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NICE's new methods: putting innovation first, but at what cost?

Traditionally the gatekeeper to the NHS, NICE has increasingly reoriented its role towards facilitating access to innovative technologies. This change has clear benefits for some patients, but the costs shouldered by others risk going unacknowledged.

Deciding when a new drug merits funding and when it does not—often to the displeasure of clinicians and patients alike—is an unenviable task. In England and Wales, it falls largely on the National Institute for Health and Care Excellence (NICE), whose recommendations shape the National Health Service's (NHS) adoption of new technologies.

Traditionally NICE has based its binding recommendations primarily, though not exclusively, on cost-effectiveness: the amount of health a technology generates per pound spent, compared with current practice. Under this approach, technologies that have not reliably demonstrated their clinical-effectiveness will generally be rejected—for example, amantadine (Lysovir/Symmetrel) for the treatment of influenza. Also rejected are those technologies considered insufficiently cost-effective: a point generally defined by NICE as £20,000–£30,000 per quality-adjusted life-year (QALY).[1] Thus, in 2016 NICE rejected the cystic fibrosis drug lumacaftor–ivacaftor (Orkambi) on the grounds that its likely clinical benefits did not justify its cost of £200,000–£350,000/QALY.[2]

This approach to priority-setting is not without its critics.[3] But it is generally accepted as sound because it gives due weight to the interests of all patients: both those who will benefit from access to a new technology, and those whose health will suffer because resources from which they were benefitting must be reallocated to pay for it.[4] In recent years, however, NICE's emphasis on cost-effectiveness has come into conflict with the drive to secure access to innovative health technologies, whose benefits are often both costly and uncertain.[5] NICE's rejection of lumacaftor–ivacaftor, for example, was later disregarded by the NHS which, in the face of pressure from patients and politicians, negotiated a confidential price discount with the manufacturer to secure access to the drug.[6]

We describe here how NICE's approach has evolved in response to such challenges and consider the implications of its January 2022 methods update, both for those who benefit directly from NICE's recommendations and the NHS as a whole.

NICE's new methods: making the exception the rule

Over time, NICE's approach to technology appraisal has evolved in two main ways.[7] The first relates to the cost-per-QALY threshold used to define cost-effectiveness. The second relates to NICE's evidential requirements.

NICE's cost-effectiveness threshold. NICE has always acknowledged that, in the interests of fairness, its decisions cannot be based on cost-effectiveness alone.[8] Accordingly, its appraisal committees have shown willingness to exceed the usual £20,000–£30,000/QALY threshold for individual cases when justified by special considerations, such as high disease severity or significant innovation.[9] In recent years, this exceptional treatment of 'special cases' has become normalised through NICE's routine use of modifiers: pre-defined multipliers that increase the value of some QALYs relative to others, effectively raising the cost-effectiveness threshold for certain technologies.[7] Most notably, since coming under criticism for its rejection of several life-extending cancer drugs in the late 2000s, NICE has used an 'end-of-life' modifier to increase the threshold for such drugs to £50,000/QALY.[10] Between 2009 and 2011, drugs recommended using this modifier delivered an estimated annual 12,401 QALYs to late-stage NHS cancer patients. However, to fund these drugs the NHS had to divert significant resources away from other activities, at an estimated annual 'opportunity cost' to other patients of between 18,330 and 27,496 QALYs.[11]

NICE states that such trade-offs should only be made in "exceptional circumstances".[12] But the end-of-life modifier was applied in 19% of appraisals between 2011 and 2019[13] and NICE's new methods seem likely to further increase the number of exceptions made. The new methods incorporate three modifiers.[12] The end-of-life modifier is replaced by a broader modifier for severity. This allows technologies that treat moderately severe diseases, such as type I diabetes, to be evaluated against a

threshold of £36,000/QALY, increasing to £51,000/QALY for very severe diseases, such as multiple sclerosis, severe rheumatoid arthritis and many advanced cancers. Two further modifiers are for use specifically in NICE's Highly Specialised Technologies (HST) programme, which evaluates technologies for very rare, and often very severe, diseases. These establish the basic cost-effectiveness threshold for such technologies as £100,000/QALY, increasing to £300,000/QALY for those expected to deliver especially large health gains. NICE's definition of cost-effectiveness has thus become considerably more generous over time.

