underwent NICE appraisal within 5 years of initial regulatory approval. We collected data on drug name, appraised indication, and specific features of both the drug and its appraisal. We noted the value for money offered by new drugs, expressed as the incremental cost-effectiveness ratio (ICER), and data on health benefits, expressed as quality-adjusted life-years (QALYs). We estimated the number of patients receiving new drugs recommended by NICE using proprietary data on the total volumes of new drugs sold in England between Jan 1, 2000, and Dec 31, 2020. We calculated the net health effect of each appraisal using the difference between the incremental QALY gains from implementing the new drug within the National Health Service (NHS) and the estimated QALYs that could hypothetically be obtained by reallocating the same funds to other NHS services or treatments. We obtained forgone QALYs by dividing the incremental cost of the new drug by the health-opportunity cost of NHS expenditure.

Findings NICE appraised 332 unique pharmaceuticals between 2000 and 2020; 276 (83%) had positive recommendations. Of these 276, 207 (75%) had a NICE appraisal within 5 years of regulatory approval. We included 183 (88%) of 207 drugs in this analysis, after excluding drugs that did not meet eligibility criteria. The median QALY gain across all 339 appraisals was 0.49 (IQR 0.15-1.13), equivalent to an additional half a year in full health. Median ICER for recommending new drugs increased from £21545 (IQR 14175–26173) per QALY gained for 14 appraisals published between 2000 and 2004 to £28555 (19556–33712) for 165 appraisals published between 2015 and 2020 (p=0.014). Median ICER varied by therapeutic area, ranging from £6478 (3526–12912) for 12 appraisals of anti-infective drugs to £30000 (22395–45870) for 144 appraisals of oncology drugs (p<0.0001). New drugs generated an estimated 3.75 million additional QALYs across 19.82 million patients who received new drugs recommended by NICE. The use of new drugs resulted in an estimated additional cost to the NHS of £75.1 billion. If the resources allocated to new drugs had been spent on existing services in the NHS, an estimated 5.00 million additional QALYs could have been generated during 2000–20. Overall, the cumulative population-health impact of drugs recommended by NICE was negative, with a net loss of approximately 1.25 million QALYs.

Interpretation During 2000–20, NHS coverage of new drugs displaced more population health than it generated. Our results highlight the inherent trade-offs between individuals who directly benefit from new drugs and those who forgo health due to the reallocation of resources towards new drugs.

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### Introduction

Few decisions in health care lead to as much controversy as those concerning the funding, or lack thereof, of new drugs. New drugs typically have a small evidence base supporting their use upon regulatory approval worldwide.<sup>12</sup> Despite uncertainties in the evidence base, new drugs typically have higher prices than existing options within health-care systems.<sup>3</sup> This combination of uncertain clinical effectiveness and higher prices has historically resulted in substantial regional and global variation in funding decisions and patient access to new drugs.<sup>45</sup>

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Department of Health Policy, London School of Economics and Political Science, London, UK (H Naci PhD); Centre for Health Economics (P Murphy PhD, B Woods PhD) and Department of Economics and Related Studies (J Lomas PhD), University of York, York, UK; Centre for Health System Sustainability, School of Public Health, Brown University, Providence, RI, USA (J Wei MSc, I Papanicolas PhD)

Correspondence to: Dr Huseyin Naci, Department of Health Policy, London School of Economics and Political Science, London WC2A 2AE, UK h.naci@lse.ac.uk

#### **Research in context**

#### Evidence before this study

Previous research has characterised clinical evidence that supports the regulatory approval and health-technology assessment of new drugs in Europe and the USA, highlighting deficiencies in the strength of the evidence underlying approval and funding decisions, and has shown that the prices of new drugs are high and increasing globally, raising questions about their cost-effectiveness. We searched MEDLINE from database inception to Sept 25, 2024, with no language restrictions using various combinations of the search terms "drugs", "medicines", "pharmacotherapy", "net health benefit", "opportunity cost", and "population health" to identify studies evaluating the net health effects of new drugs worldwide. Although some observational studies indicated that new drugs have contributed to increases in life expectancy at the population level during the past four decades, no research has examined the overall population health impact of new drugs while considering both health benefits and health forgone from allocating finite resources towards the new drugs and away from alternative health-care priorities.

# Added value of this study

We estimated the number of patients who received new drugs recommended by the National Institute for Health and Care

The National Institute for Health and Care Excellence (NICE), originally established as the National Institute for Clinical Excellence in 1999, aimed explicitly to address this "post-code prescribing" in England.<sup>6</sup> One of the primary responsibilities of NICE is to provide funding recommendations for the National Health Service (NHS) in England. NICE bases its recommendations on "an assessment of population benefits and value for money".<sup>7</sup> A core principle guiding NICE's work is consideration of "the 'opportunity cost' of recommending one intervention instead of another", as is accounting for the forgone benefits of spending finite resources.<sup>7</sup>

The value for money of new drugs recommended by NICE has consequences for population health. Under a constrained budget, the choice to fund a new drug for one patient group might mean forgoing the funding of interventions and services that would deliver benefits for others.8 NICE advises its committees to consider new drugs as offering value for money, and thus suitable for funding within the NHS, if they cost less than £20000-30000 per additional year of full health gained, measured as quality-adjusted life-years (QALYs).9 Historically, there has not been any empirical basis for NICE's funding threshold.10 Analyses examining the relationship between NHS expenditure and health outcomes have suggested that the NHS spends approximately £15000 to generate an additional year of full health with existing services, which is used by the UK Department of Health and Social Care.11,12 Thus, spending more than this amount could harm population health as

Excellence (NICE) in England during 2000–20, documenting the population-level health and economic impacts of new drugs across multiple therapeutic areas. We also estimated the health effects of services that could not be funded due to the allocation of resources to new drugs. We estimated that new drugs displace more health than they generate at the population level. To our knowledge, this is the first evaluation of the overall population health impact of new drugs.

#### Implications of all the available evidence

Our finding emphasises the trade-offs and implicit prioritisation of people who will directly benefit from new drugs at the expense of people who will not. An important policy consideration is whether NICE's threshold should better align with the estimate of health-opportunity costs of National Health Service expenditure of the Department of Health and Social Care. Presenting NICE recommendations relative to the health-opportunity cost threshold would convey trade-offs in funding decisions. Future research should explore the implementation of NICE funding recommendations by decision makers.

it might displace more health than it generates. Understanding the net health effects of the funding decisions of NICE on population health is essential, considering both the value for money of new drugs and the implication of disinvestment in other areas.

