

# TRANSPARENCY IN HEALTH TECHNOLOGY ASSESSMENT

## NICE, IQWIG and HAS in comparison

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### Executive Summary

This report examines assessments of a novel breast cancer drug's efficacy by three different European health technology assessment agencies (HTAs) in order to gauge these agencies' comparative levels of transparency and identify best practices in HTA transparency.

#### Key findings at a glance

- Overall, the assessment processes of NICE (England & Wales), IQWIG (Germany) and HAS (France)<sup>1</sup> have a high level of transparency. All three agencies disclose who reviewed the evidence underlying their assessments, and how possible conflicts of interest were managed. They also detail what evidence they reviewed, and how they evaluated it. The literature suggests that many other European HTAs do not meet these transparency standards.
- Against this positive backdrop, some gaps remain:
  - *NICE redacted some efficacy data* from its drug assessment reports; disclosure of similar data by the other two HTAs shows that such redactions are not inevitable.
  - Meanwhile, the assessment report of *HAS provided less detail* and thus insight into the agency's reasoning than those of NICE and IQWIG.

#### Policy recommendations

- **European-level HTA assessments.** Any future European-level HTA assessments should raise the bar on transparency by matching or exceeding the strongest transparency policies and practices of the individual Member State that is most advanced in that area. Notably, European-level HTA should adopt IQWIG's approach of routinely publishing all clinical trial data used within its assessment reports.
- **NICE redactions.** In the short term, NICE should put into place a system that automatically un-redacts all clinical trial data cited in its documents after a [12 month embargo period](#).<sup>(1)</sup> In the medium term, NICE should follow the positive example of its German counterpart and stop redacting any clinical trial data in the first place.
- **NICE patient group involvement.** NICE should follow up on its recent pledge to take into account concerns about undisclosed industry funding for patient groups in the ongoing review of its conflict of interest policies (see box further below).

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<sup>1</sup> NICE = [National Institute for Health and Care Excellence \(https://www.nice.org.uk/\)](https://www.nice.org.uk/); IQWIG = [Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen \(https://www.iqwig.de/en/home.2724.html\)](https://www.iqwig.de/en/home.2724.html); HAS = [Haute Autorité de santé \(https://www.has-sante.fr/\)](https://www.has-sante.fr/)

## Introduction

### What is health technology assessment?

Health technology assessment agencies (HTAs) are tasked with evaluating whether any given drug, medical device or treatment is clinically better than other treatments currently in use for the patient group in question.

For example, the UK's National Institute for Health and Care Excellence (NICE, <https://www.nice.org.uk/>) assesses drugs, devices and treatments "to ensure that all NHS patients have equitable access to the most clinically- and cost-effective treatments that are viable". De facto, if NICE determines that a new treatment adds little or no value, the NHS is unlikely to provide it to patients.

### Different HTAs may reach different conclusions

Individual national HTAs sometimes reach different conclusions about the same drug licensed by the European Medicines Agency. There are several reasons for this. For example, HTAs may be looking at different bodies of evidence as new data becomes available over time. Also, different HTAs have different mandates. Some HTAs only assess whether a drug works better than alternative treatments, while others – like NICE – also assess whether their added benefits justify the additional cost of providing them. Furthermore, clinical practice (and thus comparator treatments) can vary from one country to the next.

In some cases, HTAs disagree about whether a drug provides any benefit at all to patients even when they are looking at the same evidence (and cost is not a factor). Palbociclib for advanced breast cancer, the drug-indication pair used as the case study in this report, is one such case.

### Importance of transparency in HTA assessments

HTA assessments help to determine whether a country's health service will pay for certain treatments. Thus, the outcomes of HTA assessments are important to individual citizens, be they patients or taxpayers. HTA transparency not only reduces corruption risks, but also enables democratic debates on public health priorities and allocations of public resources, and the social values underlying these. In a democracy, the public should have access to information on who makes important decisions, based on what evidence base, following which reasoning, and what has been decided.

In addition, HTA transparency can further medical progress. For example, in the field of oncology, there is currently a lively scientific debate about the [limited added value provided by many new cancer drugs](#) in general,(2) and the [salience of surrogate endpoints](#),(3) including [progression-free survival](#),(4) in particular. The assessment documents for palbociclib compiled by NICE and IQWiG are valuable research outputs in their own right, and can help to inform

these scientific debates, future [regulatory](#)(5) and HTA decision-making, and individual treatment decisions.

### Scope and limitations of this report

This report gauges the three HTAs' *comparative levels of transparency* to identify gaps and best practices, using public documents on their assessment of palbociclib for breast cancer as a case study. This report does *not* seek to evaluate the soundness of HTAs' internal decision-making processes or the validity of their conclusions regarding palbociclib with an aromatase inhibitor for previously untreated, hormone receptor-positive, HER2-negative, locally advanced or metastatic breast cancer.

The mandate of NICE and HAS (but not IQWiG) also includes making reimbursement decisions. This report focuses exclusively on HTAs' technical assessments. Pharmacoeconomic assessments, pricing negotiations, or reimbursement decisions by NICE and HAS are beyond its scope.

### Background of this report

This report was commissioned and funded by HealthWatch and written by Till Bruckner. The author would like to thank Kirstine McDermid, who helped to locate relevant publications, and Ron Akehurst, Susan Bewley, Mike Drummond, John Graham, Leeza Osipenko, Richard Sullivan, staff members at IQWiG, and additional anonymous reviewers, some of whom provided extremely helpful and detailed comments on an earlier draft. The responsibility for the content lies with the author alone.

## Case study: three HTA decisions on palbociclib for breast cancer

### Advanced breast cancer: background

Breast cancer is the [most common type of cancer in the UK](#).<sup>(6)</sup> About one in eight women are diagnosed with breast cancer during their lifetime. Most women diagnosed with breast cancer are over fifty years old. There are many different kinds of breast cancer.

Around [two thirds of breast cancers](#) are hormone receptor (HR) positive,<sup>(7)</sup> meaning that high estrogen levels help the cancer cells grow and spread. On a second dimension, most breast cancers are classed as ‘HER2 negative’, meaning that they have cells that contain little or none of the human epidermal growth factor receptor 2 protein. Roughly half of advanced breast cancers are both HR-positive and HER2-negative.

Advanced breast cancer is cancer that is locally advanced, has spread from the breast to another part of the body, or has come back in another location within the same or the other breast. Most women with advanced breast cancer die within a few years of diagnosis. It is incurable but medical treatment can extend the life span of patients. Thus, the aim of current treatments is to extend patients’ life span, improve their quality of life, or both.

### Palbociclib: a new breast cancer drug

The drug palbociclib (brand name Ibrance) was developed to treat women with advanced breast cancers that are both HR-positive and HER2-negative.<sup>2</sup> Some relevant trials are still ongoing and their overall survival data are not yet available. In November 2016, the European Medicines Agency [gave palbociclib a marketing authorisation](#),<sup>(8)</sup> allowing the pharmaceutical company Pfizer to sell it within the European Union.

### Three different HTAs, three different decisions on palbociclib

Health technology assessment agencies across Europe subsequently evaluated evidence on palbociclib provided by the pharmaceutical company Pfizer to help national decision-makers determine whether it should be provided to patients. This report covers the assessments made by three HTAs:

- The HTA of England and Wales, the National Institute for Health and Care Excellence (NICE), [recommended palbociclib](#) “as an option for treating hormone receptor-positive, human epidermal growth factor receptor 2-negative, locally advanced or metastatic breast cancer as initial endocrine-based therapy in adults.” (December 2017)<sup>(9)</sup>
- The German HTA, the Institute for Quality and Efficiency in Health Care (IQWiG) concluded that while palbociclib [provided no proven added benefit to any group of patients](#),<sup>(10)</sup> it caused more severe side effects than alternative treatment options did, and therefore did not recommend its use in breast cancer patients. (February 2017)
- The French HTA, the Haute Autorite de Sante (HAS) concluded that palbociclib [did provide “minor” benefits](#) compared to alternative treatment options,<sup>(11)</sup> but only in the case of post-menopausal women. However, HAS found that no added benefits had been proven for pre-menopausal women. Thus, it recommended its use in only some patient sub-groups (May 2017).

## Transparency of NICE’s assessment (England and Wales)

### Who reviewed the evidence?

The members of the relevant committee are [publicly listed by name](#),<sup>(12)</sup> as are external experts and other participants in committee meetings.

