1 Clarification on Canadian Considerations in Risk Management Plans

The government of Canada has issued a notice of clarification for drug manufacturers and sponsors preparing Canadian-specific considerations in risk management plans (RMPs) for certain drug products. It elaborates on the Submission of Risk Management Plans and Follow-up Commitments guidance document released in Canada in 2015, which outlines requirements for submitting a Canadian RMP, and describes the requirements and process for RMP follow-up commitments and updates to Health Canada.

A Canadian RMP should specify any notable differences from global RMPs in the epidemiology of the medical condition, risk factors for the authorised indication in Canada, and when the drug is intended for use in a small patient population in Canada. It should indicate if safety concerns listed in an EU RMP or other recognised RMP can be applied to Canada, or explain why not. It should describe reasons for the addition or removal of safety concerns, such as genetic or external factors unique to a population and proposed or approved indications, including: potential harm from overdose, transmission of infectious agents or medication errors, or off-label use; and risks associated with the drug class or during pregnancy and lactation and in children. Post-authorisation experience in Canada and globally should be included, if applicable.

Canadian-specific RMP requirements are also described for biosimilars and prescription opioids.

Routine pharmacovigilance activities (PVAs) and additional PVAs should be listed in the RMP; each additional PVA should state how it applies in Canada and timelines for reporting to Health Canada; reasons should be given if PVAs for a product differ from international PVAs, and additional PVAs should be tabulated. Routine risk minimisation activities should also be listed in the RMP and refer to the most recent Canadian product monograph, product packaging and product labelling. Additional risk minimisation activities should also be compared with those in other jurisdictions.

Government of Canada. Notice of clarification to drug manufacturers and sponsors: Canadian-specific considerations in risk management plans. 12 Nov 2020. https://www.canada.ca/en/health-canada/services/drugs-health-products/reports-publications/medeffect-canada/profile-guidance-document-submission-risk-management-plans-follow-commitments/notice-clarification-drug-manufacturers-sponsors.html. Accessed 22 Dec 2020.

2 Cardiac Advisories from Regulatory Agencies Differ Between Countries

Post-marketing cardiac safety advisories from regulatory authorities differ between Australia, Canada, the UK and USA, according to findings of a study published in Pharmacology Research and Perspectives.

Recommendations including monitoring advice in all safety advisories on cardiac-related adverse events which were issued between 2010 and 2016 by the Therapeutic Goods Administration (TGA) in Australia, Health Canada, the UK Medicines and Healthcare products Regulatory Agency (MHRA) and the US Food and Drug Administration (FDA) were compared.

In total, 164 safety advisories on cardiac-related adverse events were released by the four regulatory authorities during the study period; 34.8% were by the MHRA, 24.4% by the FDA, 21.3% by the TGA and 19.5% by Health Canada. The advisories involved 61 drugs, but only 14.7% of these drugs had advisories from all regulatory agencies in countries in which they were approved.

The most frequently reported adverse events in cardiac advisories were arrhythmias (59%; including tachycardia, QT interval prolongation and heart arrest), coronary artery disorders (24%), heart disorders, signs or symptoms (12.8%) and health failure (10.4%). The most frequent types of advisories were alerts in Australia (54.3%), the UK (50.9%) and the US (75%), and direct health professional communications in Canada (68.8%).
Overall, 58.4% of cardiac advisories were about 11 drugs: rosiglitazone (7.3%), dextropropoxyphene (6.1%), fingolimod (6.1%), domperidone (5.5%), denosumab (4.8%), dronedarone (4.3%), ondansetron (4.3%), citalopram (3.7%) and dabigatran (3.7%). Although the most frequent advice to healthcare professionals was to monitor patients (45%), only 41% of these advisories gave advice on monitoring.

In a case study on citalopram and escitalopram, all regulators issued advisories on the risks of QT prolongation and torsades de pointes, but only the FDA and Health Canada advised on the risk of death, and the agencies provided differing advice on monitoring.

“There was a low level of concordance between regulators in the decision to warn clinicians, leading to potential differences in knowledge and care between patients in different countries. Monitoring information was also often inadequate. This is particularly concerning considering the potentially fatal nature of many cardiac adverse effects”, concluded the authors.

Hooimeyer A, Bhasale A, Perry L, et al. Regulatory post-market drug safety advisories on cardiac harm: a comparison of four national regulatory agencies. Pharmacol Res Perspective. 2020;8(6):e00680.

3 NICE Consulting on Methods Used for Health Technology Evaluation

The UK National Institute for Health and Care Excellence (NICE) has initiated public consultation on proposals for changing its methods and processes used for evaluating and developing guidance on health technologies.

“As we develop a new regulatory and access environment for medicines, medical devices, diagnostics and digital health technologies, our methods should be aimed at supporting early patient access at a reasonable cost to the NHS, for example by encouraging companies to launch their products in the UK first”, commented Meindert Boysen, director of the Centre for Health Technology Evaluation at NICE. “Ensuring that our methods are clear, transparent and predictable should allow us to speed up evaluation processes for new and emerging technologies. This is particularly important in our response to COVID-19, but also allows us to further consider how to best evaluate the value of specific new technologies such as cell and gene therapies”, he said.

An online consultation event was hosted by NICE on 24 November 2020 and the consultation period closed on 18 December 2020.

National Institute for Health and Care Excellence. NICE’s methods of technology evaluation—presenting a case for change. 6 Nov 2020. https://www.nice.org.uk/news/article/nice-s-methods-of-technology-evaluation-presenting-a-case-for-change. Accessed 22 Dec 2020.

4 EMA and ICMRA Urge Continuation of COVID-19 Vaccine Safety Trials

The European Medicines Agency (EMA) and the International Coalition of Medicines Regulatory Authorities (ICMRA) are urging stakeholders including researchers, academia, regulators and drug companies to continue COVID-19 vaccine trials beyond the time when the predefined cases of COVID-19 disease for final analysis of the trial have been reached, to gain additional long-term safety and efficacy data.

“The work of ICMRA in streamlining regulatory requirements for vaccines through global cooperation has supported the rapid development of COVID-19 vaccines … Vaccines will be a key component in overcoming COVID-19, and we must ensure that robust and convincing evidence is being generated to enable the continuous assessment of their benefits and risks”, said Emer Cooke, Chair of ICMRA and Executive Director of the EMA.

