## Supplementary materials

Supplementary Table 1 Search strategy

Ovid MEDLINE, 1946 to June Week 4 2020

|  |  |  |
| --- | --- | --- |
| Search No. | Searches | Results |
| 1 | (health technolog$ adj6 assessment$).ti,ab. | 3790 |
| 2 | (health technolog$ adj6 recommend$).ti,ab. | 90 |
| 3 | (health technolog$ adj6 adopt$).ti,ab. | 97 |
| 4 | (health technolog$ adj6 appraisal$).ti,ab. | 74 |
| 5 | (pharmaceutical$ adj6 subsidy).ti,ab. | 28 |
| 6 | (pharmaceutical$ adj6 coverage).ti,ab. | 113 |
| 7 | (pharmaceutical$ adj6 reimbursement).ti,ab. | 242 |
| 8 | (pharmaceutical$ adj6 listing).ti,ab. | 45 |
| 9 | (pharmaceutical$ adj6 market access$).ti,ab. | 12 |
| 10 | (pharmaceutical$ adj6 decision make$).ti,ab. | 30 |
| 11 | (drug$ adj6 subsidy).ti,ab. | 85 |
| 12 | (drug$ adj6 coverage).ti,ab. | 1684 |
| 13 | (drug$ adj6 reimbursement).ti,ab. | 899 |
| 14 | (drug$ adj6 listing).ti,ab. | 163 |
| 15 | (drug$ adj6 market access$).ti,ab. | 29 |
| 16 | (drug$ adj6 decision make$).ti,ab. | 53 |
| 17 | (medicine$ adj6 subsidy).ti,ab. | 15 |
| 18 | (medicine$ adj6 coverage).ti,ab. | 238 |
| 19 | (medicine$ adj6 reimbursement).ti,ab. | 247 |
| 20 | (medicine$ adj6 listing).ti,ab. | 49 |
| 21 | (medicine$ adj6 market access$).ti,ab. | 13 |
| 22 | (medicine$ adj6 decision make$).ti,ab. | 46 |
| 23 | (medication$ adj6 subsidy).ti,ab. | 11 |
| 24 | (medication$ adj6 coverage).ti,ab. | 393 |
| 25 | (medication$ adj6 reimbursement).ti,ab. | 214 |
| 26 | (medication$ adj6 listing).ti,ab. | 61 |
| 27 | (medication$ adj6 market access$).ti,ab. | 1 |
| 28 | (medication$ adj6 decision make$).ti,ab. | 18 |
| 29 | (coverage adj5 decision$).ti,ab. | 783 |
| 30 | (reimbursement adj5 decision$).ti,ab. | 776 |
| 31 | value for money.ti,ab. | 1391 |
| 32 | 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 | 10329 |
| 33 | framework$.ti,ab. | 194075 |
| 34 | model$.ti,ab. | 2343559 |
| 35 | priorit$.ti,ab. | 99748 |
| 36 | priority setting$.ti,ab. | 2023 |
| 37 | criteri$.ti,ab. | 550684 |
| 38 | preference$.ti,ab. | 125985 |
| 39 | weight$.ti,ab. | 872657 |
| 40 | importance$.ti,ab. | 600478 |
| 41 | contribution$.ti,ab. | 343046 |
| 42 | impact$.ti,ab. | 885968 |
| 43 | factor$.ti,ab. | 2890428 |
| 44 | attribute$.ti,ab. | 216860 |
| 45 | determinant$.ti,ab. | 208218 |
| 46 | driver$.ti,ab. | 51350 |
| 47 | (tradeoff$ or trade off$).ti,ab. | 21576 |
| 48 | 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 | 7260623 |
| 49 | decision maker$.ti,ab. | 11760 |
| 50 | payer$.ti,ab. | 12562 |
| 51 | policy maker$.ti,ab. | 18089 |
| 52 | (committee adj5 member$).ti,ab. | 2397 |
| 53 | expert$.ti,ab. | 160007 |
| 54 | appraisal$.ti,ab. | 30309 |
| 55 | decision$.ti,ab. | 309387 |
| 56 | submission$.ti,ab. | 7956 |
| 57 | evaluation$.ti,ab. | 1075634 |
| 58 | 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 | 1527993 |
| 59 | cancer$.ti,ab. | 2400229 |
| 60 | neoplasm$.ti,ab. | 171264 |
| 61 | tumor$.ti,ab. | 1778205 |
| 62 | oncology$.ti,ab. | 183588 |
| 63 | 59 or 60 or 61 or 62 | 3402145 |
| 64 | 32 and 48 and 58 and 63 | 678 |
| 65 | limit 64 to English language | 641 |
| Outcome |  | 641 |

