Evidence Summary on Subcutaneous Rituximab for the Treatment of Non-Hodgkin's Lymphoma

Service Line	Evidence Summary
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Background

What is Non-Hodgkin's lymphoma (NHL)?

Non-Hodgkin's Lymphoma (NHL) is a large group of cancers that start in the lymphocytes. The cancers can grow quickly or slowly and can form from B cells or T cells. It is more common than Hodgkin lymphoma and its most common subtypes include *diffuse large B-cell lymphoma (DLBCL)* and *follicular lymphoma*. Follicular lymphoma is the most common type of low grade lymphoma described as slow growing. Meanwhile, diffuse large B-cell lymphoma is characterized by its quick progression and diffuse pattern of cancer cells.

NHL can either be aggressive (i.e., DLBCL) or indolent (i.e., follicular lymphoma). Aggressive lymphomas are commonly present as acutely or sub-acutely with a rapidly growing mass, systemic B symptoms (i.e, fever, night sweats, weight loss), and/or elevated levels of serum lactate dehydrogenase (LDH) and uric acid. While indolent lymphomas are characterized only with slow growing lymphadenopathy, hepatomegaly, splenomegaly, or cytopenia. NHL is commonly diagnosed through bone marrow exam, histology, Hans algorithm and Tally method. (ASCO, 2017)

What is the standard of care for NHL?

The drugs used in the treatment of NHL include (1) chlorambucil; (2) methotrexate; (3) vincristine; (4) etoposide; (5) doxorubicin; (6) carboplatin and (7) rituximab. The aforementioned drugs are already listed in the Philippine National Formulary (DOH, 2019). However, similar to the WHO Essential Medicines List, only the intravenous form of rituximab is listed but not the subcutaneous form. For patients diagnosed with diffuse large B-cell NHL, rituximab IV therapy requires 8 cycles for a total of 8 doses of 500 mg/500 mL and 16 doses of 100 mg/100 mL of rituximab IV. On the other hand, for patients diagnosed with follicular type NHL, rituximab IV therapy requires 20 cycles for a total of 20 doses of 500 mg/500 mL and 40 doses of 100 mg/100 mL of rituximab IV.

What is the potential of subcutaneous rituximab as treatment for NHL?

Based on the 2015 European Society for Medical Oncology (ESMO), rituximab *(not indicated if IV or SC*) can be used for first relapse and progress of NHL, alongside platinum- and/or gemcitabine-based regimens. On the other hand, according to the 2021 National Comprehensive Cancer Network (NCCN) Guidelines, rituximab subcutaneous (SC) can be used as substitute to rituximab intravenous (IV) for first-line treatment of NHL among patients with minimal/ no prior chemotherapy. It is important to note that using the rituximab SC regimen includes intravenous administration of rituximab for the first cycle, then the subcutaneous administration for the succeeding cycles. Specifically, the dosing regimen are as follows:

1. Diffuse large B-cell NHL
    - rituximab IV: One (1) 500 mg vial and two (2) 100 mg vials on the first cycle
    - rituximab SC: One (1) 1,400 mg vial per cycle, for the next seven (7) cycles [number of cycles per PSMO, 2021]

2. Follicular type NHL
    - rituximab IV: One (1) 500 mg vial and two (2) 100 mg vials on the first cycle
    - rituximab SC: One (1) 1,400 mg vial per cycle, for the next nineteen (19) cycles [number of cycles per PSMO, 2021]

As of publishing this evidence summary, rituximab SC is not listed in the 22nd WHO Essential Medicines List (WHO, 2021) and in the current Philippine National Formulary (8th ed). The current WHO EML and PNF-listed medicine for NHL includes rituximab IV (DOH, 2019). The 22nd WHO EML (2021) also listed quality-assured biosimilars of Rituximab IV.

Policy Question

Should subcutaneous rituximab be included in the Philippine National Formulary for the treatment of patients with non-Hodgkin's lymphoma (NHL)?

Research Questions

Clinical efficacy, effectiveness and safety

- In patients with NHL, what is the efficacy, and safety of rituximab subcutaneous (SC) therapy compared to IV rituximab therapy?

Economic Impact

- What is the associated medication cost per patient of using rituximab subcutaneous (SC) therapy compared to IV rituximab therapy as first-line treatment for patients with NHL?
- What is the total medication cost for the expected number of patients using rituximab subcutaneous (SC) therapy compared to IV rituximab therapy as first-line treatment for patients with NHL?

Ethical, Legal, Social and Health System Impact

- What are the potential ethical, legal, social and health system impact of rituximab subcutaneous (SC) therapy for NHL?

Responsiveness to Disease Magnitude and Severity

According to the latest GLOBOCAN data, NHL was responsible for 544,352 new cases and 259,793 deaths worldwide in 2020. The cumulative risk of developing NHL before the age of 75 years was estimated to be 0.62%, while the cumulative risk of death due to NHL was estimated to be 0.27%. Males had a 0.73% cumulative risk of developing NHL and a 0.33% cumulative risk of mortality which were both higher than the cumulative risk in females (0.52% risk of NHL and 0.21% risk of death). Lower middle income countries accounted for 17.5% of new cases and 21.4% of deaths in 2020 (International Agency for Research on Cancer, 2020). Age is a risk factor for NHL, with more than half of new cases diagnosed at the age of 65 or older. Other risk factors for NHL include gender, family history, exposure to certain chemicals and drugs, exposure to radiation, immune deficiency, autoimmune diseases, obesity, and certain bacterial and viral infections (American Cancer Society, 2022).

Locally, there are 2 to 3 cases in every 100,000, and Filipino men are more likely to have the disease than women. The median age is 60 years (PSMO, 2020). Further, the 2020 GLOBOCAN data ranked NHL as the 12th leading type of cancer and the 12th leading cause of death due to cancer in the Philippines, with a cumulative risk of 0.46% and 0.27%, respectively (International Agency for Research on Cancer, 2020)

Efficacy, Effectiveness and Safety

Review of published evidence on clinical efficacy and safety

Rituximab works by attaching to the CD20 marker of B-lymphocytes which then causes its death. Adverse events that may occur in using this drug are bacterial and viral infection, neutropenia, leukopenia, nausea, and rash. Adverse reactions during infusion include bronchospasm and hypotension, which can be severe or life-threatening. (MIMS, 2021)

The National Comprehensive Cancer Network (NCCN, 2021) recommended the use of rituximab IV as a first-line agent (except for patients with prior multiple lines of chemotherapy), and rituximab SC as substitute for patients who have received at least one full dose of rituximab IV. Meanwhile the European Society of Medical Oncology (ESMO, 2015) recommends the use of rituximab (not specified if IV or SC) for the first relapse of chemotherapy in combination with platinum and/or gemcitabine-based regimens. Rituximab IV including quality-assured biosimilars are also listed in the 22nd WHO Model List of Essential Medicines published in 2021.

A notable difference between the subcutaneous and intravenous formulation is that the SC form has an excipient called *hyaluronidase* which helps facilitate the dispersion and absorption of the drug between cells underneath the skin. However, in terms of the occurrence of adverse events, there is no difference between the two preparations (Davies, 2017 [*Phase III RCT*]).

Table 1 below shows the HTA reports considered by the HTA Council in the review. In summary, the Council has deemed that the clinical evidence on rituximab SC has shown non-inferior efficacy and safety versus rituximab IV. Aside from this, it also offers additional benefits such as convenience and less healthcare professional administration time and chair time for the patient. Hence, the review also looked into costing data.

