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Promoting innovation while controlling cost: The UK's approach to health technology assessment

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ABSTRACT

New technologies, including pharmaceuticals and medical devices, can improve treatment options in healthcare but also bring concerns about rising healthcare costs. We undertake a narrative review of the United Kingdom's (UK) approach to appraising new health technologies. We find that the National Institute for Health and Care Excellence (NICE), Scottish Medicines Consortium (SMC) and All Wales Medicines Strategy Group (AWMSG) have contributed to the UK's robust and transparent approach towards the evaluation of new health technologies using the cost per QALY approach. However, there are limitations to this approach including several external benefits not captured, bias against less treatable diseases, and deciding the appropriate level of the threshold. NICE, SMC, and AWMSG have attempted to overcome some of these limitations by considering additional factors such as end-of-life criteria, highly specialised treatments, and populations that experience unmet need. Looking to the future, the advent of 'personalised' and 'genomic' medicine, will likely mean the UK has to accommodate an increasing number of 'step-change' and 'highly specialised' technologies as well as respond to changes in pharmaceutical licensing and increasing use of real-world evidence.

1. Introduction

New health technologies, including pharmaceuticals, devices and procedures, can expand the treatment options in health care and improve patient outcomes. New health technologies also bring concerns about rising health care costs, and governments may make attempts to contain expenditure. However, governments have to balance cost containment policies against other priorities including improving quality of care, ensuring equitable access to treatments, and considerations of industrial policy, such as encouraging research and development, and supporting local manufacturing and employment [1]. Over several decades, the United Kingdom (UK) has attempted to balance multiple priorities by developing structured approaches to assess the value of new health technologies conducted by the National Institute for Health and Care Excellence (NICE) in England, the Scottish Medicines Consortium (SMC) in Scotland and the All Wales Medicines Strategy Group (AWMSG) in Wales [2]. The development and application of scientific methods by these institutions has led to the UK's approach to health technology assessment becoming internationally renowned as transparent, robust, and inclusive [3]. Moreover, the UK has been successful in controlling pharmaceutical expenditure, which as a proportion of total health spending has remained stable, at around 12%, and one of the lowest levels seen in Organisation for Economic Co-operation and Development (OECD) countries [4,5]. International surveys also reveal that the UK provides relatively quick access to most new medicines, although at a rate slower than some European countries such as Germany, Denmark, and the Netherlands [6]. However, looking forward, the UK, like many other countries, is facing several important challenges and opportunities when introducing new technologies such as accommodating 'step-change' and 'highly specialised' technologies, and responding to changes in pharmaceutical licensing and increasing use of real-world evidence. Therefore, at the crucial time where the UK may look to re-evaluate its' approach to health technology assessment (HTA) during a period of uncertainty created by leaving the European Union and the COVID-19 pandemic, the purpose

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of this paper is two-fold. First, we review academic and grey literature to profile the current approach to HTA in the UK. Second, we identify what potential future opportunities and challenges exist for HTA, as well as discuss potential policy responses.

2. Methods

We undertook a narrative review, that combines both academic and grey literature, to synthesise the available evidence on HTA developments in the UK. We separated our results into two sections. The first section profiles the current approach to HTA, and the second section involves a discussion of future challenges and opportunities for HTA. The second section was informed both by the narrative review and the expertise and insights of the co-authors. Co-authors were selected by convenience sampling from a wider set of health policy experts that were convened to review future challenges and opportunities for the National Health Service (NHS) across the UK in the 2020s for the London School of Economics and Political Science (LSE)- Lancet Commission on "The Future of the NHS". They were selected according to their expertise and exposure to pharmaceutical research and policy in the UK over the last two decades. The LSE-Lancet Commission produced a series of working papers that take a similar format to this paper on issues related to workforce [7], changing health needs [8], digital health [9], and financing [10]. The final commission report, recommendations, and complete list of health policy experts is also publicly available [11]. The co-authors discussed the format and content of this second section during four in-person meetings in Belfast, Cardiff, Edinburgh, and London held between 2018 and 2019, and several follow-up virtual meetings held between 2020 and 2021.

