



## **HTA barriers for conditional approval drugs**

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# **HTA BARRIERS FOR CONDITIONAL APPROVAL DRUGS**

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### **Conflicts of Interest/Competing interests**

The authors have no conflict of interest or competing interests.

### **Availability of data and materials**

All data sources used are publicly available. Regulatory agency websites were screened to identify marketing authorisation reports. This included the European Medicines Agency (EMA) and Health Canada. HTA agency websites were screened to identify HTA recommendations. This included the National Institute of Health and Care Excellence (NICE), the Scottish Medicines Consortium (SMC), the Haute Autorité de Santé, (HAS), the Canadian Agency for Drugs and Technologies in Health (CADTH), and the Institut national d'excellence en santé et en services sociaux (INESSS).

### **Ethics approval and consent to participate**

Not applicable

### **Consent for publication**

Not applicable

### **Author contributions**

Mackenzie Mills – Conceptualisation, Methodology, Data Collection, Data Analysis, Writing – Original Draft

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## **ABSTRACT**

**Introduction:** Conditional approval pathways facilitate accelerated marketing authorisation based on immature clinical evidence for drugs that address an unmet medical need in a life-threatening or chronically debilitating condition. Lowering evidence requirements for marketing authorisation results in higher clinical uncertainty, which may present challenges for the health technology assessment of these products.

**Objectives:** The objective of this study is to assess whether conditionally approved drugs face higher probabilities of HTA rejection or delays in HTA approval relative to drugs with standard marketing authorisation.

**Methods:** This paper adopts a mixed-methods approach to provide a meta-analysis of HTA outcomes across 80 drug-indication pairs in France, England, Scotland, and Canada. Differences in the characteristics (i.e. disease rarity and clinical trial design) of conditionally approved drugs and drugs with standard marketing authorisation and drivers of HTA outcomes are assessed through logistics regressions. Delays in HTA approval are assessed through survival analysis.

**Results:** Relative to standard approval drugs, conditionally approved drugs are less likely to include phase III trial designs, less likely to include clinical endpoints, and less likely to include an active comparator. Uncertainties in clinical and economic evidence are raised more frequently by HTA agencies for conditionally approved drugs, which have a marginally lower probability of receiving HTA approval relative to drugs with standard approval. Conditionally approved drugs face moderate delays (an average of 6 months) in receiving HTA approval relative to standard approval drugs.

**Conclusion:** Overall, conditionally approved drugs likely face increased barriers at HTA level.

## **KEY POINTS FOR DECISION-MAKERS**

- Conditionally approved drugs have high levels of unresolved clinical uncertainties related to the magnitude of clinical benefit, appropriateness of clinical trial design, and adverse event profile.
- Conditionally approved drugs likely face a slightly increased probability of receiving a negative HTA outcome.
- Delays in HTA approval were identified for conditionally approved drugs, although the extent of delay varies across settings.

## INTRODUCTION

Firm entry in the pharmaceutical market, and by extension diffusion of innovative medicines to patients, is heavily influenced by the presence and structure of regulatory institutions [1]. In an increasing number of settings globally, innovative medicines must pass through two key milestones before adoption into a healthcare system: marketing authorisation (MA) and health technology assessment (HTA) [2-3]. Marketing authorisation review is undertaken by regulatory institutions such as the European Medicines Agency (EMA) and the U.S. Food and Drug Administration in order to confirm that drugs have a positive benefit-to-risk ratio (i.e. that they are safe and efficacious for human use) [4]. HTA agencies on the other hand, such as the National Institute of Care and Health Excellence (NICE) in England, evaluate the relative clinical and, in some instances, economic effectiveness of a drug in order to inform resource allocation decisions [5,6].

The presence of two sets of institutions with distinct objectives increases the transaction costs firms face in overcoming regulatory hurdles [7,8]. Within the pharmaceutical market, institutional alignment (between MA and HTA agencies) is inversely correlated with transaction cost (i.e. the cost associated with research and development) [9]. Strong alignment between marketing authorisation agencies and HTA agencies on evidence requirements reduces firm evidence generation costs, while poor alignment increases costs.

Potential issues arising from institutional alignment are well illustrated by the case of conditional approval pathways. Conditional approval pathways, a type of marketing authorisation, provide medicines with provisional authorisation in an effort to reduce regulatory delays in instances where medicines address an unmet medical need in a serious, life-threatening or chronically debilitating disease [10,11]. Approval is granted on the basis of pre-mature or early phase clinical evidence on the condition that evidence generation is

completed post-authorisation; effectively shifting the evidence generation transaction cost from pre-approval to post-approval [12]. Depending on how stringently post-marketing requirements are enforced, transaction costs may be lower; recent research on FDA accelerated approval drugs identified several instances where confirmatory trials were never completed [13].

The extent to which firms benefit from this shift, and by extension the extent to which conditional approval policies achieve their intended effect of accelerating access to drugs that address an unmet medical need, is contingent on whether firms meet evidence requirements at HTA level. However, HTA outcomes and approval timelines for conditionally approved oncology drugs in Europe are extremely fragmented [14].

Fragmented HTA outcomes have important consequences for public health, leading to differences in patient access and time to access of medicines across settings [15,16]. Differences in HTA methodology across agencies may account for some of the heterogeneity, leading to differences in the interpretation of evidence [17-19]. Magnitude of clinical efficacy, clinical trial design, disease area and cost-effectiveness, have all been reported as significant determinants of HTA outcomes in single-setting analyses [20-26]. More recently, some empirical studies have attempted to explain difference HTA outcomes across settings through mixed-methods approaches [27,28], although findings are limited by sample size and the difficulty of quantitatively assessing HTA coverage decisions.

This study has the following objectives:

- 1) To compare and contrast the health technology assessment of drugs that have received conditional marketing authorisation relative to those that have received standard marketing authorisation.



- 2) To examine whether differences in the quality and strength of evidence of conditionally approved drugs and standard approval drugs lead to a higher probability of HTA rejection or delays in HTA approval.

Existing literature on conditional approval pathways has predominantly focused on characterising levels of clinical evidence [29-32], clinical development and approval timelines [32,33], post-approval safety warnings [34,35] and completion of confirmatory studies [13,35, 36]. A small body of literature has begun to explore HTA decision-making on conditionally approved drugs, focusing on single setting evaluations of conditionally approved medicines [37,38], descriptive analysis of HTA timelines and outcomes [14], and the impact of study design [39] and post-approval studies [40] on HTA outcomes in Europe. The scope of these studies was restricted to conditionally approved drugs, limiting our understanding of whether these drugs face barriers at HTA level over and above drugs with standard marketing authorisation. The present study provides an empirical analysis comparing HTA decision-making on a cohort of conditionally approved and standard approval drugs.

## **METHODS**

This research was undertaken as a follow-up to the IMPACT-HTA Horizon 2020 project [41] as part of a team of researchers tasked with developing methodology on clinical and economic evidence uncertainties in the context of HTA.

### **i) Conceptual Framework**

We employ a mixed-methods approach to the data-collection and meta-analysis of HTA outcomes [19], which accounts for differences in the type of evidence submitted, the interpretation of evidence, and the impact of interpretation on the final recommendation. The

mixed-methods approach involves two stages. In the first stage, publicly available HTA decision reports are qualitatively analysed in order to collect data on the evidence submitted to HTA bodies (both clinical and economic), the interpretation of the evidence from HTA bodies (including the scientific and the social value judgements made) and to identify components of uncertainty as well as elicited and non-elicited additional considerations that may have played a role in the assessment/appraisal process for each drug-indication pair. In the second stage, quantitative analysis is performed to identify key drivers of HTA decision-making. Table 1.0 provides a conceptual framework which informs model specification.

**Table 1 – Conceptual Framework for Empirical Analysis of HTA Outcomes**

|  | Negative Effect on HTA Outcome | Ambiguous Effect on HTA Outcome | Positive Effect on HTA Outcome | Hypothesis of predicted impact on HTA outcome  |
|--|--------------------------------|---------------------------------|--------------------------------|--|
| <b>A. Disease Characteristics<sup>1</sup></b>                      |                                |                                 |                                |  |
| Therapeutic Area<br>(Non-cancer=0, Cancer=1)                       |                                | X                               |                                | Evidence generation in oncology is limited by disease severity and short patient expectancy, which create ethical barriers to conducting large head-to-head clinical trials. Higher levels of clinical uncertainty in this disease area are expected to have a negative impact on HTA outcomes. However, disease severity and higher perception of unmet need for new cancer drugs may have a positive effect.   |
| Orphan Status<br>(Non-orphan=0, Orphan=1)                          |                                | X                               |                                | Evidence generation in orphan disease is limited by issues in patient recruitment for clinical trials. Higher levels of clinical uncertainty in this disease area are expected to have a negative impact on HTA outcomes. However a higher perception of unmet need and low budget impact may have a positive effect.  |
| <b>B. Pivotal Trial Characteristics<sup>2</sup></b>                |                                |                                 |                                |  |
| Trial Phase<br>(Single arm Phase I/II=0, Randomized Phase III = 1) |                                |                                 | X                              | Phase III trials are larger and longer than phase I or II trials and have greater statistical power to evaluate the clinical efficacy of a product. HTA agencies are predicted to look more favorably on evidence generated from a phase III study relative to phase I or II.  |
| Endpoint<br>(Surrogate=0, Clinical=1)                              |                                |                                 | X                              | Surrogate endpoints can be both validated or un-validated and are designed to provide an indication that a treatment is working at earlier stages in the treatment pathway. Surrogate endpoints may not always represent true indicators of clinical benefit and as such the inclusion of hard clinical endpoints is expected to have a positive impact on HTA outcomes.   |
| Comparator<br>(Placebo/No comparator=0, Active comparator=1)       |                                |                                 | X                              | HTA agencies seek to evaluate the clinical and economic impact of a drug against the current standard of care. Submissions with clinical trials including active comparators are expected to have a positive impact on HTA outcomes.   |
| <b>C. Uncertainties<sup>3</sup></b>                                |                                |                                 |                                |  |
| Clinical Uncertainties Overcome<br>(Total number)                  |                                | X                               |                                | Clinical uncertainties relate to issues raised by HTA agencies on magnitude of clinical benefit, absence of clinical evidence, study design, indirect comparisons, generalizability or safety. Uncertainties coded as overcome were raised by HTA agencies in decision reports, but dismissed based on supplemental data, patient submission, clinical expert submission or recognition of disease context. Overcome uncertainties are not expected to have a positive or negative impact on HTA outcomes. |
| Clinical Uncertainties Not Overcome<br>(Total number)              | X                              |                                 |                                | Clinical uncertainties coded as not-overcome relate to all clinical issues that are not dismissed by HTA agencies. Uncertainties that are not-overcome are expected to have a negative impact on HTA outcomes.   |
| Economic Uncertainties Overcome<br>(Total number)                  |                                | X                               |                                | Economic uncertainties relate to issues raised by HTA agencies on modelling assumptions, modelling type, model inputs including costs, utilities and clinical evidence, cost-effectiveness estimates and sensitivity analysis. Uncertainties coded as overcome were raised by HTA agencies in decision reports, but dismissed based on supplemental data, patient submission, clinical expert submission or recognition of disease context   |

or minimal impact on model outputs. Overcome uncertainties are not expected to have a positive or negative impact on HTA outcomes.

Economic Uncertainties Not Overcome  
(Total number) X

Economic uncertainties coded as not-overcome relate to all economic issues that are not dismissed by HTA agencies. Uncertainties that are not-overcome are expected to have a negative impact on HTA outcomes.

#### D. Social Value Judgements<sup>4</sup>

|  |  |
|--|--|
| Disease Severity<br>(not-raised=0, raised=1) X         | The HTA agency acknowledged the severity of disease during the appraisal of evidence. HTA agencies may show greater leniency or willingness to approve of products that address a serious, life-threatening or chronically debilitating disease, given higher levels of patient morbidity and mortality. |
| Unmet Need<br>(not-raised=0, raised=1) X               | The HTA agency acknowledged there is an unmet clinical need for effective treatments in the therapeutic indication. HTA agencies may show greater leniency or willingness to approve products that address unmet clinical needs.   |
| Administration Advantage<br>(not-raised=0, raised=1) X | The HTA agency acknowledged that the product under evaluation provides a benefit to patients in terms of the route of administration that is not captured by the clinical or economic evidence. This is expected to have a positive impact on HTA outcome.   |
| Innovation<br>(not-raised=0, raised=1) X               | The HTA agency acknowledges that the product has an innovative mechanism of action. The impact of innovation on decision making is ambiguous. It is beneficial for patients to have access to therapies with varied mechanisms of actions, particularly if they fail to respond to one treatment.        |
| Quality of Life<br>(not-raised=0, raised=1) X          | The HTA agency acknowledges that the product improves patient quality of life in ways not captured by the clinical evidence submitted. This is expected to have a positive impact on HTA outcome.  |
| Special Demographics<br>(not-raised=0, raised=1) X     | The HTA agency acknowledges that the product is to be used in a special patient demographic (e.g. pediatric patients or elderly patients). It is unclear if HTA agencies will prioritize special demographics differently during decision-making.  |

Source: The authors, adapted from [19]. Abbreviations: HTA – Health Technology Assessment

<sup>1</sup>Disease characteristics considered include therapeutic area and orphan status. Data on ATC code was collected for all drugs included in the sample. Given low sample size, therapeutic area was considered as a binary variable (cancer vs non-cancer indications). Data on orphan status was collected at EMA level, as no such designation exists in Canada.

<sup>2</sup>Pivotal trial characteristics considered include trial phase, comparator, and endpoint. Trial phase was considered as a binary variable (phase I/II vs Phase III) to provide an approximate measure of trial size and length. Comparator was considered in terms of whether an active comparator was present in the trial, in order to provide an indication of whether direct comparative evidence was available. Endpoint was considered in terms of whether the primary endpoint consisted of a surrogate or clinical endpoint.

