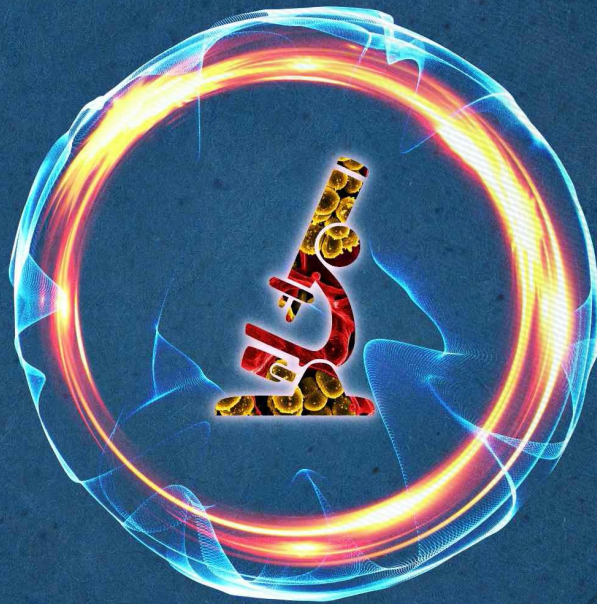# THE ORACLE PROJECT

## Student Workbook

# The Oracle Project

## ❖ Context

The world is on the verge of a new pandemic following the identification of a new emerging virus. Several outbreaks are already spreading across borders. Your team of scientists has been selected to quickly develop an effective vaccine to protect the population.



## ❖ Overall objectives

To develop up to three vaccines and to immunize the population against the circulating viral strains. You will have 4 rounds in total to achieve these goals.

## ❖ Online vaccine development game

You will be using an online serious game called Immunization that simulates the vaccine development process. The game is available on the Tabletopia platform.

---

1. Download the **Tabletopia App** on your tablet and search for The Immunization Game.

**Note:** For labtops, go to https://tabletopia.com/games/immunization.

2. Create a free account if necessary and select Solo Mode (Cooperative Mode - 1 Player)

**Note:** if you use a private virtual game room, access it via the URL link provided by the Immunitarium team.

---

## ❖ Set up of the gameplay

The gameplay is divided into 5 areas:

**(1)** The Disease cards

**(2)** The Player's biotech area where vaccines are developed and produced

**(3)** The Research reagents and Tox/Clinical study cards

**(4)** The Turn Counting board

**(5)** The rule summary
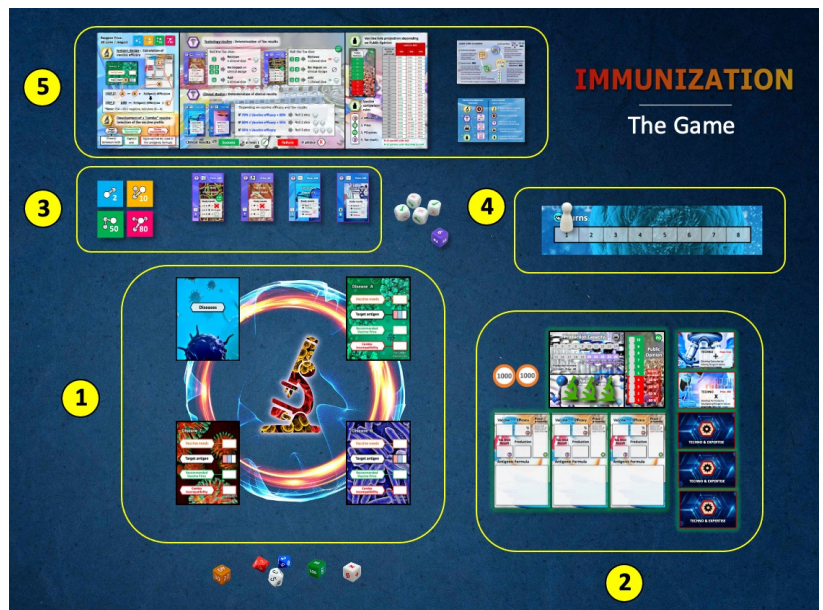


▶️ 🎦 For more details about the game rules, click **here** to watch a video tutorial.