We aimed to evaluate the population-health impact of NICE recommendations for new drugs during 2000–20. We aimed to characterise the additional health benefits and value for money offered by new drugs by systematically reviewing publicly available appraisal reports. We then aimed to quantify the net health effects per patient across different therapeutic areas and estimate their net population health effects by considering the number of patients who received drugs recommended by NICE.

### Methods

#### Data sources

For this retrospective analysis, we manually searched for and identified technology appraisals for new drugs in England published from 2000 in NICE's publicly available database of appraisals.<sup>13</sup> To account for the increasing frequency of redacted information in NICE documents, we included appraisals published up to 2020.<sup>14,15</sup> We excluded products with terminated appraisals, not recommended, or subsequently withdrawn from the market. Appraisals in NICE's Highly Specialised Technologies programme and other programmes focusing on medical devices, diagnostics, or interventional procedures were not included.

We included drugs that underwent NICE appraisal within 5 years of initial regulatory approval. We therefore differentiated between new drugs, often associated with higher prices and less comprehensive evidence,23 and those that have been available on the market for longer durations (appendix p 3).

To identify all approved indications of new drugs, we reviewed the British National Formulary and mapped the corresponding indications appraised by NICE.16 We included all subsequent appraised indications of drugs as long as the initial NICE appraisal for any indication occurred within the first 5 years of regulatory agency approval. For indications with updated appraisals, we considered the year of the first positive appraisal. Our final dataset included one technology appraisal per indication appraised by NICE with a positive funding recommendation.

#### **Data extraction**

We collected data on drug name, appraised indication, and specific features of both the drug and its appraisal. We established whether the drug indication had an orphan designation (ie, a designation for the treatment of rare diseases) from the European Medicines Agency at the time of NICE appraisal,17 whether the NICE technology appraisal committee concluded that the drug was innovative,<sup>18</sup> and whether the appraisal met NICE's end-of-life criteria that had been in place since 2009 and remained in place for the duration of our analysis.<sup>19</sup> The data extraction process was conducted independently by two researchers, one of which was PM. Consensus was reached through discussion, and a third researcher (HN) verified all extracted data.

We noted the value for money offered by new drugs, expressed as the incremental cost-effectiveness ratio (ICER; panel),<sup>20,21</sup> which is calculated by dividing the difference in total costs (ie, the incremental cost) by the difference in health benefits (ie, the incremental health benefits). This process provides a ratio that shows the extra cost per additional unit of health. NICE uses QALYs as the measure of health benefit; one QALY represents 1 year in full health.<sup>22</sup> Use of QALYs facilitates comparison of ICERs across therapeutic areas and with alternative uses of health system resources. OALYs, costs, and ICERs are typically estimated for the lifetime of a patient. As the clinical-trial evidence used to support approval of new drugs provides a much shorter period of follow-up, NICE generally considers lifetime outcomes estimated with decision-analytical models that combine evidence from a range of sources, such as randomised clinical trials, observational studies, and resource-use studies. Comparators in NICE costeffectiveness analyses represent the NHS standard of care.9

We extracted the preferred ICER of the NICE technology appraisal committee from the final appraisal document. If the preferred ICER of the committee was unavailable, we conducted a hierarchical review considering public committee slides summarising the available data, evidence review group reports, and manufacturer submissions (appendix p 3).

We then extracted incremental QALYs and costs corresponding to the extracted ICERs from NICE See Online for appendix documentation following the same hierarchical approach. When matching incremental QALYs were unavailable in NICE documentation, we systematically checked corresponding information from other sources (appendix p 3). We back-calculated missing incremental costs using imputed incremental QALYs and extracted ICERs. When manufacturers offered confidential price reductions during the NICE appraisal process, the final ICERs reflected these reductions and were factored into the incremental costs used in our analysis. The costs and ICERs reflected the actual prices in nominal terms at the time of appraisal, with discounting already applied.

#### Panel: Key terms

#### Incremental cost-effectiveness ratio

A summary measure that represents the additional cost required to achieve an additional unit of health outcome with a new treatment, compared with an alternative. Calculated by dividing the difference in total costs (ie, the incremental cost) by the difference in health benefits (ie, the incremental health benefits). Low incremental cost-effectiveness ratios indicate better value for money than high incremental costeffectiveness ratios.

#### Net health effect

A summary measure that quantifies the impact of a new treatment, considering both the health benefits of the new treatment and the health benefits forgone elsewhere due to allocation of resources to the new treatment. A negative net health effect indicates that the health benefits of the new treatment do not sufficiently offset the health losses incurred from diverting resources away from alternative health-care services.

#### Opportunity cost

Health benefits that are forgone because of the implementation of a new treatment. In a health system with a fixed budget, increased costs required to pay for a new treatment might displace other health-care services that are already being provided or could be provided if funds were available. In such cases, opportunity cost refers to the health benefits lost due to the displacement of existing activities to fund the new treatment.

#### Quality-adjusted life-years

A health-outcome measure that combines the effects of improvements in both the quantity and quality of life associated with a treatment. Full health is assigned a value of 1 and death is assigned a value of 0. A year spent with a guality of life that is considered to be half that of someone in full health would be equal to 0.5 quality-adjusted life-years.

Therefore, we did not apply additional discounting, as our goal was to assess the reasonableness of the decisions at the time they were made.

## Estimation of patient numbers

As the NHS does not centrally collect information on prescription drug use in both primary and secondary care settings,23 we procured proprietary data on the total volumes of new drugs sold in England between Jan 1, 2000, and Dec 31, 2020, from IQVIA Multinational Integrated Data Analysis System (MIDAS). MIDAS records data on the volume of branded and generic products dispensed in both retail and hospital pharmacies. Data sources are manufacturers, wholesalers, and hospital and retail pharmacies. MIDAS is not limited to NHS sales, as it captures the small number of private prescriptions dispensed by community pharmacists and used for patients treated privately on NHS wards (but not in private hospitals). This dataset is the most comprehensive source of pharmaceutical sales volume data in England and is used to evaluate drug use by the UK Government.24-26

Sales data were available in standard units, a measure of volume defined by IQVIA to represent the smallest common dose of a product form. To calculate the total patient days on therapy, we divided the standard units for each drug by the defined daily doses (DDDs). DDDs represented the assumed mean maintenance dose per day for a drug used in its approved indication. The DDD is a method developed by WHO to standardise medicines