Table 1. Clinical evidences on the safety and efficacy of Rituximab IV and SC

Study/Report	Findings
International Network of Agencies for Health Technology Assessment (INAHTA, 2002)	• Rituximab IV achieves clinical responses (generally defined as at least 50% reduction in the size of lesions and no new lesions) in some patients with Stage III or IV follicular lymphoma that is chemoresistant or in its second or subsequent relapse after chemotherapy. • Mild-to-moderate adverse events occur in most patients; severe adverse events occur in a minority of patients; fatal adverse events are very rare but do occur. • The absence of direct comparative data makes it very difficult to assess whether the ratio of benefits to disbenefits with rituximab is better, worse or the same as for currently used alternatives.
National Institute for Health Care Excellence (NICE, 2011)	• Evidence shows that first-line maintenance treatment with rituximab IV versus no treatment (observation) improves progression-free survival (36 months' median PFS: 74.9% vs 57.6% respectively; HR 0.55; $p < 0.0001$). • However, the size of the overall survival benefit could not be determined.
NICE, 2012	• Rituximab IV in various combinations of treatment options with cyclophosphamide, vincristine, prednisolone, doxorubicin, mitoxantrone, etoposide, and interferon-alfa or chlorambucil is recommended as an option for the treatment of symptomatic stage III and IV follicular lymphoma in previously untreated people.
NICE, 2014	• The recommendation of NICE in 2014 included results from the Phase III randomized controlled non-inferiority trial (SABRINA) of rituximab SC versus rituximab IV. Compared to rituximab IV, rituximab SC was reported to be non-inferior based on observed mean rituximab serum trough concentrations (C_{trough}) between the groups at induction

	cycle 7 [Geometric mean ratio: 1.62 (90% CI: 1.36 to 1.94)]. In addition, rituximab SC was associated with a similar overall response rate (84% with IV form compared with 90% with SC form); however, the trial was not powered to detect differences between the two groups. ● Compared with rituximab IV, rituximab SC offers a quicker, less invasive mode of administration. However, administration-related reactions are more common with the subcutaneous injection compared with the intravenous infusion. ● The subcutaneous injection offers benefits in terms of healthcare professional time and associated costs saved compared with administration of the intravenous infusion. However, these benefits may not be as great if rituximab is used with other drugs given intravenously.
De Cock et. al., 2016	● Compared with rituximab IV, rituximab SC was associated with reduced chair time and active healthcare provider (HCP) time.
(UK Electronic Medicines Compendium, 2021	● *Special warning noted in the UK Electronic Medicines Compendium on the use of rituximab SC:* The rituximab SC formulation as monotherapy in patients with stage III-IV follicular lymphoma who are chemoresistant or are in their second or subsequent relapse after chemotherapy cannot be recommended as the safety of the once weekly subcutaneous administration has not been established.

Household Financial Impact

Based on the case rate list of PhilHealth, there were 10 case rates relevant to the management of NHL. PhilHealth data on claims and hospital bills on these case rates were reviewed in order to estimate the cost-of-illness and the out-of-pocket costs. Overall, based on our analysis, the cost of treating NHL ranges from **Php 8,098.75 to Php 70,706.38**. Of these, out-of-pocket expense ranges between **Php 1,148.75 and Php 60,601.51** for patients diagnosed with NHL was noted across all identified case rates.

Based on these data, the support value for NHL cases varies depending on the specific diagnosis. Some cases were noted to have out-of-pocket payments as high as Php 60,601.51. Details per case rate are summarized below:

For large cell, follicular non-Hodgkin's lymphoma Follicular lymphoma grade III, unspecified

- PhilHealth has issued a case rate of **Php 13,900** for patients with *large cell, follicular NHL follicular lymphoma grade III, unspecified (C82.2)*.
- There were a total of 12 claims for this case rate from 2016 to 2020. The median claims cost for *large cell, follicular NHL follicular lymphoma grade III, unspecified* for the same period was **Php 13,900.**
- Reviewing the hospital bills collected by PhilHealth from 2016-2020, the median amount spent by patients with *large cell, follicular NHL follicular lymphoma grade III, unspecified* is at **Php 33,852.57.**
- From the same dataset, the calculated median out-of-pocket spending for patients with *large cell, follicular NHL follicular lymphoma grade III, unspecified* is at **Php 19,952.57.**

For other types of follicular non-Hodgkin's lymphoma

- PhilHealth has issued a case rate of **Php 13,900** for patients with *other types of follicular NHL (C82.7)*.
- There were a total of 38 claims for this case rate from 2016 to 2020. The median claims cost for *other types of follicular NHL* for the same period was **Php 13,900.**
- Reviewing the hospital bills collected by PhilHealth from 2016-2020, the median amount spent by patients with *other types of follicular NHL* is at **Php 28,972.59.**
- From the same dataset, the calculated median out-of-pocket spending for patients with *other types of follicular NHL* is at **Php 15,072.59.**

For follicular non-Hodgkin's lymphoma, unspecified; nodular non-Hodgkin's lymphoma NOS

- PhilHealth has issued a case rate of **Php 13,900** for patients with *follicular NHL, unspecified; nodular NHL NOS (C82.9)*.
- There were a total of 92 claims for this case rate from 2016 to 2020. The median claims cost for *follicular NHL, unspecified; nodular NHL NOS* the same period was **Php 14,810.**
- Reviewing the hospital bills collected by PhilHealth from 2016-2020, the median amount spent by patients with *follicular NHL, unspecified; nodular NHL NOS* is at **Php 60,980.18.**
- From the same dataset, the calculated median out-of-pocket spending for patients with *follicular NHL, unspecified; nodular NHL NOS* is at **Php 46,586.92.**

For small cell diffuse non-Hodgkin's lymphoma; small cell B-cell lymphoma

- PhilHealth has issued a case rate of **Php 13,900** for patients with *small cell diffuse NHL; small cell B-cell lymphoma (C83.0)*.
- There were a total of 42 claims for this case rate from 2016 to 2020. The median claims cost for *small cell diffuse NHL; small cell B-cell lymphoma* the same period was **Php 13,900.**

- Reviewing the hospital bills collected by PhilHealth from 2016-2020, the median amount spent by patients with *small cell diffuse NHL; small cell B-cell lymphoma* is at **Php 43,534.35.**
- From the same dataset, the calculated median out-of-pocket spending for patients with *small cell diffuse NHL; small cell B-cell lymphoma* is at **Php 27,207.68.**

For mixed small and large cell diffuse non-Hodgkin's lymphoma

- PhilHealth has issued a case rate of **Php 13,900** for patients with *mixed small and large cell diffuse NHL* (C83.2).
- There were a total of 2 claims for this case rate from 2016 to 2020. The median claims cost for *mixed small and large cell diffuse NHL* the same period was **Php 13,900.**
- Reviewing the hospital bills collected by PhilHealth from 2017-2020, the median amount spent by patients with *mixed small and large cell diffuse NHL* is at **Php 8,098.75.**
- From the same dataset, the calculated median out-of-pocket spending for patients with *mixed small and large cell diffuse NHL* is at **Php 1,148.75.**

For large cell diffuse non-Hodgkin's lymphoma; diffuse large B-cell lymphoma

- PhilHealth has issued a case rate of **Php 13,900** for patients with *large cell diffuse NHL; diffuse large B-cell lymphoma (C83.3).*
- There were a total of 414 claims for this case rate from 2016 to 2020. The median claims cost for *large cell diffuse NHL; diffuse large B-cell lymphoma* in the same period was **Php 15,624.21.**
- Reviewing the hospital bills collected by PhilHealth from 2017-2020, the median amount spent by patients with *large cell diffuse NHL; diffuse large B-cell lymphoma* is at **Php 76,908.80.**
- From the same dataset, the calculated median out-of-pocket spending for patients with *large cell diffuse NHL; diffuse large B-cell lymphoma* is at **Php 60,601.51.**

For immunoblastic diffuse non-Hodgkin's lymphoma

- PhilHealth has issued a case rate of **Php 13,900** for patients with *immunoblastic diffuse NHL (C83.4).*
- There were a total of 3 claims for this case rate from 2016 to 2020. The median claims cost for *immunoblastic diffuse NHL* in the same period was **Php 13,900.**
- Reviewing the hospital bills collected by PhilHealth from 2017-2020, the median amount spent by patients with *immunoblastic diffuse NHL* is at **Php 32,617.57.**
- From the same dataset, the calculated median out-of-pocket spending for patients with *immunoblastic diffuse NHL* is at **Php 18,717.57.**

For lymphoblastic diffuse non-Hodgkin's lymphoma

- PhilHealth has issued a case rate of **Php 13,900** for patients with *lymphoblastic diffuse NHL (C83.5).*
- There were a total of 50 claims for this case rate from 2016 to 2020. The median claims

cost for *lymphoblastic diffuse NHL* in the same period was **Php 16,326.67.**
- Reviewing the hospital bills collected by PhilHealth from 2017-2020, the median amount spent by patients with *lymphoblastic diffuse NHL* is at **Php 33,818.22.**
- From the same dataset, the calculated median out-of-pocket spending for patients with *lymphoblastic diffuse NHL* is at **Php 20,121.**