The review of academic literature involved a search of publications between January 1st 2000 and December 31st 2020 carried out using two databases: MEDLINE (a biomedical database) and EconLit (an economics database). The search terms were applied to titles and abstracts and included combinations of the words; "medicines", "drugs", "pharmaceuticals", "health technology", "reform", "policy", "regulation", "reimbursement", "assessment", "appraisal", "regulating", "England", "Scotland", "Wales", "Northern Ireland", "United Kingdom", "Great Britain", "NICE", "SMC", "AWMSG", "National Institute for Health and Care Excellence", "Scottish Medicines Consortium", "All Wales Medicines Strategy Group". The specific search criteria are listed in Supplementary Material. The inclusion criteria were any articles whereby the primary focus was to comparatively review the approach undertaken by one of the three UK HTA agencies, specifically NICE, SMC, or AWMSG. For feasibility purposes we excluded articles whereby the primary focus was international comparisons of HTA processes or decisions (unless the article compared one UK HTA agency with another), articles which were concerned with local level HTA, resource management, or priority setting, and articles which were case studies of individual novel medicines or technologies. All article types and methodologies were considered with the exception of editorials or commentaries. We also undertook a review of reference lists in key articles to identify other relevant publications. One reviewer applied the search criteria and screened articles, with a second reviewer screening a random sample of 25% of articles identified using the search criteria. Any disagreements between these two reviewers were discussed with a third reviewer who is the senior author of this paper. The review of grey literature focused on documents retrieved from the websites for NICE [12], SMC [13], and AWMSG [14], and health authorities in the UK including NHS England [15], Healthcare Improvement Scotland [16], NHS Wales [17], and the Northern Ireland Health and Social Care Board [18]. The inclusion criteria for grey literature also included any relevant technical or guidance documents which detailed the processes utilised by UK HTA agencies to assess the value of new health technologies. We summarised our findings narratively, and did not include a PRISMA statement, as per guidance on narrative reviews [19].

3. Results

Our search of academic literature using MEDLINE and EconLit yielded 5155 results. After screening titles and abstracts 113 articles were identified as potential candidates for meeting the inclusion criteria. After reviewing the full text of these articles we identified 21 articles which met our inclusion criteria. A further 4 articles were identified from reviewing reference lists. Our search of grey literature identified 27 documents, and webpages which detailed the approach towards HTA in the UK. We summarised these identified references narratively below in two sections. The first section is concerned with the current approach to HTA in the UK, whereas the second is focused on what potential future opportunities and challenges exist for the UK when introducing new health technologies.

3.1. The current approach to health technology assessment in the UK

3.1.1. Scope and activities of UK health technology assessment agencies

In England, NICE is responsible for assessing the clinical and cost-effectiveness of new health technologies and has a number of programmes, including for drugs, devices, diagnostic procedures and public health interventions (Table 1). All the programmes [20–23], with the exception of the Interventional Procedures Programme (which considers only clinical evidence) [24], consider both clinical and cost-effectiveness. The remit of NICE also extends to pre-existing technologies through its clinical guidelines programmes [25], which explicitly considers costs through a systematic review of economic evaluation literature, and identifies candidates for disinvestment. However, unlike the technology appraisal programmes, adoption of clinical guidance recommendations is not mandatory for the NHS [26]. When assessing new health technologies NICE will commission an external review of the evidence, usually undertaken an independent academic centre. For single technology appraisals (STA) [20], the independent academic centre will critique the manufacturer's evidence submission and cost-effectiveness model, whereas for multiple technology appraisals (MTA), which is used when a health technology is particularly complex with several comparator treatments or indications, the independent academic centre is required to combine evidence submissions from multiple manufacturers and develop their own comparative cost-effectiveness model [27].

Similar bodies assess health technologies in other parts of the UK, including the SMC in Scotland and AWMSG in Wales, which both assess pharmaceuticals. The remit of AWMSG is complementary to that of NICE, only including the assessment of new pharmaceuticals that are not on the 12-month work programme of NICE [28,29]. Moreover, NICE guidance can supersede AWMSG recommendations [28]. In contrast, the scope of SMC is not explicitly complementary to NICE, and each organisation issues separate recommendations on new pharmaceuticals [30]. SMC can however endorse selected assessments by NICE on a case by case basis. To date, SMC has chosen to endorse several MTAs undertaken by NICE, likely because these assessments are particularly resource intensive [21]. The arrangement in Northern Ireland is that the local Department of Health endorses NICE guidance, unless it is not found to be locally applicable.

The central feature for appraising technologies that is utilised by NICE, SMC, and AWMSG is the calculation of the incremental cost per quality-adjusted life-year (QALY) gained, over and above the current standard of care, and to compare this with a decision-making threshold [2,31]. The QALY is intended to provide

Table 1
Key differences between United Kingdom Health Technology Assessment Agencies.

	National Institute for Health and Care Excellence (NICE)	Scottish Medicines Consortium (SMC)	All Wales Medicines Strategy Group (AWMSG)
Year Established	1999	2002	2002
Remit	England, Wales, and Northern Ireland	Scotland	Wales
Scope	Appraises all newly licensed medicines Publishes evidence-based guidance on clinical practice, quality standards and performance metrics for health, public health and social care	Appraises all newly licensed medicines	Appraises newly licensed medicines when NICE does not plan to publish an appraisal within 12 months of the medicine's market authorisation. Advice is superseded by NICE guidance once published
Timelines	40–60 weeks	18–26 weeks	20–21 weeks
Additional considerations	Flexibility in cost per QALY threshold for end-of-life, and highly specialised treatments (see below)	SMC uses six modifiers (see below), alongside its consideration of the incremental cost per QALY	Similar to NICE, flexibility in cost per QALY threshold for end-of-life, and highly specialised treatments (see below)
Implementation	There is a legal requirement that local commissioning bodies in England, and health boards and health trusts in Wales and Northern Ireland provide access to new medicines recommended by NICE	Recommendations are not mandatory and understood as only advisory	There is a legal requirement that health boards in Wales provide access to new medicines recommended by AWMSG

