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How do HTA agencies perceive conditional approval of medicines? Evidence from England, Scotland, France and Canada

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ABSTRACT

There is a growing disconnect between regulatory agencies that are promoting expedited approval to medicines based on early phase clinical evidence and health technology assessment (HTA) agencies that require robust clinical evidence to inform coverage decisions. This paper provides an assessment of the evidence gap between regulatory and HTA agencies on medicines receiving conditional marketing authorisation (CMA) and examines how HTA agencies in France, England, Scotland, and Canada interpret and appraise evidence for these medicines. A mixed methods research design was used to identify the types and frequency of parameters raised in the context of HTA decision-making for all conditional approvals in Europe and Canada between 2010 and 2017. Significant heterogeneity was found across the HTA agencies in England, Scotland, France, and Canada in the assessment of medicines receiving CMA, with the highest likelihood of rejection present in Quebec (50%) and Scotland (25%). Rejected medicines were more likely to have unresolved uncertainties related to the magnitude of clinical benefit, study design, and issues in economic modelling. More systematic use of joint early dialogue and conditional reimbursement pathways would help clarify evidence requirements and avoid delays in patient access to innovative medicines.

1. Background

Conditional approval pathways aim to promote faster entry to market for innovative medicines that treat serious or life-threatening diseases and address unmet medical needs. They do so by reducing the clinical development time of innovative medicines and shifting some evidence generation activities from pre- to post-marketing authorisation [1]. While conditional approval pathways, such as the U.S. Food and Drug Administration's (FDA) Accelerated Approval (AA), the European Medicines Agency's (EMA) Conditional Marketing Authorisation (CMA) and the Health Canada's Notice of Compliance with Conditions (NOC/C) are well established [2–5], they can produce considerable challenges for health technology assessment (HTA) and resource allocation decisions, given that only immature and/or early phase clinical data is typically available at the time of regulatory submission [6].

Existing literature on conditional approval pathways raises several points of potential concern in the trade-off between strength of evidence and speed of access to technologies that address an unmet need in serious and life-threatening diseases. Randomised controlled trials (RCTs), the gold standard for evaluating safety and efficacy of medicines, typically only represent a minority of the evidence available for conditionally approved medicines with approval instead granted on the basis of small and, increasingly non-randomised, studies [7]. Conditionally approved medicines granted FDA approval are also more likely to experience post-market safety events than standard approval medicines [8]. Further, confirmatory trials for conditionally approved medicines, required according to the conditions of authorization, frequently either have study designs which do yield significant improvements in

Abbreviations: ATC, Anatomic Therapeutic Chemical; ATU, Temporary Authorisation for Use (France); CADTH, Canadian Agency for Drugs and Technologies in Health; CDF, Cancer Drugs Fund (England); CMA, Conditional Marketing Authorisation; CUP, Compassionate Use Programme; EAA, Early Access Authorisation (France); EAMS, Early Access to Medicines (England); EMA, European Medicines Agency; FDA, Food and Drug Administration; HAS, Haute Autorité de Santé; HTA, Health Technology Assessment; INESSS, The Institut National d'Excellence en Santé et en Services Sociaux; MA, Marketing Authorisation; MAEC, Marketing Authorisation under Exceptional Circumstances (EMA); MCDA, Multiple Criteria Decision Analysis; MCL, Mantle Cell Lympoma; NOC, Notice of Compliance; NOC/c, Notice of Compliance/Conditional; pCODR, pan-Canadian Oncology Drug Review; RCC, Renal Cell Carcinoma; RCT, Randomised Control Trial; SMC, Scottish Medicine Consortium; SVJ, Social Value Judgement.

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the quality of evidence or are not completed [9].

Importantly, it remains unclear if conditional approval pathways achieve their primary aim to promote faster patient access to medicines due to requirements at HTA level [10–12]. When comparing across countries, significant heterogeneity exists in both the types of coverage recommendation and the timelines between EMA approval and reimbursement for cancer medicines approved through the CMA pathway in Germany, France, England, Scotland and Italy [10]. Overall, conditionally approved medicines tend to have poor success at HTA level within Europe [13], suggesting a disconnect between regulatory and HTA agencies relating to their value [10–13].

Delays in access to medicines that address an unmet need may be partially alleviated by the presence of other types of expedited regulatory pathways (e.g. FDA priority review), which aim to expedite approval through alternative mechanisms (see Appendix A1 for a detailed overview and comparison of expedited regulatory pathways), or through compassionate use programmes (CUPs) such as France's Early Access Authorisation (EAA), formerly known as Temporary Authorisation for Use (ATU), and England's Early Access to Medicines Scheme (EAMS) [14,15]. CUPs, distinct from conditional approval pathways, provide access to unauthorised medicines on compassionate grounds to patients with chronically debilitating or life threatening diseases, which cannot be treated satisfactorily by an authorised medicinal product. While CUPs may act as a stop gap for medicines that address an unmet need by accelerating access to new technologies, they should not be mistaken for MA providing access to an entire patient population. CUPs tend to be restricted to individual patients or narrowly defined patient populations and requirements to offer medicines free-of-charge (e.g. England EAMS) often further limit uptake into these schemes [15]. Although some patients may be eligible to receive conditionally approved medicines prior to reimbursement through clinical trial enrolment or on compassionate grounds, routine access of these medicines through reimbursement procedures remains an issue.

HTA agencies have frequently issued negative recommendations for conditionally approved medicines, however the salient features driving these decisions are unknown [13]. The potential disconnect between regulatory and HTA agencies is of particular significance in Europe, where the CMA pathway was implemented in 2006 and in Canada, where the NOC/C was implemented in 2002 [4,5]. In both settings, HTA plays a fundamental role in resource allocation decisions [16,17].

While some differences are present between the CMA and NOC/C pathway, both are similar in their eligibility criteria and their capacity to reduce clinical development time relative to medicines that receive standard marketing authorisation. Importantly, pre-mature or early phase clinical evidence is only accepted provided the medicine still demonstrates a positive benefit-risk ratio, one of the fundamental characteristics of all regulatory approval pathways. A full comparison of the CMA and NOC/C pathways is provided in Table 1.

In both Canada and in several settings across Europe, the impact of conditional regulatory approval on health technology assessment remains unclear. This study has two objectives: first, to examine the evidence gap between regulatory and HTA agencies for conditionally approved medicines in England, Scotland, France, and Canada; and, second, to determine how HTA agencies in these four countries interpret and appraise clinical and economic evidence submitted for conditionally approved medicines. In doing so, this study provides an important empirical assessment of the critical issues that CMA generates at HTA level and enhances our understanding of the alignment (or lack thereof) that needs to happen between regulatory and HTA on innovative medicines.

Table 1
Comparison of EMA conditional marketing authorisation pathway and Health Canada notice of compliance with conditions pathway.

Agency	EMA	Health Canada
Expedited Approval Pathway	Conditional Marketing Authorisation	Notice of Compliance with Conditions
Eligibility Criteria	1. Medicinal products which aim at the treatment, the prevention or the medical diagnosis of seriously debilitating diseases or life-threatening diseases; 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 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.
Evidence Requirements	For a product to be granted a conditional marketing authorisation it must fulfil all of the criteria set out in Article 4(1) of the same Regulation: (a) The risk–benefit balance of the medicinal product, as defined in Article 1(28a) of Directive 2001/83/EC, is positive; (b) It is likely that the applicant will be in a position to provide comprehensive clinical data; (c) Unmet medical need will be fulfilled; (d) The benefit to public health of the immediate availability on the market of the medicinal product concerned outweighs the risk inherent in the fact that additional data are still required. A conditional marketing authorisation may be granted, where comprehensive pre-clinical or pharmaceutical data have not been supplied.	Potential of a therapy can be demonstrated with: (a) Trials with surrogate markers that require validation; (b) Phase II trials that would require confirmation with Phase III trials consistent with the normal course of development of a therapeutic entity; (c) Phase III trials where a single small to moderately sized trial would require confirmation of either the efficacy or safety of the agent under question. Furthermore, there are multiple ways whereby clinical evidence may be established including literature review, expert opinions, panels or pharmacokinetic/pharmacodynamic studies.
Limitations	Restricted to the first indication approved for a new molecule	N/A
Duration	One year	Case-by-case

Source: The authors adapted from [4,5].