### How were conflicts of interest managed?

NICE has detailed conflict of interest policies for [board members and employees](#),<sup>(13)</sup> and for [external actors](#).<sup>(14)</sup> COI data is published and may only be redacted in “exceptional circumstances”. COI are disclosed both in written form and verbally; the latter disclosures are [considered during meetings](#).<sup>(15)</sup> Appraisal committee members may be excluded from participating further in an appraisal if the committee considers them to have a substantial conflict of interest. In addition, NICE has a [gifts and hospitality policy](#),<sup>(16)</sup> and maintains a [database of gifts and hospitality](#) provided to board members and directors.<sup>(17)</sup>

In April 2019, NICE started charging pharmaceutical companies for appraisals of their drugs.<sup>3</sup> Some NHS organisations [voiced fears](#) that industry fees might give companies inappropriate influence over NICE.<sup>(20)</sup> The government rejected these concerns, arguing that companies will be charged before appraisals begin, so NICE revenues will not be dependent on assessment outcomes.

<sup>2</sup> Palbociclib with an aromatase inhibitor for previously untreated, hormone receptor-positive, HER2-negative, locally advanced or metastatic breast cancer.

<sup>3</sup> The move was preceded by a [government consultation](#)<sup>(18)</sup> that drew [78 responses](#),<sup>(19)</sup> 41 of which came from industry.

### Concerns about gaps and omissions in patient organisation disclosures

A [study published by BMJ](#) in January 2019 examined industry funding for 53 patient organisations contributing to 41 NICE technology appraisals during 2015-2016.(21) The team found that on 79% occasions that patient organisations contributed to appraisals in 2015 and 2016, they had accepted funding from the manufacturer(s) of a technology or a competitor product in the same year that they had contributed to the appraisal of that technology, or the previous year.

Current NICE policy requires individuals to declare any money or grants they have received, but does not require the patient organisation itself to reveal its funding. Most patient organizations assessed had not voluntarily disclosed their potential conflicts of interests on [Disclosure UK](#).(22) online, or in response to direct enquiries.

NICE's decision-making committees were aware of only 21% of these specific interests. For nearly two thirds of these unrecognised specific interests, disclosure by patient organisations was not required by NICE's policy. Scotland and France already have relevant mandatory disclosure rules in place, the lead author [told the Guardian](#).(23)

In an [accompanying editorial](#).(24) the BMJ recommended that NICE policies should "require disclosure in all circumstances and not just in the nomination of patient and clinical experts. Furthermore, NICE must ensure complete enforcement with compliance from all patient organizations." Noting that almost all of the nominated patient and clinical experts who declared financial conflicts of interest were selected to attend NICE committee meetings, the editorial concluded that: "Disclosure alone does not provide a robust enough safeguard to ensure public trust, and additional legislation and organizational policies are needed for all stakeholders to react in a meaningful way to the information disclosed."

NICE responded that an ongoing review of its disclosure policies would take the study's findings and recommendations into account. NICE's deputy chief executive [told the Guardian](#) that: "Ensuring that organisations and individuals declare potential conflicts of interests in accordance with our policies is central to how we develop guidance and is essential in maintaining public and professional confidence in our work."(23)

### What evidence was reviewed?

NICE reviewed evidence from two clinical trials: PALOMA-1, an open-label study involving 165 patients, and PALOMA-2, a placebo-controlled, double-blind trial involving 666 patients. Results from PALOMA-3 were not considered as they were not relevant to the assessment question. NICE reviewed trial registry data, journal articles, Clinical Study Reports, and additional information provided by Pfizer. NICE's [response to a Freedom of Information](#)

[request](#) confirms that it fully listed all sources of evidence used on its website.(25)

### How was the evidence evaluated?

The committee's conclusions about the strengths and weaknesses of the evidence and how uncertainties were dealt with are detailed, and [are available online](#).(26)

### Will palbociclib actually benefit patients?

NICE concluded that there was no evidence that palbociclib has an effect on overall survival, but recommended the drug based on its positive effect on progression-free survival.

Multiple studies show that surrogate endpoints such as progression-free survival have only [a low or modest correlation](#)(2) with overall survival in cancer drugs.<sup>4</sup> However, changes to NICE rules adopted in 2016 had the effect of lowering evidence standards specifically for cancer drugs. End-of-life technologies assessed by NICE must now only demonstrate "the prospect of" providing a three month extension to life. One observer [has warned that](#):

"This implies that such a drug should only be rejected outright if it can be shown to have no prospect of offering the required extension to life... This shifts the burden of proof from the manufacturer, who was previously responsible for demonstrating that their drug likely met the criteria for cost-effectiveness, towards the appraisal committee, which in order to reject such a drug now needs to demonstrate that it likely does not."(27)

Interestingly, in the case of palbociclib, NICE argued that progression-free survival in and of itself has substantial benefits for NHS patients with advanced breast cancer (irrespective of whether or not it extends their overall life span), for example by delaying the need for chemotherapy.<sup>5</sup>

This view was shared by the (few) patients and patient groups who submitted evidence to NICE that is publicly available. However, research has shown many patients [do not fully understand the meaning of progression-free survival](#), nor recognize its distinction from overall survival. (28)

NICE's [Final Appraisal Determination](#) does not make any reference to an expected increase of Quality-Adjusted Life Years (QALYs) among patients receiving the new treatment.(29)

While written assessment reports and the rationale for committee's conclusions (see above) are highly detailed and available online, the committee's discussions leading up to those conclusions took place in closed session and have not been made public. The [published minutes](#) of the meeting reveal little: "*Discussion on confidential information continued. This information was supplied by the company [Pfizer]. The Committee continued to discuss the clinical and cost effectiveness of Palbociclib*".(15)

<sup>4</sup> A clinical oncologist who anonymously reviewed an earlier draft of this paper commented that clinical trial outcome data often overestimates the efficacy of new drugs: "One can wipe off between 30 to 70% of the efficacy of a drug

once it gets in the real world and adverse events also often radically increase."

<sup>5</sup> An anonymous reviewer of an earlier draft commented that: "There is no doubt that quality of life on aromatase plus palbociclib is much better than any chemotherapy regimen."

### Tug-of-war over appropriate cost-effectiveness baseline

Pfizer argued in its submission that a straightforward comparison of the cost-effectiveness of palbociclib against its trial comparator and alternative treatment option, letrozole, was misplaced. Pfizer claimed that because letrozole is available as a (comparatively) cheap generic, “no new treatments are likely to achieve cost-effectiveness,” threatening to perpetually lock the NHS into the current therapeutic status quo.” Pfizer essentially suggested that in order to incentivise future innovation and drug development in England and Wales, NICE should take the one-off step of resetting the cost-effectiveness baseline at palbociclib’s higher price level. NICE rejected this suggestion.

### What information was redacted?

NICE redacted substantial amounts of information in its [appraisal document for palbociclib](#).<sup>(30)</sup> Redactions include not only pricing information, but also data on the drug’s efficacy generated by clinical trials:

Survival probability at 1 year was [redacted] in the palbociclib plus letrozole arm, and [redacted] in the letrozole alone arm [redacted] and at 2 years was [redacted] in the palbociclib plus letrozole arm, and [redacted] in the letrozole alone arm [redacted]. At 3 years, survival probability was [redacted] in the palbociclib plus letrozole arm, and [redacted] in the letrozole alone arm [redacted].<sup>6</sup>

NICE’s online [compilation of policies and procedures](#) does not list a stand-alone policy on redactions,<sup>(31)</sup> and NICE’s current approach to redactions reportedly [lacks consistency](#).<sup>(1)</sup>

A 2011 [agreement between NICE and ABPI](#) distinguishes between “commercial in confidence” and “academic in confidence” information, the latter referring to instances, such as the one above, “where disclosure could prejudice future publication of the information in a scientific publication”.<sup>(32)</sup> (See also [here](#).<sup>(33)</sup>) The agreement does not comment on the desirability of using non-peer-reviewed data to inform an assessment.

Under the terms of the agreement, “the data owner [company] retains the right to make a final decision in relation to the release of confidential information into the public domain.” It states that “Incremental costs, quality adjusted life years and cost effectiveness ratios are not expected to be marked as provided in confidence,” but some documents published by NICE in fact [do contain redactions of QALY data](#).<sup>(34)</sup>

The agreement also states that “NICE will seek the express permission of the company before placing any data in relation

to unpublished trials in the public domain. The data owner retains the right to make a final decision in relation to the release of confidential information into the public domain.” This provision only holds for 12 months “after the sign-off by the company of the trial report,” but NICE [lacks a process for un-redacting its documents](#) after that time period has elapsed.<sup>(1)</sup>

In addition, a 2012 NICE [guide for manufacturers](#) states:

*“Under exceptional circumstances, unpublished evidence is accepted under agreement of confidentiality... NICE will ask manufacturers and sponsors to reconsider restrictions on the release of data if there appears to be no obvious reason for the restrictions, or if such restrictions would make it difficult or impossible for NICE to show the evidential basis for its guidance.”*<sup>(35)</sup>

A 2014 [guidelines manual](#) cautions that “Confidential information should be kept to an absolute minimum.”<sup>(36)</sup>

Reportedly, on at least one occasion, NICE has redacted data from an NHS-funded trial as “academic in confidence”.<sup>6</sup>

### Using Freedom of Information requests to challenge NICE redactions

In response to a Freedom of Information (FOI) request filed by the author, NICE [initially refused to release the data](#) redacted in the passage above.<sup>(37)</sup> NICE argued that the data is exempt from disclosure under both Section 41 (information provided in confidence) and Section 43 (commercial interests) of the Act.

