CLINICAL PROTOCOL

A Real-World Evidence Study Evaluating Quality of Life Parameters Following treatment with Otrivine (Xylometazoline hydrochloride)

Protocol Number:	218317
Compound/Product Name:	Otrivine Congestion Relief 0.1% Nasal Spray (1 mg/ml of xylometazoline hydrochloride)
United States (US) Investigational New Drug (IND) Number:	N/A
European Clinical Trials Database (EudraCT) Number:	N/A
Other Regulatory Agency Identified Number:	N/A
Phase:	N/A

Sponsor Information

Sponsor Name & Legal Registered Address	**GlaxoSmithKline Consumer Healthcare (UK) Trading Limited** 980 Great West Road, Brentford, Middlesex, TW8 9GS, United Kingdom (UK)
Sponsor Contact Details	**GlaxoSmithKline Consumer Healthcare (GSK CH)** St. George's Avenue Weybridge KT130DE United Kingdom (UK)

Document History

Document	Version
Original protocol	1.0
Amendment 1	2.0

Amendments incorporate all revisions to date, including amendments made at the request of country health authorities, institutional review boards/ethics committees (IRBs/ECs), etc.

Principal Investigator Protocol Agreement Page

- I confirm agreement to conduct the study in compliance with the protocol and any amendments according to the current International Conference on Harmonisation Good Clinical Practice (ICH GCP) guidelines.
- I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described study.
- I agree to ensure that all associates, colleagues, and employees assisting in the conduct of the study are informed about their obligations. Mechanisms are in place to ensure site staff receive all appropriate information throughout the study.
- I agree to conduct this study in full conformance with the laws and regulations of the country in which the research is conducted and the Declaration of Helsinki.

Principal Investigator Name:	PPD
Principal Investigator Qualifications:	
Principal Investigator Signature:	PPD
Date of Signature/Agreement:	PPD DD-Mmm-YYYY

Table of Contents

List of in text tables

Summary of Changes

Amendment 1

The purpose of this non-substantial amendment is to clarify that the 125 number of subjects refers to eligible enrolled subjects throughout the protocol. An eligible subject is one who confirms that they have nasal congestion of severity 5, which they wish to treat, once they have received the product. These changes are listed in the table below.

Section	Original	Revision
1.1 Synopsis (Page 12: Study Design)	The study expects to enroll 125 subjects to ensure that 100 subjects complete the study.	The study expects to enroll 125 eligible subjects. A total of 100 subjects are expected to complete the study.
12.1 Synopsis (Page 14: Type and Planned Number of Subjects)	It is anticipated that a total of 125 eligible subjects will be enrolled.	This study intends to enroll approximately 125 eligible subjects.
4.1 Overall Design (Page 19)	The study expects to enroll approximately 125 subjects to ensure that 100 subjects complete the study.	The study intends to enroll approximately 125 subjects. A total of 100 subjects are expected to complete the study.
5.1 Type and Planned Number of Subjects (Page 22)	It is anticipated that a total of 125 eligible subjects will be enrolled into the trial.	This study intends to enroll approximately 125 eligible subjects.
12.1 Sample Size Determination (Page 43)	Sufficient individuals will be screened to enroll approximately 125 healthy subjects assuming an estimated 20% drop out rate. Using the above parameters, we obtain a sample size N =125 subjects to retain 100 completed subjects.	Sufficient individuals will be screened to enroll approximately 125 healthy eligible subjects assuming an estimated 20% drop out rate. Using the above parameters, we obtain a sample size N =125 eligible subjects to retain 100 completed subjects.

1 PROTOCOL SUMMARY

1.1 Synopsis

Short Title:

Otrivine: QoL impact in a real-world setting

Background and Rationale:

This study is designed to generate real world data from subjects with nasal congestion acquired from common cold following treatment with a marketed nasal spray. The main aim of this study is to evaluate the effectiveness of a nasal spray on quality of life (QoL) factors.

Objectives and Endpoints:

Objective(s)	Endpoint(s)
Primary	
To evaluate the over-time effects of Otrivine on QoL factors and common cold symptoms among individuals experiencing nasal congestion associated with common cold, following up to 7 days of treatment using WURSS-21.	Scores over time on Days 0, 1, 2, 3, 4, 5, 6, 7 in: - WURSS-21 total score - WURSS-21 total symptom domains - WURSS-21 total QoL domains - Each of the WURSS-21 symptom domains (10 in total)
Secondary	
To evaluate the over-time effects of Otrivine on additional measures of QoL factors among individuals experiencing nasal congestion associated with common cold, following up to 7 days of treatment, using additional QoL factors.	Post Otrivine use score on Days 1, 2, 3, 4, 5, 6, 7, for each of the following additional health related QoL factors: - snoring - alertness the morning after - feeling self-conscious about how you sound - smell - taste - feeling self-conscious around people - energy - motivation
Safety	
To record adverse events (AEs) during study period	Number and percent of patients reporting Aes or serious AEs (SAEs) while on treatment • Related to product • Not related to product

Study Design:

This is a longitudinal, open-label study evaluating the effect on QoL factors in subjects with the common cold using Otrivine nasal spray (xylometazoline hydrochloride 0.1%), in a real-world setting. A sufficient number of adults aged 18 years and over with symptoms of common cold will be screened for eligibility. The study expects to enroll approximately 125 eligible subjects. A total of 100 subjects are expected to complete the study.