❖ **Set up of the 1ˢᵗ Disease card (A)**

**(1)** Enter **20** in the "Vaccine needs" field

**(2)** Enter **435** as the Target antigen

**(3)** Leave the "Recommended Vaccine Price" case empty or ignore it as you will not use the coins during this project

**(4)** Enter Ø in the "Combo Incompatibility" field (this feature will be introduced during Round 2)

This disease A represents the first circulating strain of the virus (wild type strain).
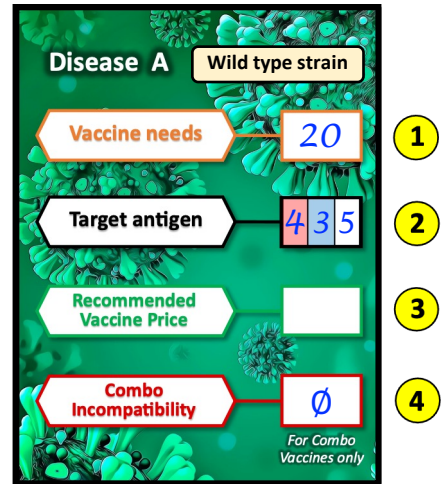
❖ **Set up of your Technologies & Expertise (T&E) cards**

1. Reveal all the T&E cards displayed in the game area.
2. Select the following ones to represent the technologies and expertise available in your biotech:

➢ **Technologies [+] [-] [x]**

These 3 technologies allow the development of vaccine formulas. Their combination helps improve the vaccine efficacy.

**Note:** You can use these technologies as often as you want to develop your vaccines.

➢ **Expertise "Clinical trial management"**

This expertise allows a player to roll the clinical dice one more time in case of Phase 1/2 or Phase 3 study failure.

**Note:** This technology can be used every time a player performs a Phase 1/2 (Ph1/2) or Phase 3 (Ph3) study.

❖ **Set up of your Manufacturing Capacity**

Before starting the game, set your production capacity at **5.**

**Note:** The coins and the public opinion score will not be used in this simulation.

## ❑ **Round 1: Development of a monovalent vaccine**

**Objective:** Develop a vaccine (A) as fast as possible against the virus that just emerged. You can perform up to **6 actions in total** to complete this task.

**The Science behind**

A monovalent vaccine is a vaccine that contains one antigen to protect against a single disease or a single pathogenic strain.

**Click here to watch a short video** to learn how to develop a vaccine formula and read explanations in **Annex 1**.

**Notes:**

- Describe each action taken in the **Action tracker table** available in **Annex 5.**

- Once a vaccine is launched, the vaccine units are produced and distributed to immunize the population at the end of each round.  The production and distribution of the vaccine units do not count as an action.

**A)** Write below the antigenic formula you have developed and calculate the vaccine efficacy.

_____

_____

**B)** At the end of the 1st round, have you been able to launch your vaccine? If so, how many vaccine units have you distributed?

_____

**C)** Update the vaccine needs on the Disease card (A) by subtracting your number of vaccine units.

**D)** During this 1st round, your team has gained some knowledge and experience. You can select one new T&E card among the list displayed in **Annex 2.**
Which T&E card have you choosen? Explain why.

_____

_____

_____

## ❑   **Round 2: Development of a bivalent vaccine**

A new mutant strain has been detected.

**Objective:** Develop a combo vaccine (A/B) against the 2 circulating variants (a bivalent vaccine). You can perform **6 actions in total** to complete this task.



A new variant is circulating.

We need to quickly develop a combo vaccine that protects against both strains.

**The Science behind**

A combination (or combo) vaccine is a vaccine that protects against multiple diseases or pathogenic strains.

The number of antigens included in a vaccine detemines the valency of the vaccine. Several vaccines have been developed based on monovalent (1 antigen), bivalent (2 antigens), trivalent (3 antigens) or quadrivalent formulations (4 antigens) and even more. Combo vaccines are also referred as multivalent vaccines.