EMBASE via Ovid, 1974 to 02 July 2020

|  |  |  |
| --- | --- | --- |
| Search No | Searches | Results |
| 1 | (health technolog$ adj6 assessment$).ti,ab. | 6826 |
| 2 | (health technolog$ adj6 recommend$).ti,ab. | 255 |
| 3 | (health technolog$ adj6 adopt$).ti,ab. | 165 |
| 4 | (health technolog$ adj6 appraisal$).ti,ab. | 232 |
| 5 | (pharmaceutical$ adj6 subsidy).ti,ab. | 42 |
| 6 | (pharmaceutical$ adj6 coverage).ti,ab. | 210 |
| 7 | (pharmaceutical$ adj6 reimbursement).ti,ab. | 579 |
| 8 | (pharmaceutical$ adj6 listing).ti,ab. | 94 |
| 9 | (pharmaceutical$ adj6 market access$).ti,ab. | 72 |
| 10 | (pharmaceutical$ adj6 decision make$).ti,ab. | 82 |
| 11 | (drug$ adj6 subsidy).ti,ab. | 124 |
| 12 | (drug$ adj6 coverage).ti,ab. | 2964 |
| 13 | (drug$ adj6 reimbursement).ti,ab. | 2407 |
| 14 | (drug$ adj6 listing).ti,ab. | 372 |
| 15 | (drug$ adj6 market access$).ti,ab. | 177 |
| 16 | (drug$ adj6 decision make$).ti,ab. | 125 |
| 17 | (medicine$ adj6 subsidy).ti,ab. | 33 |
| 18 | (medicine$ adj6 coverage).ti,ab. | 436 |
| 19 | (medicine$ adj6 reimbursement).ti,ab. | 593 |
| 20 | (medicine$ adj6 listing).ti,ab. | 92 |
| 21 | (medicine$ adj6 market access$).ti,ab. | 53 |
| 22 | (medicine$ adj6 decision make$).ti,ab. | 78 |
| 23 | (medication$ adj6 subsidy).ti,ab. | 33 |
| 24 | (medication$ adj6 coverage).ti,ab. | 787 |
| 25 | (medication$ adj6 reimbursement).ti,ab. | 450 |
| 26 | (medication$ adj6 listing).ti,ab. | 115 |
| 27 | (medication$ adj6 market access$).ti,ab. | 5 |
| 28 | (medication$ adj6 decision make$).ti,ab. | 32 |
| 29 | (coverage adj5 decision$).ti,ab. | 1348 |
| 30 | (reimbursement adj5 decision$).ti,ab. | 2006 |
| 31 | value for money.ti,ab. | 2392 |
| 32 | 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 | 19708 |
| 33 | framework$.ti,ab. | 299731 |
| 34 | model$.ti,ab. | 3634527 |
| 35 | priorit$.ti,ab. | 157233 |
| 36 | priority setting$.ti,ab. | 2836 |
| 37 | criteri$.ti,ab. | 1018440 |
| 38 | preference$.ti,ab. | 184496 |
| 39 | weight$.ti,ab. | 1340198 |
| 40 | importance$.ti,ab. | 880669 |
| 41 | contribution$.ti,ab. | 458731 |
| 42 | impact$.ti,ab. | 1559325 |
| 43 | factor$.ti,ab. | 4326684 |
| 44 | attribute$.ti,ab. | 328677 |
| 45 | determinant$.ti,ab. | 283132 |
| 46 | driver$.ti,ab. | 91489 |
| 47 | (tradeoff$ or trade off$).ti,ab. | 30724 |
| 48 | 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 | 11016583 |
| 49 | decision maker$.ti,ab. | 18501 |
| 50 | payer$.ti,ab. | 26511 |
| 51 | policy maker$.ti,ab. | 26840 |
| 52 | (committee adj5 member$).ti,ab. | 4097 |
| 53 | expert$.ti,ab. | 273247 |
| 54 | appraisal$.ti,ab. | 42717 |
| 55 | decision$.ti,ab. | 514223 |
| 56 | submission$.ti,ab. | 18095 |
| 57 | evaluation$.ti,ab. | 1715512 |
| 58 | 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 | 2461473 |
| 59 | cancer$.ti,ab. | 2711579 |
| 60 | neoplasm$.ti,ab. | 190069 |
| 61 | tumor$.ti,ab. | 2076295 |
| 62 | oncology$.ti,ab. | 206788 |
| 63 | 59 or 60 or 61 or 62 | 4002025 |
| 64 | 32 and 48 and 58 and 63 | 1580 |
| 65 | limit 64 to English language | 1519 |
| Outcome |  | 1519 |

