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An evaluation of the use of the Universal Benefit–Risk Assessment Framework by the Zambia Medicines Regulatory Authority for documenting and communicating benefit–risk decisions

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ABSTRACT

Transparent and consistent medicines approval processes support stakeholder trust in National Medicines Regulatory Authorities (NMRAs). Structured benefit–risk assessment frameworks may strengthen such transparency and consistency. One example is the Universal Methodology for Benefit–Risk Assessment (UMBRA) developed by the Centre for Innovation in Regulatory Science in collaboration with four regulatory authorities.

This study evaluated the feasibility, usability and perceived value of applying UMBRA within the Zambia Medicines Regulatory Authority (ZAMRA) and compared the explicitness and structure of UMBRA benefit–risk documentation with the existing narrative approach.

In this exploratory comparative case study, two ZAMRA assessors applied UMBRA retrospectively to two previously reviewed applications and prospectively, alongside routine assessment, to two applications. Documentary comparison and directed content analysis of assessor feedback were conducted.

Across the four cases, UMBRA made the decision context, selected benefits and risks, their relative importance, uncertainties and the basis for the benefit–risk conclusion more explicit than narrative assessments. Both assessors found the template useable and considered its structured format potentially valuable for reviewer training and implementation. One assessor initially required clarification on recording adverse events. These findings represent four cases and two assessors' perceptions and do not establish improvements in decision quality, inter-assessor consistency, review time or regulatory outcomes.

1. Introduction

The benefit–risk assessment of medicines is a dynamic, multi-stage process for evaluating a medicine's therapeutic advantages against potential harmful effects throughout its lifecycle (Piccirillo and Parish, 2022). The review process involves assessing the relative importance of a medicine's therapeutic benefits compared to its potential risks, including adverse drug reactions (Kumar, 2018). Regulatory approval decisions are grounded in an assessment of whether the anticipated benefits outweigh the potential harms, and are strengthened by structured evaluation of the relative importance of key benefits in relation to identified risks (United States Food and Drug Administration (US FDA), 2018). The assessment evolves from initial clinical trials to post-marketing surveillance, applying methods ranging from qualitative to quantitative approaches incorporating key evidence sources such as randomized clinical trial and real-world pharmacoepidemiologic data (Franklin et al., 2021; Zink et al., 2021). The benefit–risk assessment process is continuous, with the medicines benefit–risk balance potentially changing over time due to factors such as long-term exposure and patient variations (Kumar, 2018). Where a medicine's benefits are clinically established and it has a well-characterised safety profile with no identified serious risks, the benefit–risk assessment may be relatively straightforward (US FDA, 2023). However, where serious risks are identified, the assessment becomes more challenging (US FDA, 2023).

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Therefore, a systematic framework is needed to support transparent documentation of benefit–risk trade-offs, strengthen the traceability of regulatory reasoning, facilitate communication to decision-makers, and enable consistent and reliable decision-making.

1.1. Evolution of benefit–risk assessment

In modern regulatory practice, structured benefit–risk evaluation became increasingly formalised from the early 1960s, alongside the expansion of independent regulatory review and strengthened evidentiary requirements for medicinal products (Califf, 2017). Early regulatory approaches were largely focused on determining whether a product's benefits outweighed its risks (Chisholm et al., 2022). Over time, authorities such as the US FDA and the European Medicines Agency (EMA) refined benefit–risk approaches to support more systematic and transparent evaluation and communication of regulatory decisions (Angelis and Phillips, 2021). However, despite ongoing development, current methodologies still rely significantly on expert judgment, with researchers actively working to create more systematic and transparent frameworks (Walker et al., 2015). Moreover, the variability in benefit–risk frameworks across NMRAs can exacerbate challenges in review harmonisation and the implementation of reliance processes (Pignatti et al., 2015). In response to this need, a consortium of four NMRAs including the Australian Therapeutic Goods Administration (TGA), Health Canada, Swissmedic, and Singapore Health Sciences Authority (HSA) approached the Centre for Innovation in Regulatory Science (CIRS) in 2008 to request their assistance in the development of a standardized benefit–risk assessment framework and template to be used in joint and shared reviews (McAuslane et al., 2017). This collaboration resulted in the development of the Universal Methodology for Benefit-Risk Assessment (UMBRA).

