Title Page

Acute Respiratory Illness Surveillance (AcRIS) by Monitoring Voice and Illness Symptom Changes using a Mobile application in a Low-Interventional Decentralized Study.

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Compound Name:	**N/A**
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Short Title: Acute Respiratory Illness Surveillance (AcRIS) with a Mobile Application in a Low-Interventional Decentralized Study.

Protocol Amendment Summary of Changes Table

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
Amendment #1	28 September 2021	**Section 1.1. Synopsis Objectives and Endpoints, Section 3 Research Questions, Objectives and Endpoints.** **Change of Primary Objective and Primary Endpoint (s)**: It reflects the change to obtain data to characterize the relationship between symptoms and voice features for participants with acute viral respiratory illness. This data will be used as the basis to build voice and symptom algorithm(s) for detection and monitoring of these illnesses. Incorporated changes throughout the protocol body to reflect update. Rationale: Due to current low attack rate of SARS-CoV-2 seen in this study thus far, the primary objective has been modified and expanded to include SARS-CoV-2, influenza virus, and RSV. **Change of Number of Participants**: The total sample size updated from 6250 to approximately 8700 to reflect the updated primary objective of the amendment, the updated overall estimate of the symptomatic attack rate for the 3 viruses, and the updated data attrition rate (as described in the updated Sample Size Determination Section 9.2). **Section 1.1 Synopsis Study Cohorts and Duration of Study Participation, Section 4.1 Overall Design:** Protocol body text updated to remove the aim of equal distribution in 4 groups

		of n=25 each: (Male >60 y/o; Male [redacted] y/o; Female >50 y/o; Female [redacted] y/o). Rationale: IA results show that recruitment of some of the age/gender groups has been challenging. Moreover, since the 100 positive symptomatic cases can now span the 3 viruses, we will no longer aim for any age and gender distribution. **Section 1.3. Schedule of Activities** Changes reflect new visit date windows. Self-swab #1 Days 2+6, Self-swab #2 symptomatic participants Days 2+40, Self-swab #2 asymptomatic participants Days 42+1, End of Study Questionnaire at Day 42+4 days. Such changes are reflected in the Schema shown in Section 1.2. Rationale: Increase flexibility and compliance with self-swabbing, increase timing for participant to receive test results and decrease potential protocol deviations. **Section 5.2. Exclusion Criteria** Changes reflect new exclusion criteria for participants who have received any investigational or licensed RSV vaccine or planning to receive during study participation. Participants who have previously been enrolled in the study cannot be re-enrolled. Rationale: To optimize enrollment of symptomatic participants. **Section 5.4. Screen Failures**

		Changes reflect that screen failure data are collected and reported to the clinical database. Rationale: Screen failures are being recorded in the clinical database. **Section 6.1.1 Performance of Diagnostic Study Interventions. Modified text for RT-PCR sample testing. New text reads as follows:** The RT-PCR samples will be used only for scientific research. Each sample will be labelled with a code so that the laboratory personnel testing the samples will not know the participant's identity. Samples that remain after performing assays outlined in the protocol may be stored by Pfizer. Unless a time limitation is required by local regulations or ethical requirements, the samples will be stored for up to 15 years after the end of the study and then destroyed. If allowed by the ICD, stored samples may be used for additional testing to better understand the immune responses to the vaccine(s) under study in this protocol, to inform the development of other products, and/or for vaccine-related assay work supporting vaccine programs. No testing of the participant's genetic material will be performed. The participant may request that his or her samples, if still identifiable, be destroyed at any time; however, any data already collected from those samples will still be used for this research. The biological samples may be shared with other researchers as long as confidentiality is maintained and no testing of the participant's genetic material is performed. Rationale: Samples will be used for additional testing to better understand the immune responses to the vaccine(s) under study in this protocol, to inform the development of other products, and/or for

		vaccine-related assay work supporting vaccine programs. **Section 8.1.1 Electronic Diary Symptoms and Voice Assessments** Changes reflect the new definition of fever in the Electronic diary: • None: less than 38.0°C or 100.4°F • Mild (Grade 1) ≥38.0°C to 38.4°C or 100.4°F to 101.1°F • Moderate (Grade 2) >38.4°C to 38.9°C or 101.2°F to 102.0°F • Severe (Grade 3) >38.9°C to 40.0°C or 102.1°F to 104.0°F • Grade 4 >40.0°C or >104.0°F • Temperature not taken. Rationale: Change from subjective definition of fever as "feeling feverish" to a more objective clinical definition to improve the data quality. **8.1.2 Nasal Self-swab** Added wheezing as a new or increased symptom for swabbing. Rationale: Wheezing is a common symptom for RSV. **9.2. Sample Size Determination** Updated to reflect the updated primary objective, PPD [redacted] The total sample estimate is updated

		accordingly (from 6250 to 8700 participants). Rationale: Since the 100 positive symptomatic cases now span the 3 viruses. **10.1.3. Milestones Updated milestones to reflect new timelines.** **11. References** Deleted reference 5. Coronavirus Disease 2019 (COVID-19) | 2020 Interim Case Definition, Approved April 5, 2020. (2020). CDC.Gov. Rationale: No longer applicable. **Changes made throughout the document body** Change of study abbreviation from ARIS to AcRIS. Corrections of typographical errors and administrative edits were made per clarity and consistency.
Original protocol	19 January 2021	N/A

This amendment incorporates all revisions to date, including amendments made at the request of country health authorities and IRBs/ECs.

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1. PROTOCOL SUMMARY

1.1. Synopsis

Short Title Acute Respiratory Illness Surveillance (AcRIS) with Mobile Application in a Low-Interventional Decentralized Study.

Rationale: The rationale for conducting the study is to better understand if there are voice features that correlate with acute viral respiratory illness symptoms. Very little work has been published using voice as an objective assessment of the status of respiratory illnesses[1,2]. To better understand if there are voice features that correlate with acute viral respiratory illness symptoms, Pfizer conducted an in-clinic and at-home exploratory study during the cold and flu season of 2018. Voice and respiratory illness symptom data were collected, and 22 voice features were identified that differed between sick and well states and corresponded to self-reported symptom changes[3]. The AcRIS mobile app is a software-based system (mobile phone app plus cloud-based transfer and storage) used to record daily participant reported symptoms of acute viral respiratory tract illness as well as brief audio recordings (scripted speech and phonemes) self-captured by participants. The Electronic diary offers an innovative approach to detect and monitor symptoms of viral respiratory tract illnesses in an out of clinic setting.

The purpose of the AcRIS study is to obtain data to characterize the relationship between symptoms and voice features for RT-PCR confirmed SARS-CoV-2, influenzavirus, or RSV positive participants with acute viral respiratory illness. This data will be used as the basis to build voice and symptom algorithm(s) for detection and monitoring of these illnesses. This would benefit vaccine development across several key disease areas, including SARS-CoV-2, influenza virus and RSV.

The study also models concepts of more efficient "flexible" clinical trials involving not only voice capture, but also web-based participant recruitment, enhanced participant engagement, and remote sample collection that could make future clinical studies more efficient. The clinical data obtained in this observational study could provide the documentation of the technology's performance needed to enable its deployment in future interventional studies.

Objectives and Endpoints

Primary Objective(s):	**Primary Endpoint(s):**
• Obtain data to characterize the relationship between symptoms and voice features for participants with acute viral respiratory illness. This data will be used as the basis to build voice and symptom algorithm(s) for detection and monitoring of these illnesses.	• Change in self-reported symptom scores in the Electronic diary from well to sick in symptomatic participants with RT-PCR confirmed SARS-CoV-2, influenza virus, or RSV. • Change in voice features such as pitch, jitter, harmonicity, entropy, flatness, shimmer from the voice collection as captured by the Electronic diary from

	well to sick in symptomatic participants with RT-PCR confirmed SARS-CoV-2, influenza virus, or RSV.
Secondary Objective(s):	**Secondary Endpoint(s):**
• Assess compliance of the participants using the Electronic diary to collect data.	• Percentage of total days of symptoms entered in the Electronic diary. • Percentage of total days of voice recordings entered in the Electronic diary.
• Test the quality of the recording from the Electronic diary to collect data that is usable for interpretation.	• Percentage of recordings with signal to noise ratio $\geq$ 20 dB that have duration $\geq$ 3 sec for phoneme and $\geq$ 10 sec for reading tasks.
• Determine rates of positivity for SARS-CoV-2/influenza virus/RSV infection.	• Percentage of participants with SARS-CoV-2; and/or influenza virus; and/or RSV RT-PCR based positivity in self-swabs.
• Evaluate the feasibility of obtaining self-swabs.	• Percentage of participants administering the self-swab at self-swab #1 and self-swab #2. • Percentage of participants reporting symptoms in the Electronic diary, who have a self-swab collected at or around symptom onset. • Percentage of self-swabs with valid (positive or negative) or invalid (non-reportable due to technical or self-collection failures) results.

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Safety Objective(s):	**Safety Endpoint(s):**
• To describe the safety profile of self-administered nasal swabs for SARS-CoV-2/influenza virus /RSV RT-PCR test among participants.	• Incidence and severity of adverse events (AEs)/research related injuries (RRIs) among all enrolled participants.

Overall Design

This is a low-interventional, observational study with planned enrollment of approximately 8700 participants 18 years of age or older.

Participants will record acute viral respiratory illness symptoms and voice data daily for up to a maximum of 8 weeks in both the well state and, should they become ill, the sick state, utilizing the electronic diary on their mobile application. Once enrolled, the participant will start recording symptoms and voice in the electronic diary, with daily time commitment to this portion of the study expected to be 2-4 minutes. Two nasal self-swab collection kits will be ordered for delivery to the participant once they are enrolled in the study. The participant will be asked to self-swab when the test kit arrives (swab #1). The kit, including the specimen, will be returned to the central lab for RT-PCR SARS-CoV2/influenza virus /RSV RT-PCR testing. The participant is expected to complete 3 phonemes and 5 lines of reading each day, in addition to score the self-reported symptoms in the Electronic diary. If participants become sick (self-report) with new or increased symptoms of respiratory illness, they will be asked to self-swab (swab #2) and return the sample for central SARS-CoV-2/influenza virus/RSV RT-PCR testing. If the participant does not develop any new or increased symptoms between swab #1 and end of Week 6, they will obtain a self-swab (swab #2) at Day 42.

