Regulatory Toxicology and Pharmacology 162 (2025) 105893

Contents lists available at ScienceDirect

Regulatory Toxicology and Pharmacology

journal homepage: www.elsevier.com/locate/yrtph

The value of a structured, systematic approach to benefit-risk assessment of medicines: A South African regulator case study

Lorraine Danks [a], Boitumelo Semete-Makokotlela [b], Donald Chuma [c], John-Joseph Borg [d], Star Khoza [e], Stuart Walker [a,f], Sam Salek [a,g,*]

[a] School of Life and Medical Sciences, University of Hertfordshire, Hatfield, United Kingdom
[b] South African Health Products Regulatory Authority (SAHPRA), Pretoria, South Africa
[c] School of Pharmacy, Department of Pharmacology and Therapeutics, University of Namibia, Namibia
[d] School of Pharmacy, University of Tor Vergata, Rome, Italy
[e] Discipline of Pharmacology and Clinical Pharmacy, School of Pharmacy, University of the Western Cape, Cape Town, South Africa
[f] Centre for Innovation in Regulatory Sciences, London, United Kingdom
[g] Institute for Medicines Development, London, United Kingdom

ARTICLE INFO

Handling Editor: Dr. Martin van den Berg

Keywords:
Universal Methodology for Benefit-Risk Assessment (UMBRA)
South African Health Products Regulatory Authority (SAHPRA)
Medicine benefit-risk assessment

ABSTRACT

This study investigates the utility of the Universal Methodology for Benefit-Risk Assessment (UMBRA) framework within the South African Health Products Regulatory Authority (SAHPRA) to determine whether adopting a structured approach improves consistency, transparency, and quality in benefit-risk assessments of new chemical entities (NCEs). The UMBRA eight-step framework was applied retrospectively and prospectively to six NCEs to systematically document the decision context, identify benefits and risks, and interpret the benefit-risk balance. Comparisons were made between initial SAHPRA narrative assessments and structured UMBRA-based evaluations. Reviewer feedback was collected through a questionnaire and group discussions. The retrospective study revealed that UMBRA provided greater clarity and alignment with decisions by global reference authorities, improving transparency in the weighting of benefits and risks. The prospective study demonstrated UMBRA's utility in highlighting local demographic and clinical considerations, enhancing regulatory reliance decisions. The UMBRA framework enhances the benefit-risk assessment process by providing a structured, transparent, and reproducible methodology. It facilitates comprehensive decision-making that aligns with global best practices, reducing reliance on subjective judgements. Implementing UMBRA at SAHPRA and other African regulatory authorities could promote harmonised regulatory practices, improve public trust, and enable transparent communication of decisions. The study recommends integrating UMBRA into routine assessments, training programs for new reviewers, and reliance strategies to ensure equitable benefit-risk evaluations across jurisdictions.

1. Recommendations

The following recommendations emerged from this study.

1. Regulators should consider using the UMBRA framework routinely to enable a systematic, structured approach for decision-making regarding the benefit-risk of innovative medicines.
2. Regulators should consider using this approach as a training tool for new reviewers.
3. With more regulators striving for transparency and efficient communication, they should review the advantages of the UMBRA framework and template as the basis for developing a public assessment report.
4. By incorporating multi-faceted input, regulators could ensure that all stakeholders contribute to the benefit-risk assessment of a medicine, that is, industry, patient, and regulator.

2. Background

It is an acknowledged fact that all medicines may present adverse effects. Therefore, it is of the utmost importance that there is sufficient evidence that the benefits of a product for a specific condition outweigh

* Corresponding author. School of Life & Medical Sciences, University of Hertfordshire, Hatfield, Herts, AL10 9AB, United Kingdom.
E-mail address: m.s.salek@herts.ac.uk (S. Salek).

https://doi.org/10.1016/j.yrtph.2025.105893
Received 26 January 2025; Received in revised form 20 May 2025; Accepted 23 June 2025
Available online 26 June 2025

its risks or potential harms and that, despite associated uncertainties, there are mechanisms to mitigate such risks (United States Food and Drugs Administration, 2023). When medicines regulators embark on the complex task of assessing a large amount of new product data to form a balanced understanding of the benefits and risks to patients, personal experts' biases and judgements may influence decision-making, making substantiating and communicating these decisions problematic (European Medicines Agency, 2008). In the absence of scientifically grounded methodologies for benefit-risk assessment, regulatory authorities may come to divergent conclusions about the same medicine, based on the same data (European Medicines Agency, 2008; Leong et al., 2013).

As far back as 1998, the Council for International Organizations of Medical Sciences (CIOMS) expressed its frustration over the lack of a defined algorithm or metric that could quantitatively verify the decisions made regarding new medicines (European Medicines Agency, 2008). Over the last two decades, the criticality of a benefit-risk assessment of medicines, and the balance between the two, have been highlighted by not only the pharmaceutical industry, but also by World Health Organization (WHO)-Listed Authorities (WLAs), the latter having the responsibility of ensuring the efficacy and safety of medicines for their populations through the review of the clinical trial data of a particular product (Leong et al., 2013). The role of Bayesian statistics, multi-criteria decision analysis (MCDA) and other quantitative methods have been considered by both sides (Leong et al., 2013), although it has been acknowledged that qualitative assessment, that is, judgements and arguments, would remain a cornerstone of benefit-risk assessment (European Medicines Agency, 2008). The perspectives of the patient have, furthermore, been highlighted as important in the ultimate benefit-risk determination (Leong et al., 2013), with patient experience data playing a role in the decision-making process (United States Food and Drugs Administration, 2023).

In March 2008, the European Medicines Agency (EMA) published a reflection paper on the benefit-risk assessment of medicines, based on the outcomes of a Committee for Medicinal Products for Human Use (CHMP) working group that investigated the manner in which EMA's benefit-risk methodology could be optimised to improve the consistency and transparency of decision-making and how the authority communicated such decisions (European Medicines Agency, 2008). Thus, one of the main recommendations from this working group was to switch from "implicit to explicit decision-making" (European Medicines Agency, 2008). The EMA Problem, Objectives, Alternatives, Consequences, Trade-Offs, Uncertainty, Risk Tolerance, Linked Decisions (PrOACT-URL) framework also took into account the principles of logical soundness, comprehensiveness, acceptability of results and generativeness (Leong et al., 2013; Walker et al., 2015).

Likewise, from around 2009 onward, the United States Food and Drug Administration (US FDA) started to explore ways to structure its benefit-risk assessments and how to effectively communicate its decisions based on this balance, which brought about their five-step approach in this area (Leong et al., 2014). This methodology took into account the nature and severity of the condition being treated, how favourably other available treatment options measured up to the product under assessment, and the clinical benefits and risks of the new drug, as well as appropriate risk management strategies for the latter (Leong et al., 2014). In its most recent guidance to the pharmaceutical industry, the US FDA described its approach as a "case-specific, multi-disciplinary assessment of science and medicine," which bears in mind the multifaceted confluence of factors that play into the benefit-risk assessment of a novel therapeutic agent, both pre-and post-marketing, across the full lifecycle of a medicine (United States Food and Drugs Administration, 2023). The agency's scope has been extended to include the health status of the intended treatment population, patient preference information, as well as the review of available Real-World Data (RWD), new safety data generated through post-marketing studies and the International Council for Harmonisation (ICH) E2C(R2) Periodic Benefit-Risk Evaluation Reports, to regularly assess whether the optimum balance between the benefits and risks has changed after the product has been authorised (United States Food and Drugs Administration, 2023; International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, 2012).