a generic measure of 'health gain' and combines data on extension of and quality of life. Quality of life is estimated using health utilities, which are values representing preferences for different health states. NICE will only accept indirect utility estimates, when patients are asked to fill in a quality of life questionnaire which are then converted to health utility values [32]. Whereas, SMC will accept both indirect and direct health utility estimates, when patients are asked directly their preferences for different health states using choice experiments such as a standard gamble or time trade off [32]. The decision-making threshold is intended to represent the opportunity cost of the current NHS budget constraint. Therefore, by comparing the incremental cost per QALY gained of a given health technology with the threshold, an assessment can be made of whether adopting the new technology will generate more QALYs than would be lost from the treatments displaced under the budget constraint.

While most health economists believe the QALY encompasses two of the most important elements of health gain, some argue that the QALY does not capture all the relevant benefits from therapy, such as external benefits to others including carers, the value of scientific spill-overs leading to other innovations, effects on the broader economy in terms of production, or other social values such as any desire for equity, or to prioritise treatments for severe disease [33]. There also remains a lack of consensus whether direct or indirect methods are the most appropriate approach to measure healthcare utilities. [32] Moreover, the QALY model does not consider the pre-treatment level of patients [34], and therefore this approach may favour those with more treatable conditions and greater capacity to benefit.

In addition, there are arguments concerning the appropriate level of the threshold. Some researchers argue that the current threshold of £20,000 per QALY to £30,000 per QALY may be set too high or low [35]. In an econometric analysis of data from NHS commissioning groups, Claxton et al. estimate that the average cost per QALY of technologies displaced across all NHS programme budgets is less than £13,000 per QALY, although this average is subject to wide variation across disease areas [35,36]. Other researchers question this analysis, given the limitations of the data. [37] Nevertheless it is worth noting the £20,000 threshold, set in 1999 by NICE and subsequently adopted by SMC and AWMSG, has not increased with inflation. By not increasing the threshold, NICE may be implicitly acknowledging the original threshold was too high. In the past, the World Health Organisation recommended that the threshold should be 1–3 times a countries' GDP per capita, which, although somewhat arbitrary, was largely aspirational and related more to presumptions about the societal willingness to pay for treatments [38].

Ultimately, the determination of a threshold is essentially a value judgement. This includes considering the trade-offs between static and dynamic efficiency. Static efficiency reflects the opportunity cost of providing existing treatments and dynamic efficiency takes account of gains in innovation and long-term benefits. While a controversial area, many argue that a threshold set through reflecting existing treatment costs is too low with respect to dynamic efficiency considerations and will discourage the necessary long-term investments required for drug development [39].

NICE allows flexibility in its decision-making (cost-effectiveness) threshold, currently set at £20,000 per QALY for routine treatments and up to £30,000 per QALY if there are other reasons in favour of recommending the technology (e.g. 'step-change' innovation). In 2009, NICE introduced its 'end-of-life guidance' [40], for therapies adding more than 3 months to the life expectancy of patients having no more than 24 months to live. This has resulted in NICE valuing QALYs gained at end-of-life at 2.5 times 'standard' QALYs, implying a decision-making threshold of £50,000 per QALY. More recently NICE introduced a new programme for Highly Specialised Technologies (HST) for treatments for small populations and rare conditions. NICE introduced a threshold of £100,000 per QALY for drugs that added more than 10 QALYs over the patient's lifetime, that can increase proportionately to £300,000 per QALY, depending on the number of QALYs added, up to 30 QALYs lifetime [41]. While this may seem like a large deviation from the standard threshold, drugs evaluated under the HST programme involve small numbers of patients and remain subject to a budget impact assessment. AWMSG have also developed policies deviating from the £20,000-£30,000 per QALY threshold for end-of-life treatments [42], and treatments for rare diseases and small populations [43], which align with the aforementioned policies developed by NICE.

Similar to NICE and AWMSG, SMC also allows flexibility in its' decision-making (cost-effectiveness) threshold. SMC applies 6 additional considerations, known as 'modifiers', alongside its consideration of the incremental cost per QALY gained: [44]

1 Evidence of a substantial improvement in life expectancy (with sufficient quality of life to make the extra survival desirable). Substantial improvement in life expectancy would normally be a median gain of 3 months but the SMC assesses the particular clinical context in reaching its decision;

2 Evidence of a substantial improvement in quality of life (with or without survival benefit);
3 Evidence that a sub-group of patients may derive specific or extra benefit and that the medicine in question can, in practice, be targeted at this sub-group;
4 Absence of other therapeutic options of proven benefit for the disease in question and provided by the NHS;
5 Possible bridging to another definitive therapy (e.g. bone marrow transplantation or curative surgery) in a defined proportion of patients;
6 Emergence of a licensed medicine as an alternative to an unlicensed product that is established in clinical practice in NHS Scotland as the only therapeutic option for a specific indication. Some possible examples include caffeine injection for the treatment of apnoea of prematurity and betaine anhydrous for the adjunctive treatment of homocystinuria.

