TERMS OF REFERENCE		
	Project Title	**Health Technology Assessment of Priority Medicines for Inclusion in the Philippine National Formulary**
I.	Background or Rationale	Pursuant to the Universal Health Care (UHC) Act, all health technologies that the government will implement and cover shall undergo health technology assessment (HTA). This aims to ensure the rational utilization of various health technologies that will be funded by the government. In 2020, DOH Administrative Order no. 2020-0041 entitled "The New Implementing Guidelines on Health Technology Assessment to Guide Funding Allocation and Coverage Decisions in support of Universal Health Care" was issued in order to define the overall framework to institutionalize and implement HTA as a priority setting mechanism that shall be recommendatory to guide DOH and PhilHealth on all coverage and funding allocation decisions. The release of the implementing guidelines was supplemented with the official release of the HTA Process and Methods Guide to lay down the details of the implementation of the process and the assessments. Under the same issuance, it is stipulated that the implementation of HTA covers alignment and linkage of its process framework with other existing programs and policies in DOH and PhilHealth which identify technologies for funding allocation or coverage, such as the Philippine National Formulary System (PNFS). Per EO no. 49 series of 1993, all government agencies have been directed to use the PNF as the basis for government procurement. The PNF serves as the national essential medicines list of the country where listed medicines have been assessed and included on the basis of safety and efficacy, cost-effectiveness, affordability and public health relevance. Currently, the assessment processes of the PNFS to review and identify which drug topic applications shall be listed (therefore be covered by the government) are subsumed under the HTA Process. Currently, there are priority drug topic applications for PNF listing needing to undergo assessment following the HTA methods, to serve as a basis for its coverage decision. As such, this project is being undertaken to assess the clinical and economic benefits of including selected drugs for inclusion in the PNFS.

II.	Objectives	*A. General Objective* To conduct health technology assessment on the following identified priority drug topics for inclusion in the Philippine National Formulary (PNF): ● Brexpiprazole (500mcg, 1mg, 2mg, 3mg, 4mg tablet / 250mcg, 1mg, 2mg, 3mg, 4mg film-coated tablet) ○ Indication: adjunct therapy for major depressive disorder (MDD) ○ Population: Patients with major depressive disorder who either not responded or only partially responded to the initial antidepressant medication ○ Intervention: Brexpiprazole as adjunct therapy ○ Comparator: Placebo / Aripiprazole / Quetiapine / olanzapine as adjunct therapy ○ Outcomes: ■ Efficacy Outcomes: ● Response rate ● Remission rate ● Severity of Depressive Symptoms (as measured by eg: HAM-D24, CGI-S, CGI-I MADRS, etc.) ● Functional impairment (based on Sheehan Disability Scale) ● Quality of life ● Relapse rate/risk of relapse ■ Safety Outcomes: ● Adverse Events ● Ideations of suicide, suicide attempt ● Systemic AEs ● Non-serious AEs ● Serious AEs ● Non-fatal SAEs ● Treatment Emergent AEs ● TEAEs leading to discontinuation ■ Economic Impact: ● Cost-effectiveness - cost per quality-adjusted life-year ● Budget impact - difference in national implementation cost between the interventions ● Cost of illness and out of pocket expenses ■ Ethical, Legal, Social, and Health System Impact: Ethical impact ● equity and fairness of coverage decisions ● considerations for special subgroups Legal impact ● Alignment or incongruence with any law or policy Social impact ● Social acceptability ● Cultural factors affecting patient and caregiver preferences and values Health systems impact ● Availability

		● Feasibility - capacity of human resources, service capacity or facilities, ● Potential to impact other roles of existing organizations ● Vortioxetine [5mg, 10mg, 15mg, 20mg film-coated tablet] ○ Indication: first-line or second-line treatment for MDD ○ Population: For adults with Major Depressive Disorder ○ Intervention: Vortioxetine as first-line or second-line treatment ○ Comparator: Placebo, Sertraline, Fluoxetine, and Escitalopram (PNF- listed drugs for MDD) ○ Outcomes: ■ Efficacy Outcomes: ● Response rate ● Remission rate ● Depression score (as measured by, eg : HAM-D24, CGI-S, CGI-I MADRS, etc.) ● Functional impairment (based on Sheehan Disability Scale) ● Quality of life ● Relapse rate/risk of relapse ■ Safety Outcomes: ● Any AEs ● Systemic AEs ● Non-serious AEs ● Serious AEs ● Non-fatal SAEs ● Treatment Emergent AEs ● TEAEs leading to discontinuation ■ Economic Impact ● Cost-effectiveness - cost per quality-adjusted life-year ● Budget impact - difference in national implementation cost between the interventions ● Cost of illness and out of pocket expenses ■ Ethical, Legal, Social, and Health System Impact Ethical impact ● Equity and fairness of coverage decisions ● Considerations for special subgroups Legal impact ● Alignment or incongruence with any law or policy Social impact ● Social acceptability ● Cultural factors affecting patient and caregiver preferences and values Health systems impact ● Availability ● Feasibility - capacity of human resources, service capacity or facilities, ● Potential to impact other roles of existing organizations ● Paroxetine [(as hydrochloride) 20mg Tablet / Film-coated Tablet] ○ Indication: first line treatment for MDD

