ANNEX OF HTA RESEARCH TOPICS

A. Draft Research Questions for the HTA of Pneumococcal Conjugate Vaccines

Topic	Population	Intervention and Comparator		Outcome	Remarks
Pneumococcal conjugate vaccines for adult indications	Adults aged 60 and above	Pneumococcal 13-valent Conjugate Vaccine (PCV13) + Pneumococcal polysaccharide vaccine (PPV23)	Pneumococcal polysaccharide vaccine (PPV23) alone	CLINICAL: - Immunogenicity assessments (OPA titers for the 13 serotypes) - Vaccine effectiveness indicated by prevention of VT-CAP - Local reactions & systemic events - Any adverse events - Impact to burden of pneumococcal disease and serotype distribution ECONOMIC: -Incremental Cost-effectiveness Ratio -Budget Impact ETHICAL, LEGAL, SOCIAL, HEALTH SYSTEMS: Ethical (equity), legal (global commitment, local laws and policies), social (acceptability, equity) and health systems (feasibility, impact to practice, human resource needs, infrastructure needs, systems support acceptability of healthcare workers, serotype surveillance mechanisms, vaccination uptake/	For finalization with relevant stakeholders (e.g. DOH, content experts)

				coverage) impact	
Pneumococcal conjugate vaccines (PCV) for pediatric indications	Infants less than 1 year old	All PCV available in the market for for the prevention of invasive disease, pneumonia, and otitis media caused by Streptococcus pneumoniae		CLINICAL: - No. of diseases and deaths averted - Vaccine effectiveness - Impact to burden of pneumococcal disease and serotype distribution ECONOMIC: -Incremental Cost-effectiveness Ratio -Budget Impact ETHICAL, LEGAL, SOCIAL, HEALTH SYSTEMS: Ethical (equity), legal (global commitment, local laws and policies), social (acceptability, equity) and health systems (feasibility, impact to practice, human resource needs, infrastructure needs, systems support acceptability of healthcare workers, serotype surveillance mechanisms, vaccination uptake/coverage) impact	For finalization with relevant stakeholders (e.g. DOH)

B. Research Questions for the Systematic Review of the Clinical Evidence for the Prioritized HTA Topics

No	Topic	Population	Intervention	Comparator	Outcome	Remarks
1	Brentuximab for relapsed or refractory CD30+ Hodgkin lymphoma	Adult patients with relapsed or refractory CD30+ Hodgkin lymphoma (HL): following autologous stem cell transplant (ASCT), or following at least two prior therapies when ASCT or multi-agent chemotherapy is not a treatment option.	Brentuximab vedotin	● Doxorubicin ● bleomycin; ● vinblastine; ● Placebo; ● SOC	*Efficacy/Effectiveness :* ● Overall survival, ● Progression free-survival ● Independent Review Facility-assessed Progression free survival ● Overall response rate ● Complete response rate *Safety:* ● Adverse events	For finalization with relevant stakeholders (e.g. DOH, content experts)
2	Erdosteine for chronic obstructive pulmonary disease	Individuals with Chronic Obstructive Pulmonary disease	Erdosteine	N-acetylcysteine (NAC) 1200mg/day Carbocysteine	Efficacy in terms of COPD management 1. Number of acute exacerbations 2. Duration of exacerbations 3. Time to first exacerbation	For finalization with relevant stakeholders (e.g. DOH, content experts)
3	High-risk human papillomavirus DNA testing	Adult women aged 30 to 65 years old	High risk HPV testing (HPV DNA test)	Cervical cytology (Pap Smear)	Early detection of cervical cancer; detection of cervical intraepithelial neoplasia grade 2 or worse (CIN2+) and CIN3+ yields	For finalization with relevant stakeholders (e.g. DOH, content experts)
4	Paliperidone palmitate (PP3M) 3-month long-acting injectable	Schizophrenia or other primary psychotic disorders ICD11 code: 6A4Z; specifically for	PP3M after at least 4 months of PP1M	PP1M alone	Efficacy: > Reduced risk of relapse > Neuropsychiatric symptoms of	For finalization with relevant stakeholders (e.g. DOH, content