These modifiers are particularly important in cancer care, where in some circumstances, new pharmaceuticals may represent little or no improvements in overall survival but instead improve quality of life [45–48]. However, NICE does argue that many of these factors are considered in its process of 'deliberative decision-making', pointing out that there is flexibility around its decision-making threshold, although this is less transparent.

Another difference between NICE and SMC is that local commissioning bodies in England, and health boards and trusts in Wales and Northern Ireland are legally required to make technologies recommended by NICE available to patients [49], whereas SMC recommendations are advisory only. This means that NICE is more open to legal challenge than SMC, and has been subject to several high profile court cases [50,51]. NICE processes therefore are typically more robust and include a longer timeline for appraising new technologies; SMC aims to issue guidance within 18–26 weeks [52], whereas for NICE the expected assessment timeline is 40–60 weeks depending upon whether a single or multiple technology appraisal is conducted [20,53]. As a result, the cost of NICE is higher than SMC, with a budget of around £50 million [54], roughly double that of Healthcare Improvement Scotland [55], which includes SMC. Although it is challenging to accurately establish the cost of each agency, particularly as both NICE and SMC rely extensively on support from the academic community, many of whom provide their support on a voluntary basis. Cairns 2006 undertook a review of the approach undertaken by NICE and SMC and concluded their recommendations should be understood as complementary and there is benefit in SMC undertaking a rapid early evaluation of new health technologies which may prevent habits by prescribers becoming established before a more extensive evaluation by NICE [56].

There is some divergence in decisions between NICE and SMC, which has, at times, led to inequitable access to new treatments [57]. Ford et al. compared decisions from SMC and NICE from establishment until 2010 and found that NICE recommended, with or without restriction, 90% of drugs compared to 80% by SMC, and that SMC published guidance more quickly than NICE (median 7.4 months compared with 21.4 months) [58]. Nicod et al. analysed all decisions by SMC and NICE between 2007 and 2009, and similarly found NICE had a higher proportion of positive recommendations (19% accepted without restrictions; 63% accepted with restrictions) compared to SMC (28% accepted without restriction; 40% accepted with restrictions) [59]. Fishcher et al. focused on a subset of drugs also reviewed by the German HTA agency between 2011 and 2014 and found that NICE recommended, with or without restrictions, 75% of drugs compared to 69% by SMC, although both agencies published more positive recommendations than the German HTA agency [60]. Griffiths et al. 2015 focused on drugs assessed between 2000 and 2014 with ICERs higher than the £20,000-£30,000 per QALY threshold and found that NICE issued a higher proportion of positive recommendations (34% accepted without restrictions; 20% with restrictions), compared to SMC (11% accepted without restrictions; 14% accepted with restrictions) [61]. Maynou and Cairns 2020 focused specifically on cancer drugs assessed between 2002 and 2014, and found that NICE issued a similar proportion of positive recommendations to SMC but SMC had a higher proportion of recommendations with restrictions (25% accepted without restriction; 48% accepted with restrictions) compared to NICE (46% accepted without restrictions; 26% accepted with restrictions) [62,63]. When focusing exclusively on orphan drugs reviewed from establishment until 2018, Stawowczyk et al. 2019, found that SMC issued a much higher proportion of negative recommendations (32%) compared to NICE (11%) [64]. Several articles have explored some of the factors underlying divergent decisions between NICE and SMC, including uncertainties about cost-effectiveness, comparator choice, and clinical benefit [65–67], differences in stakeholder input [68], additional considerations such as the innovative nature of the treatment, unmet need, indirect benefits of the treatment, and the nature of adverse events [68,69], and the negotiation of confidential price discounts or market entry agreements (MEAs) [70,71].

Despite consensus amongst many articles identified that SMC is more likely to issue negative recommendations than NICE, it appears that in more recent years that SMC has begun to issue a higher proportion of positive recommendations. Macaulay 2016 undertook a time-trend analysis of SMC submissions up to 2015 and found SMC approval rates for new drugs peaked in 2014 at 86% from 59% in 2007, and found a positive correlation for SMC approval rates over time [72]. The article suggested this may be linked to the introduction of the Patient and Clinician Engagement Group (PACE) process for end-of-life and rare disease indications in 2014 [73], which aims to describe added benefits from medicines from both patient and clinician's perspectives that may not be fully captured within conventional clinical and economic evaluation. Manufacturers are invited to request a PACE meeting if the draft advice from SMC is a negative recommendation. However, other analysis has suggested that the introduction of the PACE process has had no impact on positive recommendations [74].

