Evidence Summary on *Sputnik V Gam-COVID-Vac COVID-19 Vaccine* for the prevention of COVID-19

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Background

The COVID-19 pandemic, caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), has led to more than two million deaths worldwide, global economic and social disruption, and unprecedented challenges in the health system. As the world continues to face these challenges, several efforts, such as developing and implementing different health technologies that will ultimately lead us to our exit strategy from the crisis, were undertaken. Among these health technologies are vaccines against COVID-19 which are currently in different phases of trials around the world. Similar to other countries, the Philippine government has been exploring all means to access these vaccines and to prepare the country for its upcoming implementation within the coming months.

On March 19, 2021, the Philippine Food and Drug Administration (FDA) released the Emergency Use Authorization (EUA) for *Sputnik V Gam-COVID-Vac COVID-19 Vaccine*.

To date, at least 13 countries (i.e., Russia, Belarus, Argentina, Bolivia, Algeria, Palestine, Paraguay, Venezuela, Turkmenistan, Hungary, Guinea, UAE, Uruguay) have issued an EUA for this product in their respective jurisdictions and have started vaccine implementation *(sponsor submission dated 09 Feb 2021 & DFA presentation dated 18 February 2021)*. This vaccine is one of the few COVID-19 vaccines which has already published its Phase III trial interim results to date.

Basic information on *Sputnik V Gam-COVID-Vac COVID-19 Vaccine* is provided below:

Table 1.1 Characteristics of *Sputnik V Gam-COVID-Vac COVID-19 Vaccine*

Trade name	Sputnik V Gam-COVID-Vac COVID-19 Vaccine
Other name	Gamaleya Sputnik V Vaccine
Manufacturer/s	Gamaleya National Center of Epidemiology and Microbiology
Vaccine platform	Viral vector vaccine [rAd26 (1st dose) and rAd5 (2nd dose) encoding the SARS-CoV-2 Spike glycoprotein)]
Dose strength and administration	One bottle of Component I and one bottle of Component II both contain 3mL - 5 dose - 0.5mL/dose of vaccine. First dose is Component I, and the second dose is Component II. Both doses are injected intramuscularly. Component II is given three weeks after Component I.

Route of administration	Solution for injection, Intramuscular (IM)
Drug delivery system	1 bottle of Component I - 3mL - 5 doses 1 bottle of Component II - 3mL - 5 doses
Storage condition	Store in a dark place at a temperature not exceeding -18°C; do not freeze; protect from light; shelf life = 6 months
Mechanism of action	Sputnik V is made up of two different viruses belonging to the adenovirus family, Ad26 and Ad5. These adenoviruses have been modified to contain the gene for making the SARS-CoV-2 spike protein. The two adenoviruses are given separately: Ad26 is used in the first dose and Ad5 is used in the second to boost the vaccine's effect. Following administration, the S glycoprotein of SARS-CoV-2 is expressed locally, stimulating neutralizing antibody and cellular immune responses. *(Source: EMA, 2021)*
Contraindications	● Hypersensitivity to any of the vaccine components, or a vaccine containing similar components; ● severe allergic reactions in the past; ● acute infectious and non-infectious diseases, flares of chronic diseases - vaccination is to be administered 2-4 weeks after recovery or remission. In non-severe ARVI or acute gastrointestinal infections - vaccination is administered after the body temperature normalizes; ● pregnancy and breastfeeding; ● age under 18 (due to lack of data on safety and efficacy) Contraindications for Dose 2 (rAd5) ● severe post-vaccination complications (anaphylactic shock, severe generalized allergic reactions, convulsive disorder, temperature above 40°C, etc.) after administering the Dose 1. *Dose 1 (rAd26) contains:* *Active substance: recombinant serotype 26 adenoviral particles, containing the SARS-CoV-2 protein S gene, in the amount of (1.0±0.5) x 10^{11} particles per dose.* *Excipients: tris- (hydroxymethyl)aminomethane - 1.21 mg, sodium chloride - 2.19 mg, sucrose - 25.0 mg, magnesium chloride hexahydrate - 102.0 µg, EDTA-disodium salt dihydrate – 19.0 µg, polysorbate 80 - 250 µg, ethanol 95% - 2.5 µL, water for injections up to 0.5 mL.* *Dose 2 (rAd5) contains:* *Active substance: recombinant serotype 5 adenoviral particles, containing the SARS-CoV-2 protein S gene, in the amount of (1.0±0.5) x 10^{11} particles per dose.* *Excipients: tris-(hydroxymethyl)aminomethane - 1.21 mg, sodium chloride - 2.19 mg, sucrose - 25.0 mg, magnesium*

	chloride hexahydrate - 102.0 µg, EDTA-disodium salt dihydrate – 19.0 µg, polysorbate 80 - 250 µg, *ethanol 95% - 2.5 µL, water for injections up to 0.5 mL.* *(Source: Ministry of Health of the Russian Federation, 2020)*
PHL EUA status	Released as of 19 March 2021 *https://www.fda.gov.ph/wp-content/uploads/2021/03/EUA-Gamaleya-Website.pdf*
PHL FDA EUA indication	For active immunization for the prevention of COVID-19 caused by SARS-CoV-2 in individuals 18 years of age and older
WHO EUL status	Not yet approved

Pursuant to the role of the Health Technology Assessment Council (HTAC) to develop coverage recommendations particularly in the selection and financing of COVID-19 vaccines using the Evaluation Framework set by the HTAC, this report presents all currently available evidence considered in the assessment of *Sputnik V Gam-COVID-Vac COVID-19 Vaccine*. This assessment follows the HTAC evaluation framework to assess COVID-19 vaccines using the following criteria: (1) responsiveness to magnitude and severity; (2) clinical efficacy and safety; (3) affordability and viability; (4) household financial impact; (5) social impact; and (6) responsiveness to equity.

Policy Question

The HTAC aims to answer the policy question:

Should ***Sputnik V Gam-COVID-Vac COVID-19 Vaccine (Gamaleya Sputnik V Vaccine)*** be recommended for emergency use to reduce COVID-19 cases, severe infection, and deaths?

Recommendation *(as of 12 April 2021)*

The HTAC **recommends the emergency use of *Sputnik V Gam-COVID-Vac COVID-19 Vaccine*** to reduce the burden of COVID-19 among eligible populations aged 18 years and older.

The HTAC considered the following criteria in formulating its recommendation for the vaccine:

Criteria	HTAC Judgment
Can *Sputnik V Gam-COVID-Vac COVID-19 Vaccine* significantly reduce the magnitude and severity of COVID-19?	**Yes**. *Sputnik V Gam-COVID-Vac COVID-19 Vaccine*, with 91.1% efficacy, has the potential to reduce the disease burden by averting a significant number of symptomatic infections and deaths assuming sufficient vaccine coverage.
Is *Sputnik V Gam-COVID-Vac COVID-19 Vaccine* efficacious and safe?	Based on the interim results of the Phase III trial on *Sputnik V Gam-COVID-Vac COVID-19 Vaccine* (Logunov et al, 2021) *[cut-off analysis: date: 24 November 2020]:* **Yes**, it is efficacious for preventing symptomatic COVID-19 based on high certainty of evidence. However, there is no reported data on the efficacy against symptomatic COVID-19 in the population with comorbidities, asymptomatic COVID-19, and hospitalization due to COVID-19. Currently, the reported evidence on vaccine efficacy of *Sputnik V Gam-COVID-Vac COVID-19 Vaccine* against severe COVID-19 has low certainty of evidence based on a wide confidence interval and short follow-up period. The duration of protection cannot be assessed given the current data. **Yes**, it is safe in the known short-term safety outcomes, based on high certainty of evidence. Meanwhile, its long term safety outcomes are inconclusive based on low certainty of evidence. It should not be given to individuals below 18 years old, to those with a known history of hypersensitivity to any component of the

	vaccine, history of severe allergic reactions, those with acute infectious and non-infectious diseases, flares of chronic diseases, and pregnant women and breastfeeding women (Ministry of Health of the Russian Federation, 2020). While vaccination is not contraindicated in other special populations, the vaccine should be used with caution in cases of the following (based on the package insert): chronic liver and kidney disease, endocrine disorders (apparent thyroid function abnormalities and diabetes mellitus in decompensation stage), serious diseases of the hematopoietic system, epilepsy and other CNS diseases, acute coronary syndrome and acute cerebrovascular event, myocarditis, endocarditis, pericarditis.
Is *Sputnik V Gam-COVID-Vac COVID-19 Vaccine* affordable and feasible to use in a national immunization program (viability)?	**Yes.** It is affordable. The share of the cost to implement vaccination using *Sputnik V Gam-COVID-Vac COVID-19 Vaccine* will constitute 21% of the total allocated budget for vaccination and will cover 21% of the 70 million target vaccinees for 2021. According to the Department of Finance, the price of *Sputnik V Gam-COVID-Vac COVID-19 Vaccine* offered to the Philippine government is equal to or better than the price offered to all countries outside of Russia. **Yes**, it is feasible as there are no significant barriers in vaccine implementation using *Sputnik V Gam-COVID-Vac COVID-19 Vaccine* in terms of storage, transport, and handling. However, there is still a need for training of vaccinators to ensure product integrity across the entire supply chain and close monitoring of adverse events.
Does *Sputnik V Gam-COVID-Vac COVID-19 Vaccine* reduce out-of-pocket (OOP) expenses of households due to COVID-19?	**Yes**. Noting its efficacy against symptomatic COVID-19, based on current evidence, *Sputnik V Gam-COVID-Vac COVID-19 Vaccine* has the potential to reduce out-of-pocket expenses of Filipino households due to averted treatment and isolation costs for mild COVID-19.
Does *Sputnik V Gam-COVID-Vac COVID-19 Vaccine* possess the characteristics desired by key stakeholders? (Social Impact)	**Yes.** Based on short term outcomes, *Sputnik V Gam-COVID-Vac COVID-19 Vaccine* possesses most of the characteristics desired by key stakeholders.
Does *Sputnik V Gam-COVID-Vac COVID-19 Vaccine* reduce or not further add to existing inequities in the health	**Yes.** Because of non-stringent logistic requirements, *Sputnik V Gam-COVID-Vac COVID-19 Vaccine* does not aggravate health inequities related to inoculation of recipients residing in isolated and disadvantaged locations. The trial population did not include important groups such as individuals aged 18 and

system?	below, immunocompromised individuals, pregnant and lactating women.

The HTA Council further emphasizes the need to enforce strict conditions for the emergency use of health products to safeguard against eventualities:

- Transparency and accountability in the processes of allowing emergency use of health products, especially for the public health response;
- Continuous collection of safety and effectiveness data in the context of clinical trials and actual use in the real world;
- Close monitoring of recipients and safeguards for expected and unexpected adverse events that may arise from the use of health products under an EUA;
- National coordination of the emergency use under the Philippine FDA and the DOH;
- Cascading of complete information to vaccinees on potential risks and benefits, and securing of informed consent with regard to receiving the intervention; and
- Just compensation mechanisms and provisions for medical management of adverse events for patients and vaccinees assured by the national government

Finally, the HTAC recommends the conduct of research to address the current gaps in evidence with regard to the use of the *Sputnik V Gam-COVID-Vac COVID-19 Vaccine*:

- Real-world effectiveness in the Philippine context particularly focused on the following:
    - Effectiveness in reducing COVID-19 cases, hospitalizations and deaths, and preventing outbreaks and transmission of disease across the population
    - Effectiveness in reducing asymptomatic infection
    - Duration of protection
    - Impact of the timing and number of doses received
    - Probable need for booster dosing
    - Differences in the effectiveness of the vaccine among special populations (i.e., elderly, individuals with comorbidities, pregnant and lactating women, immunocompromised patients)
    - Effectiveness of the vaccine against emerging SARS-CoV-2 viral strains

- Continuous safety surveillance and monitoring of all adverse events especially severe allergic reactions, Bell's palsy, serious adverse events and adverse events of special interest (AESI) following vaccination
    - Across the general population
    - In special populations: elderly, patients with comorbidities, pregnant and lactating women, immunocompromised individuals
- Randomized controlled trials should also be done among populations not currently included in clinical trials: children below 18 years of age
- Best practices, challenges, and barriers in implementation across different localities
- Monitoring of unexpected or additional costs associated with vaccine implementation.

Current Evidence on *Sputnik V Gam-COVID-Vac COVID-19 Vaccine*

The table below summarizes the appraisal of available evidence on *Sputnik V Gam-COVID-Vac COVID-19 Vaccine* against the HTAC evaluation framework.