NICE's evidential requirements. NICE has historically required the technologies that it recommends to have reliably demonstrated their benefit, strongly preferring evidence from randomised controlled trials (RCTs) and advising its committees not to recommend technologies when "evidence of clinical-effectiveness is either absent or too weak for reasonable conclusions to be reached."[8] The seemingly cost-effective flu drug amantadine, for example, was rejected in 2003—and again in 2009—because its clinical-effectiveness was not "sufficiently proven".[14] Over the past decade, however, NICE's evidential requirements have eased. The new methods manual accepts the use of non-randomised studies as the primary source of clinical evidence, despite acknowledging their "high risk of bias".[12] It also encourages committees to accept "a higher degree of uncertainty" when considering technologies deemed "innovative and complex" or indicated for rare diseases or paediatric populations—a potentially large proportion of appraisals.[12] Under these more lenient standards, some technologies that NICE would previously have rejected may be made available, sometimes to large patient populations: for example, the 'innovative' anti-obesity drug naltrexone-bupropion (Mysimba), which NICE rejected in 2017 due to uncertainty over its long-term effectiveness.[15]

NICE has also extended its use of 'managed access' arrangements, a mechanism embraced by many countries to allow technologies with uncertain benefits to be provisionally adopted while research continues.[12 16] Initially used in the NHS for a handful of technologies, primarily in the context of the Cancer Drugs Fund (CDF), such arrangements now constitute the intended norm for all promising technologies which cannot currently demonstrate clinical- and/or cost-effectiveness.

NICE positions these changes as improvements designed to "deliver excellence for patients, the NHS and the life sciences industry."[17] But not all patients stand to benefit from NICE's new approach.

Benefitting the few at a cost to many: flaws in NICE's use of modifiers

NICE has a responsibility to uphold the interests of all patients and recognises that its use of modifiers should be "morally and ethically supported by reason, coherence, and available evidence."[12] The end-of-life modifier arguably failed to meet these requirements because its narrow focus on terminally-ill cancer patients did not properly reflect society's preference for treating the severely ill.[18] Its replacement by the more inclusive severity modifier partially addresses this issue. (Figure 1). But there remain several logical and ethical flaws in NICE's use of modifiers.

First, whenever NICE recommends a new technology, the NHS will likely have to stop doing something else to pay for it. While access to a new cancer drug may improve the health of some severely ill cancer patients, other very ill patients may find that their health decreases because funds are diverted away from interventions that were benefitting them, such as high-quality palliative care or drugs for other severe diseases. Under NICE's approach, modifiers are applied to the health gains of the first group of patients but not the health losses of the second group.[19] This is unfair and illogical, as it leads to the health of similar patients being valued differently.

Second, the special treatment of technologies for very rare diseases (HSTs) does not reflect public preference and lacks coherence. While there is strong evidence that society supports the prioritisation of severe diseases, evidence of a similar preference for rare diseases is limited: NICE acknowledges that "there is no case for a specific modifier for rarity."[20] Nevertheless, NICE evaluates HSTs against a significantly higher cost-effectiveness threshold than other technologies and applies an additional 'magnitude of benefit' modifier that has also been shown to lack public support.[13] These modifiers facilitate disproportionate, and potentially unjustified, expenditure on treatments for very rare diseases and are inconsistent with NICE's approach to other technologies.

Third, while modifiers may increase the ease and predictability of NICE decision-making by decreasing the need for case-based deliberation, reducing ethically complex scenarios to a few quantified variables is contentious and limits NICE's ability to balance ethically relevant considerations.[21] In relying on such an approach, NICE risks replacing rather than enhancing the nuanced reasoning for which its appraisal committees have historically received praise and which has been central to justifying its recommendations to those affected.

Giving innovation the benefit of the doubt

NICE's increasing reliance on modifiers is an understandable—if perhaps unjustified—response to high drug prices.[22] Other challenges for NICE include the demand for earlier access to new medicines, regulators' willingness to approve drugs based on limited evidence of clinical benefit[23], and NICE's commitment to issuing its recommendations "as quickly as possible" after regulatory approval.[12]