		○ Population: Adults with Major Depressive Disorder ○ Intervention: Paroxetine as first line treatment ○ Comparator: SSRIs (Escitalopram; Fluoxetine; Sertraline)/ Placebo ○ Outcomes: ■ Efficacy Outcomes ● Response rate ● Remission rate ● Depression score (as measured by, eg : HAM-D24, CGI-S, CGI-I MADRS, etc.) ● Functional impairment (based on Sheehan Disability Scale) ● Quality of life ● Relapse rate/risk of relapse ■ Safety Outcomes ● Ideations of suicide, suicide attempt ● Any AEs ● Systemic AEs ● Non-serious AEs ● Serious AEs ● Non-fatal SAEs ● Treatment Emergent AEs ● TEAEs leading to discontinuation ■ Economic Impact ● Cost-effectiveness - cost per quality-adjusted life-year ● Budget impact - difference in national implementation cost between the interventions ● Cost of illness and out of pocket expenses ■ Ethical, Legal, Social, and Health System Impact Ethical impact ● Equity and fairness of coverage decisions ● Considerations for special subgroups Legal impact ● Alignment or incongruence with any law or policy Social impact ● Social acceptability ● Cultural factors affecting patient and caregiver preferences and values Health systems impact ● Availability ● Feasibility - capacity of human resources, service capacity or facilities, ● Potential to impact other roles of existing organizations ● Paroxetine [(as hydrochloride) 20mg Tablet / Film-coated Tablet] ○ Indication: for Post-Traumatic Stress Disorder (PTSD) ○ Population: Adults with Major Depressive Disorder ○ Intervention: Paroxetine for PTSD ○ Comparator: SSRIs (Escitalopram; Fluoxetine; Sertraline)/ Placebo ○ Outcomes: ■ Efficacy Outcomes

		● Clinical-Administered PTSD Scale (CAPS) score ● Clinical Global Impressions (CGI) Scale ● Quality of life ■ Safety Outcomes ● Any AEs ● Systemic AEs ● Non-serious AEs ● Serious AEs ● Non-fatal SAEs ● Treatment Emergent AEs ● TEAEs leading to discontinuation ■ Economic Impact ● Cost-effectiveness - cost per quality-adjusted life-year ● Budget impact - difference in national implementation cost between the interventions ● Cost of illness and out of pocket expenses ■ Ethical, Legal, Social, and Health System Impact Ethical impact ● Equity and fairness of coverage decisions ● Considerations for special subgroups Legal impact ● Alignment or incongruence with any law or policy Social impact ● Social acceptability ● Cultural factors affecting patient and caregiver preferences and values Health systems impact ● Availability ● Feasibility - capacity of human resources, service capacity or facilities, ● Potential to impact other roles of existing organizations *B. Specific Objectives:* 1. To perform review of reviews or a systematic review on the clinical efficacy and safety of the identified drug topics for inclusion in the PNF. 2. To perform review of international guidelines (NRA guidelines, country guidelines and clinical practice guidelines) of other countries and HTA Agencies. 3. To conduct cost minimization analysis or cost-effectiveness analysis, a 5-year budget impact analysis, and a household financial impact analysis, for drugs that will show comparable or significant benefit based on Specific Objective 1. 4. To develop an evidence summary for each identified drug or each drug class, containing the clinical and costing evidence, following the specified format.
III.	Scope of Work	The Consultants shall:

		1. Prepare a research protocol, with study design and methodologies (following the Philippine HTA Methods Guide 2020) including the research timeline and work plan with budget requirements; 2. Conduct of stakeholder consultation to validate the scope of the research question (Population, Intervention, Comparator, Outcomes) 3. Develop corresponding necessary data collection tools and conduct appropriate pre-testing activities 4. Implement the research project as per the developed and approved (with technical and ethical clearances) research protocols; 5. Conduct necessary expert consultations on the economic evaluation modelling (choice of model and assumptions; input parameters) 6. Coordinate with the DOST Health Technology Assessment Division (HTA Division) on the finalization of the research protocol, research implementation, and completion; 7. Develop the final report for the study. 8. Communicate results through reports and oral presentations to the HTA Division; 9. Submit all research project deliverables according to the prescribed timelines.

<table>
<tr>
<td>IV.</td>
<td>Methodology</td>
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Research question (Population, Intervention, Comparator, Outcomes) expert validation
Conduct of initial scoping of clinical evidence to determine if the clinical assessment will be de novo systematic review, adoption of existing reviews or updating of existing reviews
Clinical assessment of efficacy. effectiveness, and safety

Review of clinical evidence:

For de novo systematic review:

Systematic review (which may include a class review, as applicable) of trials and observational studies on the clinical efficacy, effectiveness, and safety

For adoption of existing systematic review:

Adoption of existing systematic review on clinical efficacy effectiveness, and safety

For updating of existing systematic review:

Updating of existing systematic review n clinical efficacy effectiveness, and safety using primary studies after the publication of the existing systematic review

Review of international guidelines (NRA guidelines, country guidelines and clinical practice guidelines) of other countries and HTA Agencies

Economic Assessment

Cost minimization analysis (for drugs which will show equivalent or not significantly different clinical outcomes) or Cost effectiveness analysis for those drug topics that will show significant added benefits in the review of clinical efficacy and safety
5-year Budget Impact analysis
Household financial impact analysis

ELSHI Assessment

Review of ethical, legal, and social implications (ELSHI) associated with the use or non-use of health technology in the local Philippine context

Conduct of systematic review of ELSHI evidence
Conduct of primary data collection (i.e., survey, survey, key informant interview, focus group discussions or participant observation)

Note: Following the HTA framework, only drug topics that have non-inferior or superior clinical evidence as determined by HTAC will proceed to economic and ELSHI assessment.
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<td>V.</td>
<td>Expected Output or Deliverables</td>
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<table>
<tr><th>Deliverable</th><th>Technical and formatting requirements</th></tr>
<tr><td>Research Protocol Per Topic</td><td><u>Outline of the Research Proposals</u>
CLINICAL ASSESSMENT
1. Research Title
2. Protocol information (Name and Signature, Contact information, Designation and Affiliation of Research</td></tr>
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Lead; Date of Submission)

3. Background
    - Description of the condition
    - Description of standard of care (SOC) and how the intervention being assessed will be part of it (CPGs may be attached in the annex)
    - Description of how the proposed intervention might work
    - Significance of the review
4. Research Question
    - For stakeholder consultation to validate PICO
    - Include brief report of the consultation/s made to finalize the scope of the PICO:
        - How was the consultation done (e.g. online or in-person discussion, written communications)
        - When the consultation happened
        - How consulted stakeholders were identified (e.g., members nominated as professional society representatives, nominated representatives of hospitals)
        - Who were the stakeholders consulted (e.g., names, representations, professional background)
        - Declaration of conflict of interest of stakeholders consulted
        - Context provided to stakeholders
        - Questionnaires used and their response
        - Key comments/ discussion points