A joint statement on continuation of vaccine trials was developed following meetings and discussions among ICMRA members on regulatory requirements to enable rapid assessment and authorisation of COVID-19 vaccines.

European Medicines Agency. Global regulators urge continuation of COVID-19 vaccine trials for longer-term safety and efficacy follow-up. 27 Nov 2020. https://www.ema.europa.eu/en/news/global-regulators-urge-continuation-covid-19-vaccine-trials-longer-term-safety-efficacy-follow. Accessed 22 Dec 2020.

5 EMA’s Safety Monitoring Plan for COVID-19 Vaccines

The EMA and national competent authorities (NCAs) in EU Member States have published a safety monitoring plan for COVID-19 vaccines, which outlines how relevant new information which becomes available after the authorisation and uptake of COVID-19 vaccines during the COVID-19 pandemic will be collected and reviewed.

According to the guidance published by the EMA and NCAs, the safety of COVID-19 vaccines will be monitored under good pharmacovigilance practices (GVP) which apply to all medicines. However, several planned activities will apply specifically to COVID-19 vaccines.

“Through the implementation of these activities, the EU medicines regulatory network will assess any safety data emerging from a range of different sources (spontaneous
reporting, observational studies, etc.). Any potential safety concerns identified will be addressed by taking appropriate regulatory action to safeguard individual and public health and communicating with the public in a transparent and timely manner”, says the EMA.

The plan requires companies to submit monthly safety reporting summaries, in addition to the regular updates, details studies for monitoring the safety, effectiveness and coverage of COVID-19 vaccines after authorisation, details transparency measures set up by EMA, and outlines how the EMA plans to engage with stakeholders.

The EMA has also published guidance for companies on the preparation of RMPs, which are required when applying for a marketing authorisation for COVID-19 vaccines. The RMP guidance for COVID-19 vaccines complements the existing guidelines which apply to all medicines, and addresses: data on vaccine safety that might be generated after the marketing authorisation in populations such as the elderly, children, or patients with comorbidities; requirements for lists of adverse events of special interest, methods used for signal detection, and follow-up of safety signals identified in trials; submission of monthly summary safety reports by marketing authorisation holders to the EMA; and traceability tools for recording which vaccine patients have received and from which batch.

For transparency, all RMPs for COVID-19 vaccines will be published on the EMA’s website.

European Medicines Agency. EMA publishes safety monitoring plan and guidance on risk management planning for COVID-19 vaccines. 13 Nov 2020. https://www.ema.europa.eu/en/news/ema-publishes-safety-monitoring-plan-guidance-risk-management-planning-covid-19-vaccines. Accessed 22 Dec 2020.

6 Drug–Drug Interactions in Patients with COVID-19

According to study results reported in Drugs & Aging, concomitant treatment of COVID-19-hospitalised patients with lopinavir/ritonavir and/or hydroxychloroquine resulted in increased numbers of potentially severe drug-drug interactions (DDIs), suggesting that their use “in patients with COVID-19 with polypharmacy needs to be carefully considered”.

The retrospective study analysed 502 patients treated at the Luigi Sacco Hospital in Milan between 30 February 2020 and 20 April 2020. There were 338 males and 164 females, 15–99 (median 61) years of age. The appropriateness of drug prescriptions was assessed using the INTER-check computerised prescription support system.

There were 399 patients (79%) who received ≥ 2 drugs, at admission (56%) and during hospitalisation (73%). At admission, the most frequently used drugs were antihypertensive agents, oral antidiabetic drugs, proton pump inhibitors, and diuretics. During hospitalisation, the use of corticosteroids, immunosuppressants, antibiotics and heparins significantly increased. Of the drugs only administered during hospitalisation, patients received hydroxychloroquine (n = 320), lopinavir/ritonavir (n = 256) and/or remdesivir (n = 70).

At least one potential DDI was identified in 271/399 patients (68%), which increased from 46% of patients at admission to 85% of patients during hospitalisation. Potentially severe DDIs were identified in 55% of patients, which increased from 22% at admission to 80% during hospitalisation.

Most DDIs at admission were associated with furosemide, amiodarone, quetiapine or β-agonist bronchodilators; all involved QT interval prolongation. During hospitalisation, 88% of events also involved QT prolongation, mainly related to lopinavir/ritonavir with azithromycin, piperacillin or hydroxychloroquine, or to hydroxychloroquine with azithromycin or piperacillin. Lopinavir/ritonavir also increased the risk of statin-induced myopathy, benzodiazepine-induced central nervous system depression, altered anti-thrombotic responses, and corticosteroid-induced Cushing-like syndrome.

The incidence of potentially inappropriate medications (PIMs) and the anticholinergic burden (ACB) were assessed in 200 patients aged > 65 years. At admission, at least one PIM was identified in 95% of patients, which reduced to 88% during hospitalisation, although the difference was not significant. There were 19% of patients with ACB scores of ≥ 3, while 2.5% of patients had scores of ≥ 5.

“The main finding of this study is that hospitalised patients with COVID-19 are at high risk of DDIs”, note the authors, "mainly because of the drugs administered" to treat the infection.

Cattaneo D, Pasina L, Maggioni AP, et al. Drug-drug interactions and prescription appropriateness in patients with COVID-19: a retrospective analysis from a reference hospital in Northern Italy. Drugs Aging. 2020. 37(12):925–33.

7 EMA Guidance on Risk Management Plans for COVID-19 Vaccines Reviewed

EMA guidance for pharmaceutical companies on how to prepare RMPs for COVID-19 vaccines have been reviewed by the Pharmacovigilance Risk Assessment Committee (PRAC), says the agency.
According to highlights from the PRAC’s recent October 2020 meeting, “companies are required to submit an RMP for COVID-19 vaccines when they apply for a marketing authorisation”, noted the EMA.

Any such RMP should explain how the market licensee of any COVID-19 vaccine “must monitor and report on its safety, and what measures they must put in place to manage any risks”, noted the EMA.

The agency also highlighted that as new information becomes available, RMPs are updated continuously across the lifetime of a vaccine.

The revised guidance is intended for COVID-19 vaccines only, and complements existing RMP format guidelines in the EU that apply to all medicines. This guidance will now be sent to the EMA’s Committee for Medicinal Products for Human Use, and it will be made available publicly once adopted by this committee.