Look for two examples of combo vaccines on the Internet and name them.

### ❖ **Set up of the 2nd Disease (Variant) card (B)**

**Note:** In the context of this Project, this 2nd Disease card and the following ones actually represent new mutant strains causing the same disease, like the viral strains (also called variants) that were identified during the Covid 19 pandemic (e.g. Alpha, Beta, Omicron).

**1**  Enter **20** in the "Vaccine needs" field

**2**  Enter **403** as the Target antigen

**3**  Enter **[ − ]** in the "Combo Incompatibility" field

**Go to Annex 3** to learn how to develop a combo vaccine by taking into account the "combo incompatibility" limitations.
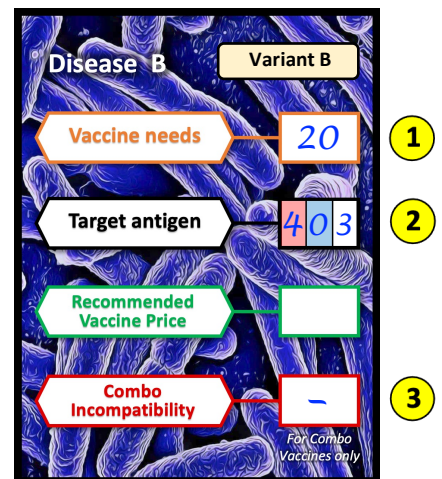


**A)** Evaluate the efficacy of your 1st vaccine (A) against the new strain. Comment on the impact of the virus mutations on the vaccine efficacy.

**B)** Write below the new antigenic formula of your 2nd vaccine (A/B) and calculate its efficacy.

_____

_____

_____

**C)** At the end of the 2nd round, have you been able to launch your combo vaccine? If so, how many vaccine units have you distributed with this vaccine?

_____

Have you also distributed vaccine units of your first monovalent vaccine? If so, how many? If not, why?

_____

_____

_____

**D)** Update the vaccine needs on the two Disease/Variant cards (A & B) by subtracting the respective numbers of vaccine units.

**Note:** Your combo vaccine units should be subtracted from the vaccine needs of <u>both</u> Disease/Variant cards.

**E)** During this 2nd round, your team has gained some knowledge and experience. You can select one new T&E card among the list displayed in **Annex 2.**
Which T&E card have you choosen? Explain why.

_____

_____

_____

_____

## ❑ Round 3: Development of a predictive vaccine

The virus is going to mutate again. The genetic evolution of the virus should be studied to predict the next variant and develop the new vaccine in advance.

**Objective:** Make a prediction of the target antigen for the next variant by studying the 2 circulating variants and develop a predictive vaccine.

You can perform **6 actions in total** to complete this task.



This virus is always one step ahead of us. We need a new strategy.

**A)** Use the graph below to plot the target antigen values of the first 2 variants (A & B) and define the function that represents the genetic evolution of the virus.

Target Antigen

450

400

350

0     1     2     3     Time
      (A)    (B)    (C)     (Viral variants)
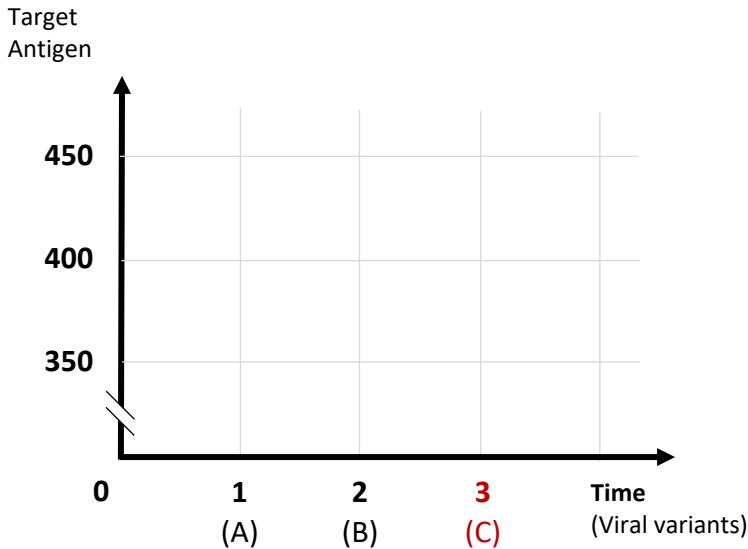
**B)** Predict the target antigen value of the next variant (C) by using the above function.