5. Results of the initial scoping of clinical evidence
    a. Methods
        - Location and Selection of systematic reviews
            - Inclusion and exclusion criteria
            - Search Strategy
            - Screening and Selection methods
        - Location and Selection of primary studies published (If an SR was detected, filter the search to detect new primary studies after the last search of the latest SR; If no SR was detected, search for all available primary studies)
            - Inclusion and exclusion criteria
            - Search Strategy
            - Screening and Selection methods

    b. Results of the Initial Scoping
    Subsections if there are SR/s detected:
        - Results of the systematic search for existing SRs

- PRISMA Flow diagram
- Tabulation of SRs selected and study characteristics (e.g., PICO, missing outcomes if any, study design of included studies, number of included studies)

- Appraisal of existing SRs *(if applicable)*
  - Critical appraisal (e.g., AMSTAR 2 tool)
  - SR's completeness of outcomes defined in the RQ
- Results of the systematic search for new primary studies published after the last search of the latest SR selected
  - PRISMA Flow diagram
  - Tabulation of primary studies and study characteristics

Subsections if there is no available SR detected (primary studies only):

- Results of the systematic search for existing SRs
  - PRISMA Flow diagram (which will show that there is no relevant SR detected)
- Results of the systematic search for primary studies
  - PRISMA Flow diagram
  - Tabulation of primary studies and study characteristics

c. Conclusion - Final conclusion for the methodology of the clinical assessment if to proceed as either of the following:
   - adoption of an existing SR
   - updating of an existing SR by adding the additional primary studies published after the date of last search
   - de novo SR

6. Methodological plan for the clinical assessment
   a. ***Part 1 of Methodological Plan for Clinical Assessment:*** Evidence Synthesis from clinical studies

IF FOR DE NOVO SYSTEMATIC REVIEW:

- Reiterate Location and Selection of Studies
  - Inclusion criteria
  - Exclusion criteria

- Search methods
  - Data sources (e.g., electronic databases, grey literature)
  - Search Terms/Strategy, including filters (if applicable)
    - MeSH (Medical Subject Headings)
    - Boolean terms
- Screening and Selection methods

- Critical appraisal plan
  - Risk of Bias (ROB) Assessment
  - GRADE rating of evidence
- Data synthesis plan
  - Data Extraction
  - Effect measures
  - Quantitative pooling techniques , tools, and software
    - Pooling method for Meta-Analysis:
      - Outcomes to be pooled
      - Method of pooling measures of treatment effect
      - Test for the presence of heterogeneity and exploration of possible sources (include list of pre-identified covariates to be explored)
      - Methods of detecting publication bias
      - Presentation of the evidence base, results, and heterogeneity
    - Pooling for Network Meta-Analysis:
      - Transitivity assumption evaluation
      - Model used
      - Method to estimate heterogeneity
      - Network inconsistency evaluation
      - Effect modifiers analysis
      - Presentation of the evidence base, results, inconsistency, and heterogeneity

<u>IF FOR ADOPTION OR APPRAISAL OF EXISTING SR:</u>

- Reiterate results of critical appraisal of SR (e.g., AMSTAR 2)
- Critical appraisal of primary studies included in the SR
  - Risk of Bias (ROB) Assessment
  - GRADE rating of evidence: *independently perform GRADE if SR was reviewed to be of low confidence using AMSTAR or GRADE result was not presented*

Note: Indicate if results will be directly adopted from the SR or additional analysis will be needed.

<u>IF FOR UPDATING OF AN EXISTING SR WITH</u>

ADDITIONAL PRIMARY STUDIES:

- Reiterate the results of systematic search for existing SRs and primary studies
  - PRISMA Flow diagram
  - List of SR selected and additional primary studies
  - Data extraction fields
- Reiterate results of critical appraisal of SR (e.g., AMSTAR)
- Critical appraisal of primary studies included in the SR and detected after the date of last search
  - Risk of Bias (ROB) Assessment
  - GRADE rating of evidence
- Data synthesis plan
  - Data Extraction fields
  - Effect measures
  - Quantitative pooling techniques , tools, and software (if re-pooling will be performed)
    - Pooling method for Meta-Analysis:
      - Outcomes to be pooled
      - Method of pooling measures of treatment effect
      - Test for the presence of heterogeneity and exploration of sources *(include list of pre-identified covariates)*
      - Methods of detecting publication bias
      - Presentation of the evidence base, results, and heterogeneity
    - Pooling for Network Meta-Analysis:
      - Transitivity assumption evaluation
      - Model used
      - Method to estimate heterogeneity
      - Network inconsistency evaluation
      - Effect modifiers analysis
      - Presentation of the evidence base, results, inconsistency, and heterogeneity

b. Part 2 Methodological Plan for Clinical Assessment: Review of Guidelines

- Search methods
  - Methodology of search
  - List of countries and/or agencies with justification
  - Data sources:
    - Drugs: NRA guidelines (if available), clinical practice guidelines, public health reimbursement programs or HTA

recommendations
    - Vaccines: NRA guidelines (if available), country guidelines in government rollouts or reimbursements, HTA recommendations
    - Devices: NRA guidelines (if available); country guidelines in government rollouts or reimbursement, HTA recommendations
- Strategy for data extraction and synthesis

7. References
8. Annexes

- Data Extraction Form
- Sample Table of Outputs

9. Declarations

- Contributions of Assessors
- Declarations of Conflict of Interest (COI)
- Sources of Support
    - Internal sources
    - External sources

10. Timelines

- Anticipated duration of the project

ECONOMIC ASSESSMENT

1. Research Title
2. Protocol information
3. Background
4. Research Question

Note: Refer to CLINICAL ASSESSMENT section above for the details of items 1 to 4.