	formulation for adult patients with schizophrenia or other primary psychotic disorders who have been adequately treated with the 1-month paliperidone palmitate injectable product for at least four months	adult patients who have been adequately treated with the 1-month paliperidone palmitate injectable product for at least four months (PP3M after the application of PP1M regimen)	treatment		schizophrenia > Symptomatic Remission	experts)
5	Reteplase for acute myocardial infarction	Patients diagnosed with ST-segment elevation myocardial infarction (STEMI)	Reteplase	Streptokinase and Alteplase	Short and long-term; mortality; stroke; hemorrhagic complications; reinfarction	For finalization with relevant stakeholders (e.g. DOH, content experts)
6	Aflibercept, Ranibizumab, and Dexamethasone implant for diabetic macular edema (DME), wet age-related macular degeneration (wAMD), macular edema secondary to retinal vein occlusion (ME-RVO)	DME: Centrally-involving diabetic macular edema ME-RVO: Macular edema secondary to retinal vein occlusion (regardless if central or branched) wAMD: Wet or neovascular age-related macular degeneration	● DME / ME-RVO: Ranibizumab vs. Aflibercept vs. Dexamethasone as first-line ● wAMD: Ranibizumab vs. Aflibercept as first-line		EFFICACY ● Improvement in visual acuity (VA) ● Reduction in Central Macular Thickness (CMT) ● Vision related Quality of life (VR-QoL) measures ● Percentage of patients achieving the desired outcome after 3 injections SAFETY ● Occurrence of severe ocular and systemic ADEs/ADRs ● Occurrence of procedure- related complications	
7	Citicoline for stroke	Adult patient who had suffered ischemic	Citicoline for the early	Standard of care	*Efficacy*	

		stroke	management of stroke in the hospital and/or home setting, regardless of route of administration, regardless of timing of initiation therapy		• All-cause mortality • Degree of disability or dependence in daily activities (mRs) • Functional recovery (BI) • Neurological function (NIHSS) • Quality of life *Safety*	
8	DPP4 inhibitors (including sitagliptin) vs sulfonylureas for adult T2DM patients inadequately controlled on metformin monotherapy	Adult type 2 diabetes mellitus patients inadequately controlled on metformin monotherapy, including subpopulations with (1) chronic kidney disease; (2) atherosclerotic cardiovascular disease	DPP4 inhibitors preferably with subgroup analysis for specific drugs such as Sitagliptin	Sulfonylureas preferably with subgroup analysis for specific drugs within the class (i.e. PNF-listed Gliclazide) SGLT2 inhibitors preferably with subgroup analysis of specific drugs within the class (i.e. Dapagliflozin)O: Clinical efficacy and safety	*Efficacy* • Glycemic control, • Health-related quality of life • All-cause mortality *Safety* • Adverse events (MACE, serious adverse events, kidney and liver function)	
9	Ivabradine for heart failure	Adult coronary artery disease (CAD) patients with chronic heart failure (NYHA class II to IV)	Ivabradine (5 mg and 7.5 mg) in combination with Beta-blockers	Beta-blockers or placebo in combination with other SOC (standard of care) medications	*Efficacy* • Lowering the risk for angina • Improving quality of life • Speed of resolution of symptoms • Lowering risk of hospitalization • Improvement in activity tolerance • Heart rate • Left Ventricular Ejection Fraction (LVEF) Safety • Reduction in mortality	