Supplementary Table 2 Definitions of explanatory factors

|  |  |  |
| --- | --- | --- |
| Factor a | Type of factor | Definitions used in the studies (category method if applicable) |
| ***Characteristics of disease*** |  |  |
| Disease prevalence | Categorical | Prevalence (ultra-orphan, orphan) [1]; |
| Continuous | Size of the target population in France [2]; Incidence rate [3]; |
| Unmet need | Categorical | Unmet need (yes, no; yes, no/ not stated) [1, 4]; PBAC judged there to be a high clinical need (yes, no) [5]; |
| Presence of alternatives | Categorical | Alternative treatment (yes, no) [6] [7] [8]; |
| ***Characteristics of technology*** |  |  |
| Administration of technology | Categorical | Administration of drug (injectable, oral) [6] [8]; |
| Treatment strategy | Categorical | first line treatment (yes, no) [6]; Treatment line (first-line, subsequent) [7]; |
| Purpose of technology | Categorical | Treatment intent (curative/adjuvant, palliative) [5]; Treatment intent (curative, palliative) [2]; |
| Submission status | Categorical | Submission type (initial submission, resubmission) [5]; |
| Type of technology | Categorical | Treatment value (orphan drug, Class 1, Class 2) [6]; regular/orphan drugs (regular, orphan) [7]; orphan designation (yes, no) [4]; |
| ***Health outcomes*** |  |  |
| Improvement on efficacy or effectiveness | Categorical | Significant primary outcome mentioned in RCT(yes, no) [6];comparative effectiveness (improved, non-inferior/similar, uncertain) [7]; overall clinical benefit(net benefit, uncertain benefit, no benefit) [8]; improvements in clinical outcomes (no/inconsistent/not measured, yes) [1]; |
| Improvement on OS | Categorical | Evidence of an OS benefit (yes, no) [5]; significant difference in survival in the interventional trials (yes, no) [6]; evidence of an OS benefit (yes, no) [4]; relative survival gain (survival>comparator, survival≤comparator) [8]; |
|  | Continuous | Gain in OS [2]; hazard ratio for OS [9]; |
| Improvement on PRO | Categorical | Improvements in PRO (no/ inconsistent/ not measured, yes) [1]; |
| Improvement on PFS | Categorical | Significant difference in PFS in the interventional trials (yes, no) [6]; |
|  | Continuous | Gain in PFS [2]; hazard ratio for PFS [9]; |
| Quality of clinical evidence | Categorical | Quality of clinical evidence (high quality, low quality) [8]; other study design issues5 (yes, no) [1]; |
| Type of clinical evidence | Categorical | Type of the trial (comparative, not comparative) [2]; availability of comparative data (yes, no) [1]; |
| Acceptance of clinical evidence | Categorical | Efficacy claim (accepted, rejected or partially accepted) [5]; toxicity claim (accepted, rejected or partially accepted) [5]; |
| Type of comparator | Categorical | Comparator type (active, inactive; placebo, active comparator) [5] [2]; |
| Acceptance of comparator | Categorical | Comparator claim (accepted, partially accepted or rejected) [5];clinical relevance of the comparator (criticized, not criticized) [2]; |
| Consistency between population in trials and indications | Categorical | Generalizability of the clinical trial results to the French population (yes, no) [2]; consistency between population in trials and indications (yes, no) [1]; |
| Quantity of clinical evidence | Continuous | The mean number of patients included in observational trials [6]; number of RCTs that provided related data [6]; the mean number of patients included in RCTs [6]; |
| Uncertainty of clincial evidence | Categorical | PBAC judged clinical evidence problematic or uncertainty (yes, no )[5]; |
| Safety | Categorical | Treatment safety (additional monitoring, no additional monitoring) [6]; safety profile (better, similar, worse; lower AE, high/uncertain AE) [2] [8]; safety issues (yes, no)[1]; |
| ***Ecomomic outcomes*** |  |  |
| Cost of technology | Categorical | Daily treatment cost ($CDN/patient): ≤ 150, 150–500, > 500 [1]; |
|  | Continuous | The price per unit of administration[6]; cost per month for experimental arm [9]; |
| Comprative cost/ICER | Categorical | ICER (≤45,000, >45,000$/QALY) [5]; Drug-price comparison (above alternative’s price, below alternative’s price)[7]; cost-effectiveness (yes, no) [3, 4]; ICER(≥ 150,000, <150,000$/QALY) [8]; |
|  | ICER (≤ 100,000, 100,000-500,000, > 500,000 $CDN/QALYs) [1]; |
| Continuous | ICER: CUA value [6]; cost/QALY [9]; ICER [9]; |
| Budget impact | Categorical | Estimated impact on the PBS budget per year (<$10 million, ≥$10 million)[5]; budget impact (high/uncertain budget impact, low budget impact) [8]; |
|  | Continuous | Budget impact of NIHDI [6]; |
| Type of economic analysis | Categorical | Type of economic analysis (CEA and/or CUA, CMA or Other) [5];CUA evaluation (yes, no) [6]; CUA/CEA evaluation (yes, no) [7]; |
| Uncertainty of economic outcomes | Categorical | PBAC judged economic evidence problematic or uncertain (yes, no) [5]; ICER quality (high/unknown uncertainty, low uncertainty) [8]; |
| Risk sharing agreement | Categorical | Risk-sharing agreement (yes, no) [7]; |
| Managed entry agreement | Categorical | Managed entry agreement (no, yes [financial schemes], yes [performance-based], yes [combination of both]) [3]; |
| ***Other variables*** |  |  |
| Decision year | Categorical | Year 2007 [3]; Year 2008 [3]; Year 2009 [3]; Year 2010 [3]; Year 2011 [3]; Year 2012 [3]; Year 2013 [3] |