5. Results of the initial scoping of evidence

5.1. Methods

- Location and Selection of systematic reviews
    - Inclusion and exclusion criteria
    - Search Strategy
    - Screening and Selection methods

5.2. Results of the Initial Scoping

Subsections if there are EE studies detected:

- Results of screening
    - PRISMA Flow diagram
    - List of Economic Evaluation selected
- Appraisal of existing economic evaluation (if applicable)
    - Philippine Reference Case (to examine adoptability)

- CHEERS Checklist

<u>*Subsections if there are no EE studies detected:*</u>

- Results of screening
  - PRISMA Flow diagram

5.3. Conclusion

Final conclusion for the methodology of the assessment if to proceed as either of the following:

- Methodological plan
  - de novo economic evaluation
  - adaptation/adoption of existing economic evaluation

- Type of economic evaluation
  - Cost Minimization Analysis (CMA)
  - Cost Effectiveness Analysis (CEA)
  - Cost Utility Analysis (CUA)

6. Methodological plan for the economic assessment

6.1. ***Part 1 of Methodological Plan for Economic Assessment:*** *Cost Minimization Analysis*

Note: Outline/ subsections here depend on the selected/ proposed methodology of economic assessment, which should be based on Section 5.

- Target population and subgroups
- Setting and location
- Study perspective
- Comparators
- Time horizon
- Estimating resources and costs
  - Year of analysis, currency conversion rate, Use of inflation rate to convert cost from year of source to year of analysis
- Other assumptions (if applicable)
- Analytical methods [e.g., methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments]
- Methods for handling population heterogeneity
- Methods for scenario analysis

6.2. Part 2 of Methodological Plan for Economic Assessment: *Cost Effectiveness Analysis or Cost Utility Analysis*

<u>IF FOR DE NOVO ECONOMIC EVALUATION</u>

- Target population and subgroups
- Setting and location
- Study perspective

- Comparators
- Time horizon
- Discount rate
- Choice of health outcomes
- Choice of model (e.g., schematic diagram)
- Model assumptions
- Methods for collecting input parameters
  - Clinical parameters
    - Measurement of treatment effect
      Note: This should be aligned with the findings from the clinical assessment stage.
    - Epidemiologic parameters
    - Transitional probabilities
  - Costing parameters
    - Year of analysis, currency conversion rate, Use of inflation rate to convert cost from year of source to year of analysis
    - Local data sources or primary data collection plan
  - Utility parameters
    - Measurement and valuation of preference based outcomes (e.g., adoption of local or international data, primary data collection plan)
- Analytical methods [e.g., methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model]
- Methods for handling population heterogeneity
- Methods for uncertainty analysis
  - Deterministic
  - Probabilistic (including choice of statistical distributions per type of parameter)

IF FOR ADOPTION OF EXISTING LOCAL ECONOMIC EVALUATION:

- Data extraction (i.e., input parameters and sources)
- Note: Local sources data are preferred. Include plan and justification in case of adoption of international data.
- Alignment with Philippine Reference Case (See HTA Methods Guide)
- Appraisal of existing economic evaluation (i.e. Drummond's checklist)

6.3. Part 3 of Methodological Plan for Economic Assessment: *Budget Impact Analysis*

- Budget Impact Analysis
  - Target population and subgroups
  - Setting and location
  - Study perspective
  - Comparators
  - Time horizon

- Estimating resources and costs
  - Year of analysis, currency conversion rate, Use of inflation rate to convert cost from year of source to year of analysis
- Other assumptions (if applicable)
- Analytical methods [e.g., methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments]
- Methods for handling population heterogeneity
- Methods for scenario analysis

6.4. Part 4 of Methodological Plan for Economic Assessment: *Household Financial Impact*

If for Cost of Illness Analysis

- Adopt Cost of Illness study
  - Search methods
    - Inclusion and Exclusion criteria
    - Search Strategy
    - Screening and Selection methods
  - Out-of-pocket expenses computation
    - Payments from government payors (i.e., PhilHealth, DOH)
  - Data analysis
- De novo Cost of Illness Analysis
  - Perspective
  - Approach
  - Time horizon

Note: Refer to CLINICAL ASSESSMENT section above for the items 7 to 10.

ELSHI ASSESSMENT

1. Title
2. Protocol Information
   - Assessors
   - Contact Information
3. Background
   - Experiences of persons with the condition
   - Description of standard of care and how the intervention being assessed will be part of it
   - Description of how the proposed intervention might work
   - Significance of the review or study
4. Research Question or Specific Objectives
   - Population or Sample
   - Intervention or Phenomenon of Interest
   - Comparator or Design
   - Outcomes or Evaluation
     - Ethical aspect
     - Legal aspect
     - Social aspect
     - Health systems aspect
5. ELSHI Assessment Methods

- If systematic review only:
  - Inclusion criteria
  - Exclusion criteria
  - Data Sources (e.g., electronic databases, grey literature)
    - At least 2 electronic databases (e.g., ScienceDirect, SCOPUS, JSTOR)
  - Search Terms/Strategy, including filters (if applicable)
    - MeSH (Medical Subject Headings)
    - Boolean terms
  - Presentation of Study Selection (i.e., ENTREQ)
  - Strategy for data synthesis
- If primary data collection:
  - Primary Data Collection (i.e., survey, key informant interview, focus group discussions, participant observation)
  - Ethical considerations
    - Plan for ethics review submission *(if applicable)*
  - Primary Data Analysis
    - Qualitative analysis technique (i.e., descriptive analysis, thematic analysis, interpretive phenomenological analysis)
    - Data analysis software (i.e., MaxQDA, nVIVO, ATLAS.ti) *(optional)*