<sup>3</sup>Uncertainties represent scientific value judgments raised by HTA agencies during the assessment of a product’s clinical and economic evidence. A full taxonomy of uncertainties is available in Appendix B

<sup>4</sup>Social Value Judgments refer to dimensions of value identified by HTA agencies beyond clinical and economic evidence, and can relate to disease severity, unmet need, administration advantage, innovation, quality of life or special demographics

## ii) Data and Sample Selection

The scope of this study was limited to France, England, Scotland and Canada. Country selection was based on the following criteria: a) Implementation of a conditional approval pathway, b) requirement to pass through HTA, c) publicly available HTA reports, d) language of HTA reports (English and French). Marketing authorisation agencies considered include the European Medicines Agency (EMA - France, England, and Scotland) [42] and Health Canada (HC - Canada) [43]. HTA agencies considered include the National Institute of Health and Care Excellence (NICE – England) [44], the Scottish Medicines Consortium (SMC – Scotland) [45], the Haute Autorité de Santé (HAS – France) [46], the Canadian Agency for Drugs and Technology in Health (CADTH – Canada) [47] and the Institut National d'Excellence en Santé et en Services Sociaux (INESSS – Canada) [48]. An overview of marketing authorisation and HTA systems in these settings is provided in Electronic Supplementary Material A.

The European Union Register of medicinal products [49] was screened to identify all new drug approvals between 01.01.2010 and 31.12.2017. The study period was set to provide sufficient time to track HTA approvals after marketing authorisation. A cut-off date of 31.12.2019 was applied for the identification of HTA reports. Indication extensions during the study period were identified through EMA annual summary reports and by screening EMA variation reports for individual drugs during the study period [42]. Veterinary products, generics, hybrids and biosimilars were excluded. Included drug indication-pairs were screened to identify drug-indication pairs with conditional marketing authorisation. Health Canada drugs with notice of compliance with conditions were identified via the Health Canada list of notice of compliance with conditions [50]. HTA agency websites across all included countries were then screened to identify matching HTA reports for the drug and therapeutic indication of interest [44-48]. Conditionally approved drugs without a minimum of one HTA report completed were excluded

from the sample. Non-conditionally approved drug-indications pairs (those with standard marketing authorisation) were then screened to identify a representative sample of standard approval drugs. Selection was based on 3 criteria: first, each drug in the sample had a minimum of one HTA recommendation across included HTA agencies; second, the total sample included a similar proportion of cancer vs non-cancer drugs relative to the conditional approval sample; finally, the total sample included a similar distribution over time (in terms of the marketing authorisation year) as the conditional approval sample. With the exception of therapeutic area and authorisation year, all details on drug-indication pairs were blinded in order to facilitate a random sampling. A flow chart, outlining the sample selection is provided in figure 1 of the results section.

HTA agency websites were screened again to identify all matching HTA reports for the final list of included drug-indication pairs. HTA reports with non-perfect matches in the therapeutic indication were screened by a second reviewer, with any disagreements on inclusion resolved by a third reviewer. In the event that an HTA agency split an indication into sub-indications, all sub-indications were included, provided separate reports were available for each sub-indication. An overview of the identification of HTA reports is provided in Electronic Supplementary Material B.

### **iii) Data Collection**

Several variables were considered as potential determinants of HTA outcomes through review of previous literature on HTA decision-making [16-26]. Positive HTA outcome were defined as unrestricted listing (L) or restricted listing (LWC) outcomes in NICE, SMC, CADTH and INESSS, and SMR ratings above insufficient in HAS. Negative HTA outcomes were defined as do not list (DNL) outcomes in NICE, SMC, CADTH, and INESSS, and an SMR rating of insufficient in HAS. Data on HTA outcome, HTA restrictions (population or economic), HTA

date, previous submissions, clinical evidence, scientific value judgements (both clinical and economic uncertainties) and social value judgements (additional dimensions of value beyond clinical and economic evidence) were collected from HTA reports. Clinical and economic uncertainties were double coded according to the type of uncertainty and the impact of the uncertainty on decision making. Uncertainties dismissed by the HTA agency due to patient submissions, clinical expert submission, supplemental data or disease context are categorised as “overcome”. Uncertainties that are not dismissed are categorised as “not-overcome”. The categorisation of clinical and economic uncertainties was reviewed and validated by a team of 4 researchers involved in WP7 of the IMPACT HTA Horizon 2020 project. A full taxonomy of clinical and economic uncertainties is provided in Electronic Supplementary Material B.

Data on marketing authorisation approval (type of authorisation, date and conversion from conditional to standard approval) were collected from publicly available marketing authorisation reports.

#### **iv) Empirical Methods**

Data was extracted into Microsoft Excel and coded. Statistical analysis was performed using STATA SE Version 17.0. The unit of analysis was defined as a drug-indication-agency trio. A single HTA outcome is specific to both a therapeutic indication and HTA agency, meaning that HTA outcomes for different therapeutic indications of a single molecule are recorded as separate entries.

Maximum likelihood logistic regression models were constructed to assess the association of collected variables with a) type of marketing authorisation pathway and b) HTA outcome. Kaplan-meier survival curves were used to compare conditionally approved drugs with standard approval drugs for time from MA to HTA outcome.

First, univariate binomial logistic regression models were used to explore the association of collected variables with type of marketing authorisation pathway. The dependent variable for univariate analysis ( $Y_{1/0}$ ) was coded as 1 for drug-indication-agency trios with conditional approval and 0 for drug-indication-agency trios with standard approval:

$$Y_{1/0} \begin{pmatrix} Y = 1, & \text{if conditional approval} \\ Y = 0, & \text{if standard approval} \end{pmatrix} \quad (1)$$

Independent variables ( $x_i$ ) included therapeutic area, orphan status, pivotal trial phase, pivotal trial comparator, pivotal trial endpoint, scientific value judgements raised by HTA agencies (clinical and economic uncertainties), social value judgements raised by HTA agencies, submission history and HTA outcome.

$$\text{Logit}(Y_{1/0} | X_1 = x_1) = \beta_o + x_1\beta_1 \quad (2)$$

Where  $x_i$  represents the independent variable,  $\beta_i$  represents the regression coefficient and  $\beta_o$  represents the intercept. Odds ratios, 95% confidence intervals and p-values are reported.

$$\text{Odds}(Y_{1/0} | X_1 = x_1) = \exp(\beta_o + x_1\beta_1) \quad (3)$$

Second, multivariate binary logistic regression models were used to explore the association of collected variables with HTA outcomes. The dependent variable for multivariate analysis ( $Z_{1/0}$ ) was coded as 1 for a drug-indication-agency trios with an HTA outcome of List (L) or List with criteria (LWC) and 0 for drug-indication-agency trios with an HTA outcome of Do not List (DNL).

$$\text{Logit}(Z_{1/0} | X_1 = x_1) = \beta_o + x_1\beta_1 \quad (4)$$



Where  $x_i$  represents the independent variable,  $\beta_i$  represents the regression coefficient and  $\beta_o$  represents the intercept. Independent variables included type of marketing authorisation pathway, therapeutic area, orphan status, pivotal trial phase, pivotal trial comparator, pivotal trial endpoint, scientific value judgements raised by HTA agencies (clinical and economic uncertainties), social value judgements raised by HTA agencies, submission history and HTA outcome. The general specification of the multivariate model was:

$$\text{Logit}(Z_{1/0} | X_{iat} = x_{iat}) = \beta_o + x_{iat}\beta' + d_i\gamma' + a_a\zeta' + t_t\eta' \quad (5)$$

Where  $x_{iat}$  is a vector of HTA characteristics (submission history, clinical evidence, scientific value judgements, and social value judgements) for drug-indication “i”, agency “a”, and assessment year “t” and  $d_i$  is a vector of disease characteristics (therapeutic area and orphan status) that are agency-invariant. To control for heterogeneity across agencies and over time, we include agency fixed effects ( $a_a$ ) and time fixed effects ( $t_t$ ).  $\beta'$ ,  $\gamma'$ ,  $\zeta'$ , and  $\eta'$  represent the regression coefficients and  $\beta_o$  represents the intercept. Odds ratios and robust standard errors adjusted for clustering at molecule level are reported. We additionally calculate average marginal effects (ME) to examine inter-agency differences and the impact of interactions in the model. As a robustness check, additional analysis were performed on cost-effectiveness countries only (excluding France) and excluding time and agency fixed effects.

Third, survival analysis using Kaplan-Meier curves was performed to assess the association of marketing authorisation type with time from marketing authorisation to HTA approval. The “death” event was defined as a positive HTA outcome (List or List with condition). The time unit was defined as days between marketing authorisation approval and HTA outcome.

## RESULTS

A total of 339 drug-indication-agency trios were included in the analysis consisting of 40 unique conditionally approved drug-indication pairs and 40 standard approval drug-indication pairs [See Figure 1]. A full list of included drug-indication pairs is provided in Electronic Supplementary Material C. A total of 58 HTA rejections (17.1%) and 281 HTA approvals (83.5%) were identified in the pooled sample. INESSS had the highest proportion of rejections (46.0%) were identified in the pooled sample. INESSS had the highest proportion of rejections (46.0% rejection vs 54.0% approval), followed by CADTH (16.4% vs 83.6%), SMC (12.1% vs 87.9%), NICE (10.6% vs 89.4%) and HAS (2.7% vs 97.3%) ( $\chi^2_{(5|N=339)} = 48.3, p < 0.01$ ). In 11 instances, conditional approval was converted to standard approval prior to publication of an HTA outcome.

### Comparing HTA Characteristics by Marketing Authorisation Pathway

Conditional approval and standard approval drugs were compared regarding disease characteristics, pivotal trial characteristics, uncertainties, social value judgements, and HTA outcomes. Results of univariate analysis are presented in table II.

Significant differences across conditional approval and standard approval drug-indication-agency trios were identified in pivotal trial characteristics, uncertainties and social value judgements, and HTA outcomes. Relative to drug-indication-agency trios with standard approval, conditionally approved drug-indication-agency trios are less likely to be based on a phase III trial, include a clinical primary endpoint, or include a direct comparator. Results for uncertainties and social value judgements were mixed, with conditionally approved drug-indication-trios statistically more likely to have a higher number of clinical uncertainties not overcome and a higher number of economic uncertainties not overcome, and more likely to have HTA agencies recognise disease severity, unmet need, and special demographics.

Health Canada

EMA

911 EMA approvals  
between 01/01/2010  
and 31/12/2017

48 drug indication pairs excluded due to marketing authorization withdrawal  
249 generic, hybrid or biosimilar drug-indication pairs excluded  
13 drug-indication pairs approved under exceptional circumstances excluded

606 drug-indication pairs  
321 new drug submissions  
285 indication extensions

52 drug indication pairs with NOC/C

17 generic, hybrid or biosimilar drug-indication pairs

582 drug-indication pairs with standard approval

35 drug indication pairs with NOC/C

24 drug-indication pairs with EMA conditional approval

6 drug-indication pairs excluded due to absence of HTA evaluation

1 drug-indication pairs excluded due to absence of HTA evaluation

29 drug-indication pairs with NOC/C and minimum of one HTA evaluation across CADTH/INESSS

23 drug-indication pairs with EMA conditional approval and min 1 HTA evaluation across NICE, SMC, ...

12 duplicates removed

40 distinct drug- indication pairs with conditional approval

40 drug-indication pairs with standard approval with a minimum of one HTA evaluation randomly selected, stratified over time and therapeutic area

CADTH - Canadian Agency for Drugs and Technologies in Health; HAS – Haute Autorité de Santé; INESS - The Institut national d'excellence en santé et en services sociaux; NICE – National Institute of Health and Care Excellence; SMC – Scottish Medicines Consortium

**Figure 1 – Flowchart illustrating identification of conditionally approved drug-indication pairs and selection of standard approval drug-indication pairs across Health Canada and the European Medicines Agency.** The European union register of medicinal products website (<https://ec.europa.eu/health/documents/community-register/html/>) was screened to identify new drug approvals between 01/01/2010 and 31/12/2017. European Medicines Agency (EMA) annual reports and variation reports were subsequently screened to identify approvals of new therapeutic indications (indication extensions) between 01/01/2010 and 31/12/2017. Products with withdrawals, generic products, hybrid products, biosimilar products and products authorised under exceptional circumstances were excluded from the sample. Remaining drug-indication pairs were stratified according to type of marketing authorisation (standard approval vs conditional approval). EMA conditionally approved products without a matching HTA report in one of NICE, SMC or CADTH were excluded from the sample. The Health Canada Notice of Compliance with conditions (NOC/C) list (<https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/notice-compliance/conditions.html>) was screened to identify drug-indication pairs with conditional approval in Canada between 01/01/2010 and 01/01/2017. Generic, hybrid and biosimilar products with conditional approval were excluded from the sample. Health Canada conditionally approved products without a matching HTA report in one of CADTH or INESS were excluded from the sample. The therapeutic indications of conditionally approved products in Health Canada and EMA were compared to identify duplicates. Matching of drug-indication pairs was performed by two reviewers, with any disagreements resolved by a third reviewer. Please refer to the supplementary material for a breakdown of the number of matching HTA reports identified per agency.