The timeline for appraisals by AWMSG is the shortest at 20–21 weeks [29], although as mentioned above, AWMSG only produces recommendations for newly licensed medicines not expected to be appraised by NICE in the next 12 months, and NICE guidance can supersede AWMSG guidance. Chamberlain et al. 2014 demonstrated some cancer drugs that were initially recommended by AWMSG and subsequently recommended by NICE were adopted faster in Wales [75], likely due to these shorter timelines for appraisals. Varnava et al. 2018 reviewed decisions by AWMSG between 2010 and 2015 and found AWMSG issued positive recommendations, with or without restrictions, for 89% of drugs [28]. For drugs recommended by AWMSG, as of May 2017, 79% had not been scheduled for assessment by NICE, 5% were in the process of being reviewed, 11% had been subsequently recommended, and 4% were not recommended. For the drugs not recommended by AWMSG, as of May 2017, 72% had not been scheduled for assessment by NICE, 6% were in the process of being assessed, 6% had been subsequently recommended, and 17% were not recommended.

3.1.2. *The appraisal of medical devices*

There has been much greater activity in the assessment of novel pharmaceuticals than of medical devices in the UK. There are a number of reasons for this. First, the expenditure of devices may not be so visible [76], in so far as some devices represent a small component of the cost of (say) a complicated surgical procedure. Secondly, whereas there is often a formal procedure, at national or local level, to approve drugs for inclusion on a formulary or ap-

proved 'list', the same is not often the case for devices. Thirdly, there are a number of particular characteristics of medical devices that make their economic assessment more challenging. These include the relative lack of controlled clinical studies estimating relative treatment effect, the incremental nature of innovation in devices, the impact of the user 'learning curve' for devices, more dynamic pricing, and the broader organisational consequences of adopting a new device [77].

In response to these challenges, the Medical Technologies Evaluations Programme (MTEP) was introduced by NICE in 2010 [22]. Whereas, the SMC and AWMSG are yet to introduce a similar programme dedicated to the evaluation of medical devices. Under this programme, sponsors (usually manufacturers) can submit medical technologies to ask for a positive recommendation if their device can be shown to reduce NHS costs, for example by switching care from an inpatient to outpatient basis [78]. This averts the need to prove clinical superiority and may be useful for those devices offering a small incremental improvement. A review of Medical Technologies Guidance between 2010 and 2017 found that NICE fully supported 45% (14/31) of technologies, partially supported 35% (11/31) and did not support 19% (6/31) [79]. 58% (18/31) of the medical technologies were reviewed on the basis of observational data only. There is selection bias associated with this sample, as NICE only assesses technologies when asked to, although medical devices are also considered within NICE's Clinical Guidelines Programme [25]. As more medical devices are developed, NICE may have to take a more proactive approach in assessing medical technologies, particularly diagnostics, where the possibility of false negatives and false positives creates risks for patients and healthcare services. To meet this challenge NICE has established a Diagnostics Assessment Programme [23], but similar to MTEP, assessment of new diagnostics is dependant on submission by a manufacturer.

3.1.3. Affordability

Since establishment, SMC has required manufacturers to estimate the budget impact of their new drug for the first five years from launch. A new drug is classified as "high impact" if it is predicted to have a budget impact of greater than £500,000 per annum [80]. Similarly, AWMSG requires manufacturers to estimate the budget impact of introducing their new drug, in a process modelled on the one developed by SMC [81]. However, in contrast there is no explicit threshold for what is considered as minimal or large budget impact set by AWMSG, and this is assessed on a case by case basis [28]. Historically, it was not required for manufacturers to estimate budget impact within submissions to NICE, however from 2017, NICE and NHS England have introduced a budget impact test to assess the affordability of new technologies within the NHS [41]. For new products where the projected budget impact exceeds £20 million per annum for each of the first three years of adoption, a discussion will then be triggered between NHS England and the company producing the technology. This discussion will cover matters of affordability, the price of the technology or ways through which the technology can be introduced via various payment mechanisms. This does not mean that £20 million is the most NHS England will pay for a new technology per annum, but rather additional arguments and (potentially) payment systems for the technology must be considered. If no agreement is reached, the new technology may be subject to a phased introduction to alleviate the short-term financial impact. This assessment will be undertaken on a case-by-case basis with NICE aiding the discussion through consultation with interested parties. These commercial negotiations have to be completed within the time that NICE issues its guidance on the technology [82].

3.2. Challenges and opportunities going forward

The following outlines several areas where the UK will face challenges and opportunities when introducing new health technologies such as pharmaceuticals and medical devices going forward. There are also other pertinent issues not covered in this paper for feasibility purposes, but covered elsewhere in other publications, such as stimulating research and development of novel antimicrobials [83], responding to developments in digital health [84,85], and reducing waste and over-treatment [86].

3.2.1. Step-change technologies

First, the NHS needs to decide on how to deal with 'step-change' technologies such as advanced therapy medicinal products (ATMPs), defined as "medicines for human use that are based on genes or cells, and offer ground-breaking new opportunities for the treatment of disease and injury" [87]. Emerging developments in immunotherapy in cancer and gene therapy, will lead to an increasing number of 'step-change' technologies and create challenges for health technology appraisal, such as increased uncertainty associated with immature evidence, incorporating additional dimensions of value, and determining appropriate discounting rates [88]. There are also affordability concerns, and the UK, like many other countries, may struggle with the acute budget impact, particularly if several highly cost-effectiveness technologies emerge simultaneously [89].