6. References
7. Annexes
   - Data gathering tool (e.g., survey questionnaire, interview guide, focus group discussion guide, field notes)
   - Informed consent form
   - Non-disclosure agreement form
8. About the Review
   - Contributions of Assessors
   - Declaration of Conflict of Interest (COI)
   - Sources of Support
     - Internal sources
     - External sources
9. Timelines
   - Anticipated start date

			○ Anticipated completion date
		Initial Research Report Per Topic	*Outline of initial research report:* **CLINICAL ASSESSMENT** **Section 1. Health problem and clinical management options** 1.1. Overview and burden of the disease (both magnitude and severity) 1.2. Current management options 1.2.1. Local (locally developed, locally adopted, or locally adapted) Clinical Practice Guidelines 1.2.2. Accessibility of treatment options (based on 5A's: Availability, Adequacy, Accessibility, Affordability, and Appropriateness) 1.2.3. Existing government policy and reimbursement mechanism **Section 2. Description, technical characteristics, and use of the health technologies** 2.1 Proposed intervention 2.2. Comparator/s *Note: Both the intervention and the comparator must have detailed information on the description, technical characteristics, and use of the health technologies.* **Section 3. Objectives and Research Questions** 3.1.Objectives 3.2. PICO (Population, Intervention, Comparator, Outcomes) of the Research Question **Section 4. Methodology** 4.1. Initial scoping of evidence 4.1.1. Methods of the initial scoping of evidence 4.1.1.1. Location and Selection of systematic reviews ● Inclusion and exclusion criteria ● Search Strategy ● Screening and Selection methods 4.1.1.2. Location and Selection of primary studies published after the search of the latest SR ● Inclusion and exclusion criteria ● Search Strategy ● Screening and Selection methods 4.1.2. Results of the initial scoping of evidence **Subsections if there are SR/s detected:** 4.1.2.1. Results of the systematic search for existing SRs ● PRISMA Flow diagram ● Tabulation of SRs selected and study characteristics (e.g., PICO, missing outcomes if any, study design of included studies, number of included studies) 4.1.2.2. Appraisal of existing SRs (if applicable) ■ Critical appraisal (e.g., AMSTAR 2 tool or

Janssen for NMA)
- SR's completeness of outcomes defined in the RQ

4.1.2.3. Results of the systematic search for new primary studies published after the last search of the latest SR selected
- PRISMA Flow diagram
- List of the detected primary studies

<u>Subsections if there is no available SR detected (primary studies only):</u>

4.1.2.1. Results of the systematic search for existing SRs
- PRISMA Flow diagram (which will show that there is no relevant SR detected)

4.1.2.2. Results of the systematic search for primary studies
- PRISMA Flow diagram
- List of Tabulation of primary studies detected and study characteristics

4.1.3. Conclusion of the initial scoping of evidence

- 4.2. Methodology of the Clinical Assessment
  - 4.2.1. Location and Selection
  - 4.2.2. Data Extraction
  - 4.2.3. Critical Appraisal
  - 4.2.4. Data Synthesis
  - 4.2.5. GRADE Rating

Section 5. Results of Synthesis of Clinical Evidence
(If methodology is de novo systematic review)

5.1.Study characteristics
5.2. ROB assessment
5.3. Results of Synthesis
Efficacy outcomes
Efficacy outcome 1
Efficacy outcome 2
Safety outcomes
Safety outcome 1
Safety outcome 2
5.4. GRADE rating of evidence

(If methodology is adoption or appraisal of an existing SR)

5.1. Study characteristics
5.2. ROB assessment of the primary studies in the adopted SR
5.3. Results of synthesis of the adopted SR
Efficacy outcomes
Efficacy outcome 1
Efficacy outcome 2
Safety outcomes
Safety outcome 1
Safety outcome 2

5.4. GRADE rating of evidence

(If methodology is updating of an existing SR with additional primary studies)
5.1. Study characteristics
5.2. Risk of Bias Assessment
5.3. Results of Synthesis
Efficacy outcomes
Efficacy outcome 1
Efficacy outcome 2
Safety outcomes
Safety outcome 1
Safety outcome 2
5.4. GRADE rating of evidence

Section 6. Discussion and Conclusion
6.1. Discussion of results
6.2. Limitations of the evidence
6.3. Limitations of the review process
6.4. Conclusion

Annexes
- Table of outputs
- List of potentially relevant studies that were excluded, including reasons for exclusion

References
Declarations
Contributions of Assessors
Declaration of Conflict of Interest (COI)
Sources of Support
Internal sources
External sources

ECONOMIC ASSESSMENT
Section 1. Health problem and clinical management options
1.1. Overview and burden of the disease (both magnitude and severity)
1.2. Current management options
1.2.1. Local (locally developed, locally adopted, or locally adapted) Clinical Practice Guidelines
1.2.2. Accessibility of treatment options (based on 5A's: Availability, Adequacy, Accessibility, Affordability, and Appropriateness)
1.2.3. Existing government policy and reimbursement mechanism
Note: The contents of this section is similar for the Clinical and Economic Assessment, thus, write-up for this section may be adopted from the clinical assessment report.

Section 2. Description, technical characteristics, and use of the health technologies

2.1 Proposed intervention

2.2. Comparator/s

Note: Both the intervention and the comparator must have detailed information on the description, technical characteristics, and use of the health technologies.