If the participant tests positive for any of the three viruses at swab #1 or swab #2, they will continue the study until end of week 8. If they test negative for any of the three viruses at swab #1 and swab #2, they will exit the study at approximately the end of week 6. Results of the RT-PCR testing will be shared with participants.

Demographic, medical history, and smoking status data will be collected. At the end of the study, voice and symptom trajectories will be analyzed to understand the infectious respiratory disease trajectory. Analysis of symptom and voice changes will be examined based on SARS-CoV-2/influenza virus/RSV test results. The study design purely contemplates capture of symptoms and voicing by a research participant. It does not involve in any respect the assessment, examination, diagnosis, prognostication or treatment of any study participant.

Number of Participants

Planned enrollment of approximately 8700 participants 18 years of age or older in order to collect a total of N= 100 participants with (1) RT-PCR confirmed negative SARS-CoV-2, influenza virus or RSV RT-PCR (swab #1) and (2) RT-PCR confirmed positive SARS-CoV-2, influenza virus and RSV, (swab #2) symptomatic completers.

Study Cohorts and Duration of Study Participation

The study has 8,700 participants to enroll to collect N=100. It is anticipated to reassess study feasibility and enrollment requirements once we have analyzed infection rate and compliance data from the first 1,000 completers. Each subject will be required to stay in the study for 6 weeks. If the participant tests positive for any of the three viruses at swab #1 or swab #2, they will continue the study until the end of Week 8.

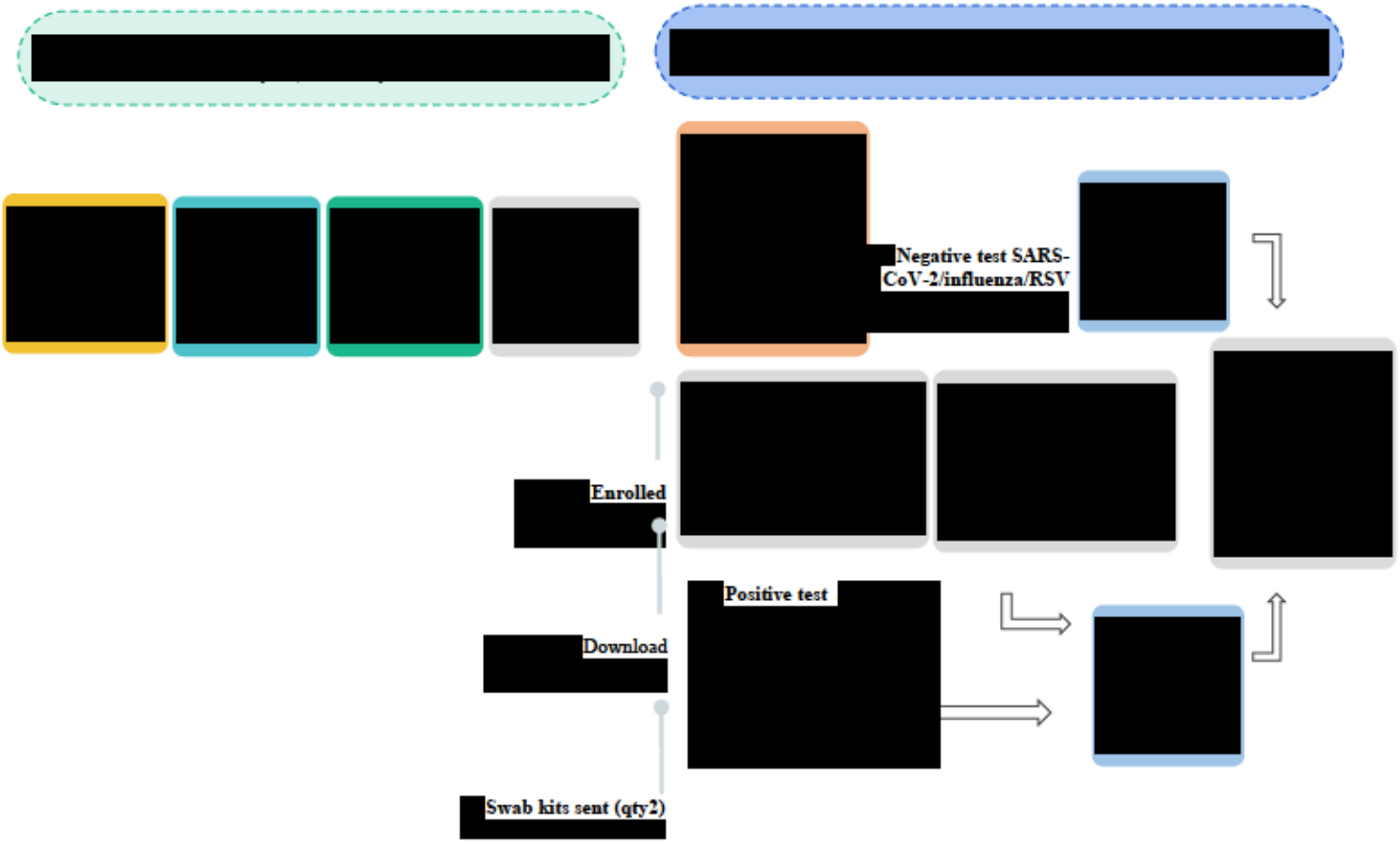
Data Monitoring Committee or Other Independent Oversight Committee: No

Statistical Method

We will be assessing changes over time in self-reported symptom scores in the electronic diary from well to sick in symptomatic participants with RT-PCR confirmed SARS-CoV-2, influenza virus, or RSV. Nonlinear models, such as exponential or sigmoid models, will be utilized to explore disease progression from well to sick and assess early detection. Mean estimates, confidence intervals, and significance tests of changes (or model parameters) will be provided. Additional models may also be considered as appropriate, and the models' goodness of fit will be assessed using Akaike/Bayesian information criteria (AIC/BIC).

Correlation between changes in symptoms and voice features will be assessed by Pearson or Spearman rank order correlations.

1.2. Schema



1.3. Schedule of Activities

The SoA table provides an overview of the protocol visits and procedures. Refer to the STUDY ASSESSMENTS AND PROCEDURES section of the protocol for detailed information on each procedure and assessment required for compliance with the protocol.

The investigator may schedule visits (unplanned visits) in addition to those listed in the SoA table, in order to conduct evaluations or assessments required to protect the well-being of the participant.

Visit Identifier	**Screening** (Day 1)	**Enrollment** (Day 1 + 1 day)	**Self-swab #1** (Day 2 + 6 days)	**Self-swab #2 Symptomatic participants** (Day 2 + 40 days)	**Self-swab #2 Asymptomatic participants** (Day 42 +1 days)	**Extended electronic diary** Only for virus positive participants[f] (Day 42 to 56)
Informed consent	X					
Inclusion and exclusion criteria	X					
Access Electronic diary		X				
Demography		X				
Enrollment Questionnaire (includes self-reported medical history)		X				
Daily symptom and voice entry on the Electronic diary		X	→	→	→	→
Obtain SARS-CoV-2/influenzavirus/RSV nasal self-swab			X[a]	X[b]	X[c]	
Enter date and time of self-swab when completed in Electronic diary			X	X	X	

Visit Identifier	Screening (Day 1)	Enrollment (Day 1 + 1 day)	Self-swab #1 (Day 2 + 6 days)	Self-swab #2 Symptomatic participants (Day 2 + 40 days)	Self-swab #2 Asymptomatic participants (Day 42 +1 days)	Extended electronic diary Only for virus positive participants[f] (Day 42 to 56)
Confirm no AE's 12 hours after self-swab; enter date and time in Electronic diary			X		X	
End of Study Questionnaire					X[d]	X[e]
Collect AEs and RRIs as appropriate	X	X	→	→	→	→

a. Participant is required to perform self-swab #1 as soon as possible once they receive the collection kit.
b. Participant is required to perform self-swab #2 if they develop new or increased symptoms.
c. Participant is required to perform self-swab #2 if they have remained asymptomatic at day 42+1.
d. Participant is required to record End of Study Questionnaire at Day 42 +4 days (for participants who have tested negative or invalid for both self-swab #1 and #2).
e. Participant is required to record End of Study Questionnaire at Day 56 (for participants who have had a positive result for either self-swab #1 or #2)
f. Participant is deemed positive for virus if biological sample is determined to contain SARS-CoV-2 and/or influenza virus and/or RSV viruses as detected by CCI RT-PCR test.

Please note for the table when the two numbers for a day are separated by a "+", what it means is that the swab may be taken as soon as the first number of the two and as late as the sum of the first and second of the numbers.

2. INTRODUCTION

The recent COVID-19 pandemic has proven to be challenging to control due to limited accessibility to testing, a prolonged asymptomatic phase in infected carriers, and non-specific symptoms. The goal of this study is to characterize the relationship of voice and symptoms for participants with acute viral respiratory illnesses, including SARS-CoV-2, influenza virus and RSV. This data will be used as the basis to build voice and symptom algorithm(s) for detection and monitoring of these illnesses. This will help vaccine development across key disease areas including SARS-CoV-2, influenza virus and RSV.
Respiratory physiology is an area with multifarious diseases ranging in morbidity and mortality. Often patients present with non-specific symptoms such as cough or shortness of breath making it difficult to objectively diagnose, prognosticate, and differentiate from infectious vs noninfectious etiology.

2.1. Study Rationale

The purpose of the AcRIS study is to characterize the relationship of symptoms and voice features for participants with acute viral respiratory illness as they progress from well to sick states. This data will be used as the basis to build voice and symptom algorithm(s) for detection and monitoring of these illnesses. This would benefit vaccine development across several key disease areas, including SARS-CoV-2, influenza virus and RSV.