In addition, the following appendices are provided for further details:

- Appendix 1. Evidence on evaluation criterion 2 - Clinical Efficacy and Safety
- Appendix 2. Evidence on evaluation criterion 3 - Affordability and Viability
- Appendix 3. References
- Appendix 4. Acknowledgment

Table 1.2 Key Findings in the Current Evidence Considered for the HTAC Evaluation of ***Sputnik V Gam-COVID-Vac COVID-19 Vaccine***

Evaluation Criteria	Question	Current Evidence	HTAC specification
1. Responsiveness to magnitude and severity	*Can the Sputnik V Gam-COVID-Vac COVID-19 Vaccine significantly reduce the magnitude and severity of COVID-19?*	As of 08 April 2021, the total number of cases has exceeded more than 132.7 million cases and breached the 2.8 million mark in terms of the total number of deaths globally. In the Philippines, the cumulative number of laboratory-confirmed COVID-19 cases has already exceeded 828,366 cases with total deaths reported at 14,119 as of 08 April 2021. Based on the DOH-Epidemiology Bureau data, the young and productive age groups (20-49 years old) have the most exposure and highest prevalence of the disease. However, the most vulnerable are the senior citizens (>60 years) who have the highest case fatality rate (CFR) at 10.2% and comprise around 63% of COVID-19 deaths. In addition, individuals with existing comorbidities such as chronic kidney disease (CKD), chronic obstructive pulmonary disease (COPD), other pulmonary, cardiovascular and blood diseases are also vulnerable with CFR reported at around 64 to 91%. COVID-19 has led to significant disruptions not only in the delivery of other priority health services (e.g., immunization, maternal and child health, noncommunicable diseases) but also in the social and economic life of the nation by arresting the growth of the economy, displacing migrant and local workers, loss of jobs, and food insecurity (NEDA, 2020; PSA 2020; TESDA, 2020). Social safety nets for the poorest and other vulnerable sectors have not been enough to compensate for these losses (TESDA, 2020). The lockdowns and community quarantines have also been shown to have an impact on the mental health of Filipinos and have affected how common Filipino households adjust under the new normal, unable to visit and	The vaccine can potentially reduce the COVID-19 disease burden (health, social and economic impact).

		freely enjoy quality time with members of their families, as captured in some focus group discussions conducted by the HTAC and the HTA Unit. The potential impact of the *Sputnik V Gam-COVID-Vac COVID-19 Vaccine* in addressing the current burden of COVID-19 disease may be gleaned from the following: ● Modeling studies in the US concluded that a vaccine efficacy of 90% can avert at least 50% of symptomatic infections and deaths due to COVID-19 at approximately 20% coverage (Matrajt, 2020). These simulations assumed that children are less susceptible to infection than middle age adults, while older adults were more susceptible, and that both natural and vaccine-induced immunity last at least one year. The study also assumed that 20% of the population have already been infected and are immune and all social distancing have been lifted, vaccinated individuals achieved full protection conferred by the vaccine and front-line healthcare workers and other essential personnel who should be prioritized, have already been vaccinated. ● Another simulation study suggests that to extinguish an ongoing epidemic, the vaccine efficacy should be at least 60% for a target coverage of 100% in order to reduce the peak by around 85%. On the other hand, a vaccine should have an efficacy of at least 80% for a target coverage of 75% to reduce the peak by almost 62%. (Bartsch et al., 2020). Locally-contextualized modelling studies are needed for more accurate projections of the potential impact of vaccination along with other interventions, under different scenarios. These can better inform decision-making.	

		HTAC Judgment: *Sputnik V Gam-COVID-Vac COVID-19 Vaccine* has the potential to reduce the disease burden by averting a significant number of symptomatic infections and deaths assuming sufficient vaccine coverage.	
2. Clinical efficacy and safety	*What is the efficacy of the Sputnik V Gam-COVID-Vac COVID-19 Vaccine in terms of reducing the incidence and/or severity of COVID-19 in the general and vulnerable populations?*	*The evidence review on efficacy was based on one published Phase I/II trial in Russia (Logunov et al, 2020) for population aged 18-60 years (N=76) using the frozen and lyophilized formulations of the vaccine; and, one published interim results from Phase III randomized clinical trial (Logunov et al., 2021) conducted in Russia (N=21,977). The median follow up period for the Phase III trial was 48 days after the 1st dose (or 27 days after second dose).* *The details of the Phase I and II trials are provided in Appendix 1.* ***PHASE III TRIAL, (N= 21,977) (Logunov et al, 2021)*** *This study was a randomised, double-blind, placebo-controlled, phase 3 trial at 25 hospitals and polyclinics in Moscow, Russia. They included participants aged at least 18 years, and with negative SARS-CoV-2 PCR and IgG and IgM tests. Participants were randomly assigned (3:1) to receive vaccine [(0.5 mL/dose) intramuscularly in a prime-boost regimen: a 21-day interval between the first dose (rAd26) and the second dose (rAd5)] or placebo. The primary outcome was the proportion of participants with PCR-confirmed COVID-19 from day 21 after receiving the first dose. Based on the interim results of the trial:* ***Clinical outcomes*** ***Critical efficacy outcomes:*** ● *Using Sputnik V Gam-COVID-Vac COVID-19 Vaccine, compared to placebo, reduces the risk of:*	The vaccine achieves the following efficacy parameters: **Preferred VE: ≥70% reduction** in the risk of symptomatic infection with vaccination versus no vaccination **Minimum acceptable VE: 50% reduction** in the risk of symptomatic infection with vaccination versus no vaccination The following factors were taken into consideration upon setting the minimum acceptability of 50% efficacy: pandemic

		○ *Symptomatic COVID-19 more than 7 days after dose 2 by 91.1% (95% CI: 83.8 to 95.1), based on high certainty of evidence* ***Important efficacy outcomes:*** ● *Using Sputnik V Gam-COVID-Vac COVID-19 Vaccine, compared to placebo, reduces the risk of:* ○ *Symptomatic COVID-19 21 days after dose 1 by 91.6% (95 CI: 85.6 to 95.2), based on high certainty of evidence* ○ *Symptomatic COVID-19 in older adults (>60 years old, n = 2,144, 10.79% of the trial population) 21 days after dose 1 by 91.8% (95% CI: 67.1 to 98.3), based on high certainty of evidence* ● *For its efficacy against moderate COVID-19 21 days after dose 1, there are 0 events out of 14,964 subjects in the intervention group and 19 events out of 4,902 subjects in the control group. The certainty of evidence is low.* ● *For its efficacy against severe COVID-19 21 days after dose 1, there are 0 events out of 14,964 subjects in the intervention group and 1 out of 4,902 subjects in the control group. The certainty of evidence is low.* *The following outcomes were not reported by the trial:* - *VE against hospitalization due to COVID-19* - *VE against severe COVID-19 after dose 2* - *VE against symptomatic COVID-19 among older adults, after dose 2* - *VE against symptomatic COVID-19 among population with comorbidity (n = 4,922, 24.78% of trial population)* - *VE against symptomatic COVID-19, Asians (n = 286, 1.44% of the population*	situation, no standard COVID-19 vaccine, limited production from each manufacturer, and the need for multiple sources of vaccines in the Philippines. Adapted from WHO, US FDA, other stringent regulatory authorities *Note: Pending legal provision allowing the use of evidence based on Phase III interim results*

		- *VE against asymptomatic COVID-19* ***Evidence on Adaptive immunity; Immunogenicity outcomes*** *Humoral immune responses were measured at 42 days after the start of vaccination. Seroconversion rates and geometric mean titers of participants were higher in the vaccine group (N=342) than in the placebo group (N=114).* ● ***RBD specific antibodies 42 days after the start of vaccination*** *(Appendix 1, Table 1.10):* ○ *Seroconversion rate:* - *Vaccine: 98.25%* - *Placebo: 14.91%* ○ *Geometric mean titer:* - *Vaccine: 8,996 (95% CI: 7,610 to 10,635)* - *Placebo: 30.55 (95% CI: 20.18 to 46.26)* ● ***Neutralizing antibodies 42 days after the start of vaccination*** *(Appendix 1, Table 1.10):* ○ *Seroconversion rate:* - *Vaccine: 95.83%* - *Placebo: 7.14%* ○ *Geometric mean titer:* - *Vaccine: 44.5 (31.8 to 62.2)* - *Placebo: 1.6 (1.12 to 2.19)* ● ***Subgroup analysis based on age and sex*** *The study reported that the age 18–30 years group (combined male and female) had a significantly higher GMT than the other age groups (p=0·0065). Meanwhile, there were no differences between the other age groups (p=0·343).* ○ ***RBD specific antibodies 42 days after the start of vaccination*** *(Appendix 1, Table 1.11)*	

		■ *18-30 years old* ● *Male - Seroconversion rate- 100%; GMT - 22,067 (95% CI: 11,971 to 40,767)* ● *Female - Seroconversion rate- 100%; GMT - 18,102 (95% CI: 7,689 to 42,616)* ■ *31-40 years old* ● *Male - Seroconversion rate- 100%; GMT - 10,106 (95% CI: 7,047 to 14,494)* ● *Female - Seroconversion rate - 100%; GMT - 10, 925 (95% CI: 6,807 to 17,532)* ■ *41-50 years old* ● *Male - Seroconversion rate- 97.87%; GMT - 6,123 (95% CI: 3,658 to 10,250)* ● *Female - Seroconversion rate- 97.78%; GMT - 7,940 (95% CI: 4,874 to 12,935)* ■ *51-60 years old* ● *Male - Seroconversion rate - 97.78%; GMT - 7,129 (95% CI: 4,466 to 11,379)* ● *Female - Seroconversion rate - 97.44%; GMT: 8,063 (95% CI: 4,715 to 13,789)* ■ *>60 years old* ● *Male - Seroconversion rate- 96.55%; GMT - 8,128 (95% CI: 4,071-16,228)* ● *Female - Seroconversion rate- 96.15%; GMT - 10,908 (95% CI: 5,462-21,785)* ■ *Placebo* ● *Seroconversion rate - 14.91%; GMT - 30.55 (95% CI: 20.18 to 46.26)* ○ ***Neutralizing antibodies 42 days after the start of vaccination*** *(Appendix 1, Table 1.12):* ■ *18-30 years old - Seroconversion rate- 85.71%; GMT - 53.84 (95% CI: 8.198 to 353.5)* ■ *31-40 years old - Seroconversion rate- 100%; GMT -*	

		72.94 (95% CI: 44.25 to 120.2) ■ *41-50 years old - Seroconversion rate- 90.91%; GMT - 48.32 (95% CI: 22.21 to 105.1)* ■ *51-60 years old - Seroconversion rate- 100.00%; GMT - 28.75 (95% CI: 16.71 to 49.49)* ■ *>60 years old - Seroconversion rate- 100.00%; GMT - 36.23 (95% CI: 13.21 to 99.35)* ■ *Placebo - Seroconversion rate - 7.14%; GMT - 1.562 (95% CI: 1.117 to 31.79)* *Cellular immune response was observed through the production of IFNγ of peripheral blood mononuclear cells (PBMC) upon SARS-CoV-2 antigen restimulation. Serum samples from 58 participants (44 from the vaccine group and 14 from the placebo group) were analysed. At day 28 after vaccination, all participants in the vaccine arm were found to have higher levels of IFNγ secretion upon antigen restimulation.* ● ***Median antigen-specific PBMC cell IFNγ production*** *(Appendix 1, Table 1.13):* ○ *<u>Before vaccination:</u>* ■ *Vaccine (n=44)* - *Unstimulated: 0.498* - *Antigen stimulated: 0.439* ■ *Placebo (n=14)* - *Unstimulated: 0.408* - *Antigen stimulated: 0.547* ○ *<u>At 28 days after administration</u>* ■ *Vaccine (n=44)* - *Unstimulated: 0.432* - *Antigen stimulated: 32.770* ■ *Placebo (n=14)* - *Unstimulated: 0.475*	

		- *Antigen stimulated: 0.410* **HTAC Judgment**: Sputnik V Gam-COVID-Vac COVID-19 Vaccine passed the minimum VE threshold against symptomatic COVID-19. The Sputnik V Gam-COVID-Vac COVID-19 Vaccine reported a minimum median follow-up period of 27 days and vaccine efficacy of 91.1%. The reported follow-up period for the said vaccine falls short of the 2-month median follow-up after completion of full vaccination regimen as set by the HTAC to exclude any effect due to innate immunity or immediate post-vaccination neutralization antibody titers of short duration. This 2-month median follow-up period that the HTAC has set is consistent with the recommendation of WHO (2020), US FDA (2021) and other regulatory agencies. However, the HTAC accepts the short follow-up period because it deems that the 91.1% vaccine efficacy is unlikely to become lower than 50% with a longer follow-up period. Rates of disease onset were similar for the vaccine and placebo groups until about 16 to 18 days after the first dose. Thereafter, the number of cases in the vaccine group increased much more slowly than in the placebo group indicating an effect of early and sustained protection over at least 80 days (Appendix 1, Figure 1). Further, the interim results reached the target number of events to trigger an interim analysis described in the trial protocol, and was the basis for the EUA issued by the Philippine FDA.	