1.2. The Universal Methodology for Benefit-Risk Assessment framework

The Universal Methodology for Benefit-Risk Assessment (UMBRA) is an eight-step systematic framework that was developed by CIRS through the Consortium on Benefit-Risk Assessment (McAuslane et al., 2017). The framework comprises eight sequential steps: (1) decision context, (2) building the value tree, (3) value tree refinement, (4) assessing relative importance, (5) evaluating options, (6) evaluating uncertainty, (7) concise presentation of results (visualisation), and (8) final recommendation (Walker and McAuslane, 2016).

The UMBRA framework was developed based on the EMA reflection paper of 2008 by consolidating benefit–risk assessment approaches from pharmaceutical companies and regulatory authorities (EMA, 2008; Danks et al., 2025; Walker et al., 2015). Subsequent to its development, the UMBRA framework has been used to communicate regulatory decisions effectively by providing a structured template for benefit–risk thereby enhancing transparency and consistency in evaluating the benefits and risks of medicines (Keyter et al., 2020). The clinical assessment templates for NMRAs in Australia, Canada, Switzerland and Singapore modified their templates to align with the eight-step UMBRA framework (Keyter et al., 2020). As shown in Fig. 1, the framework provides a structured methodology that systematically documents decision contexts, identifies benefits and risks, as well as assesses the relative importance of the benefits and risks to interpret their balance (CIRS, 2012; Danks et al., 2025).

By guiding assessors through these eight stages, UMBRA supports regulators in documenting how clinical benefits and risks were considered, how conclusions were reached, and how the underlying rationale can be communicated to stakeholders (Keyter et al., 2020).

1.3. Current Benefit–Risk Assessment Practice at the Zambia Medicines Regulatory Authority (ZAMRA)

The Zambia Medicines Regulatory Authority (ZAMRA) is the statutory body mandated by law to regulate and register medicines for the Zambian population (Medicines and Allied Substances Act (MASA), 2013). At present, ZAMRA does not apply a formally defined structured framework for benefit–risk assessment of medicines submitted for