Subjects will be recruited through targeted advertising on social media channels. This study is entirely decentralized, and subjects will not be required to physically attend any on-site visits. All study data will be collected remotely through a study app using the subject's own mobile device.

Pre-screening & Informed Consent

Adult subjects reporting early symptoms of the common cold including nasal congestion and at least one other common cold symptom (scratchy throat, sore throat, dry cough or watery nasal discharge) within the previous 24 hours, who respond to a social media ad, complete the pre-screening questionnaire, and are seeking relief of their nasal congestion symptoms, and are eligible to take part in the study will be sent an email invitation to download the study app and complete the study registration process.

Once in the study app, an electronic informed consent (eIC) interview phone call will be scheduled, and investigator/designee will release the eIC form that will be made available to the subject through the study app. During the eIC phone call subjects will have the opportunity to ask any questions they may have. Subject identification will be checked during the consent interview phone call. Subjects that sign the eIC form will have the option to download the signed eIC to save a copy for local reference and/or access the signed eIC through the study app once the investigator/designee countersigns and attests that the consent interview phone call was completed.

Screening & Baseline Assessments

Subjects that provide informed consent will be asked to complete the Wisconsin Upper Respiratory Symptom Survey (short version) (WURSS-21) and, if eligible, they will be prompted to complete the screening questionnaire, confirm their medical history and concomitant medication via a phone call with the investigator/designee, and complete their demographics and shipping form. If the responses to all screening criteria are fulfilled, the subject will be considered enrolled and will move forward to training on how to use the study app. Once this training is complete, they will complete the additional QoL questions as baseline assessments.

Upon completion of baseline assessments and questionnaires, the subject will be shipped the study product. Once the shipment is received, the subject will need to confirm receipt and usability of the product via the app.

Treatment Period

Upon receipt of the study product, the subjects will re-confirm their eligibility to continue in the study based on the previous screening criteria including completion of the WURSS-21 questionnaire (see appendix section 15.2.1). Those with nasal congestion (described as plugged nose on WURSS-21) of at least moderate (score 5) based on WURSS-21 and who exhibit at least one other common cold symptom of at least mild (score 3) based on WURSS-21 and who self-select to treat their nasal congestion symptoms, will be asked to start treatment with the product according to the label instructions.

Subjects who do not satisfy these criteria will be considered dropouts.

Each morning the subject will be prompted to complete the WURSS-21 questionnaire, the additional QoL questions (considering the effects of the product used during the day before).

End of Treatment Period

As per leaflet instruction, xylometazoline hydrochloride (0.1%) nasal spray may be used for up to 7 treatment days.

Subjects will have the option to discontinue treatment at their discretion. The reasons for discontinuing treatment will captured in the app whenever possible.

Subjects may choose to discontinue treatment if:

- they feel that their symptoms do not warrant further use of the study product
- their nasal symptoms/congestion is considered resolved

Subjects that continue to use the study product will be prompted to discontinue treatment after 7 days of continuous use and seek advice from their general practitioner for further assessment and treatment.

Subjects will also be informed that the study will end on Day 7 (or the day after the last treatment, if earlier than 7 days), and will be asked to fill in an exit survey.

Study Product:

Otrivine Congestion Relief 0.1% Nasal Spray (Xylometazoline Hydrochloride), Menthol (UK Marketplace)

Product code: CCI

The study product is to be used as per leaflet instructions: 1 spray in each nostril up to 3 times per day until resolution of symptoms or up to a maximum of 7 days, whichever occurs first. This product is currently on the market for over-the-counter consumer purchase in the United Kingdom.

Type and Planned Number of Subjects:

Adult subjects aged 18 years and over, reporting early symptoms of the common cold including nasal congestion and at least one other common cold symptom (scratchy throat, sore throat, dry cough or watery nasal discharge) within the previous 24 hours will be screened for enrollment into the study. The study intends to enroll approximately 125 eligible subjects. This study assumes an approximate 20% drop out rate. A total of 100 subjects are expected to complete the study.

Statistical Analyses:

Sample size: The sample size determination was performed using a non-parametric Paired Wilcoxon test. The sample size is based on a significance level (α) of 0.05, 80% power (1-β) and an estimated standardized effect size of 0.27.

Population for analysis: A modified intention-to-treat (mITT) analysis will be performed and will include all subjects who received at least one dose of the study product and have at least one post-baseline QoL questionnaire data to support at least one of the primary endpoint assessments. Primary and secondary analyses will be summarized using the mITT population only. Safety population will include all subjects who receive at least one dose of study product. Adverse events will be summarized using the Safety population.

1.2 Schedule of Activities:

Schedule of activities tables provide an overview of the study procedures.