AE, Adverse Event; CEA, Cost-Effectiveness Analysis; CMA, Cost Minimization Analysis; CRM, Commission of Reimbursement of Medicines; CUA, cost-utility analysis; ICER, Incremental Cost-Effectiveness Ratio; NIHDI, National Institute of Health and Disability Insurance; OS, Overall Survival; PBAC, Pharmaceutical Benefits Advisory Committee; PFS, Progression-Free Survival; PRO, Patient-Reported Outcome; QALY, Quality-Adjusted Life-Year; RCT, Randomized Controlled Trial

a This table only inculded the definitions of factors which were analyzed in more than one study or were found as the significant predictors in one study.

Supplementary Table 3 Analysis and modeling methods

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Study | Dependent variables | |  | Univariable analysis | | | Multivariable analysis | | |
| levels | Definition | Unit of analysis | Method | Number of explanatory variables | Data souce | Method | Number of explanatory variables | Varible Selection method |
| Karikios et al [5] | 2 | Recommendation vs. rejection (rejections and deferrals) | Item, indication | Univariable logistic regression analyses | 16 | HTA guidelines and literautures | 1) Recursive partitioning analysis;  2) Multivariable logistic regression analysis | 1) 3  2) 5 | Significant variables on univariable analysis (P<0.05); backward elimination |
| Pauwels et al [6] | 2 | Recommendation vs. rejection (negative or no advice) | Item, indication | Univariate analysis | 23 | Reimbursement dossiers and literauture | Multivariate logistic regression model | 3 | Significant variables on univariable analysis (P<0.25);  forward selection; |
| Kim et al [7] | 2 | List vs. non-list | Item, indication | Univariable logistic regression analyses | 13 | Reimbursement dossiers and literauture | Multivariate logistic regression model | 1) 13  2) 3 | 1) all the explanatory variables  2) Significant variables on univariable analysis (P<0.25);  stepwise backward elimination |
| Li et al. [2] | 3 | ASMR level (level II and III, IV, V)a | Item | Univariate analysis | 12 | Dossiers from reimbursement commission | NAa | NA | NA |
| Maynou et al [3] | 3 | Recommendation vs. restricted recommendation vs. rejection | Item, indication | NA | NA | NA | A Multi-level mixed-effects ordered probit | 1) 15  2) 22b | t-test and the log-likelihood test |
| Pinto et al [4] | 2 | Recommendion vs. rejection | Item, indication |  |  |  | Linear probability model | 4 | NA |
| Skedgel et al [8] | 3,2,2 | 1) Recommendation vs. conditional recommendation vs. rejection; b  2) Rejection vs. non-rejection (full and conditional recommendation);  Full vs. conditional recommendation c | Item, indication | Univariate analysis | 11 | NA | Multivariate logistic  regression | 11 | test all possible main  effects combinations and plausible interaction terms |
| Niraula et al [9] | 2;2 | 1) Recommendation vs. rejection;d  2) Recommendation vs. conditional recommendation vs. rejection e | Item, indication | Wilcoxon 2-sample test | 6 | NA | Linear regression analysis | 3 | NA |
| Nagase et al [1] | 2 | Recommendation (full and conditional recommendation) vs. rejection | Item, indication | Univariate analysis | 14 | NA | NA | NA | NA |