**Predicted Target Antigen =**

**C)** Use your 3rd Vaccine Board to develop the predictive vaccine (C), ideally up to the Ph1/2 study stage.

Write below the antigenic formula of your predictive vaccine and calculate its predicted efficacy.

**Notes:**

**-** Use 2 clinical dice for the validation of the predictive vaccine during the Ph1/2 study (+/- 1 dice depending on your Tox score).

- The Ph3 study will be initiated during the 4th round once the new strain is detected.

**D)** At the end of the 3rd round, have you been able to test your predictive vaccine in a Ph1/2 study?

Have you also distributed vaccine units of your monovalent and/or combo vaccines? If so, how many units?

**E)** Update the vaccine needs on the two Disease/Variant cards (A & B) by subtracting the respective numbers of vaccine units.

**F)** Select a new T&E card among the list displayed in **Annex 2**. Which T&E card have you choosen? Explain why.

# ❑ Round 4: Control & Eradication of the Pandemic

As expected, a new variant has been detected among the population.



**Objective:** Finalize the development of your predictive vaccine and try to eradicate all the circulating variants.

You can perform **6 actions in total** to achieve this objective.

Let's stop this pandemic once and for all.

**The science behind**

The concept of predicitve vaccinology is not new and is actually used to predict the Influenza strains that circulate every seasons.

Read this **CDC article[1]** to learn more about the average efficacy of the seasonal Flu vaccines.

## ❖ Set up of the 3rd Disease (Variant) card (C)



**(1)** Enter **20** in the "Vaccine needs" field

**(2)** Enter **357** as the Target antigen

**(3)** Enter **[x]** in the "Combo Incompatibility" field

**A)** Evaluate the "real" efficacy of your predictive vaccine against the new strain. Comment on the accuracy of your prediction.

**B)** Perform the Ph3 study with your predictive vaccine.

**Note:** The number of clinical dice for the Ph3 study is determined based on the "real" vaccine efficacy (+/- 1 dice based on your Tox score).

**C)** At the end of the 4th round, have you been able to eradicate all the circulating strains?
If not, how many vaccine needs does it remain?

_____

Read this **article**[2] and comment on the approach used by these pharmaceutical companies to fight the Covid19 pandemic.

_____

_____

_____

**D)** Based on this reading and assuming you were playing with other groups, what could you have done differently to stop this pandemic more efficiently?

_____

_____

_____

How would you have allocated the T&E cards to each group to form an optimal consortium?

_____

_____

_____

_____

**E)** Find an article that illustrates the "Rapid response platform" T&E card that you may have used during your vaccine development simulation.
In your opinion, which vaccine technology(ies) falls into this category?

_____

_____

_____

**F)** Do you think that a virus mutates randomly or do you believe that the genetic evolution of a virus can be predicted? Explain your opinion.

_____

_____

_____

_____

_____

Read this **research article**[3] about applications of physical principles & laws to biological systems like DNA/RNA genomes (Section IV of the article). Discuss as a group the conclusions of this study and the similarities you see with this vaccine development simulation.

Find additional articles that support your arguments related to the existence of deterministic (predictable) patterns or stochastic (not predictable) patterns in the evolution process of viruses.

Read this **article**[4] from CEPI about the development of a Global Vaccine Library based on AI-generated antigens.