For other types of diffuse non-Hodgkin's lymphoma; other non-follicular lymphoma
- PhilHealth has issued a case rate of **Php 13,900** for patients with *other types of diffuse NHL; other non-follicular lymphoma (C83.8).*
- There were a total of 47 claims for this case rate from 2016 to 2020. The median claims cost for *other types of diffuse NHL; other non-follicular lymphoma* in the same period was **Php 13,900.**
- Reviewing the hospital bills collected by PhilHealth from 2017-2020, the median amount spent by patients with *other types of diffuse NHL; other non-follicular lymphoma* is at **Php 67,822.25.**
- From the same dataset, the calculated median out-of-pocket spending for patients with *other types of diffuse NHL; other non-follicular lymphoma* is at **Php 51,842.25.**

For diffuse non-Hodgkin's lymphoma unspecified; non-follicular lymphoma unspecified
- PhilHealth has issued a case rate of **Php 13,900** for patients with *diffuse NHL unspecified; non-follicular lymphoma unspecified* (C83.9).
- There were a total of 82 claims for this case rate from 2016 to 2020. The median claims cost for *diffuse NHL unspecified; non-follicular lymphoma unspecified* in the same period was **Php 14,708.89.**
- Reviewing the hospital bills collected by PhilHealth from 2016-2020, the median amount spent by patients with *diffuse NHL unspecified; non-follicular lymphoma unspecified* is at **Php 70,706.38.**
- From the same dataset, the calculated median out-of-pocket spending for patients with *diffuse NHL unspecified; non-follicular lymphoma unspecified* is at **Php 54,986.38.**

Cost-effectiveness

The HTA Council has deemed that rituximab SC is non-inferior to rituximab IV. Thus, cost-minimization analysis (CMA) was intended based on the Philippine HTA Methods Guide. A costing analysis was performed which is presented in the next section.

Affordability and viability

Scoping of prices among the different countries identified by the HTA Council was conducted. A total of 11 countries (i.e., Australia, Canada, Indonesia, Malaysia, Japan, South Korea, Thailand, the United Kingdom, and Vietnam) were included in the scoping review for prices. Of these, only Malaysia and Australia were found to have publicly available pricing of rituximab IV. The lowest prices detected for rituximab IV both domestic and overseas were used in this assessment. Table 2.1 presents the different pricing cited.

Table 2.1 Comparison of unit prices of Rituximab IV 100 mg and 500 mg (2021)

Country	Rituximab IV 100 mg (in Php)	Rituximab IV 500 mg (in Php)	Source
RITUXIMAB IV INNOVATOR			
Australia	14,536.62 *[388.87 AUD]*	36,341.37 *[972.17 AUD]*	Pharmaceutical Benefits Scheme 2020
Malaysia	13,702.83 *[1,150 MYR]*	68,514.13 *[5,750 MYR]*	Ministry of Health Malaysia - Pharmaceutical Service Program 2020 and 2021
Philippines	9,783.74	47,673.39	Maximum Drug Retail Price (EO 104)
	8,363.00	**40,757.00**	Drug Price Reference Index (DPRI), 2021

Note: Foreign currency conversions based on the Reference Exchange Rate Bulletin of Bangko Sentral ng Pilipinas as of 15 January, 2021: https://www.bsp.gov.ph/statistics/rerb/15%20Jan%202021.pdf

Costing analysis was performed for the two types of NHL to which rituximab is indicated based on the PH FDA approved package insert i.e. (1) patient diagnosed with diffuse large B-cell NHL, and (2) patient diagnosed with follicular type NHL. Separate costing analysis was performed for the two indications since the drug regimen and number of eligible patients (and therefore the costing calculation) between these two subgroups under our population of interest are different.

We calculated the incremental cost of using the SC preparation using the sponsor list price versus the IV preparation using the reference price in the Philippines for the innovator IV preparation (i.e., 2021 DPRI).

INITIAL COSTING CALCULATION: SC vs IV

Costing comparison for diffuse large B-cell NHL (SC versus innovator IV)

At the patient level, the comparison of the total cost of drug therapy per patient (i.e., cost of drug regimen + other costs) between the IV and SC form for patients diagnosed with diffuse large B-cell NHL shows that the use of rituximab SC will result in a higher cost at Php 768,148.56 compared to rituximab IV at Php 733,996.84. This results in an incremental cost of Php 34,151.72 per patient associated with the use of rituximab SC vs its IV form.

Meanwhile, at the government level, the projected overall cost of using Rituximab SC for all expected users is at Php 2,635,517,709.36 whereas the IV preparation will incur Php 2,518,343,158,04, resulting in an incremental cost of Php 117,174,551.32 to the government. This is assuming that the government will cover 3,431 estimated patients with diffuse large B-cell NHL which were determined by deriving 31% of the 11,065 total 5-year prevalence of NHL cases reported in GLOBOCAN 2020.

Table 2.2 Comparison of medication costs for diffuse large B-cell (8 cycles)

Cost Parameters	Intervention: **Rituximab SC therapy**	Current Treatment: **Rituximab IV therapy**	Remarks	References
Cost of Drug Therapy per patient				
Unit Cost of Drug per dose				
Rituximab SC vial (1400 mg/ 11.7 mL solution for subcutaneous (SC) injection)	PHP 62,500.00			Sponsor submission

Rituximab IV 10 mL (100 mg)	PHP8,363.00	PHP 8,363.00	The average BSA of a Filipino male is 1.659 square meter, which was computed using the average Filipino male weight (54.3 kg) and height (151.4 cm) using the Dubois and Dubois method. Hence the dose per cycle of rituximab IV is 685 mg, corresponding to one (1) 500 mg vial and two (2) 100 mg vials per cycle.	DPRI, 2021
Rituximab IV 50 mL (500 mg)	PHP 40,757.00	PHP 40,757.00		DPRI, 2021
Cost of Drug Regimen Per Patient				
Rituximab SC vial (7 units) + Rituximab IV 100 mg (2 units) + Rituximab IV 500 mg (1 unit)	PHP 494,893.00		TOTAL: rituximab SC: seven (7) units of 1,400 mg vial rituximab IV: two (2) units of 100 mg vials + one (1) unit of 500 mg vial	NCCN, 2021
Rituximab IV 100 mg (16 units) + Rituximab 500 mg (8 units)		PHP 459,864.00	TOTAL: rituximab IV: Sixteen (16) units of 100 mg vials + Eight (8) units of 500 mg vial	NCCN, 2021
Cost of Drug Per Patient Per Cycle	**PHP 61,872.88**	**PHP 57,483.00**		
Drug Administration Cost per cycle	PHP 123.30	PHP 205.50	Administration time difference of 40% (Italy) was adopted based on expert opinion. The hourly rates were computed using the monthly salaries under the Salary Standardization Law: Nurse: SG 15-1 (PhP 32,053) Registered Pharmacist: SG 11-1 (PhP 22,316)	De Cock et al., 2016 Salary Standardization Law, 2021 Expert opinion

Number of Cycles	8	8		PSMO, 2021
Total Drug Administration Cost	PHP 986.40	PHP 1,644.00		
Total Cost of Drug Regimen Per Patient	**PHP 495,969.40**	**PHP 461,508.00**		
Other costs				
Cost of diagnostic tests	PHP 244,887.00	PHP 244,887.00		Expert opinion
Cost of consumables	PHP 1,780.16	PHP 2,089.84		Philippine General Hospital, 2021
Cost of Management for Most Common Treatment-Related Adverse Events (per patient)	PHP 25,512.00	PHP 25,512.00	Cost per patient who will experience AE	Expert opinion
Total cost of other cost items per patient	***PHP 272,179.16***	***PHP 272,488.84***		
Total Drug Therapy Cost Per Patient *(Total Cost of Drug Regimen per patient + Total cost of other cost items per patient)*	**PHP 768,148.56**	**PHP 733,996.84**		

Incremental cost per patient	**PHP 34,151.72**			
Cost of Drug Therapy <u>for all expected number of users</u>				
No. of Patients Eligible for Treatment	3,431	3,431	Based on the Globocan 2020 report, NHL's 5-year prevalence in the Philippines is at11,065. With 31% of NHL cases expected to be DLBC, 5-year prevalence of diffuse B-cell is estimated at 3,431.	GLOBOCAN, 2020 PSMO, 2021
Total Cost of Drug Therapy for all expected number of users	**PHP 2,635,517,709.36**	**PHP 2,518,343,158.04**		
Total incremental cost	**PHP 117,174,551.32**			

Costing comparison for follicular type NHL (SC versus <u>innovator IV</u>)

At the patient level, the comparison of the total cost of drug therapy per patient (i.e., cost of drug regimen + other costs) between the IV and SC form for patients diagnosed with follicular type NHL shows that the use of rituximab SC will result in a higher cost at Php 1,538,006.00 compared to rituximab IV at Php 1,445,168.00. This results in an incremental cost of Php 92,838.00 per patient associated with the use of rituximab SC vs its IV form.