2. Methods

2.1. Analytical framework

HTA agencies vary not only in the types of evidence they consider, but also in their interpretation of such evidence. Upon completion of an assessment, many HTA agencies publish detailed assessment reports which outline the evidence submitted (clinical as well as economic, the latter if applicable), the agencies' interpretation of the evidence, and the results of the assessment to add legitimacy and transparency to the decision-making process. Beyond clinical and economic evidence, HTA agencies also discuss other contextual considerations (e.g. relating to disease severity, unmet need, or ethical considerations, among others), known as social value judgements (SVJs).

Large volumes of unstructured data present in HTA reports and

Table 2
List of variables deployed in analysis.

Variable	Type	Variable Abbreviation	Definition/Explanation
Marketing Authorisation Reports			
Therapeutic Area	Categorical	ATC	The therapeutic area according to the Anatomical Therapeutic Chemical (ATC) classification system
Study Design of Pivotal Trial[1]	Categorical	PIVOTAL	1 = Observational study; 2= Phase I Study; 3 = Single armed phase II study; 4= Controlled phase II study; 5= Placebo controlled randomised phase III study; 6 = Actively controlled randomised phase III study
Marketing Authorisation Conditions[2]	Categorical	CONDITIONS	1 = Submission of follow-up data from ongoing studies; 2 = Completion of confirmatory phase II trial; 3 = Completion of confirmatory phase III trial
Health Technology Assessment Reports			
HTA Outcome[3]	Categorical	HTAOUTCOME	1 = List (L); 2 = List with conditions (LWC); 3 = List with conditions through a resubmission following an initial rejection (LWC after resubmission); 4 = Do not list (DNL); 5 = Do not list through a resubmission following an initial rejection (DNL after resubmission); 6 = No HTA submission.
Study Design of Main Trial for HTA[4]	Categorical	HTATRIAL	1 = Observational study; 2= Phase I Study; 3 = Single armed phase II study; 4= Controlled phase II study; 5= Placebo controlled randomised phase III study; 6 = Actively controlled randomised phase III study
Clinical Uncertainties Raised in HTA			
Size of clinical benefit[5]	Continuous	CLINBEN	Number of uncertainties raised around the size of clinical benefit extrapolated from the evidence submitted
Generalisability[6]	Continuous	GENERAL	Number of uncertainties raised related to generalisability to the country's population
Study Design[7]	Continuous	DESIGN	Number of uncertainties raised related to clinical trial study design
Indirect Comparison[8]	Continuous	INDIRECT	Number of uncertainties raised related to suitability of indirect comparisons
Clinical evidence[9]	Continuous	CLINEV	Number of uncertainties raised related to the availability of clinical evidence
Clinical Practice[10]	Continuous	CLINPRAC	Number of uncertainties raised related to generalisability to the country's local clinical practice
Comparator Used[11]	Continuous	COMP	Number of uncertainties raised related to the compactor in the clinical trial
Economic Uncertainties Raised in HTA			
Modelling[12]	Continuous	MODELLING	Number of uncertainties raised related to the economic model structure and assumptions
Model Type[13]	Continuous	MODELTYPE	Number of uncertainties raised related to the appropriateness of the type of model employed
Comparator[14]	Continuous	COMPECON	Number of uncertainties raised related to the compactor employed in the economicmodel
Cost[15]	Continuous	COST	Number of uncertainties raised related to the cost estimates used in the economic model
Utilities[16]	Continuous	UTILITIES	Number of uncertainties raised related to the utilities estimates used in the economic model
Cost-effectiveness[17]	Continuous	COSTEFFECT	Number of uncertainties raised related to the cost-effectiveness estimate in the model
Sensitivity analysis[18]	Continuous	MODEL	Number of uncertainties raised related to the sensitivity analysis performed
Social Value Judgments Identified in HTA			
Severity	Binary	SEVERITY	1= Severity of the disease explicitly recognised by HTA agency; 0 = Severity not recognised.
Administration route/ frequency	Binary	ADMINAD	1= Route and the frequency of administration of the treatment explicitly recognised by HTA agency as offering advantage; 0 = Not recognised as offering advantage.
Unmet need	Binary	UNEED	1= Unmet need for the new treatment (e.g. few or no alternatives exist, need for additional treatments, high BoD) explicitly recognised by HTA agency; 0 = Unmet need not recognised.
Innovation	Binary	INNOVATION	1= Novel mechanism of action and overall innovativeness of the treatment explicitly recognised by HTA agency; 0 = Not recognised.
Rarity	Binary	RARITY	1 = Small patient population or disease rarity explicitly recognised by HTA agency; 0 = Not recognised
Short Life Expectancy	Binary	EXPECTANCY	1 = Short duration of life expectancy explicitly recognised by HTA agency; 0 = Not recognised
Special Demographics	Binary	DEMOGRAPHICS	1 = Special demographics of patient population in terms of age, sex, race or socioeconomic status explicitly recognised by HTA agency; 0 = Not recognised

Source: The author, adapted from mixed methods framework developed by Nicod and Kanavos [10]

[1] The study design of the pivotal trial used to support conditional regulatory approval. Study designs are classified according to study phase (phase I, phase II, phase III, phase IV, or N/A for non-interventional studies), study blinding (open label or double blind), randomisation (randomised or non-randomised/single arm), and comparators (placebo controlled, actively controlled or uncontrolled).

[2] The specific post-marketing obligations imposed by regulatory agencies in order to fulfil the conditions of marketing authorisation. Conditions are classified according to the type of evidence generation requested (submission of follow-up data or completion of additional clinical trials).

[3] HTA outcomes are classified as list (L), list with conditions (LWC), list with conditions through a resubmission following an initial rejection (LWC after resubmission), do not list (DNL), do not list through a resubmission following an initial rejection (DNL after resubmission), or No HTA submission. In France, the HAS assigns a rating based on the absolute clinical benefit (SMR) and relative clinical benefit (ASMR). SMR ratings include insufficient, low, moderate, and important and determines the reimbursement rate for a product (not reimbursed, 15%, 30% and 65% respectively). The ASMR rating ranges from V (non-existent added benefit) to I (major added benefit) and determines a products price. In order to qualify for a price premium an ASMR rating of I or II is needed. HTA outcomes for France are classified according to SMR and ASMR ratings (DNL – SMR insufficient, L – SMR important and ASMR I or II, or LWC- all other combinations).

[4] The study design of the main trial used to support HTA assessment. Study designs are classified according to study phase (phase I, phase II, phase III, phase IV, or N/A for non-interventional studies), study blinding (open label or double blind), randomisation (randomised or non-randomised/single arm), and comparators (placebo controlled, actively controlled or uncontrolled).

[5] 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.

[6] 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.

[7] 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.

[8] 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).

[9] 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.

[10] 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).

[11] 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

[12] 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.

[13] Concerns around the use of a certain model (cost-minimization or cost-utility etc) that may not suitable for the analysis.

[14] 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.

[15] 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.

[16] 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.

[17] 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.

[18] Sensitivity analysis performed to demonstrate robustness of model inappropriate or missing. It may comprise but it's not limited to: (1) Any issues around the sensitivity analysis performed by the manufacturer or by the HTA body experts; (2) The sensitivity analysis produced cost-effectiveness ratios outside of acceptable levels; (3) The sensitivity analysis did test the deterministic sensitivity of a key variable or assumption.

Source: The authors.

complex decision-making processes based on multiple implicit and explicit criteria present limitations towards quantitative analysis of HTA outcomes. We adopt a sequential mixed-methods research design, as outlined in the analytical framework developed by Nicod and Kanavos [18], in order to mitigate these limitations and capture the widest possible range of criteria which may influence HTA outcomes. First, HTA reports are qualitatively analysed to capture: (a) the quality of evidence being submitted to HTA agencies; (b) how HTA agencies interpret this evidence; (c) the influence this evidence has on the final decision; and (d) additional social value judgements considered beyond clinical and economic evidence. Second, categorised and coded data is analysed quantitatively. When implemented across a large sample of medicines and their respective indications, the framework enables a meta-analysis of HTA decision-making and identification of key parameters considered in the HTA process.