European Medicines Agency. Meeting highlights from the Pharmacovigilance Risk Assessment Committee (PRAC) 26–29 October 2020. 30 Oct 2020. https://www.ema.europa.eu/en/news/meeting-highlights-pharmacovigilance-risk-assessment-committee-prac-26-29-october-2020. Accessed 22 Dec 2020.

8 Quality of AE Reporting Evaluated for Remdesivir Trials of COVID-19

Remdesivir may have potential for the treatment of COVID-19 but “the medical community is heavily relying on the clinical trials to inform the possible harms of remdesivir”, say researchers from Malaysia, the UK and Australia.

In a Letter to the Editor of the European Journal of Clinical Pharmacology, the researchers explained how they evaluated the adequacy of the four clinical trials of remdesivir in patients with COVID-19 fulfilling each of the Consolidated Standards of Reporting Trials (CONSORT) harms recommendations.

The researchers’ evaluation of the total harm reporting score [where the total harm reporting score could range from 0 (i.e. worst possible score) to 19 (best possible score)] revealed that only one of the remdesivir clinical trials (Wang et al.) had “moderate” (i.e. score of 10–14) quality of adverse event (AE) reporting, while the remaining three clinical trials (Beigel et al.; Goldman et al. + Spinner et al.) had a “low” (score of 5–9) quality of AE reporting.

The trial by Wang et al. had a total harm reporting score of 10, the trials by Beigel et al. and Goldman et al. both had a corresponding score of 9, and the trial by Spinner et al. had a score of 8. None of the clinical trials provided information on AEs in the introduction section (i.e. CONSORT recommendation 2). While all the clinical trials used a validated scale to measure the severity of AEs, none of the clinical trials defined AEs (i.e. CONSORT recommendation 3). Only one of the clinical trials each described how AE-related data were collected (Beigel et al.; CONSORT recommendation 4a) and described AEs leading to withdrawals (Wang et al.; CONSORT recommendation 6b). All of the clinical trials provided denominators for AEs (CONSORT recommendation 7a), but none described any subgroup analyses and exploratory analyses for harms, nor presented a balanced discussion on both safety and efficacy of the drug (CONSORT recommendations 9 and 10).

In conclusion, the researchers “urge that future and ongoing clinical trials on remdesivir in COVID-19 should follow the ten CONSORT harm recommendations in terms of reporting adverse events for a better understanding of the safety of remdesivir in its use in COVID-19 patients. This is of utmost importance such that the potential clinical benefits of remdesivir are not negated by the development of adverse events in susceptible patients”.

Kow CS, Aldeyab M, Hasan SS. Quality of adverse event reporting in clinical trials of remdesivir in patients with COVID-19. Eur J Clin Pharmacol. Epub 4 Oct 2020. https://doi.org/10.1007/s00228-020-03008-6. Accessed 22 Dec 2020.

9 RPS Urges Action to Prevent Influx of Post-Brexit Counterfeit Drugs

The Royal Pharmaceutical Society (RPS) of Great Britain is calling on the UK government to take “immediate action” to stop the introduction of counterfeit medicines into the supply chain following the exit of the UK from the European Union (EU).

Ahead of the European Council’s deliberations on the future of the UK–EU relationship, the RPS has sent a letter to the UK Secretary for State for Health, Matt Hancock, emphasising the urgent need for robust plans to be put in place to maintain formal links with the EU to assist with authenticating the legitimacy of medicines that move between the EU and UK.

Based on current plans, the UK will no longer benefit from the provisions of the Falsified Medicines Directive (FMD) after the EU Exit transition period has ended. The RPS is concerned that the removal of the FMD safeguards, which ensure that EU medicines are safe, legitimate and of high quality, could expose the UK to an influx of counterfeit medicines and lead to patient care being impacted in the UK and EU. Currently, over 45 million packs of medicines move between the EU and the UK every month.

“It is unacceptable that in the final months of the Brexit transition period, robust plans have not been put in place to
prevent falsified or counterfeit medicines entering the UK”, commented RPS President, Sandra Gidley. “We have made it clear that the ideal way forward is for continuity of the provisions of the Falsified Medicines Directive, enabling ongoing connectivity between the UK and Europe”.

Royal Pharmaceutical Society of Great Britain. RPS calls for action to fight counterfeit medicines. 13 Oct 2020. https://www.rpharms.com/about-us/news/details/RPS-calls-for-action-to-fight-counterfeit-medicines. Accessed 22 Dec 2020.

10 Consensus Guidelines on Acute Drug-Induced Liver Injury in Trials

Consensus guidelines on best practices for the detection, assessment and management of suspected drug-induced liver injury (DILI) in clinical trials in adults with chronic viral hepatitis, and cirrhosis secondary to hepatitis B (HBV), hepatitis C (HCV) or non-alcoholic steatohepatitis (NASH), developed by the IQ DILI Initiative, are reported in Drug Safety.

The IQ DILI Initiative, comprised of members from 16 drug companies in collaboration with DILI experts from academia and regulatory agencies, conducted an extensive literature review and discussions between pharmaceutical industry members and experts from outside industry to achieve a consensus on recommendations.

Key conclusions and consensus recommendations include:

- Establishing laboratory criteria that signal potential DILI events and fit the disease indication studied in a clinical trial, based on knowledge of test fluctuations in patients with that disease.
- Establishing a pretreatment baseline value based on more than one screening determination, and revising that baseline during the trial if a new nadir is achieved during treatment.
- Basing rules for increased monitoring, and for stopping a drug due to potential DILI, on multiples of baseline liver test values and/or a threshold value rather than on multiples of the upper limit of normal (ULN).
- Using more sensitive tests of liver function including direct bilirubin (DB), or combined parameters such as AST:ALT ratio, or model for end-stage liver disease (MELD) to signal potential DILI (particularly in trials in patients with cirrhosis); and
- Awareness of potential confounders related to disease complications that may masquerade as DILI events.

