In recent years, technology appraisals and reimbursement recommendations from established health technology assessment (HTA) organizations around the globe are taking on an increasingly prominent role in cost-containment and seem to have become more restrictive in nature. In order for important new health technologies to reach patients, innovative research companies must achieve market access not only through stringent regulatory processes, but also by gaining reimbursement approval from many countries around the world. While navigating this complex process, it is important to consider whether the evaluations and decisions of agencies in different countries are aligned around the same key clinical and economic components. As HTAs have become a prominent element of health care decision-making in many countries, attention is turning to whether they assess outcomes and measures that are most meaningful to patients and their physicians.

Given the current climate and a growing interest in HTA policy, Context Matters initiated a research initiative to examine trends in global HTA with a specific focus on established global HTA models that are often referenced in domestic conversations regarding access and reimbursement. The United Kingdom’s (UK) National Institute for Health and Care Excellence (NICE) was a particular focus in this endeavor, given their high level of activity and their role as a leading HTA body.

It is understandable that HTA processes will differ from country to country as each seeks to best serve the public health and economic interests of its population. We wanted to better understand how HTA agencies assess the clinical aspects of a drug and whether those assessments vary from agency to agency. Clinical assessments are based upon clinical trial data and outcomes and are an important driver of reimbursement decisions. While we empirically understood that there would be some variability due to different HTA approaches and standards, we were still surprised as to the extent of the variability. As global market access for innovative therapies is highly dependent on gaining reimbursement approval from many countries with HTA processes, it was important to consider how the evaluations and decisions of agencies in different countries are aligned around key clinical components. That is, if the clinical components are similar, how much variability should we expect in clinical assessments?

Methods

In order to gauge alignment, Context Matters examined the HTA decisions for pharmaceutical interventions for four key global agencies in relation to the UK’s NICE: SMC (Scottish Medicines Agency; Scotland), PBAC (Pharmaceutical Benefits Advisory Committee; Australia), HAS (Haute Autorité de Santé; France), and CADTH’s Common Drug Review (Canadian Agency for Drugs and Technologies in Health; Canada). Therapeutics were matched on indication, and the most recent review released since 2007 was included if it was reviewed by NICE and at least one other agency. Two hundred and thirteen reviews met these criteria.1

“Agreement” and “disagreement” was defined as follows: NICE and another agency agreed on the reimbursement decision if both agencies issued a positive decision or if both agencies issued a negative decision. Otherwise, they disagreed.

Results

There is variability in agreement between NICE and other agencies

All agencies in this study rendered positive decisions more than 50% of the time, ranging from 62% (PBAC) to 95% (HAS). CADTH issued positive decisions for 67% of the reviews; NICE for 72%.

This variability resulted in levels of disagreement between NICE and the other agencies studied. NICE disagreed with HAS on 41% of the reviews, but disagreed with SMC only about half as often, on 19% of the reviews. From 2007 to 2013, HAS became less aligned in their decisions with NICE, while CADTH, SMC, and PBAC became more closely aligned. When the time period is divided into two eras, 2007-2010 and 2011-2013, interesting trends emerge. The rate of disagreement between NICE and SMC decreased from 25% (2007-2010) to 15% (2011-2013). Similarly, the rate of disagreement between NICE and PBAC decreased from 37% (2007-2010) to 35% (2011-2013). HAS became less aligned with NICE; their disagreement rate increased from 33% (2007-2010) to 46% (2011-2013).

Disagreement rates between agencies are significantly higher for oncology medicines

NICE agreed with other agencies more frequently in non-oncology disease conditions than in oncology conditions. Rates of disagreement in oncology reviews were 55% with PBAC, 50% with HAS, and 23% with SMC, indicating that SMC aligns closely with NICE.2 Overall, the five agencies agreed with NICE on the final decision for 81% of the reviews for non-oncology drugs and for only 56% of the reviews for oncology drugs. Economic factors, including the use of patient access schemes, seemed to have a more prominent role in reimbursement determinations for oncology products.