The study also models concepts of more efficient "flexible" trials involving not only voice capture but also web-based participant recruitment, enhanced participant engagement, and remote sample collection that could make future clinical studies more efficient. The clinical data obtained in this observational study could provide the documentation of the technology's performance needed to enable its deployment in future interventional studies.

2.2. Background

2.2.1. Clinical Overview

The rationale for conducting the study is to better understand if there are voice features that correlate with acute respiratory illness symptoms. Very little work has been published using voice as an objective assessment of the status of respiratory illness[1,2].
To better understand if there are voice features that correlate with acute respiratory illness symptoms, Pfizer conducted an in-clinic and at-home exploratory study during the cold and flu season of 2018. Voice and respiratory illness symptom data were collected, and 22 voice features were identified that differed between sick and well states and corresponded to self-reported symptom changes[3]. The AcRIS mobile app is a software-based system (mobile phone app plus cloud-based transfer and storage) used to record daily participant reported symptoms of acute respiratory tract illness as well as brief audio recordings (scripted speech and phonemes) self-captured by participants. The electronic diary offers an innovative approach to detect and monitor symptoms of respiratory tract illness in an out of clinic setting.

2.3. Benefit/Risk Assessment

- We do not anticipate any obvious risks from participating in this study. The nasal swab diagnostic procedure is standard of care, however, there is the possibility of discomfort with this procedure.

The benefits of this study include development of easily accessible tools that can be utilized to detect and monitor respiratory illnesses.

3. RESEARCH QUESTIONS, OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary Objective(s):	**Primary Endpoint(s):**
• Obtain data to characterize the relationship between symptoms and voice features for participants with acute viral respiratory illness. This data will be used as the basis to build voice and symptom algorithm(s) for detection and monitoring of these illnesses.	• Change in self-reported symptom scores in the Electronic diary from well to sick in symptomatic participants with RT-PCR confirmed SARS-CoV-2, influenza virus, or RSV. • Change in voice features such as pitch, jitter, harmonicity, entropy, flatness, shimmer from the voice collection as captured by the Electronic diary from well to sick in symptomatic participants with RT-PCR confirmed SARS-CoV-2, influenza virus, or RSV.
Secondary Objective(s):	**Secondary Endpoint(s):**
• Assess compliance of the participants using the Electronic diary to collect data.	• Percentage of total days of symptoms entered in the Electronic diary. • Percentage of total days of voice recordings entered in the Electronic diary.
• Test the quality of the recording from the Electronic diary to collect data that is usable for interpretation.	• Percentage of recordings with signal to noise ratio $\geq$ 20 dB that have duration $\geq$ 3 sec for phoneme and $\geq$ 10 sec for reading tasks.
• Determine rates of positivity for SARS-CoV-2/influenza virus/RSV infection.	• Percentage of participants with SARS-CoV-2; and/or influenza virus; and/or RSV RT-PCR based positivity in self-swabs.
• Evaluate the feasibility of obtaining self-swabs.	• Percentage of participants administering the self-swab at self-swab #1 and self-swab #2.

	• Percentage of participants reporting symptoms in the Electronic diary, who have a self-swab collected at or around symptom onset. • Percentage of self-swabs with valid (positive or negative) or invalid (non-reportable due to technical or self-collection failures) results.
CCI	
Safety Objective(s):	**Safety Endpoint(s):**

• To describe the safety profile of self-administered nasal swabs for SARS-CoV-2/influenza virus/RSV RT-PCR among participants.	• Incidence and severity of adverse events (AEs)/research related injuries (RRIs) among all enrolled participants.

3.1. Variables

Variable	Role	Data source(s)	Operational definition
Demographics	Baseline characteristic	Electronic diary	Self-reported questionnaire
Enrollment Questionnaire (includes self-reported medical history)	Baseline characteristic	Electronic diary	Self-reported questionnaire
Self-swab 1 test result status at study beginning	Baseline characteristic	Covance	Diagnostic test
Change in self-reported symptom scores in the Electronic diary from well to sick, in symptomatic participants with RT-PCR confirmed SARS-CoV-2, influenza virus, or RSV	Primary outcome endpoint	Electronic diary	Details provided in the SAP
Change in voice features such as pitch, jitter, harmonicity, entropy, flatness, shimmer from the voice collection in the Electronic diary from well to sick in symptomatic participants with RT-PCR confirmed SARS-CoV-2, influenza virus, or RSV	Primary outcome endpoint	Electronic diary	Details provided in the SAP
Percentage of total days of symptoms entered in the Electronic diary	Secondary outcome endpoint	Electronic diary	Details provided in the SAP
Percentage of total days of voice recordings entered in the Electronic diary	Secondary outcome endpoint	Electronic diary	Details provided in the SAP
Percentage of recordings with signal to noise ratio ≥ 20 dB that have duration ≥ 3 sec for phoneme and ≥ 10 sec for reading tasks	Secondary outcome endpoint	Electronic diary	Details provided in the SAP

Variable	Role	Data source(s)	Operational definition
Percentage of participants with SARS-CoV-2 and/or influenza virus and/or RSV RT-PCR based positivity in self-swabs	Secondary outcome endpoint	Covance	Details provided in the SAP
Percentage of participants administering the self-swab at self-swab #1 and self-swab #2	Secondary outcome endpoint	Electronic diary	Details provided in the SAP
Percentage of participants reporting symptoms in the Electronic diary, who have a self-swab collected at or around symptom onset	Secondary outcome endpoint	Electronic diary	Details provided in the SAP
Percentage of self-swabs with valid (positive or negative) or invalid (non-reportable due to technical failures) results	Secondary outcome endpoint	Covance	Details provided in the SAP
CCI [redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

CCI [redacted]	[redacted]	[redacted]	[redacted]
[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
Incidence and severity of adverse events (AEs)/research related injuries (RRIs) among all enrolled participants	Safety outcome endpoint	CRF	Details provided in the SAP
Death details	Safety outcome endpoint	CRF	Details provided in the SAP

4. STUDY DESIGN

4.1. Overall Design

This is a low-interventional, observational study with planned enrollment of approximately 8700 participants 18 years of age or older in order to collect a total N=100 participants with (1) RT-PCR confirmed negative SARS-CoV-2, influenza virus and RSV (swab #1) and (2) RT-PCR confirmed positive SARS-CoV-2, influenza virus and RSV (swab #2 or any subsequent swab) symptomatic completers.

Each subject will be required to stay in the study for 6 weeks. If the participant tests positive for any of the three viruses at swab #1 or swab #2, they will continue the study until the end of Week 8.

Participants will record acute respiratory illness symptoms and voice data daily for up to a maximum of 8 weeks in both the well state and, should they become ill, the sick state, utilizing the Electronic diary on their Mobile application. Once enrolled, the participant will start recording symptoms and voice in the Electronic diary, with daily time commitment to this

portion of the study expected to be 2-4 minutes. Two nasal self-swab collection kits will be ordered for delivery to the participant once they are enrolled in the study. The participant will be asked to self-swab when the test kit arrives (swab #1). The kit, including the specimen, will be returned to the central lab for RT-PCR SARS-CoV2/influenza virus/RSV RT-PCR testing. The participant is expected to complete 3 phonemes and 5 lines of reading each day, in addition to score the self-reported symptoms in the Electronic diary. If participants become sick (self-report) with new or increased symptoms of respiratory illness , they will be asked to self-swab (swab #2) and return the sample for central SARS-CoV-2/influenza virus/RSV RT-PCR testing. If the participant does not develop any new or increased symptoms between swab #1 and end of Week 6, they will obtain a self-swab (swab #2) at Day 42.

If the participant tests positive for any of the three viruses at swab #1 or swab #2, they will continue the study until end of week 8. If they test negative for the three viruses at swab #1 and swab #2, they will exit the study at approximately the end of week 6 when the test results are returned. The results of the RT-PCR testing will be shared with participants.

Demographic, medical history, and smoking status data will be collected. At the end of the study, voice and symptom trajectories will be analyzed to understand the SARS-CoV-2/influenza virus/RSV respiratory disease trajectories. Analysis of changes in symptoms and voice characteristics will be stratified by SARS-CoV-2/influenza virus/RSV test results. The study design purely contemplates capture of symptoms and voicing by a research subject. It does not involve in any respect the assessment, examination, diagnosis, prognostication or treatment of any study participant.

4.2. Scientific Rationale for Study Design

This is a low-interventional study design looking at collecting voice and respiratory symptoms data in participants who become infected with SARS-CoV-2/influenza virus/RSV. The rationale behind the design is to characterize the relationship between symptoms and voice features for participants with acute viral respiratory illnesses as they progress from well to sick states. This data will be used as the basis to build voice and symptom algorithm(s) for detection and monitoring of these illnesses. Furthermore, the study is completely remote and decentralized allowing flexibility and less burden to participants.

4.2.1. Limitations of the Study Design and Methods

One limitation of this study's methods is its dependence on participants' recording voice and symptoms in their Electronic diary and collecting nasal self-swabs if they develop any new or increased symptoms. Daily reminders to the participant via the Electronic diary will also serve to reinforce and remind participants of the need to complete the tasks. Data entry will be closely monitored, study personnel will follow up with the participants if noncompliance is noted despite issuance of automated reminders. As this study is not provisioning devices, another limitation would be if the participant fails to connect their device to the cloud.

4.2.2. Participant Input Into Design

Not Applicable

4.3. Justification for Dose

Not applicable

4.4. End of Study Definition

A participant is considered to have completed the study if he/she has completed all phases of the study, including the last scheduled procedure shown in the SoA.

The end of the study is defined as the date of the last scheduled procedure shown in the SoA for the last participant in the trial globally.

The participant is required to complete the End of Study Questionnaire as scheduled in the SoA.

5. STUDY POPULATION

This study can fulfill its objectives only if appropriate participants are enrolled. The following eligibility criteria are designed to select participants for whom participation in the study is considered appropriate.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Age and Sex:

1. Male or female participants ≥18 years of age (or the state's minimum specific age of consent if >18), at Screening visit.

