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Complete List of Authors:	Polak, Tobias; Erasmus Medical Center Department of Epidemiology, Biostatistics Cucchi, David; Amsterdam UMC Locatie VUmc, Haematology; Franciscus Gasthuis en Vlietland, Darrow, Jonathan; Harvard Medical School, Department of Medicine Versteegh, Matthijs; Institute for Medical Technology Assessment, Erasmus University Rotterdam
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The incremental therapeutic value of novel pharmaceuticals: a cross-sectional study of government QALY estimates

Tobias B. Polak, MSc[1], David G.J. Cucchi, MD[2], Jonathan J. Darrow, SJD, LLM, JD, MBA[3], Matthijs M. Versteegh, PhD[4]

Corresponding author:
Tobias Boy Polak
Department of Biostatistics, Na28
Doctor Molewaterplein 40
3015 GD Rotterdam, the Netherlands Phone: +31 10 704 0 704
Email: t.polak@erasmusmc.nl

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[1] Erasmus School of Health Policy & Management, Erasmus University of Rotterdam, Rotterdam, The Netherlands

[2] Department of Haematology, Amsterdam UMC, Vrije Universiteit Amsterdam, Cancer Center Amsterdam, Amsterdam, The Netherlands

[3] Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts

[4] institute for Medical Technology Assessment, Erasmus University of Rotterdam, Rotterdam, The Netherlands

Abstract

Objectives: To evaluate the incremental value of new drugs across disease areas receiving favourable coverage decisions by the United Kingdom's National Institute for Health and Care Excellence (NICE) over the past decade.

Design, setting, and participants: This cross-sectional study assessed favourable appraisal decisions of drugs between January 1, 2010 and December 31, 2020. Estimates of incremental benefit were extracted from NICE's evidence review groups reports.

Primary outcome measure: Incremental benefit of novel drugs relative to the best alternative therapeutic option, expressed in Quality Adjusted Life Years (QALYs).

Results: 184 appraisals of 129 drugs provided QALYs. The median incremental value was 0·27 QALY (interquartile range[IQR]: 0·07-0·73). Benefits varied across drug-indication pairs (range: -0·49-5·22 QALYs). The highest median benefits were found in haematology (0·70 QALY, IQR: 0·55-1·22) and oncology (0·49 QALY, IQR: 0·21-0·87), the lowest in ophthalmology (0·11 QALY, IQR: 0·04-0·26) and endocrinology (0·02 QALY, IQR: 0·01-0·06). Eight appraisals (4·3%) found contributions of more than two QALYs, but one in four (50/184) drug-indication pairs provided less than the equivalent of one month in perfect health compared to existing treatments.

Conclusions: In our review period, the median incremental value of novel drugs was equivalent to three to four months of life in perfect health, but data were heterogeneous. Objective evaluations of therapeutic value helps patients and physicians to develop reasonable expectations of drugs and delivers insights into disease areas where medicinal therapeutic progress has had the most and least impact.

Strengths and limitations of this study

- This is the first study systematically comparing QALY data derived from all single technology appraisals of novel pharmaceuticals recommended for use within the NHS between January 1st 2010 and December 31st 2020.
- Our analysis enables direct comparison of health benefits across conditions for individual patients receiving novel treatments.
- QALYs gained were calculated based on the best alternative therapy.
- Analysis is limited to appraisals that disclose information on incremental QALYs.
- Benefits are analysed from the perspective of individual patient. We do not take into account effects on the population level, e.g. disease prevalence and market share.

Introduction

Before a novel treatment is allowed on the market, its clinical benefit is assessed by regulatory agencies such as the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA). However, clinical benefit evaluations do not provide insight into issues deemed relevant by payers, such as comparative effectiveness, cost effectiveness, or lifetime benefit. Therefore, several countries have created independent health technology assessment bodies to conduct drug value assessments, commonly referred to as cost effectiveness analyses.[1] Through these value assessments, publicly-funded experts help to clarify the incremental clinical benefit and incremental costs of selected new therapies according to their approved indications, which professional societies may then rely on when revising treatment guidelines to include the new drug.

Despite the increased focus on incremental drug value, surprisingly little attention has been devoted to understanding the magnitude and distribution of their clinical benefits across disease areas. The limited scholarship in this area can be explained in part by the fact that, until recently, it has been difficult to compare the benefit of drugs intended to treat widely divergent diseases or conditions.

However, the emergence of official government drug value assessments over the past two decades, rigorously conducted following a consistent set of health economic modelling guidelines, now makes such comparisons feasible. These assessments utilize the Quality Adjusted Life Year (QALY), a common metric of patient health. One QALY, for example, represents the equivalent of one additional year of life in perfect health, or some longer period of time in less-than-perfect health.[2,3] Although the QALY has long been available as a measure and is frequently used in individual economic evaluations,[4] the QALY can, in combination with forecasts over the lifetime of patients from health economic models, be used to compare health benefits across medical disciplines in a consistent and transparent manner. QALYs are primarily used to calculate incremental cost-effectiveness ratio's (ICER), which signals the efficiency with which a health technology produces health by dividing incremental costs by incremental benefits expressed as QALYs. However, it is often overlooked that the QALY part of an ICER is, in and of itself, a parameter that provides relevant insights into the size of forecasted health benefit. In the case of the UK, QALYs are produced following specific modelling guidance by the National Institute for Health and Care Excellence (NICE), enhancing their comparability across diseases.

NICE is a British governmental organization that assesses the value of novel drugs and the impact on the National Health System (NHS) of adopting them. Since NICE was established in 1999, drug manufacturers have been invited to submit evidence on the health benefits and costs of their drugs in comparison to the standard of care.[5] An evidence review group—generally a group of university based researchers contracted by NICE—then appraises the evidence in "single technology appraisals" and produces independent estimates of health benefits, measured in QALYs.

Using data from NICE evidence review groups, we sought to better understand the incremental value of all new therapies assessed between 2010 and 2020. Although these data are used to inform public health decisions, we here present their implications from a patient's perspective. Specifically, we sought to identify disease areas where the greatest gains from novel therapies have occurred, and the differing average amounts of gain per drug for individual patients in each disease area.

Materials and methods

We identified all single technology appraisals of novel pharmaceuticals that were submitted to NICE between January 1, 2010 and December 31, 2020. Data were extracted on May 1, 2021. We excluded drug appraisals resulting in negative coverage decisions, appraisals for which no data were available because of termination, withdrawal, or reconsideration, and appraisals that addressed only cost-saving issues and lacked QALY data.

Two authors (TBP and DGJC) independently extracted QALY estimates from each drug's appraisal documents. Discordance was resolved by discussion with the last author (MMV). When appraisal documents included multiple comparators, we extracted the QALY value that corresponded to the best alternative therapy. As a sensitivity analysis, in the case of multiple comparators, we also computed the added value compared with the next-best alternative. We disregarded cost, as we focused on health gains for individual patients and not on health care systems.

The evidence review group usually specified which of the modelled QALYs was its preferred estimate of health benefit (i.e. which modelling assumptions were deemed most appropriate to the review group). If the evidence review group did not clearly document their preference and this could not be determined after deliberation with a third author (MMV), we discarded the appraisal from our analysis. Although manufacturers frequently report the incremental cost-effectiveness ratio in cost (British pounds) per QALY, they are not required to disclose the individual components of this ratio. We therefore removed appraisals in which the manufacturer redacted all estimates of incremental QALYs. A schematic overview of our appraisal selection and data extraction method is depicted in Figure 1.

Each appraisal was categorized according to its medical discipline: cardiology, endocrinology, gastroenterology, haematology, nephrology, neurology, oncology, ophthalmology, rheumatology, vascular medicine, and other (dermatology, infectious diseases, psychiatry, pulmonology, urology). Summary statistics were calculated and visualized in R version 4·0·5.

Patient and Public Involvement

No patients were involved during the planning and writing of this work; all data were derived from NICE single technology appraisals. Therefore the study did not require ethical approval by the institutional review board.

Results

Between January 1st, 2010 and December 31st, 2020, 436 single technology appraisals were submitted to NICE associated with 212 drugs. No documentation was available for 115 appraisals, including 14 that were withdrawn, 56 that were terminated, and 45 that were later reconsidered or updated. Another 37 appraised drug-indication pairs received a negative reimbursement determination, meaning they were not considered a cost-effective use of NHS resources and thus did not become available to patients in the UK. An estimate of QALY gain could not be extracted in 19 appraisals, because QALYs were not reported in cost-saving appraisals or because the evidence review group did not specify its preferred estimate out of several reported outcomes. After these exclusions, there were 265 appraisals available for evaluation associated with 171 drugs. Of these appraisals, 81 had their incremental QALY estimates redacted, which can occur at the company's request, leaving 184 appraisals associated with 129 drugs for inclusion in our data set (different appraisals can review the same drug for different indications).

Of the 184 drug-indication pairs, the median incremental QALY gain was 0·27 QALY (interquartile range [IQR]: 0·07-0·73) (Figure 2). The highest median benefits were associated with drugs developed for medical disciplines such as haematology (0·70, IQR: 0·55-1·22), oncology (0·46, IQR: 0·19-0·87), and neurology (0·45, IQR: 0·13-1·15), and the lowest for drugs associated with medical disciplines such as vascular medicine (0·11, IQR: 0·01-0·19), ophthalmology (0·10, IQR: 0·04-0·26) and endocrinology (0·02, IQR: 0·01-0·06).

In our review period, eight (4·3%) positive coverage decisions were granted to drugs contributing more than the equivalent of two life years in perfect health. Both dinutuximab beta to treat neuroblastoma and nusinersen used to treat children with spinal muscular atrophy led patients to accumulate 5·2 incremental QALYs.

On the other hand, 50 (27%) drugs contributed no more than the equivalent of one month in perfect health (≤ 0·082 QALY) (Table 1). Eight drugs were estimated to provide lower QALY gains than their next best alternative. Government decision makers may nevertheless be willing to pay for such products thanks to the uncertainty around point estimates, together with strategic pricing by manufacturers. For example, one drug, venetoclax, was estimated to be inferior to its direct comparator (ibrutinib) in the treatment of chronic lymphocytic leukaemia. Although this negative point estimate was considered most plausible by the evidence review group, there was still considerable uncertainty remaining as the group also provided higher estimates (an incremental benefit of 0·51 when idelalisib was the comparator) and lower estimates (-1·75 when treatment effects of venetoclax were assumed to be waning faster than expected) under varying assumptions. Venetoclax was offered at a lower price than ibrutinib, and NICE concluded that the new drug was likely a cost-effective use of NHS resources in the treatment of lymphocytic leukaemia.[6]

When selecting the next-best drug as a comparator instead of the best available comparator, the median added value slightly increases (0·31, IQR: 0·09 – 0·73, range: -0·39 – 5·22), suggesting our results are robust under these different choices of comparators.

Discussion

Novel pharmaceuticals that became publicly available to patients in the NHS over the past 11 years and that were favourably evaluated by NICE contributed the equivalent of between three to four months of life in perfect health. The added benefit varied greatly, including eight drugs that were inferior in some cases to its already-available counterpart, and two that provided the equivalent of over five years in perfect health. To our knowledge, this analysis is the first to compare the therapeutic value of drugs across diverse disease areas using QALYs extracted from independent cost-effectiveness analyses conducted through a standardized framework.

The largest benefits were observed in areas such as haematology or oncology, where drugs were shown to improve quality or duration of life by 0·70 and 0·46 QALY. Patients have least profited from pharmaceutical innovations in endocrinology and ophthalmology, where novel pharmaceuticals were associated with a median incremental benefit of 0·02 to 0·10 QALYs.

The nature of each treatment (curative, palliative, symptomatic, preventive) may impact the incremental QALY. For example, adult patients that have undergone total hip or knee replacements may be treated with apixaban (TA245) to prevent venous thromboembolism. When used for this indication, apixaban provides an incremental benefit of 0·0016 QALY over the standard of care (low-molecular-weight heparin), equivalent to an additional fourteen hours of life in perfect health. The very low benefit reflected estimates that one venous thromboembolism event would be prevented for every 110–250 patients treated prophylactically for ten days following surgery.[7–9] Although apixaban may prevent serious outcomes (death) in some patients, outcome heterogeneity led to the extremely low average incremental QALY.

Due to selection bias and other factors, the median QALY estimates reflected in our study may substantially overstate the average benefit of new drugs. QALY evaluations are necessarily based on the data available at the time of drug approval, which is in turn increasingly based on earlier phase trials, but later-generated evidence often fails to confirm promising early results.[10] Furthermore, most (59%) drugs are now approved on the basis of surrogate endpoints,[11] such as progression free survival, which for purposes of QALY calculations are assumed to correlate with clinical outcomes such as increased survival. However, studies have shown that this correlation is often poor or fair, particularly in oncology.[12,13]

A recent assessment of oncology drugs approved via the FDA's accelerated approval pathway demonstrated that only half (48%, 45/93) of drug-indication pairs subsequently became reimbursed within the NHS, suggesting their therapeutic benefit was not sufficiently important or well established in relation to the associated cost to receive a positive reimbursement decision.[14] Not all FDA-approved drugs are subsequently approved by the EMA, and not all EMA-approved drugs are assessed by NICE.

Due to the time it takes to conduct clinical trials, the best available comparators used in the cost-effectiveness analyses may no longer be the most relevant drugs at the time the new drug is approved. When similar treatments are assessed for different indications despite having similar effects on the body, average benefits may appear larger than if those treatments had been assessed for the same indication. For example, secukinumab, brodalumab, ixekizumab, apremilast, tofacitinib, and certolizumab pegol have all been individually appraised in the treatment of plaque psoriasis, yet all these biologicals compete for a different line of therapy and were assessed using different therapies as comparators.