	What is the duration of protection of the Sputnik V Gam-COVID-Vac COVID-19 Vaccine in terms of reducing the incidence and/or severity of COVID-19?	Current interim evidence shows protection against laboratory-confirmed symptomatic COVID-19 infection based on a median follow up period of 48 days after dose 1. Data on the duration of protection will be reassessed as more evidence becomes available. **HTAC Judgment:** Cannot be assessed based on current data	**Minimum acceptable duration of protection:** confers at least 6 months protection **Preferred:** ≥1-year protective immunity *Reference: WHO Target Product Profile for COVID-19 Vaccines, 2020*
	What are the safety issues and incidence of adverse events caused by the Sputnik V Gam-COVID-Vac COVID-19 Vaccine?	The evidence review on efficacy was based on both trials and real world data. For the evidence from trials, we reviewed the same phase I/II trial (Logunov et al, 2020); and, one phase III trials which reported its interim results in a published manuscript (Logunov et al., 2021) and in an unpublished report (sponsor submission) which reports the same data set but with more details on adverse events. The median follow up period for the trial was 48 days after the 1st dose (or 27 days after second dose). *The details of the Phase I and II trials are provided in Appendix 1.* **EVIDENCE FROM TRIALS** ***PHASE III trial (N=21,977) (Logunov et al, 2021)*** **Short-term outcomes:** Based on the computed risk ratio, *Sputnik V Gam-COVID-Vac COVID-19 Vaccine* shows higher risk of systemic and local	Local and systemic reactions are tolerable, self-limiting and do not require hospitalization. No serious adverse events were caused by the vaccine. **Short term outcomes** (e.g., reactogenicity and allergic reactions): at least 2 months **Long term outcomes** (e.g., serious AEs): at least 1 year

		reactogenicity when compared to placebo: ● Systemic reactogenicity [RR: 1.76 (95% CI: 1.67 to 1.85)], based on high certainty of evidence ● Local reactogenicity [RR: 5.23 (95% CI: 4.56 to 6.00)], based on high certainty of evidence **Long-term outcomes:** *Sputnik V Gam-COVID-Vac COVID-19 Vaccine* shows inconclusive safety for the following: ● Serious adverse events [RR: 0.65 (95% CI: 0.39 to 1.07)], based on low certainty of evidence ● Death (all-cause mortality) [RR: 0.99 (95% CI: 0.10 to 9.54)], based on low certainty evidence ○ A total of four deaths were reported in the trial publication. Three deaths were in the vaccine group - one from a fractured thoracic vertebra and two from COVID-19 infection. Meanwhile, one death occurred in the control group due to a hemorrhagic stroke. The trial reported that there were no vaccine-related deaths. **EVIDENCE FROM REAL WORLD DATA** ● Regulatory agencies and ministries of health were searched for reports on safety of *Sputnik V Gam-COVID-Vac COVID-19 Vaccine* after its rollout in the following countries: Algeria, Argentina, Bolivia, Pakistan, Russia and UAE. However, as of this writing, only Argentina had published a report. ● **Argentina** (as of 15 March 2021) - 22,912 adverse events were reported. - Of these, 96.8% were events related to the vaccine. - The most common AEs were headache and/or myalgia	

		and/or arthralgia (36.5%) and fever with headaches and/or myalgia (34.1%). *(Source: Argentina Ministerio de Salud, 2021)* **HTAC Judgment:** Short term safety of *Sputnik V Gam-COVID-Vac COVID-19 Vaccine* is acceptable**.** However, further follow-up data is needed to establish longer-term safety. It should not be given to individuals below 18 years old, to those with a known history of hypersensitivity to any component of the vaccine, history of severe allergic reactions, those with acute infectious and non-infectious diseases, flares of chronic diseases, and pregnant women and breastfeeding women (Ministry of Health of the Russian Federation, 2020). While vaccination is not contraindicated in other special populations, the vaccine should be used with caution in cases of the following (based on the package insert): chronic liver and kidney disease, endocrine disorders (apparent thyroid function abnormalities and diabetes mellitus in decompensation stage), serious diseases of the hematopoietic system, epilepsy and other CNS diseases, acute coronary syndrome and acute cerebrovascular event, myocarditis, endocarditis, pericarditis.	
	Does the Sputnik V Gam-COVID-Vac COVID-19 Vaccine provide a highly favorable benefit/risk profile in the context of observed	The current evidence shows that the likely clinical benefits, such as decreased risk of symptomatic COVID-19 infection after 2 doses in the overall study population by 91.1%, outweigh the known short term risks based on data available at the time of evaluation. Evidence on the vaccine efficacy against hospitalization due to	Favorable benefit/risk profile The benefit of preventing morbidity

	vaccine efficacy?	COVID-19 infection, symptomatic COVID-19 in older adults after 2nd dose (n=2,144, 10.79% of trial population), symptomatic COVID-19 in the population with comorbidities (n=4,922, 24.81% of trial population), and, asymptomatic COVID-19 infection were not reported. Further, evidence on long term safety outcomes are still inconclusive; thus, we cannot determine the benefit/risk profile in terms of the long term outcomes. **HTAC Judgment:** PASSED	of at least 50% far outweighs the reported risk of adverse events
3. Affordability and viability	*Is Sputnik V Gam-COVID-Vac COVID-19 Vaccine affordable?*	Based on the projected calculations, the total cost of rolling out vaccination with *Sputnik V Gam-COVID-Vac COVID-19 Vaccine* for 15M Filipinos in 2021 (i.e., target vaccinees for this vaccine profile identified in the vaccination roll out plan) will amount to about Php **17.4 billion.** **HTAC Judgment:** Yes. The vaccine is affordable since the budget for the target number of vaccinees has been allocated.	Affordability will be measured using the sufficiency of the allocated amount to achieve vaccination targets.
	What are the budget implications of using the Sputnik V Gam-COVID-Vac COVID-19 Vaccine?	The total cost of vaccination per individual, which accounts for other costs such as consumables, hauling and storage, and operations, was computed at Php 1,160.85. The potential budget impact of the use of *Sputnik V Gam-COVID-Vac COVID-19 Vaccine* to the national government to cover 15 million Filipinos was calculated at about Php 17.4 billion. It is estimated that **21.1%** of the total allocated budget for	The share of the cost to implement the COVID-19 vaccine within the total vaccination budget is not too disproportionate to the share of the population to be

		vaccination will go to **21%** of the 70 million target vaccinees for 2021. According to the Department of Finance, the price of *Sputnik V Gam-COVID-Vac COVID-19 Vaccine* offered to the Philippine government is equal to or better than the price offered to all countries outside of Russia. **HTAC Judgment:** The share of the cost of the *Sputnik V Gam-COVID-Vac COVID-19 Vaccine* to the total vaccine budget is considered proportionate to the share of the population to be vaccinated using the said vaccine.	vaccinated using the said vaccine in the total population to be vaccinated. **The vaccine unit cost is comparable with those in other ASEAN countries.*
	Does the Sputnik V Gam-COVID-Vac COVID-19 Vaccine represent good value for money in terms of: *a. preventing COVID-19 mortality* *b. lowering hospitalization (moderate, severe and critical cases)* *c. lowering incidence of symptomatic (mild) and asymptomatic cases (RT-PCR*	Whether *Sputnik V Gam-COVID-Vac COVID-19 Vaccine* represents good value for money in terms of preventing COVID-19 mortality, lowering hospitalization (moderate, severe, and critical cases), and lowering the incidence of symptomatic (mild) and asymptomatic cases (RT-PCR confirmed cases) cannot be fully assessed at the moment. Rough estimates of the vaccination cost per case averted are high. However, HTAC has bases to conclude that these will be offset by averted healthcare costs (i.e., total COVID-19-related PhilHealth claims, out of pocket expenditures), economic gains (i.e., in terms of recovery in GDP), and social gains. **HTAC Judgment:** Yes. The HTAC deems that the health, economic, and social benefits of the vaccination program using *Sputnik V Gam-COVID-Vac COVID-19 Vaccine* outweigh the negative impacts such as deaths due to COVID-19, medical costs, loss of productivity, social disruption and unprecedented challenges in the health system.	The health, economic, and social benefits of the vaccination program outweigh the costs. The vaccine is likely cost-effective. *Note: A full-blown cost-effectiveness analysis is currently not done for rapid reviews under a pandemic situation due to its emergency nature. A full-blown cost-effectiveness analysis that takes on a societal perspective (i.e.,*

	confirmed cases)		*including the economic and social impacts) will be performed once sufficient evidence is available and when full market authorization has been granted.*
	Are there significant barriers to vaccine implementation in terms of vaccine storage and transport, handling; adequacy, skills and training of vaccinators; and access of the target population to the health care facility? Are there plans to overcome significant barriers?	The vaccine can be readily stored in a freezer at -18 degrees Celsius. Given this, it is expected that the *Sputnik V Gam-COVID-Vac COVID-19 Vaccine* can be widely distributed to facilities with the said equipment. Like any vaccine implementation, there is still a need for training on vaccine storage and handling to ensure product integrity across the entire supply chain. Trained personnel in handling unreported or rare adverse reactions that could occur following vaccination should also be in place. Further, training on medical supervision and management of special populations such as immunocompromised individuals should be conducted. **HTAC Judgment:** There are no significant barriers in vaccine implementation using *Sputnik V Gam-COVID-Vac COVID-19 Vaccine* in terms of storage, transport, and handling. However, there is still a need for training to: ensure product integrity across the entire supply chain; and, close monitoring of adverse events with emphasis on medical supervision and management on special populations.	There are no significant barriers and if there are, the plans to address the barriers are clearly reflected in the vaccine roadmap and other relevant documents.
4. Household Financial Impact	*Will the Sputnik V Gam-COVID-Vac COVID-19 Vaccine reduce or not*	**<u>For mild COVID-19 pneumonia:</u>** ● PhilHealth has issued the following packages and case rates related to mild COVID-19:	The adoption of the vaccine can reduce out-of-pocket

	add further to the out-of-pocket expenses of Filipino households?	- Isolation Package (C19CI): Php 22,499.00 - Mild COVID-19 pneumonia for elderly and with comorbidities (C19IP1): Php 43,997.00 ● Looking at the actual PhilHealth claims as of January 2021, the isolation package amounted to a median cost of **Php 22,499,** while claims for mild COVID-19 pneumonia for elderly and those with comorbidities amounted to a median cost of **Php 43,997.** ● Reviewing the hospital bills data collected by PhilHealth as of January 2021, the median amount spent by patients for isolation is at **Php 22,499** while mild cases among elderly and those with comorbidities is at **Php 60,020.25.** ● From the same dataset, the calculated median out-of-pocket spending for patients with mild COVID-19 pneumonia is at **Php 16,023.25.** Meanwhile, the median out-of-pocket reported for patients availing of an isolation package is 0. **<u>For moderate COVID-19 pneumonia:</u>** ● PhilHealth has issued a benefit package C19IP2 for moderate COVID-19 pneumonia with a case rate of Php 143, 267. ● Looking at the actual PhilHealth claims for moderate COVID-19 pneumonia as of January 2021, they amounted to a median of **Php 143, 267.00**. ● Reviewing the hospital bills data collected by PhilHealth as of January 2021, the median amount spent by patients with moderate COVID-19 is at **Php 234, 925.13**. ● From the same dataset, the calculated median out-of-pocket spending for patients with moderate COVID-19 pneumonia is at **Php 63,371.30**. **<u>For severe COVID-19 pneumonia:</u>** ● PhilHealth has issued a benefit package C19IP3 for severe	spending of individuals and families due to averted COVID-19 disease and/or hospitalization.