**Table 2 – Univariate Analysis Comparing HTA Assessment of Conditional Approval and Standard Approval Drugs**

|  |                       | Standard Approval<br>Drug-Indication-<br>Agency Trios |             | Conditional Approval<br>Drug-Indication-Agency<br>Trios |             | Univariate |             |              |
|--|-----------------------|---|-------------|---|-------------|------------|-------------|--------------|
|  |                       | No  | (%)         | No  | (%)         | OR         | [95% CI]    | P-value      |
| <b>A. Disease Characteristics</b>                |                       |   |             |   |             |            |             |              |
| Therapeutic Area                                 | Cancer                | 164   | (75.9%)     | 104   | (83.2%)     | 1.57       | [0.89-2.76] | 0.116        |
|  | Non-Cancer            | 52  | (24.1%)     | 21  | (16.8%)     | 1.00       | [Reference] |              |
| Orphan Status                                    | Orphan                | 52  | (24.1%)     | 34  | (27.2%)     | 1.18       | [0.71-1.95] | 0.52         |
|  | Non-Orphan            | 164   | (75.9%)     | 91  | (72.8%)     | 1.00       | [Reference] |              |
| <b>B. Pivotal Trial Characteristics</b>          |                       |   |             |   |             |            |             |              |
| Trial Phase <sup>1</sup>                         | Phase III             | 182   | (84.2%)     | 67  | (53.6%)     | 0.22       | [0.13-0.36] | <b>0.000</b> |
|  | Phase I/II            | 34  | (15.7%)     | 58  | (46.4%)     | 1.00       | [Reference] |              |
| Endpoint <sup>2</sup>                            | Clinical              | 60  | (27.8%)     | 13  | (10.4%)     | 0.30       | [0.16-0.56] | <b>0.000</b> |
|  | Surrogate             | 156   | (72.2%)     | 112   | (89.6%)     | 1.00       | [Reference] |              |
| Comparator                                       | Active                | 109   | (50.5%)     | 49  | (39.2%)     | 0.63       | [0.40-0.99] | <b>0.045</b> |
|  | Placebo/No comparator | 107   | (49.5%)     | 76  | (60.8%)     | 1.00       | [Reference] |              |
| <b>C. Uncertainties</b>                          |                       |   |             |   |             |            |             |              |
| Clinical Uncertainties Overcome                  | Mean [95%CI]          | 2.33  | [1.98-2.68] | 2.77  | [2.26-3.27] | 1.06       | [0.98-1.15] | 0.151        |
| Clinical Uncertainties Not Overcome              | Mean [95%CI]          | 3.11  | [2.73-3.48] | 4.62  | [4.06-5.19] | 1.19       | [1.10-1.28] | <b>0.000</b> |
| Economic Uncertainties Overcome <sup>3</sup>     | Mean [95%CI]          | 1.37  | [1.10-1.62] | 1.40  | [0.98-1.83] | 1.01       | [0.89-1.15] | 0.871        |
| Economic Uncertainties Not Overcome <sup>3</sup> | Mean [95%CI]          | 2.44  | [2.14-2.73] | 3.11  | [2.67-3.56] | 1.17       | [1.04-1.33] | <b>0.011</b> |
| <b>D. Social Value Judgements</b>                |                       |   |             |   |             |            |             |              |
| Disease Severity                                 | Considered            | 108   | (50.0%)     | 79  | (68.1%)     | 2.14       | [1.33-3.43] | <b>0.002</b> |
|  | Not-considered        | 108   | (50.0%)     | 37  | (31.9%)     | 1.00       | [Reference] |              |
| Unmet Need                                       | Considered            | 163   | (75.5%)     | 101   | (87.1%)     | 2.19       | [1.17-4.09] | <b>0.014</b> |
|  | Not-considered        | 53  | (24.5%)     | 15  | (12.9%)     | 1.00       | [Reference] |              |
| Administration Advantage                         | Considered            | 62  | (28.7%)     | 43  | (37.1%)     | 1.46       | [0.91-2.36] | 0.119        |
|  | Not-considered        | 154   | (71.3%)     | 73  | (62.9%)     | 1.00       | [Reference] |              |
| Innovation                                       | Considered            | 72  | (33.3%)     | 47  | (41.2%)     | 1.40       | [0.88-2.24] | 0.156        |
|  | Not-considered        | 144   | (66.7%)     | 64  | (58.7%)     | 1.00       | [Reference] |              |
| Quality of Life                                  | Considered            | 82  | (38.1%)     | 60  | (48.0%)     | 1.50       | [0.96-2.34] | 0.076        |
|  | Not-considered        | 133   | (61.9%)     | 65  | (52.0%)     | 1.00       | [Reference] |              |
| Special Demographics                             | Considered            | 10  | (4.7%)      | 17  | (13.6%)     | 3.22       | [1.43-7.29] | <b>0.003</b> |
|  | Not-considered        | 205   | (95.3%)     | 108   | (86.4%)     | 1.00       | [Reference] |              |
| <b>E. HTA Outcomes</b>                           |                       |   |             |   |             |            |             |              |

|                          |                  |     |          |    |         |      |             |              |
|--------------------------|------------------|-----|----------|----|---------|------|-------------|--------------|
| Submission History       | Prior-rejection  | 34  | (15.7%)  | 27 | (21.6%) | 1.47 | [0.84-2.59] | 0.175        |
|                          | First submission | 182 | (84.3%)  | 98 | (78.4%) | 1.00 | [Reference] |              |
| HTA Outcome <sup>4</sup> | L or LWC         | 186 | (86.11%) | 97 | (77.6%) | 0.56 | [0.32-0.99] | <b>0.046</b> |
|                          | DNL              | 30  | (13.9%)  | 28 | (22.4%) | 1.00 | [Reference] |              |

Abbreviations: L – List; LWC - List with Conditions; DNL – Do not List;

HTA characteristics of conditional vs standard approval across NICE, SMC, HAS, CADTH and INESSS. Conditional approval status defined based receipt of a conditional marketing authorisation in EMA or notice of compliance with condition (NOC/C) in Health Canada. The dependent variable, type of marketing authorisation, is coded as 1 for conditionally approved drug-indication-agency trios, and 0 for standard approval drug-indication-agency trios. Odds ratios reflect the likelihood of differences in disease characteristics, pivotal trial characteristics, uncertainties, social value judgements and HTA outcomes across conditionally approved and standard approval drugs. Results are pooled across all agencies.

<sup>1</sup> Where multiple pivotal trials are available, highest phase is recorded

<sup>2</sup> According to primary endpoint in pivotal trial

<sup>3</sup> Statistical tests on economic uncertainties calculated excluding HAS

<sup>4</sup> In HAS, products with a medical service rendered (SMR) rating of insufficient are not reimbursed and are considered as DNL. All other SMR ratings are considered in the L/LWC category.

Conditionally approved drug-indication-agency trios were statistically more likely to receive a negative HTA outcome relative to standard approval drug-indication-agency trios. This result remains significant when removing HAS from analysis (CEA countries only). No statistically significant differences were identified for disease characteristics or submission history.

As a robustness check, the 11 drug-indication-agency trios with converted MA were reclassified as standard approval drugs and univariate analysis was repeated. Results were consistent with the original classification, with statistically significant differences identified for trial phase, endpoint, comparator, clinical uncertainties not overcome, economic uncertainties not overcome, disease severity, unmet need, special demographics and HTA outcome.

### **Multivariate Regression Examining Drivers of HTA Outcomes**

In order to capture the impact of respective groups of variables on HTA outcomes, regression models were constructed in a step-wise manner. A baseline model (Model 0) included type of marketing authorisation pathway, with agency and time fixed-effects, to provide a benchmark. Type of marketing authorisation pathway was excluded from subsequent models given high collinearity with the other independent variables. Disease characteristics and submission history (Model 1), pivotal trial characteristics (Model 2), uncertainties (Model 3), and social value judgements (Model 4) were added sequentially. Model 5 presents results of cost-effectiveness countries only (excluding HAS). All models controlled for agency and time fixed effects. Results of the multivariate models are presented in table III. Additional models without fixed effects are presented in Electronic Supplementary Material E

**Table 3 – Multivariate logistic regression models comparing positive and negative HTA outcomes across NICE, HAS, SMC, CADTH and INESSS.**

|   | Model 0          | Model 1             | Model 2             | Model 3              | Model 4              | Model 5              |
|---|------------------|---------------------|---------------------|----------------------|----------------------|----------------------|
| <i>Dependent Variable: HTA Outcome (List or List with condition: 1, Do not list: 0)</i> |                  |                     |                     |                      |                      |                      |
| <b>A) Regulatory Approval</b>   |                  |                     |                     |                      |                      |                      |
| Conditional Approval  | 0.714<br>(0.256) |                     |                     |                      |                      |                      |
| <b>B) Disease Characteristics</b>   |                  |                     |                     |                      |                      |                      |
| Cancer  |                  | 2.724**<br>(1.107)  | 2.605**<br>(1.034)  | 2.631**<br>(1.219)   | 2.625*<br>(1.363)    | 3.628**<br>(2.061)   |
| Orphan  |                  | 2.323<br>(1.281)    | 3.452**<br>(1.965)  | 4.019**<br>(2.742)   | 6.217**<br>(5.006)   | 9.119**<br>(9.274)   |
| <b>C) Submission History</b>  |                  |                     |                     |                      |                      |                      |
| Resubmission  |                  | 3.921***<br>(1.953) | 3.731***<br>(1.910) | 10.567***<br>(8.570) | 10.223***<br>(7.948) | 10.634***<br>(8.401) |
| <b>D) Pivotal Trial Characteristics</b>   |                  |                     |                     |                      |                      |                      |
| Trial Phase   |                  |                     | 1.999<br>(0.876)    | 2.474*<br>(1.283)    | 3.365**<br>(2.064)   | 3.528*<br>(2.384)    |
| Endpoint  |                  |                     | 1.344<br>(0.673)    | 1.491<br>(0.799)     | 1.278<br>(0.748)     | 1.211<br>(0.743)     |
| Comparator  |                  |                     | 1.305<br>(0.593)    | 1.657<br>(0.877)     | 1.306<br>(0.670)     | 1.097<br>(0.593)     |
| <b>E) Uncertainties</b>   |                  |                     |                     |                      |                      |                      |
| Clinical Overcome   |                  |                     |                     | 1.493***<br>(0.165)  | 1.504***<br>(0.199)  | 1.505***<br>(0.196)  |
| Clinical Not-Overcome   |                  |                     |                     | 0.780***<br>(0.062)  | 0.760***<br>(0.070)  | 0.760***<br>(0.072)  |
| Economic Overcome   |                  |                     |                     | 1.935***<br>(0.433)  | 2.431***<br>(0.570)  | 2.440***<br>(0.532)  |
| Economic Not-Overcome   |                  |                     |                     | 0.845*<br>(0.084)    | 0.830*<br>(0.094)    | 0.845<br>(0.104)     |
| <b>F) Social Value Judgements</b>   |                  |                     |                     |                      |                      |                      |



|                          |       |       |       |       |                  |                  |
|--------------------------|-------|-------|-------|-------|------------------|------------------|
| Disease Severity         |       |       |       |       | 1.102<br>(0.592) | 1.275<br>(0.690) |
| Unmet Need               |       |       |       |       | 0.489<br>(0.310) | 0.337<br>(0.203) |
| Administration Advantage |       |       |       |       | 2.052<br>(1.175) | 2.153<br>(1.229) |
| Innovation               |       |       |       |       | 0.958<br>(0.567) | 0.919<br>(0.574) |
| Quality of Life          |       |       |       |       | 1.588<br>(0.862) | 1.437<br>(0.814) |
| Special Demographics     |       |       |       |       | 4.157<br>(3.794) | 4.051<br>(3.935) |
| Number of Observations   | 339   | 339   | 339   | 339   | 339              | 256              |
| Pseudo-R <sup>2</sup>    | 0.178 | 0.221 | 0.252 | 0.408 | 0.448            | 0.435            |
| AIC                      | 282.9 | 273.5 | 270.1 | 220.9 | 216.9            | 199.9            |
| Time FE                  | Yes   | Yes   | Yes   | Yes   | Yes              | Yes              |
| Agency FE                | Yes   | Yes   | Yes   | Yes   | Yes              | Yes              |

Abbreviations: CADTH - Canadian Agency for Drugs and Technologies in Health; FE – Fixed Effects; HAS – Haute Autorité de Santé (HAS); NICE – National Institute of Health and Care Excellence; SMC – Scottish Medicines Consortium

Model 0 is a reference case controlling only for type of marketing authorisation with country and time fixed effects. Disease characteristics and submission history (Model 1), pivotal trial characteristics (Model 2), Uncertainties (Model 3) and Social Value Judgments (Model 4) were added sequentially. Model 5 presents results for cost-effectiveness countries only (excluding France). Odds ratios and robust standard errors adjusted for clustering (in brackets) are reported. Results are pooled across all agencies.

P-Values \*p<0.1; \*\*p<0.05; \*\*\*p<0.01

See supplementary material for regression models without time and agency fixed effects.

### ***Disease Characteristics and Submission History***

In the aggregate sample, HTA approval was marginally higher for oncology drugs (85.0%) vs non-oncology drugs (75.3%). This effect was significant in all multivariate models (1-5), although in model 4 significance was only achieved at a level of  $p < 0.1$  (OR 2.631, 95% CI [0.948-7.27]). HTA approvals were also higher for orphan drugs (94.1%) vs non-orphan drugs (79.2%). In the final model (model 4), this effect was statistically significant (OR 6.22, 95% CI [1.28 – 30.1],  $p = 0.023$ ). Finally, HTA approvals are marginally more likely in drug-indication-agency trios with a previous rejection (85.3%) compared to drugs without previous rejection (82.5%). This effect was significant in all multivariate models (OR 10.223, 95% CI [2.27 – 46.9],  $p = 0.001$ ). Interpretation of magnitude of effect (particularly for orphan status and resubmission status) is limited in later models (3-5), given high robust standard errors and wide confidence intervals.

### ***Clinical Evidence***

The association of pivotal trial characteristics and HTA approvals was mixed across multivariate models. In the aggregate sample, HTA approvals were a) slightly higher for drug-indication-agency trios supported by phase III trials (85.5%) vs phase I or II trials (76%), b) similar for drug-indication-agency trios supported by at least one clinical endpoint (86.3%) vs surrogate (82.1%), and c) slightly higher for drug-indication-agency trios supported with a trial including an active comparator (89.2%) vs placebo control (77.60%). Odds ratios in multivariate models for pivotal trial characteristics are predominantly non-significant with the exception of trial phase, which achieved significance at  $p < 0.05$  in model 4 (OR 3.365, 95% CI [1.01 – 11.2]). Wide confidence intervals are present across all pivotal trial characteristic variables, and were largest in models 3, 4 and 5.