**Figure 1: Incremental health benefits of new drugs recommended by NICE in England during 2000-20** Incremental health benefits per patient associated with appraisals of new drugs recommended by NICE over time (A) and by therapeutic area (B). The figure includes all 339 appraisals for 183 new drugs recommended by NICE in our sample. The figure excludes outliers (ie, values that deviated from the IQR by more than 1-5; appendix p 13). High values indicate greater health benefits than existing alternatives. Boxes show median and IQR. Whiskers show minimum and maximum. NICE=National Institute for Health and Care Excellence. QALYs=quality-adjusted life-years.

of varying doses.<sup>27</sup> If DDD factors were not available from WHO, we used those calculated by IQVIA to monitor global use of new medicines.<sup>28</sup>

To estimate the number of patients receiving the new drugs in their appraised indications, we divided the total patient days on therapy by the mean duration of treatment. Information on treatment duration was sourced from NICE documents and targeted literature searches (appendix p 4). We used IQVIA MIDAS Disease to obtain information on the relative share of use in different indications. This dataset estimates indication-level use based on repeated cross-sectional surveys of prescribers in European countries. We allocated total patient days based on share of use within each indication. We then divided the total patient days on therapy by its corresponding treatment duration (appendix p 4).

### Statistical analysis

We summarised appraisal-level incremental QALY gains and ICERs using median (IQR) data over time, by therapeutic area, and by features of the drug and appraisal (ie, orphan, innovation, and end-of-life criteria). We compared medians using a non-parametric *k*-sample test in Stata version 18.

We then calculated the net health effect per patient for each appraisal.<sup>29</sup> Net health effect represents the difference between the incremental QALY gains from implementing the new drug within the NHS and the estimated QALYs that could hypothetically be obtained by reallocating the same funds to other NHS services or treatments. We obtained forgone QALYs by dividing the incremental cost of the new drug by the healthopportunity cost of NHS expenditure. We used £15000 per QALY gained as the estimate of healthopportunity cost, consistent with the UK Department of Health and Social Care impact assessments and empirical evidence on the productivity of NHS spending.<sup>11,12,30-32</sup> This process implies that for every  $f15\,000$  allocated to new medicines expenditure, 1 QALY is forgone by patients elsewhere in the health system. A positive net health effect indicates that the appraisal recommendation improves health outcomes, whereas a negative net health effect suggests that the health benefits of the new drug do not adequately offset the health losses resulting from the reallocation of health-care funding to accommodate the new drug.29

We then estimated the total number of QALYs gained with each drug at the population level by multiplying the patient numbers by the incremental QALYs. Similarly, we calculated the total additional spending on each drug by multiplying the patient numbers by incremental costs.

To estimate the total number of QALYs that could have been gained if the same costs had been allocated elsewhere, we divided the total additional cost of the new drugs by the Department of Health and Social Care's health-opportunity cost estimate (ie,  $\pounds$ 15 000 per QALY). Finally, we estimated the population health impact of

For **IQVIA MIDAS** see https:// www.iqvia.com/solutions/ commercialization/brandstrategy-and-management/ market-measurement/midas] new drugs recommended by NICE by comparing the total QALYs gained and the total QALYs that could have been gained during 2000–20.

We conducted multiple sensitivity analyses (appendix p 6). First, we restricted our analysis to data from 2010 to 2020, to focus on the population health impact of more recently appraised drugs. Second, we evaluated the impact of more or fewer patients receiving the new drugs by changing the mean treatment duration. Third, we considered the impact of reduced incremental costs for drugs with generic or biosimilar alternatives. Fourth, we considered how alternative opportunity cost thresholds impact net health effects. Fifth, for drugs with multiple indications, we assumed that all use occurred in the indication with the lowest or highest ICER.

All analyses were done in Stata version 18.

#### Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

# Results

NICE appraised 332 unique pharmaceuticals between 2000 and 2020; 276 (83%) had positive recommendations. Of these 276, 207 (75%) had a NICE appraisal within 5 years of regulatory approval. We included 183 (88%) of 207 drugs in this analysis, after excluding drugs that did not meet eligibility criteria (appendix p 9).

The 183 drugs included had regulatory approvals for use across 385 indications. 287 (75%) of 385 indications received positive recommendations in 339 separate NICE appraisals conducted between 2000 and 2020 and were included in our analysis (appendix p 9). Oncology comprised 154 (45%) of 339 appraisals, followed by 71 (21%) appraisals for immunology, and 27 (8%) appraisals for the vascular system. 191 (56%) of the 339 appraisals were published between 2015 and 2020. During 2000–20, 35 (19%) of 183 NICE-recommended new drugs had generic or biosimilar alternatives.

The median QALY gain across all 339 appraisals was 0.49 (IQR 0.15–1.13), equivalent to an additional half a year in full health (figure 1A). Median QALY gains were 0.35 (0.17–0.78) for 16 appraisals published between 2000 and 2004 and 0.59 (0.17–1.30) for 191 appraisals published between 2015 and 2020 (p=0.046). There was significant variation across therapeutic areas, ranging from 0.07 (0.02–0.22) additional QALYs gained for the 27 appraisals of vascular-system drugs to 0.74 (0.32–2.53) for 16 appraisals of anti-infective drugs (p<0.0001; figure 1B).

Median ICER for recommending new drugs increased from £21545 (IQR 14175–26173) per QALY gained for 14 appraisals published between 2000 and 2004 to £28555 (19556–33712) for 165 appraisals published between 2015 and 2020 (p=0.014; figure 2A). Median ICER varied by therapeutic area, ranging from £6478



*Figure 2*: Value for money of new drugs recommended by NICE in England during 2000–20

ICERs over time (A) and by therapeutic area (B). The figure includes only 292 appraisals in the northeast quadrant, where new drugs generated more health gains but were more expensive; it excludes 47 appraisals with ICERs outside of the northeast quadrant (ie, 40 cost-saving drug indications, four appraisals with cost comparisons for drug indications that incurred costs but added QALYs, and three QALY-reducing drug indications). The figure excludes outliers (ie, values that deviated from the IQR by more than 1-5; appendix p 16). High values indicate less cost-effective results than comparator treatments. Boxes show median and IQR. Whiskers show minimum and maximum. Black dotted lines show the NICE end-of-life criteria threshold (ie, £50 000 per QALY). Green dashed lines show the NICE cost-effectiveness threshold (£15 000 per QALY). Red dashed lines show the National Health Service health-opportunity cost threshold (£15 000 per QALY). Red and life-years.