		COVID-19 pneumonia with a case rate of Php 333,519. ● Looking at the actual PhilHealth claims for severe COVID-19 pneumonia as of January 2021, they amounted to a median of **Php 333,519.00**. ● Reviewing the hospital bills data collected by PhilHealth as of January 2021, the median amount spent by patients with severe COVID-19 pneumonia is at **Php 388,904.20**. ● From the same dataset, the calculated median out-of-pocket spending for patients with severe COVID-19 pneumonia is at **Php 388,903.20**. Interim results from the clinical trial have shown its clinical benefit in decreasing the risk of symptomatic COVID-19. However, current interim results did not report vaccine efficacy to reduce the risk of hospitalization due to COVID-19. **HTAC Judgment**: Based on current evidence, *Sputnik V Gam-COVID-Vac COVID-19 Vaccine* has the potential to reduce out-of-pocket expenses of Filipino households due to averted treatment and isolation costs for mild COVID-19.	
5. Social Impact	*Does the Sputnik V Gam-COVID-Vac COVID-19 Vaccine possess the characteristics desired by key stakeholders (i.e., policy- and decision makers, health workers, program managers and/or*	Based on the results of the focus group discussions conducted by the HTAC among *healthcare workers, patient groups, civil society organizations and community leaders* from low- and high-prevalence areas, the results from the deliberations in congressional inquiries on the COVID-19 vaccination roadmap, public hearings, and consultations with government decision-makers and implementers, the following are the important and desirable attributes of COVID-19 vaccines and the corresponding evidences for the *Sputnik V Gam-COVID-Vac COVID-19 Vaccine*:	The vaccine possesses all or most of the characteristics desired by key stakeholders Qualitative responses will contextualize the

	implementers, patient groups, CSOs, communities, general public)? ● *Safety* ● *Efficacy* ● *Transparency in the regulatory/approval process and information on the vaccines* ● *Availability* ● *Potential for high and equitable coverage* ● *Ease in logistical and implementation requirements* ● *Cost-efficiency to the government* ● *Public acceptability* ● *Availability of mechanisms to compensate vaccine recipients for any untoward*	1) Safe and efficacious for the general population (18 years old and older). Evidence: Clinical trial shows acceptable safety profile for known short-term risks and significant efficacy to reduce risk of symptomatic COVID-19. However, there is insufficient efficacy data on hospitalization due to COVID-19 and asymptomatic COVID-19; as well as its efficacy and safety among older adults and populations with comorbidities. 2) Underwent a transparent regulatory process of being evaluated and approved by health authorities - Evidence: The Philippine FDA has issued an EUA for *Sputnik V Gam-COVID-Vac COVID-19 Vaccine*. 3) Potential for high and equitable coverage across the population - Evidence: *Sputnik V Gam-COVID-Vac COVID-19 Vaccine* can be made more available since vaccine handling and storage are within the capacity of the RHUs. 4) Ease in logistics and administration - Evidence: *Sputnik V Gam-COVID-Vac COVID-19 Vaccine* can be stored at -18 degrees Celsius which is present in most RHUs. 5) Cost-effective - Evidence: The health, economic, and social benefits of implementing vaccination program using *Sputnik V Gam-COVID-Vac COVID-19 Vaccine* outweigh the negative impact of COVID-19 such as deaths due to COVID-19, medical costs, loss of productivity, social disruption and unprecedented challenges in the health system	Filipino experience and may impact on implementation strategy

	event following vaccination • *Appropriateness of the vaccine to special at-risk groups and patients with comorbidities*	6) Public acceptability - Evidence: No brand-specific study has been conducted to provide evidence on this characteristic. Available data for COVID-19 vaccines in general based on COVID-19 Vaccine Sectoral surveys conducted by the DOH-Health Promotion Bureau among specific groups shows that: - 70.54% of participants from the Philippine National Police responded that they are willing to get COVID-19 vaccine (February 5-14, 2021). This is an increase from the 56.94% acceptance rate in a similar survey conducted last 29 December 2020 to 8 January 2021. - 68.62% of participants from the Civil Service Commision (excluding DOH, PNP and AFP employees) responded that they are willing to get COVID-19 vaccine (6 February to 3 March 2021). This is an increase from the 44.85% acceptance rate in a similar survey conducted previously (Duration of survey not reported). 7) Availability of mechanisms to compensate vaccine recipients for any untoward event following vaccination - Evidence: The Republic Act 11525 or the COVID-19 Vaccination Program Act of 2021 establishes the COVID-19 National Vaccine Indemnity Fund to provide funds and authorize PhilHealth to pay compensation to any person inoculated through the vaccination program, in the case of death and permanent disability.	

		8) Appropriateness of the vaccine to special at-risk groups and patients with comorbidities
		- Evidence: The latest interim results of *Sputnik V Gam-COVID-Vac COVID-19 Vaccine* did not report the specific vaccine efficacy for the following special populations included in their trial:
		  - older adults *(N =2,144, 10.79% of the trial population) after the 2nd dose*
		  - people with stable comorbidities *(N=4,922, 24.81% of the trial population)*
		  - Asian population *(N=286, 1.44% of the trial population)*
		- Meanwhile, the trial has excluded the following populations:
		  - immunosuppressive or immunodeficient state;
		  - with uncontrolled comorbidities; and
		  - pregnant and lactating women
		
		HTAC Judgment: Based on short-term outcomes, *Sputnik V Gam-COVID-Vac COVID-19 Vaccine* possesses most of the characteristics desired by key stakeholders.	

6. Responsiveness to equity	*How will the Sputnik V Gam-COVID-Vac COVID-19 Vaccine and its use impact pre-COVID and COVID-generated health and socioeconomic inequities?*	While the VE of *Sputnik V Gam-COVID-Vac COVID-19 Vaccine* against symptomatic COVID from the interim results is 91.1% (95% CI: 83.8 to 95.1), it did not report its VE (after 2 doses) for special subpopulation of interest. Further, there may be issues/gaps in access for special and vulnerable populations such as individuals below 18 years old and those with allergy to one of the components of the vaccine.	Ideally, health interventions can be fairly adopted and distributed/ implemented for eligible populations without aggravating existing health

	Which groups might be unfairly disadvantaged in relation to the COVID-19 disease burden and delivery of the Sputnik V Gam-COVID-Vac COVID-19 Vaccine?	*Sputnik V Gam-COVID-Vac COVID-19 Vaccine* can be stored at normal freezing storage conditions (-18 degrees Celsius). This will make vaccine distribution more logistically feasible which in turn does not aggravate inequities for patients living in geographically isolated and disadvantaged areas. Compared to other new vaccines, the price per dose and the logistical and operational cost of *Sputnik V Gam-COVID-Vac COVID-19 Vaccine* allow it to be utilized widely. **HTAC Judgment:** Because of non-stringent logistic requirements, *Sputnik V Gam-COVID-Vac COVID-19 Vaccine* does not aggravate health inequities related to inoculation of recipients residing in isolated and disadvantaged locations. The trial population did not include important vulnerable groups such as individuals with immunosuppressive or immunodeficient state, people with uncontrolled comorbidities, and pregnant and lactating women.	inequities especially for vulnerable sectors of our society.

Appendix 1. Evidence on criterion 2 - Clinical Efficacy and Safety

Evidence from trials were considered on the review of efficacy, while evidence from both trials and available real world data were considered on the review of the safety of this vaccine.

EVIDENCE FROM TRIALS

Available trials on the efficacy and safety included: one published manuscript covering two substudies for Phase I/II trials in Russia which assessed the two formulations of the vaccine (i.e., frozen and lyophilized) among the population aged 18-60 years (N=76) (Logunov et al., 2020); and, interim results from one Phase III randomized clinical trial conducted in Russia (N=21,977) available as a published manuscript (Logunov, et al., 2021) and in an unpublished report version (sponsor submission) which reports the same data set but with more details on adverse events. The median follow up period for the trial was 48 days after the 1st dose.

Phase I/II trials (Logunov et al., 2020)

Study characteristics

The Phase I/II trial of *Sputnik V Gam-COVID-Vac COVID-19 Vaccine* included two open non-randomised sub-studies in selected hospitals in Russia to assess the two formulations of the vaccine - frozen [Gam-COVID-Vac] and lyophilized [Gam-COVID-Vac-Lyo]). For each study, 120 healthy adult volunteers aged 18-60 years were preselected for screening. The trial included adult volunteers of both sexes with body mass index between 18.5 and 30.0 kg/m^2 who had negative PCR test and tested negative for IgG and IgM to SARS-CoV-2, with no history of COVID-19 or contact with patients diagnosed with COVID-19, with no infectious diseases at the time of vaccination and 14 days prior to vaccination, and did not receive any other vaccinations within 30 days of participation in the study. After preliminary screening, 100 volunteers were selected for inclusion in the trial, with 50 participants in each trial.

In Phase I of both sub-studies, participants received one dose of either rAd26-S or rAd5-S intramuscularly. The primary outcome measures for Phase I were safety *(i.e., adverse events from day 0 to day 28 after vaccination)* and immunogenicity *(i.e., change from baseline in antigen-specific antibody levels from day 0 to day 28; virus neutralizing antibody titres on days 0, 14, and 28 after vaccination; and, the determination of antigen-*

specific cellular immunity [specific T-cell immunity and interferon-γ production or lymphoproliferation] on days 0, 14, and 28 after vaccination).

Meanwhile, Phase II of both sub-studies began 5 days after phase 1 vaccination where in participants received prime-boost vaccination with one dose of rAd26-S administered intramuscularly on day 0 and one dose of rAd5-S administered intramuscularly on day 21. The primary outcome measures for Phase II were safety *(i.e., adverse events from day 0 to day 42 after vaccination)* and immunogenicity *(i.e., change from baseline in antigen-specific antibody levels from day 0 to day 42; virus neutralizing antibody titres on days 0, 14, 28, and 42 after vaccination; and, the determination of antigen-specific cellular immunity [specific T-cell immunity and interferon-γ production or lymphoproliferation] on days 0, 14, and 28 after vaccination).* For post-vaccination immunity, RBD-specific and neutralizing antibody titers of vaccinated participants were compared with titres measured from the convalescent plasma of recovered COVID-19 patients.

Findings from the Trials

The Phase I/II trials of the two sub-studies enrolled 38 participants each (18 participants in Phase I and 20 in Phase II). In the Phase I trial, 9 participants received rAd26-S and 9 participants received rAd5S. Meanwhile, in the Phase II trial, all 20 participants received rAD26-S as their first dose and rAd5-S as their second dose. All participants were included in the safety and immunogenicity evaluation.

Phase I

Seroconversion rates and Geometric Mean Titre of RBD-specific antibodies (Table 1.1.)

Analysis of Phase I results of the substudy on the frozen formulation (Gam-COVID-Vac) show that:

- At 14 days after administration, SARS-CoV-2 Receptor-Binding Domain (RBD) -specific antibodies were detected in 100% (GMT 400.0) of participants who were given rAd26-S (n=9) and in 77.8% (GMT 147.0) of participants who received rAd5-S (n=9).
- At 28 days after administration, seroconversion rates for both groups were reported to reach 100% (rad26-S GMT 1866; rad5-S GMT 2352).

Meanwhile for the lyophilized formulation (Gam-COVID-Vac-Lyo) substudy:

- At 14 days after administration, the seroconversion rates were:
  - 77.8% (GMT 46.29) for participants administered with rAd26-S (n=9)
  - 88.9% for those given rAd5-S (GMT 158.7) (n=9)
- At 28 days after administration, both groups reached 100% seroconversion rates (rad26-S GMT 1372; rad5-S GMT 2963).

Seroconversion rates and Geometric Mean Titre of Neutralizing Antibodies (Table 1.1.)

Administration of frozen (Gam-COVID-Vac) demonstrated at 28 days after administration that:

- The seroconversion rate for participants administered with frozen rAd26-S is at 66.7 % (GMT 4.286) (n=9).
- The seroconversion rate for participants administered with frozen rAd5-S was also reported to be at 66.7% (GMT 6.300) (n=9).

For the substudy on the lyophilized formulation at 28 days after administration:

- The seroconversion rates in participants administered with lyophilized rAd26-S was reported to be 55.6% (GMT 3.674) (n=9).
- The seroconversion rates in participants administered with lyophilized rAd5-S was reported to be 88.9% (GMT10.80) (n=9).

Table 1.1. Phase I data on seroconversion rates of RBD- specific antibodies at days 0, 14, 21 and 28 and Neutralizing Antibodies (NtAb) at days 0, 14 and 28. Titer of 12.5 (RBD- specific antibodies) and 1.25 (NtAb) are baseline characteristics that correspond with volunteers "non-responder".

Days after vaccination	**Gam-COVID -Vac** (Frozen Formulation)				**Gam-COVID-Vac-Lyo** (Lyophilized Formulation)			
	rAd26-S (n=9)		**rAd5-S (n=9)**		**rAd26-S (n=9)**		**rAd5-S (n=9)**	
	% Sero-conversion rate	**Geometric Mean Titer (95% C)I**	**% Sero-conversion rate**	**Geometric Mean Titer (95% C)I**	**% Sero-conversion rate**	**Geometric Mean Titer (95% C)I**	**% Sero-conversion rate**	**Geometric Mean Titer (95% C)I**
RBD-Specific Antibodies								
Day 0	0	12.5	0	12.5	0	12.5	0	12.5
Day 14	100	400.0 (142.6 to 1122)	77.8	147.0 (26.09 to 828.0)	77.8	46.29 (19.57 to 109.5)	88.9	158.7 (39.77 to 633.7)
Day 21	100	1,866 (1,122 to 3,132)	100	2,177 (1,020 to 4,650)	100	1089 (509.8 to 2325)	100	2,016 (5,32.1 to 7,637)

Day 28	100	1,866 (1,122 to 3,132)	100	2,352 (1,052 to 5,255)	100	1372 (685.5 to 2744)	100	2,963 (1,366 to 642)
Neutralizing Antibodies								
Day 0	0	1.250	0	1.250	0	1.250	0	1.250
Day 14	55.6	3.402 (1.52 to 7.60)	55.6	4.286 (1.44 to 12.76)	22.2	1.984 (:0.93 to 4.22)	66.7	4.286 :2.94 to 9.01)
Day 28	66.7	4.286 (1.95 to 9.44)	66.7	6.30 (2.33 to 17.07)	55.6	3.674 (1.58 to 8.57)	88.9	10.80 (4.39 to 26.6)

Median cell proliferation of antigen-specific T-helper (CD4+) and T-killer (CD-8+) cells (Table 1.2.)