**G)** Based on your literature review and on what you have learned during this vaccine development simulation, describe in one concise paragraph the concept of predictive vaccinology as if you were explaining it to a non-specialist audience.
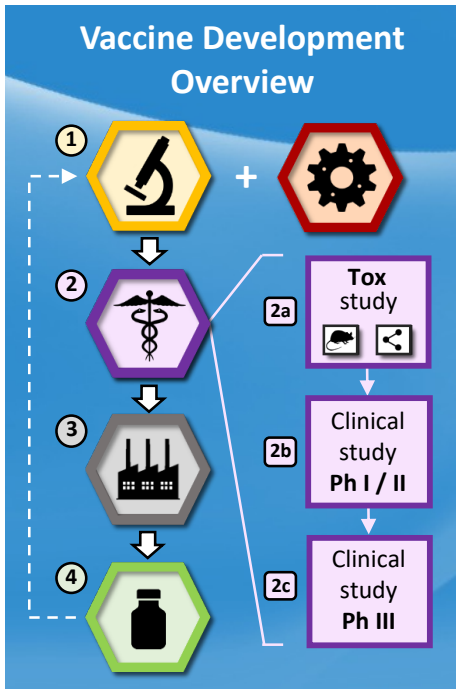
_____

_____

_____

_____

_____

## Annex 1 - **Vaccine development process summary and Action list**

### Vaccine Development Overview



A vaccine is developed in 4 steps. (1) The 1st step consists in developing the vaccine formula. (2) The vaccine is then tested in a toxicology study: an animal model or an in vitro model should be selected. The vaccine is then evaluated in a Ph1/2 clinical study followed by a Ph3 clinical study. Once the vaccine is successfully validated, (3) it can be produced and (4) distributed to immunize the population.

**During each round, you can perform 6 actions** to be selected among the following list:

**Order Research Reagents** (up to 3 reagents per action) – Code: **REA**
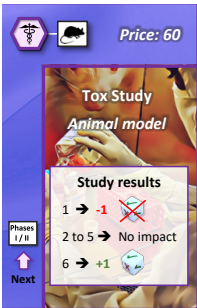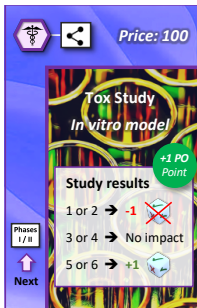
Four types of reagents are available:



**Note:** Reagents are consumables that cannot be re-used.

---

**Perform a Toxicology study**
- Code: 🐭 **Tox AM** or ◁ **Tox IVM**

- Tox study in an animal model
- Tox study in an in vitro model

*Price: 60*

**Tox Study**
*Animal model*

**Study results**
1 ➔ -1
2 to 5 ➔ No impact
6 ➔ +1

*Price: 100*

**Tox Study**
*In vitro model*

+1 PO Point

**Study results**
1 or 2 ➔ -1
3 or 4 ➔ No impact
5 or 6 ➔ +1
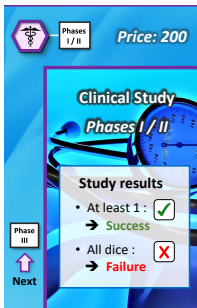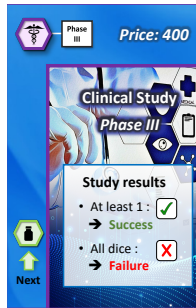
**Perform a Clinical study**
- Code: **Ph1/2** or **Ph3**

- Ph1/2 Clinical study
- Ph3 Clinical study

*Price: 200*

**Clinical Study**
*Phases I / II*

**Study results**
• At least 1 : ✓ ➔ Success
• All dice : ✗ ➔ Failure

*Price: 400*

**Clinical Study**
*Phase III*

**Study results**
• At least 1 : ✓ ➔ Success
• All dice : ✗ ➔ Failure

---

**Increase Production Capacity** (up to 2 units per action) – Code: **INC PROD CAP**

---

**Launch a new vaccine for distribution** – Code: **LAUNCH**

---

**Note:** When you develop your vaccines, you will need to use Technologies & Expertise ( ⚙ ) represented by T&E cards. The use of T&E cards does not count as an action (except for the Digital Manufacturing card). You can use your T&E cards as many time as you want during the gameplay.