Section 3. Objectives and Research Questions

3.1.Objectives

3.2. PICO (Population, Intervention, Comparator, Outcomes) of the Research Question

Section 4. Methodology

4.1: Cost Minimization Analysis (if applicable)

- 4.1.1. Validation or consultation of the disease model, inputs, and assumption with experts
- 4.1.2. Target population and subgroups
- 4.1.3. Setting and location
- 4.1.4. Study perspective
- 4.1.5. Comparators
- 4.1.6. Time horizon
- 4.1.7. Inputs to costing analysis
  - 4.1.7.1. Cost items
  - 4.1.7.2. Estimation of the target population to be covered
  - 4.1.7.3. Resource Utilization
  - 4.1.7.4. Costing scenarios
- 4.1.8. Other assumptions (if applicable)
- 4.1.9. Analytical methods [e.g., methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments]
- 4.1.10. Methods for handling population heterogeneity
- 4.1.11. Methods for scenario analysis

(Cost-effectiveness Analysis / Cost-utility Analysis)

4.1: De novo Economic Evaluation (if applicable)

- 4. 1.1. Validation or consultation of the disease model, inputs, and assumption with experts
  - 4.1.1.1. How was the consultation done (e.g. online or in-person discussion, written communications)
  - 4.1.1.2. When the consultation happened
  - 4.1.1.3. How consulted stakeholders were identified (e.g., members nominated as professional society representatives, nominated representatives of hospitals)
  - 4.1.1.4. Who were the stakeholders consulted (e.g.,

				names, representations, professional background) 4.1.1.5. Declaration of conflict of interest of stakeholders consulted 4.1.1.6. Context provided to stakeholders 4.1.1.7. Questionnaires used and their response 4.1.2. Study characteristics 4.1.2.1. Target population and subgroups 4.1.2.2. Setting and location 4.1.2.3. Study perspective 4.1.2.4. Comparators 4.1.2.5. Time horizon 4.1.2.6. Discount rate 4.1.2.7. Model and model assumptions 4.1.2.8. Input parameters 4.1.2.9. Methods for collecting input parameters 4.1.2.9.1. Clinical parameters 4.1.2.9.1.1. Measurement of treatment effect *Note: This should be aligned with the findings from the clinical assessment stage.* 4.1.2.9.1.2. Epidemiologic parameters 4.1.2.9.2. Costing parameters 4.1.2.9.2.1. Year of analysis, currency conversion rate, Use of inflation rate to convert cost from year of source to year of analysis 4.1.2.9.2.2. Local data sources or primary data collection plan 4.1.2.9.3. Utility parameters 4.1.2.9.3.1. Measurement and valuation of preference based outcomes (e.g., adoption of local or international data, primary data collection plan) 4.1.3. Analytical methods [e.g., methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model] 4.1.4. Methods for handling population heterogeneity 4.1.5. Methods for uncertainty analysis 4.1.5.1. Deterministic 4.1.5.2. Probabilistic (including choice of statistical distributions per type of parameter). Probabilistic Sensitivity Analysis is preferred. 4.1. Adoption of Existing Economic Evaluation (if applicable) 4.1.1. Selection of EE Study 4.1.2. Quality Assessment 4.1.2.1. Alignment with Philippine Reference Case (See HTA Methods Guide)

				4.1.2.2. Appraisal of existing economic evaluation (i.e. Drummond's checklist) 4.2. Budget Impact Analysis 4.2.1. Target population and subgroups 4.2.2. Setting and location 4.2.3. Study perspective 4.2.4. Comparators 4.2.5. Time horizon 4.2.6. Inputs to costing analysis 4.2.6.1. Cost items 4.2.6.2. Estimation of the target population to be covered 4.2.6.3. Resource Utilization 4.2.6.4. Costing scenarios 4.2.7. Other assumptions (if applicable) 4.2.8. Analytical methods [e.g., methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments] 4.2.9. Methods for handling population heterogeneity 4.2.10. Methods for scenario analysis 4.3. Household Financial Impact Analysis 4.3.1. Adoption of Cost of Illness study (if applicable) 4.3.1.1. Search methods 4.3.1.1.1. Inclusion and Exclusion criteria 4.3.1.1.2. Search Strategy 4.3.1.1.3. Screening and Selection methods 4.3.1.2. Out-of-pocket expenses computation 4.3.1.2.1. Payments from government payors (i.e., PhilHealth, DOH) 4.3.1.3. Data analysis 4.3.1. De novo Cost of Illness Analysis (if applicable) 4.3.1.1. Perspective 4.3.1.2. Approach (i.e, Incidence-based approach, Prevalence-based approach) 4.3.1.3. Time horizon 4.3.1.4. Data collection methods 4.3.1.4.1. Sampling plan (sample size, sampling strategy) 4.3.1.5. Inputs to costing analysis 4.3.1.6. Out-of-pocket expenses computation 4.3.1.6.1. Payments from government payors (i.e., PhilHealth, DOH)

Section 5. Results of Synthesis of Cost Minimization Analysis (if applicable)

5.1. Results of Costing Analysis

5.1.1. Cost per user (Intervention vs Comparator)

5.1.2. Cost of implementation for the target population (Intervention vs Comparator)

5.2. Results of Scenario Analysis

5.3. Heterogeneity

5.4. Limitations

Section 5. Results of Cost Effectiveness Analysis or Cost Utility Analysis (if applicable)

Results and Discussion

IF FOR DE NOVO ECONOMIC EVALUATION

5.1. Validation or consultation of the disease model, inputs, and assumption with experts

5.1.1. Discussion points

5.1.2. Key agreements

5.2. Cost-effectiveness/ Cost-utility analysis results

5.2.1. Incremental costs and outcomes

5.3. Characterizing uncertainty

5.4. Characterizing heterogeneity

5.5. Limitations

IF FOR ADOPTION OF EXISTING ECONOMIC EVALUATION:

5.1. Study characteristics of adopted EE

5.1.1. Target population and subgroups

5.1.2. Setting and location

5.1.3. Study perspective

5.1.4. Comparators

5.1.5. Time horizon

5.1.6. Discount rate

5.1.7. Model and model assumptions

5.1.8. Input parameters

5.2. Quality Assessment

5.2.1. Alignment of the study to the Philippine reference case

5.2.2. Appraisal of existing economic evaluation

5.3. Cost-effectiveness/ Cost-utility analysis results

5.3.1. Incremental costs and outcomes

5.4. Limitations

Section 6. Results of Budget Impact Analysis

6.1. Budget impact analysis results

6.1.1. Cost of treatment

6.1.2. Incremental cost (Intervention vs comparator)
6.2. Results of Scenario analysis
6.3. Heterogeneity
6.4. Limitations