On the other hand, our study may underestimate average QALY benefit. QALY values have been challenged for not taking into account non-health related benefits, such as the value derived by patients from the hope that a new treatment can grant them long-term survival (whether realized or not).[15] However, if non-health related benefits are included, then so too should be non-health related harms.[16] These could include treatment discomfort, the burdens of managing daily dosing, psychosocial distress from receiving treatment,[17] difficulties in transport to and from treatment (especially for seriously-ill patients), or, in contexts without universal health care coverage, surprise medical billing.[18] QALY values reported by NICE are generated from a health care perspective and hence only incorporate costs and benefits within the health care system. [19,20] Benefits in those other than patients (such as caregivers) are generally excluded.[21] Our findings must be interpreted in this larger context.

Our study has a few limitations. First, our analysis was restricted to data presented to NICE of drugs that subsequently obtained a positive coverage decision. Therefore, drugs in our review are a subset of the drugs covered

in other analyses of medication approved by the FDA or EMA—our drugs are more stringently selected as they needed to be EMA approved and also have a favourable cost profile.

Second, we could not retrieve all estimates of health benefit as some were concealed by the manufacturer, the implications of which are unclear. It seems some companies maintain a policy of not disclosing QALY figures for any indications or drugs, whereas other companies consistently provide full disclosure. There may be greater incentives to conceal QALY values when they are small, but other factors could also be relevant, such as a desire to maintain in confidence the incremental cost of their treatment, which would implicitly be made evident if both cost/benefit ratios and QALY values were simultaneously disclosed.

Third, our results are sensitive to the choice of relevant comparator: a different choice of comparator will lead to different results. Alternatively, one may not be interested in the overall population, but only in specific (sub)populations reported in the appraisal documentation. This may give more specific estimates for individual patients, but impedes the comparison of drugs across diseases.

Our findings provide insight into the relative benefits of new pharmaceuticals across therapeutic areas. Additional health gains may be hindered by the difficulty of developing novel drugs for specific diseases, perhaps because major improvements have already been generated prior to our review period—or have yet to come. QALYs are a useful tool for comparison, but the measure omits important health-related variables, such as the extent to which a patient remains unable to live out a "normal" life expectancy or achieve complete health. Other factors, such as lack of fundamental understanding of disease pathologies,[22,23] or the abundance or absence of sufficient research funding may also limit health gains. Our figures evaluate the health-related benefits of drug development over the past decade. In combination with indices measuring health needs, such as the Global Burden of Disease,[24] as well as cost-effectiveness/cost-saving data of novel drugs that might produce similar QALYs as already available therapies, our findings can help provide context for the allocation of research funding and thereby shape health policy.

Eight drugs improved life by more than two incremental QALYs, which may justify their superlative epithets of "ground-breaking" or "game-changing."[25] Half of the drugs in our study were likely to improve life by three to four months in perfect health, and 84·8% of novel drugs do not add more than one such year. Unfortunately, 25% of appraisals have covered drugs that contributed the equivalent of no more than one month in perfect health, and 23 (12·5%) drug-indication pairs were estimated to add several hours to just a week of perfect health. For example, eluxadoline for prevention of diarrhoea and abdominal pain in patients with irritable bowel syndrome yielded a total QALY gain of 0·015—equivalent to 5·5 days in perfect health—compared with placebo. Given the uncertainty around cost-effectiveness estimates—models that require ample assumptions and extrapolations over lifetime horizons can hardly be expected to accurately forecast a week of health gained—drafting extensive cost-effectiveness reports in these situations is not likely to be a cost-effective use of time.

Drugs that have little health benefit relative to the best alternative may still promote price competition and thereby free funds for other public health initiatives or treatments. To avoid wasting public resources in needless evaluations, guideline committees could determine a threshold of incremental benefit that is clinically relevant to each disease area.[26] Drugs that do not pass this threshold based on early assessments of their value should be rejected without a full evaluation unless they are offered at lower cost.

Patients and physicians can use the QALY data presented here to put the effectiveness of treatments in perspective. The frequently employed metric of "number needed to treat" provides important information about the effectiveness of drugs on the principal disease-specific outcome. For example, the efficacy of eluxadoline could be described in terms of the number of patients that would need to be treated three months to avoid one episode of abdominal pain or diarrhoea, in this case between eight and 33 patients over three months.[27] Metrics such as this, however, do not account for adverse events. Using the incremental QALY estimate that integrates gains and losses into a single measure (for eluxadoline, 0·015), it is possible to calculate that 67 patients would need to be treated over their lifetime horizons to gain the equivalent of one year in perfect health. As such, the QALY provides an estimate of both duration and quality of life, which are arguably the two most important factors from the perspective of a patient.

Conclusions

Novel pharmaceuticals that received a positive coverage decision by NICE between 2010 and 2021 provided patients with an average of 0·27 QALYs, the equivalent of three to four additional months of life in perfect health. One in

four drugs does not improve quality of life by more than one month, and incremental benefit varies greatly across disease areas and compounds. Several novel drugs do not provide additional QALY gains over available therapies, but if offered at a lower price could still be of interest from a public cost-saving perspective even if not from the patient's perspective. Providing transparent information on the added value of novel therapies enables patients and physicians to have reasonable expectations about the average net benefits of therapies at their disposal. Objectively evaluating the benefits contributed by novel pharmaceuticals provides insight not only into whether a given drug is worth its price once approved, but also into the therapeutic return on investment reaped by society from the substantial public and private sums expended on research and development. Finally, these figures provide a benchmark for future innovations.

Ethics approval statement

No patients were involved during the planning and writing of this work. Therefore the study did not require ethical approval by the institutional review board.

Declaration of interests

TBP is employed part-time by myTomorrows, which facilitates expanded access programs for the pharmaceutical industry. TBP holds stock in myTomorrows (<0.1%). TBP has received funding for research from the Dutch government (grant EMCLSH20012). The research of TBP is conducted independently and TBP is contractually free to publish any results for all the conducted work. None of the recent work concerns the topic in this analysis. DGJC has no interests to declare. MMV is director of the institute of Medical Technology Assessment (iMTA). iMTA conducts cost-effectiveness research funded by international governments, pharmaceutical industry, and med-tech industry. All research is conducted independently and iMTA is contractually free to publish any results for all conducted work. None of the recent work concerns the topic in this analysis. Jonathan Darrow receives funding from Arnold Ventures, the Greenwall Foundation, the Kaiser Permanente Institute for Health Policy, West Health, and the Novo Nordisk Foundation (grant for a scientifically independent Collaborative Research Programme; grant NNF17SA0027784).

Author contributions

TBP and MMV conceived the paper. TBP and DGJC collected, analysed and visualised the data. TBP drafted the first version of the manuscript; JJD and DGJC critically revised the first version of the paper; all authors discussed the results and contributed to the final manuscript. All authors had full access to all the data in the study and accept responsibility for submission for publication.

Data sharing

All raw data is available through the NICE website. Aggregated data will be made available upon reasonable request.

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Figure legends

Figure 1 : Flowchart
Flowchart of the selection and retrieval of estimates of Quality-Adjusted Life Years (QALYs) from NICE technology appraisals.

Figure 2: The added value of all novel pharmaceuticals over the past decade
Display of the distribution (boxplot) of added value in Quality Adjusted Life Years (QALYs) of novel pharmaceuticals per medical discipline that have received a positive coverage decision of NICE between January 1st, 2010 and January 1st, 2021. Medical disciplines with fewer than eight appraisals were classified as 'Other'.

Tables

Table 1
Top-10 pharmaceuticals that produced most and least incremental health benefit, ranked according to their added Quality-Adjusted Life Years (QALYs) extracted from NICE Technology Appraisals (TAs).

TA	Product	Disease	QALY	Specifics
TA538	dinutuximab beta	neuroblastoma	5.22	Dinutuximab beta for treating high-risk neuroblastoma in people aged 12 months and over whose disease has at least partially responded to induction chemotherapy, followed by myeloablative therapy and stem cell transplant, only if they have not already had anti-GD2 immunotherapy.
TA588	nusinersen	spinal muscular atrophy	5.20	Nusinersen for treating 5q spinal muscular atrophy (SMA) only if people have pre-symptomatic SMA, or SMA types 1, 2 or 3.
TA443	obeticholic	primary biliary cholangitis	4.22	Obeticholic acid for treating primary biliary cholangitis in combination with ursodeoxycholic acid for people whose disease has responded inadequately to ursodeoxycholic acid or as monotherapy for people who cannot tolerate ursodeoxycholic acid.
TA507	sofosbuvir–velpatasvir–voxilaprevir	chronic hepatitis C	3.76	Sofosbuvir–velpatasvir–voxilaprevir for treating chronic hepatitis C in direct-acting antivirals experienced patients.
TA589	blinatumomab	acute lymphoblastic leukaemia	2.96	Blinatumomab for treating Philadelphia-chromosome-negative CD19-positive B-precursor acute lymphoblastic leukaemia in adults with minimal residual disease (MRD) of at least 0.1%, only if the disease is in first complete remission.
TA537	ixekizumab	psoriatic arthritis	-0.10	Ixekizumab (alone or with methotrexate) for treating active psoriatic arthritis in adults who have not responded to, or are ineligible for, a TNF-alpha inhibitor.
TA220	golimumab	psoriatic arthritis	-0.30	Golimumab for the treatment of active and progressive psoriatic arthritis.
TA512	tivozanib	renal cell carcinoma	-0.38	Tivozanib for treating advanced renal cell carcinoma in adults, only if they have had no previous treatment.
TA561	venetoclax	chronic lymphocytic leukaemia	-0.39	Venetoclax (with rituximab) for treating chronic lymphocytic leukaemia in adults who have had at least 1 previous therapy.

TA	Product	Disease	QALY	Specifics
TA543	tofacitinib	psoriatic arthritis	-0.49	Tofacitinib (with methotrexate) for treating active psoriatic arthritis in adults who have not responded to, or are ineligible for, a TNF-alpha inhibitor.

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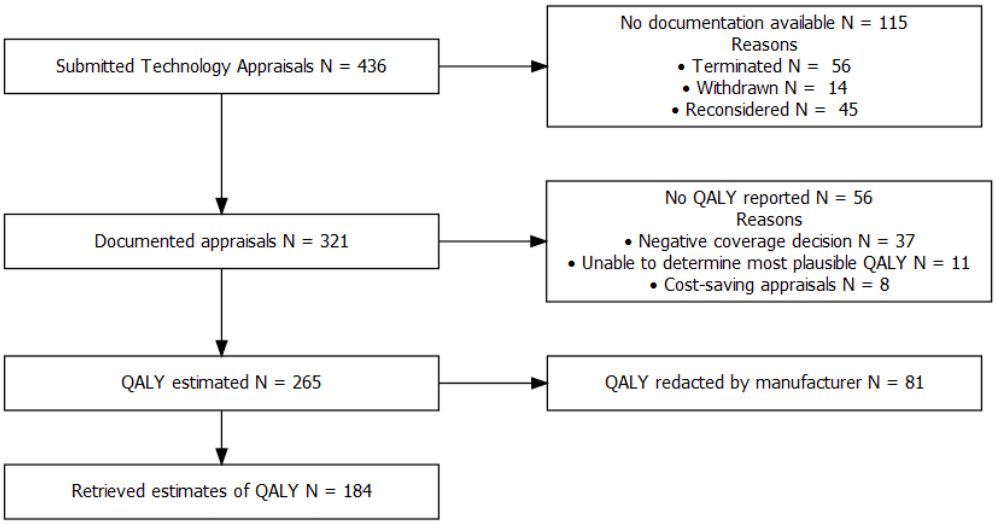

Figure 1 : Flowchart
Flowchart of the selection and retrieval of estimates of Quality-Adjusted Life Years (QALYs) from NICE technology appraisals

292x153mm (72 x 72 DPI)

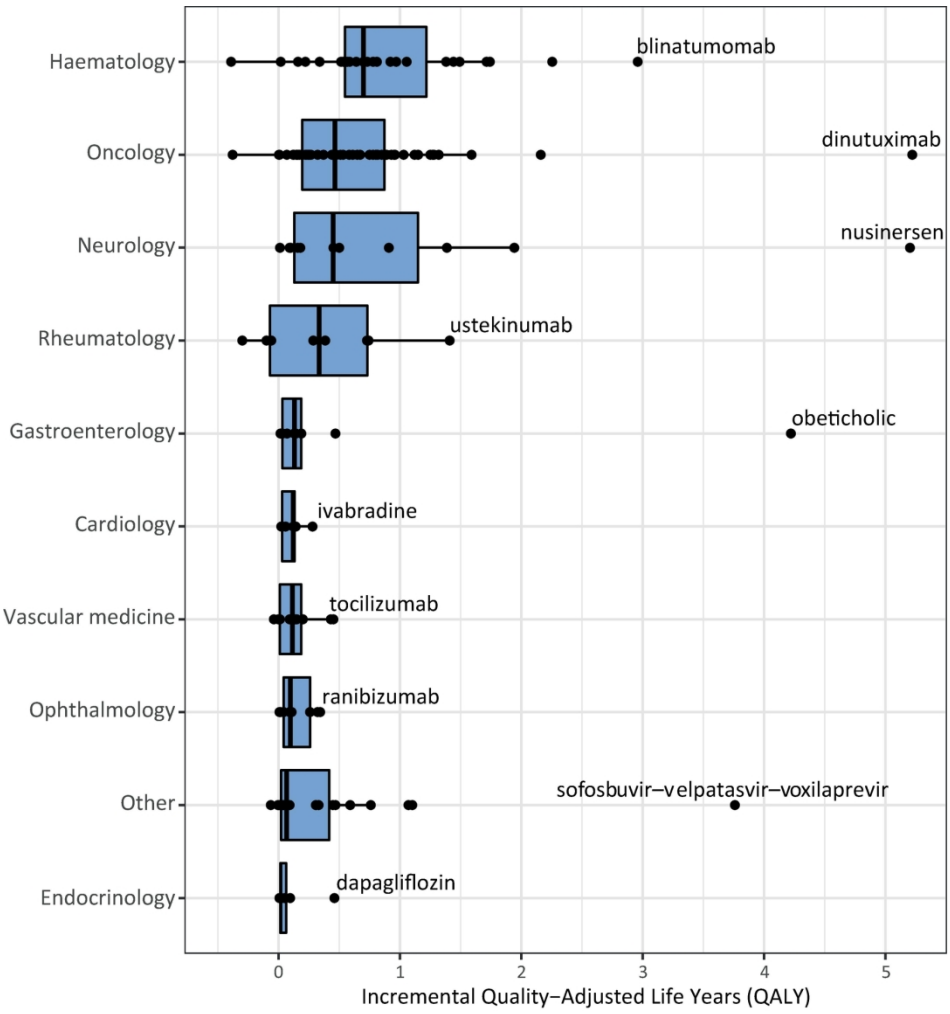

Figure 2: The added value of all novel pharmaceuticals over the past decade
Display of the distribution (boxplot) of added value in Quality Adjusted Life Years (QALYs) of novel pharmaceuticals per medical discipline that have received a positive coverage decision of NICE between January 1st, 2010 and January 1st, 2021. Medical disciplines with fewer than eight appraisals were classified as 'Other'.