Figure 3: Net health effects of new drugs recommended by NICE in England during 2000-20 Net health effects per patient of 183 new drugs recommended by NICE over time (A) and by therapeutic area (B). The figure includes all 339 appraisals for 183 new drugs recommended by NICE in our sample. The figure excludes outliers (ie, values that deviated from the IQR by more than 1-5; appendix p 20). Positive values indicate more health is gained than lost per patient. Boxes show median and IQR. Whiskers show minimum and maximum. NICE=National Institute for Health and Care Excellence. (IQR 3526–12912) for 12 appraisals of anti-infective drugs to  $f_{30000}$  (22395–45870) for 144 appraisals of oncology drugs (p<0.0001; figure 2B).

When considering the anticipated loss of QALYs elsewhere in the NHS due to increased costs of new drugs, 233 (69%) of 339 appraisals resulted in negative net health effects. Median net health effect per patient was -0.06 (IQR -0.49 to 0.04) for appraisals published between 2000 and 2004; -0.15 (-0.40 to 0.01) for appraisals published between 2005 and 2009; -0.07 (-0.49 to 0.06) for appraisals published between 2010 and 2014; and -0.30 (-1.19 to 0.01) for appraisals published between 2010 and 2014; and -0.30 (-1.19 to 0.01) for appraisals published between 2015 and 2020 (p=0.080; figure 3A). Median net health effect per patient varied by therapeutic area, ranging from -0.52 (IQR -1.52 to -0.18) for appraisals in oncology to 0.97 (0.15 to 1.99) for appraisals in anti-infectives (p<0.0001; figure 3B).

During 2000–20, we estimated that 19.82 million patients received new drugs recommended by NICE. The estimated number of patients receiving these drugs varied by therapeutic area, ranging from 0.17 million for anti-infectives to 7.53 million for vascular-system treatments.

The use of new drugs resulted in an estimated additional cost to the NHS of  $\pounds$ 75.1 billion. The therapeutic areas that contributed most to these additional costs were immunology ( $\pounds$ 25.7 billion), oncology ( $\pounds$ 22.7 billion), and the vascular system ( $\pounds$ 16.0 billion; figure 4A).

New drugs generated an estimated 3.75 million additional QALYs (figure 4B). Of these, an estimated 1.10 million additional QALYs were attributable to new

drugs used in immunology, 0.97 million additional QALYs were attributable to those used for the vascular system, and 0.64 million additional QALYs were attributable those used in oncology. If the resources allocated to new drugs had been spent on existing services in the NHS, an estimated 5.00 million additional QALYs could have been generated during 2000–20 (figure 4C). 1.71 million QALYs were forgone in immunology, 1.51 million QALYs were forgone in oncology, and 1.07 million QALYs were forgone in the vascular system.

The net health effect of the use of new drugs recommended by NICE in the NHS was positive for antiinfectives, ophthalmological treatments, and drugs that we categorised as others (ie, respiratory, gastrointestinal, endocrine, orthopaedic, urology, dermatology, and mental health), which together resulted in approximately 0.36 million additional QALYs at the population level (figure 4D). However, the remaining therapy areas had a negative net health effect, with the use of oncology drugs accounting for a loss of 0.87 million QALYs at the population level.

The net health effect of new drugs became progressively more negative over time (figure 5A), driven primarily by the net impact of wider use of oncology and immunology drugs (figure 5B). Overall, the cumulative population health impact of drugs recommended by NICE was negative during 2000–20, resulting in a net loss of approximately 1.25 million QALYs. Incremental costs would have needed to be lowered by a median of 42% (IQR 13–53) at the time of NICE appraisal to ensure new drugs contributed positively to population health during 2000–20.



Figure 4: Additional costs, health benefits, and net health effects of new drugs recommended by NICE at the population level in England during 2000–20 Population-level additional costs (A), accrued health benefits (B), potential health benefits not realised (C), and net health effects (D) of 179 new drugs recommended by NICE, by therapeutic area. The figure excludes four drugs for which patient numbers could not be estimated (appendix p 9). We calculated additional costs and benefits by multiplying incremental costs and QALYs by the estimated number of patients receiving each drug for each indication. Health benefits not realised represent total QALYs that could have been achieved, assuming that the National Health Service spent £15000 to generate one QALY with existing treatments and services. We calculated net health effects as the difference between health benefits accrued and not realised, with negative values indicating a loss in population-level health. NICE=National Institute for Health and Care Excellence. QALYs-equality-adjusted life-years.

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Figure 5: Population-health impact of new drugs recommended by NICE in England during 2010-20

(A) Overall net health effects of 179 new drugs recommended by NICE over time and by therapeutic area. (B) Sum of net health effects for drug indications with positive and negative effects by therapy and year. The figure excludes four drugs for which patient numbers could not be estimated (appendix p 9). Negative values indicate that more QALYs could be gained if the additional resources required for new drugs were reallocated to other National Health Service treatments. NICE=National Institute for Health and Care Excellence. QALYs=quality-adjusted life-years.

In sensitivity analyses, the only scenarios yielding a positive health impact were when we assumed all use for each drug was in the most cost-effective indication, with the lowest ICER, and when we considered  $\pm 30\,000$  as an alternative measure of opportunity cost (figure 6).

### Discussion

We quantified the population health impact of new drugs recommended by NICE during 2000–20. New drugs generated the equivalent of 3.75 million additional years of full health. However, reallocating the extra expenditures on these new drugs to other NHS treatments and services could have potentially generated the equivalent of 5.00 million additional years of full health. Although the new drugs could have benefited patients who received them, their access came at a considerable cost for others who might have missed out on potential health gains due to necessary disinvestment or underinvestment in other forms of care to fund these newly recommended drugs.