Section 7. Results of Household Financial Impact Analysis
IF ADOPTION OF COST OF ILLNESS STUDY
7.1. Study Characteristics (Study design, Study setting, etc)
7.2. Cost of treatment of condition
7.3. Out-of-pocket expenses
7.3.1. Payments from government payors (i.e., PhilHealth, DOH)
7.4. Limitations

IF DE NOVO COST OF ILLNESS ANALYSIS
7.1. Inputs to costing analysis
7.2. Cost of treatment of condition
7.3. Out-of-pocket expenses
7.3.1. Payments from government payors (i.e., PhilHealth, DOH)
7.4. Limitations

Section 8. Discussion and Conclusion
8.1. Discussion of results
8.2. Limitations of the evidence
8.3. Conclusion

References
Annexes
- Table of outputs
- List of potentially relevant studies that were excluded, including reasons for exclusion (if applicable)

Declarations
- Contributions of Assessors
- Declaration of Conflict of Interest (COI)
- Sources of Support
  - Internal sources
  - External sources

ELSHI ASSESSMENT
Section 1. Health problem and clinical management options
1.1. Overview and burden of the disease (both magnitude and severity)
1.2. Current management options
1.2.1. Local (locally developed, locally adopted, or locally adapted) Clinical Practice Guidelines

1.2.2. Accessibility of treatment options (based on 5A's: Availability, Adequacy, Accessibility, Affordability, and Appropriateness)

1.2.3. Existing government policy and reimbursement mechanism

Section 2. Description, technical characteristics, and use of the health technologies

2.1 Proposed intervention

2.2. Comparator/s

Note: Both the intervention and the comparator must have detailed information on the description, technical characteristics, and use of the health technologies.

Section 3. Objectives and Research Questions

3.1. Objectives

3.2. PICO (Population, Intervention, Comparator, Outcomes) or SPIDER (Sample, Phenomenon of Interest, Design, Outcomes/Evaluation, Research Type) of the Research Question

Section 4. Methodology

4.1. Scoping review

- 4.1.1. Ethical
  - 4.1.1.1. Targeted search strategy
  - 4.1.1.2. Strategy for data synthesis
    - 4.1.1.2.1. Type of analysis
    - 4.1.1.2.2. Analytical techniques, tools, and software
  - 4.1.1.3. Data sources
- 4.1.2. Legal
  - 4.1.2.1. Targeted search strategy
  - 4.1.2.2. Strategy for data synthesis
    - 4.1.2.2.1. Type of analysis
    - 4.1.2.2.2. Analytical techniques, tools, and software
  - 4.1.2.3. Review of existing local policies (if applicable)
  - 4.1.2.4. Data sources
- 4.1.3. Social
  - 4.1.3.1. Targeted search strategy
  - 4.1.3.2. Strategy for data synthesis
    - 4.1.3.2.1. Type of analysis
    - 4.1.3.2.2. Analytical techniques, tools, and software
  - 4.1.3.3. Data sources
- 4.1.4. Health Systems
  - 4.1.4.1. Targeted search strategy

				4.1.4.2. Strategy for data synthesis 4.1.4.2.1. Type of analysis 4.1.4.2.2. Analytical techniques, tools, and software 4.1.4.3. Data sources *(Note: Please specify which aspect the method (i.e. ethical, legal, social, or health systems) will cover)* *(Qualitative systematic review)* 4.2. Adoption or appraisal of existing qualitative SR (if applicable) 4.2.1. Critical appraisal of qualitative SR 4.2.1.1. Methodological quality assessment 4.2.2. Critical appraisal of primary studies included in the qualitative SR and detected after the date of last search 4.2.2.1. Methodological quality assessment 4.2.2.2. GRADE CERQual rating of evidence 4.2.3. Strategy for data synthesis 4.2.3.1. Data extraction 4.2.3.2. Analytical techniques , tools, and software 4.3. Updating of an existing qualitative SR with additional primary studies (if applicable) 4.3.1. Reiterate the results of systematic search for existing SRs and primary studies 4.3.1.1. PRISMA/ENTREQ flow diagram 4.3.1.2. List of selected SR/s and additional primary studies 4.3.1.3. Data extraction 4.3.2. Reiterate results of critical appraisal of qualitative SR 4.3.3. Critical appraisal of primary studies included in the qualitative SR and detected after the date of last search 4.3.3.1. Methodological quality assessment 4.3.3.2. GRADE CERQual rating of evidence 4.3.4. Data synthesis plan 4.3.4.1. Data extraction 4.3.4.2. Analytical techniques, tools, and software 4.4. De novo qualitative SR 4.4.1. Location and selection of studies 4.4.1.1. Inclusion criteria 4.4.1.2. Exclusion criteria 4.4.1.3. Data Sources (e.g., electronic databases, grey literature) 4.4.1.3.1. At least 2 electronic databases (e.g.,

ScienceDirect, SCOPUS, JSTOR)
4.4.1.4. Search Terms/Strategy, including filters (if applicable)
4.4.1.4.1. MeSH (Medical Subject Headings)
4.4.1.4.2. Boolean terms
4.4.1.5. Screening and selection methods
4.4.2. Critical appraisal of primary studies
4.4.2.1. Methodological quality assessment
4.4.2.2. GRADE CERQual rating of evidence
4.4.3. Data synthesis plan
4.4.3.1. Data extraction
4.4.3.2. Analytical techniques, tools, and software

4.5. Primary data collection (if applicable)
4.5.1. Research design (e.g., mixed methods, qualitative)
4.5.2. Primary Data Collection Method (e.g., survey, key informant interview, focus group discussions, participant observation)
4.5.2.1. Sampling
4.5.2.1.1. Sample size
4.5.2.1.2. Selection criteria
4.5.2.2. Study setting
4.5.2.3. Process of data gathering
4.5.2.4. Brief description on data gathering tool
4.5.3. Ethical considerations
4.5.3.1. Adherence to existing ethical research guidelines
4.5.3.2. Ethical clearance (if applicable)
4.5.4. Primary Data Analysis
4.5.4.1. Qualitative analysis technique (i.e., descriptive analysis, thematic analysis, interpretive phenomenological analysis)
4.5.4.2. Data analysis software (i.e., MaxQDA, nVIVO, ATLAS.ti) *(optional)*