“It is critical that clear inclusion/exclusion criteria that define and control enrollment be applied in clinical trials in patients with cirrhosis from HCV, HBV, or NASH to ensure the population conforms to compensated or decompensated cirrhosis”, commented the authors. “It is also imperative that any cases of possible, probable, or likely DILI in clinical trials be thoroughly evaluated and adjudicated by experts. Such cases need to be followed closely to discern patterns and trends that illuminate early warning signals in patients with cirrhosis. They also need to be followed for clinical and laboratory signatures of reversal of drug-related worsening upon study drug discontinuation or dose modification that may differ based on the underlying liver disease and that potentially differ from the noncirrhotic population”, they said.

Treem WR, Palmer M, Lonjon-Domanec I, et al. Consensus guidelines: best practices for detection, assessment and management of suspected acute drug-induced liver injury during clinical trials in adults with chronic viral hepatitis and adults with cirrhosis secondary to hepatitis B, C and nonalcoholic steatohepatitis. Drug Saf. Epub 3 Nov 2020. https://doi.org/10.1007/s40264-020-01014-2. Accessed 22 Dec 2020.

11 MHRA Reports a Milestone: 1 Million Yellow Card Reports

The UK MHRA has reported a major milestone: 1 million Yellow Card reports of suspected AEs in patients receiving drugs or medical devices since the scheme was initiated 50 years ago.

The milestone coincided with the launch of the annual #MedSafetyWeek, which encourages reporting of adverse events to regulatory authorities in 73 countries throughout the world. The campaign is led by Uppsala Monitoring Centre (UMC), a WHO Collaborating Centre for International Drug Monitoring.

Medicines and Healthcare products Regulatory Agency. Milestone 1 million Yellow Card report for suspected side effects in MedSafetyWeek. 2 Nov 2020. https://www.gov.uk/government/news/milestone-1-million-yellow-card-report-for-suspected-side-effects-in-medsafetyweek. Accessed 22 Dec 2020.

12 REGIMS Immunotherapy Registry for MS Allows AE Comparisons

The REGIMS immunotherapy registry, a prospective, national, multicentre, pharmacovigilance registry implemented in Germany, allows comparisons of adverse events (AEs) between immunotherapies for the treatment of multiple sclerosis (MS), say authors of an article published in Drug Safety.
Patients treated with MS medication approved in Germany are recruited to the registry by physicians during routine visits to hospitals, outpatient clinics and specialist MS practices. REGIMS incorporates electronic physician-based documentation in each centre as well as paper-based patient documentation at baseline and follow-up visits. Patients regularly complete questionnaires on patient-reported outcomes (PROs).

A fee of €50 (2019 Euros) is paid to centres for baseline documentation, and €15 is paid for follow-up documentation. AE reports are provided and a newsletter with centre-specific recruitment information is sent to centres regularly.

By the end of 2019, 43 REGIMS centres had recruiting 1562 adults diagnosed with MS or clinically isolated syndrome who were treated with de novo MS medication including alemtuzumab, dimethyl fumarate, fingolimod, mitoxantrone, natalizumab, ocrelizumab or teriflunomide, irrespective of duration, or treated with azathioprine, glatiramer acetate, interferon-β-1a or interferon-β-1b for up to 3 years. Two to four new centres were joining the registry each year.

Overall, 69% of first 1000 patients in the REGIMS registry were female, and 90% of patients had relapsing-remitting MS. The most frequently administered drugs at baseline were natalizumab (33.1%), fingolimod (21.7%), alemtuzumab (15.9%), dimethyl fumarate (10.1%), ocrelizumab (5.3%), interferons (4.4%), teriflunomide (3.5%) and glatiramer acetate (3.4%). Most patients were treated with a second-line therapy.

“Data from registries such as the REGIMS registry allow the comparison of AEs and SAEs of newly approved drugs for which there is limited experience, especially regarding their long-term use. It is possible to directly analyze drug history and treatment switches, as well as interruptions in the treatment, to assess therapy adherence and safety and to collect PROs. Future newly approved immune therapies can easily be added into the REGIMS documentation, and its results shall support physicians in finding the most appropriate therapy for a selected patient”, concluded the authors.

Simbrich A, Thibaut J, Khil L, et al. Chances and challenges of registry-based pharmacovigilance in multiple sclerosis: lessons learnt from the implementation of the multicenter REGIMS registry. Drug Saf. Epub 23 Oct 2020. https://doi.org/10.1007/s40264-020-01007-1. Accessed 22 Dec 2020.

13 Decisions by ICER and NICE Discordant for Some Cancer Drugs

The US Institute for Clinical and Economic Review (ICER) and the UK NICE are in concordance for most cost-effectiveness recommendations on new cancer drugs but some of their decisions are discordant, primarily due to higher drug prices in the US and a higher cost-effectiveness threshold used by ICER, say authors of a study published in EClinicalMedicine.

There is no formal HTA agency in the US but private health insurers are increasing relying on ICER’s evaluations on new drugs to make coverage decisions. In England, NICE evaluates the cost-effectiveness of new drugs and makes reimbursement decisions on public coverage within the National Health Service. This analysis compared methods and outcomes of cost-effectiveness evaluations performed by ICER and NICE on 11 cancer drugs between 2016 and 2019 (atezolizumab, axicabtagene ciloleucel, enzalutamide, ixazomib, niraparib, nivolumab, olaparib, panobinostat, pembrolizumab, rucaparib and tisagenleucel), based on the method of economic evaluation, incremental cost-effectiveness ratios, comparator drugs, drug price, and recommendations made.

For all 11 drugs, cost effectiveness was assessed by both ICER and NICE in terms of incremental cost per QALY gained. ICER used a willingness-to-pay threshold of $100 000–$150 000 per QALY gained, whilst NICE used a threshold of £20 000–£30 000 ($28 471–$42 857) per QALY gained. ICER and NICE used similar economic models, payer perspectives and time horizons, as well as similar comparators for most drugs.

ICER and NICE were in concordance for evaluations on seven drugs but were discordant with regard to cost effectiveness and recommendations for four drugs.

Overall, seven of the 11 drugs were not considered cost effective in the US or England. However, NICE was able to negotiate drug price discounts and patient access schemes with drug manufacturers which reduced the cost per QALY gained for some drugs. As a result, NICE made favourable recommendations for ten drugs, while ICER made favourable recommendations for only four drugs. Seven of the ten recommendations made by NICE were subject to additional evidence gathered by use under the Cancer Drugs Fund.