Analysis of Phase I results of the substudy on the frozen formulation (Gam-COVID-Vac) show that at 28 days after vaccination:

- rad26-S (n=9) arm showed median cell proliferation of 0.60% and 0.30% for CD4+ and CD8+ cells, respectively.
- rad5-S (n=9) arm demonstrated median cell proliferation of 1.10% and 1.40% for CD4+ and CD8+ cells, respectively.

Meanwhile, for the lyophilized formulation (Gam-COVID-Vac-Lyo) substudy at 28 days after vaccination:

- rad26-S (n=9) arm showed median cell proliferation of 0.20% and 0.40% for CD4+ and CD8+ cells, respectively.
- rad5-S (n=9) arm was found to have median cell proliferation of 0.40% and 0.80% for CD4+ and CD8+ cells, respectively.

Table 1.2. Detected CD4+ and CD8+ proliferative cellular immune response and median cell proliferation of antigen specific CD4+ and CD8+ cells at days 0, 14, and 28 in participants immunized with rAd26-S (n=9) or rAd5-S (n=9) only

Days after vaccination	**Gam-COVID -Vac** (Frozen Formulation)		**Gam-COVID-Vac-Lyo** (Lyophilized Formulation)	
	rAd26-S (n=9)	**rAd5-S (n=9)**	**rAd26-S (n=9)**	**rAd5-S (n=9)**
CD4+				
Day 0	0	0	0	0
Day 14	0	0	0	0
Day 28	0.60	1.10	0.20	1.60
CD8+				
Day 0	0	0	0	0
Day 14	0	0	0	0
Day 28	0.30	1.40	0.40	0,80

Adverse events

Adverse events among the study participants from day 0 to day 28 after vaccination were observed. Among the reported local and systemic adverse events, the most common were vaccination site pain (24 [66.7%]), headache (16 [44.4%]), and hyperthermia (12 [33.3%]). Meanwhile, reported changes in laboratory variables were mild and transient. No occurrence of adverse events led to the withdrawal of any participant from the study. No serious adverse events were also reported in this trial.

Phase II

Seroconversion rates and Geometric Mean Titres of RBD-specific antibodies (Table 1.3).

Analysis of Phase II results of the substudy on the frozen formulation [COVID-Vac (rAd26-S + rAd5-S)] and lyophilized formulation [Gam-COVID-Vac-Lyo(rAd26-S + rAd5-S)] show that:

- At 14 days after administration of rAd26-S and rAd5-S, SARS-CoV-2 RBD-specific antibodies were detected in 95% (GMT 132.0) of participants given

with the frozen formulation (n=20), and in 75% (GMT 50.0) of participants given with the lyophilized formulation (n=20).

- At 21 days after administration of rAd26-S and rAd5-S, seroconversion rates for both frozen and lyophilized formulation arms were reported to reach 100% (frozen GMT 1,345; lyophilized GMT 951.4).

Meanwhile upon comparison of RBD- specific antibody levels between vaccinated participants and recovered COVID-19 patients (through convalescent plasma) at 28 and 42 days after administration, post-vaccination ELISA titres (at 28 days after administration: frozen GMT 5,382; lyophilized GMT 5,322; at 42 days after administration, frozen GMT 14,703; lyophilized GMT 11,143) were observed to be significantly higher than titres after COVID-19 infection (at 28 and 42 days after administration, GMT 1,266) (p<0·0001).

Seroconversion rates Geometric Mean Titres of Neutralizing Antibodies (Table 1.3.)

Administration of either frozen formulation [COVID-Vac (rAd26-S + rAd5-S)] or lyophilized formulation [Gam-COVID-Vac-Lyo(rAd26-S + rAd5-S)] at 28 days after vaccination shows that:

- The seroconversion rate for participants administered with frozen formulation [COVID-Vac (rAd26-S + rAd5-S)] is at 95% (GMT 16.25) (n=20).
- The seroconversion rate for participants administered with lyophilized formulation [Gam-COVID-Vac-Lyo(rAd26-S + rAd5-S)] was also reported to be at 95% (GMT 21.44) (n=20).

Meanwhile participants from both the frozen formulation [COVID-Vac (rAd26-S + rAd5-S)] (GMT 49.25) and lyophilized formulation [Gam-COVID-Vac-Lyo(rAd26-S + rAd5-S)] (GMT 45.95) groups showed 100% seroconversion at 42 days after administration.

Table 1.3. Phase II data on Seroconversion rates of RBD- specific antibodies at days 0, 14, 21, 28 and 42; and Neutralizing Antibodies at days 0, 14, 28 and 42 in patients immunized with rAd26-S + rAd5-S (n=20) and in COVID-19 convalescents at ~1 month after recovery. Titer of 12.5 (RBD-specific) and 1.25 (NtAb) are baseline characteristics that correspond with volunteers "non-responder".

Days after vaccination	**COVID-Vac (rAd26-S + rAd5-S)** (Frozen Formulation) **n=20**		**Gam-COVID-Vac-Lyo (rAd26-S + rAd5-S)** (Lyophilized Formulation) **n=20**		**Convalescent n=4,817**	
	% Sero-conversion rate	**Geometric Mean Titer (95% C)I**	**% Sero-conversion rate**	**Geometric Mean Titer (95% C)I**	**% Sero-conversion rate**	**Geometric Mean Titer (95% C)I**
RBD-Specific Antibodies						
Day 0	0	12.5	0	12.5	85.8	1,266 (1,066 to1,504)
Day 14	95	132.0 (69.32 to 251.2)	75	50.00 (28.37 to 88.13)		
Day 21	100	1,345 (756.9 to 2,392)	100	951.4 (485.4 to1.865)		
Day 28	100	5,382 (3,538 to 8,185)	100	5,322 (3,184 to 8,894)		
Day 42	100	14,703 (9,576 to 22,576)	100	11,143 (7,786 to 15,947)		
Neutralizing Antibodies						
Day 0	0	1.250	0	1.250	90.9	32.96 (31.49 to 34.50)
Day 14	65	4.83 (2.78 to 8.39)	25	1.96 (1.34 to 2.88)		
Day 28	95	16.25 (10.38 to 25.42)	95	21.44 (13.91 to 33.04)		
Day 42	100	49.25 (33.17 to 73.12)	100	45.95 (32.11 to 65.76)		

Formation of antigen-specific T-helper (CD4+) and T-killer (CD-8+) cells

Cellular immune response was demonstrated by the formation of antigen-specific cells of both T-helper (CD4+) and T-killer (CD8+) cells. Particularly, cells from vaccinated participants proliferated significantly in response to glycoprotein S on day 28 for both formulations. The number of participants with CD4+ and CD8+ proliferative cellular immune response to antigen can be seen in Table 1.4.

Meanwhile, median cell proliferation at day 28 was also reported to be higher in the frozen formulation with 2.50% and 1.30% for CD4+ and CD8, respectively, than in the lyophilized formulation with 1.30% and 1.10% for CD4+ and CD8+, respectively. Detected median cell proliferation at days 14 at 28 for both formulations are found in Table 1.4.

Table 1.4. Detected CD4+ and CD8+ proliferative cellular immune response and **median cell proliferation** of antigen specific CD4+ and CD8+ cells at days 14 and 28 in participants immunized with frozen or lyophilized formulation of Gam-COVID-Vac

Days after vaccination	**Gam-COVID -Vac** (Frozen Formulation) **(rAd26-S + rAd5-S) n = 20**		**Gam-COVID-Vac-Lyo** (Lyophilized Formulation) **(rAd26-S + rAd5-S) n = 20**	
	CD4+	**CD8+**	**CD4+**	**CD8+**
Detected cellular immune response				
Day 14	11 (55.00%)	13 (65.00%)	12 (60.00%)	12 (60.00%)
Day 28	17 (85.00%)	17 (85.00%)	20 (100.00%)	20 (100.00%)
Median cell proliferation				
Day 14	0.25	0.15	0.20	0.30
Day 28	2.50	1.30	1.30	1.10

Safety (adverse events, Table 1.4.)

Adverse events among participants were observed from day 0 to day 42 after vaccination. Given its two-dose dosing schedule (one dose of rAd26-S on day 0 and one dose of rAd5-S on day 21), it was observed that most adverse events have occurred after the second vaccination. However, no occurrence of adverse events led to the withdrawal of any participant from the study. No serious adverse events were also reported in Phase II of the trial. Generally, the adverse events observed were characteristic of other vaccines. Table 1.4 shows the result of the Phase I/II safety evaluation.

Table 1.4 Number of participants who reported systemic and local adverse events on healthy adults aged 18-60 years (from day 0 to 42)

Outcomes	Gam-COVID-Vac (Frozen Formulation)			Gam-COVID-Vac-Lyo (Lyophilized Formulation)		
	rAd26-S (n=9)	rAd5-S (n=9)	rAd26-S plus rAd5-S (n=20)	rAd26-S (n=9)	rAd5-S (n=9)	rAd26-S plus rAd5-S (n=20)
Systemic reactions						
Hyperthermia	8	3	20	1	1	7
Headache	6	3	11	3	4	5
Asthenia	3	3	11	0	0	4
Muscle and joint pain	3	2	5	1	2	6
Heartbeat (subjective palpitation)	3	1	0	0	0	0
Diarrhea	1	0	3	0	0	0
Rhinorrhea	0	0	4	0	0	0
Loss of appetite	2	0	1	0	0	0
Pharyngalgia	0	1	1	0	0	0
Malaise	0	0	2	0	0	0
Sore throat	0	0	2	0	0	0
Hives	1	0	0	0	0	0
Nasal congestion	0	0	1	0	0	0
Cough	0	0	1	0	0	0
Sneezing	0	0	1	0	0	0
Changes in laboratory variables	9	9	20	7	6	18
Local reactions						
Pain	7	5	8	5	7	12
Edema	0	0	0	2	1	0
Hyperthermia	0	0	2	0	1	0
Itch	1	0	0	0	0	0
Swelling	0	0	1	0	0	0

Phase III trial (Logunov et al., 2021)

Study characteristics

The trial is a randomized, double-blind (patient and assessor) placebo-controlled, Phase III trial to study the efficacy, immunogenicity and safety of the *Sputnik V Gam-COVID-Vac COVID-19 Vaccine* combined vector vaccine involving 21,977 in adults aged 18 to 111 years (mean age = 45.3 years). The trial was initiated on September 7, 2020 across 25 hospitals and polyclinics in Moscow, Russia. The trial sought to determine the efficacy of *Sputnik V Gam-COVID-Vac COVID-19 Vaccine* against the SARS-CoV-2 infection, based on the severity of the clinical course of COVID-19 from day 21 after receiving the first dose (i.e at the time of the 2nd dose), and 7 days after the 2nd dose, and the incidence and severity of adverse events. The median follow up time when the first interim results were published on February 20, 2021 was 48 days.

The trial was funded by the Moscow City Health Department, Russian Direct Investment Fund, Sberbank and RUSAL. They declared to have no role in study design, data collection, data analysis, data interpretation, or writing of the report. The manuscript declared the following: All of the authors were affiliated with the Ministry of Health of the Russian Federation, and were responsible for the design and conduct of the trial, data collection, analysis and interpretation of the data, write-up of the manuscript and approval of the final version of the paper. Some of the authors reported patents for an immunobiological expression vector, pharmaceutical agent and its method of use to prevent COVID-19. The declared study sponsors were the Gamaleya Research Institute of Epidemiology and Microbiology and the Health Ministry of the Russian Federation. Apart from the published trial results, we also referred to the supporting documents submitted by Gamaleya in its application for emergency use authorization to the Food and Drug Association Philippines.