Table 1-1 Schedule of Activities

Procedure/ Assessment	Screening/ Baseline	Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Informed Consent	x								
Screening Questionnaire	x								
Demographics	x								
Subject eligibility	x								
Enrollment	x								
WURSS-21 questionnaire (baseline, pre-treatment)	x								
Additional QoL Questions (baseline, pre-treatment)	x								
Study product shipped [a]	x								
Confirmation of eligibility [b]		x							
Study product treatment usage [c]		x	x	x	x	x	x	x	
WURSS-21 questionnaire (post-treatment) [d]			x	x	x	x	x	x	x
Additional QoL Questions (post-treatment) [e]			x	x	x	x	x	x	x
Subject diary completion			x	x	x	x	x	x	x
Change in Medication Reporting			x	x	x	x	x	x	x
Adverse Event (AE) Review [f]		x	x	x	x	x	x	x	x
End of symptoms reporting [g]									x
End of study questions									x
Study Conclusion and/or Subject Exit from Study [h]									x
Medical History [i]	[i]x								
Concomitant Medication [i,j]	[i]x	[j]x	[j]x	[j]x	[j]x	[j]x	[j]x	[j]x	[j]x
Return of used/unused product [k]									x

Footnotes:

[a] Study product (Otrivine Congestion Relief 0.1% Nasal Spray) will be shipped only after baseline assessments and questionnaires have been completed.
[b] Confirmation of eligibility means WURSS-21 (plugged nose at least moderate, cold symptoms at least mild) AND blocked nose that they still wish to treat.
[c] 1 spray in each nostril up to 3 times per day and up to 7 days or until resolution of symptoms, whichever occurs first.
[d] WURSS-21 (post-treatment) will be completed each day in the morning.
[e] Additional QoL questions (post-treatment) will be asked each day in the morning.
[f] Adverse Events (AEs) and therefore all Serious Adverse Events (SAEs) will be collected immediately from the time of first use of the product by the PI/designee.
[g] End of study reporting will occur upon resolution of symptoms or Day 8 (whichever is sooner).
[h] Study Conclusion and/or Subject Exit from Study will occur at subject's completion of study or resolution of symptoms, whichever occurs first.
[i] Once subjects are eligible for enrolment into the study, the PI/designee will record the subjects medical history and concomitant medication use via a phone call scheduled through the study app. Subjects will be given an opportunity to report any changes in health, concomitant medications, or non-drug treatments/procedures.
[j] Subjects will be given an opportunity to report any changes in health, concomitant medications, or non-drug treatments/procedures.
[k] Will be returned to CCI via a pre-paid package.

2 INTRODUCTION

2.1 Study Rationale

Real world evidence (RWE) studies offer an opportunity to gather information of a marketed product in real-world heterogeneous populations that can complement clinical evidence, consumer insight data, and post-marketing surveillance. Real world data (RWD) generation is increasingly important in determining effectiveness outside of the tightly controlled conditions of randomized clinical trials (RCTs), that do not always reflect real-world patient populations, limiting their generalizability and external validity (Sherman et al., 2016)

This study is designed to generate real world data from subjects with nasal congestion associated with the common cold, evaluating the effects of a commercially available nasal spray on health-related quality of life.

In line with UK Regulations informed consent will be conducted via a phone call with the investigator/designee and subjects will be instructed to return the study product after treatment discontinuation or on Day 7 in a self-addressed envelope/packet.

Otrivine is a marketed nasal decongestant spray used for treatment of nasal congestion associated with common cold. Although this is a non-life-threatening condition, it impacts individuals' ability to function normally in day-to-day activities (physical, social, occupational, and emotional).

Based on a large national on-line survey conducted in the United States (ACHOO survey) (Blaiss et al., 2015, Dicpinigaitis et al., 2015), nasal congestion was one of the most bothersome symptoms of the common cold; and it has been shown to have a significant impact on the quality of life, work productivity, absenteeism, and sleep quality.

This study will generate data to support the decongestant effectiveness of the Otrivine nasal spray in the real-world setting among individuals with common cold to understand how the effect can influence their quality of life.

2.2 Background

Otrivine (xylometazoline hydrochloride) is a nasal decongestant spray that constricts nasal blood vessels and increases nasal airflow, enabling individuals with a blocked nose to breathe more easily. This is a well-known and commonly used decongestant; different versions of this product have been marketed in numerous countries and used by consumers for decades.

A double-blind, placebo-controlled, parallel group study by Eccles (Eccles et al., 2008) investigated the efficacy of the Otrivine nasal spray in patients with common cold. Twenty-nine patients were treated with xylometazoline hydrochloride 0.1%, and 32 patients treated with a placebo (saline solution); 1 spray 3 times a day for up to 10 days was the posology used. The primary objective of the study was to determine the

decongestant effect (via nasal conductance); and the secondary objectives were to determine the peak subjective effects (visual analog scale), duration of relief of nasal congestion and total and individual cold symptoms. In addition, any effects on sleep, tiredness, general well-being and smell/taste were studied as exploratory variables with a daily diary, Adverse events (AEs) were also assessed. The decongestant effect of xylometazoline hydrochloride was significantly greater than placebo, as shown by the nasal conductance at 1 hour. Peak subjective effect (VAS assessment) was also significantly positive. Nasal conductance was significantly superior for up to 10 hours. Compared with placebo, xylometazoline hydrochloride significantly improved the total common cold symptom score on day 1 of treatment (xylometazoline hydrochloride 25.71 versus placebo 35.79; (p=0.0221)) and significantly improved individual common cold symptoms on day 1 (blocked nose, sore throat, and earache), day 2 (blocked nose), day 5 (runny nose), and day 10 (runny nose) of treatment. Xylometazoline hydrochloride-associated significant improvement of total and some individual common cold symptoms scores lead to significantly greater patient general evaluation and satisfaction with treatment.