### *Scientific and Social Value Judgements*

Uncertainties showed significant differences for clinical uncertainties overcome, clinical uncertainties not overcome, and economic uncertainties overcome. HTA approvals were more likely to have a higher number of clinical uncertainties overcome (OR 1.504, 95% CI [1.16 – 1.95],  $p=0.002$ ), a lower number of clinical uncertainties not overcome (OR 0.760, 95% CI [0.63 – 0.91],  $p<0.003$ ), and a high number of economic uncertainties overcome (OR 2.431, 95%CI [1.54 – 3.85],  $p<0.001$ ). No significant differences (at  $p<0.05$ ) were detected for number of economic uncertainties not overcome. Relative to other covariates, confidence intervals were narrower for clinical and economic uncertainties and effect sizes were relatively consistent across models. Results remain consistent in model 5, which assessed CEA countries only.

Sub-analysis according to type of clinical and economic uncertainty is provided in Electronic Supplementary Material D. The positive association between the aggregate of clinical uncertainties overcome and HTA outcomes appears to be driven largely by uncertainties in clinical benefit, which showed a significantly positive effect across both models. Overcome uncertainties in clinical evidence also contribute positively, although high robust standard error on the odds ratios limit interpretation of results. Conversely, the negative association between the aggregate clinical uncertainties not overcome and HTA outcomes appears to be driven largely by unresolved uncertainties in clinical benefit, study design, and adverse events, which significantly lower the probability of a positive outcome across both models. The positive association between the aggregate of economic uncertainties overcome is largely driven by overcome uncertainties in modelling. Overcome uncertainties in utilities and cost-effectiveness also contribute positively, although high robust standard error on the odds ratios limit interpretation of results.

Social value judgements were not significantly associated with HTA outcomes. Most SVJs are raised with similar frequency in HTA approvals and rejections. HTA approvals are a) similar when severity is raised (85.6%) vs not raised (80.0%); b) similar when unmet need is raised (82.6%) vs not raised (85.3%); c) similar when administration advantage is raised (86.7%) vs not raised (81.5%); slightly higher when innovation is raised (89.1%) vs not raised (79.6%) and similar when special demographics are raised (83.8%) vs not raised (82.3%). Effects were insignificant in models 4 and 5 for all social value judgements. Widest confidence intervals were present for administration advantage (only raised in 32% of all HTA assessments) and special demographics (only raised in 8.6% of all HTA assessments).

### ***Model Fit***

Pseudo  $R^2$  values suggest that disease characteristics and submission history account for 6.2% of the variation in HTA outcomes. Pivotal trial characteristics account for a further 3.1% of the variation. Scientific value judgements (uncertainties) increased the Pseudo  $R^2$  by a further 15.6%. Social value judgements only accounted for 4.0% of variation and did not contribute substantially to model fit, as shown by only a marginal decrease in the AIC when this group of variables was added. Agency and fixed effects account for approximately 15% of variation (see Electronic Supplementary Material E).

### ***Inter-Agency Effects***

The interaction of a set number of predictors with agency dummies is presented in Table 4. Conditional approval appears to reduce the probability of approval across each agency, although no effects were statistically significant. All agencies also appear to favour oncology drugs, although only INESSS showed significance (at  $p < 0.1$ ). CADTH, INESSS, SMC and NICE appear to favour orphan drugs in HTA approvals over non-orphan drugs. The effect of

uncertainties is consistent across most agencies with clinical and economic uncertainties overcome increasing the probability of approval, clinical uncertainties not overcome reducing the probability of approval, and no effect shown for economic uncertainties not overcome. The exception was HAS, where no significance was seen for uncertainties.

### **Survival Analysis of Time from Marketing Authorisation to Positive HTA Outcome**

Results from survival analysis for the pooled sample and agency specific models are presented in Figure 2. Within the pooled sample, and in each of the agency-specific models, conditionally approved drugs have a longer median time to HTA approval than standard approval drugs. The difference was statistically significant in the pooled sample (median time from MA to HTA approval of 458 days (conditional) vs 265 days (standard),  $p < 0.001$ ), in CADTH (median time from MA to HTA approval of 391 days (conditional) vs 144 days (standard),  $p=0.01$ ) and HAS (median time from MA to HTA approval of 338 days (conditional) vs 229 days (standard),  $p=0.01$ ). Differences were non-significant in INESSS (605 days (conditional) vs 511 days (standard)), NICE (583 days (conditional) vs 385 days (standard)), and SMC (323 days (conditional) vs 263 days (standard)).

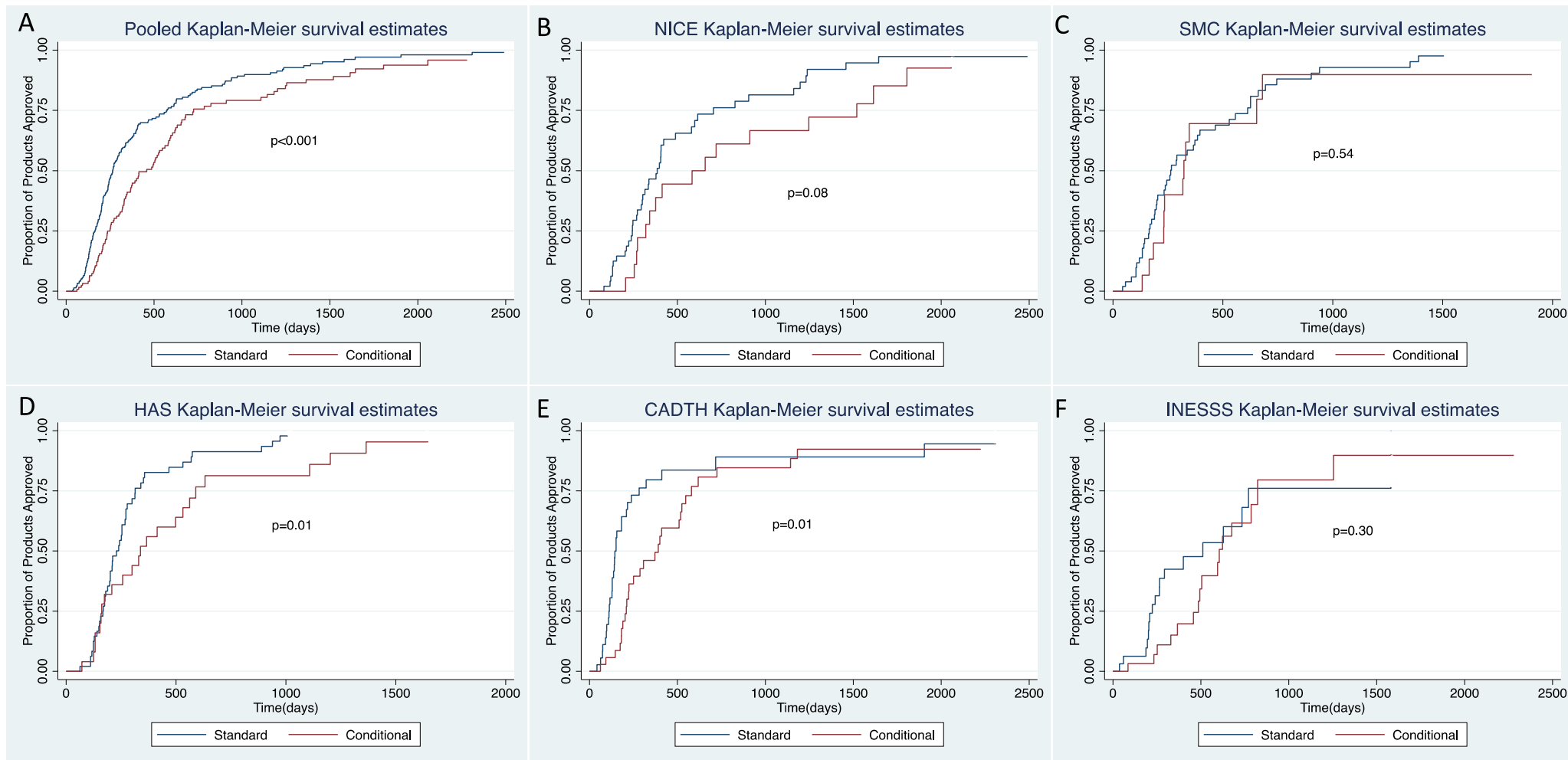
Table 4 – Average marginal effects of selected predictor variables interacting with agency dummies

| <b>Average Marginal Effects (dydx) – Interaction of Predictors with Agency</b> |                   |                   |                     |                    |                  |                        |                       |                        |                    |
|--|-------------------|-------------------|---------------------|--------------------|------------------|------------------------|-----------------------|------------------------|--------------------|
|  | Type of MA        | Cancer            | Orphan              | Trial Phase        | Comparator       | Clinical Uncertainties |                       | Economic Uncertainties |                    |
|  |                   |                   |                     |                    |                  | Overcome               | Not-overcome          | Overcome               | Not-overcome       |
| <b>CADTH</b>   | -0.044<br>(0.048) | 0.104<br>(0.067)  | 0.118***<br>(0.038) | 0.136*<br>(0.078)  | 0.018<br>(0.035) | 0.040***<br>(0.014)    | - 0.027***<br>(0.009) | 0.088***<br>(0.121)    | - 0.017<br>(0.012) |
| <b>INESSS</b>  | -0.079<br>(0.085) | 0.130*<br>(0.071) | 0.217***<br>(0.082) | 0.167**<br>(0.083) | 0.037<br>(0.070) | 0.055***<br>(0.015)    | - 0.037***<br>(0.011) | 0.121***<br>(0.029)    | - 0.023<br>(0.017) |
| <b>HAS</b>   | -0.009<br>(0.012) | 0.032<br>(0.025)  | 0.028<br>(0.023)    | 0.042<br>(0.035)   | 0.007<br>(0.014) | 0.011<br>(0.007)       | - 0.007<br>(0.005)    | -                      | -                  |
| <b>SMC</b>   | -0.038<br>(0.045) | 0.077<br>(0.050)  | 0.111**<br>(0.049)  | 0.097<br>(0.060)   | 0.018<br>(0.035) | 0.028**<br>(0.012)     | - 0.019**<br>(0.007)  | 0.060***<br>(0.021)    | - 0.011<br>(0.008) |
| <b>NICE</b>  | -0.033<br>(0.038) | 0.060<br>(0.037)  | 0.094**<br>(0.046)  | 0.077*<br>(0.042)  | 0.015<br>(0.029) | 0.022***<br>(0.008)    | - 0.015***<br>(0.005) | 0.050***<br>(0.013)    | - 0.009<br>(0.007) |
| <b>Number of observations</b>  | 323               | 323               | 323                 | 323                | 323              | 323                    | 323                   | 256                    | 256                |

Abbreviations – MA – Marketing authorisation

Average marginal effects of Type of Marketing authorization after interacting with agency dummies, controlling only for agency and time fixed effects. Average marginal effects of Cancer, Orphan, Trial Phase, Comparator, Clinical Uncertainties, and Economic Uncertainties after interacting with agency dummies, controlling for covariates specified in model [4].

P-Values \*p<0.1; \*\*p<0.05; \*\*\*p<0.01



**Figure 2 - Kaplan Meier plots of HTA approval time conditional approval and standard approval drug-indication-agency trios, defined as time from marketing authorisation to HTA approval.** A – HTA approval time of conditional vs standard approval products in pooled sample. B – HTA approval time of conditional vs standard approval products in NICE, C – HTA approval time of conditional vs standard approval products in SMC. D – HTA approval time of conditional vs standard approval products in HAS. E – HTA approval time of conditional vs standard approval products in CADTH. F – HTA approval time of conditional vs standard approval products in INESSS. Abbreviations: CADTH - Canadian Agency for Drugs and Technologies in Health, HAS – Haute Autorité de Santé (HAS), NICE – National Institute of Health and Care Excellence, SMC – Scottish Medicines Consortium.

## **DISCUSSION**

Availability of innovative medicines across settings remains extremely fragmented [14]. With a rising number of targeted therapies, personalised medicines, immunotherapies and cell and gene therapies under development, policy makers must take appropriate steps to ensure that patients do not face unnecessary delays in access to life-saving treatments [2]. At the same time, financing of healthcare must be sustainable and health insurers must make coverage decisions with confidence that they are allocating resources in an optimal way [51]. Conditional approval pathways provide an excellent case study for exploring this trade-off, requiring HTA agencies to contend with higher levels of uncertainty in their decision-making.

This paper provided a meta-analysis of HTA coverage decisions for 80 drug-indication pairs, 40 of which received conditional marketing authorisation, and 40 which received standard marketing authorisation, across five HTA agencies. Our empirical approach to analysing HTA outcomes provides an important preliminary contribution to our understanding of how scientific and social value judgements shape HTA decision-making, which will benefit from further validation across other settings and larger cohorts of drug-indication pairs. Further, our multi-country approach validates previous findings that agencies vary systematically in their interpretation and assessment of health technologies. There are a number of important take-aways from our results.

### **HTA agencies raise uncertainties more frequently for conditionally approved drugs**

First, conditionally approved drugs in our sample had a higher average number of unresolved clinical and economic uncertainties raised relative to standard approval drugs. A wide range of clinical issues or uncertainties are raised during HTA, including but not limited to uncertainty in magnitude of clinical benefit, absence of clinical evidence, inadequate study design, limitations in indirect comparisons, and issue in generalisability of trial results. In an attempt



to measure the extent to which this weaker evidence base translates into a higher level of uncertainty during HTA, decision text was qualitatively analysed to identify different types of clinical and economic uncertainties. This enables us to a) examine the frequency with which different clinical and economic are raised, and b) explore the association between uncertainties and HTA outcomes. While we are not able to assign specific weights of individual uncertainties on decision-making, our findings that conditionally approved drugs have a higher average number of unresolved clinical uncertainties are consistent with the differences seen in pivotal trial characteristics.