The participant inclusion criteria of the study were as follows: age 18 years or older; negative HIV, hepatitis B and C, and syphilis test results; negative anti-SARS-CoV-2 IgM and IgG antibody and SARS-CoV-2 PCR tests; no history of COVID-19; no contact with anyone with COVID-19 in the preceding 14 days; consent to use effective contraceptive methods; negative urine pregnancy test (for women of child-bearing potential); negative drug and alcohol tests at screening visit; no history of vaccine-induced reactions; and no acute infectious or respiratory disease in the 14 days before enrolment. Exclusion criteria were any vaccination in the 30 days before enrolment; steroids or

immunoglobulins in the 30 days before enrolment; immunosuppression in the three months before enrolment; pregnancy or breastfeeding; acute coronary syndrome or stroke in the year before enrolment; tuberculosis or chronic systemic infections; allergy or hypersensitivity to the drug or components; neoplasms; blood donation in the two months before enrolment; splenectomy; neutropenia, agranulocytosis, significant blood loss, severe anaemia, or immunodeficiency in the 6 months before enrolment; active form of a disease caused by HIV, syphilis, or hepatitis B or C; anorexia or protein deficiency; large tattoos at the injection site; history of alcohol or drug addiction; participation in any other clinical trial; study centre staff or other employees directly involved in the trial or their families; or any other condition deemed a problem by the study physician.

Randomization was performed in a ratio of 3:1 to the vaccine group or the placebo group. The vaccine group received a full dose of 10^{11} viral particles per dose administered intramuscularly with a 21-day interval. The first dose contained the rAd26-S vector component and the second dose, the rAd5-S. The placebo group consisted of the vaccine buffer composition, but without the recombinant adenoviruses. The planned follow up visits were at day 28, day 42 and day 180 after dose 2. The primary and secondary outcomes of interest in the trial are as follows:

- *Primary Outcome:* Proportion of participants with COVID-19 confirmed by PCR from day 21 after receiving the first dose.
- *Secondary Outcomes*: Severity of COVID-19; Changes in antibody levels against SARS-CoV-2 glycoprotein; proportion of participants with antibodies against SARS-CoV-2 N-protein; changes (increase) in SARS-CoV-2 neutralizing antibody titers; changes (increase) in antigen-specific cellular immunity level and incidence and severity of adverse events.

  Vaccine efficacy (VE) was calculated using the formula: (1-OR) x 100, where OR is as follows :

  OR = (a/b) / (c/d) = (a x d) / (b x c)
  where :
  a = number of vaccinated participants with COVID-19
  b = number of vaccinated participants without COVID-19
  c – number of unvaccinated participants with COVID-19
  d – number of unvaccinated participants without COVID-19

Primary efficacy and safety analysis included all participants who had received at least two doses at the time of database lock (November 24, 2020), excluding those with protocol violations. On the other hand, analysis of serious adverse events included all participants who had received at least one dose without protocol violations. Generally, per protocol analysis was utilized for all outcomes.

Appraisal Methodology

The HTAC's clinical research question elements are as follows:

Population: General and vulnerable population

Intervention: Gam-COVID-Vac vaccine

Comparator: Placebo (vaccine buffer)

Outcomes: Vaccine efficacy (VE) and safety (see table below for details)

Table 1.5. Definitions and rating of importance of efficacy outcomes of interest

Name of outcome	Definition	HTAC rating of outcome importance
Vaccine efficacy (VE) against symptomatic COVID-19 after dose 2	Positive Nucleic Acid Amplification Test (NAAT) and the following symptoms after dose 2: ● Acute onset of any of three or more signs and symptoms: fever, cough, general weakness/fatigue, headache, myalgia, sore throat, coryza, dyspnea, anorexia/nausea/vomiting, diarrhea, altered mental status ● Anosmia (loss of smell), ageusia (loss of taste) in the absence of any other identified cause *Reference: WHO COVID-19 case definitions*	**CRITICAL** to decision making
VE against Hospitalization due to COVID-19	Hospital admission for the management of COVID-19	**CRITICAL** to decision making
VE Severe COVID-19 Occurrence after dose 1	Symptomatic COVID-19 after dose 1 with the addition of the following clinical manifestations: pneumonia, severe acute respiratory syndrome, multi-organ failure, and death *Reference: US FDA*	**CRITICAL** to decision making
VE Severe COVID-19 Occurrence after dose 2	Symptomatic COVID-19 after dose 2 with the addition of the following clinical manifestations: pneumonia, severe acute respiratory syndrome, multi-organ failure, and death *Reference: US FDA*	**CRITICAL** to decision making

VE against symptomatic COVID-19 after Dose 1	Positive Nucleic Acid Amplification Test (NAAT) and the following symptoms after dose 1: ● Acute onset of any of three or more signs and symptoms: fever, cough, general weakness/fatigue, headache, myalgia, sore throat, coryza, dyspnea, anorexia/nausea/vomiting, diarrhea, altered mental status ● Anosmia (loss of smell), ageusia (loss of taste) in the absence of any other identified cause *Reference: WHO COVID-19 case definitions*	**IMPORTANT** but not critical to decision-making
VE against symptomatic COVID-19 among older adults after dose 2	Positive Nucleic Acid Amplification Test (NAAT) and the following symptoms after dose 2 in older adults as defined in the trials: ● Acute onset of any of three or more signs and symptoms: fever, cough, general weakness/fatigue, headache, myalgia, sore throat, coryza, dyspnea, anorexia/nausea/vomiting, diarrhea, altered mental status ● Anosmia (loss of smell), ageusia (loss of taste) in the absence of any other identified cause *Reference: WHO COVID-19 case definitions*	**IMPORTANT** but not critical to decision-making
VE against symptomatic COVID-19 among population with comorbidities after dose 2	Positive Nucleic Acid Amplification Test (NAAT) and the following symptoms after dose 2 in population with comorbidities: ● Acute onset of any of three or more signs and symptoms: fever, cough, general weakness/fatigue, headache, myalgia, sore throat, coryza, dyspnea, anorexia/nausea/vomiting, diarrhea, altered mental status ● Anosmia (loss of smell), ageusia (loss of taste) in the absence of any other identified cause *Reference: WHO COVID-19 case definitions*	**IMPORTANT** but not critical to decision-making
VE against asymptomatic COVID-19	Absence of COVID-19 symptoms but with positive NAAT results	**IMPORTANT** but not critical to decision-making

Table 1.6. Definitions and rating of importance of safety outcomes of interest

Name of outcome	Definition	HTAC rating of outcome importance
Serious adverse events	An adverse event is any undesirable experience associated with the use of a vaccine. The event is serious when the patient outcome is: ● Death ● Life threatening ● Hospitalization (initial or prolonged) ● Disability of permanent damage ● Congenital anomaly/ birth defect ● Required intervention to prevent permanent impairment of damage ● Other serious events which may jeopardize the patient and may require medical or surgical intervention to prevent one of the other outcomes *Reference: US FDA*	**CRITICAL** to decision making
Death (All-cause mortality)	Reported deaths regardless of cause	**CRITICAL** to decision making
Systemic reactogenicity (Dose 1)	General systemic reactions to injectable products such as vaccines include nausea/vomiting, diarrhea, headache, fatigue, and myalgia *Reference: US FDA*	**CRITICAL** to decision making
Systemic reactogenicity (Dose 2)		
Local reactogenicity (Dose 1)	Local reaction to injectable products such as vaccines include pain, tenderness, erythema/redness, and induration/ swelling *Reference: US FDA*	**IMPORTANT** but not critical to decision-making
Local reactogenicity (Dose 2)		

Table 1.7. presents which of the study outcomes match the HTAC outcomes of interest.

Table 1.7. HTAC outcomes of interest and the corresponding outcomes reported by Logunov et al., 2021

HTAC outcome of interest	**Matching reported outcome from the *Gam-COVID-Vac Vaccine* trial** *(Logunov, et al., 2021)*	**Definition of outcome from the*Gam-COVID-Vac Vaccine* trial** *(Logunov, et al., 2021)*
Efficacy outcomes		
VE against symptomatic COVID-19 after dose 2	VE against first COVID-19 occurrence after dose 2 (28 days after dose 1) (includes those who received both doses)	COVID-19 in participants ≥7 days after dose 2 Assumed to be the sum of cases of Mild, Moderate, Severe and Extremely Severe COVID. Mild COVID: body temp below 38.5 degrees Celsius, cough, weakness, sore throat; no symptoms of moderate and severe course Moderate COVID : Fever over >38.5'C, RR >22/min, shortness of breath during physical exertion, pneumonia (confirmed by lung CT), O2sat <95%, CRP >10ml/l Severe COVID: RR >30/min, O2sat <= 93%, O2 partial pressure / F1O2 <= 300mmHg, progression of changes in the lungs by X-ray. CT, ultrasonography; decreased level of consciousness, agitation; unstable hemodynamics (SBP< 90mmHg or DBP <60mmHg, diuresis <20ml/hr), arterial blood lactate >2 mmol/L, more than 2 points on the SOFA scale Extremely severe COVID: ARF with the need for respiratory support (invasive mechanical ventilation), septic shock, multiorgan failure, changes in the lungs on CT (xray) typical of a critical viral lesion (lesion volume Is significant or subtotal; 4 (CT) or an evidence on ARDS
VE against hospitalization due to COVID-19	Not reported	Not reported
VE against severe COVID-19 after dose 1	Not reported	Not reported

VE against severe COVID-19 after dose 2	Reported as VE against first moderate OR severe COVID-19 occurrence from 21 days after dose 1 (day of dose 2), includes those who received both doses	Separate VEs for Moderate and Severe COVID derived and calculated based on the separate counts for moderate and severe cases provided by Gamaleya to the Philippine FDA. Definitions for moderate and severe as above
VE against symptomatic COVID-19 after dose 1	VE against first COVID-19 occurrence after dose 1 (includes participants who received at least one dose) - at anytime after dose 1 - from 14 days after dose 1	First COVID-19 occurrence after dose 1 COVID-19: assumed to include mild, moderate, severe and extremely severe, as defined above
VE against symptomatic COVID-19 after dose 2 in older adults	VE against against first COVID-19 occurrence from 21 days after dose 1 (day of dose 2), includes those who received both doses, among >60 years	First occurrence of COVID-19 21 days after dose 1: mild, moderate, severe and extremely severe infections (as defined above), in participants over 60 years old
VE against symptomatic COVID-19 after dose 2 in population with comorbidities	Not reported	Not reported
VE against asymptomatic COVID-19	Not reported	Asymptomatic – participants with a positive PCR test result done on the day of the second dose, without signs of respiratory infection
Safety outcomes		
Serious adverse events	Serious adverse events (rates provided)	Diagnosed on the basis of the event requiring hospitalization, adjudicated
Death (all-cause mortality)	Deaths (counts and descriptions)	Reported as all cause
Systemic reactogenicity	Adverse events (counts)	Reported as adverse events (i.e., influenza-like illness, hyperthermia, asthenia, chills pyrexia, sensation of fever, hyperhidrosis, malaise, disorder of the regulation of the autonomic nervous system, headache, myalgia, musculoskeletal pain, pain on

		the back side, nausea, diarrhea and decreased appetite)
Local reactogenicity	Adverse events (counts)	Reported as adverse events (i.e., reaction at injection site)

The methodological assessment of the quality of the evidence was based on the evaluation of the trial publication using the Cochrane risk of bias tool (RoB version1) which was performed by the Living CPG Group and independently appraised by the HTAC. Two reviewers independently appraised the study and any disagreements between the reviewers were resolved through consensus. After which, certainty of the evidence was appraised by two reviewers through the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) Approach.

Findings from the Trial

Clinical efficacy and safety outcomes

The interim results covered data gathered from 7 September 2020 to 24 November 2020, during which 21,977 adults were randomly assigned to receive the vaccine (n=16,501) or placebo (n=5,476), in a 3:1 distribution. The participants included in the outcome analysis totalled 19,866 (vaccine group = 14964, placebo group = 4902). The mean ages in both treatment groups was 45.3 years, with 10.8% older than 60 years of age. Nearly all were White (98.5%) and Asians comprised only 1.4% of the study population. There were slightly more males (61.2% vs 38.8%). One fourth of the study population had concomitant diseases. Less than 1% of the population were considered to be of high risk of COVID infection (defined as those whose work involves interaction with patients with a confirmed diagnosis of COVID-19). Demographic characteristics were well balanced between the vaccine and the placebo groups. The median follow up for the interim report was 48 days after the first dose.

Of the eight efficacy outcomes and four safety outcomes of interest to the HTAC, the current trial has measured and reported six. For this report, the vaccine efficacy against severe COVID-19 was calculated based on the breakdown of the reported cases of moderate and severe cases in the placebo group provided for by the sponsor

in its FDA EUA application. Below are the outcomes measured and reported by the trial and the matching outcomes of interest in our research question:

The results of our appraisal of the clinical evidence on the efficacy and safety of the *Sputnik Gam-COVID-Vac COVID-19 Vaccine* using the GRADE approach (in collaboration with the Living CPG Group) are shown in Table 1.8 and Table 1.9. respectively. Methodological assessment of the quality of the evidence showed a low risk of bias in the domains concerning randomization, allocation concealment, blinding and selective reporting.