Type of Participant and Disease Characteristics:

2. Participants who are willing and able to comply with daily symptom and voice assessments on the electronic diary application and other study procedures, including self-collection of nasal swabs.

3. Expected to be available for the duration of the study.

Informed Consent:

4. Capable of giving signed informed consent as described in Appendix 1.

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions:

1. Participants who self-report any medical condition, recreational substance use, or medication use which would prevent them from completing study tasks or impair the providing of informed consent, or in the investigator's judgment, make the participant inappropriate for the study.

Prior/Concomitant Therapy:

2. Participants who have been vaccinated with COVID-19 vaccine or are planning to get vaccinated during study participation.

Participants can continue to use all other prescription or non-prescription medications.

Prior/Concurrent Clinical Study Experience:

3. Previous vaccination with any licensed or investigational RSV vaccine or are planning to get vaccinated during study participation.

4. Previous administration with an investigational drug within 30 days of enrollment (or as determined by the local requirement) or planning to participate in an interventional trial during study conduct.

Diagnostic Assessments:

5. Screening diagnostic assessments are not required for eligibility purposes.

Other Exclusions:

6. Investigator site staff or Pfizer employees directly involved in the conduct of the study, site staff otherwise supervised by the investigator including vendors, and their respective family members.

7. Participants who use a mobile device that does not meet the minimum requirements of the Electronic diary.

8. Participants who have previously been enrolled in the study cannot be re-enrolled.

5.3. Lifestyle Considerations

No restrictions are required during the course of study participation.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently enrolled in the study.

Screen failure data are collected and reported to the clinical database.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened.

5.5. Criteria for Temporarily Delaying Enrollment.

The following conditions may allow a participant to be enrolled once the conditions rendering the participant ineligible have resolved and the participant becomes eligible:

- Acquire an appropriate mobile device
- Become eligible based on age
- No longer self-reporting medical conditions preventing from enrollment.

6. STUDY INTERVENTIONS

In this study, there are no therapeutic study interventions, however the study does involve protocol-required diagnostic or monitoring procedures (study interventions) that are considered to be low risk or burden to the study participant; specifically:

- Nasal Swab Testing
- Electronic Diary Voice and Symptoms Entry.

6.1. Study Intervention(s)

6.1.1. Performance of Diagnostic Study Interventions

Participants will be required to administer two nasal swab tests for clinical diagnostic purposes during the duration of the study.

Two nasal swab samples will be self-collected by the subject at home using a nasal swab that is stored in UTM media. The first swab collection is required as soon as the participant receives the kits. The second swab collection is required either if the subject self-reports new or increased symptoms or at end of week 6 if they have remained asymptomatic

The RT-PCR samples will be used only for scientific research. Each sample will be labelled with a code so that the laboratory personnel testing the samples will not know the participant's identity. Samples that remain after performing assays outlined in the protocol may be stored by Pfizer. Unless a time limitation is required by local regulations or ethical requirements, the samples will be stored for up to 15 years after the end of the study and then destroyed. If allowed by the ICD, stored samples may be used for additional testing to better understand the immune responses to the vaccine(s) under study in this protocol, to inform the development of other products, and/or for vaccine-related assay work supporting vaccine programs. No testing of the participant's genetic material will be performed.

The participant may request that his or her samples, if still identifiable, be destroyed at any time; however, any data already collected from those samples will still be used for this research. The biological samples may be shared with other researchers as long as confidentiality is maintained and no testing of the participant's genetic material is performed.

The participant will be notified of their results for swab #1 and #2. If they were to have any questions after receiving their results, a contact number will be made available to them so they can contact the investigator or designated study member to answer any questions that the participant might have.

Electronic Diary Voice and Symptoms Entry:

Participants will perform their voice and symptom tasks once a day. Instructions and training in the Electronic diary will guide the participants on how and when to complete these tasks. The participant will be expected to record their daily voice and symptoms until they finish the participation in the study.

6.1.2. Medical Devices

Not Applicable

6.2. Preparation/Handling/Storage/Accountability

Instructions for the collection, handling, storage, and shipment of biological samples will be provided in the home collection kit provided by the sponsor. Samples will be analyzed using the emergency use authorized (EUA) CCI [redacted] SARS-CoV-2/Flu/RSV multiplex respiratory RT-PCR assay for detection of the presence or absence of SARS-CoV2 /influenza virus A and B/RSV infection. The assay will be validated at a CLIA accredited central laboratory. Samples must be collected and shipped as indicated to maintain sample integrity. Any deviation from the handing instructions should be reported to the sponsor.

6.2.1. Preparation and Dispensing

- Study interventions should be stored in their original containers.
- Site staff will instruct participants on the proper storage requirements for take home study intervention.
- The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance of all study interventions to be accounted for using a study intervention accountability form/record. All study intervention that is taken home by the participant, both used and unused, must be returned to the investigator or designee by the participant. Returned study intervention must not be re-dispensed to the participants.

6.3. Methods to Minimize Bias

6.3.1. Allocation to Study Intervention

All enrolled participants will be assigned to the same study arm. This is a low interventional study all participants will receive the same emergency use authorized (EUA) CCI [redacted] SARS-CoV-2/Flu/RSV multiplex respiratory RT-PCR assay.

7. PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM STUDY

7.1. Participant Discontinuation/Withdrawal From the Study

A participant may withdraw from the study at any time at his/her own request. Reasons for discontinuation from the study include the following:

- Refused further follow-up;
- Lost to follow-up;
- Death;
- Study terminated by sponsor;

If a participant withdraws from the study, he/she may request destruction of any remaining samples taken and not tested, and the investigator must document any such requests in the site study records and notify the sponsor accordingly.

If the participant withdraws from the study and also withdraws consent for disclosure of future information (see Section 7.1.1), no further evaluations should be performed, and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

Lack of completion of all or any of the protocol-required withdrawal/early termination procedures will not be viewed as protocol deviations so long as the participant's safety was preserved.

7.1.1. Withdrawal of Consent

Participants should notify the investigator in writing of the decision to withdraw consent for future follow-up, whenever possible. The withdrawal of consent should be explained in detail in the site study records by the investigator, as to whether the withdrawal was from study procedures and/or study follow-up, and this information should be entered on the appropriate CRF page. In the event that vital status (whether the participant is alive or dead) is being measured, publicly available information should be used to determine vital status only in a manner that is in accordance with local law.

7.2. Lost to Follow-up

A participant will be considered lost to follow-up if he or she fails to return the 2 swabs after approximately at the end of week 6. The following actions must be taken:

- The investigator or designated study member will attempt to contact the participant to ask the participant to return the unused swabs. Should the participant be unreachable or not respond to contact, he/she will be considered to have withdrawn from the study.
- If the participant cannot be contacted or refuses to return the swabs, a report will be filed in the CSR to account for the unreturned swabs

A participant will be considered lost to follow-up if he or she repeatedly fails to comply with study activities or is unable to be contacted by the study site.

The following actions must be taken if a participant fails to complete electronic diary entries for 3 consecutive days:

- The site must attempt to contact the participant and ascertain whether or not the participant wishes to and/or should continue in the study;Before a participant is deemed lost to followup, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's site study record.

- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

8. STUDY ASSESSMENTS AND PROCEDURES

The investigator (or an appropriate delegate at the investigator site) must obtain a signed and dated ICD before performing any protocol-required procedure.

Protocol-required study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed.

Safety issues related to protocol-required procedures should be discussed with the sponsor immediately upon occurrence or awareness to determine whether the participant should continue or discontinue from the study.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Every effort should be made to ensure that protocol required tests and procedures (study interventions) are completed as described. However, it is anticipated that there may be circumstances outside the control of the investigator that may make it infeasible to perform the test. In these cases, the investigator must take all steps necessary to ensure the safety and wellbeing of the participant. When a protocol required test cannot be performed, the investigator will document the reason for the missed test and any corrective and preventive actions that he or she has taken to ensure that required processes are adhered to as soon as possible. The study team must be informed of these incidents in a timely manner.

For samples being collected and shipped, detailed collection, processing, storage, and shipment instructions and contact information will be provided to the investigator site prior to initiation of the study.

8.1. Efficacy Assessments

8.1.1. Electronic Diary Symptoms and Voice Assessments:

Participants will perform their voice and symptom tasks once a day. Instructions and training in the Electronic diary will guide the participants on how and when to complete these tasks. The participant will be expected to record their daily voice and symptoms until they finish the participation in the study.

The following voice and symptom assessments will be entered daily by the participant in the Electronic diary:

Daily Symptoms: Fever, cough, shortness of breath or difficulty breathing, fatigue, nasal congestion, runny nose, sore throat, loss of taste or smell, chills, muscle pain, diarrhea, vomiting, headache, nausea, rigors, wheezing. In addition, the participant will rate each of the symptoms from None, Very Mild, Mild, Moderate, Severe. The definitions of the symptoms and rating severity are provided in the Electronic diary. For fever, the definition below will be followed:

- None: less than 38.0°C or 100.4°F
- Mild (Grade 1) ≥38.0°C to 38.4°C or 100.4°F to 101.1°F
- Moderate (Grade 2) >38.4°C to 38.9°C or 101.2°F to 102.0°F
- Severe (Grade 3) >38.9°C to 40.0°C or 102.1°F to 104.0°F
- Grade 4 >40.0°C or >104.0°F
- Temperature not taken.

Daily Voice Assessments: 2 phonemes: 'eee' and 'mmm' for 4 seconds (minimum 3 seconds), 1 phoneme: "ahh" sustained (as long as possible) and a 5-sentence reading passage: "When the sunlight strikes raindrops in the air, they act as a prism and form a rainbow. The rainbow is a division of white light into many beautiful colors. These take the shape of a long round arch, with its path high above, and its two ends apparently beyond the horizon. There is, according to legend, a boiling pot of gold at one end. People look, but no one ever finds it. When a man looks for something beyond his reach, his friends say he is looking for the pot of gold at the end of the rainbow".

8.1.2. Nasal Self-swab

Participants will need to complete two nasal self-swabs.