“Our analysis shows that NICE’s capacity to negotiate price discounts and access schemes result in much lower cost per QALY valuations and more favourable recommendations than those of ICER for similarly assessed cancer drugs—largely due to its sanctioned role in healthcare decisions for England in contrast to ICER’s voluntary non-profit role which has no enforcement over pricing or coverage decisions in the US”, said the authors. “While differences in health system and sociopolitical context may prevent US acceptance of a lower cost-effectiveness threshold or public integration of an HTA body, NICE provides an important perspective for how much lower other countries pay for pharmaceuticals and provides examples of policy tools that may help US health insurers, particularly Medicare and Medicaid, achieve better value”, they commented.
Cherla A, Renwick M, Jha A, et al. Cost-effectiveness of cancer drugs: comparative analysis of the United States and England. EClinicalMedicine. Epub 5 Nov 2020. https://doi.org/10.1016/j.eclinm.2020.100625. Accessed 22 Dec 2020.

14 UK NHS Advised to Consider New Models of Cancer Drug Pricing

The UK NHS should vary the price it pays for cancer drugs to improve patient access to new cancer treatments, suggests a group of experts.

This is one of several recommendations that were made following a summit held by the Institute of Cancer Research, London. The panel consisted of experts from academic institutions, charities, stakeholder groups and drug companies.

The panel suggests that new pricing models may improve patient access to new cancer treatments. More flexibility to vary the price of drugs for different indications should be explored. The panel also suggests introducing outcome-based pricing, where the NHS would pay the full agreed price for a drug only if the drug proves as effective as claimed by the manufacturer. This was seen as a way of ensuring the NHS gets value for money for innovative new cancer medicines while improving access to the newest cancer treatments. Such new drug-pricing models, however, would require better digital infrastructure within the NHS to collect detailed prescribing data so that drug prices can be varied by indication or aligned with outcomes. Another recommendation was the advice for the Competition and Markets Authority to provide clear guidance to make it easier for companies to collaborate on new combination treatments. Furthermore, the panel suggests a drug’s degree of innovation in its mechanism of action should be adequately considered when evaluating new treatments for use on the NHS.

Iacobucci G. NHS should vary price it pays for cancer drugs to improve access, say experts. BMJ. 2020;375:m4322.

15 Estimation of CE Threshold Based on Health Opportunity Costs in USA

Treatments with incremental cost-effectiveness ratios (ICERs) above $100 000–$150 000 (2019 US dollars) per QALY gained are not likely to be cost effective in the US, according to findings of a cost-utility study published in Annals of Internal Medicine.

The US cost-effectiveness (CE) threshold based on health opportunity costs was evaluated using a simulation model of short-term mortality and morbidity attributable to termination of health insurance due to insurance premium increases totalling $100 000 000 ($100 per member per year) in a hypothetical cohort of in 100,000 adults with private health insurance.

It was estimated that 1860 adults would become uninsured per $10,000,000 increase in healthcare expenditure (due to premium increases), leading to five deaths, 81 QALYs lost due to death and 15 QALYs lost due to morbidities.

This resulted in an estimated CE threshold of $104,000 per QALY gained for a new treatment with an incremental cost of $100,000,000. There was 49% probability that the CE threshold was less than $100,000 per QALY gained, but only 14% probability that the threshold was over $150,000 per QALY gained.

“We believe that it is reasonable to expect that when an authority, be it a government agency or a private insurance plan, agrees on whether or how much to pay for a treatment, that decision will “first, do no harm” to population health. Setting cost-effectiveness thresholds too high (or ignoring them altogether) sustains current conditions for a self-reinforcing cycle of escalating health care costs and continued disappointing progress on improving population health”, commented the authors.

Vanness DJ, Lomas J, Ahn H. A health opportunity cost threshold for cost-effectiveness analysis in the United States. Ann Intern Med. Epub 3 Nov 2020. https://doi.org/10.7326/M20-1392. Accessed 22 Dec 2020.

16 Factors Influencing HTA Decisions Differ Between Countries

Clinical factors primarily influence reimbursement decisions made by HTA organisations on cancer drugs and hepatitis C therapies, but other factors vary between countries, according to findings of a Pfizer Japan-funded study published in PharmacoEconomics—Open.

Investigators identified economic evaluation types and factors considered by HTA organisations in assessing four cancer drugs (nivolumab, palbociclib, pembolizimab and trastuzumab emtansine), and five hepatitis C therapies (asunaprevir, daclatasvir, ledipasvir/sofosbuvir, ombitasvir and sofosbuvir) in Australia (Pharmaceutical Benefits Advisory Committee [PBAC]), Canada (Canadian Agency for Drugs and Technologies in Health [CADTH]; pan-Canadian Oncology Drug Review [pCODR]), France (Haute Autorité de Santé [HAS]), Germany (Institute for Quality and Efficiency in Healthcare [IQWiG]), Italy (Agenzia Italiana del Farmaco [AIFA]), Japan (Center for Outcomes Research and Economic Evaluation for Health [C2H]), Spain (Agen-cia de Evaluación de Tecnologías Sanitarias de Andalucía [AETSA]) and the UK (NICE). Factors included special circumstances factors considered by the NICE such as end-of-life and innovation, and International Society for
Pharmacoeconomics and Outcomes Research (ISPOR) additional value elements.

PABC, CADTH, C2H and NICE based economic evaluations on incremental cost-effectiveness ratios (ICERs) assessing cost per QALY gained. IQWiG used cost-only analysis for all cancer drugs, while HAS used ICERs for 55% of dossiers. PABC used ICERs in 85% of cancer-related dossiers and 75% of hepatitis C-related dossiers. AETSA and AIFA did not mention economic evaluations.

PABC, CADTH/pCODR, HAS and NICE considered factors such as unmet needs and stakeholder persuasion. NICE also considered end-of-life, issues concerning current treatments, and innovation. IQWiG reported manageable or clinically insignificant adverse events more frequently than other countries. Australia was the only country which considered fear of contagion, equity, and scientific spillover value. PBAC was the only HTA organisation that used most of the additional elements of value for healthcare suggested by the ISPOR Special Task Force.