166x166mm (300 x 300 DPI)

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3, 4
Objectives	3	State specific objectives, including any prespecified hypotheses	3, 4
Methods			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	4
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	4
Bias	9	Describe any efforts to address potential sources of bias	6
Study size	10	Explain how the study size was arrived at	4
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	4
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	4
		(*b*) Describe any methods used to examine subgroups and interactions	4
		(*c*) Explain how missing data were addressed	4
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	N/A
		(*e*) Describe any sensitivity analyses	N/A
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	4, 5
		(b) Give reasons for non-participation at each stage	4, 5
		(c) Consider use of a flow diagram	Figure 1 (page 4)
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	5
		(b) Indicate number of participants with missing data for each variable of interest	5
Outcome data	15*	Report numbers of outcome events or summary measures	5
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	5
		(*b*) Report category boundaries when continuous variables were categorized	5
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	8
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	N/A
Discussion			
Key results	18	Summarise key results with reference to study objectives	8
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	8
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	7,8
Generalisability	21	Discuss the generalisability (external validity) of the study results	6-9
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	9

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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The incremental therapeutic value of novel pharmaceuticals: a cross-sectional study of UK NICE QALY estimates from 2010 to 2020

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The incremental therapeutic value of novel pharmaceuticals: a cross-sectional study of UK NICE QALY estimates from 2010 to 2020

Tobias B. Polak, MSc[1], David G.J. Cucchi, MD, PhD[2],
Jonathan J. Darrow, SJD, LLM, JD, MBA[3], Matthijs M. Versteegh, PhD[4]

Corresponding author:
Tobias Boy Polak
Department of Biostatistics, Na28
Doctor Molewaterplein 40
3015 GD Rotterdam, the Netherlands Phone: +31 10 704 0 704
Email: t.polak@erasmusmc.nl

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Keywords: Health Technology Assessment; QALY; novel pharmaceuticals; incremental value

[1] Erasmus School of Health Policy & Management, Erasmus University of Rotterdam, Rotterdam, The Netherlands

[2] Department of Haematology, Amsterdam UMC, Vrije Universiteit Amsterdam, Cancer Center Amsterdam, Amsterdam, The Netherlands

[3] Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts

[4] institute for Medical Technology Assessment, Erasmus University of Rotterdam, Rotterdam, The Netherlands

Abstract

Objectives: To evaluate the incremental value of new drugs across disease areas receiving favourable coverage decisions by the United Kingdom's National Institute for Health and Care Excellence (NICE) over the past decade.

Design, setting, and participants: This cross-sectional study assessed favourable appraisal decisions of drugs between January 1, 2010 and December 31, 2020. Estimates of incremental benefit were extracted from NICE's evidence review groups reports.

Primary outcome measure: Incremental benefit of novel drugs relative to the best alternative therapeutic option, expressed in Quality Adjusted Life Years (QALYs).

Results: 184 appraisals of 129 drugs provided QALYs. The median incremental value was 0·27 QALY (interquartile range[IQR]: 0·07-0·73). Benefits varied across drug-indication pairs (range: -0·49-5·22 QALYs). The highest median benefits were found in haematology (0·70 QALY, IQR: 0·55-1·22) and oncology (0·46 QALY, IQR: 0·20-0·88), the lowest in ophthalmology (0·09, IQR: 0·04-0·22) and endocrinology (0·02, IQR: 0·01-0·06). Eight appraisals (4·3%) found contributions of more than two QALYs, but one in four (50/184) drug-indication pairs provided less than the equivalent of one month in perfect health compared to existing treatments.

Conclusions: In our review period, the median incremental value of novel drugs approved for use within the English NHS, relative to the best alternative therapeutic option, was equivalent to three to four months of life in perfect health, but data were heterogeneous. Objective evaluations of therapeutic value helps patients and physicians to develop reasonable expectations of drugs and delivers insights into disease areas where medicinal therapeutic progress has had the most and least impact.

Strengths and limitations of this study

- We systematically compared QALY data from NICE appraisals of all novel pharmaceuticals recommended for use within the English NHS between January 1, 2010 and December 31, 2020.
- Incremental QALYs were calculated based on the best alternative therapy.
- We analysed expected health benefits from the individual patient's perspective and did not consider effects on the population level, e.g. disease prevalence and market share.
- Our analysis is limited to appraisals that disclose information on incremental QALYs.

Introduction

Before a novel treatment is allowed on the market, its clinical benefit is assessed by regulatory agencies such as the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA). However, clinical benefit evaluations do not provide insight into issues deemed relevant by payers, such as comparative effectiveness, cost effectiveness, or lifetime benefit. Therefore, several countries have created independent health technology assessment bodies to conduct drug value assessments, commonly referred to as cost effectiveness analyses.[1] Through these value assessments, publicly-funded experts help to clarify the incremental clinical benefit and incremental costs of selected new therapies according to their approved indications, which professional societies may then rely on when revising treatment guidelines to include the new drug.

Despite the increased focus on incremental drug value, surprisingly little attention has been devoted to understanding the magnitude and distribution of their clinical benefits across disease areas. The limited scholarship in this area can be explained in part by the fact that, until recently, it has been difficult to compare the benefit of drugs intended to treat widely divergent diseases or conditions.

However, the emergence of official government drug value assessments over the past two decades, rigorously conducted following a consistent set of health economic modelling guidelines, now makes such comparisons feasible. These assessments utilize the Quality Adjusted Life Year (QALY), a common metric of patient health. One QALY, for example, represents the equivalent of one additional year of life in perfect health, or some longer period of time in less-than-perfect health.[2,3] Although the QALY has long been available as a measure and is frequently used in individual economic evaluations,[4] the QALY can, in combination with forecasts over the lifetime of patients from health economic models, be used to compare health benefits across medical disciplines in a consistent and transparent manner. QALYs are primarily used to calculate incremental cost-effectiveness ratios (ICER), which signals the efficiency with which a health technology produces health by dividing incremental costs by incremental benefits expressed as QALYs. However, it is often overlooked that the QALY part of an ICER is, in and of itself, a parameter that provides relevant insights into the size of forecasted health benefit. In the case of the UK, QALYs are produced following specific modelling guidance by the National Institute for Health and Care Excellence (NICE), enhancing their comparability across diseases.

NICE is a non-departmental public body that assesses the value of novel drugs and the impact on the English National Health System (NHS) of adopting them. Since NICE was established in 1999, drug manufacturers have been invited to submit evidence on the health benefits and costs of their drugs in comparison to the standard of care.[5] An evidence review group—generally a group of university based researchers contracted by NICE—then appraises the evidence in "single technology appraisals" and produces independent estimates of health benefits, measured in QALYs.

Using data from NICE evidence review groups, we sought to better understand the incremental value of all new therapies assessed from 2010 to 2020. Although these data are used to inform public health decisions, we here present their implications from a patient's perspective. Specifically, we sought to identify disease areas where the greatest gains from novel therapies have occurred, and the differing average amounts of gain per drug for individual patients in each disease area.

Materials and methods

We identified all single technology appraisals of novel pharmaceuticals that were submitted to NICE between January 1, 2010 and December 31, 2020.[6] Data were extracted on May 1, 2021. We excluded drug appraisals resulting in negative coverage decisions, appraisals for which no data were available because of termination, withdrawal, or reconsideration, and appraisals that addressed only cost-saving issues and lacked QALY data.

Two authors (TBP and DGJC) independently extracted QALY estimates from each drug's appraisal documents. Discordance was resolved by discussion with the last author (MMV). As per NICE guidance,[7] QALYs are calculated over the remainder lifetime of patients, and future health benefits are discounted at a 3.5% annual rate. We extracted these 'net present' values. When appraisal documents included multiple comparators, we extracted the QALY value that corresponded to the best alternative therapy. As a sensitivity analysis, in the case of multiple comparators, we also computed the added value compared with the next-best alternative. We disregarded cost, as we focused on health gains for individual patients and not on health care systems.

The evidence review group usually specified which of the modelled QALYs was its preferred estimate of health benefit (i.e. which modelling assumptions were deemed most appropriate to the review group). If the evidence review group did not clearly document their preference and this could not be determined after deliberation with the last author (MMV), we discarded the appraisal from our analysis. Although manufacturers frequently report the incremental cost-effectiveness ratio in cost (British pounds) per QALY, they are not required to disclose the individual components of this ratio. We therefore removed appraisals in which the manufacturer redacted all estimates of incremental QALYs (also see: Supplementary Material). A schematic overview of our appraisal selection and data extraction method is depicted in Figure 1.

Each appraisal was categorized according to its medical discipline: cardiology, endocrinology, gastroenterology, haematology, neurology, oncology, ophthalmology, rheumatology, vascular medicine, infectious diseases and other (benign haematology, dermatology, internal medicine, nephrology, psychiatry, pulmonology, urology). Summary statistics were calculated and visualized in R version 4·0·5.

Patient and Public Involvement

No patients were involved during the planning and writing of this work; all data were derived from NICE single technology appraisals.

Results

Between January 1, 2010 and December 31, 2020, 436 single technology appraisals were submitted to NICE associated with 212 drugs. No documentation was available for 115 appraisals, including 14 that were withdrawn, 56 that were terminated, and 45 that were later reconsidered or updated. Another 37 appraised drug-indication pairs received a negative reimbursement determination, meaning they were not considered a cost-effective use of NHS resources and thus did not become available to patients in the UK. An estimate of QALY gain could not be extracted in 19 appraisals, because QALYs were not reported in cost-saving appraisals or because the evidence review group did not specify its preferred estimate out of several reported outcomes. After these exclusions, 265 appraisals were available for evaluation, associated with 171 drugs. Of these appraisals, 81 had their incremental QALY estimates redacted (Supplementary Material), which can occur at the company's request, leaving 184 appraisals associated with 129 drugs for inclusion in our data set (different appraisals can review the same drug for different indications).

Of the 184 drug-indication pairs, the median incremental QALY gain relative to the best alternative therapy was 0·27 QALY (interquartile range [IQR]: 0·07-0·73) (Figure 2). The highest median benefits were associated with drugs developed for medical disciplines such as haematology (0·70, IQR: 0·55-1·22), oncology (0·46, IQR: 0·20-0·88), and neurology (0·45, IQR: 0·13-1·15), and the lowest for drugs associated with medical disciplines such as vascular medicine (0·11, IQR: 0·01-0·19), ophthalmology (0·09, IQR: 0·04-0·22) and endocrinology (0·02, IQR: 0·01-0·06).

In our review period, eight (4·3%) positive coverage decisions were granted to drugs contributing more than the equivalent of two life years in perfect health. Both dinutuximab beta to treat neuroblastoma and nusinersen used to treat children with spinal muscular atrophy led patients to accumulate 5·2 incremental QALYs.

On the other hand, 50 (27%) drugs contributed no more than the equivalent of one month in perfect health over the best alternative therapeutic option (≤ 0·082 QALY) (Table 1). Eight drugs were estimated to provide lower QALY gains than their next best alternative. Government decision makers may nevertheless be willing to pay for such products thanks to the uncertainty around point estimates, together with strategic pricing by manufacturers. For example, one drug, venetoclax, was estimated to be inferior to its direct comparator (ibrutinib) in the treatment of chronic lymphocytic leukaemia. Although this negative point estimate was considered most plausible by the evidence review group, there was still considerable uncertainty remaining as the group also provided higher estimates (an incremental benefit of 0·51 when idelalisib was the comparator) and lower estimates (-1·75 when treatment effects of venetoclax were assumed to be waning faster than expected) under varying assumptions. Venetoclax was offered at a lower price than ibrutinib, and NICE concluded that the new drug was likely a cost-effective use of NHS resources in the treatment of lymphocytic leukaemia.[8]

When selecting the next-best drug as a comparator instead of the best available comparator, the median added value slightly increases (0·31, IQR: 0·09 – 0·73), suggesting our results are robust under these different choices of comparators.

Discussion

Novel pharmaceuticals that became publicly available to patients in the NHS over the past eleven years and that were favourably evaluated by NICE contributed the net present equivalent of between three to four months of life in perfect health relative to the best alternative therapy. The added benefit varied greatly, including eight drugs that were inferior in some cases to its already-available counterpart, and two that provided the equivalent of over five years in perfect health. To our knowledge, this analysis is the first to compare the therapeutic value of drugs across diverse disease areas using QALYs extracted from independent cost-effectiveness analyses conducted through a standardized framework.

The largest benefits were observed in areas such as haematology or oncology, where drugs were shown to improve quality or duration of life by 0·70 and 0·46 QALY. Patients have least profited from pharmaceutical innovations in endocrinology and ophthalmology, where novel pharmaceuticals were associated with a median incremental benefit of 0·02 to 0·09 QALYs.