					• adverse events (dyspnea, fatigue, hypotension)	
10	Ivabradine for angina	Adult coronary artery disease (CAD) patients with chronic stable angina pectoris	Ivabradine (5 mg and 7.5 mg) in combination with Beta-blockers and other anti-anginal drugs	Trimetazidine (35 mg) alone or in combination with Beta-blockers and/or other anti-anginal drugs (excluding Ivabradine)	*Efficacy* • Lowering the risk for angina • Improving quality of life • Speed of resolution of symptoms • Lowering risk of hospitalization • Improvement in activity tolerance • Heart rate • Left Ventricular Ejection Fraction (LVEF) *Safety* • Reduction in mortality • adverse events (dyspnea, fatigue, hypotension)	
11	Nilotinib for chronic myeloid leukemia	Adult patients (18 years old and above) with Philadelphia-positive Chronic Phase CML, confirmed using any of the following tests: conventional cytogenetics, fluorescence in situ hybridization (FISH) analysis, or reverse transcription polymerase chain reaction (RT-PCR).	Nilotinib (and its other names), regardless of preparation or strength	Imatinib (and its other names), regardless of preparation or strength	Overall survival, progression-free survival, event-free survival,treatment-free remission, hematologic response, progression to accelerated phase/blast phase, adverse events	
12	Short-acting insulins (insulin aspart,	Patients with T1DM	*Short acting insulins:*	regular insulin (NPH)	*Efficacy/Effectiveness* • HbA1c	

	insulin lispro, insulin glulisine) for T1DM		• Insulin aspart, • insulin lispro, • insulin glulisine		• postprandial glucose • FBS, • survival, • quality of life *Safety* • hypoglycemia	
13	Short-acting insulins (insulin aspart, insulin lispro, insulin glulisine) for T2DM	patients with T2DM on metformin	*Short acting insulins in combination with oral anti-hypoglycemic agents (i.e., metformin and gliclazide):* • Insulin aspart, • insulin lispro, • insulin glulisine	Regular insulin in combination with oral anti-hypoglycemic agents (i.e., metformin and gliclazide)	*Efficacy/Effectiveness* • HbA1c • postprandial glucose • FBS, • survival, • quality of life *Safety* • hypoglycemia	
14	TACE with mitomycin C for unresectable hepatocellular carcinoma	Non-resectable (unresectable) hepatocellular carcinoma patients stage B or stage C	Transarterial Chemoembolization (TACE) with Mitomycin only	For hepatocellular carcinoma Stage B • TACE plus combination therapy of doxorubicin; or mitomycin C and doxorubicin For hepatocellular carcinoma Stage C • Open comparator	*Efficacy/Effectiveness* • Overall survival • Progression-free survival • Tumor response • Health-related QoL *Safety* • Adverse events	

15	Ticagrelor for acute coronary syndrome	For adults with acute coronary syndrome (unstable angina, non-ST-elevation myocardial infarction, ST-Elevation myocardial Infarction) or stroke treated with medical management, percutaneous coronary intervention, or coronary artery by-pass grafting	Ticagrelor (90mg) alone or in combination with aspirin	Clopidogrel + aspirin	*Efficacy/Effectiveness* ● Death from vascular causes ● MI or stroke ● Myocardial infarction ● Stroke ● Other thrombotic events ● Target vessel failure ● MACE (major adverse cardiac events) ● QoL (CHF, Angina, and Functional Capacity) *Safety* ● Major bleeding ● All-cause mortality ● Perioperative bleeding ● Non-procedure major bleeding event ● Dyspnea, Bradycardia ● Non-procedure-related bleeding (CNS bleed ● GI bleed) ● Procedure-related bleeding (puncture site bleeding, CABG related bleeding) ● GI upset ● Embolism	
16	Ticagrelor for prevention of thrombotic events	Adult, high risk post-MI patients for the prevention of thrombotic events (cardiovascular death, myocardial infarction and stroke) in patients with a history of myocardial infarction (MI occurred at least one year ago) and a	Ticagrelor (60mg) alone or in combination with aspirin	Aspirin	Efficacy/Effectiveness ● Death from vascular causes ● MI or stroke ● Myocardial infarction ● Stroke ● Other thrombotic events ● Target vessel failure ● MACE (major adverse cardiac events) ● QoL (CHF, Angina, and Functional Capacity)	