“Although clinical factors play a predominant role in the decision to reimburse medicines, NICE and PBAC were found to be the HTA organizations with the most comprehensive list of additional criteria. Furthermore, CADTH/pCODR, HAS and IQWiG also showed a direction for decision making that extends beyond clinical evidence. If the decision-making process of HTA were clearly outlined with more public accessibility or transparency into the considered factors, there would be more transparency in HTA systems, leading to better understanding amongst stakeholders about decision making”, concluded the authors.

Yuasa A, Yonomoto N, LoPresti M, et al. Use of productivity loss/gain in cost-effectiveness analyses for drugs: a systematic review. Pharmacoeconomics. Epub 24 Nov 2020. https://doi.org/10.1007/s40273-020-00986-4. Accessed 22 Dec 2020.

18 Global Access to Orphan Drugs: Disparities in Policies

The number of countries with orphan drug policies (ODPs) is growing but policies are more common in wealthier countries or areas, and incentives are required to improve the affordability of orphan drugs throughout the world, say authors of systematic review published in Value in Health.

Investigators conducted a systematic literature search and obtained information from national pharmacovigilance centres up to July 2019 to identify policies on access to and regulation of orphan drugs for rare diseases in 194 WHO member countries and six non-member areas (Hong Kong, Taiwan, Macau, Kosovo, Palestine and Sahrawi Republic), in order to evaluate global ODPs on development, licensing, pricing and reimbursement of orphan drugs. Data from 172 drug regulatory documents and 77 publications were included in the analysis.

Overall, 69% of studies reported the impact of productivity losses/gains on ICERs; 53% of studies reported that the inclusion of productivity losses/gains contributed to more favourable ICERs.

“Further examination and discussion is needed to consider the optimal framework for considering productivity losses/gains in CEA, including the appropriate cost elements to include (e.g., patient absenteeism, caregiver absenteeism, presenteeism, unemployment) and how those costs should be estimated. Moreover, an analysis by country may be important given the different context and background of healthcare systems in each country”, concluded the authors.

Yuasa A, Yonomoto N, LoPresti M, et al. Use of productivity loss/gain in cost-effectiveness analyses for drugs: a systematic review. Pharmacoeconomics. Epub 24 Nov 2020. https://doi.org/10.1007/s40273-020-00986-4. Accessed 22 Dec 2020.

17 Including Productivity Losses and Gains in CEAs

Including productivity losses/gains in cost-effectiveness analyses (CEAs) may have an impact on ICERs of drugs, but as yet there is no universal framework for including these losses and gains in CEAs, say authors of a systematic review published in Pharmacoeconomics.

MEDLINE, Embase, and the Cochrane Library were searched for CEAs and cost-utility analyses published between January 2010 and October 2019 that included indirect costs such as productivity losses/gains. Approaches used to estimate productivity losses/gains, and their impact on ICERs were reviewed.
The establishment of OPs increased in non-high-income countries between 2013 and 2019; 54% of the 37 ODPs established during that period were in low- or middle-income countries/areas and 27% were in upper-middle income countries/areas. Only 19% of low-income countries/areas established ODPs. Countries/areas with ODPs had greater national incomes than those without ODPs (gross income per capita $10,875 vs $3,950; p < 0.001).

ODPs primarily covered orphan drug designation, marketing authorisation of orphan drugs, efficacy and safety requirements, price regulation, and incentives to encourage market availability and research and development of orphan drugs. National income was significantly correlated with the scope of ODPs (p < 0.001).

“While observing the global growth of ODP establishment, drug authorities should be prepared to develop or refine current policies to optimize patient access to orphan drugs. In particular, policy improvements in the thematic areas of price regulation, incentives that encourage market availability, and incentives that encourage research and development are recommended to ensure affordability for payers with sufficient returns for manufacturers”, concluded the authors.

Chan AYL, Chan VKY, Olsson S, et al. Access and unmet needs of orphan drugs in 194 countries and 6 areas: a global policy review with content analysis. Value Health. Epub 30 Oct 2020. https://doi.org/10.1016/j.jval.2020.06.020. Accessed 22 Dec 2020.

19 ADR Reporting by Patients Increased by Use of a Mobile App

Reporting of adverse drug reactions (ADRs) by patients with MS receiving a first-line disease-modifying drug (DMD) can be increased by the use of a mobile device app, according to the results of a study from France.

The cluster-randomised controlled study examined whether the use of a mobile app (My eReport France®) would increase ADR reporting by adults with relapsing-remitting MS who initiated, or switched to, treatment with a first-line DMD (including interferon-β-1a [Avonex; Rebif], peginterferon-β [Plegridy], glatiramer acetate [Copaxone], teriflunomide [Aubagio] and dimethyl fumarate [Tecfidera]), compared with traditional reporting. The study was conducted in 24 centers in France and included 159 patients (91 in the experimental arm and 68 in the control arm).

Over a 6-month follow-up period, there were 64 ADRs in 43 reports in the experimental arm versus 3 ADRs in 2 reports in the control arm. All suspected ADR events were assessed as possibly related to the first-line DMD. The analysis at centre level showed that the mean number of ADR reports per patient was significantly higher in the experimental arm (0.47 vs 0.03). The analysis at individual level indicated that the relative risk for the app effect, as compared with the control, was 18.6 (95% CI 4.1, 84.2) after adjusting for female sex and DMD. The study also showed that 16 ADRs (24%) were unlisted in the Summary of Product Characteristics of the respective DMD. The clinical quality of the ADRs reported using the mobile app was moderate.

Defer G, Fedrizzi S, Chevanne D, et al. Adverse drug reaction reporting using a mobile device application by persons with multiple sclerosis: a cluster randomized controlled trial. Drug Saf. Epub 13 Oct 2020. https://doi.org/10.1007/s40264-020-01009-z. Accessed 22 Dec 2020.

20 Health Canada Advises No Use of NSAIDs After ≥ 20 weeks’ Gestation

Health Canada is advising against the use of NSAIDs at 20 weeks’ gestation or later in pregnancy due to the risk of kidney damage in the fetus. Prescription and over-the-counter (OTC) NSAIDs to be avoided include aspirin, celecoxib, diclofenac, ibuprofen and naproxen.

The US FDA is requiring labelling changes for all prescription and OTC NSAIDs at ≥ 20 weeks’ gestation and is warning that kidney problems in the fetus can result in low levels of amniotic fluid and complications including impaired lung maturation and limb contractures.