NICE acknowledged that there is “a public interest in understanding how our guidance recommendations have been made,” but argued that this was outweighed by “a strong public interest in drug companies participating in the development of NICE technology appraisals to enable us to fully evaluate the clinical and cost effectiveness of a drug for the NHS.” If it disclosed this information, NICE argued, “drug companies would be less likely to participate fully in future technology appraisals.”<sup>7</sup>

NICE’s weighing of the public interest omitted to take into account the interests of NHS patients with breast cancer in accessing information on whether the drug was shown to increase overall survival in trial participants.

However, a few months later, NICE [did release the data](#) in response to a separate FOI request filed by an associate of the author.<sup>(38)</sup> NICE’s responses to a [series of FOI requests](#) for similar data recently filed by the author,<sup>(39)</sup> expected in late November 2019, may shed light on whether or not this reflects a broader change in NICE’s approach to the transparency of clinical trial data.

<sup>6</sup> An anonymous reviewer of an earlier draft recalled an instance in which the confidentiality of data from a publicly funded trial that “radically changed the patient pathway” for a disease nearly delayed publication of a new treatment guideline. The data had been supplied to NICE as ‘academic in confidence’, “but publication dates kept moving back because the authors were determined to get it into a high impact journal.”

<sup>7</sup> An anonymous reviewer of an earlier draft challenged this claim, arguing that if companies “are obliged to participate in technology appraisals anyway, then there is no public interest in making it easier for them. Are drug companies threatening to walk away from their markets?” The same reviewer also noted that unpublished data “MIGHT NOT SURVIVE the peer review process, or the post-publication process,” warning that as a result, “dangerous innovations might be introduced too early.”

## Transparency of IQWiG's assessment (Germany)

Note: In contrast to NICE, which both performs the technical assessment and makes reimbursement decisions for England, Germany splits those roles between two separate entities. Assessments are performed by IQWiG, a nominally independent institute, while subsequent reimbursement decisions are the purview of the [Gemeinsame Bundesausschuss](#),<sup>(40)</sup> which *can and often does* reject IQWiG's recommendations.<sup>(41)</sup><sup>8</sup> The scope of this report is limited to IQWiG documentation.

The below review of IQWiG's transparency is based on German language documentation. IQWiG has additionally published an [English language summary of its palbociclib assessment](#).<sup>(42)</sup>

### Who reviewed the evidence?

IQWiG staff and an external expert involved in the assessment are publicly listed by name. IQWiG had invited comments from patients and patient groups, but none were submitted.

### How were conflicts of interest managed?

IQWiG has [detailed conflicts of interest disclosure requirements](#).<sup>(43)</sup> which vary according to participants' role in the assessment process, and may cover the institution a person is associated with as well as the person him/herself. COI disclosures are made public, albeit only in summary form, and without disclosing the names of counterparts or financial amounts. IQWiG considers previous participation in studies or guideline development related to the assessment topic as a potential COI, and its [COI forms](#) include a separate field for disclosing these.<sup>(44)</sup><sup>9</sup> Patients providing testimony also have to declare COI, but their names are redacted before publication.

### What evidence was reviewed?

IQWiG evaluated the evidence base with respect to four potential sub-groups of patients with breast cancer. Pfizer submitted evidence from three clinical trials: PALOMA-1 and PALOMA-2, and PALOMA-3. For PALOMA 1+2, IQWiG reviewed trial registry data, journal articles, Clinical Study Reports, and additional information provided by Pfizer. IQWiG excluded PALOMA-3 from its assessment, arguing that it was not relevant for the treatment contexts covered.

<sup>8</sup> An anonymous reviewer of an earlier draft commented that the Gemeinsame Bundesausschuss has on more than one occasion recommended treatments that IQWiG previously found to confer no added benefit.

<sup>9</sup> An anonymous reviewer of an earlier draft commented that: "NICE also asks experts and committee members if they

### How was the evidence evaluated?

IQWiG's analyses of the strengths and weaknesses of the available evidence, and how it evaluated the evidence, are detailed and are [available online](#).<sup>(45)</sup> In a nutshell, IQWiG concluded that taking palbociclib actually left patients worse off.

IQWiG noted that PALOMA-1 had a high risk of bias and therefore gave far stronger weight to the evidence from PALOMA-2. It also noted that it could not assess efficacy for one sub-group due to the lack of data relevant to that group.

Pfizer had submitted overall survival data for PALOMA-1 only. Pfizer did not submit equivalent data for PALOMA-2, arguing that the data available at that point were insufficient to permit a statistical analysis. Rejecting this argument, IQWiG itself extracted and analysed survival data from the trial's Clinical Study Report.

#### **IQWiG dismisses efficacy claims based on invisible evidence**

IQWiG noted that Pfizer's submission did not include overall survival data from PALOMA-2. Pfizer had explained that this data was not yet available at the time evidence for the dossier was compiled, but also stated that the same data was already available to an external data monitoring committee. IQWiG concluded that "This procedure is incomprehensible [nicht nachvollziehbar]. The dossier is incomplete in terms of overall survival." See page 80 [here](#).<sup>(46)</sup>

IQWiG concluded that existing data fails to provide sufficient evidence for an overall survival benefit, as differences in overall survival were not statistically significant in either trial. At the same time, according to IQWiG's analysis, compared to the standard of care, the new treatment exposes patients to a [very high risk of severe side effects](#).<sup>(47)</sup>

In contrast to NICE, IQWiG explicitly rejected Pfizer's argument that progression-free survival in and of itself conferred any benefits to patients, and pointedly noted that based on PALOMA-2 outcomes (which included a [QoL-related endpoint](#))<sup>(48)</sup> there was no evidence that palbociclib improved patients' overall health or health-related quality of life.

have 'academic conflicts' where they have already expressed in print or broadcast a view about whether a treatment should be available. This is quite similar to the German requirement."

**What information was redacted?**

None of the data or analyses in IQWiG’s assessment were redacted prior to publication. The assessment document contains overall survival data aggregated across both trials:

<b>Mortalität</b>		
Gesamtüberleben	37,5 vs. 33,3 Monate <sup>c</sup> 21,4–35,7 % vs. 17,1–38,3 % <sup>d</sup> heterogene Ergebnisse <sup>e</sup> In keiner der 2 relevanten Studien lag ein statistisch signifikanter Effekt vor.	geringerer Nutzen / Zusatznutzen nicht belegt

Under a German national [law](#) in force since 2011,(49) companies are required to share all relevant Clinical Study Reports – including – all their appendices with the German authorities, [including reports of trials conducted abroad](#).(50) [Under the law](#),(51) IQWiG [publishes all data used within its assessment reports](#).(52)

IQWiG [has noted](#) that as a result,(53) its assessments “provide considerably more information on the methods and outcomes of clinical studies on new drugs than other publicly available sources,” especially as access to Clinical Study Reports through regulators [remains difficult or impossible](#).(54) However, IQWiG does not publish the full Clinical Study Reports themselves.

## Transparency of HAS' assessment (France)

*Note: The below review of HAS' transparency is based on French language documentation.*

### Who reviewed the evidence?

Efficacy assessments are conducted by a committee whose members are [listed by name](#) on the HAS website.(55) However, in published meeting minutes, [some names of HAS staff are redacted](#).(56)

### How were conflicts of interest managed?

HAS has a [detailed conflicts of interest policy](#) covering all staff and external contributors.(57) COI declarations by key players are [publicly available](#).(58) albeit without detailed financial data.

### What evidence was reviewed?

HAS reviewed the evidence from the PALOMA-1, PALOMA-2 and PALOMA-3 trials. (As its analysis of PALOMA-3 data relates to a drug-indication pair not covered in depth by NICE or IQWiG, the subsequent discussion excludes HAS' analysis of that trial.) While it appears likely that HAS reviewed the Clinical Study Reports for these trials, the assessment report does not explicitly state this.

### How was the evidence evaluated?

The [HAS assessment report](#) stated that the treatment goal for advanced breast cancer was improving quality of life and overall survival.(59) HAS accepted that PALOMA-2 demonstrated benefits on progression-free survival, but noted that available data did not show any benefits in terms of overall survival or improved QoL. HAS also noted that palbociclib caused significantly more serious side effects than the comparator treatment.