2.2. Sample selection

The European Medicines Agency (EMA) and Health Canada's medicines approval databases were screened to identify all medicine-indication pairs that have received Conditional Marketing Authorisation (CMA) or Notice of Compliance with Conditions (NOC/C), respectively, between January 1st, January 1st,J2010 and December 31st, 2017. The study period was selected in order to: (a) provide sufficient time for HTA evaluations to have been completed following marketing authorisation; (b) provide sufficient sample size for analysis; and (c) limit the impact of regulatory and HTA reforms on results. Medicines which have received Marketing Authorisation Under Exceptional Circumstances (MAEC), which is part of EMA's regulatory approval processes pro, where excluded from the study (See appendix for details on the MAEC pathway). A medicine-indication pair is defined as a molecule and the specific indication where the molecule's use is authorised.

The scope of this study is restricted to England, Scotland, France, and Canada. Country selection is based on the presence of an accelerated access regulatory pathway, public availability of marketing authorisation reports, public availability of HTA reports, and language (English and French). Three HTA agencies from Europe were included in the study, notably, the National Institute for Health and Care Excellence (NICE) [19], the Haute Autorité de Santé (HAS) [20], and the Scottish Medicines Consortium (SMC) [21], and two HTA agencies from Canada, notably the Canadian Agency for Drugs and Technology in Health (CADTH)/pan-Canadian Oncology Drug Review (pCODR) [22], and the Institut National d'Excellence en Santé et Services Sociaux (INESSS) [23]. European HTA agencies were screened to identify HTA reports for CMA medicine-indication pairs and Canadian HTA agencies were screened to identify HTA reports for NOC/C medicine-indication pairs. CMA and NOC/C medicine-indication pairs that had not been evaluated by at least one HTA agency were excluded from the study.

2.3. Data collection and coding

In order to enable (a) an assessment of the evidence gap between MA and HTA and (b) an evaluation of how HTA agencies interpret and appraise evidence of conditionally approved medicines, a number of parameters were extracted from publicly available MA reports and publicly available HTA reports (Table 2). Evidence was extracted into a database created in Microsoft Excel for coding and analysis. The parameters extracted from MA reports were: (1) the molecule name, (2) the brand name, (3) the exact wording of indication, (4) the therapeutic area, (5) the MA date, (6) the study name (trial identifier code) and study design of the pivotal clinical trial (trial phase, trial blinding, trial randomisation, and type of comparators) and (7) the conditions applied to the marketing authorisation. The parameters extracted from HTA reports were: (8) HTA outcome (List (L), List with conditions (LWC), Do not List (DNL)), (9) the number of resubmissions following a rejection if applicable, (10) the study name (trial identifier code) and study design of the main trial submitted (trial phase, trial blinding, trial randomisation, and type of comparators), (11) the assessment of clinical evidence in terms of the clinical uncertainties raised regarding the magnitude of clinical benefit, lack of clinical evidence, study design, choice of comparator, generalizability of trial population, and applicability local clinical practice, (12) the assessment of economic evidence in terms of uncertainties raised regarding modelling, the type of model, the choice of comparator, the estimation of costs and utilities, the cost-effectiveness ratio, and the sensitivity analysis performed, and (13) the consideration of additional elements of value including disease rarity, disease severity, unmet need, innovative mechanism of action, short life expectancy, administration advantages, and special demographics.

2.4. Data analysis

Data analysis followed a sequential mixed-methods approach for

Table 3
Descriptive statistics.

HTA/funding outcome Outcome type (DNL/LWC/L) N (% of total)	Do Not List (DNL) 30 (29%)	List With Criteria (LWC) 72 (71%)	List (L) 0 (0%)	Total *n* = 102 (100%)
Country (Agency)				
$\chi^2 = 10.1737$ ($p =$ ***0.038***)				
Canada (CADTH)	6 (20%)	22 (31%)	0 (0%)	28 (27%)
Canada (INESS)	13 (43%)	13 (18%)	0 (0%)	26 (25%)
Scotland (SMC)	3 (10%)	9 (13%)	0 (0%)	12 (12%)
France (HAS)	7 (23%)	14 (19%)	0 (0%)	21 (21%)
England (NICE)	1 (3%)	14 (19%	0 (0%)	15 (15%)
Therapeutic area				
$\chi^2 = 0.6209$ ($p = 0.431$)				
Non-oncology[1]	7 (23%)	12 (17%)	0 (0%)	19 (19%)
Oncology	23 (77%)	60 (83%)	0 (0%)	83 (81%)
Prior rejection by HTA				
$\chi^2 = 0.3998$ ($p = 0.527$)				
No	25 (83%)	56 (78%)	0 (0%)	81 (79%)
Yes	5 (17%)	16 (22%)	0 (0%)	21 (21%)
Trial phase				
$\chi^2 = 3.2583$ ($p = 0.353$)				
Phase 1	0 (0%)	1 (3%)	0 (0%)	1 (1%)
Phase II	15 (50%)	35 (49%)	0 (0%)	50 (49%)
Phase III	14 (47%)	35 (39%)	0 (0%)	49 (48%)
Other (Observational)	0 (0%)	2 (3%)	0 (0%)	2 (2%)
Social value judgments				
Severity				
$\chi^2 = 2.0668$ ($p = 0.151$)				
Not considered	4 (13%)	19 (26%)	0 (0%)	23 (23%)
Considered	26 (87%)	53 (74%)	0 (0%)	79 (77%)
Unmet need				
$\chi^2 = 0.0731$ ($p = 0.787$)				
Not considered	3 (10%)	6 (8%)	0 (0%)	9 (9%)
Considered	27 (90%)	66 (92%)	0 (0%)	93 (91%)
Administrative advantage				
$\chi^2 = 0.1158$ $p = (0.734)$				
Not considered	19 (63%)	43 (60%)	0 (0%)	62 (61%)
Considered	11 (37%)	29 (40%)	0 (0%)	40 (39%)
Innovation				
$\chi^2 = 3.4358$ ($p = 0.064$)				
Not considered	21 (70%)	36 (50%)	0 (0%)	57 (56%)
Considered	9 (30%)	36 (50%)	0 (0%)	45 (44%)
Rarity				
$\chi^2 = 7.0247$ ($p =$ **0.008**)				
Not considered	26 (87%)	43 (60%)	0 (0%)	69 (68%)
Considered	4 (13%)	29 (40%)	0 (0%)	33 (32%)
Short Life Expectancy				
$\chi^2 = 0.0000$ ($p = 1.000$)*				
Not considered	20 (67%)	48 (67%)	0 (0%)	68 (67%)
Considered	10 (33%)	24 (33%)	0 (0%)	34 (33%)
Special Demographics				
$\chi^2 = 0.0000$ ($p = 1.000$)*				
Not considered	25 (83%)	60 (83%)	0 (0%)	85 (83%)
Considered	5 (17%)	12 (17%)	0 (0%)	17 (17%)
Clinical uncertainties				
Clinical benefit				
$t = -1.2346$ ($p = 0.2199$)				
Observations	30	72	0	102
Mean (SD)	2.5 (1.63)	2.1 (1.29)	-	2.2 (1.4)
Generalizability				
$t = -1.3526$ ($p = 0.1792$)				
Observations	30	72	0	102
Mean (SD)	0.7 (0.60)	0.5 (0.71)	-	0.56 (0.68)
Study Design				
$t = -3.5819$ ($p =$ ***0.0005***)				
Observations	30	72	0	102
Mean (SD)	3.2 (2.81)	1.65 (1.53)	-	2.11 (2.1)
Indirect Comparison				
$t = 0.2724$ ($p = 0.7859$)				
Observations	30	72	0	102
Mean (SD)	0.33 (0.66)	0.375 (0.72)	-	0.36 (0.70)
Clinical Evidence				
$t = -0.5378$ ($p = 0.5919$)				
Observations	30	72	0	102

(*continued on next page*)

Table 3 (*continued*)