Also in 2008, the Centre for Innovation in Regulatory Sciences (CIRS) was consulted to assist four medium-sized National Regulatory Authorities (NRAs), that is, the Australian Therapeutic Goods Administration (TGA), the Singapore Health Sciences Authority (HSA), Health Canada, and Swissmedic in developing "a systematic qualitative approach" when assessing the benefits and risks of medicines, with the ultimate view of enabling joint reviews so as to maximise their resources (McAuslane et al., 2017). This cohort became known as the Consortium on Benefit-Risk Assessment (COBRA), and utilising the work done by the EMA CHMP working group, a benefit-risk documentation template was developed (McAuslane et al., 2017). After establishing its feasibility, the COBRA benefit-risk template was deployed retrospectively and prospectively to determine its applicability in highlighting the benefits and risks associated with new medicinal products (McAuslane et al., 2017). This template evolved into the Universal Methodology for Benefit-Risk Assessment (UMBRA), an all-encompassing benefit-risk framework that holistically incorporates the aspects determining the pre-marketing clinical benefits and risks of a medicine in its eight-step framework (Fig. 1) (Keyter et al., 2020a; Walker and McAuslane, 2016). The UMBRA framework encompasses four pivotal stages to elucidate the benefit-risk ratio of a medicine.

1) Framing the treatment decision within the given context (decision context);
2) Identifying the benefits and risks associated with a medicine;
3) Assessing the relevant benefits and risks;
4) Interpreting the information gathered in 1–3 and providing recommendations in terms of the benefit-risk balance that a certain product has for a target population (Keyter et al., 2020a).

The UMBRA framework assists medicines regulators to clearly document their approaches when assessing the essential clinical benefits and risks, the conclusions they come to and how these are communicated to stakeholders (Keyter et al., 2020a). In light of this, Keyter and colleagues recommended that national regulatory authorities (NRAs), with specific reference to the South African Health Products Regulatory Authority (SAHPRA), adopt the UMBRA framework for benefit-risk (BR) assessment, as this should have "a major impact on ensuring consistency in the BR assessment of new active substances," resulting in transparent quality decision-making, which may be publicly communicated with confidence and could form the basis of a public assessment report (Keyter et al., 2020a).

When SAHPRA was established in 2018, it inherited a backlog of product applications from its predecessor, the Medicines Control Council (MCC), which led to a standalone Backlog Clearance Project (BCP) being set up to effectively and efficiently clear this build-up (South Africa Government, 2008; The Boston Consulting Group, 2019; Danks et al., 2023). Within the backlog were several innovative products awaiting registration, for which clinical data had been submitted for regulatory review. In the absence of a scientifically validated benefit-risk framework for clinical assessment, the review outcomes varied considerably from those by the WLAs, such as the US FDA, Swissmedic, and especially the EMA, which was specified as the principal SAHPRA reference for clinical reliance (Danks et al., 2023; Keyter et al., 2020b; SAHPRA, 2024).

The SAHPRA-approved labelling diverged significantly from the EMA Summary of Product Characteristics (SmPC) in terms of therapeutic indications (40 % divergence demonstrated by the study cohort), contraindications (74 %), special warnings and precautions for use (60 %) and fertility, pregnancy and lactation (84 %) (Danks et al., 2023). The subjective judgement of the SAHPRA clinical assessors gave rise to

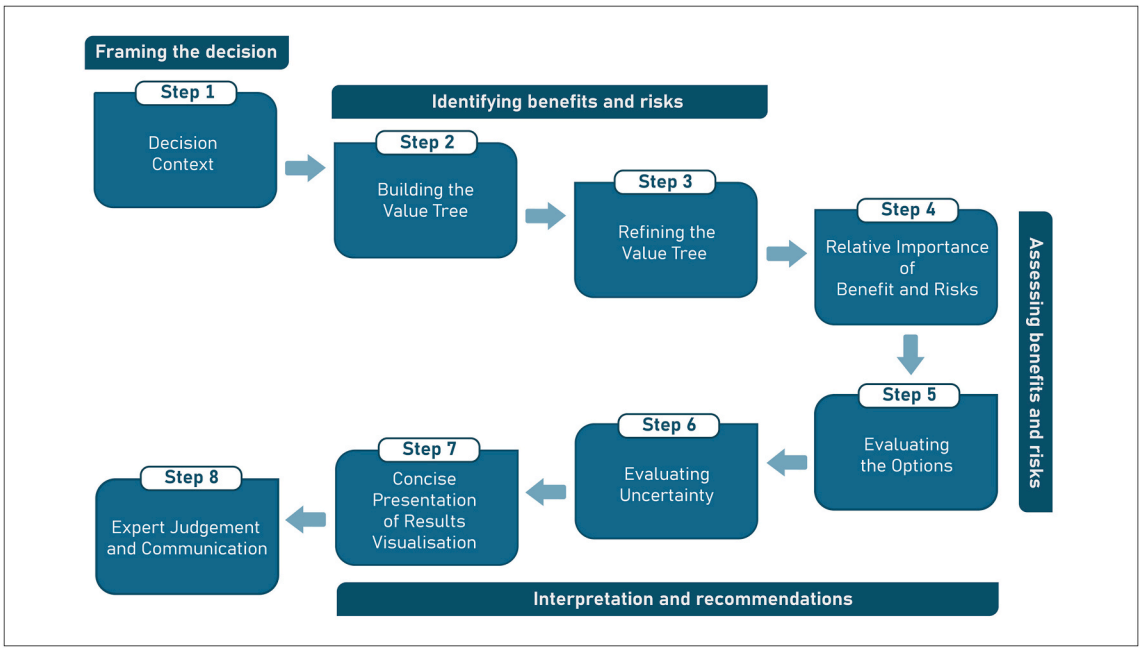

Fig. 1. The UMBRA Eight-Step Benefit-Risk Framework [adopted from Walker and McAuslane (2016)].

these disparities (Danks et al., 2023), and through employing a purely qualitative approach by "making a 'gut decision' on the benefit-risk profile of each product" (Leong et al., 2013), although the decisions were documented, the rationale could be challenged. Without a structured benefit-risk tool, the clinical judgement and risk tolerance of the reviewer, which among other factors is based on many years of clinical expertise rather than transparency of decision-making, informed the decisions, resulting in divergence in the assessment outcomes (Danks et al., 2023). Given the diverse regulatory decisions, not only between assessors, but also between different medicines regulators, there is a need for agency transparency and accountability, enabled by robust tools, in terms of benefit-risk decision-making (Walker et al., 2015).