# Annex 2 – Technologies & Expertise Cards (see next page as well)

➢ **Technologies [+] [-] [x] [÷]**

These technologies allow the development of antigenic formulas. Their combination can be useful to improve the vaccine efficacy.



**TECHNO** **Price: Free** **+** Develop Formulas by Adding Reagent values

**TECHNO** **Price: 200** **X** Develop Formulas by Multiplying Reagent Values

**TECHNO** **Price: 200** **−** Develop Formulas by Substracting Reagent Values

**TECHNO** **Price: 200** **÷** Develop Formulas by Dividing Reagent Values



**TECHNO** **Price: 200** **High-Throughput Screening** +2 Free Reagents per Turn

➢ **Techno "High-throughput screening"**

This technology allows a player to obtain two reagents (of any type) at no cost <u>each round</u>. The procurement of these reagents does not count as an action.



**TECHNO** **Price: 300** **Combo Development** Solve Incompatibility Issues (For one Vaccine only)

➢ **Techno "Combo development"**

This technology allows a player to develop <u>one</u> "combo" vaccine by bypassing the incompatibility constraints.



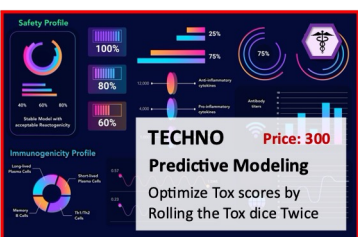**TECHNO** **Price: 400** **Digital Manufacturing** Increase up to 3 Production Units per Action

➢ **Techno "Digital Manufacturing"**

This technology allows a player to purchase up to 3 Production units per action (instead of 2) to increase his/her manufacturing capacity.



**TECHNO** **Price: 400** **Rapid Response Platform** Tox studies Not Required Anymore (Tox Score = 4 by default)

➢ **Techno "Rapid Response Platform"**

This technology allows a player to waive the Tox evaluation. The vaccine platform has been consistently demonstrated as safe and can be granted a Tox score of 4 by default. The player is <u>not obliged to use this techno</u> during the development of a vaccine.



**TECHNO** **Price: 300** **Predictive Modeling** Optimize Tox scores by Rolling the Tox dice Twice

➢ **Techno "Predictive Modeling"**

This technology allows a player to roll the Tox dice twice and to select the highest score. This technology can be used every time a player performs a Tox study (in vitro or animal models).

# Annex 2 – Technologies & Expertise Cards



➢ **Expertise "Clinical trial management"**

This expertise allows a player to roll the clinical dice one more time in case of study failure. This technology can be used every time a player performs a Ph1/2 or Ph3 study.



➢ **Expertise "Quality by Design"**

This expertise allows a player to increase the vaccine efficacy by 5% for <u>one</u> vaccine only.
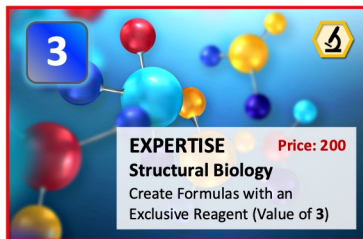


➢ **Expertise "Structural Biology"**

This expertise allows a player to use an exclusive reagent of a value equal to **3**. This reagent can be used indefinitely in the vaccine formulas without extra cost.



➢ **Expertise "Regulatory"**

This expertise means that your Company has mastered the regulatory procedures required to launch new vaccines. Any launch can be performed without counting as an action.



➢ **Expertise "Supply Chain Management"**

This expertise allows a player to immediately gain 2 production units (only once) and to expand the production capacity of his/her manufacturing facility with 6 additional units (Maximum Capacity = 24 units). However, the player still needs to purchase the production units to reach this extra level of production capacity.