Collection of Self-swab #1

Participants will need to perform Self-swab #1 as soon as possible, once they receive the home collection kit.

The collection of Self-swab #2 might occur at 2 different points in the study:

a) If participant develops new or increased symptoms, the participant will perform Self-swab #2 (after Self-swab #1 and before day 42). Self-swab #2 Criteria: An illness involving any 1 or more of the following symptoms will trigger self-swab collection:

- New or increased fever
- New or increased cough
- New or increased shortness of breath or difficulty breathing.
- New or increased fatigue
- New or increased nasal congestion
- New or increased runny nose
- New or increased sore throat
- New or increased loss of taste or smell
- New or increased chills
- New or increased rigors
- New or increased muscle pain
- New or increased diarrhea
- New or increased vomiting
- New or increased headache
- New or increased nausea
- New or increased wheezing

b) If participant does not develop any new or increased symptoms, the participant will be asked to self-swab at day 42.

Detailed instructions on collection, processing, storage, and shipment for the nasal self-swab and contact information will be provided to the participant.

Depending on the results of the self-swab, the following results will determine the end of study for the participant (positive and negative refer to all viruses tested):

a) All negative or invalid results from self-swab #1 and #2, the participant will stop the study at approximately the end of week 6.

b) Any positive self-swabs #1 or #2, the participant will continue the study until end of Week 8.

c) If both self-swabs are invalid the participant will exit the study at approximately the end of Week 6.

d) If one self-swab is negative and another is invalid, the participant will exit the study at approximately the end of Week 6.

8.1.3. Other Electronic diary Activities

The following activities are to be completed by the participant on the Electronic diary.

- Prescreening questionnaire
- Consent
- Inclusion/exclusion criteria
- Enrollment
- Demographics
- Enter date and time self-swab #1 and #2 performed.
- Confirm no health events occurred within 12hrs following self-swab #1 and #2.
- Enrollment and end of study questionnaires

The Electronic diary will have the following AE reminders after a swab for the participants:

- Report any health events occurring 12hrs following self-swab #1 and #2. Instructions and reminders on when and how to report any health events will be given to the participant, as well as a contact telephone number.

The Electronic diary will have the following daily reminders for the participants:

- Remind participant to collect swab if new or increased symptoms occur.
- Remind the participant to call 911 if any medical emergency.
- Remind the participant to complete daily symptom and voice entries on Electronic diary.

8.1.4. Rater Qualifications

Not Applicable

8.1.5. Imaging Assessments

Not Applicable

8.2. Safety Assessments

Unscheduled clinical laboratory measurements or other safety assessments may be obtained at any time during the study to assess any perceived safety issues.

8.2.1. Protocol-Required Clinical Safety Laboratory Assessments

Protocol-required clinical safety laboratory assessments will not be performed in this study.

8.3. Adverse Events and Serious Adverse Events

The definitions of an AE, SAE and research related injury (RRI) can be found in Appendix 2. The investigator is required to assess whether any AE may be related to participation in the study. All AEs (i.e., serious and non-serious, including those attributed to a protocol-required procedure identified as RRI) are collected in the clinical study database. Should a participant, in the investigator's opinion, suffer a medically important research related injury caused by their participation in the study, the designated Pfizer clinician or medical monitor must be notified immediately by telephone or email.

AEs may arise from symptoms or other complaints reported to the Investigator by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative) or they may arise from clinical findings of the Investigator or other HCPs (clinical signs, test results, etc.).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible to pursue and obtain adequate information both to determine the outcome and to assess whether the event meets the criteria for classification as an SAE or caused the participant to discontinue the study intervention (see Section 6.1).

During the active collection period for safety events (see Section 8.3.1), each participant will be questioned about the occurrence of AEs in a nonleading manner.

In addition, the investigator may be requested by Pfizer Safety to obtain specific follow-up information in an expedited fashion.

8.3.1. Time Period and Frequency for Collecting AE and SAE Information

Procedure-Observation Time Table:

Procedure	Minimum Observation Time for Section 8.3.1.
Nasal self-swab collection	Up-to 12 Hours following swab

The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each participant begins at the time that the nasal self-swab #1 and #2 are performed and ends 12 hours after that procedure/intervention has completed.

The investigator is required to perform appropriate follow-up of each adverse event throughout and after the active collection period and until the AE/SAE or its sequelae resolve or stabilize at a level acceptable to the investigator and Pfizer concurs with that assessment.

If the participant withdraws from the study and also withdraws consent for the collection of future information, the active collection period ends when consent is withdrawn.

If a participant definitively discontinues or temporarily discontinues study intervention because of an AE or SAE, the AE or SAE must be recorded on the CRF and the SAE reported using the NIS AE Report form.

Since there is no product under study, there is no post-study active reporting period for the SAEs to be communicated to Pfizer Safety.

Symptoms of respiratory illness will be collected from the time of consenting to the clinical research through the end of the study daily through the Electronic diary. This information will not be reported on an AE CRF unless that they occur within the 12 hrs following swab.

8.3.1.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a participant during the active collection period (see Section 8.3.1) are reported to Pfizer Safety on the NIS AE Report form immediately upon awareness, as indicated in Appendix 2; under no circumstance should the time between awareness and reporting of the SAE exceed 24 hours. The investigator will also submit any updated SAE data to the sponsor within 24 hours of it being available.

Reportable SAEs include events related to an approved Pfizer product taken by the participant under routine care, during the time they are participating in the study, should such events come to the attention of the Investigator (including an overdose or a medication error that led to the SAE). Refer to Appendix 2 for the definition of an overdose or medication error.

8.3.1.2. Recording Nonserious AEs and SAEs on the CRF

All applicable SAEs and nonserious AEs, as described in Appendix 2, that are directly observed and/or spontaneously reported by the participant during the active collection period (described in Section 8.3.1) will be recorded on the AE page of the CRF.

8.3.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 2.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open -ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. For each event, the investigator must pursue and obtain adequate information until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.2).

In general, follow-up information will include a description of the event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Any information relevant to the event, such as concomitant medications and illnesses, must be provided. In the case of a participant death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer Safety.

Further information on follow-up procedures is given in Appendix 2.

8.3.4. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country -specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/ECs, and investigators.

8.3.5. Exposure During Pregnancy or Breastfeeding, and Environmental Exposure

The requirements for reporting pregnancy or breastfeeding and environmental exposure apply throughout the entire active collection period and are outlined below; when such reports are required per protocol, the report must be transmitted to Pfizer Safety within 24 hours of investigator awareness.

8.3.5.1. Exposure During Pregnancy

An EDP occurs if:

- A female participant is found to be pregnant while taking any Pfizer product under routine care, at any time during the study period (e.g., a concomitant medication that is not required by the study protocol); or,
- A male participant uses any Pfizer product under routine care during the study period (i.e., a concomitant medication that is not required by the study protocol) and his partner subsequently becomes pregnant.

The investigator must report the EDP to Pfizer Safety within 24 hours of the investigator's awareness, whether or not an SAE has occurred.

- The initial information submitted should include the anticipated delivery date of the baby (see below for information related to termination of pregnancy).
- An EDP report is not required if the Pfizer product taken under routine care is specifically approved for use in pregnant women (e.g., vitamins) and is administered in accord with authorized use. However, if the infant experiences an SAE associated with such a drug, the SAE must be reported along with the EDP.

The Investigator must report the EDP to Pfizer Safety on the NIS AE Report Form and the EDP Supplemental Form. Relevant details of the exposure and the pregnancy will be collected from the time informed consent was provided until final study follow-up. If there is an SAE associated with the EDP, then the SAE is reported to Pfizer Safety using the NIS AE Report Form.

Follow-up must be conducted to obtain general information on the pregnancy and its outcome for all EDP reports. The investigator will follow the pregnancy until completion (or until pregnancy termination) and notify Pfizer Safety of the outcome as a follow-up to the initial EDP Supplemental Form. For a live birth, information regarding the structural integrity of the neonate at the time of birth should be provided. In the event of a termination, the reason(s) for termination should be provided and information regarding the structural integrity of the terminated fetus should be included in the report (if available; not required if pre-procedure test findings were conclusive for a congenital anomaly and those findings are provided in the report).

Abnormal pregnancy outcomes are considered SAEs. If the outcome of the pregnancy meets the criteria for an SAE (i.e., ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly), then the investigator should follow the procedures for reporting SAEs.

Additional pregnancy outcomes that must be reported to Pfizer Safety as SAEs include:

- Spontaneous abortion including miscarriage and missed abortion;
- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death may be related to exposure to the Pfizer product used under routine care during the study

Additional information regarding the EDP may be requested by the sponsor. Further follow up of birth outcomes will be handled on a case-by-case basis (e.g., follow up on preterm infants may be requested to identify developmental delays). In the case of paternal exposure, the investigator will provide the participant with the Pregnant Partner Release of Information Form to deliver to his partner. The investigator must document in the source documents that the participant was given the Pregnant Partner Release of Information Form.

8.3.5.2. Exposure During Breastfeeding

- An EDB occurs if female participant is found to be breastfeeding while taking any Pfizer product under routine care, at any time during the study period (e.g., a concomitant medication that is not required by the study protocol).
- An EDB report is not required when a Pfizer product specifically approved for use in breastfeeding women (e.g., vitamins) is administered in accord with authorized use. However, if the infant experiences an SAE associated with such a drug, the SAE must be reported along with the EDB.

The investigator must report an EDB to Pfizer Safety within 24 hours of the investigator's awareness, whether or not an SAE has occurred.

- The investigator must report EDB to Pfizer Safety using the NIS AE Report form.
- If the EDB is associated with a SAE, then the SAE must be reported using the same NIS AE Report form.

8.3.5.3. Environmental Exposure

Not Applicable. Environmental or occupational exposure is not reportable in this study since there is no Pfizer product under study.

8.3.6. Cardiovascular and Death Events

Not applicable

8.3.7. Disease Related Events and/or Disease Related Outcomes Not Qualifying as AEs or SAEs

Not applicable

8.3.8. Adverse Events of Special Interest

Not applicable

8.3.8.1. Lack of Efficacy

Lack of efficacy is the failure of expected pharmacologic action or therapeutic benefit. In this study, lack of efficacy is reportable to Pfizer Safety for an approved Pfizer product used by the participant under routine care, if the Investigator is made aware.