The aim of this research was to investigate the value of a structured benefit-risk assessment of new chemical entities (NCEs) within the SAHPRA Backlog Clearance Project (BCP) by using the UMBRA tool, and how this assessment framework would enhance the quality of decision-making by regulators.

The specific objectives were to.

- Provide, through a retrospective introduction of the UMBRA framework, an alignment comparison between the original SAHPRA narrative reviews and the UMBRA template assessments, particularly in terms of the respective outcomes and the clarity with which the individual product benefits and risks were highlighted;
- Determine whether prospective implementation of the UMBRA framework, in parallel to SAHPRA's standard narrative approach, could improve the objectivity and clarity in delineating the benefits and risks of the medicine;
- Garner feedback from the clinical assessor cohort on whether a structured, systematic benefit-risk framework is of value in communicating a medicines regulator's decision outcome.

3. Methods

3.1. Study design

For this qualitative study, the UMBRA template (Walker and McAuslane, 2016) was employed within the SAHPRA BCP retrospectively, where the clinical assessment of NCEs had already taken place, as well as prospectively, upon initial review of the clinical data. Three BCP expert clinical assessors were selected (two African-based and one European Union-based assessor) to determine the benefits and risks of six NCE applications submitted to SAHPRA, and to clearly document the information using the mentioned template, with Table 1 providing an outline of the data gathered to inform the benefit-risk balance for each product. Table 2 further provides a visualisation of the UMBRA effects table through which the assessors weighted the benefits and risks of a particular medicine.

3.2. Study setting

The South African medicines regulator has a structured process for the review of NCE clinical data, which is performed via a narrative template completed by its assessors. The reporting template provides space for the reviewer to detail their observations in a general narrative manner without explicit benefit-risk weighting and determination sections. While the assessment of the quality attributes of a product occurs separately from that of the clinical data review, for NCEs, the input of specifically the external expert reviewers on the Advisory Clinical Committee (ACC) plays a pivotal role. This cohort assesses approximately 50 NCE applications per year, with the majority of the products previously authorised by SAHPRA reference authorities (SAHPRA, 2024).

3.3. Retrospective study

For the retrospective analysis, clinical data for three products, containing tofacitinib, brexpiprazole, and venetoclax, were evaluated by Assessors A, B and C, respectively, using the UMBRA framework and completing the associated assessment template. Each assessor carried out a benefit-risk analysis on one of the products. These products had already been reviewed and authorised by SAHPRA and a comparison was made between the two decision outcomes, that is, the initial SAHPRA decision versus the decision made retrospectively using the UMBRA approach. Notwithstanding the decision outcome alignment, it was also of importance to appraise the manner in which the medicines' benefits and risks were highlighted during the two types of reviews, with a view of enabling clear communication of these to physicians and patients.

Table 1
The outline of the UMBRA template populated by the assessors (Walker and McAuslane, 2016).

	Information Documented
Compound Information	• Compound identifier(s) • Product name/brand name/generic name • Active ingredient(s)/strength(s)/dosage form • Proposed indication by the company • Approved indication • Regulatory history—reference agencies that have reviewed the product and outcome
Background (Decision Context)	• Proposed therapeutic indication(s) • Treatment modalities evaluated in submission • Unmet medical need—specify reasons • Local clinical guideline or other issues to be considered to contextualize the decision context • Previous review of the active substance by the agency—details on the outcome of the review, the indication(s) and any issues raised • Reference agency regulatory history—reference agency, outcome at agency, approved indication(s), approved doses, contraindications, warnings and precautions, product sameness, key documents referenced
Overall Summaries	• Quality Overall Summary—details only if significantly affect the benefit-risk assessment • Non-Clinical Overall Summary—details only if significantly affect the benefit-risk assessment • Human Pharmacology—overall summary and conclusions • Assessment of ethnic factors
Clinical Study Summary	• Clinical Overall Summary—study reference/type, study design and duration, treatment, conclusion, key benefit (s) and/or risk(s) identified by study • Clinical Conclusion—only important results and issues that impact the benefit-risk balance
Risks: Overall Summary	• Table of pooled overall incidence—investigated product, comparator(s), placebo (if appropriate)
Identified Benefits and Risks	• List of all benefits of treatment as inferred in the submission, justification of inclusion in the benefit-risk assessment and main reason(s) for inclusion/exclusion • List of all risks of treatment as inferred in the submission, justification of inclusion in the benefit-risk assessment and main reason(s) for inclusion/exclusion
Weights and values	**Benefits** • Assignation of relative importance (weighting of high, medium or low) to the benefits identified, valuation of the options (investigated product, comparator(s), placebo (if appropriate)), commentary on strength and uncertainty of benefit **Risks** • Assignation of relative importance (weighting of high, medium or low) to the risks identified, valuation of the options (investigated product, comparator(s), placebo (if appropriate)), commentary on strength and uncertainty of risk • Determination on whether the value or weight of the risks were mitigated by the ability to control the use of the medicine once on the market
Conclusion	• Effects table—documentation of the effects (benefits and risks) and their relative importance in the benefit-risk balance • If negative benefit-risk balance, documentation of the harm (e.g., lack of efficacy, toxicity) • Evolution of the benefit-risk balance over time (e.g., when late side effects emerge or long-term efficacy decreases) • Evaluation of pharmacovigilance and risk minimization plans, if available, and restrictions to product availability or usage • Outstanding significant information—additional reports by the company, hearings and advisory group recommendations, information from other jurisdictions (scientific experts, patients, consumers, consumer advocates and other stakeholders) • Any further studies required—to improve the benefit-risk balance with further optimisation studies, the need for intensive additional follow-up measures or specific obligations, and the need for further development including any paediatric development plans • Any other information considered by the agency relevant to the benefit-risk decision that is not covered elsewhere in the template • Clear conclusion on the benefit-risk being positive or not for the proposed indication • Recommendation of the outcome of the benefit-risk balance • Indication of outcome alignment with reference agencies

3.4. Prospective study

The same assessor cohort then proceeded to complete the UMBRA template in parallel with their initial review of three other NCEs, namely icatibant (Assessor A), neratinib (Assessor B), and cabozantinib (Assessor C), following the same process.

At the conclusion of the two studies, a feedback questionnaire (Table 3) was shared with the three assessors to comment on the applicability and advantages and/or disadvantages of the UMBRA template in an NRA setting, followed by a virtual group discussion to further determine the value of this methodology.

4. Results

The results are presented in three parts: Part I - the retrospective study; Part II - the prospective study; and Part III – the clinical reviewers' evaluation of the universal methodology of benefit-risk assessment.