Fundamentally, conditionally approved drugs are expected to have weaker evidence bases than standard approval drugs, given the respective regulatory requirements [10,11]. Our univariate analysis provides validation of previous literature on the extent of the evidence gap [29-32] showing that conditionally approved drugs are less likely to have a phase III trial design, less likely to utilise a clinical endpoint and less likely to include a direct comparator. The potential impact of this difference in clinical evidence, both in terms of development time and cost, is significant, ranging from US\$ 1.4 to US\$ 6.6 million for phase 1 trials, US\$ 7.0 to US\$ 19.6 million for phase II trials and US\$ 11.5 to US\$ 52.9 million depending on therapeutic area [52]. Inclusion of clinical endpoints, such as overall survival, can dramatically increase the length, and cost of a trial [53]. In the absence of HTA (i.e. in the USA), conditional approval, when paired with other accelerated marketing authorisation pathways such as priority review, reduces clinical development time by an average of nearly two years [33].

### **HTA barriers for conditionally approved drugs?**

Second, our results indicate that conditional approval drugs likely face increased barriers at HTA level relative to standard approval drugs, although interpretation of the size of effect is limited by study sample size and frequency of HTA rejections (only 17.1% of evaluations).

HTA barriers were measured in two ways: first, whether conditionally approved drugs have an increased probability of rejection at HTA level; and second, whether conditionally approved drugs face delays in receiving HTA approval. Based on the conceptual framework and results of the univariate analysis, conditionally approved drugs were predicted to have characteristics that both improved probability of approval (unmet need and disease severity) and reduced probability of approval (orphan status, pivotal trial characteristics, number of clinical uncertainties not overcome).

The alignment of our empirical results with the conceptual framework informing this study was mixed. Pivotal trial characteristics, which were expected to have a positive impact on HTA outcomes predominantly did not exhibit a significant effect in multi-variate models and only account for a marginal part of the variation in the sequential models. There are some indications that trial phase contributes positively towards HTA approval, however there is considerable uncertainty in the magnitude of effect (given high standard error and wide confidence intervals). A marginal or limited impact of pivotal trial characteristics is consistent with findings from previous single-setting studies of HTA outcomes in France and England [22,24].

The impact of scientific value judgements on HTA outcomes was more closely aligned with hypothesised effects. Drugs with higher unresolved clinical uncertainty, particularly surrounding clinical benefit, study design and adverse events, face a significantly lower probability of HTA approval, an effect which holds in each HTA agency apart from HAS. However analysis of marginal effects in the HAS is likely limited by a small number of rejections in the sample (n=2). Meanwhile, uncertainties that were dismissed by HTA agencies (clinical and economic overcome) had a positive impact on probability of HTA approval, an effect which again holds in each HTA agency apart from HAS. Overall, the strength of

evidence was highest for this group of variables, given the total proportion of variance explained and relatively low robust standard errors.

These findings suggest that the interpretation of evidence, rather than the evidence itself drives decision-making at HTA level (i.e. a phase II single arm trial may or may not be acceptable depending on the disease context). This narrative is aligned with a recent study which found a positive correlation between HTA outcomes and implementation of managed entry agreements (tools which help to mitigate clinical and economic uncertainty) [28]. Health systems have a wide range of managed-entry tools available to them to help mitigate clinical and economic uncertainties, including outcome-based payment, price-volume-caps, and coverage with evidence development [54,55]. In theory, one might expect that managed entry agreement implementation would occur more frequently with conditionally approved drugs to mitigate higher levels of uncertainty. Within our sample, the presence of managed entry agreement (patient access scheme or commercial access agreement) was recorded for NICE and SMC (CADTH and INESSS are advisory bodies without direct links to healthcare payers, while HAS evaluations are issued independently of managed entry agreements). The vast majority of positive HTA outcomes in NICE and SMC included a patient access scheme (98% and 91% respectively). While all conditionally approved drugs had managed entry agreements, the high frequency of application in the standard approval cohort prevents us from drawing meaningful conclusions about their differential application across type of marketing authorisation. Further, the terms of managed entry agreements in both settings are commercial in confidence, limiting our ability to fully assess how these tools can mitigate additional uncertainty present in conditionally approved drugs.

Surprisingly, no association was detected between social value judgements and HTA outcome. Unmet need and disease severity, key eligibility criteria for conditional approval pathways,

were predicted to have a positive impact on the probability of HTA approval. These findings contrast with previous case study analysis which indicate that social value judgements render clinical and economic certainties more acceptable [56]. Indeed, supplementary analysis (Electronic Supplementary Material D) exploring the association of SVJs and uncertainties indicate that disease severity, unmet need, innovation and quality of life are positively associated with the total number of clinical uncertainties overcome. The absence of effect on HTA outcomes could partially be explained by imprecision in the model estimates, which consider social value judgements as a binary variable, while the true effect of these parameters may be variable or weighted. Alternatively, this could reflect a lack of statistical power to detect significant effects.

Univariate analysis indicates that conditional approval is associated with a reduced probability of HTA approval across the aggregate sample. Interestingly, the effect lost significance in the multi-variate model after adding country and fixed effects, signalling that effect size is likely small and that the model may be underpowered to detect positive associations of existing variables. Analysis of average marginal effects suggest a tendency for each agency to be biased against conditionally approved drugs, although no significance was reached. This highlights the need to validate findings in larger cohorts of drugs and other settings.

Finally, conditionally approved drugs face marginal delays (on average 6 months longer) in receiving HTA approval relative to standard marketing authorisation drugs. In theory, delays from receipt of marketing authorisation to receipt of HTA approval can occur through three broad mechanisms: 1) initial rejection requiring resubmission for HTA approval, 2) delays in HTA review and 3) delays in manufacturer submission.

Evidence from our dataset does not provide strong support of the first mechanism, given only marginal and non-statistically significant increases in the number resubmissions for

conditionally approved drugs vs standard approval (21.6% of conditionally approved drugs had multiple submissions vs 15.7% of standard approval). It is possible that review timelines are longer for drugs with conditional approval. Despite published target timelines for HTA review across each of the included HTA agencies, a number of factors can delay the HTA process including requirements for supplemental data, requirements for revisions to economic modelling, and clinical expert and patient consultation [57].

Launch times for pharmaceuticals have been shown to relate to market size [58,59], firm size [60] firm location [61,62] and price controls (external reference pricing) [59]. While these factors may help to explain inter-agency differences in average time from MA to HTA, they do not offer an explanation for differences in HTA approval timelines of conditional drugs vs standard approval drugs. Perceived institutional barriers to entry at HTA level may result in submission delays, as manufacturers seek to avoid initial rejections and resubmissions. Manufacturers with immature clinical evidence, provided there is transparency and awareness of HTA evidence requirements, may elect to delay submission until more mature clinical evidence is available. Greater involvement of HTA agencies earlier in clinical development pathways through the use of joint-early dialogue and scientific advice may help to clarify evidence requirements and avoid unnecessary delays in HTA approval [63].

### **Strengths and limitations**

This study relies on a meta-analysis of 339 HTA decisions, spanning 5 HTA agencies and 80 drug-indication pairs. The mixed-methods approach enabled collection of an extensive set of variables relating to scientific and social value judgements, providing novel insights on determinants of HTA decision-making. To the best of our knowledge this is the first empirical study that examines health technology assessment of conditionally approved drugs in comparison to a cohort of standard approval medicines. Our study a) provides important

insights to health regulators, insurers, policy makers, and pharmaceutical companies; and b) offers a methodological approach towards future research on health technology assessment.

The present study is not without limitations. Unavoidably, the small number of conditionally approved drugs present across Europe and Canada limits our sample size. There was a low frequency of HTA rejections within the sample, which places limitations on the precision of model estimates and statistical power. This is evident in the later multivariate models where some covariates have high odd ratios and wide confidence intervals. While the effect of variable groups on explaining variance in HTA outcome are still informative, individual effect sizes in the multivariate model must be interpreted with caution and model power may not have been sufficient to detect all relevant effects. The external validity of findings may be limited by sample selection of standard approval drugs (matching according to therapeutic area and over time) and agency selection. Inclusion of all standard approval drug-indication pairs was not feasible given the extent of data that is collected for each HTA evaluation. Further research including other settings and a more recent sample of drugs would help to validate findings. Finally, exclusion of conditionally approved drugs without HTA assessments (and therefore without HTA data) may bias findings on the extent to which conditionally approved drugs face barriers at HTA level. Manufacturers may elect not to submit drugs that are unlikely to receive HTA approval. Further research is needed to investigate the characteristics of non-submitted conditionally approved drugs.

## **CONCLUSIONS**

Our empirical results indicate that conditionally approved drugs likely face increased barriers at HTA level relative to drugs with standard marketing authorisation, both in terms of HTA outcomes and time to HTA approval. Conditionally approved drugs tend to have lower levels of clinical evidence than drugs with standard marketing authorisation, which likely translates

into a higher level of clinical and economic uncertainties at HTA level and reduced probability of HTA approval. Delays in HTA approval may offset some of the reductions in clinical development time facilitated by the conditional approval pathway. Greater and earlier involvement of HTA agencies in scientific advice processes should be explored as an option to clarify evidence requirements and help to mitigate delays in HTA approval.

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## Electronic Supplementary Material A – Overview of Regulatory and HTA systems

**Table A1 – Comparison of Marketing authorisation and HTA systems across England, Scotland, France, and Canada**

|  | England   | Scotland      | France                  | Canada (Ontario)  | Canada (Quebec)  |
|--|---|---------------|-------------------------|---|------------------|
| <b>A. Regulatory System</b>                    |   |               |                         |   |                  |
| Agency   | European Medicines Agency (EMA)   |               |                         | Health Canada   |                  |
| Conditional Approval Pathway                   | Conditional Marketing Authorisation (CMA)   |               |                         | Notice of Compliance with Conditions (NOC/C)  |                  |
| Conditional Approval Criteria                  | 1. Medicinal products which aim at the treatment, the prevention or the medical diagnosis of seriously debilitating diseases or life-threatening diseases;<br>2. medicinal products to be used in emergency situations, in response to public health threats duly recognised either by the World Health Organisation or by the Community in the framework of Decision No 2119/98/EC; or<br>3. medicinal products designated as orphan medicinal products in accordance with Article 3 of Regulation (EC) No 141/2000. |               |                         | Promising new drug therapies intended for the treatment, prevention or diagnosis of serious, life-threatening or severely debilitating diseases or conditions for which a) there is no alternative therapy available on the Canadian market or, b) where the new product represents a significant improvement in the benefit/risk profile over existing products. |                  |
| <b>B. HTA System</b>                           |   |               |                         |   |                  |
| Agency   | NICE  | SMC           | HAS                     | CADTH   | INESSS           |
| Products selection                             | By submission   | By submission | All authorized products | By submission   | By submission    |
| Publicly available decision reports (language) | Yes (English)   | Yes (English) | Yes (French)            | Yes (English)   | Yes (French)     |
| Clinical evaluation                            | Yes   | Yes           | Yes                     | Yes   | Yes              |
| Economic evaluation                            | Yes   | Yes           | No <sup>1</sup>         | Yes   | Yes <sup>2</sup> |

|                           |                      |                      |                       |                       |                       |
|---------------------------|----------------------|----------------------|-----------------------|-----------------------|-----------------------|
| Type of decision          | Binding <sup>3</sup> | Binding <sup>4</sup> | Advisory <sup>5</sup> | Advisory <sup>6</sup> | Advisory <sup>7</sup> |
| Target review time        | 12 months            | 6 months             | 3 months              | 6 months              | 6 months              |
| Parallel review available | Yes                  | No                   | No                    | Yes                   | Yes                   |

Abbreviations: CADTH - Canadian Agency for Drugs and Technologies in Health; EC- European Commission; HAS – Haute Autorité de Santé; INESS - The Institut national d'excellence en santé et en services sociaux; NICE – National Institute of Health and Care Excellence; SMC – Scottish Medicines Consortium.

Source: The authors, based on a review of regulatory and HTA websites across France, England, Scotland, and Canada.

<sup>1</sup> Cost-effectiveness is not considered as a key criterion during HTA evaluation by the HAS. Products claiming an ASMR (Improvement in medical service rendered) of III or higher must submit an economic dossier which may be used to inform price negotiations following completion of HTA.

<sup>2</sup> Economic evaluation is only appraised by INESSS if the agency determines there is clinically meaningful benefit.

<sup>3</sup> Positively recommended products must be made available to patients by the NHS within 3 months of the decision.