The nature of each treatment (curative, palliative, symptomatic, preventive) may impact the incremental QALY. For example, adult patients that have undergone total hip or knee replacements may be treated with apixaban (TA245) to prevent venous thromboembolism. When used for this indication, apixaban provides an incremental benefit of 0·0016 QALY over the standard of care (low-molecular-weight heparin), equivalent to an additional fourteen hours of life in perfect health. The very low benefit reflected estimates that one venous thromboembolism event would be prevented for every 110–250 patients treated prophylactically for ten days following surgery.[9–11] Although apixaban may prevent serious outcomes (death) in some patients, outcome heterogeneity led to the extremely low average incremental QALY.

QALY evaluations are necessarily based on the data available at the time of drug approval, which are in turn increasingly based on earlier-phase trials, but later-generated evidence often fails to confirm promising early results.[12] Furthermore, most (59%) drugs are now approved on the basis of surrogate endpoints,[13] such as progression free survival, which for purposes of QALY calculations are assumed to correlate with clinical outcomes such as increased survival. However, studies have shown that this correlation is often poor or fair, particularly in oncology.[14,15] Additionally, data on infrequent or longer-term harms cannot be known with certainty or incorporated in the appraisals, as these data only become apparent when the drug is available for broader use. Furthermore, fitter patients are often recruited for clinical trial participation and the outcomes for more vulnerable patients are not known. Factors such as these could cause QALY values to be lower than NICE estimates suggest.

Three additional issues can also lead to overestimations in incremental therapeutic benefit. First, during the time it takes to plan and conduct a trial, approve a drug, and complete a cost-effectiveness assessment, the standard of care may have shifted and the best available comparator may no longer provide the relevant baseline for comparison. Second, a drug may have different benefits for different indications, a factor of particular relevance when off-label use is widespread or where marketing authorization is granted for a population that is broader than the tested population. Third, trials may be designed to demonstrate incremental benefit even when available treatments might demonstrate similar efficacy if tested with a different trial design.

Our findings should be interpreted with caution and cannot easily be interpreted from a population health perspective, as drug-indication pairs may be reimbursed within some health systems only for specific patient populations. For example, some of these large incremental benefits mainly occur for drugs that were not considered cost-effective in earlier lines of therapy – but when all prior therapies fail, these drugs are estimated to provide substantial benefit. From the examples in Table 1, sofosbuvir-velpatasvir-voxilaprevir is estimated to generate 3.76 incremental QALYs for patients who have previously been treated with direct-acting antivirals. However, the Marketing Authorisation has been granted to treat patients regardless of cirrhosis status and treatment history. These benefits must be seen in this larger context.

Our study has a few limitations. First, our analysis was restricted to data presented to NICE of drugs that subsequently obtained a positive coverage decision, excluding medicine that may be accessed via private health insurance. Therefore, drugs in our review are a subset of the drugs covered in other analyses of medication approved by the FDA or EMA, a subset that is likely to be associated with higher QALY estimates than the average new drug. Not all FDA-approved drugs are subsequently approved by the EMA, and not all EMA-approved drugs are assessed by NICE. A recent assessment of oncology drugs approved via the FDA's accelerated approval pathway

demonstrated that only half (48%, 45/93) of drug-indication pairs subsequently became reimbursed within the English NHS, suggesting their therapeutic benefit was not sufficiently important or well established in relation to the associated cost to receive a positive reimbursement decision.[16]

Second, we could not retrieve all estimates of health benefit as some were concealed by the manufacturer, the implications of which are unclear. It seems some companies maintain a policy of not disclosing QALY figures for any indications or drugs, whereas other companies consistently provide full disclosure. The desire to maintain in confidence the incremental cost of their treatment, which would implicitly be made evident if both cost/benefit ratios and QALY values were simultaneously disclosed, may be the driving force behind redactions. In the Supplementary Material, we provide examples where we could retrieve estimates due to ineffective redaction. We also list the number of redacted estimates by disease area. The rates of redaction in oncology (37.2%) and haematology (44.9%), compared with other disease areas (such as cardiology, vascular medicine, endocrinology) where none of the values were redacted, may either represent the unwillingness to disclose high drug prices in these indications,[17] or the unwillingness to disclose low benefits, the latter of which may make average QALY figures appear larger than they are for these disease areas. For withdrawn or terminated appraisals, no detailed information is available to the public on cost or QALYs. Although speculative, it is unlikely these appraisals discussed drugs that were cheaper and more effective than the current standard of care.

Third, QALY estimates of individual products are sensitive to the choice of relevant comparator. Our results, however, show that the choice of comparator does not significantly affect the overall estimated QALY gain in our dataset. Alternatively, one may not be interested in the overall population, but only in specific (sub)populations reported in the appraisal documentation. This may give more specific estimates for individual patients, but impedes the comparison of drugs across diseases.

Fourth, estimates of median incremental QALY for each drug are associated with varying degrees of uncertainty. Although we have extracted the 'preferred' estimate from the evidence review group, the variance of these estimates is not routinely reported. Furthermore, distinct preferences in modelling choices, may result in substantial differences in benefit estimates.

Our findings provide insight into the relative benefits of new pharmaceuticals across therapeutic areas. Additional health gains may be hindered by the difficulty of developing novel drugs for specific diseases, perhaps because major improvements have already been generated prior to our review period,[18,19] or because scientific breakthroughs have not yet occurred. QALYs are a useful tool for comparison, but the measure omits important health-related variables, such as the extent to which a patient remains unable to live out a "normal" life expectancy or achieve complete health. Other factors, such as lack of fundamental understanding of disease pathologies,[20,21] or the abundance or absence of sufficient research funding may also limit health gains.[22] Our figures evaluate the net present health-related benefits of drugs that are considered cost-effective by NICE over the past decade. In combination with indices measuring health needs, such as the Global Burden of Disease,[23] as well as cost-effectiveness/cost-saving data of novel drugs that might produce similar QALYs as already available therapies, our findings can help provide context for the allocation of research funding and thereby shape health policy.

Eight drugs improved life by more than two incremental QALYs, which may justify their superlative epithets of "ground-breaking" or "game-changing".[24] Half of the drugs in our study were likely to improve life by the equivalent of three to four months in perfect health, and 84·8% of novel drugs did not add more than one such year. Unfortunately, 25% of appraisals have covered drugs that contributed the equivalent of no more than one month in perfect health, and 23 (12·5%) drug-indication pairs were estimated to add several hours to just a week of perfect health. For example, eluxadoline for prevention of diarrhoea and abdominal pain in patients with irritable bowel syndrome yielded a total QALY gain of 0·015—equivalent to 5·5 days in perfect health—compared with placebo. Given the uncertainty around cost-effectiveness estimates—models that require ample assumptions and extrapolations over lifetime horizons can hardly be expected to accurately forecast a week of health gained—drafting extensive cost-effectiveness reports in these situations is not likely to be a cost-effective use of time.

Drugs that have little health benefit relative to the best alternative may still promote price competition and thereby free funds for other public health initiatives or treatments. To avoid wasting public resources in needless evaluations, guideline committees could determine a threshold of incremental benefit that is clinically relevant to each disease area.[25] Drugs that do not pass this threshold based on early assessments of their value should be rejected without a full evaluation unless they are offered at lower cost.

Patients and physicians can use the QALY data presented here to put the effectiveness of treatments in perspective. The frequently employed metric of "number needed to treat" provides important information about the effectiveness of drugs on the principal disease-specific outcome. For example, the efficacy of eluxadoline could be described in terms of the number of patients that would need to be treated three months to avoid one episode of abdominal pain or diarrhoea, in this case between eight and 33 patients over three months.[26] Metrics such as this, however, do not account for adverse events. Using the incremental QALY estimate that integrates gains and losses into a single measure (for eluxadoline, 0·015), it is possible to calculate that 67 patients would need to be treated over their lifetime horizons to gain the equivalent of one year in perfect health. As such, the QALY provides an estimate of both duration and quality of life, which are arguably the two most important factors from the perspective of a patient.

Conclusions

Novel pharmaceuticals that received a positive coverage decision by NICE from 2010 to 2020 provided patients with an average of 0·27 additional QALYs over the best alternative therapy, the equivalent of three to four additional months of life in perfect health. One in four drugs does not improve quality and quantity of life by more than one month, and incremental benefit varies greatly across disease areas and compounds. Several novel drugs do not provide additional QALY gains over available therapies, but if offered at a lower price could still be of interest from a public cost-saving perspective even if not from the patient's perspective. Providing transparent information on the added value of novel therapies enables patients and physicians to have reasonable expectations about the average net benefits of therapies at their disposal. Objectively evaluating the benefits contributed by novel pharmaceuticals provides insight not only into whether a given drug is worth its price once approved, but also into the therapeutic return on investment reaped by society from the substantial public and private sums expended on research and development. Finally, these figures provide a benchmark for future innovations.

Ethics approval statement

No patients were involved during the planning and writing of this work. Therefore the study did not require ethical approval by the institutional review board.

Declaration of interests

TBP is employed part-time by myTomorrows, which facilitates expanded access programs for the pharmaceutical industry. TBP holds stock in myTomorrows (<0.1%). TBP has received funding for research from the Dutch government (grant EMCLSH20012). The research of TBP is conducted independently and TBP is contractually free to publish any results for all the conducted work. None of the recent work concerns the topic in this analysis. DGJC has no interests to declare. MMV is director of the institute of Medical Technology Assessment (iMTA). iMTA conducts cost-effectiveness research funded by international governments, pharmaceutical industry, and med-tech industry. All research is conducted independently and iMTA is contractually free to publish any results for all conducted work. None of the recent work concerns the topic in this analysis. Jonathan Darrow receives funding from Arnold Ventures, the Greenwall Foundation, the Kaiser Permanente Institute for Health Policy, West Health, and the Novo Nordisk Foundation (grant for a scientifically independent Collaborative Research Programme; grant NNF17SA0027784).

Author contributions

TBP and MMV conceived the research. TBP and DGJC collected, analysed and visualised the data. TBP drafted the first version of the manuscript; JJD and DGJC critically revised the first version of the paper; all authors discussed the results and contributed to the final manuscript. All authors had full access to all the data in the study and accept responsibility for submission for publication.

Data sharing

All raw data are available through the NICE website. Aggregated data will be made available upon reasonable request.

Acknowledgements

We thank Dr. Noor Gieles and Ms. Rozemarijn Berends for critically reviewing the manuscript.

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Figure legends

Figure 1 : Flow diagram
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Tables

Table 1
Pharmaceuticals that produced most and least incremental health benefit, ranked according to their added Quality-Adjusted Life Years (QALYs) extracted from NICE Technology Appraisals (TAs).

TA	Product	Disease	QALY	Specifics
Top-5 pharmaceuticals with the largest incremental health benefits, compared with their next-best alternative.				
TA538	dinutuximab beta	neuroblastoma	5.22	Dinutuximab beta for treating high-risk neuroblastoma in people aged 12 months and over whose disease has at least partially responded to induction chemotherapy, followed by myeloablative therapy and stem cell transplant, only if they have not already had anti-GD2 immunotherapy.
TA588	nusinersen	spinal muscular atrophy	5.20	Nusinersen for treating 5q spinal muscular atrophy (SMA) only if people have pre-symptomatic SMA, or SMA types 1, 2 or 3.
TA443	obeticholic	primary biliary cholangitis	4.22	Obeticholic acid for treating primary biliary cholangitis in combination with ursodeoxycholic acid for people whose disease has responded inadequately to ursodeoxycholic acid or as monotherapy for people who cannot tolerate ursodeoxycholic acid.
TA507	sofosbuvir–velpatasvir–voxilaprevir	chronic hepatitis C	3.76	Sofosbuvir–velpatasvir–voxilaprevir for treating chronic hepatitis C in direct-acting antivirals experienced patients.
TA589	blinatumomab	acute lymphoblastic leukaemia	2.96	Blinatumomab for treating Philadelphia-chromosome-negative CD19-positive B-precursor acute lymphoblastic leukaemia in adults with minimal residual disease (MRD) of at least 0.1%, only if the disease is in first complete remission.
Top-5 pharmaceuticals with the smallest incremental health benefits compared with their next-best alternative.				
TA537	ixekizumab	psoriatic arthritis	-0.10	Ixekizumab (alone or with methotrexate) for treating active psoriatic arthritis in adults who have not responded to, or are ineligible for, a TNF-alpha inhibitor.
TA220	golimumab	psoriatic arthritis	-0.30	Golimumab for the treatment of active and progressive psoriatic arthritis.

TA	Product	Disease	QALY	Specifics
TA512	tivozanib	renal cell carcinoma	-0.38	Tivozanib for treating advanced renal cell carcinoma in adults, only if they have had no previous treatment.
TA561	venetoclax	chronic lymphocytic leukaemia	-0.39	Venetoclax (with rituximab) for treating chronic lymphocytic leukaemia in adults who have had at least 1 previous therapy.
TA543	tofacitinib	psoriatic arthritis	-0.49	Tofacitinib (with methotrexate) for treating active psoriatic arthritis in adults who have not responded to, or are ineligible for, a TNF-alpha inhibitor.

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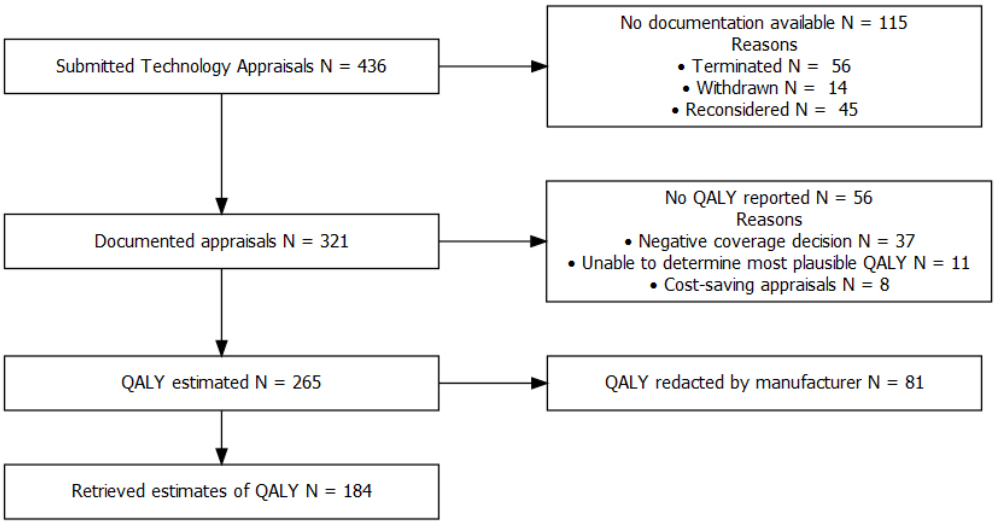

Figure 1. Flow diagram.
Flow diagram of the selection and retrieval of estimates of Quality-Adjusted Life Years (QALYs) from NICE technology appraisals between January 1, 2010 and December 31, 2020.