To date, the Department of Health and Social Care and NICE in England, and equivalent bodies in other parts of the UK, have used cost control measures such as restricting access to new treatments to those who will benefit the most, and/or securing confidential price discounts [90]. However, it might be possible to drive the cost of these new technologies down further. More aggressive use of tendering at a national or local level, or the greater use of financial MEAs and price discounts are potential mechanisms. Research has, however, shown that the UK is a relatively low user of financial MEAs [91,92]. This may reflect lack of enthusiasm after a previous risk- sharing scheme between the UK government and the pharmaceutical industry to make interferon beta and glatiramer available for use in patients with multiple sclerosis following a negative recommendation from NICE in 2002 [93], did not result in any renegotiation of prices after initial results were worse than predicted [94]. Alternatively, this could reflect the various objectives pursued by the UK government when dealing with the pharmaceutical industry, which include promoting innovation and supporting a sector that is estimated to add around £14 billion to the economy and create 60,000 jobs [95].

3.2.2. Highly specialised technologies

Secondly, it is increasingly apparent that NICE's value for money approach does not easily accommodate highly specialised technologies, which target small groups of patients with very rare conditions that could include some ATMPs. To date, NICE in England has addressed this by establishing a new Highly Specialised Technologies programme with a different decision making threshold [96]. As of June 2021, only 14 health technologies have been assessed by this programme. However, one concern of decision-makers is that, with the advent of personalised medicine, more and more small groups of patients will be identified as potential beneficiaries from a new, expensive technology by use of gene expression tests. More broadly, there needs to be a more active debate in the UK concerning whether the NHS should devote funds to highly specialised technologies and, if so, on what basis. There may be good reasons for making these therapies available, but this may involve a sacrifice of health gain to the population as a whole [97]. In the absence of substantial increases in funding, the NHS may face a choice between two vastly different approaches to

the allocation of resources. The current approach, embodied in the calculation of incremental cost per QALY and the use of a cost-effectiveness threshold, focuses on allocating resources to maximize the total health gain to the population. It embodies a notion of horizontal equity, in that (with the exception of NICE's 'end of life' guidance) a QALY is valued the same no matter whom receives it. However, it does not acknowledge variations in relative capacity to benefit across different patients or guarantee equal access to health care for all members of the population.

An alternative approach to resource allocation might be based on a notion of vertical equity, or 'unequal treatment of unequals'. This approach would focus on those individuals in the greatest need [98], suffering from the most severe illnesses and may result in more funding being available for the treatment of orphan diseases and various kinds of specialised treatment. Since these treatments tend to be expensive this approach to resource allocation would involve some loss of health overall within the population but may be preferred by those members of the population who feel that some funding should be made available to those suffering from the most serious or life-threatening diseases. In this respect, the higher "end-of-life" thresholds have already established a principle of vertical equity within the NHS. In reality, the NHS will have to consider the relative trade-offs and seek an optimal balance between these two approaches.

3.2.3. Changes to pharmaceutical licensing and the use of real-world data

Thirdly, the NHS needs to respond to drugs which are now being approved more quickly by licensing authorities, often on the basis of less mature clinical evidence [99]. The UK government has committed to provide faster access to breakthrough technologies and treatments [100], through accelerated pathways to market [101]. This has occurred in part, due to lobbying by patient groups and the pharmaceutical industry [102]. Evaluation of similar initiatives by the US Food and Drug Administration (FDA) found that expedited drugs did not offer a step change improvement in patient outcomes and were more likely have safety issues than drugs approved through regular pathways [103–106]. Moreover, it was found that expedited drugs were based on early studies which relied on surrogate outcomes [107,108], which do not necessarily translate to long-term clinical benefits [109]. Irrespective of this, analyses to data has indicated that both NICE and SMC are willing to grant positive recommendations to novel medicines based on uncertain evidence such as prospective case studies [110]. Therefore, it is important that any move towards accelerated access to medicines is combined with thorough monitoring of real-world efficacy, and if necessary renegotiation of prices.

NICE and the Department of Health and Social Care have already responded to this challenge for cancer drugs, by reforming the Cancer Drugs Fund to collect long term data on promising new therapies [111]. This has been supported by development of the NHS Systemic Anti-Cancer Treatment (SACT) dataset, which includes data on all cancer drugs administered in England linked to cancer registration and survival data, facilitating monitoring throughout the total patient pathway [112]. With increased investment in health information technology infrastructure and capabilities, this approach could be developed and applied to other therapeutic areas, to develop a more seamless approach to the approval, reimbursement and long-term evaluation of health technologies. Indeed, in 2021, the UK government announced £340 million of funding to develop an Innovative Medicines Fund modelled on the Cancer Drugs Fund to focus on other therapeutic areas, including for rare and genetic diseases [113]. However, challenges associated with the use of real-world data will need to be considered, including the funding of studies, the collection and reporting of data, the risk of observational bias and analytical methods [114].