On the other hand, at the government level, the projected overall cost of using rituximab SC for all expected users is at Php 3,745,044,610.00 whereas the IV preparation will incur Php 3,518,984,080.00, with an incremental cost of Php 226,060,530.00 to the government. This is assuming that the government shall cover 2,435 estimated patients with follicular type NHL which were determined by deriving 22% of the 11,065 total 5-year prevalence of NHL cases reported in GLOBOCAN 2020.

Table 2.3 Comparison of medication costs for follicular type NHL (20 cycles)

Cost Parameters	Intervention: **Rituximab SC therapy**	Current Treatment: **Rituximab IV therapy**	Remarks	References
Cost of Drug Therapy <u>per Patient</u>				
Unit Cost of Drug per dose				
Rituximab SC vial (1400 mg/ 11.7 mL solution for subcutaneous (SC) injection)	PHP 62,500.00			Sponsor submission
Rituximab IV 10 mL (100 mg)	PHP 8,363.00	PHP 8,363.00	The average BSA of a Filipino male is 1.659 square meter, which was computed using the average Filipino male weight (54.3 kg) and height (151.4 cm) using the Dubois and Dubois method. Hence the dose per cycle of rituximab IV is 685 mg, corresponding to one (1) 500 mg vial and two (2) 100 mg vials per cycle.	DPRI, 2021
Rituximab IV 50 mL (500 mg)	PHP 40,757.00	PHP40,757.00		DPRI, 2021
Cost of Drug Regimen Per Patient				
Rituximab SC vial (19 units) + Rituximab IV 100 mg (2 units) + Rituximab IV 500 mg (1 unit)	PHP 1,244,983.00		TOTAL rituximab SC: Nineteen (19) 1,400 mg vials PLUS: rituximab IV: Two (2) 100 mg vials One (1) 500 mg vial	NCCN, 2021

Rituximab IV 100 mg (40 units) + Rituximab 500 mg (20 units)		PHP 1,149,660.00	TOTAL rituximab IV: Forty (40) 100 mg vials Twenty (20) 500 mg vials	NCCN, 2021
Cost of Drug Per Patient Per Cycle	**PHP 62,249.15**	**PHP 57,483.00**		cycle
Drug Administration Cost per cycle	PHP 123.30	PHP 205.50	Administration time difference of 40% (Italy) was adopted based on expert opinion. The hourly rates were computed using the monthly salaries under the Salary Standardization Law: Nurse: SG 15-1 (Php 32,053) Registered Pharmacist: SG 11-1 (Php 22,316)	De Cock et al., 2016 Salary Standardization Law, 2021 Expert opinion
Number of Cycles	20	20		PSMO, 2021
Total Drug Administration Cost	PHP 2,466.00	PHP 4,110.00	Administration time difference of 40% (Italy) was adopted based on expert opinion. The hourly rates were computed using the monthly salaries under the Salary Standardization Law: Nurse: SG 15-1 (Php 32,053) Registered Pharmacist: SG 11-1 (Php 22,316)	Expert opinion De Cock et al., 2016 Salary Standardization Law, 2021
Total Cost of Drug Regimen Per Patient	***PHP 1,247,449.00***	***PHP 1,153,770.00***		
Other Costs				

Cost of diagnostic tests	PHP 244,887.00	PHP 244,887.00		Expert opinion
Cost of consumables	PHP 4,384.00	PHP 5,225.00		Philippine General Hospital, 2021
Cost of Management for Most Common Treatment-Related Adverse Events (per patient)	PHP 41,286.00	PHP 41,286.00	Cost per patient who will experience AE	Expert opinion
Total cost of other cost items per patient	***PHP 290,557.00***	***PHP 291,398.00***		
Total Drug Therapy Cost Per Patient *(Total Cost of Drug Regimen per patient + Total cost of other cost items per patient)*	**PHP 1,538,006.00**	**PHP 1,445,168.00**		
Incremental cost per patient	**PHP 92,838.00**			
Cost of Drug Therapy <u>for all expected number of users</u>				
No. of Patients Eligible for Treatment	2,435	2,435	Based on the Globocan 2020 report, NHL's 5-year prevalence in the Philippines is at 11,065. With 22% of non-Hodgkin lymphoma expected to be FL, 5-year prevalence of can reach 2,431.	GLOBOCAN 2020 PSMO, 2021

Total Cost of Drug Therapy for all expected number of users	**PHP 3,745,044,610.00**	**PHP 3,518,984,080.00**		
Total incremental cost	**PHP 226,060,530.00**			

PROPOSAL FOR PRICE NEGOTIATION

Considering the non-inferiority of rituximab subcutaneous (SC) to rituximab intravenous in terms of clinical efficacy and safety, and the price disparity of the applied dosage form (rituximab subcutaneous form) to the intravenous form, the HTA Council agreed to endorse rituximab SC to the Price Negotiation Board (PNB) on 05 October 2021. The official PNB response was received on 02 December 2021 to no longer proceed with price negotiation given the non-prioritization of the DOH Disease Prevention and Control Bureau (DPCB) - Cancer Control Division (CCD) considering the expiration of the patent of rituximab IV and increased availability of cheaper biosimilars. The non-prioritization of the program for rituximab SC resulted in the non-submission of indicative or committed volume for the price negotiation. As the proponent of the assessment, the Philippine Society for Medical Oncology (PSMO) was consulted for confirmation of interest and the corresponding target beneficiaries for price negotiation on 09 December 2021. Despite the confirmation and information on the target beneficiary from PSMO, the DPCB CCD maintained its position not to prioritize rituximab SC given the above mentioned reasons. The HTAC then agreed on 06 January 2022 to ask the PNB to explore the possibility of requesting indicative volume from PhilHealth as another health financing entity. As of 11 February 2022, PhilHealth responded that they cannot provide an indicative volume since there is no history of reimbursement for rituximab SC as this drug is not part of the current benefits package.

The PNB provided its final directive on 15 February 2022 to not proceed with the price negotiation for rituximab SC.

COMPARATIVE COSTING RE-ANALYSIS: SC vs IV biosimilar

With the rationale from the DPCB CCD to not prioritize rituximab SC due to increased availability of biosimilars, a costing reanalysis was conducted to compare rituximab SC to rituximab IV biosimilars. In the reanalysis, we calculated the incremental cost of using

the SC preparation (using the sponsor list price) versus the IV biosimilar preparation (using the cheapest publicly available prices of biosimilars in other countries) [i.e. Pharmaceutical Benefit Scheme Australia prices].

Table 2.4 Comparison of unit prices of Rituximab IV 100 mg and 500 mg (2021)

Country	Rituximab IV 100 mg (in Php)	Rituximab IV 500 mg (in Php)	Source
Australia	**8,028.14** *[216.17 AUD]*	**20,070.54** *[540.43 AUD]*	Pharmaceutical Benefits Scheme 2022
New Zealand	9,534.02 [275.33 NZD]	23,830 [688.20 NZD]	Pharmaceutical Management Agency, 2022

Note: Foreign currency conversions based on the Reference Exchange Rate Bulletin of Bangko Sentral ng Pilipinas as of 23 February 2022: https://www.bsp.gov.ph/statistics/rerb/23Feb2022.pdf

In summary, based on our calculations, the incremental cost of using rituximab SC will be greater once the IV biosimilars become available which rationalizes the DPCB CCD's decision to not prioritize the SC formulation. Details of the costing analysis for diffuse large B-cell NHL and follicular type NHL are presented below.