NICE increasingly recommends drugs with ICERs that exceed its regular cost-effectiveness threshold.<sup>33</sup> Through explicit QALY weighting and other mechanisms, NICE prioritises patients with greater unmet needs and who could benefit from new drugs, valuing their health gains more than those of patients whose needs can be met



#### Figure 6: Sensitivity analyses

Sensitivity of net population health effects of 179 new drugs recommended by NICE considering different assumptions and scenarios. The figure excludes four drugs for which patient numbers could not be estimated (appendix p 9). Negative values indicate that more QALYs could be gained if additional resources required for new drugs were reallocated to alternative National Health Service treatments. ICER=incremental cost-effectiveness ratio. NICE=National Institute for Health and Care Excellence. QALYs=quality-adjusted life-years.

elsewhere in the NHS.<sup>34,35</sup> However, national surveys and qualitative studies have found no societal support for such prioritisation.<sup>36-38</sup> Moreover, this approach does not consider that the opportunity costs of drugs for patients with substantial unmet needs might affect others with similar needs in the NHS, thereby undermining the moral justification for funding recommendations.<sup>39</sup>

Our analysis makes an important contribution to the literature. We not only documented incremental QALY gains and ICERs over time, thereby expanding upon previous studies,40-43 but also used data on prescribing volumes to evaluate impacts at the population level for the first time, to our knowledge. Contrary to earlier studies suggesting that new drugs are associated with substantial population-level health gains worldwide,44-47 contributing to more than a third of life-expectancy gains in the past four decades,48 we found that the use of new drugs recommended by in England by the NHS had a negative overall impact on population health. Our results differ because earlier studies solely quantified the benefits of drugs, neglecting their potential healthopportunity costs. We considered the health benefits that could be derived from alternative uses of pharmaceutical expenditures, enabling us to calculate net health effects. Future research should explore the implementation of NICE's funding recommendations and document the trade-offs experienced by decision makers.

Our estimate of the forgone health benefits associated with funding new drugs is based on the UK Department of Health and Social Care's estimate of the health-opportunity cost of NHS expenditure.<sup>30</sup> This is the current best estimate of the expected health impact of reducing available health-care expenditures in the NHS.<sup>11,12</sup> Drugs recommended by NICE incur additional

costs and directly reduce resources available for the rest of the NHS. Therefore, we can use this figure to estimate the expected impact on health outcomes due to the displacement of other NHS services. Extensive literature has shown the robustness of the  $\pounds$ 15000 per QALY estimate.<sup>49-52</sup> By contrast, the established threshold of NICE (ie,  $\pounds$ 20000–30000 per QALY) has no empirical basis.<sup>53</sup>

The 2024 agreement between the UK Government and the pharmaceutical industry has committed NICE to retaining its cost-effectiveness threshold until 2029. An important policy consideration is whether NICE's threshold should better align with the Department of Health and Social Care's estimate of the healthopportunity cost of NHS expenditure.54 Doing so would ensure that the NHS does not pay more for the benefits of new drugs than it pays for the benefits of existing treatments and services. However, there is substantial opposition from the industry as reducing the threshold would result in reduced prices and, therefore, reduced industry profits. The NHS should balance promoting pharmaceutical innovation and ensuring the capacity of the system to deliver all forms of care that offer good value for money. Although a single threshold might not be the best approach to balance the objectives of population health and innovation, an appropriate price level would likely be equivalent to or less than the value commensurate with a threshold of  $f_{15000}$  per QALY for most products.55

The discrepancy between NICE's cost-effectiveness threshold and the health system's opportunity cost threshold highlights the incoherence in NICE's approach—its overt commitment to the principle of opportunity cost and population benefits despite using a threshold that does not accurately reflect NHS opportunity cost.<sup>39</sup> This discrepancy could jeopardise the legitimacy of NICE in supporting the NHS objective of maximising health gain with scarce resources.<sup>56–58</sup> The concept of opportunity cost remains challenging to implement in practice, and is often overlooked in decision-making processes.<sup>59–63</sup> Currently, NICE does not acknowledge the population-health consequences of recommendations that exceed the opportunity cost threshold of the health system.

Presenting committee recommendations relative to the health-opportunity cost threshold (ie,  $\pounds$ 15 000 per QALY) would convey the trade-off between individuals who directly benefit and other NHS users who might be deprioritised as existing interventions and NHS services are displaced to accommodate new drugs.<sup>64</sup> For example, NICE recommended trastuzumab for treatment of people with metastatic gastric cancer in 2010, with the committee considering an ICER of  $\pounds$ 43 206 per QALY gained as cost-effective. Expressing this outcome as 2.88 QALYs forgone per QALY gained would better elucidate the relative importance assigned to patients benefiting from the treatment compared with others

expected to forgo health.<sup>64</sup> At the population level, use of trastuzumab in people with gastric cancer led to an estimated 4000 QALYs lost during 2010–20. However, presenting recommendations in this way might be challenging for policy makers because of historical and ongoing commitments to the £20000–30000 per QALY threshold.

A prevailing perspective in pharmaceutical policy suggests that the negative health impact of high prices during the patent-protection period could be an acceptable trade-off if subsequent price reductions after patent expiration would mitigate any negative effects on population health.65 However, evidence relating to the availability, use, and pricing of generics and biosimilars suggests that this mitigation is often insufficient.66 During 2000-20, only 35 (19%) of 183 NICE-recommended new drugs had generic or biosimilar alternatives. Accounting for cost reductions after generic or biosimilar entry did not meaningfully change the population health impact. Overall, incremental costs would have needed to be lowered by a median of 42% (IQR 13-53) at the time of NICE appraisal to ensure new drugs contributed positively to population health during 2000-20.

Our findings reflect the features of the English NHS, which operates under a constrained budget and intense resource constraints.<sup>67</sup> The most important performance indicators of the NHS are no longer met.68 In this environment, paying high prices for new drugs can adversely affect population health, potentially more so than in systems with more budgetary flexibility. However, other health systems have similar challenges.69 As new innovations emerge with increased prices, opportunity cost will become even more important if the goal is to improve the health of many, not the few who will benefit from the new drug. Even in settings where additional funding can be made available to pay for new drugs, these resources could potentially yield greater health benefits if allocated to other treatments and services.70 Consequently, the concept of opportunity cost-and our methodology-is relevant for other health systems with higher and more flexible budgets.