292x153mm (72 x 72 DPI)

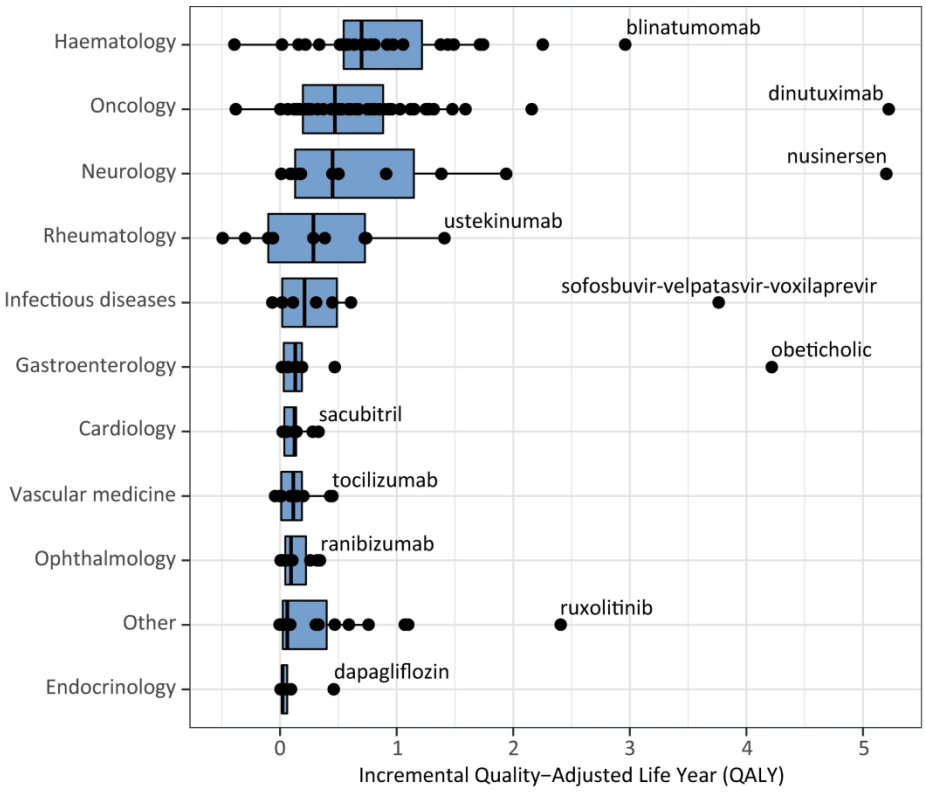

Figure 2: The added value of novel pharmaceuticals approved by NICE from 2010 to 2020

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218x171mm (300 x 300 DPI)

Supplementary Material to the manuscript:

The incremental therapeutic value of novel pharmaceuticals: a cross-sectional study of UK NICE QALY estimates from 2010 to 2020

Tobias B. Polak MSc, David G.J. Cucchi MD, PhD,

Jonathan Darrow SJD, LLM, JD, MBA and Matthijs M. Versteegh, PhD

This supplementary material provides more background information regarding the redaction of estimates of cost, Quality-Adjusted Life Years (QALYs) and Incremental Cost-Effectiveness Ratios (ICERs) available in Technology Appraisals (TAs) as available from the National Institute of Care and Excellence (NICE) in the United Kingdom.

A. Overview of redacted technology appraisals by disease area

	Estimate Redacted		
	Yes, N = 81[1]	No, N = 184[1]	Overall, N = 265
Disease area			
Oncology	35 (37%)	59 (63%)	94
Hematology	22 (45%)	27 (55%)	49
Neurology	4 (27%)	11 (73%)	15
Ophthalmology	4 (29%)	10 (71%)	14
Rheumatology	5 (36%)	9 (64%)	14
Gastroenterology	2 (18%)	9 (82%)	11
Cardiology	0 (0%)	10 (100%)	10
Dermatology	3 (30%)	7 (70%)	10
Vascular medicine	0 (0%)	10 (100%)	10
Endocrinology	0 (0%)	8 (100%)	8
Infectious diseases	0 (0%)	8 (100%)	8
Pulmonology	2 (29%)	5 (71%)	7
Benign hematology	1 (25%)	3 (75%)	4
Psychiatry	0 (0%)	4 (100%)	4
Internal medicine	2 (67%)	1 (33%)	3
Nephrology	0 (0%)	2 (100%)	2
Urology	1 (50%)	1 (50%)	2

[1]n (%)

B. Examples of various redaction strategies

I. Complete redaction

Here we provide examples of TAs where all estimates are redacted.

Table 28: Scenario analyses for prolonged post-treatment overall survival benefit (including ERG corrections)

Extension	Total			Incremental			ICER (£/QALY)
Treatment	*Costs*	*QALYs*	*Life years*	*Costs*	*QALYs*	*Life years*	
Base case							
Hydroxycarbamide	[redacted]	[redacted]	[redacted]	—	—	—	—
Bosutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
+1 month							
Bosutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
+2 months							
Bosutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
+3 months							
Bosutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
−1 month							
Bosutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year

Figure 1: Completely redacted estimates (ICER, QALY, cost) from TA401: Bosutinib for previously treated chronic myeloid leukaemia. Table from Evidence Review Group Report.

Table 62. Deterministic results using the PAS for dacomitinib and the list prices for the comparators

Treatment	Expected mean costs (£)	Incremental costs (£)	Expected mean QALY	Incremental QALY	ICER (£)
Erlotinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dacomitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gefitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Afatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life years gained					

Figure 2: Completely redacted estimates (ICER, QALY, cost) from TA595: Dacomitinib for untreated EGFR mutation-positive non-small-cell lung cancer. Table from Evidence Review Group Report.

II. Incomplete redaction

Here we provide examples of TAs where two out of three unknowns are redacted. We could not find examples where cost was the only revealed estimate.

ERG base case compared to BSC
no 17p deletion/TP53 mutation (pop. 4)

	Incremental costs	Incremental QALYs	ICER	Δ ICER
Company base case*	[redacted]	3.529	[redacted]	-
Correcting hazard ratios*	[redacted]	3.385	[redacted]	[redacted]
Using post progression data after idelalisib for BSC*	[redacted]	2.377	[redacted]	[redacted]
Changing PFS utility value from 0.853 to 0.71*	[redacted]	3.025	[redacted]	[redacted]
Changing cost of some AEs*	[redacted]	3.465	[redacted]	[redacted]
ERG's preferred base case*	[redacted]	1.741	[redacted]	[redacted]

Abbreviations: BSC, best supportive care; PFS, progression free survival; AE, adverse event

*analyses include corrected starting age and proportion male

Figure 3: Redacted estimates (ICER, cost) from TA487: Venetoclax for treating chronic lymphocytic leukaemia. Table from the Public Committee Slides Appraisal Consultation.

Table 64: Exploratory Analysis 4 – ERG-preferred base case

Probabilistic model					
Option	**QALYs**	**Costs**	**Incremental QALYs**	**Incremental costs**	**Incremental cost per QALY gained**
Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	**£61,219**
Rituximab/chemotherapy	[redacted]	[redacted]	-	-	-
Deterministic model					
Option	**QALYs**	**Costs**	**Incremental QALYs**	**Incremental costs**	**Incremental cost per QALY gained**
Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	**£61,050**
Rituximab/chemotherapy	[redacted]	[redacted]	-	-	-

QALY - quality-adjusted life year

Figure 4: Redacted estimates (QALY, cost) from TA491: Ibrutinib for treating Waldenstrom's macroglobulinemia. Table from Evidence Review Group Report.

III. Ineffective redaction

Here we provide examples of TAs where one out of three unknowns is redacted. Because the ICER is the ratio of incremental cost and incremental QALYs, the unknown is not 'unknown' and can be derived.

Table 5-1 Effect of corrections and amendments made by ERG to the manufacturer's model for the base case analysis (paclitaxel/carboplatin as comparator) over 6 years

	Gefitinib / carboplatin		Paclitaxel / carboplatin		Incremental		ICER	Changes (from 6 year horizon base case)		
Model amendment	Costs	QALYs	Costs	QALYs	Costs	QALYs	(£/QALY)	Costs	QALYs	ICER
Submitted base case	[redacted]	**1.1110**	**£27,902**	**0.9235**	**£3,637**	**0.1874**	**£19,402**			
Base case with 6 year horizon	[redacted]	**1.1110**	**£27,947**	**0.9235**	**£3,751**	**0.1874**	**£20,010**			
Amend 1st line CTX costs	[redacted]	1.1110	£24,563	0.9235	£7,135	0.1874	£38,063	+£3,498	0.0000	+£18,054
Reduced cycles of CTX	[redacted]	1.1110	£25,527	0.9270	£6,170	0.1839	£33,544	+£2,420	-0.0035	+£13,535
Revise OS models	[redacted]	1.2219	£32,985	1.0834	£2,268	0.1384	£16,381	-£1,483	-0.0490	-£3,628
Revise PFS models	[redacted]	1.0923	£28,149	0.9181	£4,989	0.1741	£28,651	+£1,238	-0.0133	+£8,641
IPASS PFS HR (not MA)	[redacted]	1.1020	£29,947	0.9235	£4,439	0.1785	£24,867	+£688	-0.0089	+£4,857
Revise discounting method	[redacted]	1.1284	£28,337	0.9378	£3,680	0.1906	£19,311	-£71	+0.0032	-£699
Omit GCSF prophylaxis	[redacted]	1.1110	£27,669	0.9235	£4,029	0.1874	£21,493	+£278	0.0000	+£1,483
Continuity correction	[redacted]	1.1110	£28,426	0.9235	£3,252	0.1874	£17,350	-£499	0.0000	-£2,660
Correct misaligned cycles	[redacted]	1.1110	£27,947	0.9235	£3,752	0.1874	£20,017	+£1	0.0000	+£7
Correct 2nd line CTX costs	[redacted]	1.1110	£25,213	0.9235	£3,975	0.1874	£21,204	+£224	0.0000	+£1,194
CTX treatment exposure	[redacted]	1.1110	£26,931	0.9235	£4,766	0.1874	£25,427	+£1,015	0.0000	+£5,417
Combined effect of all changes	[redacted]	**1.2223**	**£24,574**	**1.0988**	**£8,746**	**0.1235**	**£70,822**	**+£4,995**	**-0.0639**	**+£50,812**

ICER= incremental cost effectiveness ratio; QALY=quality adjusted life year; CTX= chemotherapy; OS= overall survival; PFS= progression free survival; granulocyte colony stimulating factor; HR=hazard ratio; MA= meta-analysis

Figure 6: Ineffective redaction of cost only from TA192: Gefitinib for the first-line treatment of locally advanced or metastatic non-small-cell lung cancer. Table from the Advisory Committee Decision Pre-meeting Briefing.

Cost-effectiveness analyses presented at 2nd committee meeting – with PAS

- Simple discount PAS agreed with Department of Health

17p deletion or TP53 mutation	Incremental		ICER
	Costs	QALYs	
Company's ACD1 response – survival based on end of life decision	[redacted]	2.38	£43,310
ERG's modified base case – PPS after idelalisib for BSC	[redacted]	1.76	£57,476

No 17p deletion or TP53 mutation	Incremental		ICER
	Costs	QALYs	
Company's ACD1 response – survival based on end of life decision	[redacted]	3.00	£49,929
ERG's modified base case – PPS after idelalisib for BSC	[redacted]	1.88	£77,779

Figure 7: Ineffective redaction of cost only from TA487: Venetoclax for treating chronic lymphocytic leukaemia. Table from the Public Committee Slides Final Appraisal Determination.