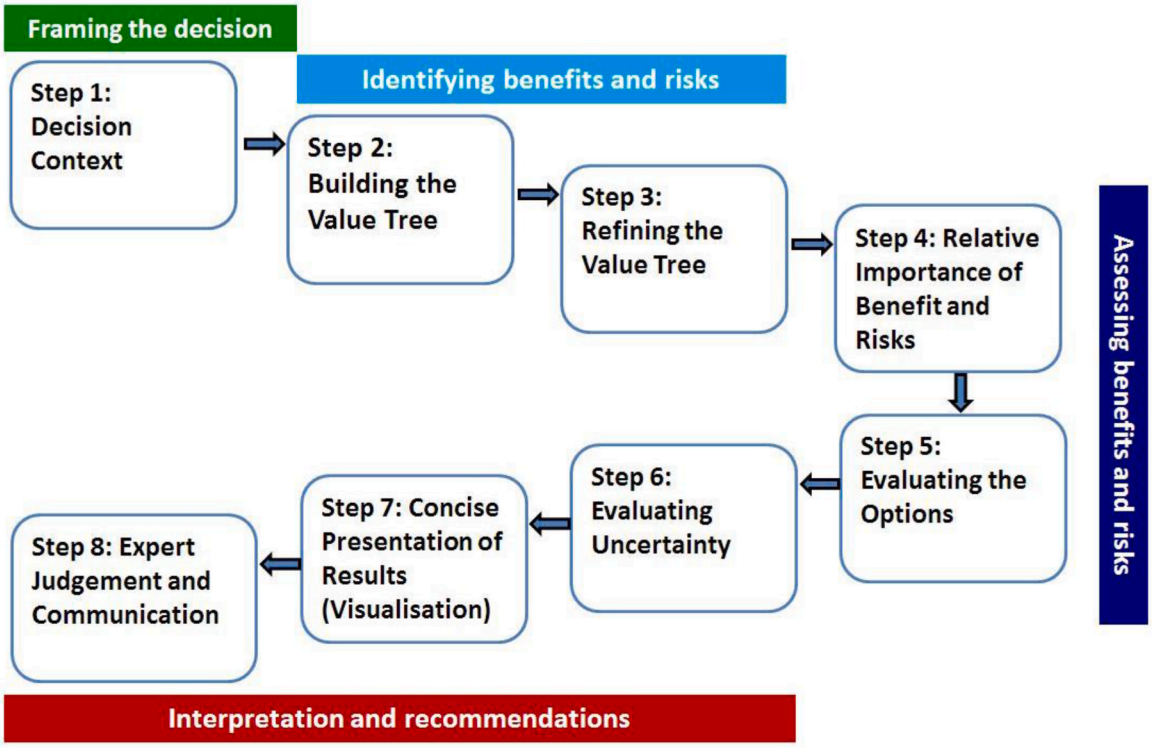

Fig. 1. The common elements of the UMBRA eight step Benefit–Risk Framework.

registration. The clinical assessment template currently in use is largely narrative, with assessors documenting observations in free-text format, which may contribute to variability and subjectivity in regulatory decision-making. Consequently, ZAMRA has not yet adopted a formal framework for systematic evaluation of medicine benefits and risks, but this study aims to provide an initial benchmark for structured benefit–risk assessment within the Authority.

The aim of this study was to evaluate the feasibility, usability and perceived value of applying the UMBRA framework within ZAMRA and to compare the structure and explicitness of benefit–risk documentation produced using UMBRA with that produced using ZAMRA's existing narrative approach.

The specific objectives were to:

- Compare, in the two retrospective cases, the content and organisation of the original ZAMRA narrative assessments with documentation produced using the UMBRA template;
- Examine, in the two prospective cases, whether parallel use of UMBRA made the decision context, selected benefits and risks, their relative importance, uncertainties and benefit–risk rationale more explicit;
- Describe the two clinical assessors' experiences of the usability and perceived value of the framework for documenting and communicating regulatory recommendations.

2. Methodology

2.1. Study design

The study was qualitative in nature and used the UMBRA template developed by CIRS. The template was applied retrospectively to two medicine applications for which the ZAMRA clinical assessments had already been completed and prospectively, in parallel with the initial clinical assessment, to two further medicine applications. Two experienced clinical assessors were purposively selected to reflect routine regulatory review practice at ZAMRA. Each assessor completed the UMBRA template for one retrospective and one prospective application, resulting in four completed UMBRA assessments. Two experienced clinical assessors were purposively selected to reflect routine regulatory review practice at ZAMRA. These assessors undertook to determine the benefits and risks of four applications submitted to ZAMRA using the UMBRA template (Table 1).

2.2. Study setting

The ZAMRA applies a structured internal procedure for the review of clinical data submitted in support of medicine registration. Clinical assessors complete a designated assessment template that is predominantly narrative in format, allowing assessors to document their observations in a general descriptive manner. However, the template does not include explicit sections for systematic benefit–risk weighting or for recording an overall benefit–risk balance for each product. In addition, quality assessment is conducted separately using a distinct template, independent of the clinical review process.

2.3. Retrospective study

For the retrospective analysis, clinical data for two previously approved products containing Atezolizumab and Eribulin Mesylate were evaluated using the UMBRA framework by two clinical assessors (Assessors A and B), with each assessor independently completing the associated UMBRA template for one allocated product. These were selected based on their complexity and their relevance in the treatment of serious conditions such as cancer whose incidence is on the increase in Zambia (Msadabwe et al., 2025). The two products included in the retrospective study had already undergone full clinical assessment and

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

Section	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 authorities that have reviewed the product and outcome)
Background (decision context)	Proposed therapeutic indication(s) Treatment modalities evaluated in the 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 authority (details on the outcome of the review, the indication(s) and any issues raised Reference authority regulatory history: reference authority, outcome at authority, 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** Assessment 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** Assessment 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

(*continued on next page*)

Table 1 (*continued*)

Section	Information documented
	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 minimisation 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 authority 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 authorities

received marketing authorisation by ZAMRA. However, the manner in which benefit–risk considerations were documented using the UMBRA framework was compared with the original narrative assessments, with particular attention to the clarity, structure, and explicitness of the benefit–risk rationale and its potential communicability to external stakeholders.