Lack of efficacy should be reported as an SAE to Pfizer Safety if the lack of efficacy involves a *vaccine, a contraceptive or a product* that is *used in the treatment of life-threatening diseases or conditions (e.g., anti-infectives) (excluding HIV and cancer).*

For Pfizer products that are not covered in paragraph above, lack of efficacy is reportable to Pfizer Safety only if associated with an SAE.

8.3.9. Medical Device Deficiencies

Not applicable

8.3.9.1. Time Period for Detecting Medical Device Deficiencies

Not applicable

8.3.9.2. Prompt Reporting of Device Deficiencies to Sponsor

Not applicable

8.3.9.3. Follow-up of Medical Device Deficiencies

Not applicable

8.3.9.4. Regulatory Reporting Requirements for Device Deficiencies

Not applicable

8.4. Treatment of Overdose

Not Applicable.

8.5. Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

8.6. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.7. Genetics

Not Applicable

8.8. Biomarkers

Two nasal swab samples will be self-collected by the subject at home using a nasal swab that is stored in UTM media. The first swab collection is required as soon as the participant receives the kits. The second swab collection is required either if the subject self-reports new or increased symptoms or at end of week 6 if they have remained asymptomatic. Instructions for the collection, handling, storage, and shipment of biological samples will be provided in the home collection kit provided by the sponsor.
Participant is deemed positive for virus if biological sample is determined to contain SARS-CoV-2 and/or influenza virus and/or RSV viruses as detected by [redacted] RT-PCR test.

The participant will be notified of their results. If they were to have any questions after receiving their results, a contact number will be made available to them so they can contact the investigator or designated study member to answer any questions that the participant might have.

8.9. Immunogenicity Assessments

Immunogenicity assessments will not be performed in this study.

8.10. Health Economics

Health economics/medical resource utilization and health economics parameters are not evaluated in this study.

9. STATISTICAL CONSIDERATIONS

9.1. Statistical Hypotheses

This is an exploratory study primarily intended to collect data to characterize the relationship between symptoms and voice features for participants with acute viral respiratory illness. The data will be used to quantify changes from well to sick using voice and self-reported symptoms collected with an Electronic diary in symptomatic SARS-CoV-2/influenza virus/RSV positive participants. The hypotheses that voice and self-reported symptoms will change with acute viral respiratory illness will be tested. This data will be used as the basis to build voice and symptom algorithm(s) for detection and monitoring of these illnesses.

9.2. Sample Size Determination

The sample size determination is based on the primary study objective, which is to obtain data to characterize the relationship between symptoms and voice features for acute viral respiratory illness for RT-PCR confirmed SARS-CoV-2, influenza virus, or RSV positive participants as they progress from well to sick states.

For this exploratory study, it is planned to obtain a total of 100 completers who are RT-PCR confirmed negative to SARS-CoV-2, influenza virus and RSV RT-PCR (at swab #1), and SARS-CoV-2, influenza or RSV RT-PCR confirmed positive (at swab #2) reporting new or increased symptoms. PPD [redacted] it is estimated that approximately 5500 participants (8700 in total including participants that have been enrolled prior to protocol amendment #1) will be needed to be enrolled in the study.

A reassessment of study feasibility and enrollment requirements is anticipated, including the required sample size, after infection rates and compliance data from the first 1000 completers analyzed.

The case definition that will be used to define cases for the primary objective of the study will be as follows:

Negative RT-PCR at swab #1 and Positive RT-PCR at swab #2 who develop 1 or more new or increased symptoms from baseline from the following list:

Fever, chills, rigors, myalgia, headache, fatigue, sore throat, rhinorrhea, congestion, vomiting, nausea, diarrhea, new olfactory and taste disorder(s), cough, wheezing, shortness of breath, or difficulty breathing.

Depending on the distribution of the 3 viruses, this sample size may be adequate to build general algorithm(s) for early detection of upper respiratory illnesses. This sample size will allow identification of any additional data required to finalize this algorithm(s).

9.3. Data Management

The sponsor or designee is responsible for the data management of this study including quality checking of the data.

9.4. Case Report Forms/Data Collection Tools/Electronic Data Record

As used in this protocol, the term CRF should be understood to refer to an electronic data record.

A CRF is required and should be completed for each included participant. The completed original CRFs are the sole property of Pfizer and should not be made available in any form to third parties, except for authorized representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer. The investigator shall ensure that the CRFs are securely stored at the study site *in* encrypted electronic and/or paper *form and will be* password protected or secured in a locked room *to* prevent access by unauthorized third parties.

The investigator has ultimate responsibility for the collection and reporting of all clinical, safety, and laboratory data entered on the CRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring, and available when required. The CRFs must be signed by the investigator or by an authorized staff member to attest that the data contained on the CRFs are true. Any corrections to entries made in the CRFs or source documents must be dated, initialed, and explained (if necessary) and should not obscure the original entry.

In this study the source documents are the site study records. In some cases, these might be the hospital or the physician's chart. In these cases, data collected on the CRFs must match the source.

In some cases, the CRF will serve as the source document. In these cases, a document should be available at the investigator site and at Pfizer that clearly identifies those data that will be recorded on the CRF, and for which the CRF will stand as the source document.

9.5. Data Analysis

The primary objective of the study is to obtain data to characterize the relationship of symptoms and voice features for symptomatic RT-PCR confirmed positive participants with SARS-CoV-2, influenza virus and/or RSV as they progress from well to sick states. The data will be used as the basis to build voice and symptom algorithm(s) for detection and monitoring of these illnesses. Depending on the actual collected data, appropriate algorithms and statistical models will be explored.

Baseline well-state characteristics (such as daily variation and confidence limits) and change over time in self-reported symptom scores in the Electronic diary from well to sick in symptomatic RT-PCR confirmed SARS-CoV-2, influenza virus, or RSV positive participants will be evaluated descriptively and graphically as appropriate. Nonlinear models, such as

exponential or sigmoid models, will be utilized to explore disease progression from well to sick and assess early detection. Mean estimates, confidence intervals, and significance tests of changes (or model parameters) will be provided. Additional models may also be considered as appropriate, and the models' goodness of fit will be assessed using Akaike/Bayesian information criteria (AIC/BIC).

The voice collection in the Electronic diary from well to sick in symptomatic RT-PCR confirmed SARS-CoV-2, influenza virus, or RSV positive participants will be first analyzed by extracting standard acoustic features such as pitch, jitter, harmonicity, entropy, flatness, shimmer, using established routines. Other voice features may also be considered as appropriate. Similar analyses and modeling considerations as for symptom scores will be conducted for the extracted acoustic features. Distance metrics based on all or most significant acoustic features will also be explored to evaluate changes over time from well to sick.

Correlation between changes in symptoms and voice features will be assessed by Pearson or Spearman rank order correlations.

Analyses for individual virus populations as well as pooled analyses across the three viruses will be assessed if deemed feasible.

Detailed methodology for summary and statistical analyses of data collected in this study will be documented in a statistical analysis plan (SAP), which will be dated, filed and maintained by the sponsor. The SAP may modify the plans outlined in the protocol; any major modifications of primary endpoint definitions or their analyses would be reflected in a protocol amendment.

9.6. Interim Analyses

The overall attack rate, attack rate by geography, attrition rate, Electronic diary and self-swab#1 and #2 compliance, SARS-COV-2/influenza virus/RSV positive rate at self-swab #1, rate of symptomatic participants at enrollment, and AEs/RRIs will be monitored on an ongoing basis in the study. If an interim analysis is performed, the study will continue whilst the analysis is being conducted. The analysis details will be provided in the SAP or in an interim analysis SAP.

9.7. Data Monitoring Committee or Other Independent Oversight Committee

This study will not use a Data Monitoring Committee.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and CIOMS International Ethical Guidelines;
- Applicable ICH GCP guidelines;
- Applicable laws and regulations, including applicable privacy laws.

The protocol, protocol amendments, ICD, SRSD(s), and other relevant documents (e.g., advertisements) must be reviewed and approved by the sponsor and submitted to an IRB/EC by the investigator and reviewed and approved by the IRB/EC before the study is initiated.

Any amendments to the protocol will require IRB/EC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC;
- Notifying the IRB/EC of SAEs or other significant safety findings as required by IRB/EC procedures;
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/EC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

10.1.1.1. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

In the event of any prohibition or restriction imposed (i.e., clinical hold) by an applicable regulatory authority in any area of the world, or if the investigator is aware of any new information that might influence the evaluation of the benefits and risks of the study intervention, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study participants against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

10.1.2. Responsible Parties

Principal Investigator(s) of the Protocol

Name, degree(s)	Job Title	Affiliation	Address
Dr. PPD PPD	PPD	PPD	PPD LA PPD

10.1.3. Milestones

Milestone	Planned date
Start of data collection	12 April 2021
End of data collection	11 April 2022
Interim report 1	Once the first 1000 participants have completed the study.
Final study report	11 March 2023

10.1.4. Financial Disclosure

Not Applicable

10.1.5. Informed Consent Process

The investigator or his/her representative will explain the nature of the study to the participant and answer all questions regarding the study. The participant should be given sufficient time and opportunity to ask questions and to decide whether or not to participate in the trial.

Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, HIPAA requirements, where applicable, and the IRB/EC or study center.

The investigator must ensure that each study participant is fully informed about the nature and objectives of the study, the sharing of data related to the study, and possible risks associated with participation, including the risks associated with the processing of the participant's personal data.

The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

The participant must be informed that his/her medical and site study records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/EC members, and by inspectors from regulatory authorities.

The investigator further must ensure that each study participant is fully informed about his or her right to access and correct his or her personal data and to withdraw consent for the processing of his or her personal data.

The site study record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICD.

Participants must be reconsented to the most current version of the ICD(s) during their participation in the study.

A copy of the ICD(s) must be provided to the participant.