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No.	Recommendation	Page No.	Relevant text from manuscript
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	**1**	
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	**2**	
Introduction				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	**3**	
Objectives	3	State specific objectives, including any prespecified hypotheses	**3**	
Methods				
Study design	4	Present key elements of study design early in the paper	**3-4**	
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	**3-4**	
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	**3-4**	
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	**N/A**	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	**3-4**	
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	**N/A**	
Bias	9	Describe any efforts to address potential sources of bias	**N/A**	
Study size	10	Explain how the study size was arrived at	**3-4**	

Continued on next page

Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	**4**
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	**4**
		(*b*) Describe any methods used to examine subgroups and interactions	**4**
		(*c*) Explain how missing data were addressed	**4**
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	**N/A**
		(*e*) Describe any sensitivity analyses	**3**
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	**4**
		(b) Give reasons for non-participation at each stage	**4**
		(c) Consider use of a flow diagram	**Figure 1**
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	**N/A**
		(b) Indicate number of participants with missing data for each variable of interest	**4**
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	**N/A**
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	**N/A**
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	**N/A**
		Cross-sectional study—Report numbers of outcome events or summary measures	**4**
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	**4**
		(*b*) Report category boundaries when continuous variables were categorized	**4**
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	**N/A**

Continued on next page

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	**4**
Discussion			
Key results	18	Summarise key results with reference to study objectives	**5-6**
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	**5-6**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	**5-6**
Generalisability	21	Discuss the generalisability (external validity) of the study results	**5-6**
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	**8**

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Incremental benefits of novel pharmaceuticals in the United Kingdom: A cross-sectional analysis of NICE technology appraisals from 2010 - 2020

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Complete List of Authors:	Polak, Tobias; Erasmus Medical Center Department of Epidemiology, Biostatistics Cucchi, David; Amsterdam UMC Locatie VUmc, Haematology; Franciscus Gasthuis en Vlietland, Darrow, Jonathan; Harvard Medical School, Department of Medicine Versteegh, Matthijs; Institute for Medical Technology Assessment, Erasmus University Rotterdam
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Incremental benefits of novel pharmaceuticals in the United Kingdom: A cross-sectional analysis of NICE technology appraisals from 2010 - 2020

Tobias B. Polak, MSc[1], David G.J. Cucchi, MD, PhD[2],
Jonathan J. Darrow, SJD, LLM, JD, MBA[3], Matthijs M. Versteegh, PhD[4]

Corresponding author:
Tobias Boy Polak
Department of Biostatistics, Na28
Doctor Molewaterplein 40
3015 GD Rotterdam, the Netherlands Phone: +31 10 704 0 704
Email: t.polak@erasmusmc.nl

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[1] Erasmus School of Health Policy & Management, Erasmus University of Rotterdam, Rotterdam, The Netherlands

[2] Department of Haematology, Amsterdam UMC, Vrije Universiteit Amsterdam, Cancer Center Amsterdam, Amsterdam, The Netherlands

[3] Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts

[4] institute for Medical Technology Assessment, Erasmus University of Rotterdam, Rotterdam, The Netherlands

Abstract

Objectives: To evaluate the incremental value of new drugs across disease areas receiving favourable coverage decisions by the United Kingdom's National Institute for Health and Care Excellence (NICE) over the past decade.

Design, setting, and participants: This cross-sectional study assessed favourable appraisal decisions of drugs between January 1, 2010 and December 31, 2020. Estimates of incremental benefit were extracted from NICE's evidence review groups reports.

Primary outcome measure: Incremental benefit of novel drugs relative to the best alternative therapeutic option, expressed in Quality Adjusted Life Years (QALYs).

Results: 184 appraisals of 129 drugs provided QALYs. The median incremental value was 0·27 QALY (interquartile range[IQR]: 0·07-0·73). Benefits varied across drug-indication pairs (range: -0·49-5·22 QALYs). The highest median benefits were found in haematology (0·70 QALY, IQR: 0·55-1·22) and oncology (0·46 QALY, IQR: 0·20-0·88), the lowest in ophthalmology (0·09, IQR: 0·04-0·22) and endocrinology (0·02, IQR: 0·01-0·06). Eight appraisals (4·3%) found contributions of more than two QALYs, but one in four (50/184) drug-indication pairs provided less than the equivalent of one month in perfect health compared to existing treatments.

Conclusions: In our review period, the median incremental value of novel drugs approved for use within the English NHS, relative to the best alternative therapeutic option, was equivalent to three to four months of life in perfect health, but data were heterogeneous. Objective evaluations of therapeutic value helps patients and physicians to develop reasonable expectations of drugs and delivers insights into disease areas where medicinal therapeutic progress has had the most and least impact.

Strengths and limitations of this study

- We systematically compared QALY data from NICE appraisals of all novel pharmaceuticals recommended for use within the English NHS between January 1, 2010 and December 31, 2020.
- Incremental QALYs were calculated based on the best alternative therapy.
- We analysed expected health benefits from the individual patient's perspective and did not consider effects on the population level, e.g. disease prevalence and market share.
- Our analysis is limited to appraisals that disclose information on incremental QALYs.

Introduction

Before a novel treatment is allowed on the market, its clinical benefit is assessed by regulatory agencies such as the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA). However, clinical benefit evaluations do not provide insight into issues deemed relevant by payers, such as comparative effectiveness, cost effectiveness, or lifetime benefit. Therefore, several countries have created independent health technology assessment bodies to conduct drug value assessments, commonly referred to as cost effectiveness analyses.[1] Through these value assessments, publicly-funded experts help to clarify the incremental clinical benefit and incremental costs of selected new therapies according to their approved indications, which professional societies may then rely on when revising treatment guidelines to include the new drug.

Despite the increased focus on incremental drug value, surprisingly little attention has been devoted to understanding the magnitude and distribution of their clinical benefits across disease areas. The limited scholarship in this area can be explained in part by the fact that, until recently, it has been difficult to compare the benefit of drugs intended to treat widely divergent diseases or conditions.

However, the emergence of official government drug value assessments over the past two decades, rigorously conducted following a consistent set of health economic modelling guidelines, now makes such comparisons feasible. These assessments utilize the Quality Adjusted Life Year (QALY), a common metric of patient health. One QALY, for example, represents the equivalent of one additional year of life in perfect health, or some longer period of time in less-than-perfect health.[2,3] Although the QALY has long been available as a measure and is frequently used in individual economic evaluations,[4] the QALY can, in combination with forecasts over the lifetime of patients from health economic models, be used to compare health benefits across medical disciplines in a consistent and transparent manner. QALYs are primarily used to calculate incremental cost-effectiveness ratios (ICER), which signals the efficiency with which a health technology produces health by dividing incremental costs by incremental benefits expressed as QALYs. However, it is often overlooked that the QALY part of an ICER is, in and of itself, a parameter that provides relevant insights into the size of forecasted health benefit. In the case of the UK, QALYs are produced following specific modelling guidance by the National Institute for Health and Care Excellence (NICE), enhancing their comparability across diseases.

NICE is a non-departmental public body that assesses the value of novel drugs and the impact on the English National Health System (NHS) of adopting them. Since NICE was established in 1999, drug manufacturers have been invited to submit evidence on the health benefits and costs of their drugs in comparison to the standard of care.[5] An evidence review group—generally a group of university based researchers contracted by NICE—then appraises the evidence in "single technology appraisals" and produces independent estimates of health benefits, measured in QALYs.

Using data from NICE evidence review groups, we sought to better understand the incremental value of all new therapies assessed from 2010 to 2020. Although these data are used to inform public health decisions, we here present their implications from a patient's perspective. Specifically, we sought to identify disease areas where the greatest gains from novel therapies have occurred, and the differing average amounts of gain per drug for individual patients in each disease area.

Materials and methods

We identified all single technology appraisals of novel pharmaceuticals that were submitted to NICE between January 1, 2010 and December 31, 2020.[6] Data were extracted on May 1, 2021. We excluded drug appraisals resulting in negative coverage decisions, appraisals for which no data were available because of termination, withdrawal, or reconsideration, and appraisals that addressed only cost-saving issues and lacked QALY data.

Two authors (TBP and DGJC) independently extracted QALY estimates from each drug's appraisal documents. Discordance was resolved by discussion with the last author (MMV). As per NICE guidance,[7] QALYs are calculated over the remainder lifetime of patients, and future health benefits are discounted at a 3.5% annual rate. We extracted these 'net present' values. When appraisal documents included multiple comparators, we extracted the QALY value that corresponded to the best alternative therapy. As a sensitivity analysis, in the case of multiple comparators, we also computed the added value compared with the next-best alternative. We disregarded cost, as we focused on health gains for individual patients and not on health care systems.

The evidence review group usually specified which of the modelled QALYs was its preferred estimate of health benefit (i.e. which modelling assumptions were deemed most appropriate to the review group). If the evidence review group did not clearly document their preference and this could not be determined after deliberation with the last author (MMV), we discarded the appraisal from our analysis. Although manufacturers frequently report the incremental cost-effectiveness ratio in cost (British pounds) per QALY, they are not required to disclose the individual components of this ratio. We therefore removed appraisals in which the manufacturer redacted all estimates of incremental QALYs (also see: Supplementary Material). A schematic overview of our appraisal selection and data extraction method is depicted in Figure 1.

Each appraisal was categorized according to its medical discipline: cardiology, endocrinology, gastroenterology, haematology, neurology, oncology, ophthalmology, rheumatology, vascular medicine, infectious diseases and other (benign haematology, dermatology, internal medicine, nephrology, psychiatry, pulmonology, urology). Summary statistics were calculated and visualized in R version 4·0·5.

Patient and Public Involvement

No patients were involved during the planning and writing of this work; all data were derived from NICE single technology appraisals.

Results

Between January 1, 2010 and December 31, 2020, 436 single technology appraisals were submitted to NICE associated with 212 drugs. No documentation was available for 115 appraisals, including 14 that were withdrawn, 56 that were terminated, and 45 that were later reconsidered or updated. Another 37 appraised drug-indication pairs received a negative reimbursement determination, meaning they were not considered a cost-effective use of NHS resources and thus did not become available to patients in the UK. An estimate of QALY gain could not be extracted in 19 appraisals, because QALYs were not reported in cost-saving appraisals or because the evidence review group did not specify its preferred estimate out of several reported outcomes. After these exclusions, 265 appraisals were available for evaluation, associated with 171 drugs. Of these appraisals, 81 had their incremental QALY estimates redacted (Supplementary Material), which can occur at the company's request, leaving 184 appraisals associated with 129 drugs for inclusion in our data set (different appraisals can review the same drug for different indications).

Of the 184 drug-indication pairs, the median incremental QALY gain relative to the best alternative therapy was 0·27 QALY (interquartile range [IQR]: 0·07-0·73) (Figure 2). The highest median benefits were associated with drugs developed for medical disciplines such as haematology (0·70, IQR: 0·55-1·22), oncology (0·46, IQR: 0·20-0·88), and neurology (0·45, IQR: 0·13-1·15), and the lowest for drugs associated with medical disciplines such as vascular medicine (0·11, IQR: 0·01-0·19), ophthalmology (0·09, IQR: 0·04-0·22) and endocrinology (0·02, IQR: 0·01-0·06). Of note, QALY estimates were redacted in 26.7% of neurology, 28.6% of ophthalmology, 37.2% of oncology and 44.9% of haematology appraisals, whereas for vascular medicine and endocrinology, QALY estimates were available in all appraisals (also see Supplementary Material).

In our review period, eight (4·3%) positive coverage decisions were granted to drugs contributing more than the equivalent of two life years in perfect health. Both dinutuximab beta to treat neuroblastoma and nusinersen used to treat children with spinal muscular atrophy led patients to accumulate 5·2 incremental QALYs.

On the other hand, 50 (27%) drugs contributed no more than the equivalent of one month in perfect health over the best alternative therapeutic option (≤ 0·082 QALY) (Table 1). Eight drugs were estimated to provide lower QALY gains than their next best alternative. Government decision makers may nevertheless be willing to pay for such products thanks to the uncertainty around point estimates, together with strategic pricing by manufacturers. For example, one drug, venetoclax, was estimated to be inferior to its direct comparator (ibrutinib) in the treatment of chronic lymphocytic leukaemia. Although this negative point estimate was considered most plausible by the evidence review group, there was still considerable uncertainty remaining as the group also provided higher estimates (an incremental benefit of 0·51 when idelalisib was the comparator) and lower estimates (-1·75 when treatment effects of venetoclax were assumed to be waning faster than expected) under varying assumptions. Venetoclax was offered at a lower price than ibrutinib, and NICE concluded that the new drug was likely a cost-effective use of NHS resources in the treatment of lymphocytic leukaemia.[8]

Table 1
Pharmaceuticals that produced most and least incremental health benefit, ranked according to their added Quality-Adjusted Life Years (QALYs) extracted from NICE Technology Appraisals (TAs).

TA	Product	Disease	QALY	Specifics
Top-5 pharmaceuticals with the largest incremental health benefits, compared with their next-best alternative.				
TA538	dinutuximab beta	neuroblastoma	5.22	Dinutuximab beta for treating high-risk neuroblastoma in people aged 12 months and over whose disease has at least partially responded to induction chemotherapy, followed by myeloablative therapy and stem cell transplant, only if they have not already had anti-GD2 immunotherapy.
TA588	nusinersen	spinal muscular atrophy	5.20	Nusinersen for treating 5q spinal muscular atrophy (SMA) only if people have pre-symptomatic SMA, or SMA types 1, 2 or 3.
TA443	obeticholic	primary biliary cholangitis	4.22	Obeticholic acid for treating primary biliary cholangitis in combination with ursodeoxycholic acid for people whose disease has responded inadequately to ursodeoxycholic acid or as monotherapy for people who cannot tolerate ursodeoxycholic acid.
TA507	sofosbuvir–velpatasvir–voxilaprevir	chronic hepatitis C	3.76	Sofosbuvir–velpatasvir–voxilaprevir for treating chronic hepatitis C in direct-acting antivirals experienced patients.
TA589	blinatumomab	acute lymphoblastic leukaemia	2.96	Blinatumomab for treating Philadelphia-chromosome-negative CD19-positive B-precursor acute lymphoblastic leukaemia in adults with minimal residual disease (MRD) of at least 0.1%, only if the disease is in first complete remission.
Top-5 pharmaceuticals with the smallest incremental health benefits compared with their next-best alternative.				
TA537	ixekizumab	psoriatic arthritis	-0.10	Ixekizumab (alone or with methotrexate) for treating active psoriatic arthritis in adults who have not responded to, or are ineligible for, a TNF-alpha inhibitor.
TA220	golimumab	psoriatic arthritis	-0.30	Golimumab for the treatment of active and progressive psoriatic arthritis.
TA512	tivozanib	renal cell carcinoma	-0.38	Tivozanib for treating advanced renal cell carcinoma in adults, only if they have had no previous treatment.

TA	Product	Disease	QALY	Specifics
TA561	venetoclax	chronic lymphocytic leukaemia	-0.39	Venetoclax (with rituximab) for treating chronic lymphocytic leukaemia in adults who have had at least 1 previous therapy.
TA543	tofacitinib	psoriatic arthritis	-0.49	Tofacitinib (with methotrexate) for treating active psoriatic arthritis in adults who have not responded to, or are ineligible for, a TNF-alpha inhibitor.