HAS concluded that PALOMA 1+2 had demonstrated significant benefits in terms of progression-free survival, but no benefits in terms of overall survival. On this basis, HAS concluded that palbociclib conferred "minor benefits" on postmenopausal women with advanced hormone receptor positive, HER2 negative breast cancer, and recommended it for treatment of this group. In the HAS' [5-scale rating system](#), a "minor benefit" comes just above the lowest rating, which is "no clinical improvement".(60)

Noting that the trials included "[very few](#)" pre- and peri-menopausal women (none in the case of PALOMA-2), HAS stated that there was insufficient evidence for these patient groups, and recommended against using palbociclib to treat them.(61) Similarly, as women with life-threatening nervous system pathologies had been excluded from the trials, they should not be given the drug.

In its report, HAS explicitly stated that the drug "is not likely to have an impact on public health" because it has "no impact on morbidity and mortality and quality of life". Nevertheless, the report concluded that palbociclib conferred an "important" treatment benefit on post-menopausal women with advanced RH+ and HER2- breast cancer, and recommended its provision by health services to that patient group. The HAS report is only 26 pages in length, and leaves unclear why HAS determined that palbociclib confers a "minor benefit" despite its reservations about efficacy on patient-relevant measures.

### What information was redacted?

None of the data in the HAS efficacy assessment commission's report were redacted. Note that while the level of benefit determined by the assessment report [does influence subsequent reimbursement decisions](#), the document does not include pharmacoeconomic analyses or pricing data.(60)<sup>10</sup>

The assessment document contains overall survival data for PALOMA-1:

Aucune différence n'a été mise en évidence dans cette étude en terme de survie globale (HR=0,813 IC95% = [0,492 ; 1,345], NS) et de pourcentage de réponse objective (OR=1,50 IC95% = [0,76 ; 2,97], NS).

It also presents interim survival data for PALOMA-2:

Seuls les résultats issus de l'analyse intermédiaire prévue au protocole et réalisée au moment de l'analyse finale de la SSP sont disponibles. Cette analyse a été effectuée après l'observation de 133 décès (soit 34% du nombre d'événements attendus pour l'analyse finale). A cette date, aucune différence n'a été mise en évidence entre les deux groupes de traitement sur ce critère : 95 décès (21%) étaient survenus dans le groupe palbociclib et 38 décès (17%) étaient survenus dans le groupe placebo. D'après le protocole, l'analyse finale de la survie globale sera effectuée après l'observation de 390 événements.

The [report](#) of a separate HAS commission dealing with pharmacoeconomy,(62) which forms the basis for subsequent price negotiations, does include pricing data; this data is redacted.

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<sup>10</sup> A French reviewer of an earlier draft commented that: "The Commission de la Transparence is not in charge of

pharmacoeconomy. In France the decision to reimburse or not a drug is not based on economy but on efficacy."

## Conclusion and Policy Recommendations

### Conclusion

Overall, the assessment processes of NICE, IQWiG and HAS have a high level of transparency. All three agencies disclose who reviewed the evidence underlying their assessments, and how possible conflicts of interest were managed. They also detail what evidence they reviewed, and how they evaluated it. The literature suggests that some other European HTAs fall short of these transparency standards.

However, scope for improvement remains. In particular, NICE could improve its transparency by shifting to the German model of never redacting clinical trial data.

### Policy recommendations for European-level HTA assessments

The European Union is currently debating the merits and drawbacks of [conducting clinical HTA assessments at a European level](#).<sup>(63)</sup> This process might eventually lead to the creation of a unified European HTA agency. How transparent such an agency would be remains unclear. Thus, the present study can contribute to informing [ongoing discussions](#) about the future shape of European HTA.<sup>(64)</sup>

Importantly, the overall high transparency of NICE, IQWiG and HAS is not mirrored by all other HTAs in Europe. For example, one HTA expert interviewed for this report noted that some smaller HTAs in Europe do not even disclose which treatments they are reviewing, and keep decisions not to fund treatments secret. This allows them to avoid public controversies over access to costly drugs that their national health systems do not want to, or cannot afford to, provide. Such opacity removes important – if difficult and sometimes painful – debates and decision-making about healthcare and public health priorities from the democratic realm. Any future European HTA should build on the best practices in transparency identified in this report and documented in the wider literature (see the Annex).

More broadly, across Europe, the pricing negotiations and decisions that follow in the wake of clinical HTA assessments remain shrouded in secrecy. It is important to highlight that this is an anomaly in democratic societies. Public

procurement transparency standards routinely applied in other economic sectors currently do not apply to pharmaceuticals; taxpayers cannot see how their money is being spent. However, ending pricing opacity in the HTA process would require political leadership; HTA bodies by themselves do not have the power to change the status quo in this area.

- **Any future European-level HTA assessments should raise the bar on transparency** by matching or exceeding the strongest transparency policies and practices of the individual Member State that is most advanced in that area. Notably, European-level HTA should adopt IQWiG's approach of routinely publishing all clinical trial data used within its assessment reports.

### Policy recommendations for NICE

This report highlights that NICE deserves its reputation as a global front-runner in transparency. However, it also flags shortcomings in NICE's redactions policy.

Notably, NICE may wish to review its stance on "academic in confidence" redactions. This currently places the interests of a small number of researchers above the competing interests of British patients and the wider scientific community, who would benefit from clinical trial outcomes being disclosed as fully and rapidly as possible. Note in this context that [few \(if any\) other HTAs in Europe recognise the "academic in confidence" category](#).<sup>(65)</sup><sup>11</sup>

- **In the short term, NICE should put into place a system that automatically un-redacts all clinical trial data** cited in its documents [after a 12 month embargo period](#).<sup>(1)</sup>
- **In the medium term, NICE should stop redacting any clinical trial data** in the first place, following the positive example of its German counterpart.<sup>12</sup>
- NICE should follow up on its recent pledge to take into account concerns about undisclosed industry funding for patient groups in the ongoing review of its conflict of interest policies.

<sup>11</sup> An anonymous reviewer of an earlier draft commented that: "It is misleading to state that that 'few (if any) other HTAs in Europe recognise the academic in confidence category.' Most of them don't release any information at all and give no reasons for their decisions. Therefore, the issue of 'academic in confidence' does not arise if you are not releasing any information." The author decided to retain the passage above nonetheless.

<sup>12</sup> The German HTA transparency approach, under which all data considered in an IQWiG assessment must be made public, is enshrined in German national law. It is beyond the scope of this report to ascertain whether a change in UK law would be required to enable NICE to also make such data public.

## Annex: Annotated Bibliography on Health Technology Assessment

The following annotated bibliography was compiled in the course of producing the report above. The literature search was not systematic, and the bibliography does not aim to be exhaustive. Its scope is limited to flagging some insightful documents relevant to the following three topics:

- HTA transparency
- Use of evidence in HTA
- Cross-country comparisons of HTAs

Publications likely to be of particular interest to readers are highlighted in grey.

### Transparency in health technology assessment

[NICE, in Confidence: An Assessment of Redaction to Obscure Confidential Information in Single Technology Appraisals by the National Institute for Health and Care Excellence](#)(1)

Ash Bullement et al, *Pharmacoeconomics*, 2019

- Analysis of redactions made in NICE documents related to 110 products
- Finds that “a large amount of information was censored as academic-in-confidence and remains so many years later”
- Warns that “censoring appears to be performed on an ad hoc basis with no consistent pattern in the information censored”
- Suggests a one-year embargo after which academic-in-confidence data will be released

[Toward transparency in health technology assessment - A checklist for HTA reports](#)(66)

David Hailey, *Int. J. of Technology Ass. in Health Care*, 2003

- Checklist of 17 questions

[The transparency of published health technology assessment-based recommendations on pharmaceutical reimbursement in Poland](#)(67)

Tomasz Bochenek et al, *Expert Rev Pharmacoecon Outcomes Res*, 2016

- Documents increasing transparency in Polish HTA over time

[Does Transparency Help or Hinder Emerging HTA Systems?](#)(68)

Wrik Ghosh, Issue Panel presentation, *ISPOR Asia Pacific 2018*

- Overview of the benefits and drawbacks of HTA transparency
- Includes an industry perspective

[Agreement between the Association of the British Pharmaceutical Industry \(ABPI\) and the National Institute for Health and Clinical Excellence \(NICE\) on guidelines for the release of company data into the public domain during a health technology appraisal](#) (32)

NICE, NICE website, 2011

- Sets ground rules for release of clinical trial evidence and economic analyses by NICE

### Use of evidence in health technology assessment

[NICE and Fair? Health Technology Assessment Policy Under the UK's National Institute for Health and Care Excellence, 1999-2018](#)(27)

Victoria Charlton, *Health Care Analysis*, 2019

- Examines changes to NICE’s approach over the years
- Finds that NICE evidence requirements have eroded over time

[Scientific Evidence in Health Technology Assessment Reports: An In-Depth Analysis of European Assessments on High-Risk Medical Devices](#)(69)

Britta Olberg et al, *Value in Health*, 2017

- Examines 93 HTA reports of medical devices 2010-2015
- “In more than half the identified studies considered in the reports, clinical evidence for demonstration of effectiveness and safety was of moderate or low quality.”