3.2.4. Leaving the European union

The most immediate consequence of leaving the European Union (EU) for the UK health sector has been the relocation of the European Medicines Agency (EMA) to Amsterdam [115]. There is a risk this could signal the end of the UK's leadership in licensing, drug safety and HTA, thereby shifting investment in pharmaceutical research away from the UK. This depends greatly on how close the UK's future relationship is with the EU 27 and whether it is able to participate in, or benefit from, the activities of the EMA. The UK's success in using temporary use authorisation processes for COVID-19 vaccines should not necessarily be seen as an indication the Medicines and Healthcare products Regulatory Agency (MHRA) has capacity to undertake robust regulatory evaluations of all novel health technologies in a timely manner. So far, in recognition of this challenge, the UK has confirmed that it will continue to recognise medicine approvals from the EMA for 2 years from Jan 1st, 2021. [116] If the UK chooses to continue to develop a separate approval process for all new drugs, there is a risk that the UK ceases to be a priority launch country for new drugs, and companies might choose to prioritise launching new drugs in the EU, which is a substantially larger market than the UK. However, a complete lack of interest by pharmaceutical companies in launching drugs in the UK seems unlikely, given that the UK is the 5th largest economy in the world, although delays in product launch are a distinct possibility.

Furthermore, the UK is also unlikely to be able to participate fully in EU HTA initiatives. To date, the UK (through NICE) has been an active partner in the EUnetHTA Joint Action [117]. However, proposals have been made to establish a permanent EU HTA capacity which would cover both drugs and medical devices and oversee cooperation in a number of areas, including horizon scanning, joint advice (between the EMA and member states) to technology manufacturers and joint clinical assessments [118]. Cooperation amongst member states in other areas of HTA, including economic evaluation, will remain voluntary. Since the UK provided some of the key skills in these areas, the country's capacity in these areas will not be denuded, although sustaining capacity depends on the level of domestic funding provided for clinical and health services research. If completely excluded from EU HTA initiatives, there is potential for the UK to establish its own, streamlined and seamless arrangements for the licensing and reimbursement of medicines and other health technologies. Indeed, this has already begun to happen with the launch of the UK Innovative Licensing and Access Pathway (ILAP), which involves collaboration between NICE and SMC to facilitate quicker access to new innovative and "step-change" medicines for patients [119]. This would help promote the UK as a world leader in the field of HTA and an attractive place for health technology companies to invest.

This leads to the most fundamental impact of leaving the EU on the NHS, its impact on economic growth, which has been compounded further by the impact of the COVID-19 pandemic. Since health and social care is one of the largest items in government expenditure, it is particularly affected by changes in economic growth and the impact of these on the tax base. Any reduction in economic growth in the UK relative to the rest of the world may limit its ability to afford expensive new health technologies.

4. Discussion

4.1. Summary of findings

Over the last two decades, through the activities of NICE, SMC, and AWMSG, the UK has developed a robust and transparent approach towards the appraisal and reimbursement of new health technologies using the cost per QALY approach. There are however some important limitations to the cost per QALY approach includ-

ing several external benefits not captured, bias against less treatable diseases, and deciding the appropriate level of the threshold. NICE, SMC, and AWMSG have attempted to overcome some of these limitations by considering a number of additional factors such as end-of-life criteria, highly specialised treatments, and populations that experience unmet need. In many respects, the activities of NICE, SMC, and AWMSG, should be understood as complementary. However, there have been divergent decisions between these HTA agencies, driven by uncertainties around clinical and cost-effectiveness, different stakeholder input, and the negotiation of confidential price discounts and MEAs, that has led to inequity in access for some treatments across the UK.

Looking to the future, we have identified several areas where the UK will face challenges and opportunities when introducing new health technologies. Developments in immunotherapy in cancer and gene therapy are likely lead to an increasing number of 'step-change' technologies with the potential to dramatically improve treatments options for many diseases. There is also growing attention towards developing highly specialised technologies which target small groups of patients with very rare conditions that currently experience unmet need for treatments. Combined with growing efforts to adapt pharmaceutical licensing pathways to provide patients with faster access to these novel treatments, NICE, SMC and AWMSG will increasingly be confronted with uncertainty regarding the clinical and cost-effectiveness of new treatments due to immature evidence and incorporating additional dimensions of value. There are also concerns regarding acute budgetary impact if several high-cost treatments are developed and reach the market simultaneously. These issues are further complicated by the UK leaving the EU, and the relocation of the EMA to Amsterdam, which may result in the end of the UK's leadership in licensing, drug safety and HTA, shifting considerable investment in pharmaceutical research away from the UK.

4.2. Strengths and limitations

A strength of this paper is that it comparatively reviews available literature on the approach undertaken by NICE, SMC, and AWMSG at a critical juncture for HTA in the UK as these agencies seek to evaluate their processes two decades post establishment in the context of significant change and uncertainty created by the UK leaving the EU, and the COVID-19 pandemic. This paper also doesn't just map of these processes, but also critically considers future challenges and opportunities for HTA in the UK, as well as potential policy responses.