Section 5. Results of Synthesis of ELSHI Evidence
5.1 Results of Scoping Review
5.1.1 Ethical implications
5.1.2. Social implications
5.1.3. Legal considerations
5.1.4. Health system implications

5.2. Results of adoption or appraisal of an existing qualitative SR (if applicable)
5.2.1. Study characteristics
5.2.2. Critical appraisal of the primary studies in the adopted SR

5.2.3. Results of synthesis of the adopted SR
Ethical outcomes
Ethical outcome 1
Ethical outcome 2
Legal outcomes
Legal outcome 1
Legal outcome 2
5.2.4. GRADE CERQual rating of evidence

5.3. Results of de novo qualitative SR (if applicable)
5.3.1. Study characteristics
5.3.2. Critical appraisal
5.3.3. Results of synthesis
Ethical outcomes
Ethical outcome 1
Ethical outcome 2
Legal outcomes
Legal outcome 1
Legal outcome 2
5.3.4. GRADE CERQual rating of evidence

5.4. Results of primary data collection (if applicable)
5.4.1. Results and Discussion
Ethical implications
Social implications
Legal implications
Health system implications

Section 6. Discussion and Conclusion
6.1. Discussion of results
6.2. Limitations of the evidence
6.3. Limitations of the review process
6.4. Conclusion

References
Annexes
- Data gathering tool (e.g., survey questionnaire, interview guide, focus group discussion guide, field notes)
- Informed consent and non-disclosure agreement form
- List of potentially relevant studies that were excluded, including reasons for exclusion (if applicable)
- Table of outputs

Declarations
- Contributions of Assessors
- Declaration of Conflict of Interest (COI)
- Sources of Support
    - Internal sources

<table>
<tr><td></td><td></td><td>
<table>
<tr><td></td><td>○ External sources</td></tr>
<tr><td>Final Research Report Per Topic</td><td>Same outline specified above.</td></tr>
<tr><td>Evidence Summary Per Topic</td><td>1. Cover page
2. Background
3. Policy Question and Research Questions
4. Summary of evidence on Responsiveness to Disease Magnitude and Severity
5. Summary of evidence on Clinical Efficacy, Effectiveness, and Safety
6. Summary of evidence on the Costing Analysis (CMA or CEA/CUA), Budget Impact Analysis and Household Financial Impact Analysis (as necessary)
7. Summary of evidence on the Ethical, Social and Health Systems Impact Analysis
8. Annexes
a. Critical appraisal of included reviews (if applicable)
b. Risk of bias assessment for included studies and outcomes
c. GRADE assessment for included outcomes
d. Detailed costing analysis and budget impact analysis</td></tr>
</table>
</td></tr>
<tr><td>VI.</td><td>Project Duration</td><td>All deliverables shall be submitted within 10 months from the date of the signed Memorandum of Agreement.</td></tr>
<tr><td>VII.</td><td>Implementation Arrangement</td><td>A. Contact Persons

ANNE JULIENNE GENUINO-MARFORI, RPh, MSc
Chief, HTA Division
4th Floor, Philippine Blood Coordinating Council, Quezon Avenue, Quezon City
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SARAH MAY OBMAÑA
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Tel. no: 533-7531
Email address: slobmana@dost.gov.ph

B. Project Management or Contract Administration
1. The DOST HTA Division and the DOH BIHC in coordination with the WHO shall monitor the overall implementation of the project.</td></tr>
</table>

<table>
<tr><td></td><td></td><td>2. WHO shall administer the service contract and settle the payment following the agreed terms.
3. All reports shall be submitted to DOST HTA Division, as well as to WHO.
4. The DOST HTA Division shall be responsible in the dissemination of these reports to all stakeholders.
C. Reporting Obligations
1. The Consultants shall be under the supervision and guidance of the DOST HTA Division and the WHO Representative in the Philippines.
2. All deliverables shall be submitted to the DOST HTA Division as well as to WHO.
3. The DOST HTA Division will facilitate the review and clearance of the final technical documents.
4. If a need for some modification arises, the respective consultant(s) shall modify the outputs and resubmit the same for DOST HTA Division's approval prior to finalization of the documents.
D. Ownership and Copyright
The DOST HTA Division shall have the sole proprietary and intellectual property rights of all the research reports and outputs to be supplied by the TA Provider, as stated herein.</td></tr>
<tr><td>VIII.</td><td>Roles and Responsibilities</td><td>The Consultant shall perform the tasks listed above under the Scope of Work section.

The DOST HTA Division shall:
1. Ensure that the objectives of this project are properly achieved;
2. Monitor and evaluate the performance of the Consultant and evaluate deliverables;
3. Extent feedback/information required for DOST Executive Committee purposes.

The WHO shall administer the service contract and settle the payment following the agreed terms.</td></tr>
<tr><td>IX.</td><td>Proposed terms of payment</td><td><table><tr><th>Scope of Work</th><th>Budget Release</th></tr><tr><td>1. Research Protocol Per Topic</td><td>30%</td></tr><tr><td>2. Initial Research Report Per Topic</td><td>40%</td></tr><tr><td>3. Final Research Report Per Topic</td><td>20%</td></tr><tr><td>4. Evidence Summary Per Topic</td><td>10%</td></tr></table></td></tr>
<tr><td>X</td><td>Estimated budget</td><td>Php 2,500,000.00</td></tr>
<tr><td>XI.</td><td>Evaluation procedure</td><td>Quality-Cost Based Evaluation Procedure (QCBE):
75% technical proposal and 25% financial proposal</td></tr>
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Prepared by:

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