2.4. Prospective study

The same two assessors then applied the UMBRA template prospectively, in parallel with their initial review of two medicines, namely Brolucizumab (Assessor A), and Epoetin alpha (Assessor B) using the same structured eight-step UMBRA process applied in the retrospective analysis.

After completing the four assessments, both assessors answered the 12-item feedback questionnaire shown in Table 2 and participated in a virtual feedback discussion. The questionnaire elicited their experience of the template, perceived advantages and disadvantages, and views on possible adoption or adaptation within ZAMRA.

2.5. Data analysis

For each case, the completed UMBRA template was compared with the corresponding narrative assessment using the main UMBRA domains as a documentary framework: decision context, identification of benefits and risks, relative importance, uncertainty and justification of the final benefit–risk conclusion. The comparison assessed whether each domain was explicitly documented; it did not score decision quality or test agreement between assessors. The questionnaire and discussion responses were analysed using directed content analysis. The questionnaire domains provided the initial coding framework, and responses were grouped into categories concerning usability and clarification needs, explicit documentation of benefits and risks, relative importance and uncertainty, implementation and training, and reliance and longitudinal use. Responses that qualified the generally favourable account were retained, including the need for initial clarification on recording adverse events. As only two assessors participated, the analysis was descriptive; no claim of thematic saturation or generalisability was made. Table 3 presents the coding framework, supporting data and interpretation.

3. Results

The results are presented in three parts: Part I - the retrospective study; Part II - the prospective study; and Part III – the clinical assessors' evaluation of the usability and perceived value of the UMBRA framework and template.

3.1. Part I - Retrospective study

The assessors first established the context within which the initial product decision was made by providing details of the active pharmaceutical ingredient, dosage form, indications being applied for and the treatment options. The assessors also determined whether the products had been approved by any WHO-listed authorities (WLAs). For the retrospective cases, they reviewed the outcomes of the original ZAMRA assessments.

3.1.1. Atezolizumab

This product was reviewed by assessor A. Atezolizumab had been approved by multiple reference agencies including the US FDA, EMA, TGA and the Pharmaceuticals and Medical Devices Agency (PMDA), for the treatment of metastatic urothelial carcinoma as monotherapy, for non-small cell lung cancer in combination with bevacizumab, paclitaxel and carboplatin, as well as small cell lung cancer combined with carboplatin and etoposide and triple-negative breast cancer (TNBC) in combination with nab-paclitaxel. An additional indication, hepatocellular carcinoma, was included in the indications for the EMA-approved product but was not reflected in the applicant's proposed summary of product characteristics (SmPC) for the product intended to be marketed in Zambia. The applicant was requested to clarify whether this was aligned to the EMA SmPC indication set.

Table 2
Feedback questionnaire on applicability and advantages and/or disadvantages of the UMBRA template for good clinical decision-making.

ZAMRA 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 ZAMRA 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 ZAMRA assessment.
7.Were you uncomfortable with documenting your assessment in specific boxes compared with a narrative approach?
8. Do you believe that utilizing 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 ZAMRA 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 a 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?

Table 3
Summary of the analytical categorisation.

Analytic category	Illustrative codes/data	Pattern across the two assessors	Interpretation and boundary
Usability and clarification needs	"Easy to use"; "specific"; initial uncertainty about whether adverse events should be separated	Both assessors reported that the format was useable; one required clarification before completion.	The template appeared feasible after orientation, but the need for clarification indicates that guidance and training would be required.
Explicit documentation of benefits and risks	Listing included/ excluded benefits and risks; structured boxes; reasons for inclusion or exclusion	Both assessors valued explicit listing and structured documentation.	The framework made the assessment trail more visible in these cases; this is a documentation finding, not evidence of better decisions.
Relative importance and uncertainty	High/medium/ low weighting; comments on strength and uncertainty	Both assessors considered the weighting prompts helpful.	Prompts supported explicit recording of judgement. Inter-assessor agreement and reproducibility were not tested.
Implementation and training	Adopt/adapt; reviewer training; future assessment practice	Both assessors supported further use and training.	Views support a larger pilot, as two favourable users cannot establish organisation-wide acceptability.
Reliance and longitudinal use	Regulatory history; comparison of reviews; post-approval updating; reliance	Both assessors perceived potential value for traceability and reliance.	These are anticipated uses. Effects on reliance, review times and stakeholder trust were not measured.