When selecting the next-best drug as a comparator instead of the best available comparator, the median added value slightly increases (0·31, IQR: 0·09 – 0·73), suggesting our results are robust under these different choices of comparators.

Discussion

Novel pharmaceuticals that became publicly available to patients in the NHS over the past eleven years and that were favourably evaluated by NICE contributed the net present equivalent of between three to four months of life in perfect health relative to the best alternative therapy. The added benefit varied greatly, including eight drugs that were inferior in some cases to its already-available counterpart, and two that provided the equivalent of over five years in perfect health. To our knowledge, this analysis is the first to compare the therapeutic value of drugs across diverse disease areas using QALYs extracted from independent cost-effectiveness analyses conducted through a standardized framework.

The largest benefits were observed in areas such as haematology or oncology, where drugs were shown to improve quality or duration of life by 0·70 and 0·46 QALY. Patients have least profited from pharmaceutical innovations in endocrinology and ophthalmology, where novel pharmaceuticals were associated with a median incremental benefit of 0·02 to 0·09 QALYs.

The nature of each treatment (curative, palliative, symptomatic, preventive) may impact the incremental QALY. For example, adult patients that have undergone total hip or knee replacements may be treated with apixaban (TA245) to prevent venous thromboembolism. When used for this indication, apixaban provides an incremental benefit of 0·0016 QALY over the standard of care (low-molecular-weight heparin), equivalent to an additional fourteen hours of life in perfect health. The very low benefit reflected estimates that one venous thromboembolism event would be prevented for every 110–250 patients treated prophylactically for ten days following surgery.[9–11] Although apixaban may prevent serious outcomes (death) in some patients, outcome heterogeneity led to the extremely low average incremental QALY.

QALY evaluations are necessarily based on the data available at the time of drug approval, which are in turn increasingly based on earlier-phase trials, but later-generated evidence often fails to confirm promising early results.[12] Furthermore, most (59%) drugs are now approved on the basis of surrogate endpoints,[13] such as progression free survival, which for purposes of QALY calculations are assumed to correlate with clinical outcomes such as increased survival. However, studies have shown that this correlation is often poor or fair, particularly in oncology.[14,15] Additionally, data on infrequent or longer-term harms cannot be known with certainty or incorporated in the appraisals, as these data only become apparent when the drug is available for broader use. Furthermore, fitter patients are often recruited for clinical trial participation and the outcomes for more vulnerable patients are not known. Factors such as these could cause QALY values to be lower than NICE estimates suggest.

Three additional issues can also lead to overestimations in incremental therapeutic benefit. First, during the time it takes to plan and conduct a trial, approve a drug, and complete a cost-effectiveness assessment, the standard of care may have shifted and the best available comparator may no longer provide the relevant baseline for comparison. Second, a drug may have different benefits for different indications, a factor of particular relevance when off-label use is widespread or where marketing authorization is granted for a population that is broader than the tested population. Third, trials may be designed to demonstrate incremental benefit even when available treatments might demonstrate similar efficacy if tested with a different trial design.

Our findings should be interpreted with caution and cannot easily be interpreted from a population health perspective, as drug-indication pairs may be reimbursed within some health systems only for specific patient populations. For example, some of these large incremental benefits mainly occur for drugs that were not considered cost-effective in earlier lines of therapy – but when all prior therapies fail, these drugs are estimated to provide substantial benefit. From the examples in Table 1, sofosbuvir-velpatasvir-voxilaprevir is estimated to generate 3.76 incremental QALYs for patients who have previously been treated with direct-acting antivirals. However, the Marketing Authorisation has been granted to treat patients regardless of cirrhosis status and treatment history. These benefits must be seen in this larger context.

Our study has a few limitations. First, our analysis was restricted to data presented to NICE of drugs that subsequently obtained a positive coverage decision, excluding medicine that may be accessed via private health insurance. Therefore, drugs in our review are a subset of the drugs covered in other analyses of medication approved by the FDA or EMA, a subset that is likely to be associated with higher QALY estimates than the average new drug. Not all FDA-approved drugs are subsequently approved by the EMA, and not all EMA-approved drugs are assessed by NICE. A recent assessment of oncology drugs approved via the FDA's accelerated approval pathway demonstrated that only half (48%, 45/93) of drug-indication pairs subsequently became reimbursed within the English NHS, suggesting their therapeutic benefit was not sufficiently important or well established in relation to the associated cost to receive a positive reimbursement decision.[16]

Second, we could not retrieve all estimates of health benefit as some were concealed by the manufacturer, the implications of which are unclear. It seems some companies maintain a policy of not disclosing QALY figures for any indications or drugs, whereas other companies consistently provide full disclosure. The desire to maintain in confidence the incremental cost of their treatment, which would implicitly be made evident if both cost/benefit ratios and QALY values were simultaneously disclosed, may be the driving force behind redactions. In the Supplementary Material, we provide examples where we could retrieve estimates due to ineffective redaction. We also list the number of redacted estimates by disease area. The rates of redaction in oncology (37.2%) and haematology (44.9%), compared with other disease areas (such as cardiology, vascular medicine, endocrinology) where none of the values were redacted, may either represent the unwillingness to disclose high drug prices in these indications,[17] or the unwillingness to disclose low benefits, the latter of which may make average QALY figures appear larger than they are for these disease areas. For withdrawn or terminated appraisals, no detailed information is available to the public on cost or QALYs. Although speculative, it is unlikely these appraisals discussed drugs that were cheaper and more effective than the current standard of care.

Third, QALY estimates of individual products are sensitive to the choice of relevant comparator. Our results, however, show that the choice of comparator does not significantly affect the overall estimated QALY gain in our dataset. Alternatively, one may not be interested in the overall population, but only in specific (sub)populations reported in the appraisal documentation. This may give more specific estimates for individual patients, but impedes the comparison of drugs across diseases.

Fourth, estimates of median incremental QALY for each drug are associated with varying degrees of uncertainty. Although we have extracted the 'preferred' estimate from the evidence review group, the variance of these estimates is not routinely reported. Furthermore, distinct preferences in modelling choices, may result in substantial differences in benefit estimates.

Our findings provide insight into the relative benefits of new pharmaceuticals across therapeutic areas. Additional health gains may be hindered by the difficulty of developing novel drugs for specific diseases, perhaps because major improvements have already been generated prior to our review period,[18,19] or because scientific breakthroughs have not yet occurred. QALYs are a useful tool for comparison, but the measure omits important health-related variables, such as the extent to which a patient remains unable to live out a "normal" life expectancy or achieve complete health. Other factors, such as lack of fundamental understanding of disease pathologies,[20,21] or the abundance or absence of sufficient research funding may also limit health gains.[22] Our figures evaluate the net present health-related benefits of drugs that are considered cost-effective by NICE over the past decade. In combination with indices measuring health needs, such as the Global Burden of Disease,[23] as well as cost-effectiveness/cost-saving data of novel drugs that might produce similar QALYs as already available therapies, our findings can help provide context for the allocation of research funding and thereby shape health policy.

Eight drugs improved life by more than two incremental QALYs, which may justify their superlative epithets of "ground-breaking" or "game-changing".[24] Half of the drugs in our study were likely to improve life by the equivalent of three to four months in perfect health, and 84·8% of novel drugs did not add more than one such year. Unfortunately, 25% of appraisals have covered drugs that contributed the equivalent of no more than one month in perfect health, and 23 (12·5%) drug-indication pairs were estimated to add several hours to just a week of perfect health. For example, eluxadoline for prevention of diarrhoea and abdominal pain in patients with irritable bowel syndrome yielded a total QALY gain of 0·015—equivalent to 5·5 days in perfect health—compared with placebo. Given the uncertainty around cost-effectiveness estimates—models that require ample assumptions and extrapolations over lifetime horizons can hardly be expected to accurately forecast a week of health gained—drafting extensive cost-effectiveness reports in these situations is not likely to be a cost-effective use of time.

Drugs that have little health benefit relative to the best alternative may still promote price competition and thereby free funds for other public health initiatives or treatments. To avoid wasting public resources in needless evaluations, guideline committees could determine a threshold of incremental benefit that is clinically relevant to each disease area.[25] Drugs that do not pass this threshold based on early assessments of their value should be rejected without a full evaluation unless they are offered at lower cost.

Patients and physicians can use the QALY data presented here to put the effectiveness of treatments in perspective. The frequently employed metric of "number needed to treat" provides important information about the effectiveness of drugs on the principal disease-specific outcome. For example, the efficacy of eluxadoline could be described in terms of the number of patients that would need to be treated three months to avoid one episode of abdominal pain or diarrhoea, in this case between eight and 33 patients over three months.[26] Metrics such as this, however, do not account for adverse events. Using the incremental QALY estimate that integrates gains and losses into a single measure (for eluxadoline, 0·015), it is possible to calculate that 67 patients would need to be treated over their lifetime horizons to gain the equivalent of one year in perfect health. As such, the QALY provides an estimate of both duration and quality of life, which are arguably the two most important factors from the perspective of a patient.

Conclusions

Novel pharmaceuticals that received a positive coverage decision by NICE from 2010 to 2020 provided patients with an average of 0·27 additional QALYs over the best alternative therapy, the equivalent of three to four additional months of life in perfect health. One in four drugs does not improve quality and quantity of life by more than one month, and incremental benefit varies greatly across disease areas and compounds. Several novel drugs do not provide additional QALY gains over available therapies, but if offered at a lower price could still be of interest from a public cost-saving perspective even if not from the patient's perspective. Providing transparent information on the added value of novel therapies enables patients and physicians to have reasonable expectations about the average net benefits of therapies at their disposal. Objectively evaluating the benefits contributed by novel pharmaceuticals provides insight not only into whether a given drug is worth its price once approved, but also into the therapeutic return on investment reaped by society from the substantial public and private sums expended on research and development. Finally, these figures provide a benchmark for future innovations.

Ethics approval statement

No patients were involved during the planning and writing of this work. Therefore the study did not require ethical approval by the institutional review board.

Declaration of interests

TBP is employed part-time by myTomorrows, which facilitates expanded access programs for the pharmaceutical industry. TBP holds stock in myTomorrows (<0.1%). TBP has received funding for research from the Dutch government (grant EMCLSH20012). The research of TBP is conducted independently and TBP is contractually free to publish any results for all the conducted work. None of the recent work concerns the topic in this analysis. DGJC has no interests to declare. MMV is director of the institute of Medical Technology Assessment (iMTA). iMTA conducts cost-effectiveness research funded by international governments, pharmaceutical industry, and med-tech industry. All research is conducted independently and iMTA is contractually free to publish any results for all conducted work. None of the recent work concerns the topic in this analysis. Jonathan Darrow receives funding from Arnold Ventures, the Greenwall Foundation, the Kaiser Permanente Institute for Health Policy, West Health, and the Novo Nordisk Foundation (grant for a scientifically independent Collaborative Research Programme; grant NNF17SA0027784).

Author contributions

TBP and MMV conceived the research. TBP and DGJC collected, analysed and visualised the data. TBP drafted the first version of the manuscript; JJD and DGJC critically revised the first version of the paper; all authors discussed the results and contributed to the final manuscript. All authors had full access to all the data in the study and accept responsibility for submission for publication.

Data sharing

All raw data are available through the NICE website. Aggregated data will be made available upon reasonable request.

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Figure legends

Figure 1 : Flow diagram
Flow diagram of the selection and retrieval of estimates of Quality-Adjusted Life Years (QALYs) from NICE technology appraisals between January 1, 2010 and December 31, 2020.

Figure 2: The added value of novel pharmaceuticals approved by NICE from 2010 to 2020

Display of the distribution (boxplot) of added value in Quality-Adjusted Life Years (QALYs) of novel pharmaceuticals per medical discipline that have received a positive coverage decision of NICE between January 1, 2010 and December 31, 2020, compared with their next-best alternative. Medical disciplines with fewer than eight appraisals were classified as 'Other'.