During both the retrospective and prospective studies, the assessors, in line with the first UMBRA stage, established the decision context by detailing the active pharmaceutical ingredient, the associated dosage regimen, the treatment options evaluated in the submission, and the indications for which were being applied. Clarification was also provided regarding the availability of therapeutic alternatives, the existence of a justified unmet need, and whether any country-specific demographic factors were relevant. Additionally, it was investigated whether the product had been approved by a SAHPRA reference agency (SAHPRA, 2024), specifically examining the licensed indications. Lastly, during the retrospective study, the assessors reviewed the outcomes of the prior assessment by the SAHPRA ACC, the indications authorised, and any concerns that had been raised.

During stage 2, the clinical data furnished to support the indications were assessed to identify key components that played into the product's benefit-risk balance, and these were clearly detailed. Furthermore, uncertainties - such as those related to study size and design, population, and comparators - were documented along with their impact on the benefit-risk balance. Stage 3 entailed assessing the listed benefits and risks, attributing a relative (low, medium, or high) value or weight to each, and providing a rationale for their inclusion or exclusion in the balance determination.

In the final stage of the UMBRA methodology, the three assessors interpreted the information gathered during stages 1–3 and offered

Table 2
Visualisation of the UMBRA effects table (Walker and McAuslane, 2016).

Effect (Benefit/ Risk)	Relative Importance (Weighting) High/Medium/ Low	Units of Measurement	Valuing the Options			Comment on Strength and Uncertainty
			Investigator Product	Comparator	Placebo	
Enter Benefit 1	Click here to enter text.	Click here to enter text.	Click here to enter text.	Click here to enter text.	Click here to enter text.	Click here to enter text.
Enter Benefit 2	Click here to enter text.	Click here to enter text.	Click here to enter text.	Click here to enter text.	Click here to enter text.	Click here to enter text.
Enter Benefit 3	Click here to enter text.	Click here to enter text.	Click here to enter text.	Click here to enter text.	Click here to enter text.	Click here to enter text.
Enter Risk 1	Click here to enter text.	Click here to enter text.	Click here to enter text.	Click here to enter text.	Click here to enter text.	Click here to enter text.
Enter Risk 2	Click here to enter text.	Click here to enter text.	Click here to enter text.	Click here to enter text.	Click here to enter text.	Click here to enter text.
Enter Risk 3	Click here to enter text.	Click here to enter text.	Click here to enter text.	Click here to enter text.	Click here to enter text.	Click here to enter text.

Table 3
Feedback questionnaire on applicability and advantages and/or disadvantages of the UMBRA template for good clinical decision-making.

SAHPRA study on benefit-risk assessment using the UMBRA template	
1	Did you find it easy and straightforward to complete the UMBRA template using information/data from the original SAHPRA assessment?
2	Were there any areas in the template that you found difficult to understand as to what should be completed?
3	Were there any questions/boxes that you believed were irrelevant to an appropriate benefit-risk assessment?
4	Did you think that it was beneficial to list the benefits and the risks/harms that you believe should be included in a benefit-risk assessment with an explanation of why certain benefits and risks were included and those that were excluded?
5	Was the documentation to indicate the relative importance/weighting of each benefit and harm helpful in making the overall benefit-risk assessment?
6	Was the section that documented the regulatory history of the product from the reference agencies of value, and was this included in your original SAHPRA assessment?
7	Were you uncomfortable with documenting your assessment in specific boxes compared with a narrative approach?
8	Do you believe that utilising the UMBRA template is of value when in the future you may want to make comparisons between different reviewers' assessments as well as the value of this approach when new data becomes available in the post-approval period?
9	Would you consider adopting or adapting parts of this template to be included in the current SAHPRA guidance for the regulatory review of new medicines?
10	Overall, did you think that this exercise was of value and has it changed the way in which you will carry out benefit-risk assessments in the future?
11	Do you believe that the UMBRA framework and template has value for the training of new reviewers?
12	Do you think that this structured and systematic approach to benefit-risk assessment has value when implementing reliance?

recommendations on the benefit-risk ratio for each of the six products.

4.1. Part I - retrospective study

4.1.1. Tofacitinib

Tofacitinib had previously been authorised by the US FDA, EMA, the Australia Therapeutic Goods Administration (TGA), and Health Canada for rheumatoid and psoriatic arthritis, as well as ulcerative colitis. The EMA approved two additional indications (European Medicines Agency, 2024a), which were not applied for in South Africa. SAHPRA had approved the product for all three indications, but had, given the local context, requested the submission of a Risk Management Plan (RMP) for the use of the medicine in an HIV setting with antiretroviral therapies.

When reviewing the benefit-risk balance using the UMBRA framework, Assessor A clearly identified "strong evidence of benefit", with these being 1) relief of symptoms in rheumatoid and psoriatic arthritis, together with physical functioning, and 2) remission in ulcerative colitis over 24 months. The assessor assigned a relative importance of "high" to all the benefits highlighted.

The characterised risks included "strong evidence of a heightened side effects profile," with the assessor ascribing a higher weighting to the majority of the more frequently reported effects. Assessor A did, however, conclude that there were sufficient measures included in the professional information to mitigate these, and that "there was a consistent demonstration of benefit across the three indications," with the benefits outweighing the risks. This decision outcome corresponded with that of the EMA, who pointed out that specific recommendations have been put in place to reduce the risks of important side effects (European Medicines Agency, 2023a). The European agency, additionally, highlighted another advantage of the product, namely that the product is an oral dosage form compared to the existing sub-cutaneous injections (European Medicines Agency, 2023a).

In the case of tofacitinib, the assessment outcomes from the independent reviewer aligned well with those of the initial review conducted by the SAHPRA ACC; however, there was clearer articulation of the benefits and risks associated with the product through the structured UMBRA template.

4.1.2. Brexpiprazole

The benefit-risk assessment of brexpiprazole was performed by Assessor B, who ascertained that out of the two indications submitted to SAHPRA for approval, only one had been approved by the EMA (treatment of schizophrenia) (European Medicines Agency, 2023b), while the US FDA had approved both (treatment of schizophrenia and of major depressive disorder as an adjunctive therapy to antidepressants) (United States Food and Drugs Administration, 2024a). However, during the prior review of the clinical data, neither of the indications had initially been approved by the SAHPRA ACC, which had prompted further consultation with the applicant to align on the EMA-authorised indication.

Supported by the UMBRA template, the assessor selected one main benefit of the product, that is, "brexpiprazole significantly delayed relapse compared to placebo." The risks associated with the product were similarly investigated and Assessor B highlighted that "brexpiprazole has a similar adverse effect profile as other approved second-generation anti-psychotics." During the weighting of the benefit and risk, the assessor, bearing in mind the value to the patient, assigned a relative importance of "high" to both. Although the weighting was the same, Assessor B still found that "the benefit-risk [was] considered positive given that the medicine was evaluated against a placebo," although still undecided as to whether the benefit-risk balance could fluctuate in relation to other authorised therapies. Ultimately, however, Assessor B aligned with the EMA decision, who had declared that "the Agency decided that [the product's] benefits are greater than its risks and it can be authorised for use in the EU" (European Medicines Agency, 2018a).