HTA/funding outcome Outcome type (DNL/LWC/L) N (% of total)	Do Not List (DNL) 30 (29%)	List With Criteria (LWC) 72 (71%)	List (L) 0 (0%)	Total *n* = 102 (100%)
Mean (SD)	1.13 (1.17)	1.01 (0.96)	-	1.04 (1.02)
Clinical Practice				
t=1.8204 (p = 0.0717)				
Observations	30	72	0	102
Mean (SD)	0.46 (0.63)	0.76 (0.80)	-	0.68 (0.76)
Comparator				
t=-1.27 (p = 0.2073)				
Observations	30	72	0	102
Mean (SD)	0.33 (0.55)	0.21 (0.41)	-	0.25 (0.45)
Economic uncertainties[2]				
Modelling				
t=1.3756 (p = 0.1720)				
Observations	30	72	0	102
Mean (SD)	1.20 (1.21)	1.68 (1.74)	-	1.54 (1.61)
Model Type				
t=0.4695. (p = 0.6397)				
Observations	30	72	0	102
Mean (SD)	0.03 (0.18)	0.06. (0.23)	-	0.05 (0.22)
Comparator				
t=0.8002 (p = 0.4255)				
Observations	30	72	0	102
Mean (SD)	0.10 (0.31)	0.17 (0.41)	-	0.15 (0.38)
Cost				
t=-0.2728 (p = 0.7856)				
Observations	30	72	0	102
Mean (SD)	0.53 (0.97)	0.49 (0.71)	-	0.50 (0.79)
Utilities				
t=0.5992 (p = 0.5504)				
Observations	30	72	0	102
Mean (SD)	0.30 (0.65)	0.375 (0.54)	-	0.35 (0.57)
Cost-Effectiveness				
*t=2.3407 (p = **0.0212**)*				
Observations	30	72	0	102
Mean (SD)	0.63 (0.67)	1.15 (1.13)	-	1.0 (1.0)
Sensitivity Analysis				
t=-0.1498 (p = 0.8812)				
Observations	30	72	0	102
Mean (SD)	0.03 (0.18)	0.03 (0.17)	-	0.03 (0.17)
Days from MA to HTA/funding decision[3]				
t= -1.5622 (p = 0.1214)				
Observations	30	72	0	102
Mean (SD)	600 (435)	453 (399)	-	496 (435)
HTA/funding decision year				
$\chi^2 = 2.1803$ *(p = 0.975)*				
2011	0 (0%)	2 (3%)	0 (0%)	2 (2%)
2012	0 (0%)	1 (1%)	0 (0%)	1 (1%)
2013	2 (7%)	8 (11%)	0 (0%)	10 (10%)
2014	3 (10%)	6 (8%)	0 (0%)	9 (9%)
2015	4 (13%)	11 (15%)	0 (0%)	15 (15%)
2016	8 (27%	16 (22%)	0 (0%)	24 (24%)
2017	8 (27%)	16 (22%	0 (0%)	24 (24%)
2018	4 (13%	10 (14%)	0 (0%)	14 (14%)
2019	1 (3%)	2 (3%)	0 (0%)	3 (3%)

Note:[1]Non-oncology medicines include alimentary track and metabolism products, anti-infective products, nervous system products, systemic hormonal preparations and products for sensory organs.

[2] France (HAS) does not conduct routine economic evaluations as part of their assessment process to determine SMR and ASMR rankings. Economic uncertainties are only recorded for CADTH, INESSS, NICE and SMC.

[3] Canadian HTA agencies (CADTH and INESSS) have the ability to undertake parallel review, whereby HTA takes place concurrently with marketing authorisation review.

[*] Equal distribution across HTA outcome categories

Sources: The authors.

decision analysis. First, text from HTA agency reports were qualitatively analysed in order to identify and code parameters that are relevant to decision-making according to the framework in Table 2. Uncertainties were double-coded based on the type of uncertainty and whether or not the uncertainty was addressed by any means in the context of the decision (e.g. with regards to the following text: "The committee was aware of the Evidence Review Group's (ERG) concerns that the trial included only a small number of patients from the UK. The Committee accepted advice from clinical specialists that the data were relevant to clinical practice in England and Wales." would be coded as "uncertainty in generalisability of trial population – overcome"). Second, descriptive quantitative analysis was performed in order to identify the frequency with which a particular coded parameter was raised in context of an HTA decision. Descriptive statistics are presented for the aggregate sample, followed by descriptive analysis of HTA outcomes, clinical evidence, clinical uncertainties, economic uncertainties and SVJs at country and agency level.

3. Results

3.1. Sample overview

Between 2010 and 2017, 25 medicine-indication pairs received CMA from the EMA and 59 medicine-indication pairs received NOC/C from Health Canada. Within Europe, 21 CMA medicine-indication pairs had at least one HTA evaluation by the HAS, SMC or NICE, 3 medicine-indication pairs were excluded due to withdrawal of marketing authorisation, and one medicine-indication pair was excluded due to lack of HTA evaluation. Within Canada, 20 of the NOC/Cs were granted to generic products and were excluded from the sample. Of the remaining 39 medicine-indication pairs, 28 had at least one HTA evaluation by either CADTH/PCODR (Ontario) or INESSS (Quebec), 7 were excluded due to lack of HTA evaluation, 2 were excluded due to withdrawal of the marketing authorisation, and 2 were excluded due to an absence of marketing authorisation reports. In total, 49 medicine-indication pairs were included in the sample, 21 from the EMA and 28 from Health Canada (See Appendix A2 and A3 for complete list of the medicine-indication pairs and a breakdown of medicines by therapeutic area).

The majority of conditional authorisations in both Europe and Canada were for oncology products, classified according to the Anatomical Therapeutic Chemical (ATC) classification system as antineoplastic and immunomodulating agents, corresponding to 86% of Health Canada NOC/C approvals and 71% of EMA CMA approvals. In Canada the remaining approvals were for alimentary track and metabolism products (Kanuma for LAL deficiency, Ocaliva for primary biliary cholangitis, and Strensiq for hypophosphatasis) and for anti-infectives for systemic use (Daklinza for the treatment of chronic hepatitis C). In Europe the remaining approvals were for sensory organs (Holoclar for chemical or physical eye burns), anti-infectives for systemic use (Deltyba and Sirturo for tuberculosis), nervous system disorders (Fampyra for Multiple Sclerosis), systemic hormonal preparations (Translarna for Duchene Muscular Dystrophy), and musculo-skeletal system (Natpar for chronic hypo-parathyroidism). Concordance between EMA and Health Canada on conditional approvals was low. Only 43% ($n = 9$) of EMA CMA medicine-indication pairs had an NOC/C for the same indication (Adcetris for 2 indications, Blincyto, Bosulif, Darzalex, Tagrisso, Votrient, Xalkori, and Zykadia).

3.2. Descriptive statistics

Descriptive analysis of the aggregate sample according to HTA outcome yielded a number of statistically significant differences (See Table 3). In the aggregate sample, HTA outcomes were found to vary significantly when comparing across HTA agencies ($p = 0.038$), according to consideration of disease rarity ($p = 0.008$), according to presence of clinical uncertainties in study design ($p = 0.0005$), and according to presence of economic uncertainties related to cost-effectiveness ($p = 0.021$).

No significant differences in HTA outcomes were identified based on oncology vs non-oncology products, prior rejection and trial phase. Further, no significant difference was found in average time between MA and HTA across HTA outcomes or according to year of evaluation.

3.3. Analysis of HTA outcomes at agency level

HTA outcomes for CMA and NOC/C medicine-indication pairs vary considerably across settings. Positive listing recommendations (L, LWC or LWC after resubmission) range from 95% (HAS) to 29% (SMC) of outcomes, and account for 78%, 67% and 46% of outcomes in CADTH, NICE and INESSS respectively (See Appendix A4). All positive listing recommendations for the sample included either clinical (prescribing or population restrictions) or economic conditions (commercial access agreement or discount to improve cost-effectiveness). INESSS has the highest frequency of negative listing decisions (46%), followed by CADTH (21%), SMC (14%), NICE (5%) and HAS (5%). HTA submissions were not present for 9 medicine-indication pairs in SMC, 6 medicine-indication pairs in NICE, and 2 medicine-indication pairs in INESSS. Approximately 15−20% of medicine-indication-pairs were subject to resubmissions, following an initial rejection. The majority of resubmissions (90%) resulted in a positive listing recommendation. Two medicine-indication pairs, Imbruvica for the treatment of patients with relapsed/refractory mantle cell lymphoma (MCL), and Votrient for the first-line treatment of advanced renal-cell carcinoma (RCC), were rejected following a resubmission by INESSS and HAS respectively.

Concordance across HTA agencies in outcomes was low. Within Europe, only 8 medicine-indication pairs (38%) had positive listing recommendations across all three HTA agencies (Adcetris, Blincyto, Bosulif, Darzalex, Tagrisso, Zykadia, Bavencio, and Xalkori). Of these medicine-indication pairs, four required at least one resubmission in either NICE, SMC, or HAS (Adcetris, Bosulif, Darzalex, and Xalkori). All medicine-indication-pairs in Europe obtained at least one positive HTA recommendation. Within Canada, 13 medicine-indication pairs (46%) had positive listing recommendations in both CADTH and INESSS and 4 medicine-indication pairs (14%) were rejected by both agencies (Darzalex, Alecensaro, Arzerra and Imbruvica). The remaining 11 medicine-indication pairs (40%) received diverging recommendations by CADTH and INESSS (32%) or were only evaluated by one agency (8%).