# Annex 3 – How to develop a "Combo" vaccine

A "Combo" vaccine is a vaccine protecting against several diseases (or variants) at the same time, in comparison with a single vaccine (or monovalent vaccine) that targets only one disease (or variant). The development of a "Combo" vaccine must respect the following game rules :

- **Only two diseases/variants** may be targeted at the same time.
- The **Target Antigen** to consider for the antigen design is **choosen by the player**.
- The **antigenic formula cannot contain any sign** displayed in the "**Combo Incompatibility" boxes** of both targeted diseases/variants.

### *Figure. Example of development of a "Combo" vaccine*



**1** John is developing a Combo vaccine against the Diseases C and D. He selects the Target Antigen from Disease D (475)

**3** John calculates the vaccine efficacy:
475 – 472 = 3
100 – 3 = **97%**

**2** As the Antigenic Formula cannot contain the signs « **X** » and « **–** », John designs an adapted formulation based on 9 reagents and the technology « **+** ».

*Notes: some diseases/variants may not have incompatibility signs (∅) and may be combined without restriction in the development of the antigenic formula. The other rules still apply.*

*During the vaccine distribution, each vaccine unit of a "Combo" vaccine is counted twice. In other words, the vaccine needs of <u>each disease/variant</u> should be updated by subtracting the number of combo vaccine units.*

## Annex 4 – References

1. CDC article about seasonal Flu vaccine Efficacy
https://www.cdc.gov/flu/vaccines-work/effectiveness-studies.htm

2. Article about partnership models during the Covid19 pandemic
https://www.biospace.com/article/sanofi-gsk-to-support-pfizer-and-biontech-vaccine-manufacturing/

3. Research article about the second law of information dynamics
https://pubs.aip.org/aip/adv/article/12/7/075310/2819368/Second-law-of-information-dynamics

4. CEPI article about Global Vaccine Library
https://cepi.net/forecasting-viral-mutations-0#:~:text=A%20study%20published%20in%20Nature,of%20SARS%2DCoV%2D2.

## Annex 5 - Action tracker related to Rounds 1 & 2

| Round # | Action # | Description (or Code) | Outcome or Score | Comments |
|---------|----------|----------------------|------------------|----------|
| *Example A* | | 3 Research Reagents ordered (or **3 REA**) | | 10 ; 50 ; 80 |
| *Example B* | | Initiation of Tox study with in vitro model (or **Tox IVM**) | Tox score = 5 | 3 Clinical dice to be used based on Tox score |
| **R1** | **A1** | | | |
| | **A2** | | | |
| | **A3** | | | |
| | **A4** | | | |
| | **A5** | | | |
| | **A6** | | | |
| **End of R1** | **Number of Vaccine Units distributed** | | **New T&E Card selected** | |
| | | | | |

| Round # | Action # | Description (or Code) | Outcome or Score | Comments |
|---------|----------|----------------------|------------------|----------|
| **R2** | **A7** | | | |
| | **A8** | | | |
| | **A9** | | | |
| | **A10** | | | |
| | **A11** | | | |
| | **A12** | | | |
| **End of R2** | **Number of Vaccine Units distributed** | | **New T&E Card selected** | |
| | | | | |

## Annex 5 - Action tracker related to Rounds 3 & 4

| Round # | Action # | Description (or Code) | Outcome or Score | Comments |
|---|---|---|---|---|
| *Example A* | | Initiation of PhI/II Clinical study (or **Ph1/2**) | Success | Monovalent vaccine against strain A with Efficacy = 98% |
| *Example B* | | Launch of my vaccine (or **VAC**) | | VAC A/B with 5 vaccine units produced for distribution |
| **R3** | A13 | | | |
| | A14 | | | |
| | A15 | | | |
| | A16 | | | |
| | A17 | | | |
| | A18 | | | |
| **End of R3** | **Number of Vaccine Units distributed** | | **New T&E Card selected** | |
| | | | | |

| Round # | Action # | Description (or Code) | Outcome or Score | Comments |
|---|---|---|---|---|
| **R4** | A19 | | | |
| | A20 | | | |
| | A21 | | | |
| | A22 | | | |
| | A23 | | | |
| | A24 | | | |
| **End of R4** | **Number of Vaccine Units distributed** | | | |
| | | | | |