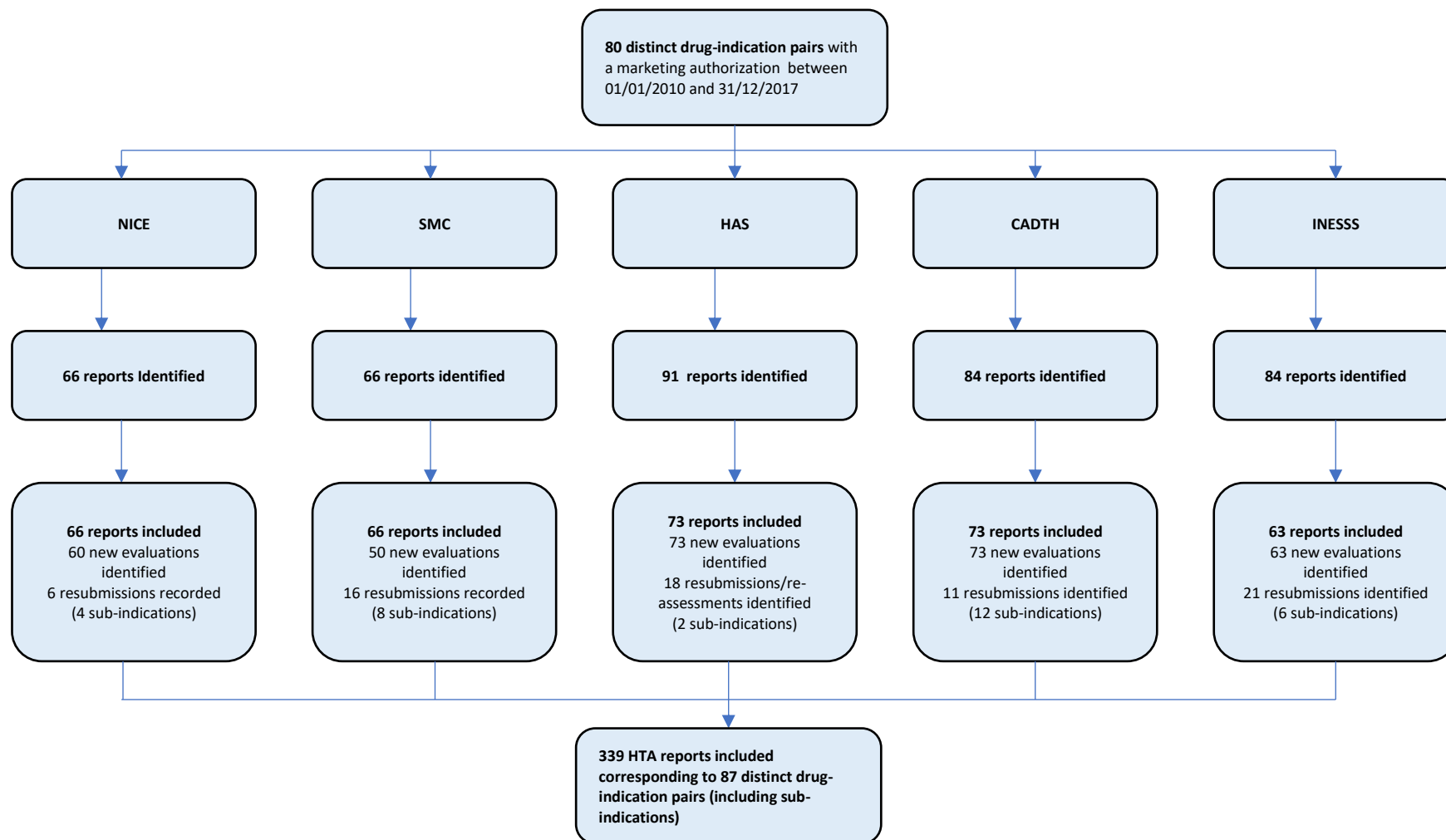
<sup>4</sup> SMC informs NHS boards of positively recommended products four weeks before publishing a decision in order to provide preparation time for introduction of a new medicine in health boards.

<sup>5</sup> The Ministry of Health makes final decisions on reimbursement of a new medicine, according to recommendations from the Transparency committee with HAS and pricing negotiations with the Economic Committee of Healthcare Products (CEPS).

<sup>6</sup> Pricing and reimbursement decisions are made at provincial level. Provinces in Canada (excluding Quebec) use CADTH recommendations to inform decision-making.

<sup>7</sup> The Ministry of Health and Social Services in Quebec makes final pricing and reimbursement decisions based on recommendations from INESSS.

## Electronic Supplementary Material B – Identification of HTA Reports



CADTH - Canadian Agency for Drugs and Technologies in Health; HAS – Haute Autorité de Santé; INESSS - The Institut national d'excellence en santé et en services sociaux; NICE – National Institute of Health and Care Excellence; SMC – Scottish Medicines Consortium

**Figure B1 – Identification of matching HTA reports in NICE, SMC, HAS, CADTH and INESSS.** NICE, SMC, HAS, CADTH, and INESSS websites were screened to identify all matching reports for the 80 included drug-indication pairs between 01/01/2010 and 31/12/2019. Identification and selection of matching reports was performed by two separate reviewers, with any disagreements resolved by a third reviewer. In the event an HTA agency split an indication into multiple sub-indications and conducted separate evaluations on the distinct sub-indications, both reports were included. In the event of a resubmission following an initial rejection, only the most recent evaluation is included. Minor re-assessments following initial positive recommendation are excluded (E.g. for a new dosage form or a re-evaluation of ASMR in the HAS).

**Table B1 – Breakdown of HTA recommendations for included drug-indication-agency trios**

| NICE                              |              |        | SMC                     |              |        | CADTH                        |              |   | INESSS                        |              |   |
|-----------------------------------|--------------|--------|-------------------------|--------------|--------|------------------------------|--------------|---|-------------------------------|--------------|---|
| HTA rejection                     | HTA approval |        | HTA rejection           | HTA approval |        | HTA rejection                | HTA approval |   | HTA rejection                 | HTA approval |   |
| DNL<br>7                          | LWC<br>58    | L<br>1 | DNL<br>8                | LWC<br>53    | L<br>5 | DNL                          | LWC<br>53    | L | DNL                           | LWC          | L |
| <b>HAS<sup>1</sup></b>            |              |        |                         |              |        |                              |              |   |                               |              |   |
| HTA rejection<br>SMR Insufficient |              |        | HTA approval<br>SMR Low |              |        | HTA approval<br>SMR Moderate |              |   | HTA approval<br>SMR Important |              |   |
| 2                                 |              |        | ASMR I                  | 0            |        | ASMR I                       | 0            |   | ASMR I                        | 0            |   |
|                                   |              |        | ASMR II                 | 0            |        | ASMR II                      | 0            |   | ASMR II                       | 4            |   |
|                                   |              |        | ASMR III                | 0            |        | ASMR III                     | 0            |   | ASMR III                      | 19           |   |
|                                   |              |        | ASMR IV                 | 0            |        | ASMR IV                      | 3            |   | ASMR IV                       | 26           |   |
|                                   |              |        | ASMR V                  | 7            |        | ASMR V                       | 0            |   | ASMR V                        | 12           |   |

ASMR – Added Medical Service Rendered; CADTH - Canadian Agency for Drugs and Technologies in Health; HAS – Haute Autorité de Santé; INESS - The Institut national d'excellence en santé et en services sociaux; NICE – National Institute of Health and Care Excellence; SMC – Scottish Medicines Consortium; SMR – Medical Service Rendered.

<sup>1</sup> The HAS issues an SMR rating, which determines the reimbursement level and an ASMR rating which determines level of added benefit. There are four possible SMR values: insufficient (0% reimbursement), Low (15% reimbursement), Moderate (30% reimbursement), Important (65% reimbursement). There are five levels of ASMR: ASMR I, II, III (eligible for price negotiations), ASMR IV (price parity to standard of care), ASMR V (priced lower than standard of care).



## Electronic Supplementary Material C – Full List of Included Drug Indication Pairs

### Conditionally Approved Drug Indication Pairs

| Molecule name       | Brand name | Indication   |
|---------------------|------------|--|
| Alectinib           | Alecensaro | As monotherapy for the treatment of patients with anaplastic lymphoma kinase (ALK) positive, locally advanced or metastatic non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib  |
| Asfotase alfa       | Strensiq   | As long-term enzyme therapy in patients with hypophosphatasia in the childhood and adolescent age to treat the bone manifestations of the disease.   |
| Ataluren            | Translarna | For the treatment of Duchenne muscle dystrophy, resulting from a nonsense mutation in the dystrophin gene, in ambulatory patients 5 years of age or more   |
| Avelumab            | Bavencio   | As monotherapy for the treatment of adult patients with metastatic Merkel cell carcinoma (MCC).  |
| Bedaquiline         | Sirturo    | For use as part of an appropriate combination regimen for pulmonary multidrug resistant tuberculosis (MDR TB) in adult patients when an effective treatment regimen cannot otherwise be composed for reasons of resistance or tolerability.  |
| Blinatumomab        | Blinicyto  | For previously treated Philadelphia-chromosome-negative acute lymphoblastic leukaemia  |
| Bosutinib           | Bosulif    | For the treatment of adult patients with chronic phase (CP), accelerated phase (AP), and blast phase (BP) Philadelphia chromosome positive chronic myelogenous leukaemia (Ph+ CML), previously treated with one or more tyrosine kinase inhibitor(s) and for whom imatinib, nilotinib and dasatinib are not considered appropriate treatment options |
| Brentuximab Vedotin | Adcetris   | For the treatment of adult patients with relapsed or refractory CD30+ Hodgkin lymphoma (HL): following autologous stem cell transplant (ASCT) or following at least two prior therapies when ASCT or multi-agent chemotherapy is not a treatment option.   |
| Brentuximab Vedotin | Adcetris   | For the treatment of adult patients with relapse or refractory systemic large cell anaplastic lymphoma (sALCL).  |
| Cabozantinib        | Cometriq   | For the treatment of medullary thyroid carcinoma in adult patients with progressive, non-resectable, locally advanced or metastatic disease.   |
| Ceritinib           | Zykadia    | For treating adult patients with anaplastic lymphoma kinase (ALK) positive advanced non-small-cell lung cancer (NSCLC) previously treated with crizotinib  |
| Crizotinib          | Xalkori    | For the treatment of advanced non-small cell lung cancer (NSCLC) with positive anaplastic lymphoma kinase (ALK+) for adult patients previously treated with at least one other lung cancer treatment   |
| Daclatasvir         | Daklinza   | In combination with sofosbuvir (SOF), be reimbursed for the treatment of patients with genotype 3 chronic hepatitis C (CHC)  |
| Daratumumab         | Darzalex   | As a monotherapy for the treatment of adult patients with recurrent and refractory multiple myeloma who have already been treated with a proteasome inhibitor and an immune modulator and have shown a disease progression during the last therapy.  |
| Delamanid           | Delyba     | for use as part of an appropriate combination regimen for pulmonary multi-drug resistant tuberculosis (MDR-TB) in adult patients when an effective treatment regimen cannot otherwise be composed for reasons of resistance or tolerability.   |
| eculizumab          | Soliris    | For the treatment of patients with atypical hemolytic uremic syndrome (atypical HUS) to inhibit complement-mediated thrombotic microangiopathy   |

|  |           |   |
|--|-----------|---|
| Everolimus   | Votubia   | For the treatment of patients aged 3 years and older with subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis complex (TSC) who require therapeutic intervention but are not amenable to surgery.   |
| ex vivo expanded autologous human corneal epithelial cells containing stem cells | Holoclar  | Treatment of patients with moderate-severe (superficial corneal neovascularisation in at least two quadrants) limbal stem cell deficiency, unilateral or bilateral with a minimum of 1-2 mm <sup>2</sup> of undamaged limbus, due to ocular burns.  |
| Fampridine   | Fampyra   | For the improvement of walking ability of adult patients with multiple sclerosis (MS) with walking impairment (EDSS 4-7).   |
| Ibrutinib  | Imbruvica | For the treatment of patients with relapsed/refractory mantle cell lymphoma (MCL)   |
| Idelalisib   | Zydelig   | For the treatment of relapsed/refractory follicular lymphoma (FL) that has progressed despite prior treatment with rituximab and an alkylating agent.   |
| Nivolumab  | Opdivo    | For the treatment of adult patients with classical Hodgkin Lymphoma (cHL) that has relapsed or progressed after: autologous stem cell transplantation (ASCT) and brentuximab vedotin, or 3 or more lines of systemic therapy including ASCT,  |
| Nivolumab  | Opdivo    | As a monotherapy or in combination with Yervoy in adults for the treatment of advanced (non-resectable or metastatic) melanoma.   |
| Obeticholic Acid   | Ocaliva   | For treating primary biliary cholangitis in combination with ursodeoxycholic acid for people whose disease has responded inadequately to ursodeoxycholic acid or as monotherapy for people who cannot tolerate ursodeoxycholic acid.  |
| Ofatumumab   | Arzerra   | To treat, in combination with chlorambucil or bendamustine, patients with CLL who have not received prior treatment and who are not suitable for fludarabine-based treatment (a type of cellular toxicity)  |
| Olaparib   | Lynparza  | As a monotherapy (alone) for maintenance therapy for ovarian cancer recurrence in patients with a specific mutation, BRCA   |
| Olaratumab   | Lartruvo  | In combination with doxorubicin for the treatment of adult patients with advanced soft tissue sarcoma who are not amenable to curative treatment with surgery or radiotherapy and who have not been previously treated with doxorubicin   |
| Osimertinib  | Tagrisso  | For the treatment of adult patients with locally advanced or metastatic epidermal growth factor receptor (EGFR) T790M mutation-positive non-small cell lung cancer (NSCLC) who have progressed on or after EGFR TKI therapy   |
| Palbociclib  | Ibrance   | Used in patients with hormone receptor (HR) positive, human epidermal growth factor receptor 2 (HER2) negative locally advanced or metastatic breast cancer   |
| parathyroid hormone  | Natpar    | For adjuvant therapy in adult patients with chronic hypoparathyroidism which cannot be adequately controlled by conventional treatment alone.   |
| Pazopanib  | Votrient  | In adults for the first-line treatment of advanced renal-cell carcinoma (RCC) and for patients who have received prior cytokine therapy for advanced disease.   |
| Pembrolizumab  | Keytruda  | As a monotherapy for the treatment of advanced (non-resectable or metastasizing) melanoma in adults.  |
| Pembrolizumab  | Keytruda  | For the treatment of locally advanced or metastatic non-small cell lung cancer (NSCLC) with PD-L1 expressing tumors after prior chemotherapy in adults. Patients with EGFR- or ALK-positive tumor mutations should already have received a therapy approved for these mutations prior to therapy with KEYTRUDA. |

|                 |           |   |
|-----------------|-----------|---|
| Pixantrone      | Pixuvri   | As monotherapy for the treatment of adult patients with multiply relapsed or refractory aggressive Non Hodgkin B cell Lymphomas (NHL). The benefit of pixantrone treatment has not been established in patients when used as fifth line or greater chemotherapy in patients who are refractory to last therapy. |
| Ponatinib       | Iclusig   | For the treatment of two types of blood cancer, chronic myeloid leukemia (KML) and Philadelphia chromosomal acute lymphocytic leukemia (Ph + ALL)   |
| Romidepsin      | Istodax   | For the treatment of recurrent peripheral T lymphoma or refractory, in people:•who are not eligible for a hematopoietic stem cell transplant at time of initiation of treatment;and•whose performance status according to ECOG is 0 to 2  |
| Sebelipase alfa | Kanuma    | For the treatment of infants, children, and adults diagnosed with LAL deficiency.   |
| Vandetanib      | Caprelsa  | For the treatment of aggressive and symptomatic medullary thyroid cancer (MTC) in patients with unresectable locally advanced or metastatic disease   |
| Venetoclax      | Venclexta | For the treatment of patients with chronic lymphocytic leukemia (CLL) with 17p deletion who have received at least one prior therapy, or patients with CLL without 17p deletion who have received at least one prior therapy and for whom there are no other available treatment options.                       |
| Vismodegib      | Erivedge  | Erivedge is indicated for the treatment of adult patients with: - symptomatic metastatic basal cell carcinoma or - locally advanced basal cell carcinoma inappropriate for surgery or radiotherapy  |