Costing comparison for diffuse large B-cell NHL (SC versus biosimilar IV)

At the patient level, the comparison of the total cost of drug therapy per patient (i.e., cost of drug regimen + other costs) between the IV biosimilar and SC form for patients diagnosed with diffuse large B-cell NHL shows that the use of rituximab SC will result in a higher cost at Php 746,792.38 compared to rituximab IV biosimilar at Php 563,147.40. This results in an incremental cost of Php 183,644.98 per patient associated with the use of rituximab SC vs its IV form.

Meanwhile, at the government level, the projected overall cost of using rituximab SC for all expected users is at Php 2,562,244,655.78 whereas the IV biosimilar preparation will incur Php 1,932,158,729.40, resulting in an incremental cost of Php 630,085,926.38to the government. This is assuming that the government will cover 3,431 estimated patients with diffuse large

B-cell NHL which were determined by deriving 31% of the 11,065 total 5 year prevalence of NHL cases reported in GLOBOCAN 2020.

Table 2.5 Comparison of medication costs for diffuse large B-cell (8 cycles)

Cost Parameters	Intervention: **Rituximab SC therapy**	Current Treatment: **Rituximab IV therapy**	**Remarks**	**References**
Cost of Drug Therapy <u>per patient</u>				
Unit Cost of Drug per dose				
Rituximab SC vial (1400 mg/ 11.7 mL solution for subcutaneous (SC) injection)	PHP 62,500.00			Sponsor submission
Rituximab IV 10 mL (100 mg)	PHP 8,028.14	PHP 8,028.14	The average BSA of a Filipino male is 1.659 square meter, which was computed using the average Filipino male weight (54.3 kg) and height (151.4 cm) using the Dubois and Dubois method. Hence the dose per cycle of rituximab IV is 685 mg, corresponding to one (1) 500 mg vial and two (2) 100 mg vials per cycle.	PBS, 2022
Rituximab IV 50 mL (500 mg)	PHP 20,070.54	PHP 20,070.54		PBS, 2022
Cost of Drug Regimen Per Patient				
Rituximab SC vial (7 units) + Rituximab IV 100 mg (2 units) + Rituximab IV 500 mg (1 unit)	PHP 473,626.82		TOTAL: rituximab SC: seven (7) units of 1,400 mg vial rituximab IV: two (2) units of 100 mg vials + one (1) unit of 500 mg vial	NCCN, 2021

Rituximab IV 100 mg (16 units) + Rituximab 500 mg (8 units)		PHP 289,014.56	TOTAL: rituximab IV: Sixteen (16) units of 100 mg vials + Eight (8) units of 500 mg vial	NCCN, 2021
Cost of Drug Per Patient Per Cycle	**PHP 59,203.35**	**PHP 36,126.82**		
Drug Administration Cost per cycle	PHP 123.30	PHP 205.50	Administration time difference of 40% (Italy) was adopted based on expert opinion. The hourly rates were computed using the monthly salaries under the Salary Standardization Law: Nurse: SG 15-1 (PhP 32,053) Registered Pharmacist: SG 11-1 (PhP 22,316)	De Cock et al., 2016 Salary Standardization Law, 2021 Expert opinion
Number of Cycles	8	8		PSMO, 2021
Total Drug Administration Cost	PHP 986.40	PHP 1,644.00		
Total Cost of Drug Regimen Per Patient	**PHP 474,613.22**	**PHP 290,658.56**		
Other costs				
Cost of diagnostic tests	PHP 244,887.00	PHP 244,887.00		Expert opinion

Cost of consumables	PHP 1,780.16	PHP 2,089.84		Philippine General Hospital, 2021
Cost of Management for Most Common Treatment-Related Adverse Events (per patient)	PHP 25,512.00	PHP 25,512.00	Cost per patient who will experience AE	Expert opinion
Total cost of other cost items per patient	***PHP 272,179.16***	***PHP 272,488.84***		
Total Drug Therapy Cost Per Patient *(Total Cost of Drug Regimen per patient + Total cost of other cost items per patient)*	**PHP 746,792.38**	**PHP 563,147.40**		
Incremental cost per patient	**PHP 183,644.98**			
Cost of Drug Therapy <u>for all expected number of users</u>				
No. of Patients Eligible for Treatment	3,431	3,431	Based on the Globocan 2020 report, NHL's 5-year prevalence in the Philippines is at 11,065. With 31% of non-Hodgkin's lymphoma expected to be DLBC, 5-year prevalence of diffuse B-cell NHL can reach 3,431.	GLOBOCAN, 2020 PSMO, 2021

Total Cost of Drug Therapy for all expected number of users	**PHP 2,562,244,655.78**	**PHP 1,932,158,729.40**		
Total incremental cost	**PHP 630,085,926.38**			

Costing comparison for follicular type NHL (SC versus biosimilar IV)

At the patient level, the comparison of the total cost of drug therapy per patient (i.e., cost of drug regimen + other costs) between the IV biosimilar and SC form for patients diagnosed with follicular type NHL shows that the use of rituximab SC will result in a higher cost at Php 1,516,649.82 compared to rituximab IV biosimilar at Php 1,018,044.40. This results in an incremental cost of Php 498,605.82 per patient associated with the use of rituximab SC vs its IV form.

On the other hand, at the government level, the projected overall cost of using rituximab SC for all expected users is at Php 3,693,042,311.70 whereas the IV biosimilar preparation will incur Php 2,478,938,114.00, with an incremental cost of Php 1,214,104,197.70 to the government. This is assuming that the government shall cover 2,435 estimated patients with follicular type NHL which were determined by deriving 22% of the 11,065 total 5-year prevalence of NHL cases reported in GLOBOCAN 2020.

Table 2.6 Comparison of medication costs for follicular type NHL (20 cycles)

Cost Parameters	Intervention: **Rituximab SC therapy**	Current Treatment: **Rituximab IV therapy**	Remarks	References
Cost of Drug Therapy per Patient				
Unit Cost of Drug per dose				

Rituximab SC vial (1400 mg/ 11.7 mL solution for subcutaneous (SC) injection)	PHP 62,500.00			Sponsor submission
Rituximab IV 10 mL (100 mg)	PHP 8,028.14	PHP 8,028.14	The average BSA of a Filipino male is 1.659 square meter, which was computed using the average Filipino male weight (54.3 kg) and height (151.4 cm) using the Dubois and Dubois method. Hence the dose per cycle of rituximab IV is 685 mg, corresponding to one (1) 500 mg vial and two (2) 100 mg vials per cycle.	PBS, 2022
Rituximab IV 50 mL (500 mg)	PHP 20,070.54	PHP 20,070.54		PBS, 2022
Cost of Drug Regimen Per Patient				
Rituximab SC vial (19 units) + Rituximab IV 100 mg (2 units) + Rituximab IV 500 mg (1 unit)	PHP 1,223,626.82		TOTAL rituximab SC: Nineteen (19) 1,400 mg vials PLUS: rituximab IV: Two (2) 100 mg vials One (1) 500 mg vial	NCCN, 2021
Rituximab IV 100 mg (40 units) + Rituximab 500 mg (20 units)		PHP 722,536.40	TOTAL rituximab IV: Forty (40) 100 mg vials Twenty (20) 500 mg vials	NCCN, 2021
Cost of Drug Per Patient Per Cycle	**PHP 61,181.34**	**PHP 36,126.82**		cycle

Drug Administration Cost per cycle	PHP 123.30	PHP 205.50	Administration time difference of 40% (Italy) was adopted based on expert opinion. The hourly rates were computed using the monthly salaries under the Salary Standardization Law: Nurse: SG 15-1 (Php 32,053) Registered Pharmacist: SG 11-1 (Php 22,316)	De Cock et al., 2016 Salary Standardization Law, 2021 Expert opinion
Number of Cycles	20	20		PSMO, 2021
Total Drug Administration Cost	PHP 2,466.00	PHP 4,110.00	Administration time difference of 40% (Italy) was adopted based on expert opinion. The hourly rates were computed using the monthly salaries under the Salary Standardization Law: Nurse: SG 15-1 (Php 32,053) Registered Pharmacist: SG 11-1 (Php 22,316)	Expert opinion De Cock et al., 2016 Salary Standardization Law, 2021
Total Cost of Drug Regimen Per Patient	***PHP 1,226,092.82***	***PHP 726,646.40***		
Other Costs				
Cost of diagnostic tests	PHP 244,887.00	PHP 244,887.00		Expert opinion
Cost of consumables	PHP 4,384.00	PHP 5,225.00		Philippine General Hospital, 2021