ASMR, Improvement in Actual Benefit; HTA, Health Technology Assessment; NA, Not Available

a Due to the small number of drugs with ASMR level II, Li et al. combined ASMR levels II (important) and III (moderate) drugs together for the analyses of ASMR drivers;

b The definition of dependent variables was used for the univariate analysis;

c The definition of dependent variables was used for the multivariate logistic regression;

d The definition of dependent variables was used for the Wilcoxon 2-sample test;

e The definition of dependent variables was used for the line regeression analysis

Supplementary Table 4 Factors only investigated in one agency †

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Agency** | **Characteristics of disease** | **Characteristics of technology** | **Health outcomes** | **Ecomomic outcomes** | **Other variables** |
| HAS | None | None | Type of the primary outcome (OS vs PFS vs RR);  Risk/benefit ratio (Important or intermediate) | None | Impact on public health (with impact vs without impact); |
| PBAC | None | List request (new listing vs extend existing listing);  Test required before drug can be used (yes vs no) | None | None | None |
| CRM | None | Treatment supply (hospital vs public pharmacy);  Treatment frequency (once a day – once in 2 weeks vs every 3 – 4 weeks or cycles vs only once) | None | None | None |
| HIRA | None | Number of indication (single vs multiple);  New Mode of Action (yes vs no);  Biological drug (yes vs no);  Type of drug (NCE vs IMD) | None | None | Listing status of reference countries;  PE data exemption (yes vs no) |
| NICE | None | None | None | None | None |
| pCODR | None | Additional costs of infrastructure or testing (high vs low) | Presence of RCTs (yes vs no) | Daily treatment cost (≤ 150 vs 150–500 vs > 500) (na)  Cost/Month: experimental arm  Cost/Month: control arm | None |

CRM, Commission of Reimbursement of Medicines; HAS, National Authority for Health; HIRA, Health Insurance Review and Assessment Service; GDP, Gross Domestic Product; IMD, Incrementally Modified Drug; NICE, National Institute for Health and Care Excellence; NCE, New Chemical Entity; OS, Overall Survival; PBAC, Pharmaceutical Benefits Advisory Committee; pCODR, pan-Canadian Oncology Drug Review; PFS, Progression-Free Survival; RR, Response Rate; RCT, Randomized Controlled Trial

† These factors were only investigated in one agency and not indentified as the signifiacant factors.

**References**

1. Nagase, F., et al., *Factors associated with positive and negative recommendations for cancer and non-cancer drugs for rare diseases in Canada.* Orphanet Journal of Rare Diseases, 2019. **14**: p. 127.

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3. Maynou Pujolras, L. and J. Cairns, *What is driving HTA decision-making? Evidence from cancer drug reimbursement decisions from 6 European countries.* Health Policy, 2018.

4. Pinto, A., et al., *Association Between the Use of Surrogate Measures in Pivotal Trials and Health Technology Assessment Decisions: A Retrospective Analysis of NICE and CADTH Reviews of Cancer Drugs.* Value in Health, 2020. **23**.

5. Karikios, D.J., et al., *Is it all about price? Why requests for government subsidy of anticancer drugs were rejected in Australia.* Intern Med J, 2017. **47**(4): p. 400-407.

6. Pauwels, K., et al., *Predictors for reimbursement of oncology drugs in Belgium between 2002 and 2013.* Expert review of pharmacoeconomics & outcomes research, 2015. **15**: p. 1-10.

7. Kim, E.-S., J.-A. Kim, and E.-K. Lee, *National reimbursement listing determinants of new cancer drugs: a retrospective analysis of 58 cancer treatment appraisals in 2007–2016 in South Korea.* Expert Review of Pharmacoeconomics & Outcomes Research, 2016. **17**.

8. Skedgel, C., W. Wranik, and M. Hu, *The Relative Importance of Clinical, Economic, Patient Values and Feasibility Criteria in Cancer Drug Reimbursement in Canada: A Revealed Preferences Analysis of Recommendations of the Pan-Canadian Oncology Drug Review 2011–2017.* PharmacoEconomics, 2018. **36**.

9. Niraula, S. and Z. Nugent, *New Cancer Drug Approvals From the Perspective of a Universal Healthcare System: Analyses of the Pan-Canadian Oncology Drug Review Recommendations.* J Natl Compr Canc Netw, 2018. **16**(12): p. 1460-1466.