The EMA-approved SmPC presented the non-small cell lung cancer (NSCLC) indication in two sections: early-stage NSCLC and metastatic NSCLC. The applicant's proposed SmPC included only metastatic NSCLC. Although the wording of the metastatic NSCLC indication was more detailed in the EMA-approved SmPC, the content was similar. The wording for metastatic NSCLC is also noted to be expanded in the EMA SmPC, although the content is similar.

When reviewing the benefit–risk balance using the UMBRA framework, the assessor focused the structured benefit–risk assessment on a single indication (metastatic urothelial carcinoma) to enable a clear comparison of identified key benefits, key risks, and their relative importance within one decision context. A positive benefit–risk balance was identified for this indication. The identified benefits included improved overall survival, less fatigue and better physical functioning, acceptable safety and good tolerability in older patients with fewer serious side effects and lower grade 3-4 adverse events. The assessor assigned high-to-medium relative importance to the identified benefits. The risks included immune-related adverse events such as hepatitis, pneumonitis, colitis, pancreatitis and endocrinopathies. Although most of these risks were assigned high relative importance, the assessor considered them manageable through appropriate monitoring and the risk-minimisation measures described in the pharmacovigilance plan. The same positive benefit–risk balance was noted for the EMA approved product (EMA, 2017).

3.1.2. Eribulin Mesylate

The benefit–risk assessment of Eribulin Mesylate was performed by Assessor B. The proposed indications were metastatic breast cancer and liposarcoma. Comparable indications were authorised by the TGA and EMA (Therapeutic Goods Administration, 2017; European Medicines Agency, 2011).

When assessing Eribulin Mesylate using the UMBRA template, Assessor B identified prolonged survival in advanced breast cancer as the principal benefit. The main risks were neutropenia, asthenia, fatigue and anaemia. Both the benefit and the risks were assigned high relative importance. The overall benefit–risk balance was assessed as positive because of the survival benefit and the availability of risk-minimisation measures, including full blood-count and electrolyte monitoring and neurological assessment for neuropathy. The assessor noted that the conclusion was aligned with the TGA and EMA assessments (Therapeutic Goods Administration, 2017; European Medicines Agency, 2011).

3.2. Part II - Prospective study

3.2.1. Brolucizumab

The benefit–risk assessment for Brolucizumab was conducted by Assessor A. Brolucizumab is indicated for neovascular (wet) age-related macular degeneration (AMD) and diabetic macular edema (DME). The same indications were approved by EMA, Health Canada, Japan, USFDA and TGA as confirmed from the submission and the public assessment reports. The focus for this assessment was the AMD indication.

The benefits identified included improvement and maintenance of best-corrected visual acuity (BCVA) compared to baseline, non-inferiority of BCVA compared with standard anti-VEGF therapy, reduction in central subfield thickness (CST), absence of intraretinal or subretinal fluid, reduced injection frequency of 12-week dosing, reduced treatment burden compared with more frequent anti-VEGF regimens, rapid onset of anatomic response, potential improvement in patient convenience and adherence, benefit in patients with high disease activity at baseline and long term maintenance of visual gains up to 96 weeks. The risks identified included intraocular inflammation (IOI), retinal vasculitis, retinal vasculitis with retinal vascular occlusion, severe vision loss secondary to occlusive retinal vasculitis, immunogenicity/immune-mediated reactions, endophthalmitis, increased intraocular pressure (IOP), retinal tear or retinal detachment, vitreous haemorrhage, immunogenicity (anti-drug antibodies development) and dose-interval associated risk (inflammation occurring after repeated dosing). When weighting the benefits and risks, the assessor assigned high relative importance to all benefits except reduction in central subfield thickness and absence of intraretinal or subretinal fluid, which were assigned medium-to-high relative importance. The risks were assigned high relative importance. The assessor documented potential mitigation through clinician awareness of early signs of intraocular inflammation, patient selection, avoidance in patients with pre-existing ocular inflammatory conditions, prompt intervention and treatment discontinuation at the earliest signs of inflammatory adverse events. The assessor considered the overall benefit–risk balance positive with these measures and noted alignment with the EMA and TGA conclusions.