Unless prohibited by local requirements or IRB/EC decision, the ICD will contain a separate section that addresses the use of samples for optional additional research. The optional additional research does not require the collection of any further samples. The investigator or authorized designee will explain to each participant the objectives of the additional research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period.

This study is planned to obtain inform consent totally remotely, the participant will "self-consent" on a secure platform and the participant will self-report and answer the questions for inclusion/exclusion criteria. It would be expected for the investigator or designated study member to be available for any questions that the participant might have during the consent process in the form of virtual contact. The consent document will have the contact number which will indicate how to get in contact with the investigator if the participants have any questions regarding the consent and the inclusion/exclusion criteria. It will be required for the investigator or designated study member to co-sign each informed consent document.

10.1.6. Data Protection

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of participant data.

Participants' personal data will be stored at the study site in encrypted electronic and/or paper form and will be password protected or secured in a locked room to ensure that only authorized study staff have access. The study site will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, the study site will be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.

To protect the rights and freedoms of participants with regard to the processing of personal data, participants will be assigned a single, participant -specific numerical code. Any

participant records or data sets that are transferred to the sponsor will contain the numerical code; participant names will not be transferred. All other identifiable data transferred to the sponsor will be identified by this single, participant -specific code. The study site will maintain a confidential list of participants who participated in the study, linking each participant's numerical code to his or her actual identity and the participant's site study record identification. In case of data transfer, the sponsor will protect the confidentiality of participants' personal data consistent with the clinical study agreement and applicable privacy laws.

10.1.7. Dissemination of Clinical Study Data

Pfizer fulfills its commitment to publicly disclose clinical study results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the EudraCT, and/or www.pfizer.com, and other public registries in accordance with applicable local laws/regulations. In addition, Pfizer reports study results outside of the requirements of local laws/regulations pursuant to its SOPs.

In all cases, study results are reported by Pfizer in an objective, accurate, balanced, and complete manner and are reported regardless of the outcome of the study or the country in which the study was conducted.

www.clinicaltrials.gov

Pfizer posts clinical trial results on www.clinicaltrials.gov for Pfizer -sponsored interventional studies (conducted in patients) that evaluate the safety and/or efficacy of a product, regardless of the geographical location in which the study is conducted. These results are submitted for posting in accordance with the format and timelines set forth by US law.

EudraCT

Pfizer posts clinical trial results on EudraCT for Pfizer -sponsored interventional studies in accordance with the format and timelines set forth by EU requirements.

www.pfizer.com

Pfizer posts public disclosure synopses (CSR synopses in which any data that could be used to identify individual participants have been removed) on www.pfizer.com for Pfizer -sponsored interventional studies at the same time the corresponding study results are posted to www.clinicaltrials.gov.

Documents within marketing authorization packages/submissions

Pfizer complies with the European Union Policy 0070, the proactive publication of clinical data to the EMA website. Clinical data, under Phase 1 of this policy, includes clinical overviews, clinical summaries, CSRs, and appendices containing the protocol and protocol amendments, sample CRFs, and statistical methods. Clinical data, under Phase 2 of this policy, includes the publishing of individual participant data. Policy 0070 applies to new marketing authorization applications submitted via the centralized procedure since 01 January 2015 and

applications for line extensions and for new indications submitted via the centralized procedure since 01 July 2015.

Data Sharing

Pfizer provides researchers secure access to patient -level data or full CSRs for the purposes of "bona-fide scientific research" that contributes to the scientific understanding of the disease, target, or compound class. Pfizer will make available data from these trials 24 months after study completion. Patient -level data will be anonymized in accordance with applicable privacy laws and regulations. CSRs will have personally identifiable information redacted.

Data requests are considered from qualified researchers with the appropriate competencies to perform the proposed analyses. Research teams must include a biostatistician. Data will not be provided to applicants with significant conflicts of interest, including individuals requesting access for commercial/competitive or legal purposes.

10.1.8. Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (e.g., laboratory data and eDiary). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must ensure that the CRFs are securely stored at the study site in encrypted electronic and/or paper form and are password protected or secured in a locked room to prevent access by unauthorized third parties.

The investigator must permit study -related monitoring, audits, IRB/EC review, and regulatory agency inspections and provide direct access to source data documents. This verification may also occur after study completion. It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

Monitoring details describing strategy (e.g., risk -based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk -based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring), are provided in the monitoring plan.

The sponsor or designee is responsible for the data management of this study, including quality checking of the data.

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is

being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including signed ICDs, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor. The investigator must ensure that the records continue to be stored securely for as long as they are maintained.

When participant data are to be deleted, the investigator will ensure that all copies of such data are promptly and irrevocably deleted from all systems.

The investigator(s) will notify the sponsor or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with the sponsor or its agents to prepare the investigator site for the inspection and will allow the sponsor or its agent, whenever feasible, to be present during the inspection. The investigator site and investigator will promptly resolve any discrepancies that are identified between the study data and the participant's site study records. The investigator will promptly provide copies of the inspection findings to the sponsor or its agent. Before response submission to the regulatory authorities, the investigator will provide the sponsor or its agents with an opportunity to review and comment on responses to any such findings.

10.1.9. Source Documents

In this study, the site study record, eDiary and electronic questionnaires will serve as a source document. A document should be available at the investigator site and at Pfizer that clearly identifies any additional records maintained at the investigator site that might also act as supportive documentation.
Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected.

Data reported on the CRF or entered in the eCRF that are from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, a participant's current site study record must be available.

Definition of what constitutes source data can be found in the study monitoring plan.

Description of the use of computerized system is documented in the Data Management Plan

10.1.10. Study and Site Start and Closure

The study site start date is the date on which the clinical study will be open for recruitment of participants study site.

The first act of recruitment is the date of the first study participant's first visit and will be the study start date.

The sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study -site closure visit has been performed.

The investigator may initiate study -site closure at any time upon notification to the sponsor if requested to do so by the responsible IRB/EC or if such termination is required to protect the health of study participants.

Reasons for the early closure of a study site by the sponsor may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/EC or local health authorities, the sponsor's procedures, or GCP guidelines;
- Inadequate recruitment of participants by the investigator;
- Discontinuation of further development.

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the ECs/IRBs, the regulatory authorities, and any CRO(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

Study termination is also provided for in the clinical study agreement. If there is any conflict between the contract and this protocol, the contract will control as to termination rights.

10.1.11. Publication Policy

The results of this study may be published or presented at scientific meetings by the investigator after publication of the overall study results or 1 year after the end of the study (or study termination), whichever comes first.

The investigator agrees to refer to the primary publication in any subsequent publications such as secondary manuscripts and submits all manuscripts or abstracts to the sponsor 30 days before submission. This allows the sponsor to protect proprietary information and to provide comments and the investigator will, on request, remove any previously undisclosed confidential information before disclosure, except for any study or Pfizer intervention related information necessary for the appropriate scientific presentation or understanding of the study results.

For all publications relating to the study, the investigator will comply with recognized ethical standards concerning publications and authorship, including those established by the International Committee of Medical Journal Editors.

The sponsor will comply with the requirements for publication of the overall study results covering all investigator sites. In accordance with standard editorial and ethical practice, the sponsor will support publication of multicenter studies only in their entirety and not as

individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship of publications for the overall study results will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

If publication is addressed in the clinical study agreement, the publication policy set out in this section will not apply.

10.2. Appendix 2: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.2.1. Definition of AE

AE Definition

- An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with a study intervention, whether or not considered related to the study intervention.

- NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with a study intervention.

Events Meeting the AE Definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator. Any abnormal laboratory test results that meet any of the conditions below must be recorded as an AE:

    - Is associated with accompanying symptoms.

    - Requires additional diagnostic testing or medical/surgical intervention.

    - *Leads to a change in the study intervention schedule (outside of any protocol-specified adjustments) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy.*

    - Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition.

- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.

- Signs, symptoms, or the clinical sequelae of a suspected drug interaction.

- Signs, symptoms, or the clinical sequelae of a suspected overdose of a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Events NOT Meeting the AE Definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.

- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE.

- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).

- Anticipated day to day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.2.2. Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that, at any dose:

a. Results in death

b. Is life threatening

The term "life threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an AE.

d. Results in persistent disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.

- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea,

influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

g. Research Related Injury

Should a participant, in the investigator's opinion, suffer a medically important research related injury caused by their participation in the study, the designated Pfizer clinician or medical monitor must be notified immediately by telephone or email.

A medically important research related injury is any untoward medical occurrence that:

- Results in death;
- Is life threatening (immediate risk of death);
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);
- Results in congenital anomaly/birth defect.

Medical and scientific judgment is exercised in determining whether an injury is an important medical event. An important medical event may not be immediately life threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the participant or may require intervention to prevent one of the other outcomes listed in the definition above, the important medical event should be reported as a research related injury.

An investigator may be requested by the designated Pfizer clinician or medical monitor to obtain specific additional follow-up information in an expedited fashion. In general, this will include a description of the injury in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible

causality. Information on other possible causes of the event, such as concomitant treatments, vaccines, and/or illnesses must be provided. In the case of a participant death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer or its designated representative.

Definition of Medication Error:

A medication error is any unintentional error in the prescribing, dispensing, or administration of a medicinal product that may cause or lead to inappropriate medication use or patient harm while in the control of the healthcare professional, patient, or consumer. Such events may be related to:

- professional practice,
- procedures,
- systems, including:
    - Prescribing
    - Order communication
    - Product labeling, packaging, and nomenclature
    - Dispensing
    - Distribution
    - Administration
    - Education
    - Monitoring
    - Use

Medication errors include near-misses involving or not involving a patient directly or confusion regarding invented names (e.g., trade name, brand name).

Definition of Overdose

An overdose is an administration of a quantity of a medicinal product given per administration or cumulatively that is above the maximum recommended dose according to the authorized product information.