[How real-world data compensate for scarce evidence in HTA](#)(70)

Elisabeth George, *Z. Evid. Fortbild. Qual. Gesundh. Wesen*, 2016

- NICE employee uses three case studies to argue that NICE is justified in using non-RCT data, in particular for devices
- RCTs can have too small sample sizes and too short time horizons
- Observational follow-up data and patient perspectives on QoL need to be taken into account

[Evidence supporting FDA approval and CMS national coverage determinations for novel medical products, 2005 through 2016](#)<sup>(71)</sup>

Aliya C. Roginiel et al, *Medicine*, 2018

- Compares the quality and quantity of evidence examined by FDA and Centers for Medicare and Medicaid Services (CMS) itself for 12 novel drugs and devices
- “[T]he majority of coverage decisions are made by regional contractors, whose determinations are not made publicly available”

[Divergent evidence requirements for authorization and reimbursement of high-risk medical devices – The European situation](#)<sup>(72)</sup>

Lisa Kruger et al, *Health Policy and Technology*, 2014 [based on 2012 data]

- Explores the authorization and reimbursement processes and associated evidence requirements for high-risk medical devices in four regions: Europe, the United States, Australia and Canada
- Weaknesses in the European approval process: “very low safety standards for market access, the exclusion of efficacy assessments and the lack of transparency of regulatory processes and their evidence requirements”
- Decentralized European ‘Notified Bodies’ system (75 offices in 2014) contrasts with centralized systems in the US (FDA), Australia (THG) and Canada (Ministry of Health)
- “In Europe, no decisions or information are publicly available through the NBs. Only in the United States is (some) information on the evidence for approval (or rejection) publicly available.”

[Improving the effectiveness and efficiency of evidence production for HTA in the light of current trends in drug and device development, health system funding, regulation and HTA](#)<sup>(73)</sup>

Karen Facey et al, *Int J Technol Assess Health Care*, 2015

- “The provision of scientific advice on HTA requirements is seen as a key initiative to support effective and efficient evidence production.”

[Clinical studies of innovative medical devices: what level of evidence for hospital-based health technology assessment?](#)<sup>(74)</sup>

Aur lie Boudard et al, *Journal of Evaluation in Clinical Practice*, 2013

- Review of 217 studies of 32 medical devices
- “most medical devices are currently released onto the EU market without high quality data”
- “the number of studies per device was highly variable, with no clinical data available for 6 medical devices and 38 clinical studies on another device”

- Mean follow-up period for studies was just 18.9 months

**Comparative health technology assessment**

[Published and unpublished evidence in coverage of decision-making for pharmaceuticals in Europe: existing approaches and way forward](#)<sup>(65)</sup>

Dimitra Panteli et al, *Health Res Policy Syst*, 2016

- Review of HTA processes in 13 European countries using data gathered in 2012
- Flags gaps in transparency and accountability, as well as best practices
- “NICE in England made it necessary to include all published and unpublished information in assessments in 2004”
- “NICE is the only institution in the sample to explicitly differentiate between commercial-in-confidence and academic-in-confidence data”
- “IQWiG does not accept commercial-in-confidence data at all, asking submitting manufacturers to sign a confidentiality waiver”
- Recommends routine checking of trial registries by HTAs (some HTAs do not do this)

[A Comparison of Reimbursement Recommendations by European HTA Agencies: Is There Opportunity for Further Alignment?](#)<sup>(75)</sup>

Nicola Allen et al, *Front. Pharmacol.*, 2017

- Two taxonomies for classifying HTAs: System and Process (with excellent charts)
- Discusses EUnetHTA Core Model
- Compares HTA decisions on new drugs across 9 countries and 102 NAS-indication pairs
- “Discrepancies between HTA recommendations may also be due to the quality of evidence available, willingness to accept uncertainty or differing methods of assessment or priorities. The methodologies and processes used to conduct HTA can vary from country to country and also between regions when decision making is decentralized (e.g., Italy and Spain).”

[European collaboration on relative effectiveness assessments: What is needed to be successful?](#)(76)

Sarah Kleijnen et al, Health Policy, 2015

- Methodological challenges for production of cross-border HTA assessments:
- The most frequently mentioned methodological problem for the production of across-border assessment was the choice of the comparator...”
- Difference between countries in accepting indirect comparisons, if direct evidence is lacking
- Countries may differ in the acceptance of intermediate or surrogate endpoints

[Policies for Use of Real-World Data in Health Technology Assessment \(HTA\): A Comparative Study of Six HTA Agencies](#)(77)

Amr Makady et al, Value in Health, 2017

- All HTAs surveyed use RWD for analysing effectiveness but only under specific circumstances
- RWD use far more prominent in pharmacoeconomic analyses

[Can a Joint Assessment Provide Relevant Information for National/Local Relative Effectiveness Assessments? An In-Depth Comparison of Pazopanib Assessments](#)(78)

Sarah Kleijnen et al, Value in Health, 2015

- Compares HTA assessments from Belgium, England/Wales, France, The Netherlands, and Scotland to explore potential for future joint European assessments
- The number of studies considered in the HTA assessments varied between 2 and 14, with only one study reviewed by all HTAs
- Apart from indirect comparison, the main methodological elements were similar

[Analysis of Duplication and Timing of Health Technology Assessments on Medical Devices in Europe](#)(79)

Katharina Hawlik et al, International Journal of Technology Assessment in Health Care, 2017

- Review of 120 HTA reports on 10 devices from 28 European HTAs from 16 countries
- Most HTA reports take place 5-10 years post CE mark award
- Some HTA reports did not identify the studies consulted
- There is no comprehensive EU database of HTA reports of devices (EUDAMED will change this)

[Leveraging EUnetHTA’s conceptual framework to compare HTA decision drivers in France, Italy, and Germany from a manufacturer’s point of view](#)(80)

Giovanni Giuliani et al, Health Economics Review, 2018

- Acceptance of endpoints other than Overall Survival differed across the three countries

[Why do health technology assessment coverage recommendations for the same drugs differ across settings? Applying a mixed methods framework to systematically compare orphan drug decisions in four European countries](#)(81)

Elena Nicod, Eur J Health Econ, 2017

- Compares 35 HTA recommendations for ten orphan drugs in England, Scotland, Sweden and France
- Six of ten drugs received diverging recommendations; only one drug got “basically similar” recommendations
- Different evidence was included by some agencies and not by others

[The difference between regulatory and market access decisions on treatment availability for new drugs in six common cancers across Australia, Canada, and Europe](#)(82)

Jan McKendrick et al, poster presentation, 2016 [[published summary here](#)]

- Discrepancies between regulatory and reimbursement decisions for 63 approved indication combinations and 65 related reimbursement decisions across 13 countries for 6 cancer types
- “The nature and extent of restrictions are not consistent across countries”
- Over 250,000 patients were estimated to be affected by the restrictions, resulting in over 70,000 years of life lost [Note: This study was industry-funded]

[Health Technology Assessment \(HTA\) Case Studies: Factors Influencing Divergent HTA Reimbursement Recommendations in Australia, Canada, England, and Scotland](#)(83)

Nicola Allen et al, Value in Health, 2017

- Looked at 89 medicine-indication pairs
- 12 medicines got a positive recommendation from all HTAs, none got a negative from all HTAs
- Documents examples of the rejection of new medicines because of uncertainties surrounding a range of factors including cost-effectiveness, comparator choice, clinical benefit, safety, trial design, and submission timing

[Relative effectiveness assessment of pharmaceuticals: similarities and differences in 29 jurisdictions](#)(84)

Sarah Kleijnen et al, Value in Health, 2012

- Only five jurisdictions state that “whatever was used in the registration trials” can be an option for the choice of the comparator
- In all jurisdictions, surrogate and composite outcomes are accepted for the assessment
- Almost all jurisdictions take safety data into account for the assessment

#### [Variation in Health Technology Assessment and Reimbursement Processes in Europe](#)(85)

Ronald Akehurst et al, Value in Health, 2017

- Study of decisions on 12 novel drugs (incl 10 cancer drugs) by 8 HTAs
- “In many cases, the rules and guidelines for HTAs, reimbursement, and pricing were not clearly defined, and practical guidance or evidence on the Websites of HTA and reimbursement bodies often contradicted the academic literature... Overall, we found the published literature insufficient to understand HTA and reimbursement processes in Europe.”