In the calculation of vaccine efficacy (VE), the point estimate was computed using the formula 100 x (1-HR), where HR is the risk ratio. Overall, *Sputnik V Gam-COVID-Vac COVID-19 Vaccine* showed benefit in the short term (median follow up of 48 days) for the identified outcomes of interest compared to placebo. *Sputnik V Gam-COVID-Vac COVID-19 Vaccine* was reported to have an efficacy of 91.1% (95% CI: 83.8 to 95.1) against symptomatic COVID-19 after dose 2 compared to placebo, based on high certainty of evidence. In terms of VE against symptomatic COVID-19 after dose 1, it has shown an efficacy of 91.6% (95% CI: 85.6 to 95.2), based on high certainty of evidence. Meanwhile, for VE against moderate COVID-19 after dose 1 is reported to be 100%, based on low certainty of evidence due to the low number of events. This is based on zero events out of 14,964 subjects in the vaccine group and 19 events out of 4,902 subjects in the control group. On the other hand, the efficacy of *Sputnik V Gam-COVID-Vac COVID-19 Vaccine* against severe COVID-19 after dose 1 is reported to be 100%, based on low certainty of evidence owing to the paucity of events recorded. This is based on zero events among 14,964 participants in the vaccine group and 1 event among 4,902 participants in the control group. Lastly, the VE against symptomatic COVID-19 after dose 2 in the older population (>60 years old) was reported to be 91.8% (95% CI: 67.1 to 98.3), based on high certainty of evidence.

Detailed adverse event data were not available for the *Sputnik V Gam-COVID-Vac COVID-19 Vaccine*, pending verification by the independent assessors in the trial. The most common adverse events reported in the trial were flu-like illness, injection site reactions, headache and asthenia and were mostly mild (grade 1) in severity. Adverse events considered as systemic and local reactogenicity were not explicitly identified in the report. Thus, the HTA Joint Subcommittee on Vaccines and Preventive and

Promotive Health identified reported adverse events which can be classified as systemic and local reactogenicity. The computed relative risks showed that the use of *Sputnik V Gam-COVID-Vac COVID-19 Vaccine* increases the risk of systemic reactogenicity by 1.76 times (95% CI: 1.67 to 1.85) compared to placebo, with a high certainty of evidence; and also increases the risk of local reactogenicity by 5.23 times (95% CI: 4.56 to 6.00) compared to placebo, with a high certainty of evidence, As for severe adverse events, participants who received the vaccine, compared to those who received placebo, and followed up for a median period of 48 days generally reported similar counts of severe adverse events, when taken in the context of the sample sizes of the two treatment groups. Ninety one severe (grade 3) adverse events were reported in the vaccine group while 31 events were reported in the placebo group. Similarly, rates for serious adverse events were similar between the two groups (0.3% vs 0.4%). No association was found between serious adverse events and vaccine administration in the trial. During the short follow up time, more deaths (3 vs 1) were reported in the vaccine group. But again, when taken in the context of a 3:1 population size distribution between the two groups, mortality rates seem equivalent. Three deaths (<0.1%) were in the vaccine group, one from a fractured thoracic vertebra and two from COVID-19 infection. The first patient developed symptoms 4 days after vaccination with the first dose and had severe cardiopulmonary disease. The second patient developed symptoms 5 days after vaccination with the first dose and had uncontrolled endocrinological and cardiopulmonary comorbidities. One death (<0.1%) occurred in the placebo group due to a hemorrhagic stroke. The computed relative risks for both serious adverse events (RR = 0.65; 95%CI: 0.39 to 1.07) and death (RR = 0.99; 95%CI: 0.10 to 9.54) were inconclusive, both with low certainty of evidence. The median follow up period of 48 days was deemed insufficient for these outcomes since a longer observation period is needed to observe such events.

Table 1.8. Summary of findings for efficacy outcomes

EFFICACY OUTCOMES										
OUTCOME	**Quality Assessment** *Note: The study design and number of studies column were collapsed since the input for these columns are the same across all outcomes*					**Summary of Findings**			**Certainty**	**Importance**
	Risk of bias	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Sputnik V Gam-COVID-Vac**	**Placebo n/N**	**Effect Size (95% CI)**		
1. VE against symptomatic COVID-19 infection (> 7 days after dose 2)	Not serious	N/A	Not serious	Not serious	None	13/14094 (0.1%)	47/4601 (1.0%)	**VE: 91.1%** (83.8 to 95.1)	⨁⨁⨁⨁ **HIGH**	CRITICAL
2. VE against hospitalization due to COVID-19 after dose 2	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	CRITICAL
3. VE against severe COVID-19 infection after dose 2	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	CRITICAL
4. VE against symptomatic COVID-19 infection (21 days after dose 1)	Not serious	N/A	Not serious	Not serious	None	16/14964 (0.11%)	62/4902 (1.26%)	**VE: 91.6%** (85.6 to 95.2)	⨁⨁⨁⨁ **HIGH**	IMPORTANT
5. VE against moderate COVID-19 infection (21 days after dose 1)	Not serious; *Some concerns (interim analysis) (incomplete ffup)*	N/A	Serious *(short follow up for this rare events)*	Serious *(very wide CI)*	None	0/14964 (0%)	19/4902 (0.39%)	**VE: 100%** (not estimable)	⨁⨁◯◯ **LOW**	IMPORTANT
6. VE against severe COVID-19 infection (21 days after dose 1)	Not serious; *Some concerns (interim analysis) (incomplete ffup)*	N/A	Serious *(short follow-up period)*	Serious *(very wide CI)*	None	0/14964 (0%)	1/4902 (<0.1%)	**VE: 100%** (not estimable)	⨁⨁◯◯ **LOW**	IMPORTANT
7A.VE against symptomatic COVID-19 infection (after dose 2) among older adults (>60 years old)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	IMPORTANT

7B. VE against symptomatic COVID-19 infection (21 days after dose 1) among older adults (>60 years old)	Not serious	N/A	Not serious	Not serious	None	2/1611	8/533	VE: **91.8%** (67.1 to 98.3)	⨁⨁⨁⨁ **HIGH**	IMPORTANT
8. VE against symptomatic COVID-19 after dose 2 in population with comorbidities	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	IMPORTANT
9. VE against symptomatic COVID-19, Asians	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	IMPORTANT
10. VE against asymptomatic COVID-19	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	IMPORTANT

Table 1.9. Summary of findings for safety outcomes

SAFETY OUTCOMES										
OUTCOME	**Quality Assessment** *Note: The study design and number of studies column were collapsed since the input for these columns are the same across all outcomes*					**Summary of Findings**			**Certainty**	**Importance**
	Risk of bias	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Sputnik V Gam-COVID-Vac**	**Placebo n/N**	**Effect Size (95% CI)**		
1. Serious adverse events	Not serious	N/A	Serious *(short follow-up period)*	Serious *(crosses value of no effect)*	None	45/16427 (0.3%)	23/5435 (0.4%)	**0.65** (0.39 to 1.07)	⨁⨁◯◯ **LOW**	CRITICAL
2. Death (All-cause mortality)	Not serious	N/A	Serious *(short follow-up period)*	Serious *(crosses value of no effect)*	None	3/16427 (<0.1%)	1/5435 (<0.1%)	**0.99** (0.10 to 9.54)	⨁⨁◯◯ **LOW**	CRITICAL
3. Systemic reactogenicity **(***time point of measurement not reported)*	Not serious Some concerns *(measurement of outcome - self-reporting outcomes: subjective outcomes)*	N/A	Not serious	Not Serious	None	6728/14964 (44.96%)	1252/4902 (25.54%)	**1.76** (1.67 to 1.85)	⨁⨁⨁⨁ **HIGH**	CRITICAL
4. Local reactogenicity *(time point of measurement not reported)*	Not serious Some concerns *(measurement of outcome- self-reporting outcomes: subjective outcomes)*	N/A	Not serious	Not Serious	None	3273/14964 (21.87%)	205/4902 (4.18%)	**5.23** (4.56 to 6.00)	⨁⨁⨁⨁ **HIGH**	IMPORTANT

Evidence on sustained protection

Rates of disease onset were similar for the vaccine and placebo groups until about 16 to 18 days after the first dose. Thereafter, the number of cases in the vaccine group increased much more slowly than in the placebo group indicating an effect of early and sustained protection over at least 80 days (Figure 1.)

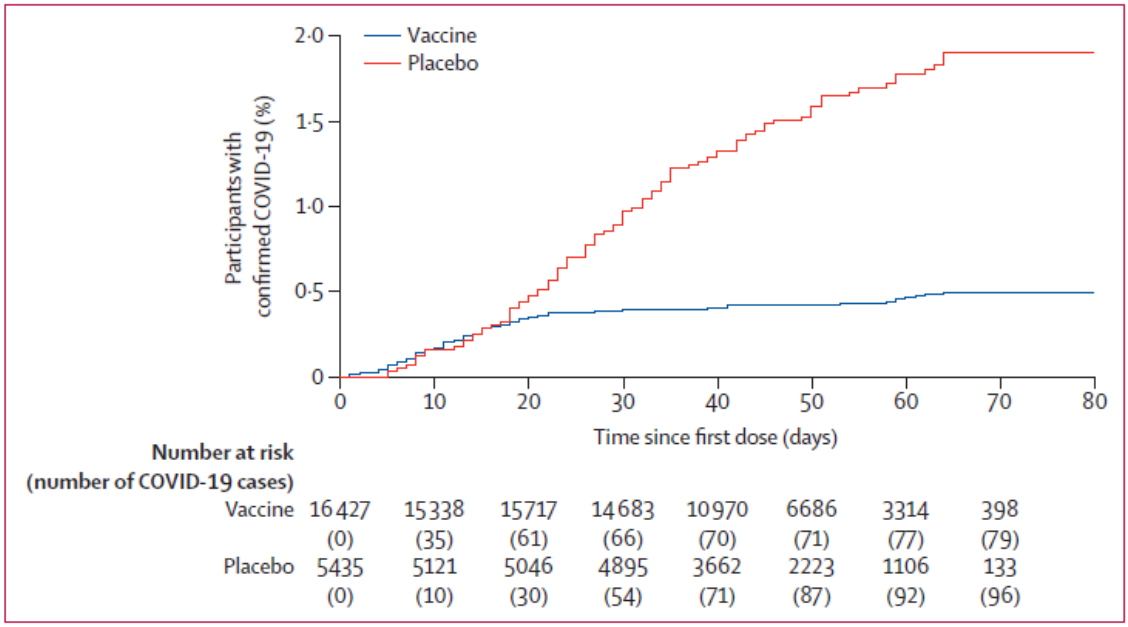

Figure 1. Kaplan-Meier cumulative incidence curves for the first symptomatic, PCR-positive COVID-19 after dose 1, in participants who received at least one dose of vaccine or placebo
Source: Logunov et al., 2021

Evidence on Adaptive Immunity

Humoral Immune Response

Humoral immune response to Sputnik V Gam-COVID-Vac was measured through presence of RBD-specific antibodies and Neutralizing antibodies. At 42 days after the start of vaccination, seroconversion rates and geometric mean titers of participants were higher in the vaccine group than in the placebo group. However, p-value comparing the vaccine and placebo was not reported. Table 1.10 details of seroconversion rates and geometric mean titers for: RBD specific antibodies [vaccine group = 342; placebo group = 114)] and neutralizing antibodies [vaccine group = 72; placebo group = 28)]

Table 1.10. Humoral immune response, measured via ELISA at 42 days after start of vaccination, in participants immunized with Sputnik V Gam-COVID-Vac or placebo

	Sputnik V Gam-COVID-Vac		Placebo	
	Seroconversion rate (%) (n/N)	Geometric Mean Titer (95% CI)	Seroconversion rate (%) (n/N)	Geometric Mean Titer (95% CI)
RBD-Specific Antibodies	98.25 (336/342)	8,996 (7,610 to 10,635)	14.91 (17/114)	30.55 (20.18 to 46.26)
Neutralizing antibodies	95.83 (69/72)	44.5 (31.8 to 62.2)	7.14 (2/28)	1.6 (1.12 to 2.19)

In a subgroup analysis of RBD-specific antibodies 42 days after the start of vaccination in participants based on age and sex, the combined male and female group aged 18-30 years showed a significantly higher GMT when compared to other age groups (p=0.0065). Meanwhile, there were no significant differences in terms of other age groups (p=0.343) as well as in terms of sex (p=0.258). In addition, placebo group (n=114) showed only 14.91% seroconversion rate [GMT 30.55 (95% CI: 20.18-46.26)] compared to the vaccine group regardless of age group (n=342) with seroconversion rate of 98.25% [GMT 8,996 (95% CI: 7,610-10,635)]. Table 1.11 presents the seroconversion rates and GMT of RBD specific antibodies (based on age group and sex) 42 days after the start of vaccination in participants immunized with the vaccine (n=342).