Our analysis had limitations. First, the reliability of the extracted data regarding additional health benefits and value for money of new drugs was affected by redactions, which have become prevalent in the past 10 years.<sup>14,15</sup> Our freedom of information request for redacted incremental QALYs for a subset of appraisals was declined by NICE. Consequently, we used a systematic hierarchical approach to impute missing information from other sources. Unless redaction practices are reversed, similar analyses cannot be conducted in the future, undermining the accountability of NICE decisions. Second, we excluded a small number of new drugs that were later incorporated into clinical guidelines and for which technology appraisals were no longer available. These drugs might have been particularly cost-effective and their exclusion might have led to an underestimation of the positive impact of new drugs recommended by NICE on population health. Third, due to limitations in data availability, we developed a novel approach to estimate patient numbers by using sales volumes and indicationlevel treatment duration. Fourth, our estimation of patient numbers did not consider drug wastage, which could particularly affect infused drugs dosed by weight or body surface area.<sup>71</sup> As vial-sharing practices are common in the UK,<sup>72</sup> we did not consider this to be a major factor. Fifth, our analysis also did not account for rebates from pharmaceutical companies to the UK Government. However, given the relatively low payment rate during this period, rebates were unlikely to substantially influence our results.<sup>73</sup>

The potential negative impact of new drugs on population health might be greater than our findings suggest. First, when the NICE committees did not prefer a single estimate, we opted for the lowest ICER, thereby assuming that new drugs offered better value for money than they might in reality. Second, our analyses might have overestimated the health benefits of new drugs. Incremental QALYs in NICE documents are based on assumptions about the future performance of new drugs, which often have little evidence at the time of appraisal.<sup>74</sup> For example, most cancer drugs do not have evidence of their survival benefits when they undergo NICE assessment.<sup>75,76</sup> Nevertheless, NICE cost-effectiveness models frequently assume long-term clinical gains on the basis of surrogate endpoints.77.78 Most new cancer drugs do not generate evidence on survival benefits during the post-marketing period.79,80 Third, we did not account for the  $f_{1\cdot 3}$  billion spent on the Cancer Drugs Fund between 2011 and 2016.<sup>81</sup> Similarly, some high-cost drugs, such as lumacaftor and ivacaftor for cystic fibrosis, were excluded from our sample as they were not recommended by NICE but, nonetheless, have been made available in the NHS and have substantially contributed to the increase in NHS drug spending in the past 5 years. We also excluded drugs considered under NICE's Highly Specialised Technologies programme, which sets a much higher cost-effectiveness threshold for recommending drugs that treat very rare conditions than their *f* 20 000–30 000 per QALY threshold.

In conclusion, our analysis of NICE appraisals during 2000–20 indicates that NICE does not fully achieve its stated objectives of basing its recommendations on "an assessment of population benefits".<sup>7</sup> The benefits derived from new drugs recommended by NICE were outweighed by the potential benefits that could have been generated from alternative uses of the resources allocated to these new drugs. During 2000–20, the population health impact of new drugs recommended by NICE deteriorated. Changes to NICE's evaluation framework are needed to ensure that the inherent health trade-offs made by NICE—and the implicit prioritisation of some patient populations over others—align with societal views and preferences.

#### Contributors

HN conceptualised the analysis, validated the data, and wrote the original draft of the manuscript. HN curated the data with support from PM. HN and JW conducted the analysis. HN, BW, JL, and IP supervised the methods. HN, PM, and JW directly accessed and verified the underlying data. All authors had full access to all data in the study, revised the final version of the manuscript, and had final responsibility for the decision to submit for publication.

#### **Declaration of interests**

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#### Data sharing

Data on incremental cost-effectiveness ratios, incremental qualityadjusted life-years, and incremental costs for every drug indication appraised by the National Institute for Health and Care Excellence and included in this analysis are available in the appendix (p 22).

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#### References

- 1 Naci H, Davis C, Savović J, et al. Design characteristics, risk of bias, and reporting of randomised controlled trials supporting approvals of cancer drugs by European Medicines Agency, 2014–16: cross sectional analysis. *BMJ* 2019; **366**: 15221.
- 2 Naci H, Salcher-Konrad M, Kesselheim AS, et al. Generating comparative evidence on new drugs and devices before approval. *Lancet* 2020; 395: 986–97.
- 3 Rome BN, Egilman AC, Kesselheim AS. Trends in prescription drug launch prices, 2008–2021. JAMA 2022; 327: 2145–47.
- 4 Lloyd DCEF, Scrivener G. Prescribing at the primary care group level: census data and prescribing indicators. J Clin Pharm Ther 2001; 26: 93–101.
- 5 Wouters OJ, Naci H, Papanicolas I. Availability and coverage of new drugs in 6 high-income countries with health technology assessment bodies. JAMA Intern Med 2024; 184: 328–30.
- 6 Rawlins M. In pursuit of quality: the National Institute for Clinical Excellence. *Lancet* 1999; 353: 1079–82.
- 7 National Institute for Health and Care Excellence. Our principles. 2024. https://www.nice.org.uk/about/who-we-are/our-principles (accessed April 9, 2024).
- 8 Barrett A, Roques T, Small M, Smith RD. How much will Herceptin really cost? *BMJ* 2006; 333: 1118–20.
- 9 National Institute for Health and Care Excellence. NICE health technology evaluations: the manual. 2023. https://www.nice.org.uk/ process/prmg36/chapter/economic-evaluation (accessed April 9, 2024).
- McCabe C, Claxton K, Culyer AJ. The NICE cost-effectiveness threshold: what it is and what that means. *PharmacoEconomics* 2008; 26: 733–44.
- 11 Claxton K, Martin S, Soares M, et al. Methods for the estimation of the National Institute for Health and Care Excellence costeffectiveness threshold. *Health Technol Assess* 2015; 19: 1–503.
- 12 Lomas J, Martin S, Claxton K. Estimating the marginal productivity of the English National Health Service from 2003 to 2012. *Value Health* 2019; **22**: 995–1002.
- 13 National Institute for Health and Care Excellence. Technology appraisal data: appraisal recommendations. 2024. https://www.nice. org.uk/about/what-we-do/our-programmes/nice-guidance/nicetechnology-appraisal-guidance/data/appraisal-recommendations (accessed May 16, 2024).