No differences were noted in the assessment of exploratory end points such as sleep, tiredness, daily activities, general well-being, and smell/taste. The study was neither designed nor powered to statistically evaluate these parameters. Nevertheless, most of the general assessment areas were rated significantly better with xylometazoline hydrochloride than with the placebo both on day 1 and on the last visit of the treatment period.

The authors concluded that xylometazoline hydrochloride is an effective and well-tolerated decongestant nasal spray that significantly relieved nasal congestion compared with placebo in the common cold and provided long-lasting relief with just 1 spray - thereby helping patients to breathe more easily for a period of time.

In the current study, GSK CH seeks to demonstrate that this level of congestion relief can provide a demonstrable improvement in QoL for those suffering from nasal congestion due to common cold. The specific goal of this study is to investigate the effect of Otrivine on QoL factors in adults with nasal congestion due to common cold.

The common cold represents the most frequent human disease (Stein, 2017). Its most relevant definition is a common viral infection of the nose or throat, with symptoms such as sore throat, runny nose, sneezing, and nasal congestion, clear discharge (mucus) from the nose, and body aches (Hemila, 2017). The trajectory of common cold symptoms caused by viruses can vary among individuals but does generally follow a familiar pattern. Cold symptoms tend to peak at 1 to 3 days after first appearance, thereafter symptoms usually last from 3 to 10 days. The mucus appearance may also change during this period. For some people the symptoms of common cold may linger a few more days, especially runny nose, stuffy nose, and coughing.

Nasal congestion and rhinorrhea are the most common complaints and start 1 to 2 days post infection and reach the maximum severity at days 2 to 3 (Eccles, 2005).

Although common cold symptoms are usually mild, they represent a huge burden for society in terms of impaired QoL and economic losses (Passioti et al., 2014, Heikkinen and Jarvinen, 2003). While rhinoviruses are the predominant cause of the common cold, the aetiologic agent remains unknown in up to half of all upper respiratory tract infections (URTIs) (Stein, 2017). For the common cold, only symptomatic treatments exist (Passioti et al., 2014, Stein, 2017). Most people require no prescription medications or doctor visits but do use a variety of over-the-counter (OTC) medications for relief of symptoms.

2.3 Mechanism of Action/Indication

Otrivine nasal spray contains 0.1% of xylometazoline hydrochloride as active ingredient. It is a direct-acting sympathomimetic that acts on alpha-adrenergic receptors on the nasal blood vessels to quickly reduce swelling in the nose, help drain the sinuses and relieve nasal congestion.

3 STUDY OBJECTIVES AND ENDPOINTS

Table 3.1 Study Objectives and Endpoints

Objective(s)	Endpoint(s)
Primary	
To evaluate the over-time effects of Otrivine on QoL factors and common cold symptoms among individuals experiencing nasal congestion associated with common cold, following up to 7 days of treatment using WURSS-21.	Scores over time on Days 0, 1, 2, 3, 4, 5, 6, 7 in: - WURSS-21 total score - WURSS-21 total symptom domains - WURSS-21 total QoL domains - Each of the WURSS-21 symptom domains (10 in total)
Secondary	
To evaluate the over-time effects of Otrivine on additional measures of QoL factors among individuals experiencing nasal congestion associated with common cold, following up to 7 days of treatment, using additional QoL factors.	Post Otrivine use score on Days 1, 2, 3, 4, 5, 6, 7, for each of the following additional health related QoL factors: - snoring - alertness the morning after - feeling self-conscious about how you sound - smell - taste - feeling self-conscious around people - energy - motivation
Safety	
To record adverse events (AEs) during study period	Number and percent of patients reporting AEs or serious AEs (SAEs) while on treatment • Related to product • Not related to product

4 STUDY DESIGN

4.1 Overall Design

This is a longitudinal, open-label study evaluating the effect on QoL factors in subjects with the common cold using Otrivine nasal spray (xylometazoline hydrochloride 0.1%), in a real-world setting. A sufficient number of adults aged 18 years and over with symptoms of common cold will be screened for eligibility. The study intends to enroll approximately 125 eligible subjects. A total of 100 subjects are expected to complete the study.

Subjects will be recruited through targeted advertising on social media channels. This study is entirely decentralized, and subjects will not be required to physically attend any on-site visits. All study data will be collected remotely through a study app using the subject's own mobile device.

Pre-screening & Informed Consent

Adult subjects reporting early symptoms of the common cold including nasal congestion and at least one other common cold symptom (scratchy throat, sore throat, dry cough or watery nasal discharge) within the previous 24 hours, who respond to a social media ad, complete the pre-screening questionnaire, and are seeking relief of their nasal congestion symptoms, and are eligible to take part in the study will be sent an email invitation to download the study app and complete the study registration process.

Once in the study app, an electronic informed consent (eIC) interview phone call will be scheduled, and investigator/designee will release the eIC form that will be made available to the subject through the study app. During the eIC phone call subjects will have the opportunity to ask any questions they may have. Subject identification will be checked during the consent interview phone call. Subjects that sign the eIC form will have the option to download the signed eIC to save a copy for local reference and/or access the signed eIC through the study app once the investigator/designee countersigns and attests that the consent interview phone call was completed.