#### [A review of health technology appraisals: case studies in oncology](#)(86)

Koonal Kirit Shah et al, J. Technol. Assess., 2013

76 HTA decisions on cancer treatments were reviewed across 5 HTAs

Documents differences between HTA assessments

- “The impact of patient voice seems only to have been incorporated formally in the HTAs conducted by NICE... We did not find any specific references to patient preferences in the HTA reports published by the other four agencies.”

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## References

1. Bullement A, Taylor M, McMordie ST, Waters E, Hatswell AJ. NICE, in Confidence: An Assessment of Redaction to Obscure Confidential Information in Single Technology Appraisals by the National Institute for Health and Care Excellence. *PharmacoEconomics*. 2019 Nov 1;37(11):1383–90.
2. Mintzes B, Vitry A. Flawed evidence underpins approval of new cancer drugs. *BMJ* [Internet]. 2019 Sep 18 [cited 2020 Feb 10];366. Available from: <https://www.bmj.com/content/366/bmj.l5399>
3. Haslam A, Hey SP, Gill J, Prasad V. A systematic review of trial-level meta-analyses measuring the strength of association between surrogate end-points and overall survival in oncology. *European Journal of Cancer*. 2019 Jan 1;106:196–211.
4. Kovic B, Jin X, Kennedy SA, Hylands M, Pędziwiatr M, Kuriyama A, et al. Evaluating Progression-Free Survival as a Surrogate Outcome for Health-Related Quality of Life in Oncology: A Systematic Review and Quantitative Analysis. *JAMA Intern Med*. 2018 Dec 1;178(12):1586–96.
5. Tanne JH. FDA cancels approval for bevacizumab in advanced breast cancer. *BMJ* [Internet]. 2011 Nov 25 [cited 2020 Feb 10];343. Available from: <https://www.bmj.com/content/343/bmj.d7684>
6. Breast cancer in women [Internet]. nhs.uk. 2017 [cited 2020 Feb 10]. Available from: <https://www.nhs.uk/conditions/breast-cancer/>
7. Hormone Therapy for Breast Cancer [Internet]. American Cancer Society. [cited 2020 Feb 10]. Available from: <https://www.cancer.org/cancer/breast-cancer/treatment/hormone-therapy-for-breast-cancer.html>
8. Ibrance - palbociclib [Internet]. European Medicines Agency. 2016 [cited 2020 Feb 10]. Available from: <https://www.ema.europa.eu/en/medicines/human/EPAR/ibrance>
9. Palbociclib with an aromatase inhibitor for previously untreated, hormone receptor-positive, HER2-negative, locally advanced or metastatic breast cancer. Technology appraisal guidance [TA495] [Internet]. NICE. 2017 [cited 2020 Feb 10]. Available from: <https://www.nice.org.uk/guidance/ta495/chapter/1-Recommendations>
10. IQWiG. Palbociclib in advanced breast cancer: Disadvantages predominate in certain patients [Internet]. [cited 2020 Feb 10]. Available from: <https://www.iqwig.de/en/press/press-releases/palbociclib-in-advanced-breast-cancer-disadvantages-predominate-in-certain-patients.7778.html>
11. IBRANCE (palbociclib), inhibiteur de protéine kinase [Internet]. Haute Autorité de Santé. 2017 [cited 2020 Feb 10]. Available from: [https://www.has-sante.fr/jcms/c\\_2761877/fr/ibrance-palbociclib-inhibiteur-de-protéine-kinase](https://www.has-sante.fr/jcms/c_2761877/fr/ibrance-palbociclib-inhibiteur-de-protéine-kinase)
12. Committee A members. Read the committee members' biographies and registered interests [Internet]. NICE. [cited 2020 Feb 10]. Available from: <https://www.nice.org.uk/get-involved/meetings-in-public/technology-appraisal-committee/committee-a-members>
13. Policy on declaring and managing interests for board members and employees [Internet]. [cited 2020 Feb 10]. Available from: <https://www.nice.org.uk/Media/Default/About/Who-we-are/Policies-and-procedures/declaring-and-managing-interests-board-and-employees.pdf>
14. Corporate Office. Policy on declaring and managing interests for NICE advisory committees [Internet]. NICE; 2019 [cited 2020 Feb 10]. Available from: <https://www.nice.org.uk/Media/Default/About/Who-we-are/Policies-and-procedures/declaration-of-interests-policy.pdf>
15. confirmed-TAC-A-minutes-october-17.pdf [Internet]. [cited 2020 Feb 10]. Available from: <https://www.nice.org.uk/Media/Default/Get-involved/Meetings-In-Public/Technology-appraisal-committee/2017/confirmed-TAC-A-minutes-october-17.pdf>
16. Governance Manager: Risk Assurance. Gifts and Hospitality Policy [Internet]. NICE National Institute for Health and Care Excellence; 2018 [cited 2020 Feb 10]. Available from: <https://www.nice.org.uk/Media/Default/About/Who-we-are/Policies-and-procedures/Gifts-Hospitality-policy.pdf>
17. Database of gifts and hospitality 2013-14 [Internet]. [cited 2020 Feb 10]. Available from: <https://www.nice.org.uk/Media/Default/About/Who-we-are/Corporate-publications/Publication-scheme/Hospitality-Database-2013-2014.xlsx>
18. NICE recommendations: charging and appeal panels [Internet]. GOV.UK. 2018 [cited 2020 Feb 10]. Available from: <https://www.gov.uk/government/consultations/nice-recommendations-charging-and-appeal-panels>
19. NICE's technology appraisal and highly specialised technology work programmes (Charging and Appeal

- Panels) - Consultation response [Internet]. Department of Health and Social Care; 2018. Available from: [https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment\\_data/file/762725/government-response-to-nice-recommendations-consultation.pdf](https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/762725/government-response-to-nice-recommendations-consultation.pdf)
20. NICE appraisal fees to be introduced despite opposition [Internet]. PMLive. 2018 [cited 2020 Feb 10]. Available from: [http://www.pmlive.com/pharma\\_news/nice\\_appraisal\\_fees\\_to\\_be\\_introduced\\_despite\\_opposition\\_1272799](http://www.pmlive.com/pharma_news/nice_appraisal_fees_to_be_introduced_despite_opposition_1272799)
  21. Mandeville KL, Barker R, Packham A, Sowerby C, Yarrow K, Patrick H. Financial interests of patient organisations contributing to technology assessment at England's National Institute for Health and Care Excellence: policy review. *BMJ* [Internet]. 2019 Jan 16 [cited 2020 Feb 10];364. Available from: <https://www.bmj.com/content/364/bmj.k5300>
  22. Disclosure Search [Internet]. [cited 2020 Feb 10]. Available from: <https://search.disclosureuk.org.uk/>
  23. Boseley S. Patient groups assessing NHS drugs receive undeclared industry funds. *The Guardian* [Internet]. 2019 Jan 17 [cited 2020 Feb 10]; Available from: <https://www.theguardian.com/society/2019/jan/17/patient-groups-assessing-nhs-drugs-receive-undeclared-industry-funds>
  24. Bruno B, Rose S. Patient organizations and conflict of interest. *BMJ* [Internet]. 2019 Jan 16 [cited 2020 Feb 10];364. Available from: <https://www.bmj.com/content/364/bmj.1129>
  25. Clinical trial data used by NICE in its palbociclib (Ibrance) assessment - a Freedom of Information request to National Institute for Health and Care Excellence [Internet]. WhatDoTheyKnow. 2018 [cited 2020 Feb 10]. Available from: [https://www.whatdotheyknow.com/request/clinical\\_trial\\_data\\_used\\_by\\_nice](https://www.whatdotheyknow.com/request/clinical_trial_data_used_by_nice)
  26. Palbociclib with an aromatase inhibitor for previously untreated, hormone receptor-positive, HER2-negative, locally advanced or metastatic breast cancer. Technology appraisal guidance [TA495] [Internet]. NICE. [cited 2020 Feb 10]. Available from: <https://www.nice.org.uk/guidance/ta495/chapter/4-Committee-discussion>
  27. Charlton V. NICE and Fair? Health Technology Assessment Policy Under the UK's National Institute for Health and Care Excellence, 1999–2018. *Health Care Anal* [Internet]. 2019 Jul 19 [cited 2020 Feb 10]; Available from: <https://doi.org/10.1007/s10728-019-00381-x>
  28. Raphael MJ, Robinson A, Booth CM, O'Donnell J, Palmer M, Eisenhauer E, et al. The Value of Progression-Free Survival as a Treatment End Point Among Patients With Advanced Cancer: A Systematic Review and Qualitative Assessment of the Literature. *JAMA Oncol*. 2019 Dec 1;5(12):1779–89.
  29. Committee A. Final appraisal determination - Palbociclib with an aromatase inhibitor for previously untreated, hormone receptorpositive, HER2-negative, locally advanced or metastatic breast cancer [Internet]. NICE; 2017. Available from: <https://www.nice.org.uk/guidance/ta495/documents/final-appraisal-determination-document>
  30. STA Palbociclib in combination with an aromatase inhibitor for previously untreated metastatic, hormone receptor-positive, HER2-negative breast cancer [ID915] [Internet]. NICE National Institute for Health and Care Excellence; Available from: <https://www.nice.org.uk/guidance/ta495/documents/committee-papers-5>
  31. Policies and procedures [Internet]. NICE. [cited 2020 Feb 10]. Available from: <https://www.nice.org.uk/about/who-we-are/policies-and-procedures>
  32. Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the National Institute for Health and Clinical Excellence (NICE) on guidelines for the release of company data into the public domain during a health technology appraisal [Internet]. 2011. Available from: <https://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/NICE-technology-appraisals/Guidelines-for-the-release-of-company-data-into-the%20public-domain-during-a-health-technology-appraisal.pdf>
  33. Glossary - Guide to the processes of technology appraisal [Internet]. NICE. [cited 2020 Feb 10]. Available from: <https://www.nice.org.uk/process/pmg19/chapter/glossary#in-confidence-material>
  34. Redacted information in NICE appraisal: Sodium Zirconium Cyclosilicate - a Freedom of Information request to National Institute for Health and Care Excellence [Internet]. WhatDoTheyKnow. 2018 [cited 2020 Feb 10]. Available from: [https://www.whatdotheyknow.com/request/redacted\\_information\\_in\\_nice\\_app\\_3](https://www.whatdotheyknow.com/request/redacted_information_in_nice_app_3)
  35. Single technology appraisal - Specification for manufacturer/sponsor submission of evidence [Internet]. NICE National Institute for Health and Care Excellence; 2012. Available from: <https://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/NICE-technology->