In Canada, use of prescription and OTC NSAIDs is currently contraindicated in the last trimester of pregnancy, and labelling advises that pregnant women should consult their healthcare professional before using these drugs during pregnancy. While Health Canada investigates the issue of kidney damage in the fetus it is extending the contraindication to ≥ 20 weeks’ gestation.

Health Canada is also recommending that, if deemed necessary by a healthcare professional, NSAID use at 20–30 weeks of pregnancy should be limited to the lowest effective dose for the shortest duration, and recommends ultrasound monitoring of amniotic fluid should be considered if the duration of NSAID treatment is over 48 h. These recommendations do not apply to the use of low-dose aspirin for pregnancy-related conditions under the direction of a healthcare professional, or to ophthalmic NSAIDs.

Health Canada. Use of non-steroidal anti-inflammatory drugs (NSAIDs) beyond 20 weeks of pregnancy and risk of kidney damage in unborn babies, leading to low amniotic fluid. 30 Oct 2020. https://healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2020/74239a-eng.php. Accessed 22 Dec 2020.
21 Codeine-Containing Medicines to be Reclassified in NZ

All codeine-containing medicines have been reclassified as prescription medicines from 5 November 2020, says New Zealand’s Medsafe.

At a Medicines Classification Committee (MCC) meeting held on 10 October, an information paper was presented and after a period of consultation and stakeholder feedback, it was recommended that “all codeine-containing medicines should be classified as prescription medicines”, said Medsafe.

Presently in New Zealand, products containing codeine only are prescription medicines. In Australia, the Therapeutic Goods Administration made this reclassification in February 2018.

MCC Chair Andi Shirtcliffe highlighted the committee’s primary concern was access to pain therapeutics for New Zealanders, and that patients requiring codeine-containing medicines will get the opportunity to receive advice from their healthcare professional before making an informed choice.

Although the implementation of this reclassification has been delayed due to New Zealand’s response to the global COVID-19 pandemic, Medsafe “will continue to work with industry representatives and other stakeholders on this change”, said the agency.

Medsafe’s Group Manager Chris James noted that “it’s important for people to know there are alternatives available for your pain management—both over the counter and as prescription medicines”.

New labelling is expected to be at the wholesale level by 5 February 2021.

Medsafe. Codeine-containing medicines to be reclassified. 21 Oct 2020. https://www.medsafe.govt.nz/publications/media/2020/CodeineReclassification.asp. Accessed 22 Dec 2020.

22 Neuropsychiatric Outcomes with Statins

There does not appear to be an association between the use of HMG-CoA reductase inhibitors (statins) and the neuropsychiatric outcomes of suicidality, seizures or anxiety, according to the results of a large population-based study reported in *Lancet Psychiatry*, but there may be a reduced risk of depressive disorders.

The study used national registers in Sweden to identify 1149 384 patients who used statins in 2006–2013. The most commonly prescribed statin was simvastatin (87.6%), followed by atorvastatin (21.3%), rosuvastatin (4.7%), pravastatin (3.6%) and fluvastatin (0.6%). Periods on and off statins (2997 545 vs 2053 310) were compared in the 625 616 males and 523 768 females who were ≥ 15 years of age.

Evaluation of unplanned hospital visits or specialised outpatient care identified anxiety disorders (2.6% of patients), seizures (2.5%), depressive disorders (2.1%) and suicidality (0.6%). The incidence per 100 patient-years was 6.0, 6.1, 5.6 and 1.0, respectively. There was no statistically significant difference between periods on and off statins for anxiety disorders (hazard ratio [HR] 0.99; 95% CI 0.95, 1.02), seizures (HR 1.0; 0.97, 1.04) or suicidality (0.99; 0.90, 1.08).

However, there was a significantly reduced risk of depressive disorder (HR 0.91; 0.87, 0.94), which was similar after adjusting for concurrent antidepressant treatment (HR 0.91; 0.88, 0.94). Sensitivity analyses revealed that significant reductions in the risk of depressive disorders occurred during periods of low- or moderate-dose statin use, but not during periods of high-dose use, “suggesting that there was no dose-response association”, note the authors.

As negative controls, the risk of depressive disorders were also calculated for thiazide users and antihistamine users, which “indicated reduces rates of depressive disorders”, note the authors, “although these associations did not reach statistical significance”. Consequently, “one interpretation of our findings could be that reductions in depression are explained by non-specific treatment factors rather than a direct neuroprotective effect”. They conclude that “this association requires further investigation to clarify the possible contribution of non-specific treatment factors”.

Malero Y, Cipriani A, Larsson H, et al. Associations between statin use and suicidality, depression, anxiety, and seizures: a Swedish total-population cohort study. *Lancet Psych*. Epub Nov 2020. https://doi.org/10.1016/S2215-0366(20)30311-4. Accessed 22 Dec 2020.
modafinil, 66 received armodafinil and one patient received both drugs.

The 122 pregnancies classified as prospective (enrolled prior to pregnancy outcome or detection of congenital abnormality) included 102 live births of which 13 had MCMs including torticollis (n = 4), congenital heart defects (3) and hypospadias (2). Rates of MCMs and cardiac malformations were greater than in the general population (13% vs 3% and 3% vs 1%, respectively).

When data from prospective pregnancies and those classified as retrospective (enrolled after pregnancy outcome or detection of congenital abnormality) were pooled, the overall prevalence of MCMs was 13%.

“Although the available data are inconclusive for causality, the potential increased risk of MCMs provides impetus for health care professionals to enhance the benefit-risk monitoring of modafinil and/or armodafinil use in pregnant individuals and individuals who may become pregnant”, concluded the authors.

“Given the risks of these medications and the high rate of unintended pregnancy, we recommend that pregnancy be considered a possibility in all individuals of reproductive age who may be prescribed a potential teratogen. To avoid major congenital malformations associated with modafinil and armodafinil, these medications should be avoided or offered along with a reliable contraceptive to individuals who could become pregnant”, said Drs. Neda Ghaffari and Patricia Robertson from the University of California, San Francisco, USA in an accompanying invited commentary published in JAMA Internal Medicine [2].