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<tr>
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<th>Oncology</th>
<th>Non-oncology</th>
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<tbody>
<tr>
<td>CADTH</td>
<td>16%</td>
<td>7%</td>
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<tr>
<td>SMC</td>
<td>32%</td>
<td>18%</td>
</tr>
<tr>
<td>HAS</td>
<td>50%</td>
<td>32%</td>
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<tr>
<td>PBAC</td>
<td>55%</td>
<td>23%</td>
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Note: Oncology represents 0% of CADTH reviews (0/15), 40% of SMC reviews (17/42), 51% of HAS reviews (20/39), and 51% of PBAC reviews (20/39).

1 The final sample included 213 reviews covering 49 unique drugs and 66 indications. The reviews span 25 disease conditions including six solid-state oncology conditions.
2 CADTH does not review oncology products.
Global Variability in HTA Decisions Poses Challenges for Innovative Biopharmaceutical Research and Development

**NICE is more closely aligned with SMC and less aligned with CADTH and HAS**

Even if two agencies issued positive and negative decisions completely randomly, they would sometimes agree just by chance. We compared actual agreement between NICE and each agency to the agreement that would be expected by chance.

These results appear to indicate that there is greater underlying similarity in assessment policy and practice between the pairs of NICE-SMC and NICE-PBAC than between the pairs of NICE-CADTH and NICE-HAS. Over time, only NICE and SMC have become more aligned by this measure, and by this measure only NICE and SMC are considerably aligned in both oncology and non-oncology decisions.

**Overall, disagreement on the clinical assessment was 50%**

Agencies were often not aligned on their clinical assessment. The clinical assessment generally includes a summary of the agency’s evaluation of the clinical evidence submitted by the manufacturer. For example, NICE determined that a Hepatitis C drug demonstrated greater efficacy/effectiveness than the comparator, while PBAC determined that there was uncertain efficacy/effectiveness for the same drug. Due to the differences in clinical assessment (greater vs. uncertain) this would be defined as a disagreement. Rates of disagreement on the clinical assessment ranged from 44% (NICE-HAS) to 56% (NICE-PBAC).

The level of variability in appraisals, even on the basis of comparative clinical effectiveness, illustrates the challenges of coming to a single, appropriate judgment of clinical value of a given test or treatment. Perspectives on clinical value vary among stakeholders and organizations, and this can have significant implications for patients and innovators. Variability makes it challenging for innovative researchers to work towards a clinical effectiveness standard.

**Time from regulatory approval to reimbursement decision**

Context Matters also examined whether NICE’s decisions notably lag behind the European Medicines Agency’s (EMA) initial market authorization. NICE took an average of 20.5 months to complete a review after EMA approval (though there was enormous variation in the corresponding intervals for individual reviews). On average, NICE took longer to issue negative decisions (27.5 months) than positive decisions (19 months). Analysis revealed that intervals for Multiple Technology Reviews averaged more than twice the length of those for Standard Technology Reviews.

**Conclusions**

Comparing NICE’s decisions to those of other agencies reveals decision and clinical assessment disagreement, particularly among oncology drugs. Across a sample of drugs reviewed by NICE and at least one of five other HTA agencies, NICE agreed with other agencies less frequently in oncology conditions than in non-oncology conditions overall (56% vs. 81%, respectively), and agreed less in oncology with each of the agencies individually. Among the oncology drugs examined, NICE agreed with SMC only 77% of the time, notable because overall SMC tends to align closely with NICE. Examination of the clinical and economic assessments that underlie these reimbursement decisions revealed notable variability in the clinical and economic evaluations across agencies.

The degree of variability in assessments illustrates the nuance and complexity of the clinical and economic data presented to HTA bodies, the element of subjectivity in how it can be interpreted, and the varying ways individual HTA organizations interpret data based on local culture, perspectives and goals. The levels of variability illustrate the challenge of making decisions based on centralized models of value assessment, even for clinical data. The challenge is particularly relevant in light of the emergence of new models of evidence-based decision-making. It will be important to continue to assess these models for their flexibility, so that they can accommodate variability in evidence, particularly with regards to patient subgroups, personalized medicine, and changes in data on clinical value. Furthermore, the rapid pace of advancing science and our increasing understanding of the underlying mechanisms of the more than 200 diseases we call cancer provide additional challenges to models for value assessment, requiring that they adapt to reflect this continual growth.