3.4. Clinical evidence–marketing authorisation vs HTA

NOC/C approvals by Health Canada were more frequently based on non-randomised clinical evidence than CMA approvals by EMA (72% vs 57% respectively). However, the most common pivotal trial design was single arm phase II trials in both the EMA (47%) and in Health Canada (57%). Only 6 medicine-indication pairs (29%) relied on phase III trial data for EMA CMA approval and only 4 medicine-indication pairs (14%) for Health Canada NOC/C approvals (See Fig. 1). In two instances, EMA CMA was granted on the basis of a phase I trial (Zykadia for ALK positive non-small cell lung cancer) and an observational study (Holoclar for the treatment of chemical or physical eye burns). In Canada, NOC/C approval was granted once on the basis of an observational study (Soliris for atypical hemolytic uremic syndrome) and three times on the basis of phase I trial data (Zykadia for ALK positive non-small cell lung cancer, Keytruda for metastatic non-small cell lung cancer and Keytruda for metastatic melanoma).

Three types of conditions were imposed by Health Canada and EMA for NOC/C and CMA approvals: (a) submission of follow-up data from pivotal clinical trials, (b) completion of a confirmatory phase II trial, or c) completion of a confirmatory phase III trial. Within Canada, 72% of NOC/C approvals required submission of follow-up data from pivotal clinical trials, 68% of approvals required completion of a confirmatory phase III trial, 21% of approvals required completion of a confirmatory phase II trial. Within Europe, 71% of CMA approvals required completion of confirmatory phase III trial, 19% required completion of a phase II trial, and 14% required submission of follow-up data from the pivotal clinical trial.

Relative to regulatory approval, HTA submissions were more frequently based on RCT designs. RCTs were the primary source of evidence in 62% of HAS submissions, 58% of INESSS submissions, 57% of CADTH submissions, 50% of SMC submissions, and 47% of NICE submissions. Across all settings, a substantial number of HTA submissions

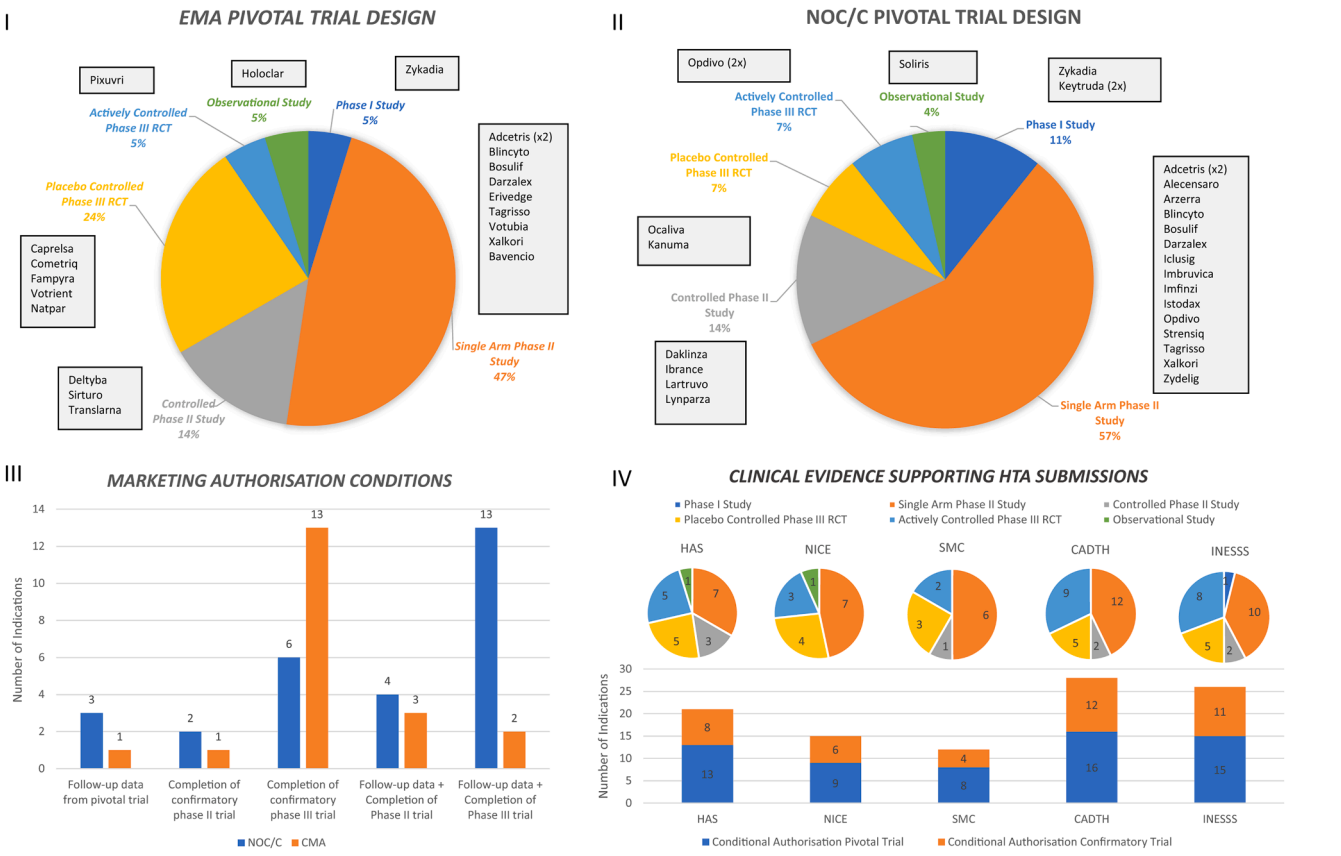

Fig. 1. Clinical Evidence Supporting Marketing Authorisation and HTA Approval of Accelerated Access Products. I – Pivotal trial design of EMA conditional marketing authorisation approvals between 2010 and 2017 with at least one HTA evaluation in France, England or Scotland. II – Pivotal trial design of Health Canada notice of compliance with conditions approvals between 2010 and 2017 with at least one HTA evaluation in Ontario (CADTH/PCODR) or Quebec (INESSS). III – Evidence generation conditions set by EMA and Health Canada for conditional marketing authorisation approvals and notice of compliance with conditions. IV – Characteristics of main clinical trial supporting HTA submissions for conditional marketing authorisation approvals and notice of compliance with conditions. Part A provides an overview of the study designs for the main trial supporting HTA approval. Part B outlines the extent to which clinical evidence supporting HTA is based on the conditional authorisation pivotal trial or based on pivotal trial confirmatory trials.

were based on single arm phase II trials. The majority of HTA submissions relied on the same trial used to support regulatory approval. However, evidence from confirmatory trials (the conditions for marketing authorisation), was available in 38% of HAS submissions, 40% for NICE submissions, 33% of SMC submissions, 43% of CADTH submissions, and 42% of INESSS submissions. Out of the 24 medicine-indication pairs that received a negative HTA recommendation across all settings, 45.8% were based on single arm phase II trials, 42% were based on randomised phase III trials, 8% were based on controlled phase II trials, and 4% were based on phase I trials.

3.5. Impact of clinical uncertainties on HTA outcomes–agency-level analysis

A total of 738 clinical uncertainties were identified across the entire sample of CMA and NOC/C medicine-indication pairs (See Fig. 2). Across all settings the most common type of clinical uncertainty raised related to the magnitude of clinical benefit (HAS, NICE, SMC and CADTH) or poor study design (INESSS).

Within HAS, uncertainty in the magnitude of clinical benefit, lack of clinical evidence, study design, and relevance to local clinical practice were the most common issues raised (47%, 15%, 18%, and 14% respectively). Over 85% of clinical uncertainties raised by HAS were not addressed in the assessment and were considered to be limitations in the clinical evidence submitted. Marginal differences in the average number and type of clinical uncertainties are present when comparing products by HTA outcome. On average, products given an ASMR rating of V had a larger number of uncertainties that were not overcome and a smaller number of addressed uncertainties relative to products given an ASMR rating of IV or III. In particular, products with an ASMR rating of V had a greater number of unaddressed uncertainties relating to evidence on the magnitude of clinical benefit and relating to issues with poor study design.