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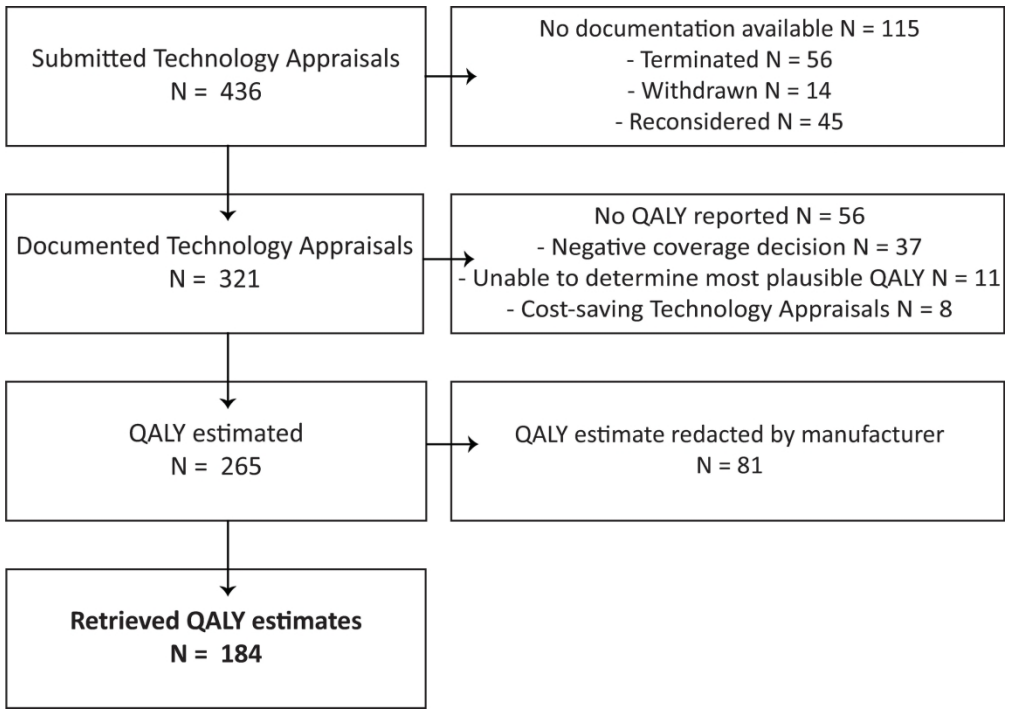

Caption : Caption : Caption : Figure 1. Flow diagram.
Flow diagram of the selection and retrieval of estimates of Quality-Adjusted Life Years (QALYs) from NICE technology appraisals between January 1, 2010 and December 31, 2020

204x143mm (300 x 300 DPI)

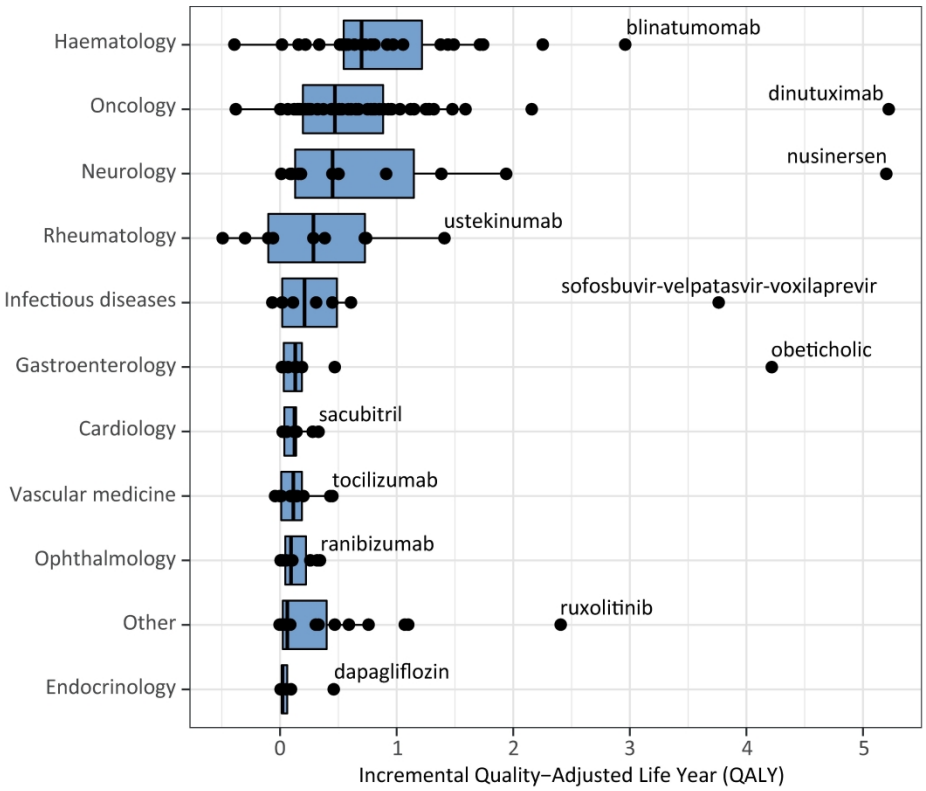

Figure 2: The added value of novel pharmaceuticals approved by NICE from 2010 to 2020

Display of the distribution (boxplot) of added value in Quality-Adjusted Life Years (QALYs) of novel pharmaceuticals per medical discipline that have received a positive coverage decision of NICE between January 1, 2010 and December 31, 2020, compared with their next-best alternative. Medical disciplines with fewer than eight appraisals were classified as 'Other'.

218x171mm (600 x 600 DPI)

Supplementary Material to the manuscript:

Incremental benefits of novel pharmaceuticals in the United Kingdom: A cross-sectional analysis of NICE technology appraisals from 2010 – 2020

Tobias B. Polak MSc, David G.J. Cucchi MD, PhD,

Jonathan Darrow SJD, LLM, JD, MBA and Matthijs M. Versteegh, PhD

This supplementary material provides more background information regarding the redaction of estimates of cost, Quality-Adjusted Life Years (QALYs) and Incremental Cost-Effectiveness Ratios (ICERs) available in Technology Appraisals (TAs) as available from the National Institute of Care and Excellence (NICE) in the United Kingdom.

A. Overview of redacted technology appraisals by disease area

	Estimate Redacted		
	Yes, N = 81[1]	No, N = 184[1]	Overall, N = 265
Disease area			
Oncology	35 (37%)	59 (63%)	94
Haematology	22 (45%)	27 (55%)	49
Neurology	4 (27%)	11 (73%)	15
Ophthalmology	4 (29%)	10 (71%)	14
Rheumatology	5 (36%)	9 (64%)	14
Gastroenterology	2 (18%)	9 (82%)	11
Cardiology	0 (0%)	10 (100%)	10
Dermatology	3 (30%)	7 (70%)	10
Vascular medicine	0 (0%)	10 (100%)	10
Endocrinology	0 (0%)	8 (100%)	8
Infectious diseases	0 (0%)	8 (100%)	8
Pulmonology	2 (29%)	5 (71%)	7
Benign haematology	1 (25%)	3 (75%)	4
Psychiatry	0 (0%)	4 (100%)	4
Internal medicine	2 (67%)	1 (33%)	3
Nephrology	0 (0%)	2 (100%)	2
Urology	1 (50%)	1 (50%)	2

[1]n (%)

B. Examples of various redaction strategies

I. Complete redaction

Here we provide examples of TAs where all estimates are redacted.

Table 28: Scenario analyses for prolonged post-treatment overall survival benefit (including ERG corrections)

Extension	Total			Incremental			ICER (£/QALY)
Treatment	*Costs*	*QALYs*	*Life years*	*Costs*	*QALYs*	*Life years*	
Base case							
Hydroxycarbamide	[redacted]	[redacted]	[redacted]	—	—	—	—
Bosutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
+1 month							
Bosutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
+2 months							
Bosutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
+3 months							
Bosutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
−1 month							
Bosutinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year

Figure 1: Completely redacted estimates (ICER, QALY, cost) from TA401: Bosutinib for previously treated chronic myeloid leukaemia. Table from Evidence Review Group Report.

Table 62. Deterministic results using the PAS for dacomitinib and the list prices for the comparators

Treatment	Expected mean costs (£)	Incremental costs (£)	Expected mean QALY	Incremental QALY	ICER (£)
Erlotinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dacomitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gefitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Afatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life years gained					

Figure 2: Completely redacted estimates (ICER, QALY, cost) from TA595: Dacomitinib for untreated EGFR mutation-positive non-small-cell lung cancer. Table from Evidence Review Group Report.

II. Incomplete redaction

Here we provide examples of TAs where two out of three unknowns are redacted. We could not find examples where cost was the only revealed estimate.

ERG base case compared to BSC
no 17p deletion/TP53 mutation (pop. 4)

	Incremental costs	Incremental QALYs	ICER	Δ ICER
Company base case*	[redacted]	3.529	[redacted]	-
Correcting hazard ratios*	[redacted]	3.385	[redacted]	[redacted]
Using post progression data after idelalisib for BSC*	[redacted]	2.377	[redacted]	[redacted]
Changing PFS utility value from 0.853 to 0.71*	[redacted]	3.025	[redacted]	[redacted]
Changing cost of some AEs*	[redacted]	3.465	[redacted]	[redacted]
ERG's preferred base case*	[redacted]	1.741	[redacted]	[redacted]

Abbreviations: BSC, best supportive care; PFS, progression free survival; AE, adverse event

*analyses include corrected starting age and proportion male

Figure 3: Redacted estimates (ICER, cost) from TA487: Venetoclax for treating chronic lymphocytic leukaemia. Table from the Public Committee Slides Appraisal Consultation.

Table 64: Exploratory Analysis 4 – ERG-preferred base case

Probabilistic model					
Option	**QALYs**	**Costs**	**Incremental QALYs**	**Incremental costs**	**Incremental cost per QALY gained**
Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	**£61,219**
Rituximab/chemotherapy	[redacted]	[redacted]	-	-	-
Deterministic model					
Option	**QALYs**	**Costs**	**Incremental QALYs**	**Incremental costs**	**Incremental cost per QALY gained**
Ibrutinib	[redacted]	[redacted]	[redacted]	[redacted]	**£61,050**
Rituximab/chemotherapy	[redacted]	[redacted]	-	-	-

QALY - quality-adjusted life year

Figure 4: Redacted estimates (QALY, cost) from TA491: Ibrutinib for treating Waldenstrom's macroglobulinemia. Table from Evidence Review Group Report.

III. Ineffective redaction

Here we provide examples of TAs where one out of three unknowns is redacted. Because the ICER is the ratio of incremental cost and incremental QALYs, the unknown is not 'unknown' and can be derived.

Table 5-1 Effect of corrections and amendments made by ERG to the manufacturer's model for the base case analysis (paclitaxel/carboplatin as comparator) over 6 years

	Gefitinib / carboplatin		Paclitaxel / carboplatin		Incremental		ICER	Changes (from 6 year horizon base case)		
Model amendment	Costs	QALYs	Costs	QALYs	Costs	QALYs	(£/QALY)	Costs	QALYs	ICER
Submitted base case	[redacted]	**1.1110**	**£27,902**	**0.9235**	**£3,637**	**0.1874**	**£19,402**			
Base case with 6 year horizon	[redacted]	**1.1110**	**£27,947**	**0.9235**	**£3,751**	**0.1874**	**£20,010**			
Amend 1st line CTX costs	[redacted]	1.1110	£24,563	0.9235	£7,135	0.1874	£38,063	+£3,498	0.0000	+£18,054
Reduced cycles of CTX	[redacted]	1.1110	£25,527	0.9270	£6,170	0.1839	£33,544	+£2,420	-0.0035	+£13,535
Revise OS models	[redacted]	1.2219	£32,985	1.0834	£2,268	0.1384	£16,381	-£1,483	-0.0490	-£3,628
Revise PFS models	[redacted]	1.0923	£28,149	0.9181	£4,989	0.1741	£28,651	+£1,238	-0.0133	+£8,641
IPASS PFS HR (not MA)	[redacted]	1.1020	£29,947	0.9235	£4,439	0.1785	£24,867	+£688	-0.0089	+£4,857
Revise discounting method	[redacted]	1.1284	£28,337	0.9378	£3,680	0.1906	£19,311	-£71	+0.0032	-£699
Omit GCSF prophylaxis	[redacted]	1.1110	£27,669	0.9235	£4,029	0.1874	£21,493	+£278	0.0000	+£1,483
Continuity correction	[redacted]	1.1110	£28,426	0.9235	£3,252	0.1874	£17,350	-£499	0.0000	-£2,660
Correct misaligned cycles	[redacted]	1.1110	£27,947	0.9235	£3,752	0.1874	£20,017	+£1	0.0000	+£7
Correct 2nd line CTX costs	[redacted]	1.1110	£25,213	0.9235	£3,975	0.1874	£21,204	+£224	0.0000	+£1,194
CTX treatment exposure	[redacted]	1.1110	£26,931	0.9235	£4,766	0.1874	£25,427	+£1,015	0.0000	+£5,417
Combined effect of all changes	[redacted]	**1.2223**	**£24,574**	**1.0988**	**£8,746**	**0.1235**	**£70,822**	**+£4,995**	**-0.0639**	**+£50,812**

ICER= incremental cost effectiveness ratio; QALY=quality adjusted life year; CTX= chemotherapy; OS= overall survival; PFS= progression free survival; granulocyte colony stimulating factor; HR=hazard ratio; MA= meta-analysis

Figure 6: Ineffective redaction of cost only from TA192: Gefitinib for the first-line treatment of locally advanced or metastatic non-small-cell lung cancer. Table from the Advisory Committee Decision Pre-meeting Briefing.

Cost-effectiveness analyses presented at 2nd committee meeting – with PAS

- Simple discount PAS agreed with Department of Health

17p deletion or TP53 mutation	Incremental		ICER
	Costs	QALYs	
Company's ACD1 response – survival based on end of life decision	[redacted]	2.38	£43,310
ERG's modified base case – PPS after idelalisib for BSC	[redacted]	1.76	£57,476

No 17p deletion or TP53 mutation	Incremental		ICER
	Costs	QALYs	
Company's ACD1 response – survival based on end of life decision	[redacted]	3.00	£49,929
ERG's modified base case – PPS after idelalisib for BSC	[redacted]	1.88	£77,779

Figure 7: Ineffective redaction of cost only from TA487: Venetoclax for treating chronic lymphocytic leukaemia. Table from the Public Committee Slides Final Appraisal Determination.

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No.	Recommendation	Page No.	Relevant text from manuscript
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	**1**	
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	**2**	
Introduction				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	**3**	
Objectives	3	State specific objectives, including any prespecified hypotheses	**3**	
Methods				
Study design	4	Present key elements of study design early in the paper	**3-4**	
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	**3-4**	
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	**3-4**	
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	**N/A**	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	**3-4**	
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	**N/A**	
Bias	9	Describe any efforts to address potential sources of bias	**N/A**	
Study size	10	Explain how the study size was arrived at	**3-4**	

Continued on next page

Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	**4**
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	**4**
		(*b*) Describe any methods used to examine subgroups and interactions	**4**
		(*c*) Explain how missing data were addressed	**4**
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	**N/A**
		(*e*) Describe any sensitivity analyses	**3**
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	**4**
		(b) Give reasons for non-participation at each stage	**4**
		(c) Consider use of a flow diagram	**Figure 1**
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	**N/A**
		(b) Indicate number of participants with missing data for each variable of interest	**4**
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	**N/A**
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	**N/A**
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	**N/A**
		Cross-sectional study—Report numbers of outcome events or summary measures	**4**
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	**4**
		(*b*) Report category boundaries when continuous variables were categorized	**4**
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	**N/A**

Continued on next page

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	**4**
Discussion			
Key results	18	Summarise key results with reference to study objectives	**5-6**
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	**5-6**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	**5-6**
Generalisability	21	Discuss the generalisability (external validity) of the study results	**5-6**
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	**8**

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.