3.2.2. Epoetin alpha

The benefit–risk assessment for Epoetin alpha was conducted by Assessor B. It was noted that Epoetin alfa is indicated for the treatment of symptomatic anaemia associated with chronic renal failure and anaemia in patients receiving chemotherapy for solid tumours, malignant lymphoma or multiple myeloma. Treatment should only be given to patients with moderate anaemia (haemoglobin [Hb] in the concentration range between 10 and 13 g/dL [6.2 to 8.1 mmol/L], no iron deficiency), if blood saving procedures are not available or insufficient when the scheduled major elective surgery requires a large volume of blood (4 or more units of blood for females or 5 or more units for males). In addition, it is also included for non-iron deficient adults prior to major elective orthopaedic surgery, having a high perceived risk for transfusion

complications in order to reduce exposure to allogeneic blood transfusions. Use should be restricted to patients with moderate anaemia (e.g. haemoglobin concentration range between 10 and 13 g/dL or 6.2 to 8.1 mmol/L) who do not have an autologous predonation programme available and with expected moderate blood loss (900 to 1800 mL). It is also indicated for the treatment of symptomatic anaemia (haemoglobin concentration of $\leq$ 10 g/dL) in adults with low- or intermediate-risk primary myelodysplastic syndromes (MDS) who have low serum erythropoietin (<200 mU/mL). The assessor confirmed from the public assessment reports that the same indications were approved by EMA, TGA and the New Zealand Medicines and Medical Devices Safety Authority (Medsafe).

The benefits identified included increased haemoglobin within 12 weeks, decreased transfusion requirements, improved quality of life, low immunogenicity and tolerable or improved adherence to the mode of administration and safety profile. The risks identified included hypertension, general erythropoietin stimulating agents' risks, as well as immunogenicity. When weighting the benefits and risks a relative high importance was assigned to all the benefits except for improved adherence to the mode of administration which was assigned as of medium importance. The risks were assigned of high relative importance. The assessor documented risk-management measures, including monitoring and management of hypertension and thromboembolic events, and considered the overall benefit–risk balance positive. The conclusion was reported to align with the EMA and TGA assessments.

3.3. Part III - Assessor feedback

To obtain feedback on the implementation of the UMBRA template for assessing the benefit–risk balance, assessors were provided with a questionnaire (Table 2) and participated in a feedback session in which the perceived advantages and disadvantages of the template were documented. Assessors were also asked whether the template could be adopted or adapted for use in ZAMRA's clinical data assessment process. For the purpose of this study, transparency referred to the explicit documentation of the decision context, identification of key benefits and risks, documentation of their relative importance, recording of uncertainties, and a clear justification of the final benefit–risk conclusion.

3.3.1. Documentary comparison and assessor feedback

Across the documentary comparison, the UMBRA templates contained dedicated fields for the decision context, explicit identification of benefits and risks, relative importance, uncertainty and the rationale for the final conclusion. These elements were not consistently separated or explicitly linked in the narrative assessments. The comparison therefore indicates a difference in the structure and traceability of documentation, not a demonstrated difference in the quality or correctness of regulatory decisions. The directed content analysis identified five categories (Table 3).

Feedback was generally favourable, particularly regarding the structured listing of benefits and risks, weighting prompts and possible use in training. However, one assessor's initial uncertainty about entering adverse events shows that implementation would require written guidance and orientation. The participants' expectations concerning reliance, transparency and reduced duplication were perceptions of potential value and were not evaluated outcomes.

4. Discussion

The application of the UMBRA framework to four medicine assessments identified substantive differences in how benefit–risk reasoning was documented relative to ZAMRA's existing narrative approach. The UMBRA template required the assessors to define the decision context, identify the benefits and risks considered relevant to the regulatory decision, record their relative importance, describe associated uncertainties and link these considerations to the final recommendation. In the narrative assessments, these elements were not consistently differentiated or explicitly connected. The principal contribution of the framework was therefore the organisation of regulatory reasoning into a structured and traceable assessment record.