Screening & Baseline Assessments

Subjects that provide informed consent will be asked to complete the Wisconsin Upper Respiratory Symptom Survey (short version) (WURSS-21) and, if eligible, they will be prompted to complete the screening questionnaire, confirm their medical history and concomitant medication via a phone call with the investigator/designee, and complete their demographics and shipping form. If the responses to all screening criteria are fulfilled, the subject will be considered enrolled and will move forward to training on how to use the study app. Once this training is complete, they will complete the additional QoL questions as baseline assessments.

Upon completion of baseline assessments and questionnaires, the subject will be shipped the study product. Once the shipment is received, the subject will need to confirm receipt and usability of the product via the app.

Treatment Period

Upon receipt of the study product, the subjects will re-confirm their eligibility to continue in the study based on the previous screening criteria including completion of the WURSS-21 questionnaire (see appendix section 15.2.1). Those with nasal congestion (described as plugged nose on WURSS-21) of at least moderate (score 5) based on WURSS-21 and who exhibit at least one other common cold symptom of at least mild (score 3) based on WURSS-21 and who self-select to treat their nasal congestion symptoms, will be asked to start treatment with the product according to the label instructions.

Subjects who do not satisfy these criteria will be considered dropouts.

Each morning the subject will be prompted to complete the WURSS-21 questionnaire, the additional QoL questions (considering the effects of the product used during the day before).

End of Treatment Period

As per leaflet instruction, xylometazoline hydrochloride (0.1%) nasal spray may be used for up to 7 treatment days.

Subjects will have the option to discontinue treatment at their discretion. The reasons for discontinuing treatment will captured in the app whenever possible.

Subjects may choose to discontinue treatment if:

- they feel that their symptoms do not warrant further use of the study product
- their nasal symptoms/congestion is considered resolved

Subjects that continue to use the study product will be prompted to discontinue treatment after 7 days of continuous use and seek advice from their general practitioner for further assessment and treatment.

Subjects will also be informed that the study will end on Day 7 (or the day after the last treatment, if earlier than 7 days), and will be asked to fill in an exit survey.

4.2 Scientific Rationale for Study Design

RWE studies reflect product use in everyday life. They offer the opportunity to gather information on currently marketed products to not only substantiate clinical evidence, but to provide additional information on the target patient population.

The Wisconsin Upper Respiratory Symptom Survey (WURSS) is an evaluative illness-specific quality of life instrument, designed to assess the negative impact of acute upper respiratory infection, presumed viral (the common cold). WURSS-21 is the short version of this validated survey.

Subjects with nasal congestion due to common cold, who seek to treat with study treatment (Otrivine) will complete WURSS-21 and an additional GSK CH designed QoL

questionnaire once every 24-hours. Study treatment use will be reported via diaries. These measures will provide GSK CH with information on the effects of Otrivine over the natural course of their common cold. This will enable GSKCH to evaluate the daily effects that may be attributable to the study treatment.

Limitations of the study

Given the natural course of the common cold, data collected during this study may be confounded by the natural resolution of the disease. Within 24 hours of cold onset, most patients report an escalation in the number of symptoms they experience, including sore throat, nasal congestion, runny nose, and headache. Over the initial days of having a cold, sore throat appears to be most bothersome on day 1 followed by nasal congestion on days 2 to 5 and cough on days 6 and 7.

Given the natural course of the disease, making sure subjects have access to treatment when nasal symptoms are at their peak will allow for subsequent QoL data capture, reducing the influence of confounding variables.

There is substantial evidence to show that different symptoms of common cold overlap during the natural course of the disease. Subjects may likely be using over-the-counter antipyretics/analgesics for fever and/or headache, which may influence their overall QoL and confound data collected. During this study patients will be prompted to report medications they take for symptom relief, along with any changes in medication over the course of their study participation, which will allow the study team to review collected data objectively.

4.3 Justification for Dose

Dosing instructions will be followed as listed on the study product commercial label.

4.4 End of Study Definition

A subject is considered to have completed the study if they have completed all procedures and assessments of the study including the last scheduled procedure shown in the Schedule of Activities.

Subjects will have the option to discontinue treatment at their discretion, if they determine they no longer want treatment. The reasons for discontinuing treatment will be captured in the app whenever possible. The end of this study per subject is tentatively defined as Day 7 but may vary based on the need/severity of nasal congestion (see section 4.1 for further details). At the end of study each subject should complete an exit survey including product satisfaction and intent to repurchase.

5 STUDY POPULATION

5.1 Type and Planned Number of Subjects

Adult subjects aged 18 years and over, displaying cold symptoms will be screened for enrollment into the study. This study intends to enroll approximately 125 eligible subjects. This study assumes an approximate 20% drop out rate. A total of 100 subjects are expected to complete the study.

The common cold has an acute onset and limited duration. Hence subjects who have been displaying cold symptoms over no longer than the previous 24 hours will be further screened for eligibility and enrollment in the study. Subjects that confirm their common cold symptoms within 24 hours of receiving the study product will be enrolled into the study. Subjects who do not meet the eligibility criteria will be considered screen-fails and withdrawn from the study.