Cost of Management for Most Common Treatment-Related Adverse Events (per patient)	PHP 41,286.00	PHP 41,286.00	Cost per patient who will experience AE	Expert opinion
Total cost of other cost items per patient	***PHP 290,557.00***	***PHP 291,398.00***		
Total Drug Therapy Cost Per Patient *(Total Cost of Drug Regimen per patient + Total cost of other cost items per patient)*	**PHP 1,516,649.82**	**PHP 1,018,044.40**		
Incremental cost per patient	**PHP 498,605.82**			
Cost of Drug Therapy <u>for all expected number of users</u>				
No. of Patients Eligible for Treatment	2,435	2,435	Based on the Globocan 2020 report, NHL's 5-year prevalence in the Philippines is at 11,065. With 22% of non-Hodgkin's lymphoma expected to be FL, 5-year prevalence for this type of NHL can reach 2,435.	GLOBOCAN 2020 PSMO, 2021
Total Cost of Drug Therapy for all expected number of users	**PHP 3,693,042,311.70**	**PHP 2,478,983,114.00**		
Total incremental cost	**PHP 1,214,104,197.70**			

5 YEAR COMPARATIVE COSTING ANALYSIS

The number of expected users per year were derived from the proportion of patients with diffuse large B-cell NHL (i.e., 31%) and the proportion of patients with follicular type NHL (i.e., 22%) out of all patients with NHL referred from the WHO GLOBOCAN data (2020). Year one consisted of the prevalent cases while the succeeding years were the cost for new cases. For the cost of rituximab SC, we used the same costing inputs in the previous section which was based on the price list from the sponsor, while the cost of rituximab IV (innovator) was based on DPRI, 2021 and the cost of rituximab IV (biosimilar) was based on the lowest list price by PBS Australia. Please note that in the costing calculation of the SC regimen which also includes using the IV preparation as its loading dose, the cost of the IV preparation is based on the cost of the IV regimen being compared to (hence, the difference in the cost of the SC regimen if compared to the IV innovator form versus if being compared to the IV biosimilar form). The cost of implementation of rituximab SC or IV over the 5-year horizon was not adjusted for inflation. We assumed that the cost of the drugs were consistent over the 5-year horizon of the calculation.

5-year Budget Impact Analysis for diffuse large B-cell NHL

The cost of implementing rituximab SC versus rituximab IV (both the innovator and biosimilar forms) for patients with diffuse large B-cell NHL was estimated over a 5-year period.

Using the innovator IV preparation, the use of rituximab SC in patients with diffuse large B-cell NHL will incur a total of Php 6,885,683,691.84, while the use of rituximab IV will incur a total of Php 6,579,547,673.76 resulting in an incremental cost of Php 306,136,018.08 over the 5-year horizon. Meanwhile, using biosimilar IV preparation, the use of Rituximab SC will incur a total of Php 6,694,246,894.32 while rituximab IV will incur a total of Php 5,048,053,293.60 resulting in an incremental cost of Php 1,646,193,600.72 The annual budget impact of rituximab SC and rituximab IV for follicular type NHL for 5 years is presented in the table below:

Year	Number of expected users of the HT	Comparative cost of Treatment Regimen (PHP): *SC vs IV innovator*		Comparative cost of Treatment Regimen (PHP: *SC vs IV biosimilar*	
		SC regimen	IV regimen (innovator)	SC regimen	IV regimen (biosimilar)

1	3431	2,635,517,709.36	2,518,343,158.04	2,562,244,655.78	1,932,158,729.40
2	1323	1,016,260,544.88	971,077,819.32	988,006,318.74	745,044,010.20
3	1362	1,046,218,338.72	999,703,696.08	1,017,131,221.56	767,006,758.80
4	1403	1,077,712,429.68	1,029,797,566.52	1,047,749,709.14	790,095,802.20
5	1445	1,109,974,669.20	1,060,625,433.80	1,079,114,989.10	813,747,993.00
TOTAL budget impact for 5 years (PHP)		6,885,683,691.84	6,579,547,673.76	6,694,246,894.32	5,048,053,293.60
Incremental cost (PHP)		**306,136,018.08**		**1,646,193,600.72**	

5-year Budget Impact Analysis for follicular type NHL

The cost of implementing rituximab SC versus rituximab IV (both the innovator and biosimilar forms) for patients with follicular type NHL was estimated over a 5-year period.

Using the innovator IV preparation, the use of rituximab SC in patients with follicular type NHL will incur a total of Php 9,786,332,178.00 while the use of rituximab IV will incur a total of Php 9,195,603,984.00 resulting in an incremental cost of Php 590,728,194.00 over the 5-year horizon. Meanwhile, using biosimilar IV preparation, the use of rituximab SC will incur a total of Php 9,650,442,804.66 while rituximab IV will incur a total of Php 6,477,816,517.20 resulting in an incremental cost of Php 3,172,626,287.46. The annual budget impact of rituximab SC and rituximab IV for follicular type NHL for 5 years is presented in the table below:

Year	Number of expected users of the HT	Comparative cost of Treatment Regimen (PHP): *SC vs IV innovator*		Comparative cost of Treatment Regimen (PHP: *SC vs IV biosimilar*	
		SC regimen	IV regimen (innovator)	SC regimen	IV regimen (biosimilar)

1	2435	3,745,044,610.00	3,518,984,080.00	3,693,042,311.70	2,478,938,114.00
2	939	1,444,187,634.00	1,357,012,752.00	1,424,134,180.98	955,943,691.60
3	967	1,487,251,802.00	1,397,477,456.00	1,466,600,375.94	984,448,934.80
4	996	1,531,853,976.00	1,439,387,328.00	1,510,583,220.72	1,013,972,222.40
5	1026	1,577,994,156.00	1,482,742,368.00	1,556,082,715.32	1,044,513,554.40
TOTAL budget impact for 5 years (PHP)		9,786,332,178.00	9,195,603,984.00	9,650,442,804.66	6,477,816,517.20
Incremental cost (PHP)		**590,728,194.00**		**3,172,626,287.46**	

Using rituximab biosimilar instead of the innovator product will result in savings of Php 1,531,494,380.16 to 191,436,797.52 for diffuse large B-cell NHL and Php 135,889,373.34 to 2,717,787,466.80 for follicular type NHL. This finding is consistent with the results of several budget impact analysis (BIA) studies across Europe, US, Canada, the Middle East and North Africa, have shown that using Rituximab IV biosimilar results in cost savings compared to the use of the innovator product.

- One study used a BIA model to estimate the expected cost savings upon introduction of Rituximab IV biosimilars in 13 countries in the Middle East and North Africa. Based on the assumption that the price of the biosimilar is 70% of the innovator drug and 100% utilization of the biosimilar, the total projected savings was 15.39 million USD for the treatment of NHL. The savings would allow access to Rituximab therapy for an additional 1,635 patients with NHL (Almaaytah, 2020). Almaaytah declared no conflict of interest regarding the data and publication of the manuscript.
- In the US, the transition to Rituximab IV biosimilars in 2020 resulted in net savings of 268.2 million USD with actual spendings on biosimilar products of 726.5 million USD against the projected spending on branded Rituximab IV of 994.7 million USD (Sanyal et al., 2021). Sanyal et al. had no research sponsor and did not declare any conflict of interest.
- In Canada, a real world budget impact analysis using rituximab utilization of 420 patients in one hospital showed that each 10% reduction in price of rituximab biosimilars will result in 0.002 to 0.50% savings (including all indications) when the biosimilar is used to replaced the innovator product (Boidart et al. 2020). The study did not receive any funding but the main

author disclosed receiving funding from Amgen and Abbvie. Amgen is a manufacturer of rituximab biosimilar while Abbvie manufactures Ibrutinib + Rituximab, a combination indicated for Waldenström's Macroglobulinemia.

- A budget impact analysis in the UK, France, Germany, Spain and Italy (Jang et al. 2020) showed that introducing the IV biosimilars into the market where the innovators market both SC and IV formulations may result in cost savings from the payer's perspective. The study by Jang et al. was sponsored by Celltrion Healthcare, a manufacturer of a rituximab biosimilar. One of the authors of Jang et al. is the founder of KU Leuven Fund on Market Analysis of Biologics and Biosimilars following Loss of Exclusivity and disclosed relationships with other pharmaceutical companies.
- Another BIA study in Italy also showed similar findings with Rituximab biosimilars producing 153.6 million EUR savings in a 5-year horizon (Rognani et al. 2018). The study was sponsored by Sandoz Italia Spa, another manufacturer of rituximab biosimilar.