4.1.3. Venetoclax

Assessor C indicated that the product had previously been approved by the EMA (European Medicines Agency, 2024b) and the US FDA (United States Food and Drugs Administration, 2019), as well as by other SAHPRA reference authorities (SAHPRA, 2024), as an "anti-cancer medicine in patients who have progressed and/or failed other treatment options." Upon authorisation, the SAHPRA indication did not fully align with that of the reference agencies, in that it was truncated and less specific. Prompted by the UMBRA template, the assessor highlighted that the SAHPRA ACC did not provide feedback on whether there was an unmet medical need within the population, while the assessor believed one existed. Assessor C also evaluated data impacting the South African demographics and determined there were no novel factors that contributed to the clinical outcomes.

Using the UMBRA template, the benefits were clearly detailed, with these being 1) clinically relevant and superior progression-free survival (PFS) and overall response rate (ORR) of the combination therapy versus standard combination therapy and 2) increased overall survival (OS) versus standard therapy. The risks comprised side effects such as neutropenia, leukopenia, lymphopenia, respiratory tract infection, and others, and Assessor C felt an RMP to manage the testicular toxicity in males would be beneficial in mitigating this risk. Identifying the relative importance of the benefits and risks according to the UMBRA framework, the benefits were valued higher, while the assessor rated the risks as medium, due to these being "manageable and common in oncology patients." This, again, aligns with the EMA's outcome, which found that in terms of safety, "the side effects of [the product] are considered acceptable" when the relevant preventative measures are adhered to (European Medicines Agency, 2021). Assessor C concluded that, given the above assessment, "the benefit/harm balance is acceptable for patients with both the monotherapy and combination therapy options."

4.2. Part II - prospective study

4.2.1. Icatibant

Assessor A noted that the icatibant injectable was authorised by most of the global reference authorities, including the EMA (European Medicines Agency, 2023c) and the US FDA (United States Food and Drugs Administration, 2024b), for the treatment of "symptoms of attacks of hereditary angioedema (HAE)," with the applicant applying for the same indication in South Africa. The assessor emphasised the need for this particular medicine, as "current treatments appear not to offer rapid onset of relief of symptoms" and, as laryngeal attacks can be life-threatening, it is critical that the time it takes for the medicine to take effect is reduced. This benefit relates to the fact that normally patients need to be treated via IV infusion in a health facility. Responding to the local context, Assessor A, prompted by the UMBRA template, further consulted the Allergy Foundation of South Africa to evaluate the current treatment guidelines and found that the "current treatment options in South Africa are limited" and that the more effective medicines are not available locally. A further consideration was the limited options for patients who wanted to conceive, as some of the current therapies are teratogenic. The assessor also documented that "no ethnic differences were observed in efficacy and safety of the medicine."

After reviewing the clinical trial data, the following were identified as benefits with high relevance compared with the comparator product and the placebo:1) the rapid onset of symptom relief, 2) the medicine's effectiveness in both non-laryngeal and laryngeal attacks, and 3) that the self-administration was safe and well tolerated by patients. Assessor A then evaluated the relative importance of the identified risks and found that only one, namely the "lack of efficacy or worsening of an HAE attack" was of medium importance, as this could potentially be life-threatening during laryngeal attacks; however, the assessor noted that most attacks are non-laryngeal. All the other side effects were deemed to be mild to moderate risks, which could be resolved without treatment. Assessor A concluded that although no RMP or pharmacovigilance plan was submitted, the risks were minimised by limiting the number of injections to eight per month and that "the product has a positive benefit-risk balance," consistent with the EMA decision that the medicine's "benefits are greater than its risks" (European Medicines Agency EMA, 2017).

4.2.2. Neratinib

In the case of this product, Assessor B found that it had been authorised for the same indication by the SAHPRA reference authorities (SAHPRA, 2024), including the EMA, who approved it as "a breast cancer medicine used to reduce the risk of the disease coming back in patients with early breast cancer who have had surgery," following prior treatment with trastuzumab (European Medicines Agency, 2018b). Guided by the UMBRA template, the assessor documented that there are "limited treatment options available for extended adjuvant therapy following treatment with trastuzumab," thus concluding that an unmet medical need existed by underscoring that ongoing therapy with trastuzumab beyond a year held no further benefit, while the risks increased significantly with longer treatment. Assessor B did, however, find that the adverse effect profile was "race dependent" and felt that, given the South African context and the low percentage of black or African Americans enrolled in the pivotal study, further studies needed to be undertaken to determine the safety profile in non-Caucasian patients.

Reviewing the data, the assessor listed three benefits of high importance, namely 1) the 2-year invasive disease-free survival (iDFS) rate was higher in the neratinib versus the placebo arm of the study, 2) neratinib resulted in disease-free survival (DFS) including a 39 % reduction in ductal carcinoma in situ (DFS-DCIS) versus placebo, and 3) it improved distant disease-free survival (DDFS) by 26 % in the studied population. Assessor B also addressed the treatment-emergent adverse events (TEAE) that occurred, that is diarrhoea, nausea, vomiting, and abdominal pain, weighting all of these of high relevance to the patient, with diarrhoea in some cases leading to treatment discontinuation. However, the EMA stated in its Pubic Assessment Report (PAR) that "there would be patients […] for whom treatment with [neratinib] after surgery and trastuzumab would be a reasonable option," and, as did Assessor B, pointed out that the measures for ensuring the safe and effective product use included in the professional information would assist in mitigating these risks (European Medicines Agency, 2018b). In view of the benefit-risk assessment conducted, Assessor B decided that the magnitude of the benefit regarding iDFS in hormone receptor-positive patients were "statistically significant and clinically relevant and, therefore, outweighs the risks."

4.2.3. Cabozantinib

The cabozantinib-containing product had been reviewed and authorised by the EMA, the United Kingdom Medicines and Healthcare products Regulatory Agency (UK MHRA) and the TGA for the treatment of advanced renal cell carcinoma (RCC) and hepatocellular carcinoma (HCC), with the EMA authorising an additional treatment regimen for differentiated thyroid carcinoma (European Medicines Agency, 2023d). Debating whether this product filled an unmet need for oncology patients, Assessor C felt strongly that, given the Southern African context of "endemic chronic hepatitis B virus infection[s]," there is a lack of effective treatment options for HCC, especially after prior therapies.