- appraisals/Specification-for-manufacturer-sponsor-submission-of-evidence-June-2012.doc
36. Developing NICE guidelines: the manual [Internet]. NICE National Institute for Health and Care Excellence; 2014. Available from: <https://www.nice.org.uk/media/default/about/what-we-do/our-programmes/developing-nice-guidelines-the-manual.pdf>
37. Redacted information in NICE appraisal: STA Palbociclib - a Freedom of Information request to National Institute for Health and Care Excellence [Internet]. WhatDoTheyKnow. 2018 [cited 2020 Feb 10]. Available from: [https://www.whatdotheyknow.com/request/redacted\\_information\\_in\\_nice\\_app\\_2](https://www.whatdotheyknow.com/request/redacted_information_in_nice_app_2)
38. Overall survival data for breast cancer drug Palbociclib - a Freedom of Information request to National Institute for Health and Care Excellence [Internet]. WhatDoTheyKnow. 2019 [cited 2020 Feb 10]. Available from: [https://www.whatdotheyknow.com/request/overall\\_survival\\_data\\_for\\_breast](https://www.whatdotheyknow.com/request/overall_survival_data_for_breast)
39. Till Bruckner - Freedom of Information requests [Internet]. WhatDoTheyKnow. [cited 2020 Feb 10]. Available from: [https://www.whatdotheyknow.com/user/till\\_bruckner/requests](https://www.whatdotheyknow.com/user/till_bruckner/requests)
40. Wer wir sind - Gemeinsamer Bundesausschuss [Internet]. [cited 2020 Feb 10]. Available from: <https://www.g-ba.de/ueber-den-gba/wer-wir-sind/>
41. AMNOG revisited [Internet]. McKinsey. [cited 2020 Feb 10]. Available from: <https://www.mckinsey.com/industries/pharmaceuticals-and-medical-products/our-insights/amnog-revisited>
42. IQWiG Reports – Commission No. A16-74. Palbociclib (breast cancer) – Benefit assessment according to §35a Social Code Book V1 [Internet]. IQWiG; 2017. Available from: [https://www.iqwig.de/download/A16-74\\_Palbociclib\\_Extract-of-dossier-assessment\\_V1-0.pdf](https://www.iqwig.de/download/A16-74_Palbociclib_Extract-of-dossier-assessment_V1-0.pdf)
43. IQWiG. Frequently asked questions about the “Form for disclosure of potential conflicts of interest” [Internet]. [cited 2020 Feb 10]. Available from: <https://www.iqwig.de/en/participation/conflicts-of-interest/frequently-asked-questions-about-the-form-for-disclosure-of-potential-conflicts-of-interest.3307.html>
44. IQWiG. Conflicts of interest [Internet]. [cited 2020 Feb 10]. Available from: <https://www.iqwig.de/en/participation/conflicts-of-interest.3074.html>
45. IQWiG Reports – Commission No. A17-15. Palbociclib (breast cancer) – Addendum to Commission A16-74 [Internet]. 2017. Available from: [https://www.iqwig.de/download/A17-15\\_Palbociclib\\_Addendum-to-Commission-A16-74\\_V1-0.pdf](https://www.iqwig.de/download/A17-15_Palbociclib_Addendum-to-Commission-A16-74_V1-0.pdf)
46. IQWiG-Berichte – Nr. 491. Palbociclib (Mammakarzinom) – Nutzenbewertung gemäß § 35a SGB V [Internet]. 2017. Available from: [https://www.iqwig.de/download/A16-74\\_Palbociclib\\_Nutzenbewertung-35a-SGB-V\\_V1-0.pdf](https://www.iqwig.de/download/A16-74_Palbociclib_Nutzenbewertung-35a-SGB-V_V1-0.pdf)
47. Information NC for B, Pike USNL of M 8600 R, MD B, Usa 20894. Palbociclib (Ibrance) for the treatment of advanced breast cancer: Overview [Internet]. Institute for Quality and Efficiency in Health Care (IQWiG); 2019 [cited 2020 Feb 10]. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK507009/>
48. Brady MJ, Cella DF, Mo F, Bonomi AE, Tulskey DS, Lloyd SR, et al. Reliability and validity of the Functional Assessment of Cancer Therapy-Breast quality-of-life instrument. JCO. 1997 Mar 1;15(3):974–86.
49. Gesetz zur Neuordnung des Arzneimittelmarktes in der gesetzlichen Krankenversicherung (Arzneimittelmarktneuordnungsgesetz – AMNOG). Bundesgesetzblatt Teil I. 2010 Dec 27;(67):2262.
50. Paul-Ehrlich-Institut - Regulation [Internet]. [cited 2020 Feb 10]. Available from: <https://www.pei.de/DE/regulation/regulation-node.html#doc3266370bodyText1>
51. BfArM - Questions and answers with regard to the Clinical Trial Result Reports according Section 42b of the Medicinal Product Act [Internet]. [cited 2020 Feb 10]. Available from: [https://www.bfarm.de/EN/Service/FAQ/\\_functions/drugs/Section42b/\\_node.html](https://www.bfarm.de/EN/Service/FAQ/_functions/drugs/Section42b/_node.html)
52. How HTA can improve access to information on medicines: Germany shows the way [Internet]. [cited 2020 Feb 10]. Available from: <https://www.transparimed.org/single-post/2018/09/11/How-HTA-can-improve-access-to-information-on-medicines-Germany-shows-the-way>
53. Köhler M, Haag S, Biester K, Brockhaus AC, McGauran N, Grouven U, et al. Information on new drugs at market entry: retrospective analysis of health technology assessment reports versus regulatory reports, journal publications, and registry reports. BMJ [Internet]. 2015 Feb 26 [cited 2020 Feb 10];350.