- 14 Osipenko L. Audit of data redaction practices in NICE technology appraisals from 1999 to 2019. BMJ Open 2021; 11: e051812.
- 15 Bullement A, Taylor M, McMordie ST, Waters E, Hatswell AJ. NICE, in confidence: an assessment of redaction to obscure confidential information in single technology appraisals by the National Institute for Health and Care Excellence. *PharmacoEconomics* 2019; 37: 1383–90.
- 16 National Institute for Health and Care Excellence. British National Formulary (BNF). 2024. https://bnf.nice.org.uk/ (accessed May 16, 2024).
- 17 European Medicines Agency. Public—list of opinions on orphan medicinal product designation. 2024. https://iris.ema.europa.eu/ odpublicregister/ (accessed May 16, 2024).
- 18 Rawlins M, Barnett D, Stevens A. Pharmacoeconomics: NICE's approach to decision-making. Br J Clin Pharmacol 2010; 70: 346–49.
- 19 Bovenberg J, Penton H, Buyukkaramikli N. 10 years of end-of-life criteria in the United Kingdom. Value Health 2021; 24: 691–98.
- 20 Sanders GD, Maciejewski ML, Basu A. Overview of costeffectiveness analysis. JAMA 2019; 321: 1400–01.
- 21 Drummond MF, Sculpher MJ, Claxton K, Stoddart GL, Torrance GW. Methods for the economic evaluation of health care programmes. Oxford University Press, 2015.
- 22 Weinstein MC, Torrance G, McGuire A. QALYs: the basics. *Value Health* 2009; **12** (suppl 1): S5–9.
- 23 Goldacre B, MacKenna B. The NHS deserves better use of hospital medicines data. BMJ 2020; 370: m2607.
- 24 NHS England. Prescribing costs in hospitals and the community 2019–2020. 2020. https://digital.nhs.uk/data-and-information/ publications/statistical/prescribing-costs-in-hospitals-and-thecommunity/2019-2020 (accessed July 6, 2021).
- 25 Department of Health and Social Care, Department for Science, Innovation, and Technology. Life sciences competitiveness indicators 2023. https://www.gov.uk/government/publications/lifesciences-sector-data-2023/life-sciences-competitivenessindicators-2023 (accessed May 13, 2024).
- 26 NHS Business Services Authority. Prescribing costs in hospitals and the community—England. 2022. https://nhsbsa-opendata.s3. eu-west-2.amazonaws.com/pchc/pchc\_2023\_background\_ information\_methodology\_v001.html (accessed May 13, 2024).
- 27 WHO. Defined Daily Dose (DDD). 2024. https://www.who.int/ tools/atc-ddd-toolkit/about-ddd (accessed May 13, 2024).
- 28 IQVIA. The global use of medicines 2024: outlook to 2028. 2024. https://www.iqvia.com/insights/the-iqvia-institute/reports-and-publications/reports/the-global-use-of-medicines-2024-outlook-to-2028 (accessed May 13, 2024).
- 29 Stinnett AA, Mullahy J. Net health benefits: a new framework for the analysis of uncertainty in cost-effectiveness analysis. *Med Decis Making* 1998; 18 (suppl): S68–80.
- 30 Department of Health and Social Care. Statutory scheme to control costs of branded health service medicines. 2020. https:// assets.publishing.service.gov.uk/government/uploads/system/ uploads/attachment\_data/file/859212/statutory-scheme-to-controlcosts-of-branded-medicines-impact-assessment.pdf (accessed April 9, 2024).
- 31 Martin S, Rice N, Smith PC. Comparing costs and outcomes across programmes of health care. *Health Econ* 2012; **21**: 316–37.
- 32 Martin S, Rice N, Smith PC. Does health care spending improve health outcomes? Evidence from English programme budgeting data. *J Health Econ* 2008; **27**: 826–42.
- 33 Charlton V, Lomas J, Mitchell P. NICE's new methods: putting innovation first, but at what cost? BMJ 2022; 379: e071974.
- 34 Paulden M, McCabe C. Modifying NICE's approach to equity weighting. *PharmacoEconomics* 2021; **39**: 147–60.
- 35 Charlton V. All health is not equal: the use of modifiers in NICE technology appraisal. BMJ Evid Based Med 2023; 28: 247–50.
- 36 Linley WG, Hughes DA. Societal views on NICE, cancer drugs fund and value-based pricing criteria for prioritising medicines: a cross-sectional survey of 4118 adults in Great Britain. *Health Econ* 2013; 22: 948–64.
- 37 Bourke SM, Plumpton CO, Hughes DA. Societal preferences for funding orphan drugs in the United Kingdom: an application of person trade-off and discrete choice experiment methods. *Value Health* 2018; 21: 538–46.

- 38 Chamberlain C, Owen-Smith A, MacKichan F, Donovan JL, Hollingworth W. "What's fair to an individual is not always fair to a population": a qualitative study of patients and their health professionals using the Cancer Drugs Fund. *Health Policy* 2019; 123: 706–12.
- 39 Charlton V, DiStefano M. An empirical ethics study of the coherence of NICE technology appraisal policy and its implications for moral justification. *BMC Med Ethics* 2024; 25: 28.
- 40 Walton MJ, O'Connor J, Carroll C, Claxton L, Hodgson R. A review of issues affecting the efficiency of decision making in the NICE single technology appraisal process. *PharmacoEconom Open* 2019; 3: 403–10.
- 41 Michaeli DT, Mills M, Kanavos P. Value and price of multiindication cancer drugs in the USA, Germany, France, England, Canada, Australia, and Scotland. *Appl Health Econ Health Policy* 2022; 20: 757–68.
- 42 Polak TB, Cucchi DGJ, Darrow JJ, Versteegh MM. Incremental benefits of novel pharmaceuticals in the UK: a cross-sectional analysis of NICE technology appraisals from 2010 to 2020. *BMJ Open* 2022; **12**: e058279.
- 43 Cherla A, Renwick M, Jha A, Mossialos E. Cost-effectiveness of cancer drugs: comparative analysis of the United States and England. *EClinicalMedicine* 2020; 29: 100625.
- 44 Lichtenberg FR. The impact of new drug launches on longevity: evidence from longitudinal, disease-level data from 52 countries, 1982–2001. Int J Health Care Finance Econ 2005; 5: 47–73.
- 45 Howard DH, Chernew ME, Abdelgawad T, Smith GL, Sollano J, Grabowski DC. New anticancer drugs associated with large increases in costs and life expectancy. *Health Aff (Millwood)* 2016; 35: 1581–87.
- 46 Chambers JD, Thorat T, Wilkinson CL, et al. Estimating population health benefits associated with specialty and traditional drugs in the year following product approval. *Appl Health Econ Health Policy* 2017; 15: 227–35.
- 47 Lichtenberg FR. Pharmaceutical innovation and longevity growth in 30 developing and high-income countries, 2000–2009. *Health Policy Technol* 2014; 3: 36–58.
- 48 Buxbaum JD, Chernew ME, Fendrick AM, Cutler DM. Contributions of public health, pharmaceuticals, and other medical care to US life expectancy changes, 1990–2015. *Health Aff (Millwood)* 2020; **39**: 1546–56.
- 49 Soares MO, Sculpher MJ, Claxton K. Health opportunity costs: assessing the implications of uncertainty using elicitation methods with experts. *Med Decis Making* 2020; 40: 448–59.
- 50 Claxton K, Lomas J, Martin S. The impact of NHS expenditure on health outcomes in England: alternative approaches to identification in all-cause and disease specific models of mortality. *Health Econ* 2018; 27: 1017–23.
- 51 Martin S, Lomas J, Claxton K, Longo F. How effective is marginal healthcare expenditure? New evidence from England for 2003/04 to 2012/13. Appl Health Econ Health Policy 2021; 19: 885–903.
- 52 Martin S, Claxton K, Lomas J, Longo F. The impact of different types of NHS expenditure on health: marginal cost per QALY estimates for England for 2016/17. *Health Policy* 2023; 132: 104800.
- 53 Devlin N, Parkin D. Does NICE have a cost-effectiveness threshold and what other factors influence its decisions? A binary choice analysis. *Health Econ* 2004; 13: 437–52.
- 54 Claxton K, Sculpher M, Palmer S, Culyer AJ. Causes for concern: is NICE failing to uphold its responsibilities to all NHS patients? Wiley Online Library, 2015.
- 55 Woods B, Lomas J, Sculpher M, Weatherly H, Claxton K. Achieving dynamic efficiency in pharmaceutical innovation: identifying the optimal share of value and payments required. *Health Econ* 2024; 33: 804–19.
- 56 Charlton V. NICE and fair? Health technology assessment policy under the UK's National Institute for Health and Care Excellence, 1999–2018. *Health Care Anal* 2020; 28: 193–227.
- 57 Michaels JA. Potential for epistemic injustice in evidence-based healthcare policy and guidance. *J Med Ethics* 2020; **47**: 417–22.
- 58 Michaels J. NICE's wrong turns: opportunity costs and missed opportunities. 2020. https://blogs.bmj.com/medicalethics/2020/11/30/nices-wrong-turns-opportunity-costs-and-missedopportunities/ (accessed June 5, 2024).
- 59 Lomas J, Ochalek J, Faria R. Avoiding opportunity cost neglect in cost-effectiveness analysis for health technology assessment. *Appl Health Econ Health Policy* 2022; 20: 13–18.