By reviewing the clinical trial data and summaries, the assessor, unsurprisingly, selected the "clinically relevant and superior PFS and ORR, and OS of combination therapy versus standard combination therapy and comparator" as the main benefit, denoting a high relative importance to this benefit. Similarly, a high weighting was attached to the benefit of having the currently unmet need fulfilled, which aligned with the EMA position (European Medicines Agency, 2022). As risks, Assessor C highlighted those for which there existed robust evidence and a strong certainty of occurrence, such as gastrointestinal perforation and fistulas, thromboembolic events, haemorrhage and wound complications, but further underscored "hypertension", which was not a risk

identified by the company and which this assessor thought warranted further investigation. In all instances, the assessor characterised the risks as manageable and common to cancer patients, again echoing the benefit-risk assessment of the EMA (European Medicines Agency, 2022). The RMP was also evaluated, and the assessor considered it deficient, in that the "safety specifications [were] not acceptable" and requested the RMP be updated with the risks highlighted during the benefit-risk assessment, as well as with missing information pertaining to certain demographics. As the applicant proposed a post-authorisation safety study in their submission to the reference authorities, Assessor C indicated that, given the time lapse, this report should now have been concluded and therefore submitted to SAHPRA for review. The assessor raised further queries in terms of the clinical data and outcomes and concluded that, until further clarification and/or data were provided by the applicant, the assessor was not confident that there existed an equitable benefit-risk balance.

4.3. Part 3 - clinical reviewer feedback

As indicated in the methodology section, feedback from the clinical reviewers was solicited to understand their experience in terms of the advantage of a universal methodology for benefit-risk assessment, and whether the UMBRA framework could be utilised by an African NRA to fulfil this function. To this end, a questionnaire and joint discussion were facilitated between the authors and the SAHPRA assessors, with the main findings and conclusions listed in Table 4.

5. Discussion

Through the six case studies, it is clear that the UMBRA template requires the assessors to pay attention to and answer specific questions around the treatment context, ethnic considerations, current treatment options available in a certain country and whether an unmet need exists that would influence the benefit-risk profile. These are not review areas explicitly dealt with through the standard SAHPRA narrative report. Furthermore, through utilisation of the effects table, each assessor could clearly identify and assign a relative importance to the benefits and risks of each product. Whilst this might have been influenced by reviewer subjectivity, it still allowed the benefit-risk balance to be documented and enabled clearer decision-making on whether or not to authorise the medicine.

Upon reviewing the assessors' comments on the value of a systematic and structured methodology to benefit-risk assessment, it became evident that there was consensus on the advantages of this approach. The assessors noted that listing the benefits and risks made it easier to reach a conclusion regarding the balance between these. One of the assessors also appreciated the inclusion of reference authorities' regulatory decisions on the product, stating that it was "helpful, especially in identifying the key safety issues that could have been missed in the assessment report." Additionally, the warnings and contraindications raised by these authorities were considered highly valuable during the benefit-risk determination process. The same reviewer acknowledged that their previous practice had been to focus primarily on "a few selected efficacy endpoints (especially the primary efficacy indicators) and [pay] little attention to the secondary endpoints," while similarly considering only serious adverse effects. However, with this structured approach, "one has to consider the moderate adverse events, which may have [a] high incidence, in making a decision on the overall risk." This shift, according to the reviewer, provided a more comprehensive understanding of the product's benefit-risk ratio.

Another assessor similarly found the structured documentation of information "very useful in situations where the evaluator cannot clearly conclude the benefit-risk profile of the assessment using the original SAHPRA template." The assessor highlighted that listing the identified benefits and risks, along with their relative importance, can endorse the conclusions derived from the SAHPRA template. When questioned about the usefulness of a benefit-risk analysis template for new reviewers, the reviewer agreed that it would simplify the process for less experienced assessors, enabling them to make more informed decisions about whether to recommend a product for approval. Two of the assessors emphasised the value of this systematic approach when implementing reliance, with one observing that "it will allow reviewers to pay more attention to certain aspects which may be more important for South Africa than for the reference agencies." The other assessor further stressed the UMBRA framework's usefulness in cases where

Table 4
The advantages and disadvantages of the UMBRA framework for benefit-risk assessment in an African NRA from a reviewer perspective.

Focus areas	Assessor feedback
Ease of use/ applicability	• The UMBRA template was found easy to complete, with pre-set questions providing useful guidance for assessors. • It was agreed the template could be used both retrospectively and prospectively, although prospective application alongside narratives were preferable. • The assessors deemed all sections relevant.
Benefits over current methods	• The template offers a structured, systematic approach to benefit-risk assessment, supplementing the current narrative methods. • It enhances objectivity and transparency, particularly in high-risk product evaluations, and in instances where the benefit-risk balance is still unclear after using the SAHPRA narrative template. • Documenting clinical trials in tabular format ensures that key issues are highlighted, which might have otherwise been missed when using a purely narrative approach. • Summarising benefits and risks systematically, especially through "Effects Tables," ensures critical information is not overlooked. • The UMBRA template also provides an opportunity to review any quality-related matters, which are not currently evaluated by the SAHPRA assessors when evaluating efficacy and safety.
Challenges identified	• Retrospective completion was challenging due to insufficient detail in previous narrative reports. • Limited resources in some authorities may require additional time to implement the template, although completing it concurrently with narrative reviews minimises this.
Reviewer perspective	• The inclusion of the regulatory history when a product had previously been authorised by a reference authority was considered helpful. • The template encourages weighing benefits and harms in terms of relative importance from both patient and societal perspectives, recognising that these views may differ. It also allows the evaluator to assess the benefit-risk profile of comparator products to the same level of scrutiny. • It fosters a more quantitative and logical approach, reducing reliance on subjective opinions. • There was consistency regarding experiences across the three independent assessors evaluating different products in parallel.
Integration with current practices	• The UMBRA template cannot replace the narrative approach but can complement it, providing a summary that enhances decision-making. • It may simplify or inform the writing of narratives and enable easier review by other assessors.
Industry submission concerns	• Current applicant submissions do not align with the UMBRA format. Encouraging structured submissions, which could include a list of the applicant's perceived benefits and harms relating to its product, would improve consistency. • The template aligns with international practices, such as the FDA five-step format and the EMA Effects Table.
Future adoption	• The template is more practical for prospective use alongside narratives.

different reference authorities have reached differing decisions regarding a product. Upon summarising the assessor feedback in terms of the advantages of UMBRA implementation in an African NRA, this had been overall positive; although, given the pilot setting of the research, the current research could benefit from future studies to explore the utility of incorporating the UMBRA approach during SAHPRA reviews to determine whether benefit-risk assessments have improved over time.

According to Leong and colleagues, Mullin from the US FDA stated that a structured and systematic benefit-risk approach has "the potential to improve the predictability and consistency of decision-making," as it considers the evidence provided and balancing this against the uncertainties (Leong et al., 2014). The same authors also pointed out that the EMA Benefit-Risk Project team indicated that "structured processes should improve transparency, the audit trail, communication, reproducibility as well as the quality and speed of decision-making" (Leong et al., 2013). It is, therefore, noteworthy to mention that the UMBRA framework used during the retrospective and prospective pilot studies aligns well with the US FDA's five-step and the EMA's seven-step approach, underpinning its universality. This is apparent from the comparison of the three methodologies in Table 5. The UMBRA framework and the documentation system were adopted for these case studies, as it is recognised that this approach incorporates all previous benefit-risk assessment models, such as the mentioned FDA and EMA approaches. In addition, the UMBRA framework presents the graduality of the observations by the assessors and these are documented in a way that enables retrospective comparisons from different reviewers.