- Available from: <https://www.bmj.com/content/350/bmj.h796>
54. Till Bruckner. After three years of struggle, scientists fail in bid to access key documents held by European regulator [Internet]. 2018 [cited 2020 Feb 10]. Available from: <https://www.transparimed.org/single-post/2018/10/04/After-three-years-of-struggle-scientists-fail-in-bid-to-access-key-documents-held-by-European-regulator>
55. Commission de la transparence [Internet]. Haute Autorité de Santé. [cited 2020 Feb 10]. Available from: [https://www.has-sante.fr/jcms/c\\_412210/en/commission-de-la-transparence](https://www.has-sante.fr/jcms/c_412210/en/commission-de-la-transparence)
56. Commission de la Transparence. Ibrance 3 mai 2017 [Internet]. [cited 2020 Feb 10]. Available from: [https://www.has-sante.fr/upload/docs/application/pdf/2017-09/ibrance\\_03052017\\_ct15873\\_transcription.pdf](https://www.has-sante.fr/upload/docs/application/pdf/2017-09/ibrance_03052017_ct15873_transcription.pdf)
57. Guide des déclarations d'intérêts et de gestion des conflits d'intérêts [Internet]. [cited 2020 Feb 10]. Available from: [https://www.has-sante.fr/upload/docs/application/pdf/guide\\_dpi.pdf](https://www.has-sante.fr/upload/docs/application/pdf/guide_dpi.pdf)
58. La HAS [Internet]. Haute Autorité de Santé. [cited 2020 Feb 10]. Available from: [https://www.has-sante.fr/jcms/fc\\_1250071/fr/commission-de-la-transparence-ct](https://www.has-sante.fr/jcms/fc_1250071/fr/commission-de-la-transparence-ct)
59. Commission de la Transparence Avis 3 mai 2017 [Internet]. [cited 2020 Feb 10]. Available from: [https://www.has-sante.fr/upload/docs/evamed/CT-15873\\_IBRANCE\\_PIC\\_INS\\_Avis3\\_CT15873.pdf](https://www.has-sante.fr/upload/docs/evamed/CT-15873_IBRANCE_PIC_INS_Avis3_CT15873.pdf)
60. Pricing & Reimbursement of drugs and HTA policies in France [Internet]. National Authority for health (Haute Autorité de Santé), France; 2014. Available from: [https://www.has-sante.fr/upload/docs/application/pdf/2014-03/pricing\\_reimbursement\\_of\\_drugs\\_and\\_hta\\_policies\\_in\\_france.pdf](https://www.has-sante.fr/upload/docs/application/pdf/2014-03/pricing_reimbursement_of_drugs_and_hta_policies_in_france.pdf)
61. Synthèse d'avis de la Commission de la Transparence - IBRANCE (palbociclib), inhibiteur de protéine kinase [Internet]. HAS Haute Autorite de Sante; 2017. Available from: [https://www.has-sante.fr/upload/docs/application/pdf/2018-04/ibrance\\_synthese\\_ct15873.pdf](https://www.has-sante.fr/upload/docs/application/pdf/2018-04/ibrance_synthese_ct15873.pdf)
62. Laëtitia - Haute Autorité de santé.pdf [Internet]. [cited 2020 Feb 10]. Available from: [https://www.has-sante.fr/upload/docs/application/pdf/2018-05/ibrance\\_11072017\\_avis\\_efficienc.pdf](https://www.has-sante.fr/upload/docs/application/pdf/2018-05/ibrance_11072017_avis_efficienc.pdf)
63. Barham L. Division on European HTA - [Internet]. 2018 [cited 2020 Feb 10]. Available from: <https://pharmaphorum.com/views-and-analysis/hta-european-health-technology-assessment-division-progress/>
64. #HTA - European Parliament backs EU-wide action but patients denied key influence [Internet]. EU Reporter. 2018 [cited 2020 Feb 10]. Available from: <https://www.eureporter.co/health/2018/10/04/hta-european-parliament-backs-eu-wide-action-but-patients-denied-key-influence/>
65. Panteli D, Nolting A, Eckhardt H, Kulig M, Busse R. Published and unpublished evidence in coverage decision-making for pharmaceuticals in Europe: existing approaches and way forward. *Health Research Policy and Systems*. 2016 Jan 26;14(1):6.
66. Hailey D. Toward transparency in health technology assessment - A checklist for HTA reports. *International journal of technology assessment in health care*. 2003 Feb 1;19:1–7.
67. Tomasz Bochenek, Ewa Kocot, Marcin Rodzinka, Brian Godman, Katarzyna Maciejewska, Susan Kamal, et al. The transparency of published health technology assessment-based recommendations on pharmaceutical reimbursement in Poland. *Expert Review of Pharmacoeconomics & Outcomes Research*. 2016 Dec 5;17(4):385–400.
68. Wrik Ghosh. IP16: Does Transparency Help or Hinder Emerging HTA Systems? In: *Asia Pacific 2018* [Internet]. Tokyo, Japan; 2018. Available from: [https://www.ispor.org/docs/default-source/conference-ap-2018/transparency\\_issue\\_panel\\_combined\\_slides\\_final.pdf](https://www.ispor.org/docs/default-source/conference-ap-2018/transparency_issue_panel_combined_slides_final.pdf)
69. Olberg B, Fuchs S, Panteli D, Perleth M, Busse R. Scientific Evidence in Health Technology Assessment Reports: An In-Depth Analysis of European Assessments on High-Risk Medical Devices. *Value in Health*. 2017 Dec 1;20(10):1420–6.
70. George E. How real-world data compensate for scarce evidence in HTA. *ZEFQ*. 2016 Jan 1;112:S23–6.
71. Roginiel A, Dhruva S, Ross J. Evidence supporting FDA approval and CMS national coverage determinations for novel medical products, 2005 through 2016: A cross-sectional study. *Medicine* [Internet]. 2018 Oct [cited 2020 Feb 10];97(40). Available from: [insights.ovid.com](https://www.ovid.com)
72. Krüger LJ, Evers SMAA, Hilgsmann M, Wild C. Divergent evidence requirements for authorization and reimbursement of high-risk medical devices – The European situation. *Health Policy and Technology*. 2014 Dec 1;3(4):253–63.

73. Facey K, Henshall C, Sampietro-Colom L, Thomas S. Improving the effectiveness and efficiency of evidence production for health technology assessment. *Int J Technol Assess Health Care*. 2015;31(4):201–6.
74. Boudard A, Martelli N, Prognon P, Pineau J. Clinical studies of innovative medical devices: what level of evidence for hospital-based health technology assessment? *Journal of Evaluation in Clinical Practice*. 2013;19(4):697–702.
75. Nicola Allen, Lawrence Liberti, Stuart R Walker, Sam Salek. A Comparison of Reimbursement Recommendations by European HTA Agencies: Is There Opportunity for Further Alignment? [Internet]. *Frontiers in Pharmacology*. 2017 [cited 2020 Feb 10]. Available from: <https://www.frontiersin.org/articles/10.3389/fphar.2017.00384/full>
76. Kleijnen S, Toenders W, de Groot F, Huic M, George E, Wieseler B, et al. European collaboration on relative effectiveness assessments: What is needed to be successful? *Health Policy*. 2015 May 1;119(5):569–76.
77. Makady A, Ham R ten, de Boer A, Hillege H, Klungel O, Goettsch W. Policies for Use of Real-World Data in Health Technology Assessment (HTA): A Comparative Study of Six HTA Agencies. *Value in Health*. 2017 Apr 1;20(4):520–32.
78. Kleijnen S, Fathallah M, van der Linden MW, Vancraeynest P, Dahmani B, Timoney A, et al. Can a Joint Assessment Provide Relevant Information for National/Local Relative Effectiveness Assessments? An In-Depth Comparison of Pazopanib Assessments. *Value Health*. 2015 Jul;18(5):663–72.
79. Hawlik K, Rummel P, Wild C. Analysis of duplication and timing of health technology assessments on medical devices in Europe. *International Journal of Technology Assessment in Health Care*. 2018 ed;34(1):18–26.
80. Leveraging EUnetHTA’s conceptual framework to compare HTA decision drivers in France, Italy, and Germany from a manufacturer’s point of view | *Health Economics Review* | Full Text [Internet]. [cited 2020 Feb 10]. Available from: <https://healtheconomicsreview.biomedcentral.com/articles/10.1186/s13561-018-0201-y>
81. Nicod E. Why do health technology assessment coverage recommendations for the same drugs differ across settings? Applying a mixed methods framework to systematically compare orphan drug decisions in four European countries. *Eur J Health Econ*. 2017 Jul 1;18(6):715–30.
82. McKendrick J, Malcolm B, Sheahan K, Katsoulis I, Song X, van Loon J. PCN307: The difference between regulatory and market access decisions on treatment availability for new drugs in six common cancers across Australia, Canada, and Europe. *Value in Health: The Journal of the International Society for Pharmacoeconomics and Outcomes Research*. 2017 Oct 1;20:A467.
83. Allen N, Walker SR, Liberti L, Salek S. Health Technology Assessment (HTA) Case Studies: Factors Influencing Divergent HTA Reimbursement Recommendations in Australia, Canada, England, and Scotland. *Value in Health*. 2017 Mar 1;20(3):320–8.
84. Kleijnen S, George E, Goulden S, d’Andon A, Vitré P, Osińska B, et al. Relative Effectiveness Assessment of Pharmaceuticals: Similarities and Differences in 29 Jurisdictions. *Value in Health*. 2012 Sep 1;15(6):954–60.
85. Akehurst RL, Abadie E, Renaudin N, Sarkozy F. Variation in Health Technology Assessment and Reimbursement Processes in Europe. *Value in Health*. 2017 Jan 1;20(1):67–76.
86. Shah KK, Mestre-Ferrandiz J, Towse A, Smyth EN. A review of health technology appraisals: case studies in oncology. *International Journal of Technology Assessment in Health Care*. 2013 Jan;29(1):101–9.