Table 1.11. RBD specific antibodies 42 days after the start of vaccination in participants immunized with vaccine (n=342), subgroup analysis by age and sex

Age strata	Male		Female	
	Seroconversion rate (%) (n/N)	Geometric Mean Titer (95% CI)	Seroconversion rate (%) (n/N)	Geometric Mean Titer (95% CI)
18-30	100 (14/14)	22,067 (11,971 to 40, 676)	100 (14/14)	18,102 (7,689 to 42, 616)
31-40	100 (44/44)	10,106 (7,047 to 14,494)	100 (35/35)	10,925 (6,807 to 17,532)
41-50	97.87 (46/47)	6,123 (3,658 to 10,250)	97.78 (44/45)	7,940 (4,874 to 12,935)

51-60	97.78 (44/45)	7,129 (4,466 to 11,379)	97.44 (38/39)	8,063 (4,715 to 13, 789)
60 and above	96.55 (28/29)	8.128 (4,071-16,228)	96.15 (25/26)	10,908 (5,462-21,785)

For neutralizing antibodies at 42 days after vaccination, high seroconversion rates were achieved across age strata (87.51 to 100%) compared to the seroconversion rate in the placebo group at 7.14% (2 out of 28 participants). Seroconversion rate in participants aged 60 years and above reached 100% (7 out of 7 participants). Geometric mean titers of neutralizing antibodies was lowest in the 51-60 years age group [(28.75 (95% CI: 16.71 to 49.49)] and highest in the 31-40 years age group [(72.94 (95% CI: 4425 to 120.2)]. Geometric mean titer of neutralizing antibodies in the 60 years old and above age group was at 36.23 (95% CI: 13.21 to 99.35). In general, geometric mean titers across all age groups were higher than placebo [1.562 (95% CI: 1.117 to 2.185)]. Table 1.12 presents neutralizing antibody seroconversion rates and geometric mean titer across age strata.

Table 1.12. Neutralizing antibodies 42 days after the start of vaccination in participants immunized with vaccine (n=72), subgroup analysis by age

Age strata	Seroconversion rate (%) (n/N)	Geometric mean titer (95% CI)
18-30	87.51 (6/7)	53.84 (8.198 to 353.5)
31-40	100.00 (15/15)	72.94 (44.25 to 120.2)
41-50	90.91 (20/22)	48.32 (22.21 to 105.1)
51-60	100.00 (21/21)	28.75 (16.71 to 49.49)
60 and above	100.00 (7/7)	36.23 (13.21 to 99.35)

Cellular immune response

Cellular immune response was observed among 58 participants through the production of IFNγ of peripheral blood mononuclear cells (PBMC) upon SARS-CoV-2 antigen restimulation. At day 28 after vaccination, all participants in the vaccine arm were found

to have higher levels of IFNɣ secretion upon antigen restimulation (median production at 32.770). Table 1.13 presents the median production of IFNɣ before and 28 days after vaccination with either *Sputnik V Gam-COVID-Vac* (n=44) or placebo (n=14).

Table 1.13. Median antigen-specific PBMC cell IFNɣ production at day of vaccination and day 28, as measured by ELISA, in participants immunized with *Sputnik V Gam-COVID-Vac* (n=44) or placebo (n=14)

Time point	Sputnik V Gam-COVID-Vac (n=44)	Placebo (n=14)
Before vaccination		
Unstimulated	0.498	0.408
Antigen stimulated	0.439	0.547
at Day 28		
Unstimulated	0.432	0.475
Antigen stimulated	32.770	0.410

EVIDENCE FROM REAL WORLD DATA

Regulatory agencies and ministries of health were searched for reports on safety of *Sputnik V Gam-COVID-Vac COVID-19 Vaccine* after its rollout in the following implementing countries: Algeria, Argentina, Bolivia, Pakistan, Russia and UAE. However, as of this writing, only Argentina had published a report.

On 15 March 2021, the Argentina Ministerio de Salud reported that as of 03 March 2021, 22,912 adverse events have been reported after inoculation of 1,181,292 doses of *Sputnik V Gam-COVID-Vac COVID-19 Vaccine*.

- Of these, 96.8% of adverse events were determined to be related to vaccination.
- The most common adverse events reported were headache and/or myalgia and/or arthralgia comprising 36.5% of the reported adverse events; and, fever with headaches and/or myalgia comprising 34.1% of the reported adverse events.
- Other common adverse events after inoculation of *Sputnik V Gam-COVID-Vac COVID-19 Vaccine* include local pain/local reaction/paresthesias/local lymphadenopathy (9.8%), fever (8.77%), gastrointestinal symptoms with or without fever including diarrhea, vomiting, nausea, metallic taste in mouth (6.07%), and mild to moderate allergic reactions (1.38%).
- There were six cases of anaphylaxis that were reported; however, one of the reports was classified as indeterminate because the event occurred 21 days post-vaccination.

Appendix 2. Evidence on Criteria 3 - Affordability and viability

Cost of Implementing *Sputnik V Gam-COVID-Vac COVID-19 Vaccine*

The following cost items were identified in calculating for the total resource requirement in implementing *Sputnik V Gam-COVID-Vac COVID-19 Vaccine* to the Philippine government: the *Sputnik V Gam-COVID-Vac COVID-19 Vaccine* and vaccine consumables; logistics (hauling and storage); and operations (recruitment and training of vaccinators). The source of these costs was derived from the DOH - Disease Prevention and Control Bureau's (DPCB) overall vaccine budget plan and the DOH - Bureau of International Health Cooperation BIHC). Overall, the projected cost of vaccine and consumables, logistics and operations based on the data is Php 17,412,676,400. The paragraphs below will detail the costing calculation for cost components.

Vaccine and Consumables

The total cost of vaccines and consumables for 15 million Filipinos will amount to Php 15,877,632,857.14. This amount takes into account 5% estimated wastage of vaccines and cost of two doses of *Sputnik V Gam-COVID-Vac COVID-19 Vaccine* for every vaccinee. Vaccine consumables include personal protective equipment (PPE) of the vaccination team and injection devices.

Logistics

Included under logistics are hauling and storage costs. Hauling cost includes the procurement of transport boxes that can contain 1,000 vials each box. Given a weight of 31.4 kg per box, the total cost for hauling *Sputnik V Gam-COVID-Vac COVID-19 Vaccine* is estimated at Php 399,596,400. This amount also includes a 1% valuation cost. For storage, the transport boxes are assumed to be stored in warehouses with storage capacity of 100 boxes per warehouse which will be used as temporary location before distribution to vaccination sites. The storage of the vaccines is assumed to last for a month at most, and is estimated to cost Php 2,800 per warehouse occupied, resulting in a storage cost of Php 882,000 per month. The overall cost for logistics is estimated to be at Php 400,478,400.

Operations

Operations cost includes mobilization, hiring costs, as well as training for vaccine implementation. Since it is projected that 15,000,000 Filipino will receive *Sputnik V Gam-COVID-Vac COVID-19 Vaccine*, it is assumed that 107,143 vaccinators will be needed

for the rollout. Further, the number of supervisors needed is estimated at 35,714, with the assumption that one supervisor is needed per three vaccinators. The duration of the activity provided by DPCB was seven (7) days. With a salary of Php 500 per day for 7 days, the cost of mobilization of these individuals is estimated to be Php 500,000,000. For the training of the vaccinators and supervisors, two days are allotted to train them with a cost of Php 1,200 per head per day. In the training costing, DPCB included an input quantity of 121,545 on top of the total number of trainees (i.e., 200,000) multiplied by the cost (in peso) of training per day. This input value is currently being validated with DPCB. In total, the operations cost is computed at Php 1,134,565,142.86. Excluded in the operations cost are the cost of conducting routine RT-PCR tests among vaccination teams, as well as their transportation or any other costs necessary for mobilization and service delivery. Table 2.1 elaborates the resource requirement costs and assumptions in the roll-out of the *Sputnik V Gam-COVID-Vac COVID-19 Vaccine* in the Philippines in 2021.

Table 2.1 Resource requirement costs in the roll-out of *Sputnik V Gam-COVID-Vac COVID-19 Vaccine* in the Philippines in 2021

Description	Cost	Assumptions/Notes	Source
Vaccine and Vaccine Consumables	Php 15,877,632,857.14	For 2 doses, with 5% wastage; consumables include syringes, personal protective equipment, hand rub, cotton *(estimated costs for vaccinating 15,000,000 Filipinos based on identified target vaccinees for this brand)*	DPCB
Logistics	Php 400,478,400.00	For -18 degrees Celsius vaccine storage temperature only. This includes hauling and storage costs. *(estimated costs for vaccinating 15,000,000 Filipinos based on identified target vaccinees for this brand)*	DPCB
Operations	Php 1,134,565,142.86	This does not include yet cost of their testing, transportation of vaccinators, or any other costs necessary for mobilization and service delivery. The duration of activity provided by DPCB was 7 days. *(estimated costs for vaccinating 15,000,000 Filipinos based on identified target vaccinees for this brand)*	DPCB
TOTAL COST	**Php 17,412,676,400.00**		
TOTAL VACCINATION COST PER INDIVIDUAL	**Php 1,160.85**		

Acronym: ***DPCB:*** *Disease Prevention and Control Bureau*

Based on the projected calculations, the total cost of rolling out vaccination with *Sputnik V Gam-COVID-Vac COVID-19 Vaccine* for 15,000,000 Filipinos would amount to Php 17,412,676,400.00 (which translates to Php 1,160.85 per individual). This would entail utilization of 21.1% of the total allocated budget for vaccination while the roll out using *Sputnik V Gam-COVID-Vac COVID-19 Vaccine* will cover 21% of the target vaccinees for 2021.

Deployment and Feasibility

The COVID-19 Vaccine Deployment Plan outlines the prioritization of eligible populations in receiving the COVID-19 vaccine which includes *Sputnik V Gam-COVID-Vac COVID-19 Vaccine*. For Stage 1 of the Vaccine Deployment Plan of COVID-19 vaccines, 22.8% (24,668,128) of the Philippine population is targeted to receive the vaccine under Priority Eligible Population A. This group includes frontline health workers (1.6% or 1,762,994), indigent senior citizens (3.5% or 3,789,874), senior citizens (5.3% or 5,678,544), indigent populations (12.0% or 12,911,193), and uniformed personnel (0.5% or 525,523). On the other hand, Stage 2 of the Vaccine Deployment Plan will increase coverage to 32.95% of the population that will include teachers and social workers (0.95% or 1,179,097), other government workers (1.66% or 1,728,641), other essential workers (1.63% or 1,690,206), other socio-demographic groups with a significantly higher risk (1.72% or 1,785,000), overseas Filipino workers or OFWs (1.66% or 1,728,641), and other remaining members of the workforce (1.25% or 1,298,729) will be inoculated with the vaccine. Finally, in Stage 3 of the Vaccine Deployment Plan, the remaining Filipinos (67.05% or 73,888,198) will be vaccinated. In terms of the priority areas for the deployment of the COVID-19 vaccine, regions determined to have a higher prevalence would be prioritized for the vaccine rollout (i.e., NCR and Region III – Central Luzon).

In the rollout of the vaccine deployment plan, the logistics involved must be taken into consideration. The required storage temperature for the *Sputnik V Gam-COVID-Vac COVID-19 Vaccine* is at -18 degrees Celsius and the shelf-life of the vaccine is 6 months stored in a dark place at -18 degrees Celsius. This temperature requirement can be addressed by use of freezers. It is expected that the *Sputnik V Gam-COVID-Vac COVID-19 Vaccine* can be widely distributed to facilities with the said equipment; examples of which include tertiary hospitals, Rural Health Units, Municipal Health Offices, and City Health Offices. *Sputnik V Gam-COVID-Vac COVID-19 Vaccine* can be accessible at the rural level.

Even though there is anticipated easier and wider distribution brought about by the storage temperature requirements, there is still a need for training on vaccine storage and handling to ensure product integrity across the entire supply chain, and a need to ensure the availability of trained personnel in handling unreported or rare adverse reactions that could occur following vaccination.

Appendix 4. References

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Appendix 5. Acknowledgement

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- DOH- Supply Chain Management Office (SCMO)
- Philippine Insurance Corporation (PhilHealth)
- Philippine Statistics Authority (PSA)
- Philippine COVID-19 Living CPG Group - Institute of Clinical Epidemiology, National Institutes of Health, University of the Philippines Manila