This study can fulfill its objectives only if appropriate subjects are eligible. The following inclusion/exclusion criteria are designed to select subjects for whom participation in the study is considered appropriate. All relevant medical and non-medical conditions will be taken into consideration when deciding whether a subject is suitable for this protocol.

5.2 Inclusion Criteria

An individual must meet all the following inclusion criteria to be enrolled in the study:

1. Individual's provision of a signed and dated eIC form indicating that the subject has been informed of all pertinent aspects of the study before any assessment is performed.
2. Individual is 18 years of age or older at the signing of the informed consent.
3. Individual reporting a nasal congestion, and at least another common cold symptom among runny nose, sore throat, cough.
4. Individual reporting a minimum score of 5 (moderate) for plugged nose associated with common cold symptoms and at least one other symptom of common cold (at least mild score of 3) as per the WURSS-21 questionnaire at screening.
5. Individual reporting initiation of cold symptoms within no longer than 24 hours of prior to initiation of screening.
6. Individuals confirm common cold symptoms within 24 hours of study product receipt of minimum score of 5 (moderate) for plugged nose associated with common cold symptoms and at least one other symptom of common cold (at least mild score of 3) as per the WURSS-21 questionnaire
7. Male and female individuals
8. Individual that owns a smart device and willing to download the study app
9. Individual who is willing and able to complete all activities as shown in the Schedule of Activities independently on own smart devices.
10. Individual is in good general and mental health.

11. Individual who has a self-reported medical diagnosis of cardiovascular disease (including those with long QT syndrome), hyperthyroidism or diabetes mellitus, may be included if deemed acceptable by a medically qualified investigator.
12. Individual who is showing a strong reaction to adrenergic substances, as manifested by signs of insomnia, dizziness, tremor, cardiac arrhythmias, or elevated blood pressure, may be included if deemed acceptable by a medically qualified investigator.

5.3 Exclusion Criteria

An individual who meets any of the following exclusion criteria will be excluded from the study:

1. Individuals under 18 years of age.
2. Individuals who are allergic to xylometazoline hydrochloride or any of the other ingredients in the spray (see product label).
3. Individuals who have had recent neurosurgery.
4. Individuals who self-report narrow angle glaucoma, chronic nasal inflammation with very dry nasal passages (rhinitis sicca or atrophic rhinitis), or enlarged prostate gland.
5. Individuals who self-report a rare tumor of the adrenal gland that produces high amounts of adrenaline and noradrenaline (phaeochromocytoma).
6. Individuals who are taking monoamine oxidase inhibitors (MAOIs) or have stopped taking them in the last 14 days.
7. Individuals who are pregnant, lactating, or plan to be pregnant or lactating during the course of the study.
8. Individual who is currently using or has used a nasal decongestant (i.e. adrenergic, steroids) within the last 7 days (or for more than 7 days) prior to initiating study treatment.
9. Individuals who have tested positive for COVID-19 within one month prior to enrollment into the study.
10. Individuals who have taken a vaccine one week prior to enrollment into the study.

5.4 Randomization Criteria

There is no randomization in this study. All enrolled subjects will be provided with the same study product.

5.5 Lifestyle Considerations

As a real-world evidence study, where will be no lifestyle considerations.

5.6 Screen Failures

Screen failures are defined as subjects who consent to participate in the study but are not subsequently enrolled in the study i.e., do not fulfill all the screening criteria.

To ensure transparent reporting of screen failure subjects, a minimal set of screen failure information will include demography (year of birth, gender, race), screen failure details (e.g., withdrawal of consent), and eligibility criteria.

Prospective subjects who do not meet the criteria for enrollment in this study (screen failure) may not be re-screened unless due to technical issues within the study app/portal. If re-screening is applicable, individuals will be re-invited with a new subject ID.

5.7 Sponsor's Qualified Medical Personnel

Contact information for the sponsor's appropriately qualified medical personnel for the study is documented in the Study Contact List held by CCI

To facilitate access to appropriately qualified medical personnel on study-related medical questions or problems, subjects will be provided with contact information in the CCI app or will be able to use the chat function in the study app.

6 STUDY PRODUCT

6.1 Study Product Supplies

The following study products will be supplied by the Clinical Supplies Department, GSK CH or preferred vendor. Subjects will be instructed to return the study product after treatment discontinuation or on Day 7 in a self-addressed envelope/packet.

Table 6-1 Study Product Supplies

	Test Product
Product Name	Otrivine Congestion Relief 0.1% Nasal Spray (Xylometazoline Hydrochloride), Menthol (UK Marketplace)
Pack Design	Labelled commercial pack
Dispensing Details	One labelled pack shipped to subject upon completion of baseline assessments and questionnaires
Product Master Formulation Code (MFC)	CCI
Dose/Application	As per label and leaflet instructions: 1 spray in each nostril up to 3 times per day until resolution of symptoms or up to a maximum of 7 days, whichever occurs first.

Route of Administration	Nasal Spray
Usage Instructions	As per directions stated on the label and Leaflet
Return Requirements	All used/unused samples to be returned

6.2 Administration

Only subjects enrolled in the study may receive study products. Product shipments to subjects will be tracked and subjects will be asked to confirm that they have received the product via the CCI app. The app will also advise subjects to follow the label and leaflet and confirm the first use of the product.