NICE's solution to these challenges has been to ease its own evidential requirements at the point of appraisal while compensating for a lack of clinical data through managed access arrangements. Though perhaps pragmatic, this response shifts much of the risk associated with adopting uncertain technologies from industry onto UK taxpayers and patients. Under managed access, the NHS pays an interim price based on a technology's "plausible potential" for cost-effectiveness given expected benefits.[12] Ideally, these benefits will be realised and cost-effectiveness will be demonstrated at this price. But products typically perform more favourably in industry-led trials than in practice,[24] so technologies may end up being less beneficial (or safe[25]) than anticipated. This puts the NHS in the problematic position of initially overpaying for new technologies and subsequently having to either renegotiate lower prices or withdraw a treatment to which patients have come to expect access. Many of the practical, political and ethical difficulties associated with this scenario were illustrated in the early 2000s through the multiple sclerosis risk-sharing scheme, in which disappointing clinical results from widespread managed access to interferon beta and glatiramer acetate triggered neither a price reduction nor withdrawal.[26]

Managed access, as currently envisaged, may also fail to resolve fundamental questions about the clinical- and cost-effectiveness of new technologies. Experience from the CDF indicates that such arrangements do not reliably address the evidence gaps identified by NICE appraisal committees, leaving them unable to reliably assess cost-effectiveness.[27] And while the 'real world' clinical data typically collected through managed access can provide valuable supplementary information on patient-reported outcomes and a technology's long-term effects, such data are ill-suited to testing different therapies' comparative effectiveness and are well-recognised as being vulnerable to bias.[28] Managed access may therefore leave patients, and NICE, unsure about the clinical value offered by many new technologies.

NICE changes, but who benefits?

The impact of NICE's new appraisal methods on patients appears mixed: while some groups of patients may stand to benefit significantly, others will suffer the costs. In contrast, the benefits to manufacturers are clear: lower evidential standards alongside increased use of managed access allows manufacturers to secure NHS uptake of their technologies earlier in the product life cycle, accelerating profits and extending the period a medicine is marketable under its patent. The routine use of modifiers to increase the price at which products are deemed 'cost-effective' further supports profitability. It is no surprise that industry has welcomed these changes to NICE's methods.[29]

What is good for industry is sometimes good for patients, and the UK is not alone in offering political support to the economically important life sciences industry through its enthusiasm for 'innovation'.[5] But if health systems are to remain fiscally sustainable given competing demands on national resources, new drugs must not come at too high a price. Research indicates that, at current levels of NHS funding, NICE's basic threshold of £20,0000–£30,000/QALY is too high and considerably underestimates the amount of health displaced to fund new technologies.[30] Consequently, many of the technologies recommended by NICE are likely to lead to a net reduction in population health.

Some technologies—such as lumacaftor–ivacaftor for cystic fibrosis—may justify this opportunity cost, and society has shown itself willing to trade off some population health in the interest of

fairness. But truly 'game-changing' innovations remain rare, with most new technologies offering only small incremental benefits.[31] They may become rarer still if payers do not maintain their expectations that new products must demonstrate both clinical- and cost-effectiveness to be adopted.

Conclusion

NICE has historically reflected carefully on the ethical implications of its methods and has enjoyed a high level of social and moral legitimacy, even though some medicines are not funded in the UK.[4] Recent changes point to a shift in NICE's priorities and values, and a step away from its gatekeeper role to focus on facilitating access to innovation. NICE owes it to those on whose behalf it acts to acknowledge and justify this shift by refreshing its public articulation of its approach: its existing statement of principles has not been updated to reflect its new methods.[32]

To maintain its reputation as a just priority-setter, NICE must also be as transparent as possible about the trade-offs its decisions involve. We do not currently know precisely how the NHS funds NICE's recommendations, or which patients suffer the opportunity costs. But we know the approximate size of these costs.[30] If NICE has confidence in its approach, it should be open about both the health gains and likely health losses generated by its recommendations. It should also monitor and publicly report how its new methods effect decision-making. Doing so would help patients and the public judge the legitimacy of NICE's approach for themselves and engage more fully in societal debates about healthcare priorities.

Key messages

- NICE's new methods suggest that its priorities and values have shifted away from its traditional gatekeeper role to focus on facilitating access to innovation.
- Higher cost-effectiveness thresholds and lower evidential standards will benefit some NHS patients and pharmaceutical manufacturers, but other NHS patients will be disadvantaged.
- NICE should be as transparent as possible about the reasons for its revised approach and the trade-offs entailed by its decisions, so that patients and the public can evaluate its legitimacy and engage fully in societal debates about healthcare priorities.

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