1. Kaplan S, Braverman DL, Frishman I, et al. Pregnancy and fetal outcomes following exposure to modafinil and armodafinil during pregnancy. JAMA Intern Med. Epub 19 Oct 2020. https://doi.org/10.1001/jamainternmed.2020.4009. Accessed 22 Dec 2020.
2. Ghaffari N, Robertson PA. Caution in prescribing modafinil and armodafinil to individuals who could become pregnant. JAMA Intern Med. Epub 19 Oct 2020. https://doi.org/10.1001/jamainternmed.2020.4206. Accessed 22 Dec 2020.

24 Antiepileptic-Related AEs Increase Total Costs in Outpatients

AEs in patients receiving antiepileptic drugs (AEDs) appear to increase total costs of prescriptions and outpatient visits, according to findings of a US study published in Drugs—Real World Outcomes.

Logistic regression analysis of US IBM Commercial and Medicare MarketScan administrative data (2014–2017) was used to investigate the association between AEs and discontinuation of AEDs (≥ 60 days without a refill) in adults with epilepsy (inpatients and outpatients) who were new users of AEDs. The economic burden of AED discontinuation was assessed in propensity score-matched patients.

The overall discontinuation rate due to AEs was 9% (0.1% based on injury codes [E-CODES], and 27% based on disease manifestation International Classification of Diseases (ICD; Ninth/Tenth Edition) codes reported in literature or product inserts [LADE]). The rate of discontinuation was highest in patients aged 65 years or over (11%). Patients who discontinued AEDs due to AEs had more outpatient claims (19.3 vs 17.8; p < 0.0001) and an increased duration of hospitalisation (6.6 vs 5.3 days; p < 0.0001).

Outpatient costs were significantly higher in patients with than without AEs, based on E-CODES ($213 vs $105 in 2017 dollars; p = 0.001) and LADE ($188 vs $161; p < 0.001), and the total cost of AEDs was significantly higher in outpatients with AEs.

No association was found between E-CODES and discontinuation of AEDs. There was a positive association between AEs based on LADE and AED discontinuation in outpatients, but a negative association in inpatients.

“We found that total costs of prescriptions claimed and outpatient visits among the outpatient cohort were higher for those with adverse drug events than for those without. The association between adverse events and discontinuation was inconclusive because it depended on the target population and how the adverse events were identified”, concluded the authors.

Peasah SK, Fishman J, Ems D, et al. Association between adverse events and discontinuation of antiepileptic drugs among drug-naive adults with epilepsy. Drugs Real World Outcomes. Epub 5 Nov 2020. https://doi.org/10.1007/s40801-020-00216-5. Accessed 22 Dec 2020.

25 Osteonecrosis of the Jaw Associated with a Variety of Drugs

A number of drugs appear to be associated with medication-related osteonecrosis of the jaw (MRONJ), according to findings of an analysis of case reports to the Australian Database of Adverse Event Notification (DAEN) published in the British Journal of Clinical Pharmacology.

The Australian TGA provided a list of all case reports of MRONJ submitted to the DAEN between 1971 and October 2019.

In total, 419 cases of MRONJ were reported between November 2015 and October 2018, and denosumab or bisphosphonates (alendronic, pamidronic, risedronic or zoledronic acid) were implicated in 405 cases.

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Denosumab was the only suspected agent in 221 cases, and was listed in addition to other possible causative agents in another 20 cases, while bisphosphonates were implicated in 163 reports. The most frequent possible secondary causative agents with antiresorptive properties included prednisolone (18 cases), cyclophosphamide (7), dexamethasone (5), lenalidomide (5) and thalidomide (5).

Another 14 reports implicated secondary agents such as adalimumab and teriparatide.

“This study presents several medications that may contribute to the pathogenesis of MRONJ, highlighting the importance of considering all possible medications that have effects on bone healing. Further research and improved MRONJ reporting are needed to verify the association of some of these drugs without anti-resorptive properties with MRONJ”, concluded the authors.

Teoh L, Moses G, Nguyen AP, et al. Medication-related osteonecrosis of the jaw - analysing the range of implicated drugs from the Australian Database of Adverse Event Notifications. Br J Clin Pharmacol. Epub 27 Nov 2020. https://doi.org/10.1111/bcp.14681. Accessed 22 Dec 2020.

26 Reports of Drug-Induced Hearing Loss in Paediatric Patients

According to the results of a study investigating paediatric drug-induced hearing loss in the French Pharmacovigilance Database (FFVD), reported in Pediatric Drugs, 80% of cases were classified as serious.

The study evaluated 51,216 ADR reports in 1985–2019 to identify 70 cases of hearing loss in paediatric patients, comprising infants (n = 5), children (n = 28) and adolescents (n = 37); 57.1% of cases were girls. There were 56 serious cases (80%), including incapacities/disabilities (n = 28), hospitalisations (n = 12) and medically important reactions (n = 16).

The most frequently reported ADR was deafness (44.3%), followed by hypoacusis (31.4%), bilateral deafness (10.0%) and auditory disorders (5.7%). There were 13 patients (18.6%) with comorbidities potentially associated with hearing loss, including brain tumour, cranial trauma, HIV infection, Lobstein disease, meningitis, otitis and prematurity.

The most commonly suspected drugs were amikacin or cisplatin (15.7% each), followed by clarithromycin, doxorubicin or vincristine (5.7% each) and ceftriaxone, MMR vaccine, isotretinoin or vancomycin (4.3% each). Ten patients were co-prescribed ototoxic drugs, mostly two antineoplastics or two antibacterials. Patients were treated for 1 day to 8 months, with hearing loss mostly detected a few days to several months after treatment initiation, although in four cases diagnosis occurred 2–9 years after drug withdrawal.

“Hearing loss with doxorubicin or ceftriaxone is an unexpected ADR not described in the literature”, note the authors; however, “our study did not allow us to draw a conclusion about these two drugs, because of their association with other ototoxic drugs or known hearing-loss risk factors”. In addition, although “the low number of ADR reports registered in the FPVD suggests an important under-reporting of drug-induced hearing loss in the pediatric population, limiting the scope of our results”, “these results underline the importance of strengthening hearing monitoring in children during and long after drug treatment”.

Gainville A, Rousseau V, Kaguelidou F, et al. Drug-induced hearing loss in children: an analysis of spontaneous reports in the French Pharmacovigilance Database. Pediatr Drugs. Epub 17 Nov 2020. https://doi.org/10.1007/s40272-020-00425-z. Accessed 22 Dec 2020.