

THE UNIVERSAL METHODOLOGY FOR BENEFIT-RISK ASSESSMENT (UMBRA): TESTING ITS IMPLEMENTATION IN A SOUTH AFRICAN AGENCY

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BACKGROUND

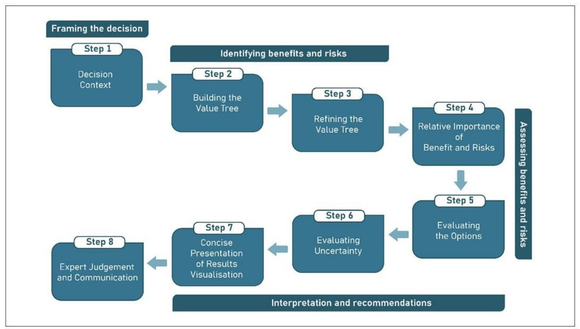
- Medicines regulators face the complex task of ensuring the benefits of medicines outweigh their risks, often hampered by subjective decision-making and inconsistent methodologies.
- In the absence of scientifically grounded methodologies for benefit-risk (BR) assessment, regulatory authorities may come to divergent conclusions about the same medicine, based on the same data
- The Universal Methodology for Benefit-Risk Assessment (UMBRA) framework was designed to standardize this process through an eight-step approach.
- UMBRA captures elements from BR frameworks utilized by the European Medicines Agency (EMA) and the United States Food and Drug Administration (US FDA), hence its universality.

AIM

This study investigates the utility of the 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).

METHODS

The UMBRA is 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:



METHODS (Cont.)

UMBRA TEMPLATE

	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 alignment with reference agencies

METHODS (Cont.)

- The UMBRA template was utilized when assessing clinical data for six new chemical entities (NCEs) submitted to SAHPRA to systematically document the decision context, identify and weigh benefits and risks, and interpret the benefit-risk balance.
- The approach was piloted both retrospectively, where the assessment of the NCEs had already taken place, as well as prospectively, upon initial review of the data.
- For the retrospective implementation, comparisons were made between initial narrative assessments and structured UMBRA-based evaluations.
- Three SAHPRA expert clinical assessors were selected to determine the benefits and risks of two products each.

Assessor	Retrospective Study	Prospective Study
A	Tofacitinib	Icatibant
B	Brexpiprazole	Neratinib
C	Venetoclax	Cabozantinib

- At the conclusion of the study, reviewer feedback was collected through a questionnaire and group discussions.

RESULTS

RETROSPECTIVE UMBRA IMPLEMENTATION

- ❑ The retrospective study revealed greater transparency, structured decision-making, and alignment with global regulatory authorities.
- ❑ Assessors identified the key benefits and risks, assigned relative weightings, and compared results to prior SAHPRA assessments.
- ❑ Tofacitinib and venetoclax showed favourable benefit-risk profiles, aligning with global approvals, while brexpiprazole's assessment raised questions on indication approval.

PROSPECTIVE UMBRA IMPLEMENTATION

- ❑ During the prospective study UMBRA facilitated systematic identification of benefits and risks, enhancing assessors' ability to justify decisions.
- ❑ Icatibant demonstrated a rapid onset of symptom relief, fulfilling an unmet medical need. Neratinib showed improved disease-free survival but had safety concerns requiring further local population studies.
- ❑ Cabozantinib addressed a regional oncology treatment gap, but additional data were requested before final approval.

REVIEWER FEEDBACK

- ❑ ADVANTAGES: enhanced objectivity, consistency and transparency in BR evaluations. The structured format complemented narrative assessments, helped highlight critical safety issues, and encouraged reliance on international regulatory decisions.
- ❑ CHALLENGES: retrospective implementation was found to be cumbersome and aligning industry submissions with the framework will be required.

CONCLUSIONS

- ❑ 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 BR decision-making.**
- ❑ **This study demonstrated that a structured, systematic approach to BR assessment enhances consistency, transparency, and decision-making quality at SAHPRA** and UMBRA helped assessors clearly document decisions, justify benefit-risk balances, and align evaluations with global regulatory standards by reducing subjectivity
- ❑ Assessors found the framework valuable for identifying key clinical benefits and risks, assigning relative weightings, and ensuring thorough evaluations. **It also enables better regulatory reliance, allowing African authorities to adopt globally accepted standards while addressing local needs.**
- ❑ Applying **a universal BR framework fosters regulatory harmonization, public trust, and clear communication of decisions** through the publication of public assessment reports (PARs).
- ❑ **The UMBRA's structured methodology can guide the African Medicines Regulatory Harmonization (AMRH) initiatives and support joint reviews across regulatory agencies.** Furthermore, with the advent of the African Medicines Agency (AMA), proliferation of **a structured and systematic approach to BR assessment into a continental best-practice would allow the AMA to publish clearly substantiated PARs**, detailing the scientific rationale for authorizing a product for use within the African population.

RECOMMENDATIONS

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.**

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