The key clinical uncertainties raised during NICE assessments of CMA products included uncertainty in magnitude of clinical benefit (25%), poor study design (24%), relevance to local clinical practice (16%), generalizability of trial population (15%) and lack of evidence (10%). Comparisons between products based on HTA outcome are limited by low sample size. The only CMA medicine-indication pair that received a negative listing decision by NICE was Erivedge for metastatic basal cell carcinoma. A total of six clinical uncertainties were raised during NICE's assessment of Erivedge. Two issues were raised on the magnitude of clinical benefit (no evidence of benefit in a subgroup and low magnitude of survival benefit), two issues on lack of evidence (no

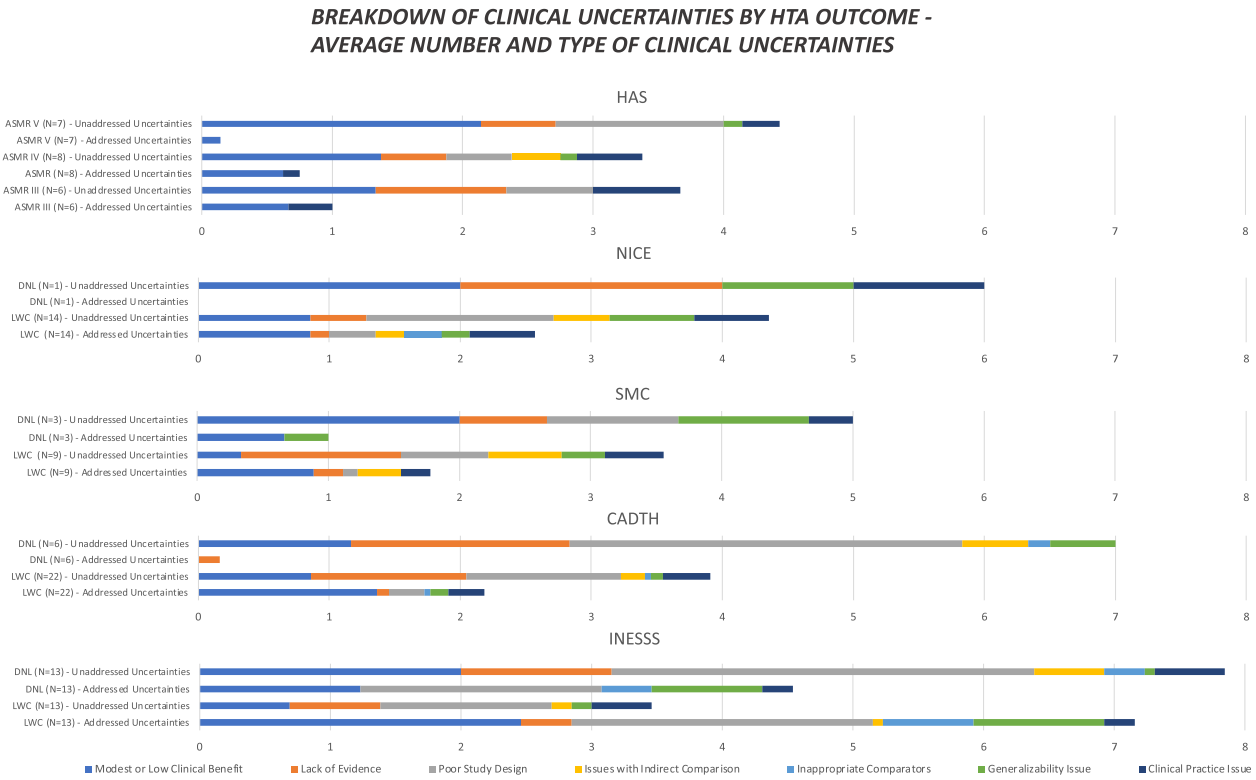

Fig. 2. Average Number and Type of Clinical Uncertainties Raised in the Assessment of CMA Approvals between 2010-2017 in France (HAS), England (NICE), and Scotland (SMC) and of NOC/C approvals in Ontario (CADTH) and Quebec (INESSS). Clinical uncertainties are categorized according to whether or not they have been addressed or remain unaddressed in the context of a decision. Data is presented at country level and according to HTA outcome: LWC = HTA recommendation to list with conditions, DNL = HTA recommendation to not list a product. ASMR = Amélioration du Service Médical Rendu (Scale of added clinical benefit ranging from V – non-existent to I – Major).

direct comparative evidence to best supportive care and no long-term OS data), one issue relating to generalizability (proportion of patients in trial with Gorlin syndrome higher than expected in the UK population), and one issue relating to clinical practice (trial not generalizable to UK clinical practice for patients with basal cell carcinoma).

The key clinical uncertainties raised during SMC assessments of CMA products included uncertainty in magnitude of clinical benefit (29%), lack of evidence (23%), issues in study design (15%), issues in indirect comparison (12%), relevance to local clinical practice (11%), and generalizability of trial population (11%). Unresolved uncertainties relating to magnitude of clinical benefit, poor study design and generalizability of trial population were more common in medicine-indication pairs that received negative recommendations relative to medicine-indications that were conditionally recommended for funding.

Within CADTH, uncertainties in magnitude of clinical benefit, lack of evidence and study design were most common (32%, 22%, and 28% respectively). Unresolved uncertainties relating to poor study design and generalizability of trial population were more common in medicine-indication pairs that received negative recommendations relative to medicine-indications that were conditionally recommended for funding. While the total average number of uncertainties raised was similar across LWC and DNL groups (7.16 vs 7), clinical uncertainties were more likely to be addressed in assessments with positive outcomes.

Similar to CADTH, uncertainties in magnitude of clinical benefit, lack of evidence and study design were the most common uncertainties raised by INESSS (28%, 10%, and 38%, respectively). Medicine-indication pairs with negative HTA outcomes are more likely to have unresolved clinical uncertainties (magnitude of clinical benefit, lack of evidence and study design) relative to medicine-indication pairs with positive HTA outcomes. Common unresolved issues in study design leading to negative recommendations by INESSS included (small number of patients ($n = 5$), issues in randomisation ($n = 3$), inappropriate outcome measure ($n = 2$), issues in study blinding ($n = 4$), confounding due to patient crossover ($n = 2$) and inadequate study duration ($n = 2$).

3.6. Impact of economic uncertainties on HTA outcomes–agency-level analysis

A total of 368 economic uncertainties were identified across the entire sample of CMA and NOC/C medicine-indication pairs (See Fig. 3). Economic analysis was not routinely performed for HAS medicine-indication pairs (only one medicine-indication pair submitted an economic evaluation – a cost-minimisation analysis of Zykadia for ALK positive NSCLC). Only one economic uncertainty was raised in relation to the appropriateness of conducting a cost-minimisation analysis, which was addressed and deemed appropriate.

The most common type of economic uncertainty raised during NICE evaluations related to modelling issues (37% of all economic uncertainties), followed by issues in cost-effectiveness estimate (29%), issues in utility estimates (24%) and issues in cost estimations (12%). Comparison across medicine-indication pairs by HTA outcome is limited due to sample size. In their negative recommendation for Erivedge, NICE