		high risk of developing a thrombotic event			Safety ● Major bleeding ● All-cause mortality ● Perioperative bleeding ● Non-procedure major bleeding event ● Dyspnea, Bradycardia ● Non-procedure-related bleeding (CNS bleed ● GI bleed) ● Procedure-related bleeding (puncture site bleeding, CABG related bleeding) ● GI upset ● Embolism	
17	Tirofiban for patients with coronary ischemic syndromes undergoing coronary angioplasty or atherectomy	For patients with coronary ischemic syndromes undergoing coronary angioplasty or atherectomy	Tirofiban in combination with heparin	Unfractionated heparin; Low-molecular-weight heparin; Fondaparinux; Abciximab (NON-PNF); Eptifibatide (NON-PNF)	Major adverse cardiovascular events (MACE) -- at least one or more of: ● All-cause mortality/death; ● Re-infarction; ● Cardiovascular mortality/death; ● Repeat revascularization; ● Stroke; ● Heart failure; ● Non-fatal re-infarction; ● Stent thrombosis; ● Major bleeding; ● Microvascular obstruction; ● Re-hospitalization for cardiovascular-related illness; ● Repeat PCI; ● Non-cardiovascular mortality/death and transient ischemic attack	
18	Tirofiban for patients with unstable angina or non-Q-wave	Patients with unstable angina or non-Q-wave myocardial infarction.	Tirofiban in combination with heparin	Unfractionated heparin; Low-molecular-weight	Major adverse cardiovascular events (MACE) -- at least one or more of: ● All-cause mortality/death;	

	myocardial infarction			heparin; Fondaparinux; Abciximab (NON-PNF); Eptifibatide (NON-PNF)	• Re-infarction; • Cardiovascular mortality/death; • Repeat revascularization; • Stroke; • Heart failure; • Non-fatal re-infarction; • Stent thrombosis; • Major bleeding; • Microvascular obstruction; • Re-hospitalization for cardiovascular-related illness; • Repeat PCI; • Non-cardiovascular mortality/death and transient ischemic attack	

C. Research Questions for the Economic and ELSHI evaluation of prioritized HTA Topics in the General Track or priority medicines for inclusion in the Philippine National Formulary which will be determined pending judgment on the clinical evidence

No.	Topic	Population	Intervention	Comparator	Outcome	Remarks
1	Colonoscopy as diagnosis of colorectal cancer as confirmatory test or procedure if found positive on fecal occult blood test	Asymptomatic healthy adults at least 45 years old	Colonoscopy as confirmatory test upon screening with FIT or FOBT	Screening and confirmatory for colorectal cancer using colonoscopy	ICER and budget impact	Change of outcome from the nomination form

2	Mammography for screening of breast cancer	Asymptomatic, apparently healthy women aged 50-69 years	Mammography/Mammography machine every one or two years	• No screening • Clinical breast examination (CBE) and breast self examination (BSE) • MRI	ICER and budget impact	Further scoping needed to determine the better Comparator Change of outcome from the nomination form
3	Newborn Pulse Oximetry for indirectly detecting hypoxemia in medically ill patients that may raise suspicion for a critical congenital heart disease (CCHD)	Newborns	Newborn pulse oximeter (fingertip, handheld, tabletop type)	2D Echo	ICER and budget impact	Change of outcome from the nomination form
4	Ultrasound with AFP for screening of patients at risk to develop hepatocellular carcinoma who have or have not progressed to cirrhosis	Adults at risk of developing hepatocellular carcinoma who have or have not progressed to liver cirrhosis	Ultrasound with alpha fetoprotein	Ultrasound alone	ICER and budget impact	Change of outcome from the nomination form
5	FOBT	Asymptomatic adults 45 yrs old and above	Guaiac-based Fecal Occult Blood Test	Fecal immunochemistry test (FIT)	ICER and Budget impact	Change of Outcome from the Nomination Form

6	FIT	Asymptomatic healthy adults, ages 45 yo and above	Fecal Immunochemical Test (FIT) or immunochemical fecal occult blood test (iFOBT)	Nearest competitor: gFOBT (guaiac Fecal Occult Blood Test), Multi-Target Stool DNA test Standard of care: Colonoscopy with biopsy or histopathology	ICER and Budget impact	Further scoping needed to determine the better Comparator Change of outcome from the nomination form
7	Visualization with Acetic Acid for screening of cervical cancer among women aged 30 to 65 years	Women aged 30 to 65 years old	Visualization with Acetic Acid	Cervical cytology (Pap Smear)	ICER and Budget impact	Further scoping needed to determine the best comparator Change of outcome from the nomination form