There are however some limitations which should be considered when interpreting the findings of this paper. First, this paper is a narrative review, and therefore lacks many characteristics of a systematic review including a PRISMA statement, results table, or assessment of quality of included studies. The second reviewer only screened a random sample of 25% of our search results, and therefore it is also possible some articles which meet our inclusion criteria have not have been included in analysis. However, these limitations do not negate the value of this paper, as this paper could be utilised as a foundation for a further more systematic review. Second, our consideration of future challenges and opportunities is heavily reliant upon the perspective of our co-authors that were selected according to their expertise in pharmaceutical research and policy by convenience sampling from a wider set of health policy experts that were convened for a more general purpose of reviewing future challenges and opportunities for the NHS across the UK in the 2020s. We also did not utilise a formal approach to reach consensus on these challenges and opportunities such as the Delphi method, and therefore the second section of our analysis should be interpreted with these limitations in mind. Third, the scope of our inclusion criteria, specifically articles which comparatively reviewed the approach undertaken by HTA agencies within the UK, did result in the exclusion of a significant body of literature which compares NICE, SMC or AWMSG with other HTA agencies internationally. While there are important lessons that can be learnt from comparing the approach taken to HTA in the UK to other countries, particularly those which do not utilise the cost per QALY approach or consider other dimensions of value, it was felt that for feasibility purposes this was outside the scope of this current review. Moreover, such international comparisons have been undertaken several times previously [31,120–122]. Finally, we also excluded articles concerned with local level HTA, resource management, or priority setting. We acknowledge that analysing factors that influence the implementation of national level recommendations at the local level is important however again argue this was not feasible to adequately cover within this review. We do however argue this should be the focus of further research as this is crucial to understanding how patients experience different levels of access to new treatments.

4.3. Policy implications

New health technology advances will continue to drive drug and medical devices expenditure in the future, and over two decades since the establishment of HTA in the UK the rationale to control costs while promoting innovation remains just as relevant. While the cost per QALY threshold approach has limitations, it still has the benefits of encompassing two crucial aspects of health gain and facilitating systematic comparisons of cost-effectiveness between alternative treatments. Looking to the future, the UK will be faced with the challenge of the increasing emergence of 'step-change' and 'highly-specialised' technologies. To overcome concerns regarding the acute budgetary impact of these technologies the UK will need to make greater use of financial MEAs and confidential price discounts. To respond to changes to pharmaceutical licensing and increasing use of real world data that aim to facilitate faster access to new treatments for patients, the UK will need to invest in the health information technology infrastructure and capabilities to successfully implement performance based MEAs to mitigate against uncertainties created by immature evidence. HTA agencies in the UK will be required to develop and evaluate the terms and conditions of such MEAs. In the context of the UK leaving the EU, and the prospect of less collaboration with European HTA agencies, the imperative for NICE, SMC, AWMSG to collaborate further will increase. These HTA agencies need to work together to respond to aforementioned challenges and opportunities in a manner that identifies synergies' and maximises HTA capacity across the UK.

Contributions

MA, MD and EM designed the study. MA, PC, and EM acted as first, second, and third reviewer. MA produced the first draft of the manuscript in conjunction with MD. All co-authors provided comments and edits to iterative drafts of the manuscript, approved the final version, and meet the ICMJE criteria for authorship.

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Supporting information

Supplementary Material 1
Search Terms:

(((medicine[*Title*/*Abstract*]) OR (medicines[*Title*/*Abstract*]) OR (drug[*Title*/*Abstract*]) OR (drugs[*Title*/*Abstract*]) OR (pharmaceuticals[*Title*/*Abstract*]) OR (health technology[*Title*/*Abstract*])) AND ((reform[*Title*/*Abstract*]) OR (policy[*Title*/*Abstract*]) OR (regulation[*Title*/*Abstract*]) OR (reimbursement[*Title*/*Abstract*]) OR (assessment[*Title*/*Abstract*]) OR (appraisal[*Title*/*Abstract*]) OR (regulating[*Title*/*Abstract*])) AND ((england[*Title*/*Abstract*]) OR (wales[*Title*/*Abstract*]) OR (scotland[*Title*/*Abstract*]) OR (northern ireland[*Title*/*Abstract*]) OR (united kingdom[*Title*/*Abstract*]) OR (UK[*Title*/*Abstract*]) OR (great britain[*Title*/*Abstract*]) OR (NICE[*Title*/*Abstract*]) OR (SMC[*Title*/*Abstract*]) OR (AWMSG[*Title*/*Abstract*]) OR (All Wales Medicines Strategy Group[*Title*/*Abstract*]) OR (National Institute for Health and Care Excellence[*Title*/*Abstract*]) OR (Scottish Medicines Consortium[*Title*/*Abstract*])))

Declaration of Competing Interest

The authors have no conflicts of interest relevant to this manuscript to declare.

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Supplementary materials

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