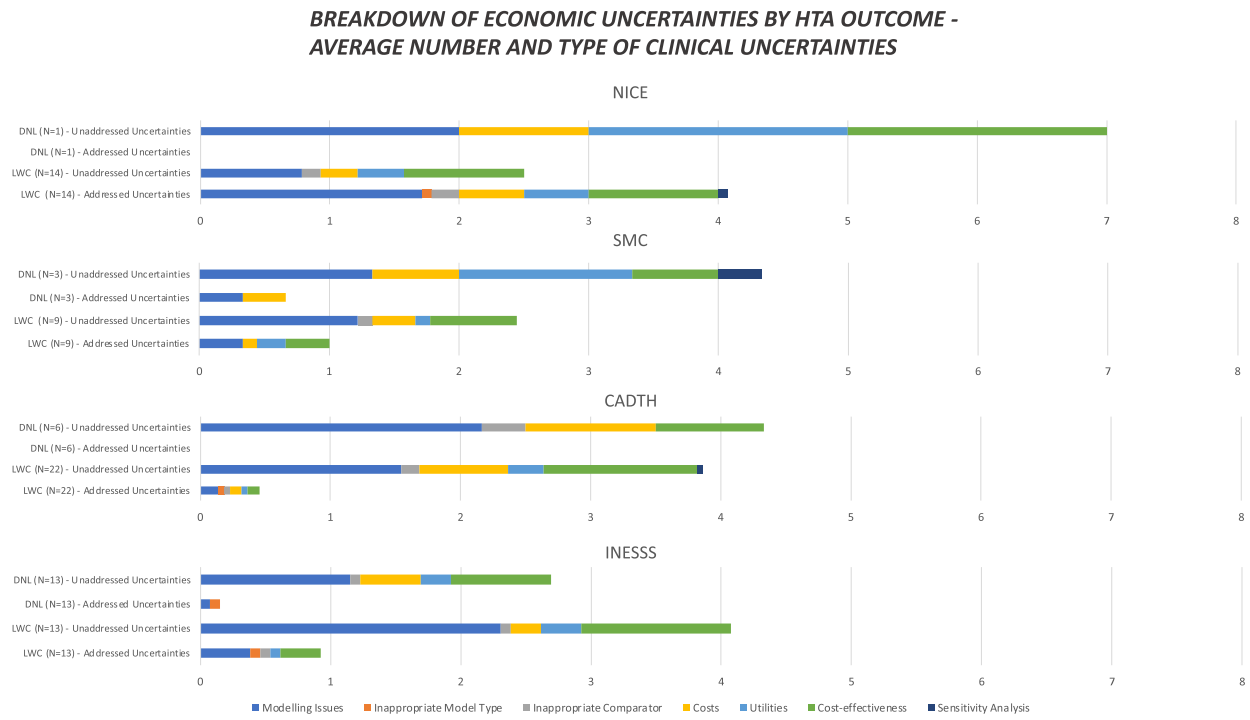

Fig. 3. Average Number and Type of Economic Uncertainties Raised in the Assessment of CMA Approvals between 2010-2017 in England (NICE), and Scotland (SMC) and of NOC/C approvals in Ontario (CADTH) and Quebec (INESSS). Economic uncertainties are categorized according to whether or not they have been addressed or remain unaddressed in the context of a decision. Data is presented at country level and according to HTA outcome: LWC = HTA recommendation to list with conditions, DNL = HTA recommendation to not list a product.

raised two uncertainties on modelling (limitations in clinical evidence used and inappropriate extrapolation method for estimating time to treatment discontinuation), two issues in cost effectiveness (ICER too high after adjustments, ICER highly uncertain), two issues in utilities (utilities not generalizable to UK and uncertainty in quality of life data), and one issue in costs (cost of best-supportive care being over-estimated). The majority of uncertainties raised for medicine-indication pairs with positive NICE outcomes were overcome.

Within Scotland, the most common type of economic uncertainty raised was also related to modelling issues (41%), followed by issues in cost-effectiveness estimates (24%), issues in utility estimates (15%) and issues in cost estimations (15%). Medicine-indication pairs with negative HTA outcomes had a larger average number of unresolved economic uncertainties than medicine-indication pairs with positive HTA outcomes. In particular, issues in cost estimation and utility estimation were more common in the negative outcome group.

Modelling issues were also the most frequently raised type of economic uncertainty by CADTH (41%) and INESSS (50%). Within CADTH, only marginal differences were seen between medicine-indication pairs with positive and negative outcomes. Unresolved uncertainties in modelling and cost estimation were slightly more common in the negative HTA outcome group. In the negative recommendation group (Darzalex, Alecensaro, Arzerra, Imbruvica, Zydelig, and Soliris), unresolved issues in modelling included majority of clinical benefit being derived post-progression ($n = 1$), uncertainty in treatment duration ($n = 3$), issues with extrapolation ($n = 5$), inappropriate time horizon ($n = 3$), and lack of clinical evidence ($n = 1$).

Within INESSS, unresolved economic uncertainties were more common in the positive HTA outcome group than the negative HTA outcome group. Economic assessment was limited for a number of medicine-indication pairs in the negative HTA outcome group. For Arzerra, Zykadia, Alecensaro, Darzalex, and Lartuvo, INESSS rejected the economic analysis submitted due to high levels of uncertainty in the clinical evidence submitted.

3.7. *Impact of social value judgments on HTA outcomes–agency-level analysis*

Social value judgments raised in the context of HTA assessments include disease rarity, disease severity, unmet medical need, innovative mechanism of action, short life expectancy for patient population, administration advantages, and special demographics (See Fig. 4). The most commonly raised SVJs in HTA assessments of CMA and NOC/C products across all settings were disease severity and unmet need. Disease severity was raised in the majority of assessments across all agencies, 81% of HAS assessments, 80% in NICE assessments, 73% of SMC assessments, 72% of CADTH assessments, and 89% of INESSS assessments. In NICE, SMC, CADTH and INESS, disease severity was mentioned more frequently in the context of negative HTA outcomes relative to positive HTA outcomes, although the difference was marginal for INESSS and NICE. Unmet need was also raised in the majority of assessments across all agencies, 82% of HAS assessments, 73% in NICE assessments, 92% of SMC assessments, 85% of CADTH assessments, and 93% of INESSS assessments. Unmet need was raised more frequently in positive HTA outcomes in HAS (ASMR III 100% vs ASMR V 57%) and in CADTH (LWC 95% vs DNL 50%).

Across all settings, disease rarity was raised more frequently in the context of positive decisions. This difference was most notable in the HAS (100% of assessments that resulted in an ASMR rating of III vs only 25% for ASMR IV and 14% for ASMR V), CADTH (41% LWC vs 17% DNL), and SMC (44% LWC vs 0% DNL), followed by NICE (21% vs 0%) and INESSS (23% vs 15%).

Fig. 4. Key Social Value Judgments (SVJs) Raised in the Assessment of CMA Approvals between 2010 and 2017 in France (HAS), England (NICE), and Scotland (SMC) and of NOC/C approvals in Ontario (CADTH) and Quebec (INESSS). SVJs are reported in terms of the frequency in which they are raised in the HTA decisions. Data is presented by country and according to HTA outcome: LWC = HTA recommendation to list with conditions, DNL = HTA recommendation to not list a product. ASMR = Amélioration du Service Médical Rendu (Scale of added clinical benefit ranging from V – non-existent to I – Major).

Innovative mechanism of action, short life expectancy, administrative advantage and special demographics were raised less frequently in the assessment of NOC/C and CMA products with a few exceptions. In SMC, innovative mechanism of action was raised in 75% of assessments, while special demographics were mentioned in 50% of assessments. Meanwhile, in INESSS, short life expectancy was raised in 63% of assessments and administration advantage was mentioned in 43% of assessments.

4. Discussion

There is a clear disconnect between expedited regulatory pathways that are promoting accelerated access to innovative medicines, and HTA agencies that still require robust clinical evidence to arrive at funding decisions. While evidence from confirmatory trials is available for use in HTA submissions in approximately 30−40% of cases, resubmissions and rejections of conditionally approved products are common, and a wide range and number of unresolved clinical and economic uncertainties are raised in the context of HTA decisions.

This study has enabled a comprehensive evaluation of the key parameters (clinical, economic and additional dimensions of value) that HTA agencies consider in the assessment and appraisal of conditionally approved medicines. Within Europe, CMA products must address an unmet medical need and demonstrate proof that the benefit to public health of the immediate availability of a product outweighs the risk associated with immature data [5]. Within Canada, NOC/C products must be used in serious or life threatening conditions where there is (a) no available therapy or (b) where the product represents a significant improvement over existing products available in Canada [4]. Despite clear criteria for fulfilling unmet medical need in serious or life threatening conditions, HTA outcomes for these products are highly variable across the HAS, NICE, SMC, CADTH and INESSS suggesting that

contextual considerations and SVJs alone, such as disease severity and unmet need, are not sufficient to overcome issues in clinical and economic evidence at HTA level.