#### Standard Approval Drug Indication Pairs

| Molecule name       | Brand name | Indication  |
|---------------------|------------|---|
| Afatinib            | Giotrif    | For treatment of locally advanced or metastatic non-small cell lung cancer with mutations of epidermal growth factor receptor (EGFR) previously untreated with other EGFR tyrosine kinase inhibitors  |
| Atezolizumab        | Tecentriq  | For the treatment of adult patients with locally advanced or metastatic non small cell lung cancer (NSCLC) after prior chemotherapy.  |
| Axitinib            | Inlyta     | Treating adults with advanced renal cell carcinoma after failure of treatment with a first-line tyrosine kinase inhibitor or a cytokine   |
| Bevacizumab         | Avastin    | In combination with carboplatin and paclitaxel for 'the front-line treatment of advanced (International Federation of Gynaecology and Obstetrics [FIGO] stages IIIB, IIIC and IV) epithelial ovarian, fallopian tube or primary peritoneal cancer   |
| Bevacizumab         | Avastin    | In combination with carboplatin and gemcitabine for 'treatment of adult patients with first recurrence of platinum-sensitive epithelial ovarian, fallopian tube or primary peritoneal cancer who have not received prior therapy with bevacizumab or other VEGF inhibitors or VEGF receptor-targeted agents |
| Bortezomib          | Velcade    | In combination with dexamethasone, or with dexamethasone and thalidomide for the induction treatment of adult patients with previously untreated multiple myeloma, who are eligible for high-dose chemotherapy with haematopoietic stem cell transplantation  |
| Brentuximab Vedotin | Adcetris   | the treatment of adult patients with Hodgkin Lymphoma (HL) at increased risk of relapse or progression following autologous stem cell transplantation (ASCT).   |
| Cabozantinib        | Cabometyx  | For the treatment of advanced renal cell carcinoma (RCC) in adults following prior vascular endothelial growth factor (VEGF)-targeted therapy   |
| Carfilzomib         | Kyprolis   | In combination with dexamethasone alone in the treatment of patients with relapsed multiple myeloma who have received 1 to 3 prior lines of therapy   |

|                             |           |   |
|-----------------------------|-----------|---|
| Cobimetinib                 | Cotellic  | In combination with vemurafenib, for the treatment of patients with unresectable or metastatic melanoma with BRAF V600 mutation   |
| Ceritinib -2                | Zykadia   | The first-line treatment of adult patients with ALK-positive locally advanced (not amenable to curative therapy) or metastatic NSCLC,   |
| Dabrafenib                  | Tafinlar  | As monotherapy for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation.  |
| Elosulfase alfa             | Vimizim   | For the treatment of mucopolysaccharidosis type IVA (MPS IVA)   |
| Eltrombopag                 | Revolade  | For the treatment of adult chronic immune (idiopathic) thrombocytopenic purpura (ITP) in patients who have had a splenectomy and whose condition is refractory to other treatments (for example, corticosteroids or intravenous immunoglobulins), and as a second-line treatment for patients who have not had a splenectomy because surgery is contraindicated |
| Enzalutamide                | Xtandi    | For the treatment of adult men with metastatic castration-resistant prostate cancer whose disease progresses during or after chemotherapy with docetaxel.   |
| Everolimus                  | Afinitor  | For treatment of postmenopausal women with hormone receptor-positive advanced breast cancer in combination with exemestane, after progression or recurrence (failure) on NSA therapy.   |
| Ibrutinib                   | Imbruvica | For previously treated chronic lymphocytic leukaemia and untreated chronic lymphocytic leukaemia with 17p deletion or TP53 mutation   |
| Idelalisib                  | Zydelig   | In combination with rituximab for the treatment of adult patients with chronic lymphocytic leukaemia (CLL): • who have received at least one prior therapy, or • as first line treatment in the presence of 17p deletion or TP53 mutation in patients unsuitable for chemo-immunotherapy  |
| Linacotide                  | Constella | For the symptomatic treatment of moderate to severe irritable bowel syndrome with constipation (RDS-O) in adults.   |
| Lisdexamfetamine Dimesilate | Elvanse   | As part of an overall therapeutic strategy for the treatment of attention deficit Hyperactivity Disorders (ADHD) in children aged six years of age if the response to a previously obtained treatment with methylphenidate is considered clinically unsatisfactory.   |
| Midostaurin                 | Rydapt    | In combination with standard induction and consolidation chemotherapy followed by Rydapt single agent maintenance therapy for adult patients with newly diagnosed acute myeloid leukaemia (AML) who are Fms-like tyrosine kinase receptor-3 (FLT3) mutation-positive;   |
| Migalastat                  | Galafold  | For the sustained treatment of adults and adolescents from 16 years of age and older with confirmed Fabry's disease ( $\alpha$ -galactosidase A deficiency), which have a mutation responsive to the treatment  |
| Nintedanib                  | Ofev      | For the treatment of idiopathic pulmonary fibrosis (IPF)  |
| Nintedanib                  | Vargatef  | In combination with docetaxel for the treatment of adult patients with locally advanced, metastatic or locally recurrent non-small-cell lung carcinoma (NSCLC) with adenocarcinoma histology after first-line chemotherapy.   |
| Nivolumab                   | Opdivo    | In adult patients with locally advanced or metastatic non-squamous non-small cell lung cancer (NSCLC) after prior chemotherapy.   |
| Nivolumab                   | Opdivo    | As monotherapy in adults for the treatment of advanced renal cell carcinoma after pretreatment.   |
| Nivolumab                   | Opdivo    | Treating squamous cell carcinoma of the head and neck in adults whose disease has progressed on platinum-based chemotherapy   |
| Nivolumab                   | Opdivo    | for the treatment of locally advanced unresectable or metastatic urothelial carcinoma in adults after failure of prior platinum-containing therapy.   |

|                        |            |  |
|------------------------|------------|--|
| Obinutuzumab           | Gazyvaro   | In combination with chlorambucil for adults with untreated chronic lymphocytic leukaemia who have comorbidities that make full-dose fludarabine-based therapy unsuitable for them  |
| Obinutuzumab           | Gazyvaro   | for treating adults with follicular lymphoma that did not respond or progressed during or up to 6 months after treatment with rituximab or a rituximab-containing regimen  |
| Pembrolizumab          | Keytruda   | First-line treatment of metastatic NSCLC with PD-L1 expressing tumours (TPS $\geq$ 50%) without activating EGFR or ALK mutations in adults   |
| Propranolol            | Hemangirol | For the treatment of proliferative infantile hemangiomas requiring systemic therapy:<br>- Life- or functional hemangioma<br>- Ulcerated hemangioma which causes pain and / or does not respond to simple wound care measures<br>- Hemangioma, Scars or distortion  |
| Regorafenib            | Stivarga   | For the treatment of a type of gastrointestinal cancer called gastrointestinal stromal cell tumors (GIST)  |
| Ramucirumab            | Cyramza    | For advanced gastric cancer or gastro–oesophageal junction adenocarcinoma previously treated with chemotherapy.  |
| Sarilumab              | Kevzara    | For the treatment of adults with moderately to severely active rheumatoid arthritis (RA) who have had an inadequate response or intolerance to one or more biologic or nonbiologic disease-modifying antirheumatic drug (DMARD), as monotherapy or in combination with methotrexate (MTX) or another non-biologic DMARD  |
| Saxagliptin/Metformin  | Onglyza    | For adult patients aged 18 years and older with type 2 diabetes mellitus to improve blood glucose control: as an oral double therapy and oral triple therapy.  |
| Selexipag              | Upravi     | For the long-term treatment of pulmonary arterial hypertension (PAH) in adult WHO-FC patients II to III, either as a combination therapy in patients whose disease is associated with an endothelin receptor antagonist (ERA) and / or a phosphodiesterase- 5 (PDE-5) inhibitor is inadequately controlled or as a monotherapy in patients who are not eligible for these therapies. |
| Tolvaptan              | Jinarc     | To slow the progression of cyst development and renal insufficiency of autosomal dominant polycystic kidney disease (ADPKD) in adults with CKD stage 1 to 3 at initiation of treatment with evidence of rapidly progressing disease.   |
| Trametinib             | Mekinist   | For treatment in combination with dabrafenib (Tafinlar) in malignant melanoma.   |
| Trifluridine–tipiracil | Lonsurf    | Lonsurf is indicated for the treatment of adult patients with metastatic colorectal cancer (CRC) who have been previously treated with, or are not considered candidates for, available therapies including fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapies, anti-VEGF agents, and anti EGFR agents.   |

## Electronic Supplementary Material D – Scientific Value Judgements in HTA

Table D1 – Taxonomy of Clinical and Economic Uncertainties

| Type of Uncertainty                   | Type of Variable | Description   |
|---------------------------------------|------------------|---|
| Clinical uncertainties                |                  |   |
| Size of clinical benefit <sup>1</sup> | Continuous       | Number of uncertainties raised around the size of clinical benefit extrapolated from the evidence submitted. Coded as overcome or not-overcome. |
| Generalisability <sup>2</sup>         | Continuous       | Number of uncertainties raised related to generalisability to the country's population. Coded as overcome or not-overcome.                      |
| Study Design <sup>3</sup>             | Continuous       | Number of uncertainties raised related to clinical trial study design. Coded as overcome or not-overcome.                                       |
| Indirect Comparison <sup>4</sup>      | Continuous       | Number of uncertainties raised related to suitability of indirect comparisons. Coded as overcome or not-overcome.                               |
| Clinical evidence <sup>5</sup>        | Continuous       | Number of uncertainties raised related to the availability of clinical evidence. Coded as overcome or not-overcome.                             |
| Clinical Practice <sup>6</sup>        | Continuous       | Number of uncertainties raised related to generalisability to the country's local clinical practice. Coded as overcome or not-overcome.         |
| Comparator Used <sup>7</sup>          | Continuous       | Number of uncertainties raised related to the compactor in the clinical trial. Coded as overcome or not-overcome.                               |
| Adverse event <sup>8</sup>            | Continuous       | Number of uncertainties raised around the adverse event profile. Coded as overcome or not-overcome.   |
| Economic uncertainties                |                  |   |
| Modelling <sup>9</sup>                | Continuous       | Number of uncertainties raised related to the economic model structure and assumptions. Coded as overcome or not-overcome.                      |
| Model Type <sup>10</sup>              | Continuous       | Number of uncertainties raised related to the appropriateness of the type of model employed. Coded as overcome or not-overcome.                 |
| Comparator <sup>11</sup>              | Continuous       | Number of uncertainties raised related to the compactor employed in the economic model. Coded as overcome or not-overcome.                      |
| Cost <sup>12</sup>                    | Continuous       | Number of uncertainties raised related to the cost estimates used in the economic model. Coded as overcome or not-overcome.                     |
| Utilities <sup>13</sup>               | Continuous       | Number of uncertainties raised related to the utilities estimates used in the economic model. Coded as overcome or not-overcome.                |
| Cost-effectiveness <sup>14</sup>      | Continuous       | Number of uncertainties raised related to the cost-effectiveness estimate in the model. Coded as overcome or not-overcome.                      |
| Sensitivity analysis <sup>16</sup>    | Continuous       | Number of uncertainties raised related to the sensitivity analysis performed. Coded as overcome or not-overcome.                                |

<sup>1</sup> Concerns raised around the magnitude of clinical benefit (e.g. is too little or confounded by other factors that are not related to the clinical design) may comprise but are not limited to: (1) Modest or low clinical benefit from trial; (2) The response of the pharmaceutical varied from study to study; (3) The response of the pharmaceutical is effective only in a sub-population; (4) The response of the pharmaceutical is not statistically significant compared with the comparator.

<sup>2</sup> Concerns raised around the **generalizability of the population** used in the clinical evidence to the country of the HTA body may comprise but are not limited to: (1) the trial population is not generalizable to the country population due to ethnicity/ baseline characteristics and prevalence; (2) The trial population is not included/underrepresented the population of the indication under review; (3) Only a subgroup of the trial is considered suitable for the indication.

<sup>3</sup> Concerns raised across the design of the trials (blinding, phase and clinical or surrogate endpoints, length, sample size, outcome measure, low patient numbers, study duration). It may comprise but it's not limited to: 1) Limitation in trial design leading to confounding in the clinical benefit (e.g. cross-over) 2) Study blinding unsuitable 3) Sample size (too small) 4) Use of surrogate endpoints vs clinical endpoints.