From Table 5, it is evident that the UMBRA framework establishes an international standard and promotes consistency among reviewers and across products within a therapeutic area, as confirmed by the assessor cohort. It corresponds favourably with ICH M4E(R2), section 2.5.6, which provides applicants with instructions on detailing their product's benefit-risk considerations during the initial submission for regulatory authorisation (International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, 2016). The UMBRA template is well-suited to evaluate the applicant's analysis of the strengths, limitations, and uncertainties of the evidence related to each key risk, as well as the implications of this information. Alternatively, the pharmaceutical industry could consider applying this approach in their submissions.

Bringing in the patient voice, an excellent example of the advantages of a focused approach is that of a benefit-risk study conducted on a hypothetical triptan regimen for the management of migraine, especially concerning the high-risk cardiovascular incidence population (Levitan et al., 2014). It called attention to the value of a structured approach to benefit-risk determination when assessing medicines, and highlighted the importance of not neglecting patient experience data (Levitan et al., 2014). Whereas the initially designed value tree focused on the typical endpoints for a "typical migraine randomized clinical trial," the patients' perspectives played an important role in refining the value tree and offsetting the benefits against the risks when it comes to making decisions about their treatment (Levitan et al., 2014). In this regard, the UMBRA template could prove invaluable for garnering feedback from patients in terms of their valuation of the benefits and risks of a treatment.

In addition, the UMBRA template systematically categorises the benefits and harms, making it much easier for another reviewer to understand the rationale behind the final decision. This approach emphasises the logic of the decision-making process rather than relying on opinion or personal experience. Reviewers in this study also expressed that the template could support a more objective evaluation, as opposed to assessments that may sometimes be perceived as subjective, potentially leading to improved decision-making. Furthermore, the benefit-risk assessment-based review can lead to consistent decision-making across different assessors and expert advisory committees.

The accompanying user manual is a supplementary advantage of the UMBRA framework that can assist medicine regulators across the African continent in implementing a structured approach to benefit-risk assessment within their authorities. As demonstrated with the COBRA group (McAuslane et al., 2017), a structured template to document benefits and harms provides a common platform for discussion, thus enhancing effectiveness in a joint review setting. Adopting the benefits of the UMBRA methodology could significantly enhance regional assessment practices, particularly within the Southern African Development Community (SADC), which will enable convergent approaches within different authorities in the same region.

Furthermore, with the advent of the African Medicines Agency (AMA), proliferation of a structured and systematic approach to benefit-risk assessment into a continental best-practice would allow the AMA to publish clearly substantiated public assessment reports, detailing the scientific rationale for authorising a product for use within the African population. At present, the African Medicines Regulatory Harmonisation (AMRH) Technical Committee for the Evaluation of Medicinal Products (EMP TC) is piloting the authorisation of new active substances, and it would be critical to ensure that the pilot incorporates a structured, systematic approach to benefit-risk assessment as part of its assessment template.

Lastly, it is important to highlight the significance of maintaining appropriate documentation of the benefit-risk assessment when a new medicine is reviewed. Such documentation could also prove valuable throughout the medicine's life cycle, providing a more effective means of identifying changes in the benefit-risk balance compared with the initial evaluation.

Table 5
Comparison between the US FDA, the EMA and the UMBRA benefit-risk assessment approaches.

Framework	Framing the decision	Identifying benefits and risks		Assessing benefits and risks		Interpretation and outcome		
	Step 1: Decision context	Step 2: Building the value tree	Step 3: Refining the value tree	Step 4: Assessing relative importance	Step 5: Evaluating the options	Step 6: Evaluating uncertainty	Step 7: Concise presentation of results (visualisation)	Step 8: Final recommendation
FDA	Analysis of conditions Unmet need	Clinical benefits and risks		Evidence and uncertainties			Words: Telling the story	Conclusions and rationale Risk management plans
EMA	Nature and framing of the problem	Objectives: Favourable and unfavourable effects		Options to be evaluated and the consequences	Trade-offs Benefit-risk balance	Evaluating uncertainty	Effects table Risk tolerance	Consistency of decisions (linked decisions)
UMBRA	Decision context	Building the value tree All benefits All risks	Rationale for benefits and risk in overall benefit-risk assessment	Weighting of benefits and risks	Valuing or scoring of options	Evaluating uncertainty throughout	Visualisation or effects table	Expert judgement and risk management

6. Conclusions

Determining the benefit response of a medicine is a critical step in the development, review, and post-approval reassessment of new medicines. The primary advantage of a systematic and structured approach to benefit-risk assessment is that it promotes a more predictable, consistent, and transparent review process. This approach helps integrate quality into decision-making, fostering trust in the regulatory process among reviewers and across authorities. Ultimately, it can also facilitate the involvement of patients in assessing the benefit-risk balance of their treatments. This study demonstrated the value to be gained by using a structured benefit-risk assessment by an African NRA.

CRediT authorship contribution statement

Lorraine Danks: Writing – review & editing, Writing – original draft, Formal analysis, Conceptualization. **Boitumelo Semete-Makokotlela:** Writing – review & editing, Formal analysis. **Donald Chuma:** Writing – review & editing, Formal analysis. **John-Joseph Borg:** Writing – review & editing, Formal analysis. **Star Khoza:** Writing – review & editing, Formal analysis. **Stuart Walker:** Writing – review & editing, Writing – original draft, Formal analysis, Conceptualization. **Sam Salek:** Writing – review & editing, Writing – original draft, Formal analysis, Conceptualization.

Ethics approval

The study was approved by Health, Science, Engineering and Technology ECDA, University of Hertfordshire, United Kingdom [Reference Protocol number: LMS/PGR/UH/05160].

Source(s) of support/funding

No external funding was utilised for this research.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

The authors acknowledge and thank Mahlodi Moropa from the SAHPRA Pre-Registration Clinical Unit for her guidance and assistance in the selection of the relevant applications and her further engagement with the ACC to socialise the concept of medicine benefit-risk determination.

Data availability

Data will be made available on request.

References

Danks, L., Semete-Makokotlela, B., Otwombe, K., Parag, Y., Walker, S., Salek, S., 2023. Evaluation of the impact of reliance on the regulatory performance in the South African Health Products Regulatory Authority: implications for African regulatory authorities. Front Med. Sci. 10. https://doi.org/10.3389/fmed.2023.1265058.

European Medicines Agency (EMA), 2017. Firazyr (icatibant). EMA/652313/2017. EPAR Summary for the Public. December 2017 https://www.ema.europa.eu/en/medicines/human/EPAR/firazyr. (Accessed 6 January 2025).

European Medicines Agency (EMA), 2024a. Xeljanz film-coated tablets. Summary of Product Characteristics (SmPC), 20 September 2024. https://www.ema.europa.eu/en/medicines/human/EPAR/xeljanz. (Accessed 6 January 2025).