Ethical, Legal, Social, and Health System Impact

Ethical Impact

Rituximab SC demonstrated non-inferior efficacy and safety compared to rituximab IV in the clinical assessment. However, the use of rituximab SC instead of rituximab IV may disadvantage patients with stage III–IV follicular lymphoma who are chemoresistant or are in their second or subsequent relapse after chemotherapy, as the safety of once weekly subcutaneous administration for this population has not been established (UK Electronic Medicines Compendium, 2021).

Due to the higher budget impact of using the SC formulation compared to the IV formulation (incremental cost of 57.8M to 111.7M), fewer patients may be accommodated especially in a resource-limited setting such as the Philippines. Further, the DOH Cancer Control Division did not prioritize the assessment of rituximab SC due to the expected availability of lower-priced biosimilars upon expiration of the patent of rituximab IV, which may translate to a more efficient allocation of resources to other essential cancer drugs and health programs.

Several budget impact analysis (BIA) studies across Europe, US, Canada, the Middle East and North Africa, have shown that using Rituximab IV biosimilar results in cost savings compared to the use of the innovator product (Almaaytah, 2020; Sanyal et al., 2021; Jang et al. 2020; Rognani et al. 2018; Boidart et al. 2020). Almaaytah declared no conflict of interest regarding the data and publication of the manuscript. Sanyal et al. had no research sponsor and did not declare any conflict of interest. Boidart et al. did not receive any funding but the main author disclosed receiving funding from Amgen and Abbvie. Amgen is a manufacturer of a rituximab biosimilar while Abbvie manufactures Ibrutinib + Rituximab, a combination indicated for Waldenström's Macroglobulinemia. The study by Jang et al. was sponsored by Celltrion Healthcare, a manufacturer of a rituximab biosimilar. One of the authors of Jang et al. is the founder of KU Leuven Fund on Market Analysis of Biologics and Biosimilars following Loss of Exclusivity and disclosed relationships with other pharmaceutical companies. Lastly, Rognani et al. was sponsored by Sandoz Italia Spa, another manufacturer of rituximab biosimilar.

Social Impact

The following reasons on the acceptability and benefits of rituximab SC over rituximab IV from the perspective of the general population and decision-makers were noted from the literature:

- *Ease of administration:* According to a multidimensional assessment by Cicchetti et. al 2018, among patients from 37 hospital centers (N= 210) in Italy, treatment with rituximab SC is preferred over the intravenous formulation as it reduces patient dosing times and increases care provider's autonomy and efficiency. Another study by Rule et al., 2014 in the UK among NHL patients (N= 700) also showed similar findings i.e. reduction in time spent in the treatment room by each patient and reduction in active

healthcare professional time with the use of the subcutaneous formulation. While both studies were funded by F. Hoffmann-La Roche Ltd., the supplier of rituximab IV and SC, Cicchetti et al. mentioned that the results of the study were not contingent on Roche's approval while Rule et al. mentioned that full editorial control was retained by the authors.

- *Patient Preference:* Based on two studies, NHL patients generally prefer rituximab SC over rituximab IV. The study of Lugtenburg et al., 2017 in 25 countries (including UK, Canada, France, Brazil, South Africa, Thailand among others) among 576 study participants showed higher rituximab Administration Satisfaction Questionnaire (RASQ) scores for all domains i.e. physical impact, psychological impact, impact on activities of daily living, convenience, satisfaction. It also showed that 90.8% of the participants stated a preference for SC over IV if given the option. In addition, the study by Rummel et al., 2017, in 32 countries worldwide (including the Philippines) among 743 participants, also showed that majority of patients preferred SC administration over IV, identifying *'requires less time in the clinic'* (68%–69%), *'feels more comfortable during administration'* (37%), and *'feels less emotionally distressing'* (28%–29%), as their main reasons. Both studies were sponsored by and provided with editorial support through Gardiner-Caldwell Communications by the F. Hoffmann-La Roche Ltd.. Additional support for third-party writing assistance for Rummel et al. was funded by Roche as well.

The following reasons on why rituximab SC might not be acceptable or not beneficial over rituximab IV from the perspective of the general population and decision-makers were noted from the literature:

- *Patient Preference:* Despite most literature supporting improved satisfaction with the SC formulation, an article by Yelvington, 2018 in the US reviewing rituximab SC use in patients with follicular lymphoma (n=197), chronic lymphocytic leukemia (n=85), and diffuse large B-cell lymphoma (n=369), mentioned that some patients may experience needle phobia with subcutaneous injection. In this situation, the IV formulation may still be more acceptable. Further, other patients may still prefer IV administration. Yelvington et al. declared no conflict of interest.
- *Equity:*
  Literature review did not indicate any specific populations that might be disadvantaged with the procurement of rituximab SC over rituximab IV. However, studies have reported that patients with low socioeconomic status (SES) generally are already more disadvantaged in accessing rituximab. Since rituximab SC is more costly, this might magnify these inequities should it be excluded from national government funding as it will be fully shouldered by the patients. Should the SC form be listed in the formulary and be eligible for government funding, public procurement entities with low SES may still have challenges procuring at its current cost.

  The specific studies supporting the impact of SES in accessing rituximab in general are as follows: First, the study by Yu-Wen et al, 2014 among NHL patients in Chinese public hospitals (N = 328) observed that patients of SES have lesser chances of receiving chemotherapy treatment. Another study in China by Hung, 2016 among 497 HL and

4,513 NHL patients, showed that patients in the post-rituximab era with lower individual and neighborhood SES are more likely to have a lower 5-year overall survival rate than patients with high individual and neighborhood SES. According to a study by Davies et al.,2017., patients in LMICs still have restricted access to healthcare resources, especially to cancer treatments which are labor-intensive and would require funding to be able to provide the appropriate service and medication. These studies show that factors such as the economic status of patients affect their access to treatment leading to less desirable clinical outcomes of chemotherapy treatment. Yu-Wen et al. and Hung et al. 2016 declared no conflict of interest, while Davies et al. was funded by the F. Hoffmann-La Roche Ltd.

- Although rituximab SC and rituximab IV have the same number of cycles of treatment **and the cost of administration of rituximab IV is higher than rituximab SC**, given that rituximab SC is more expensive than rituximab IV **by Php 35,119.00 (innovator) to 184,612.26 (biosimilar) per patient for diffuse large B-cell NHL and Php 95,323.00 (innovator) to 501,090.42 (biosimilar) per patient for follicular NHL**, the total cost of treatment using the subcutaneous formulation will still be higher. If rituximab SC will not be subsidized by the government, indigent patients will still have access to the PNF-listed rituximab IV but the high cost of rituximab SC will be a barrier to this treatment option for NHL patients who cannot afford it.
- *Availability of alternative treatment options:* Currently, the PhilHealth has 10 benefit packages for the different forms of non-Hodgkin's lymphoma (ICD Codes: C82.2, C82.7, C82.9, C83.0, C83.3, C83.3, C83.4, C83.5, C83.8, C83.9). Each of these packages has a case rate of **Php 13,900** per patient which utilizes PNF-listed drugs for the treatment of NHL(chlorambucil, methotrexate, vincristine, etoposide, doxorubicin, carboplatin, and rituximab IV).
- *Out-of-pocket expenses:* Given that there is currently no health financing entity that prioritizes rituximab SC, opting to use this treatment instead of PNF-listed drugs will mean that use of this intervention will incur out of pocket expenses to the patient.

Legal Impact

Recognizing that cancer is one of the leading causes of mortality in the Philippines, Republic Act 11215 or the National Integrated Cancer Control Act (NICCA) was signed last February 2019 to further strengthen cancer control programs in the healthcare system, and improve cancer survivorship by scaling up essential programs, likewise make cancer treatment and care more equitable and affordable for all. Article V of the act mandates PhilHealth to expand its benefit packages to include treatment assistance among others in both adults and children. This expansion, however, shall go through "*proper, transparent and standardized prioritization setting process, such as the Health Technology Assessment and actuarial feasibility study, to avoid inequitable allocation of funds for health care services*". Likewise, Article VI of the act mandates the DOH, and other concerned government agencies to "*implement reforms supporting early access to essential medicines, innovative medicines, and health technologies, to ensure the*

highest possible chance of survival among people with cancer". With this, the possible PNF inclusion and implementation of rituximab SC align with the mandate of the NICC Act. Furthermore, the RA 11215 is also aligned to the overarching mandate that all health technologies for DOH and PhilHealth financing must go through HTA (per RA 11223 or the Universal Health Care Act), and that all drugs for reimbursement by the government must refer to the PNF (EO 49, series of 1993).