6.2.1 Medication/Dosing Errors

Medication/dosing errors may result, in this study, from the administration or consumption of:

- the wrong product,
- by the wrong subject,
- at the wrong time,
- or at the wrong dosage.

In the event of medication dosing error, the sponsor should be notified **immediately and under no circumstance should this exceed 24 hours** and information should be captured in the electronic case report form (eCRF).

If a medication/dosing error is accompanied by an AE, as determined by the investigator, the medication/dosing error and, any associated AEs are to be captured in the eCRF AE form.

6.2.2 Overdose

An overdose is a deliberate or inadvertent administration of a product at an amount higher than specified in the protocol.

Overdose is not likely to occur in this study.

6.3 Study Product Storage

Subjects will be instructed to:

- Keep this medicine out of sight and reach of children.
- Store the product below 25°C.

- Store the product in its original package.
- Not dispose this medicine via wastewater or household waste.

6.4 Study Product Accountability

All products supplied are for use only in this clinical study and should not be used for any other purpose.

CCI preferred distributing vendor must maintain adequate records documenting the receipt, shipment, loss, or other disposition of all the product supplies.

CCI preferred distributing vendor is responsible for accountability, reconciliation, and record maintenance of study products stored/non-dispensed at the vendor site.

6.4.1 Destruction of Study Product Supplies

At the end of the study, the investigator/designee, and a representative of GSK CH (study monitor) or designated vendor will inventory all used and unused study products. The study product accountability record for returned study products will then be completed. All study product (used and unused) for this clinical study, will be returned for destruction to the GSK CH Clinical Supplies Department or designated vendor using the return instructions provided. Detailed instructions for the return of study product for the accountability checks and subsequent destruction will be provided by GSK CH during the study in time for study close out visit.

6.5 Blinding and Allocation/Randomization

This is an open label study, and no blinding is required.

6.6 Breaking the Blind

Not applicable.

6.7 Compliance

Subjects will be asked to follow the label and leaflet instructions as recommended for nasal congestion relief. Compliance will be determined by treatment consumption, as reported in the study app. Subjects eligible for the treatment will be asked to complete an eDiary documenting specifics of product use each day. Although subjects may use the product for up to 7 days, those who report resolution of nasal symptoms sooner will be discouraged from continuing to use the study treatment. Compliance calculations will take symptom resolution into account.

Missed assessments will be recorded as such. Exceptions will be made for subjects who report having experienced technical or connectivity issues that prevented them from accessing the app. Compliance will be calculated as an ongoing measure throughout the treatment. For subjects who are withdrawn or withdraw prior to the end of the treatment

period, percent adherence will be based on the number of days active in the study intervention prior to withdrawal.

6.8 Concomitant Medication/Treatment(s)

At screening, subjects will confirm their medical history and concomitants medication use via a phone call with the investigator/designee, and subjects on exclusionary medications will not move forward based on their responses. Thereafter, if any change in concomitant medication is reported while the subject is still enrolled in the study, the investigator/designee will be alerted to fill out the concomitant medications form.

In the event that the concomitant medication needs to be noted, this form will be available for investigator/designee to fill-out. If the subject reports to the investigator/designee incidences of being administered medication, supplements, or vaccines due to a health reason after signing consent, the investigator/designee will note this in concomitant medication form with its indication, unit dose, daily dose, and start and stop dates of administration in the study portal. Please see section 8.1.4 for details on noting medical history and section 12 for AE/SAE monitoring.

7 DISCONTINUATION OF STUDY INTERVENTION AND SUBJECT DISCONTINUATION/WITHDRAWAL

7.1 Subject Discontinuation/Withdrawal

A subject may withdraw from the study at any time at their own request or may be withdrawn at any time at the discretion of the local PI or sponsor for safety, behavioral reasons, or the inability of the subject to comply with the protocol-required schedule of study activities.

The following circumstances require discontinuation of study product and/or premature subject withdrawal:

- Protocol violation that may impact the subject's safety
- Withdrawal of informed consent
- Subject lost to follow-up
- Pregnancy

If a subject is discontinued or prematurely withdraws from the study, the reason(s) for discontinuation or withdrawal and the associated date will be recorded in the CCI portal.

7.2 Lost to Follow-Up

A subject will be considered lost to follow-up if he or she is repeatedly unable to be contacted by CCI or designee within the permitted missed reminders (logins).

Before a subject is deemed lost to follow-up, CCI or designee must make every effort to regain contact (up to 3 attempts to contact the subject will be made). These contact attempts should be documented if they occur outside of the study app. If contact is made with the subject, the investigator/designee should inquire about the reason for missing login, and if appropriate, request that the subject to follow-up regarding any unresolved adverse events (AEs).

Should the subject continue to be unreachable, they will be considered to have withdrawn from the study and lost to follow-up.

If the subject withdraws from the study and withdraws consent for disclosure of future information, 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.

8 STUDY PROCEDURES

This section lists the procedures to be completed for each planned study time point. However, as per nature of RWE studies, if a subject fails to complete their daily questionnaires at any timepoint post-baseline, subjects will be permitted to continue in the study. The timing of each procedure is listed in the Schedule of Activities section.