Out of the five agencies in our sample, NICE was the most favourable towards conditionally approved products, providing positive recommendations to 93% (14/15) medicine-indication pairs that were appraised. While HAS also had a high frequency of approval in terms of reimbursement (only one product received an SMR rating of "insufficient"), no products received an ASMR of I or II (indicating a "major" or "important" added benefit, respectively) and 33% of medicine-indication pairs received an ASMR rating of V indicating non-existent added benefit or "lack of therapeutic progress". This indicates a clear disconnect between the HAS and EMA on the value of conditionally approved products. Conditionally approved products had mixed success with the SMC, as only half of the products appraised received a positive coverage rercommendation upon completion of the process, while an additional 3 products received a positive coverage recommendation following resubmission. CADTH was also relatively favourable towards NOC/C products, although 21% of medicine-indication pairs received a negative recommendation and a further 21% required a resubmission for a positive HTA outcome. INESSS was the least favourable towards conditionally approved products, providing a positive recommendation to only 50%.

It is clear that HTA agencies do not rely on a single metric to arrive at an assessment outcome, but, rather, a combination of multiple parameters. Products with negative HTA outcomes (DNL and SMR insufficient) frequently had several dimensions of value that were remarked upon positively by HTA agencies, most frequently disease severity and unmet need. Nevertheless, SVJs alone, may not compensate for concerns related to clinical and economic evidence. Across the aggregate sample, products with negative HTA outcomes have a high tendency to have unresolved study design issues and unresolved issues in the cost-effectiveness estimates, even for products identified for use in severe diseases with high unmet need.

Within the HAS, uncertainties in magnitude of clinical benefit, issues in study design, disease rarity, and unmet need were key parameters in distinguishing products by ASMR rating. Within NICE, uncertainties in the magnitude of clinical evidence, uncertainties related to lack of evidence, uncertainties in cost estimation, and uncertainties in utilities estimates were notable parameters in the rejection of Erivedge. Within the SMC, uncertainties in magnitude of clinical benefit, issues in study design, issues in generalisability of the trial population, uncertainty in cost estimation, uncertainty in utilities estimates, disease rarity, and administration advantage were key parameters in distinguishing products with positive and negative HTA outcomes. In CADTH, uncertainty in study design, uncertainty in generalisability of trial population, uncertainties in modelling, and unmet need were key parameters in distinguishing products with positive and negative HTA outcomes. Finally in INESSS, uncertainties in magnitude of clinical benefit, uncertainties in study design, uncertainties in cost estimation, innovative mechanism of action and administration advantage were key parameters in distinguishing products with positive and negative HTA outcomes.

The heterogeneity in HTA outcomes reported here is consistent with other empirical studies that have compared HTA assessment and outcomes across settings [24–27], and raise questions around whether or not current frameworks employed by HTA agencies adequately capture all elements of value that a product provides. This is particularly important in the context of conditionally approved products where patients often have no therapeutic alternatives and are suffering from life-threatening or chronically debilitating conditions.

Several policy priorities emerge from our analysis. First, greater alignment between regulatory bodies and HTA agencies is needed on evidence requirements for conditionally approved medicines. The extent to which conditional marketing authorisation pathways reduce clinical development time is currently limited by stringent HTA evidence requirements, resulting in reduced or delayed availability of conditionally approved medicines. HTA agencies and regulatory bodies serve fundamentally different functions with distinct objectives. While complete harmonization of evidence requirements is not pragmatic, more can be done to tailor HTA processes to conditionally approved products. Conditional reimbursement pathways, such as England's Cancer Drugs Fund (CDF), provide temporary reimbursement to products with high levels of clinical uncertainty to allow time for evidence maturation and could be implemented more widely [30]. While conditional reimbursement pathways produce greater administrative burden, due to the need for resubmission and reassessment following evidence maturation, their use may be warranted in limited cases for medicines that address an unmet medical in a serious or life-threatening condition.

Second, HTA agencies need to play a more active role in evidence generation planning for conditionally approved medicines. In a recent EMA report on experience with the CMA from 2006-2016, the EMA calls for greater engagement with HTA agencies and increased use of early dialogue [31]. A number of initiatives on joint early dialogue between regulators and HTA agencies and involving multiple HTA agencies have been launched recently in Europe including the EMA-EUnetHTA Parallel Consultation procedure and the EUnetHTA-Multi HTA Early Dialogue procedure [32,33]. HTA agencies should have more systematic and earlier involvement in joint early dialogue processes to clarify evidence expectations earlier in the clinical development pathway and to help mitigate negative HTA outcomes for conditionally approved medicines.

Finally, there is a need for increased transparency and consistency in HTA decision-making, particularly in the incorporation of parameters beyond clinical and cost effectiveness. SVJs are consistently raised during the HTA decision-making process, providing contextual considerations. However, methods of incorporating social value judgements are not explicitly defined in HTA processes, leading to uncertainty in the impact of these parameters on decision-making. A recent review of HTA systems and methods highlighted that while HTA agencies routinely consider economic and clinical evidence, other elements of value are often considered implicitly [28]. Novel approaches to HTA such as multiple criteria decision analysis (MCDA) could help to improve the transparency of decision-making through explicit consideration and weighting of a range of different value dimensions [29]. While MCDA could help to clarify questions around what constitutes value in the context of conditionally approved medicines, it does not guarantee that different HTA agencies or regulatory agencies will align on their definition of value. Alternatively, HTA agencies should explore alternative mechanisms of explicitly scoring or weighting social value parameters, with clearly defined criteria and impact on decision-making (e.g. sliding cost-effectiveness thresholds).

There are several limitations in the present study which highlight areas for future research. First, while the analytical framework employed in the present study allows for the identification of the frequency with which a particular parameter is raised in the context of HTA, the weight of particular parameters on the final decision may be variable. In particular, the relative impact of clinical vs non-clinical parameters (social value judgements) on the final decision remains unknown. For instance, the level of unmet need and ethical obligations to fund a novel medicine is unlikely to uniform across all disease areas. By extension, the extent to which unmet need modifies HTA outcomes is likely to vary from medicine-to-medicine. As such, while the results presented here help to explain some of the heterogeneity seen across settings in the evaluation of conditionally approved products and what parameters are likely to be important, they do not fully account for the discrepancies seen across settings. Second, the results are unique to the HTA agencies considered and to conditionally approved products approved between 2010-2017, and, as such, are not generalizable to other HTA agencies or types of products including those with standard regulatory approval. While outside the scope of the present study, which was limited to the characteristics, evidence and evaluation of conditionally approved products, an evaluation of how HTA agencies compare in their assessment of standard vs conditionally approved

products would present a natural extension and offer further clarity on how HTA agencies balance uncertainties in clinical and economic evidence with additional dimensions of value such as disease severity and unmet need. There would also be added value in considering the impact of alternative regulatory pathways including priority review and authorisation under exceptional circumstances. Third, while the Health Canada NOC/C pathway and the EMA CMA pathway are not asimilar, they each have distinct eligibility criteria, as evidenced by differences in the products that received conditional approval in the respective settings. As a result, it is possible that the differences identified across HTA agencies in the evaluation of conditionally approved products are partially caused to differences at regulatory level, rather than differences in evidence thresholds and consideration of uncertainty and additional dimensions of value. Finally, marketing authorisation for a small number of conditionally approved products was withdrawn and, because of that, they were excluded due to redaction of HTA reports. This may bias the results slightly in favour of products with positive HTA outcomes.

5. Conclusion

This study explored the disconnect between regulatory and health technology assessment agencies on the value of conditionally approved products through application of a mixed-methods analytical framework. Significant heterogeneity was noted in terms of parameters considered by HTA agencies and HTA outcomes. The push for accelerated access to medicines for serious and life-threatening conditions by regulatory agencies is often stalled by HTA agencies that require robust evidence to inform resource allocation recommendations or decisions.

As more innovative and life-saving medicines are developed, it will be critical to improve the dialogue between all stakeholders in order to clarify evidence requirements and avoid delays in patient access.

Availability of data and material

All data sources used are publicly available. Regulatory agency websites were screened to identify marketing authorisation reports for all indications approved for the selected multi-indication medicines. This included the European Medicines Agency (EMA) and Health Canada. HTA agency websites were screened to identify HTA recommendations issued for all indications for the selected multi-indication medicines. This included the National Institute of Health and Care Excellence (NICE), the Scottish Medicines Consortium (SMC), the Haute Authorité 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

Not applicable.

CRediT authorship contribution statement

Mackenzie Mills: Conceptualization, Methodology, Data curation, Formal analysis, Writing – original draft, Writing – review & editing. **Panos Kanavos:** Conceptualization, Methodology, Supervision, Writing – review & editing.

Declaration of Competing Interest

The authors have no conflict of interest or competing interests.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.healthpol.2022.08.005.

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