- <sup>4</sup> Concerns raised around the type of indirect comparison, adjustment methods, or studies included in indirect comparison. It may comprise but it's not limited to: 1) indirect comparison not well designed 2) population across different studies non comparable 3) Statistical analysis performed not suitable (e.g. butcher vs Bayesian model)
- <sup>5</sup> Concerns raised around lack of comparative clinical evidence, lack of evidence on a subgroup, or lack of long-term clinical evidence. It may comprise but it's not limited to: 1) Lack of comparative clinical data 2) Unsuitable data 3) Lack of long-term evidence 4) Lack of safety data
- <sup>6</sup> Concerns raised around **generalizability of the clinical practice** of the clinical trials submitted by the manufacturer (e.g. administration route or pre- and concomitant medication or a different use of the resource of the health system) may comprise but are not limited to: (1) differences in the pathway in the clinical practice of the country; (2) differences in the administration and dose in comparison with the standard of care; (3) When the treatment criteria (e.g. baseline of the patients for starting the treatment) differed between the study and clinical practice; (4) A pharmaceutical may have limited use in the study country (e.g. PBAC clinical pathways).
- <sup>7</sup> Comprises all the concerns raised across the comparator(s) such as use of placebo or the use of a comparator different from the one preferred by the HTA bodies or used routinely in the clinical practice. Comparator used in clinical trial was inappropriate. It may comprise but it's not limited to: 1) comparator not marketed in the country 2) comparator not suitable because not used in the clinical practice 3) comparator is not the standard of care in the country 4) Placebo-controlled trial
- <sup>8</sup> Concerns around the safety profile of the medicine under evaluation stemmed from the clinical benefit evidence or the EPAR. It may comprise but is not limited to: (1) Substantial number of patients discontinuing the therapies due to adverse events; (2) EPAR with too many safety issues in comparison with current treatment used; and (3) There are notable adverse events that would lead to specific monitoring.
- <sup>9</sup> Concerns around the modelling used (e.g. in Markov/ partitioned survival model), or the extrapolation technique used for the clinical data may comprise but is not limited to: (1) the modelling used is not suitable; (2) the use of curves is not appropriate; (3) extrapolations method is not appropriate; (4) misrepresentation of the population under review or of some specific subgroup; (5) any computational errors.
- <sup>10</sup> Concerns around the use of a certain model (cost-minimization or cost-utility etc) in that may not suitable for the analysis.
- <sup>11</sup> Concerns around the appropriate comparator used within an economic model. It may comprise but it's not limited to: 1) comparator used in the economic model is not marketed in the country 2) comparator used in the economic model is not suitable because not used in the clinical practice 3) comparator used in the economic model is not the standard of care in the country.
- <sup>12</sup> Concerns around the **cost data** used to build the model leading to over- or under-estimation of the ICER may comprise but is not limited to: (1) some costs included in the model are too low or too high; (2) the model does not include specific cost that would lead to a over-estimation or under-estimation of the cost-effectiveness such as administration cost or wastage.
- <sup>13</sup> Concerns around the **utility data** used to build the model leading to over- or under-estimation of the ICER may comprise but are not limited to: (1) the utility values used in the model are not suitable leading to over-estimation or under-estimation of the ICER; (2) the utility source is not suitable/ or the measured was not appropriate.
- <sup>14</sup> Concerns around the magnitude of ICER to high or too much uncertainty in ICER estimate. It may comprise but it's not limited to: 1) cost-effectiveness over the threshold 2) ICER too high even after testing with sensitivity analysis or re-evaluation carried out by manufacturer/HTA body/ external reviewers
- <sup>15</sup> Concerns around the clinical evidence used in the economic model. It may comprise but it's not limited to: 1) the clinical evidence used in the economic model is not suitable due to limitations such as sample size, poor trial design etc. 2) there is a lack of evidence following the nature progression of the disease (e.g. lack of long-term evidence) 3) the indirect comparison used to populate the clinical input of the model is poorly design/with an unsuitable design
- <sup>16</sup> Sensitivity analysis performed to demonstrate robustness of model inappropriate or missing. It may comprise but it's not limited to: any issues around the sensitivity analysis performed by the manufacturer or by the HTA body experts. The sensitivity analysis produced cost-effectiveness ratios outside of acceptable levels The sensitivity analysis did test the deterministic sensitivity of a key variable or assumption.

**Source:** The authors, adapted from [19].

Table D2 – Multivariate logistic regression of HTA outcomes across France, England, Scotland, Canada, controlling for clinical uncertainties

|                            |              | Model 0             | Model 4               |
|----------------------------|--------------|---------------------|-----------------------|
| <b>Clinical Benefit</b>    | Overcome     | 3.051***<br>(0.958) | 9.071***<br>(4.618)   |
|                            | Not-overcome | 0.557**<br>(0.142)  | 0.331***<br>(0.1239)  |
| <b>Clinical Evidence</b>   | Overcome     | 5.588<br>(6.229)    | 12.582*<br>(19.26)    |
|                            | Not-overcome | 0.961<br>(0.236)    | 1.754<br>(0.685)      |
| <b>Study Design</b>        | Overcome     | 1.297<br>(0.402)    | 1.440<br>(1.397)      |
|                            | Not-overcome | 0.559***<br>(0.101) | 0.132***<br>(0.055)   |
| <b>Indirect Comparison</b> | Overcome     | 1.197<br>(1.139)    | 0.238<br>(0.279)      |
|                            | Not-overcome | 1.631<br>(0.764)    | 4.090**<br>(2.487)    |
| <b>Comparator</b>          | Overcome     | 2.077<br>(1.158)    | 0.796<br>(0.824)      |
|                            | Not-overcome | 4.972**<br>(3.689)  | 155.43***<br>(197.59) |
| <b>Generalisability</b>    | Overcome     | 0.660<br>(0.372)    | 2.367<br>(3.302)      |
|                            | Not-overcome | 1.019<br>(0.407)    | 0.853<br>(0.398)      |
| <b>Clinical Practice</b>   | Overcome     | 12.276<br>(0.713)   | 1.712<br>(1.607)      |
|                            | Not-overcome | 0.817<br>(0.320)    | 1.712<br>(1.670)      |
| <b>Adverse Events</b>      | Overcome     | 0.732<br>(0.368)    | 0.808**<br>(0.564)    |
|                            | Not-overcome | 0.275**<br>(0.142)  | 0.036***<br>(0.045)   |
| Number of Observations     |              | 326                 | 326                   |
| Pseudo-R <sup>2</sup>      |              | 0.436               | 0.656                 |
| AIC                        |              | 233.2               | 184.3                 |
| Time FE                    |              | Yes                 | Yes                   |
| Agency FE                  |              | Yes                 | Yes                   |

Association between clinical uncertainties and HTA outcomes without controlling for covariates (Model 0) and controlling for covariates specified in model 4. Odds ratios and robust standard errors adjusted for clustering (in brackets) are reported. Results are pooled across all agencies. Only coefficients for clinical uncertainties are reported.

P-Values \*p<0.1; \*\*p<0.05; \*\*\*p<0.01



Table D3 – Multivariate logistic regression of HTA outcomes across England, Scotland, Canada, controlling for economic uncertainties

|                             |              | Model 0             | Model 4             |
|-----------------------------|--------------|---------------------|---------------------|
| <b>Modelling</b>            | Overcome     | 3.900***<br>(2.027) | 5.166**<br>(3.591)  |
|                             | Not-overcome | 1.047<br>(0.178)    | 1.112<br>(0.212)    |
| <b>Model Type</b>           | Overcome     | 1.222<br>(1.659)    | 0.948<br>(0.990)    |
|                             | Not-overcome | 1.410<br>(1.384)    | 1.006<br>(1.22)     |
| <b>Comparator</b>           | Overcome     | 3.971<br>(3.544)    | 2.421<br>(2.482)    |
|                             | Not-overcome | 0.769<br>(0.405)    | 0.676<br>(0.388)    |
| <b>Costs</b>                | Overcome     | 1.913<br>(1.759)    | 0.673<br>(0.271)    |
|                             | Not-overcome | 0.743<br>(0.219)    | 7.481<br>(5.819)    |
| <b>Utilities</b>            | Overcome     | 5.396<br>(6.181)    | 7.481***<br>(5.819) |
|                             | Not-overcome | 0.412<br>(0.148)    | 0.346**<br>(0.164)  |
| <b>Cost-effectiveness</b>   | Overcome     | 3.010*<br>(1.802)   | 2.431<br>(1.672)    |
|                             | Not-overcome | 1.272<br>(0.320)    | 1.11<br>(0.283)     |
| <b>Sensitivity Analysis</b> | Overcome     | -                   | -                   |
|                             | Not-overcome | 1.101<br>(1.302)    | -                   |
| Number of Observations      |              | 326                 | 326                 |
| Pseudo-R <sup>2</sup>       |              | 0.304               | 0.421               |
| AIC                         |              | 264.4               | 241.9               |
| Time FE                     |              | Yes                 | Yes                 |
| Agency FE                   |              | Yes                 | Yes                 |

Association between economic uncertainties and HTA outcomes without controlling for covariates (Model 0) and controlling for covariates specified in model 4. Odds ratios and robust standard errors adjusted for clustering (in brackets) are reported. Results are pooled across all agencies. Only coefficients for economic uncertainties are reported.

P-Values \*p<0.1; \*\*p<0.05; \*\*\*p<0.01

Table D4 – Linear regression models exploring association of SVJs and uncertainties

|   | Model 1             | Model 2             | Model 3           |
|---|---------------------|---------------------|-------------------|
| <i>Dependent Variable: Total number of uncertainties raised</i> |                     |                     |                   |
| <b>Disease Severity</b>   | 0.68**<br>(0.296)   | 1.274***<br>(0.313) | -0.001<br>(0.296) |
| <b>Unmet Need</b>   | 0.507*<br>(0.291)   | 0.461<br>(0.419)    | -0.001<br>(0.313) |
| <b>Administration Advantage</b>                                 | -0.127<br>(0.349)   | -0.119<br>(0.368)   | -0.501<br>(0.127) |
| <b>Innovation</b>   | 1.500***<br>(0.280) | -0.197<br>(0.348)   | 1.481<br>(0.280)  |
| <b>Quality of Life</b>  | 0.689**<br>(0.337)  | 0.483<br>(0.406)    | -0.001<br>(0.337) |
| <b>Demographics</b>   | -0.125<br>(0.580)   | 0.659<br>(0.420)    | -0.501<br>(0.580) |

Linear regressions exploring the association SVJs with total clinical uncertainties overcome (Model 1), total clinical uncertainties not overcome (Model 2), total economic uncertainties overcome (Model 3) and total economic uncertainties not overcome (Model 4). Coefficients and robust standard errors adjusted for clustering (in brackets) are reported. Results are pooled across all agencies

P-Values \*p<0.1; \*\*p<0.05; \*\*\*p<0.01

## Electronic Supplementary Material E – Sensitivity Analysis and Robustness Checks

### E1 – Multivariate logistic regression models without fixed effects comparing positive and negative HTA outcomes across NICE, HAS, SMC, CADTH and INESSS.

|   | Model E0 | Model E1           | Model E2 | Model E3 |
|---|----------|--------------------|----------|----------|
| <i>Dependent Variable: HTA Outcome (List or List with condition: 1, Do not list: 0)</i> |          |                    |          |          |
| <b>A) Regulatory Approval</b>   |          |                    |          |          |
| Conditional Approval  |          | 0.558**<br>(0.162) |          |          |
| <b>B) Disease Characteristics</b>   |          |                    |          |          |

|   |       |                     |                     |                     |
|---|-------|---------------------|---------------------|---------------------|
| Cancer                                  |       | 2.399**<br>(0.872)  | 2.181**<br>(0.767)  | 1.755<br>(0.671)    |
| Orphan                                  |       | 5.257***<br>(2.313) | 7.154***<br>(3.217) | 5.921***<br>(2.911) |
| <b>C) Submission History</b>            |       |                     |                     |                     |
| Resubmission                            |       | 1.529<br>(0.667)    | 1.488<br>(0.647)    | 1.654<br>(0.736)    |
| <b>D) Pivotal Trial Characteristics</b> |       |                     |                     |                     |
| Trial Phase                             |       |                     | 2.025*<br>(0.757)   | 1.974<br>(0.849)    |
| Endpoint                                |       |                     | 1.268<br>(0.514)    | 1.153<br>(0.485)    |
| Comparator                              |       |                     | 2.173**<br>(0.727)  | 1.769<br>(0.686)    |
| <b>E) Uncertainties</b>                 |       |                     |                     |                     |
| Clinical Overcome                       |       |                     |                     | 1.135<br>(0.097)    |
| Clinical Not-Overcome                   |       |                     |                     | 0.813***<br>(0.048) |
| Economic Overcome                       |       |                     |                     | 1.420***<br>(0.165) |
| Economic Not-Overcome                   |       |                     |                     | 0.817***<br>(0.059) |
| <b>F) Social Value Judgements</b>       |       |                     |                     |                     |
| Disease Severity                        |       |                     |                     |                     |
| Unmet Need                              |       |                     |                     |                     |
| Administration Advantage                |       |                     |                     |                     |
| Innovation                              |       |                     |                     |                     |
| Quality of Life                         |       |                     |                     |                     |
| Special Demographics                    |       |                     |                     |                     |
| <hr/>                                   |       |                     |                     |                     |
| Number of Observations                  | 339   | 339                 | 339                 | 339                 |
| Pseudo-R <sup>2</sup>                   | 0.127 | 0.062               | 0.108               | 0.224               |
| AIC                                     | 311.1 | 299.66              | 291.4               | 262.7               |
| <hr/>                                   |       |                     |                     |                     |
| Time FE                                 | No    | No                  | No                  | No                  |
| Agency FE                               | No    | No                  | No                  | No                  |

Abbreviations: CADTH - Canadian Agency for Drugs and Technologies in Health; FE – Fixed Effects; HAS – Haute Autorité de Santé (HAS); NICE – National Institute of Health and Care Excellence; SMC – Scottish Medicines Consortium

Model E0 is a reference case controlling only for type of marketing authorisation. Disease characteristics and submission history (Model E1), pivotal trial characteristics (Model E2), Uncertainties (Model E3) and Social Value Judgments (Model E4) were added sequentially. Model E5 presents results for cost-effectiveness countries only (excluding France). Odds ratios and robust standard errors adjusted for clustering (in brackets) are reported. Results are pooled across all agencies. No time or agency fixed effects are included in any model.

P-Values \* $p < 0.1$ ; \*\* $p < 0.05$ ; \*\*\* $p < 0.01$

See supplementary material for regression models without time and agency fixed effects.