10.2.3. Recording/Reporting and Follow-up of AEs and/or SAEs

AE and SAE Recording/Reporting During the Active Collection Period

The table below summarizes the requirements for recording adverse events on the CRF and for reporting serious adverse events on the NIS AE Report form to Pfizer Safety throughout the active collection period(s). These requirements are delineated for 3 types of events: (1) SAEs; (2) nonserious adverse events (AEs); and (3) exposure to a Pfizer product used under routine care during pregnancy or breastfeeding.

It should be noted that the NIS AE Report form for reporting of SAE information is not the same as the AE page of the CRF. Wherever the same data or information are to be collected, the forms must be completed in a consistent manner. AEs should be recorded using concise medical terminology and, when referring to a specific event, the same AE term should be used on both the CRF and the NIS AE Report form.

Safety Event	Record on the *CRF*	Report on the NIS AE Report Form to Pfizer Safety within 24 hours of awareness
SAE	Any SAE that occurs during the active collection period(s). Any SAE that occurs outside the active collection period(s) that the investigator suspects may be related to the protocol-required procedure/intervention.	Any SAE that the investigator suspects may be related to any Pfizer product used by the participant under routine care during and outside any active collection period.
Non-serious AEs	Any non-serious AE that occurs during the active collection period(s). Any AE that occurs outside the active collection period(s) that the investigator suspects may be related to the protocol-required procedure/intervention.	None

Safety Event	Record on the *CRF*	Report on the NIS AE Report Form to Pfizer Safety within 24 hours of awareness
Scenarios involving exposure during pregnancy (EDP) and exposure during breast feeding (EDB).	Instances of EDP or EDB are not captured in the CRF.	All instances of EDP (whether or not there is an associated SAE). * All instances of EDB are reported (whether or not there is an associated AE/SAE). **

***EDP** (with or without an associated AE or SAE): any pregnancy information is reported to Pfizer Safety using the NIS AE Report Form and the EDP Supplemental Form; if the EDP is associated with an SAE, then the SAE is reported to Pfizer Safety using the NIS AE Report Form.

****EDB** is reported to Pfizer Safety using the NIS AE Report Form, which would also include details of any SAE that might be associated with the EDB.

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g, hospital progress notes, laboratory reports, and diagnostic reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the CRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to Pfizer Safety in lieu of completion of the NIS AE Report form or the Adverse Event CRF page.
- There may be instances when copies of medical records for certain cases are requested by Pfizer Safety. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Pfizer Safety.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.

- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.

- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The investigator is obligated to assess the relationship between any study intervention (or Pfizer product used under routine care) and each occurrence of each AE/SAE.

- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.

- The investigator will use clinical judgment to determine the relationship.

- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration, will be considered and investigated.

- In making his/her assessment, the investigator will also consult the product information for a marketed Pfizer product used under routine care.

- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.

- There may be situations in which an SAE has occurred, and the investigator has minimal information to include in the initial report to the sponsor. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor.**

- The investigator may change his/her opinion of causality in light of followup information and send an SAE followup report with the updated causality assessment.

- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

- If the investigator does not know whether or not the study intervention caused the event, then the event will be handled as "related to study intervention" for reporting purposes, as defined by the sponsor. In addition, if the investigator determines that an SAE is associated with study procedure/intervention, the investigator must record this causal

relationship in the source documents and CRF, and report such an assessment in the NIS AE Report form and in accordance with the SAE reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other healthcare providers.

- If a participant dies during participation in the study or during a recognized followup period, the investigator will provide Pfizer Safety with a copy of any postmortem findings including histopathology.

- New or updated information will be recorded in the originally completed CRF.

- The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

10.2.4. Reporting of SAEs

SAE Reporting to Pfizer Safety via an Electronic Data Collection Tool

- The primary mechanism for reporting an SAE to Pfizer Safety will be the electronic data collection tool.

- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) in order to report the event within 24 hours.

- The site will enter the SAE data into the electronic system as soon as the data become available.

- After the study is completed at a given site, the electronic data collection tool will be taken offline to prevent the entry of new data or changes to existing data.

- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken offline, then the site can report this information on a paper SAE form (see next section) or to Pfizer Safety by telephone.

SAE Reporting to Pfizer Safety via NIS AE Report Form

- Facsimile transmission of the NIS AE Report form is the preferred method to transmit this information to Pfizer Safety.

- In circumstances when the facsimile is not working, notification by telephone is acceptable with a copy of the NIS AE Report form sent by overnight mail or courier service.

- Initial notification via telephone does not replace the need for the investigator to complete and sign the NIS AE Report form pages within the designated reporting time frames.

10.3. Appendix 3: Liver Safety: Suggested Actions and Follow-up Assessments

LFTs are not required as a routine safety monitoring procedure in this study. However, should an investigator deem it necessary to assess LFTs because a participant presents with clinical signs/symptoms that the investigator suspects may be due to a Pfizer product used under routine care, then, such LFT results should be managed and followed as described below.

Humans exposed to a drug who show no sign of liver injury (as determined by elevations in transaminases) are termed "tolerators," while those who show transient liver injury, but adapt are termed "adaptors." In some participants, transaminase elevations are a harbinger of a more serious potential outcome. These participants fail to adapt and therefore are "susceptible" to progressive and serious liver injury, commonly referred to as DILI. Participants who experience a transaminase elevation above 3 × ULN should be monitored more frequently to determine if they are an "adaptor" or are "susceptible."

In the majority of DILI cases, elevations in AST and/or ALT precede TBili elevations (>2 × ULN) by several days or weeks. The increase in TBili typically occurs while AST/ALT is/are still elevated above 3 × ULN (i.e., AST/ALT and TBili values will be elevated within the same laboratory sample). In rare instances, by the time TBili elevations are detected, AST/ALT values might have decreased. This occurrence is still regarded as a potential DILI. Therefore, abnormal elevations in either AST OR ALT in addition to TBili that meet the criteria outlined below are considered potential DILI (assessed per Hy's law criteria) cases and should always be considered important medical events, even before all other possible causes of liver injury have been excluded.

The threshold of laboratory abnormalities for a potential DILI case depends on the participant's individual baseline values and underlying conditions. Participants who present with the following laboratory abnormalities should be evaluated further as potential DILI (Hy's law) cases to definitively determine the etiology of the abnormal laboratory values:

- Participants with AST/ALT and TBili baseline values within the normal range who subsequently present with AST OR ALT values >3 × ULN AND a TBili value >2 × ULN with no evidence of hemolysis and an alkaline phosphatase value <2 × ULN or not available.

- For participants with baseline AST **OR** ALT **OR** TBili values above the ULN, the following threshold values are used in the definition mentioned above, as needed, depending on which values are above the ULN at baseline:

    - Preexisting AST or ALT baseline values above the normal range: AST or ALT values >2 times the baseline values AND >3 × ULN; or >8 × ULN (whichever is smaller).

    - Preexisting values of TBili above the normal range: TBili level increased from baseline value by an amount of at least 1 × ULN **or** if the value reaches >3 × ULN (whichever is smaller).

Rises in AST/ALT and TBili separated by more than a few weeks should be assessed individually based on clinical judgment; any case where uncertainty remains as to whether it represents a potential Hy's law case should be reviewed with the sponsor.

The participant should return to the investigator site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history, and physical assessment.

In addition to repeating measurements of AST and ALT and TBili for suspected cases of Hy's law, additional laboratory tests should include albumin, CK, direct and indirect bilirubin, GGT, PT/INR, total bile acids, and alkaline phosphatase. Consideration should also be given to drawing a separate tube of clotted blood and an anticoagulated tube of blood for further testing, as needed, for further contemporaneous analyses at the time of the recognized initial abnormalities to determine etiology. A detailed history, including relevant information, such as review of ethanol, acetaminophen/paracetamol (either by itself or as a co-formulated product in prescription or --over-the-counter medications), recreational drug, supplement (herbal) use and consumption, family history, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and potential occupational exposure to chemicals, should be collected. Further testing for acute hepatitis A, B, C, D, and E infection and liver imaging (e.g., biliary tract) and collection of serum samples for acetaminophen/paracetamol drug and/or protein adduct levels may be warranted.

All cases demonstrated on repeat testing as meeting the laboratory criteria of AST/ALT and TBili elevation defined above should be considered potential DILI (Hy's law) cases if no other reason for the LFT abnormalities has yet been found. **Such potential DILI (Hy's law) cases are to be reported as SAEs, irrespective of availability of all the results of the investigations performed to determine etiology of the LFT abnormalities.**

A potential DILI (Hy's law) case becomes a confirmed case only after all results of reasonable investigations have been received and have excluded an alternative etiology.

10.4. Appendix 4: Abbreviations

The following is a list of abbreviations that may be used in the protocol.

Abbreviation	Definition
AcRIS	Acute Respiratory Illness Surveillance
AIC	Akaike information criteria
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BIC	Bayesian information criteria
CLIA	Clinical Laboratory Improvement Amendments
CFR	Code of Federal Regulations
CIOMS	Council for International Organizations of Medical Sciences
CK	creatine kinase
CRF	case report form
CRO	Contract Research Organization
COVID-19	Coronavirus Disease 2019
CSR	Clinical Study Report
DILI	drug-induced liver injury
EC	ethics committee
ECG	electrocardiogram
eCRF	electronic case report form
EDB	exposure during breastfeeding
eDiary	electronic diary
EDP	exposure during pregnancy

EMA	European Medicines Agency
EOS	End of Study
EUA	emergency use authorization
EudraCT	European Union Drug Regulating Authorities Clinical Trials Database
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
HCP	health care provider
HIPAA	Health Insurance Portability and Accountability Act
IA	interim analysis
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICD	informed consent document
INR	international normalized ratio
IRB	Institutional Review Board
LFT	liver function tests
CCI	[redacted]
n, N	number
N/A	not applicable
NIS	non-interventional study
PT	prothrombin time
RRI	research related injury
RT-PCR	reverse transcription polymerase chain reaction
RSV	respiratory syncytial virus
SAE	serious adverse event

SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SoA	schedule of activities
SOP	standard operating procedures
SRSD	single reference safety document
TBili	total bilirubin
ULN	upper limit of normal
CCI	[redacted]
y/o	years old

11. REFERENCES

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