European Medicines Agency (EMA), 2024b. Venclyxto film-coated tablets. Summary of Product Characteristics (SmPC), 17 April 2024. https://www.ema.europa.eu/en/documents/product-information/venclyxto-epar-product-information_en.pdf. (Accessed 6 January 2025).

European Medicines Agency (EMA), 2023a. Xeljanz (tofacinitib). EMA/351521/2022. An overview of Xeljanz and why it is authorised in the EU. April 2023. https://www.ema.europa.eu/en/medicines/human/EPAR/xeljanz. (Accessed 6 January 2025).

European Medicines Agency (EMA), 2023b. Rxulti film-coated tablets. Summary of Product Characteristics (SmPC). 14 June 2023. https://www.ema.europa.eu/en/documents/product-information/rxulti-epar-product-information_en.pdf. (Accessed 6 January 2025).

European Medicines Agency (EMA), 2023c. Firazyr solution for injection. Summary of Product Characteristics (SmPC), 21 April 2023. https://www.ema.europa.eu/en/documents/product-information/firazyr-epar-product-information_en.pdf. (Accessed 6 January 2025).

European Medicines Agency (EMA), 2023d. Cabometyx film-coated tablets. Summary of Product Characteristics (SmPC), 10 October 2023. https://www.ema.europa.eu/en/documents/product-information/cabometyx-epar-product-information_en.pdf. (Accessed 6 January 2025).

European Medicines Agency (EMA), 2021. Venclyxto (venetoclax). EMA/256462/2021. An overview of venclyxto and why it is authorised in the EU. June 2021. https://www.ema.europa.eu/en/medicines/human/EPAR/venclyxto. (Accessed 6 January 2025).

European Medicines Agency (EMA), 2018a. Rxulti (brexpiprazole). EMA/393168/2018. An overview of Rxulti and why it is authorised in the EU. July 2018. https://www.ema.europa.eu/en/documents/overview/rxulti-epar-medicine-overview_en.pdf. (Accessed 6 January 2025).

European Medicines Agency (EMA), 2018b. Nerlynx (neratinib). EMA/455200/2018. An overview of Nerlynx and why it is authorised in the EU. September 2018. https://www.ema.europa.eu/en/medicines/human/EPAR/nerlynx. (Accessed 6 January 2025).

European Medicines Agency (EMA), 2008. Reflection paper on benefit-risk assessment methods in the context of the evaluation of marketing authorisation applications of medicinal products for human use. In: http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2010/01/WC500069634.pdf. (Accessed 6 January 2025).

International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), 2016. Guideline on enhancing the format and structure of benefit-risk information in ICH. Efficacy - M4E(R2). https://database.ich.org/sites/default/files/M4E_R2__Guideline.pdf. (Accessed 6 January 2025).

European Medicines Agency (EMA), 2022. Cabometyx (cabozantinib). EMA/237818/2022. An overview of cabometyx and why it is authorised in the EU. June 2022. https://www.ema.europa.eu/en/medicines/human/EPAR/cabometyx. (Accessed 6 January 2025).

International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), 2012. ICH harmonised tripartite guideline. Periodic benefit-risk evaluation report (PBRER) E2C(R2). https://database.ich.org/sites/default/files/E2C_R2_Guideline.pdf. (Accessed 6 January 2025).

Keyter, A., Salek, S., Banoo, S., Walker, S., 2020a. Can standardisation of public assessment reports improve benefit-risk communication? Front. Pharmacol. 17, 855. https://doi.org/10.3389/fphar.2020.00855.

Keyter, A., Salek, S., McAuslane, N., Banoo, S., Azatyan, S., Walker, S., 2020b. Implementation of a framework for an abridged review using good reliance practices: optimising the medicine regulatory review process in South Africa. Ther Innov Regul Sci. 54, 1199–1207. https://doi.org/10.1007/s43441-020-00144-0.

Leong, J., Salek, S., Walker, S., 2014. Strategy for communicating benefit-risk decisions: a comparison of regulatory agencies' publicly available documents. Front. Pharmacol. https://doi.org/10.3389/fphar.2014.00269.

Leong, J., McAuslane, N., Walker, S., Salek, S., 2013. Is there a need for a universal benefit–risk assessment framework for medicines? Regulatory and industry perspectives. Pharmacoepidemiol. Drug Saf. 22, 9. https://doi.org/10.1002/pds.3464.

Levitan, B., Phillips, L., Walker, S., 2014. Structured approaches to benefit-risk assessment: a case study and the patient perspective. Ther Innov Regul Scie 1–10. https://doi.org/10.1177/2168479014536500.

McAuslane, N., Leong, J., Liberti, L., Walker, S., 2017. The benefit-risk assessment of medicines: experience of a consortium of medium-sized regulatory authorities. Ther Innov Regul Sci. 51, 635–644. https://doi.org/10.1177/2168479017696260.

South Africa Government, 2008. Report of the ministerial task team on the restructuring of the medicines regulatory affairs and medicines control council and recommendation for the new regulatory authority for health products for South Africa. https://www.gov.za/documents/other/report-ministerial-task-team-restructuring-medicines-regulatory-affairs-and. (Accessed 6 January 2025).

South African Health Products Regulatory Authority (SAHPRA), 2024. SAHPGL-BAU-01_v4 reliance guideline (version 4). https://www.sahpra.org.za/document/reliance-guideline/. (Accessed 6 January 2025).

The Boston Consulting Group (BCG), 2019. The backlog clearance program strategy document, the South African Health Products Regulatory Authority. Internal Document.

United States Food and Drugs Administration (US FDA), 2024a. Rexulti Film-Coated Tablets. Prescribing Information. May 2024. www.accessdata.fda.gov/drugsatfda_docs/label/2024/205422s011lblcorrection.pdf. (Accessed 6 January 2025).

United States Food and Drugs Administration (US FDA), 2024b. Firazyr Injection. Prescribing Information. January 2024. www.accessdata.fda.gov/drugsatfda_docs/label/2024/022150s016lbl.pdf. (Accessed 6 January 2025).

United States Food and Drug Administration (US FDA), 2023. Benefit-risk assessment for new drug and biological products. Guidance for industry. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/benefit-risk-assessment-new-drug-and-biological-products. (Accessed 6 January 2025).

United States Food and Drugs Administration (US FDA), 2019. Venclexta Film-Coated Tablets. Prescribing Information. May 2019. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/208573s013lbl.pdf. (Accessed 6 January 2025).

Walker, S., McAuslane, N., 2016. Center for Innovation in Regulatory Science (CIRS) in collaboration with Leong, J., Centre of Regulatory Excellence, Duke-NUS Medical School. Summary Template for the Benefit Risk Assessment of Medicines. v0.9.0. Internal Document.

Walker, S., McAuslane, N., Liberti, L., Leong, J., Salek, S., 2015. A universal framework for the benefit-risk assessment of medicines: is this the way forward? Ther Innov Regul Sci 1–9. https://doi.org/10.1177/2168479014547421.