- 60 Persson E, Tinghög G. Opportunity cost neglect in public policy. *J Econ Behav Organ* 2020; **170**: 301–12.
- 61 Culyer AJ. Cost, context, and decisions in health economics and health technology assessment. Int J Technol Assess Health Care 2018; 34: 434–41.
- 62 Palmer S, Raftery J. Economic notes: opportunity cost. BMJ 1999; 318: 1551–52.
- 63 Bryan S, Williams I, McIver S. Seeing the NICE side of costeffectiveness analysis: a qualitative investigation of the use of CEA in NICE technology appraisals. *Health Econ* 2007; 16: 179–93.
- 64 Siverskog J, Henriksson M. On the role of cost-effectiveness thresholds in healthcare priority setting. Int J Technol Assess Health Care 2021; 37: e23.
- 65 Neumann PJ, Podolsky MI, Basu A, Ollendorf DA, Cohen JT. Do cost-effectiveness analyses account for drug genericization? A literature review and assessment of implications. *Value Health* 2022; 25: 59–68.
- 66 Woods B, Fox A, Sculpher M, Claxton K. Estimating the shares of the value of branded pharmaceuticals accruing to manufacturers and to patients served by health systems. *Health Econ* 2021; 30: 2649–66.
- 67 Charlesworth A, Anderson M, Donaldson C, et al. What is the right level of spending needed for health and care in the UK? *Lancet* 2021; 397: 2012–22.
- 68 Department of Health and Social Care. Independent Investigation of the National Health Service in England. 2024. https://assets. publishing.service.gov.uk/media/66f42ae630536cb92748271f/Lord-Darzi-Independent-Investigation-of-the-National-Health-Service-in-England-Updated-25-September.pdf (accessed Nov 21, 2024).
- 59 Vanness DJ, Lomas J, Ahn H. A health opportunity cost threshold for cost-effectiveness analysis in the United States. Ann Intern Med 2021; 174: 25–32.
- 70 Sculpher M, Claxton K, Pearson SD. Developing a value framework: the need to reflect the opportunity costs of funding decisions. *Value Health* 2017; 20: 234–39.
- 71 Bach PB, Conti RM, Muller RJ, Schnorr GC, Saltz LB. Overspending driven by oversized single dose vials of cancer drugs. *BMJ* 2016; **352**: i788.
- 72 Gilbar PJ, Chambers CR, Musicco F. Preventing drug vial wastage and reducing expenditure associated with injectable cancer drugs: international oncology pharmacy survey. J Oncol Pharm Pract 2022; 28: 1332–39.
- 73 Angelis A, Lomas J, Woods B, Naci H. Promoting population health through pharmaceutical policy. 2023. https://www.lse.ac.uk/lsehealth/assets/documents/Reports/23-0275-Pharma-Report-V10.pdf (accessed June 7, 2024).
- 74 Grigore B, Ciani O, Dams F, et al. Surrogate endpoints in health technology assessment: an international review of methodological guidelines. *PharmacoEconomics* 2020; 38: 1055–70.
- 75 Davis C, Naci H, Gurpinar E, Poplavska E, Pinto A, Aggarwal A. Availability of evidence of benefits on overall survival and quality of life of cancer drugs approved by European Medicines Agency: retrospective cohort study of drug approvals 2009–13. *BMJ* 2017; 359: j4530.
- 76 Naci H, Zhang Y, Woloshin S, Guan X, Xu Z, Wagner AK. Overall survival benefits of cancer drugs initially approved by the US Food and Drug Administration on the basis of immature survival data: a retrospective analysis. *Lancet Oncol* 2024; 25: 760–69.
- 77 Latimer NR, Adler AI. Extrapolation beyond the end of trials to estimate long term survival and cost effectiveness. *BMJ Med* 2022; 1: e000094.
- 78 Prasad V. Overestimating the benefit of cancer drugs. JAMA Oncol 2017; 3: 1737–38.
- 79 Salcher-Konrad M, Naci H, Davis C. Approval of cancer drugs with uncertain therapeutic value: a comparison of regulatory decisions in Europe and the United States. *Milbank Q* 2020; 98: 1219–56.
- 80 Gyawali B, Hey SP, Kesselheim AS. Assessment of the clinical benefit of cancer drugs receiving accelerated approval. *JAMA Intern Med* 2019; **179**: 906–13.
- 81 Aggarwal A, Fojo T, Chamberlain C, Davis C, Sullivan R. Do patient access schemes for high-cost cancer drugs deliver value to society? Lessons from the NHS Cancer Drugs Fund. Ann Oncol 2017; 28: 1738–50.