The retrospective assessments of Atezolizumab and Eribulin Mesylate illustrated the distinction between the regulatory conclusion and the documentation supporting that conclusion. Reassessment using UMBRA did not alter the positive benefit–risk conclusions previously reached by ZAMRA. It did, however, provide a more explicit account of the benefits and risks considered decisive, the relative importance assigned to each, the uncertainties affecting their interpretation and the risk-minimisation measures supporting the final recommendation. The structured assessment consequently provided greater visibility of the evaluative judgements underlying decisions that had previously been recorded predominantly in a narrative format.

The prospective assessments of Brolucizumab and Epoetin alpha indicated that the framework could also be applied during the initial clinical assessment rather than only after completion of the regulatory review. In both cases, the assessors documented the principal benefits and risks, assigned their relative importance and considered whether the identified risks could be managed through appropriate monitoring and risk-minimisation measures. Prospective application permitted the benefit–risk rationale to be developed concurrently with the clinical assessment, thereby reducing reliance on subsequent reconstruction of the reasoning underlying the recommendation. These finding support the further evaluation of UMBRA as an integrated component of the clinical assessment process.

These findings are consistent with previous evaluations of structured benefit–risk assessment in regulatory settings. Danks et al. (2025) reported that the application of UMBRA within SAHPRA supported systematic documentation of the decision context, benefits, risks and overall benefit–risk conclusion. Walker et al. (2015) described UMBRA as a common framework through which the evidence, value judgements and uncertainties contributing to a regulatory decision could be organised. McAuslane et al. (2017) similarly reported that the framework provided a common structure that could be aligned with the assessment approaches of participating regulatory authorities. The present study extends this evidence to ZAMRA and indicates that the framework can be applied within an authority whose clinical assessment process has historically relied on narrative documentation.

The value of structured documentation is not limited to the identification of benefits and risks. A benefit–risk conclusion is influenced by the clinical relevance of the outcomes, the magnitude and certainty of the treatment effects, the seriousness and manageability of the risks, the availability of alternative treatments and the context in which the medicine is intended is to be used. Recording these considerations separately allows the relationship between the evidence and the final recommendation to be examined more readily. The UMBRA framework also requires assessors to document uncertainty and the relative importance assigned to individual benefits and risks, thereby making the evaluative component of the assessment more explicit. The study did not determine whether this structure produced more accurate or consistent decisions, but it identified differences in the completeness and organisation of the documented rationale.

The assessors' feedback indicated that the framework was generally acceptable and that its structured format assisted them in identifying and documenting the considerations contributing to the benefit–risk conclusion. Both assessors regarded the explicit listing of benefits and risks and the assignment of relative importance as useful. They also identified a potential application of the framework in the training of new assessors and in the comparison of assessments when additional evidence becomes available. These findings support the feasibility of further implementation but should be interpreted as the experiences of the two participating assessors rather than as evidence of organisation-wide acceptability.

One assessor initially required clarification regarding whether

adverse events should be recorded separately or grouped within the template. This finding identifies a practical requirement for implementation in that the framework would need to be accompanied by completion guidance, standardised definitions and worked examples. Adaptation to ZAMRA's assessment procedures may also be required to ensure consistent interpretation of the sections addressing the selection, weighting and presentation of benefits and risks. Maloney et al. (2019) reported differing views regarding the use of ranking or weighting within a structured benefit–risk framework in a health-technology reassessment setting, indicating that the application of these elements may be influenced by institutional context and user expectations. Evaluation during a broader ZAMRA pilot study would assist in determining which components can be adopted directly and which require modification.