Health system Impact

Existing health system support for the management of NHL

Currently, the PhilHealth reimburses for 10 benefit packages for the different forms of non-Hodgkin's lymphoma (ICD Codes: C82.2, C82.7, C82.9, C83.0, C83.3, C83.3, C83.4, C83.5, C83.8, C83.9). Each of these packages has a case rate of **Php 13,900** per patient.

Meanwhile, the PNF currently lists several drug treatments for NHL which can be reimbursed by the patient through PhilHealth or can be supported by government health facilities: (1) chlorambucil; (2) methotrexate; (3) vincristine; (4) etoposide; (5) doxorubicin; (6) carboplatin and (7) rituximab IV. (DOH, 2019).

With the signing of NICCA in 2019, these efforts in ensuring access to healthcare for cancer patients, in general, are anticipated to be further strengthened by the health system.

Impact of Rituximab SC on Medicine Access

In terms of access, should this drug be listed in the PNF, the existing policies and programs of the DOH, and Philhealth on financing support will be utilized. Therefore, the adoption of this health technology will not require any organizational changes except for the need for additional budget as this is more expensive than the currently listed IV form.

Based on the CPR issued by the Philippine FDA of rituximab SC, the product can be stored at refrigerator temperature (2 °C – 8 °C) which is widely available in different healthcare facilities locally. Hence, it will not require specialized storage equipment.

Impact of Rituximab SC on the procurement process

To some degree, adding this new form may result in a more complex procurement process since the government will have to procure both the SC and IV formulations.

Impact of Rituximab SC on End-user Training

Literature reviewed did not indicate whether the rituximab SC administration will not require additional training. However, subcutaneous injections are routinely done in healthcare facilities, thus administration of rituximab SC will not likely pose significant difficulties in training human resources.

Impact of Rituximab SC on Patient and HCP Time

Based on the studies of De Cock et al., 2016 [8 European countries, N=30 oncology units], Stewart et al., 2020 [Canada, N=55 HCPs], Sanchez, et al., 2019 [US, N=130 patients (527 cycles)], and Rule et al., 2014 [UK, N=3 oncology units], rituximab SC was associated with reduced patient chair time and active healthcare provider time compared with rituximab IV. Furthermore, the study of Sanchez, et al., 2019 showed that the reduced preparation and administration time for rituximab SC resulted in a significant reduction in the median total cost per cycle ($p < 0.001$) as compared with using the rituximab IV. The Rule et al., 2014 study also consistently showed time and cost savings in the rituximab SC formulation as compared to IV and estimated reduced total mean staff costs by £115.17 (95% CI: 98.95–136.93) per cycle or equivalent to Php 8,063.55 (1 UK Pound to Php 70.01). All four studies disclosed their affiliations with F. Hoffmann-La Roche Ltd. The study by De Cock et al., including communications, was funded by F. Hoffmann-La Roche Ltd and two of its authors were also indicated to be former or current employees of the company. The authors of Stewart et al. disclosed receiving honoraria and writing support funded by F. Hoffmann-La Roche Ltd. One of the authors was also employed at F. Hoffmann-La Roche Ltd. at the time of the study. The study by Rule et al., including the data analysis and editorial assistance, were funded by Roche Products Ltd. Lastly, four authors of the study by Sanchez et al. have provided consultant services or have received research support and personal fees from F. Hoffmann-La Roche Ltd. during the conduct of the study.

Similarly, the UK NICE review also concluded that rituximab SC injection offers benefits in terms of HCP time and associated cost savings as compared with rituximab IV infusion. However, it was noted that these incremental cost benefits may not be as great if rituximab is used with other drugs given intravenously. (UK NICE, 2014)

Overall, it can be inferred that adoption of the health technology will likely provide time and cost savings in the local health system as compared to rituximab IV.

Impact of Rituximab SC on Adverse events Management

Based on the UK NICE 2014 review, treatment-related adverse events are more common with rituximab SC as compared with rituximab IV although most were mild to moderate. The proportion of people who experienced a serious adverse event did not differ between the treatment groups. On the other hand, the study of Stewart et al., 2020 in Canada among healthcare providers (N=55) associates rituximab SC with a reduced risk of infusion-related reactions. Stewart et al. declared that they previously received honoraria from Hoffmann–La Roche Ltd. Further, one author was employed at Hoffmann–La Roche Ltd. at the time of the study. Medical writing support was provided by Impact Medicom Inc. which was also funded by Hoffmann–La Roche Ltd.

No studies or guidelines indicating an additional post-monitoring requirement for adverse events related to rituximab SC was found.

Recommendation [as of 04 March 2022]

The Health Technology Assessment Council (HTAC) **cannot recommend the inclusion** of rituximab 1400 mg/ 11.7 mL solution for subcutaneous (SC) injection in the Philippine National Formulary.

The HTAC recognizes the comparable clinical efficacy and safety of rituximab SC vs rituximab IV. The advantages of rituximab SC also include its ease of administration, and the need for less healthcare professional administration time and chair time for the patients with non-Hodgkin's lymphoma.

However, the HTAC acknowledges the disadvantages of rituximab SC to patients with advanced stages of follicular lymphoma given its limited safety profile for this population. Several studies also report varying preference of patients between rituximab SC and rituximab IV. There are also available health system support through existing PhilHealth benefit packages (ICD Codes: C82.2, C82.7, C82.9, C83.0, C83.3, C83.3, C83.4, C83.5, C83.8, C83.9) and PNF-listed drugs (rituximab IV, chlorambucil, methotrexate, vincristine, etoposide, doxorubicin, and carboplatin) for non-Hodgkin's lymphoma.

The high cost of rituximab SC compared to rituximab IV results in a high budget impact to the government. The incremental cost per patient (i.e., Php 34,151.72 to 92,838.00) and the total incremental cost for 1 year for all expected users (i.e., Php 117,174,551.32 to Php 226,060,530.00) of using the SC therapy for both diffuse large B-cell and follicular type non-Hodgkin's lymphoma are significantly higher than the current standard of care (i.e., more than 1.04 times more expensive than rituximab IV therapy). Based on the sponsor-listed price of rituximab SC and the DPRI 2021 price of rituximab IV, the HTAC considered further price reduction through the Price Negotiation Board.

While efforts have been made for the drug to be affordable, price parity of the subcutaneous form with the intravenous form was not achieved since the price negotiation did not proceed due to the following reasons:

- DOH Cancer Control Division did not prioritize the drug due to its preference for more affordable biosimilars which are anticipated to be available with the expiration of the patent of rituximab IV
- PhilHealth Benefits and Research Department stated that it has no current benefit package requiring modification to indicate or include reimbursement of rituximab SC.

Following this, a costing analysis of rituximab SC versus rituximab IV biosimilars was conducted which showed that incremental cost per patient (i.e., Php 183,644.98 to Php 498,605.82) and the total incremental cost for 1 year for all expected users (i.e., Php 630,085,926.38 to Php 1,214,104,197.70) of using the SC therapy for both diffuse large B-cell and follicular type non-Hodgkin's lymphoma is further increased when the biosimilar form of the current standard of care is used (i.e., more than 1.33 times more expensive than rituximab IV therapy).

Comparative costing analysis over a 5-year period showed that using rituximab SC versus rituximab IV incurs a total incremental cost of Php 306,136,018.08 diffuse large B-cell NHL, and Php 590,728,194.00 for follicular type NHL provided that the innovator IV formulation will be used. The incremental cost of rituximab SC is further increased when IV biosimilar is used (i.e., Php 1,646,193,600.72 for diffuse large B-cell NHL and Php 3,172,626,287.46 for follicular type NHL).

In light of the non-prioritization of the DPCB CCD, the lack of Philhealth benefit package requiring modification to indicate or include reimbursement of rituximab SC, and the high budget impact to the government, the HTAC **cannot recommend the inclusion** of rituximab SC to the Philippine National Formulary.

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