Structured benefit–risk documentation may also support the use of regulatory reliance by providing a transparent account of the evidence and judgements underpinning a recommendation. Reliance requires the receiving authority to determine whether an assessment performed elsewhere is sufficiently relevant, complete and applicable to its own regulatory context. Consistent documentation of the decision context, key benefits and risks, uncertainties and final rationale may facilitate this determination. Previous research has identified access to suitable assessment reports and an adequate understanding of the reference authority's evaluation as relevant considerations in reliance-based review (Vaz et al., 2022). The participating assessors perceived the potential value of UMBRA for reliance; however, the study did not include receiving authorities or measure its effect on duplication, review timelines or reliance decisions. The contribution of a structured benefit–risk documentation to reliance therefore requires prospective evaluation.

The findings also have implications for the communication of regulatory decisions. Standardised assessment reports can improve the organisation and accessibility of the rationale provided to regulatory and public stakeholders (Keyter et al., 2020). The UMBRA framework provides a potential structure for presenting the principal benefits, risks, uncertainties and reasons supporting a decision in future ZAMRA public assessment reports. The present study evaluated internal assessment documentation but did not obtain feedback from decision committees, applicants, healthcare, professionals or the public. Further evaluation is required to determine whether information generated through the UMBRA framework is sufficiently clear and relevant for these audiences.

A larger prospective pilot study is warranted before the integration of UMBRA into routine ZAMRA practice. The pilot study should include a wider range of therapeutic areas, product types, assessment pathways and assessors with different levels of regulatory experience. The same applications should be evaluated independently by more than one assessor to determine whether the framework supports consistency in the identification, weighting and documentation of key benefits and risks. Predefined indicators should be used to assess the completeness and clarity of the documented rationale, the time required to complete the template and the need for additional guidance. Evaluation by regulatory decision-making committees would further establish whether the structured assessment provides sufficient information to understand and appraise the basis of the recommendation. Findings from such a pilot study would inform whether the UMBRA framework should be adopted in full or adapted for incorporation into ZAMRA's existing clinical assessment template and assessor-training programme.

5. Conclusion

This study established the feasibility and value of applying the UMBRA framework within ZAMRA's clinical assessment process. Compared with the existing narrative approach, the framework provided a more structured and explicit account of the decision context, key benefits and risks, their relative importance, associated uncertainties and the rationale supporting the final benefit–risk conclusion. The participating assessors found the framework to be useful and identified its potential to strengthen clinical assessment documentation and support the training of assessors.

These findings provide a foundation for the progressive integration of UMBRA principles into ZAMRA's existing clinical assessment template and training programme. Further application across a broader range of products and assessors will support a refinement of the framework for routine use and inform its contribution to consistent benefit–risk documentation, regulatory reliance and regional harmonisation.

6. Recommendations

The following recommendations resulted from the study:

1. ZAMRA should consider using the UMBRA framework routinely, upon successful completion of the larger-scale pilot study, in the clinical assessment of medicines in order to enable a systematic, structured approach for decision-making regarding the benefit-risk of new active substances.
2. The UMBRA framework should be incorporated in the training module for new assessors.
3. The aspect of benefit–risk assessment should be included in the public assessment reports template once the Authority starts publishing these reports so as to enhance consistency and transparency for stakeholders.

Ethics declaration

Informed consent and patient details

Written informed consent to take part in the study and to publish the article has been obtained from all participants or their legal representatives. The privacy rights of participants have been observed.

Studies in Human

This study was performed in compliance with relevant laws, regulatory frameworks and guidelines where the research took place. This study was approved by the WITS Human Research Ethics Committee. (Approval No. R14/49 Chisha).

Ethical approval

The study was granted ethical approval by the Human Research Ethics Committee (Medical) of the University of Witwatersrand, Johannesburg, South Africa (Waiver number: R14/49 Chisha).

Permission was granted by the ZAMRA for the collection of data and for its subsequent publication.

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CRediT authorship contribution statement

Constance Sakala Chisha: Conceptualization, Data curation, Formal analysis, Writing – original draft. **Stephanie Leigh:** Conceptualization, Formal analysis, Supervision, Writing – review & editing. **Prudence Musonda Mubanga:** Data curation, Writing – review & editing. **Bernice Mumbi Chilufya:** Data curation, Writing – review & editing. **Makomani Siyanga:** Supervision, Writing – review & editing. **Stuart Walker:** Conceptualization, Formal analysis, Supervision, Writing – review & editing.

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.

Data availability

The data that has been used is confidential.

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