8.1 Screening

The following data will be collected in the study app for screening:

- Informed Consent
- Demographics & Shipping information
- Screening Questionnaire
- WURSS-21 Questionnaire
- Medical History/Concomitant medication checklist

8.1.1 Informed Consent

e-Consent is a tool that assists in the consent process by using multimedia components delivered by an electronic system. The multimedia components may consist of video, audio, knowledge review, dictionary, and electronic signature.

The eIC process for this study will be performed using the study app on the subject's mobile device.CCI will provide training on the study app and portal.

Once the subject downloads the study app and completes the registration process, an eIC interview phone call will be conducted, and the eIC form will be made available to the subject through the study app. During the eIC phone call subjects will have the opportunity to ask any questions they may have. Subject identification will be checked during the

consent interview phone call. Subjects that sign the eIC will have the option to download the signed eIC to save a copy for local reference and/or access the signed eIC through the study app once the investigator/designee countersigns and attests that the consent interview phone call was completed.

Subjects will be able to electronically sign the eIC in the study app and email a signed copy of the eIC to themselves. The signed eIC will also be available at all times within the study app for immediate access.

Any identifiable subject data are isolated to a special team at CCI designated for that purpose. Any such data will not be transferred or available to the sponsor (GSK CH).

If, during participation in the study, any new information becomes available that may affect the subjects' willingness to continue with the study, each ongoing subject will receive this new information and be re-consented into the study.

After signing the eIC, subjects will undergo the screening procedures. Subjects that meet the screening criteria are considered enrolled to participate in the study.

8.1.2 Demographics

The following demographic information will be recorded in the study app: year of birth, gender, and race.

Ethnicity and race of subjects will be recorded in accordance with FDA Guidance for Industry: Collection of Race and Ethnicity Data in Clinical Trials, 2005.

8.1.3 Inclusion/Exclusion Criteria

Inclusion and exclusion criteria information will be collected in a screening questionnaire in the study app.

8.1.4 Medical History

Subjects that continue to be eligible for participation in this study after providing eIC will confirm their medical history and concomitant medication use via a phone call with the investigator/designee. Subjects meeting any of the exclusionary criteria will be excluded from the study.

If a health change is reported after signing the consent and if the event qualifies as a medical history, the investigator/designee will fill out the medical history form to document this. Relevant medical and surgical history, including allergies or drug sensitivity can be documented by the investigator/designee in the medical history form.

Please refer to section 12 for further details on Adverse Event and Serious Adverse Event Monitoring and to section 6.8 for further details on concomitant medications.

8.1.5 Subject Eligibility

Relevant inclusion/exclusion criteria, medical history, and medications to assess subjects with common cold eligibility and enrollment will be assessed at baseline and confirmed upon receipt of study product.

8.2 Study Period

8.2.1 Days 0-7

The number of days each subject will actively engage with the study will vary according to the resolution of their nasal symptoms. Subjects will use the nasal spray for up to 7 days (as per leaflet instructions) unless their nasal symptoms resolve prior to that. If symptoms and subject reporting continues for the full 7 days, subjects will complete the questionnaire for 7 days (baseline + 6 post treatment days). Subjects with nasal symptoms resolved sufficiently to no longer warrant product use or those who determine they no longer wish to medicate for nasal congestion symptoms will complete daily forms from baseline through one day after the last dose of study. This will complete their "study period".

The following assessments will be completed in the study app during the study period:

- Subjects will report any changes in health, concomitant medications, or non-drug treatments/procedures
- Subjects will complete WURSS-21 questionnaire and additional QoL questions each day
- Subjects will complete an eDiary to record product use each day
- Subjects will report any adverse events
- Subjects will report the end of nasal symptoms (or sufficiently reduced)/stop of product use and answer end of the study questions prior to exiting the study

8.3 Study Conclusion

The Study Conclusion page of the eCRF (CCI portal) will be completed for all subjects by the study team. If the subject discontinued early, at any point during the study, the primary reason for discontinuation (if available) should be recorded on the Study Conclusion page.

If a subject experiences any AEs, at the end of the study, GSK CH will be notified. AEs may be marked as unresolved and local study PI will ask the subject to seek appropriate healthcare professional care, if applicable.

8.4 Follow-Up Phone Call

The local PI will contact a subject to follow up on any reported AE/SAE post-study completion/withdrawal to ensure any issues are resolved as soon as possible. The local PI

must make every effort to regain contact with the subject (where possible, 3 notifications). Should the subject continue to be unreachable, the AE/SAE will be considered unresolved.

9 STUDY ASSESSMENTS

Every effort should be made to ensure that protocol required procedures and assessments are completed as described.

9.1 Screening Assessments

Subject enrollment will be determined based on the inclusion/exclusion criteria and screening questionnaire responses.

9.2 Quality of Life Assessments

The following quality of life tools will be completed by subjects daily the study app from receipt of product to study conclusion.

- WURSS-21 Questionnaire
- Additional QoL Questions (in appendix section 15.2.2)

9.3 Safety and Other Assessments

Subjects will report any adverse events throughout the study from eConsent to study conclusion in the study app.

Subjects will complete eDiary to record product use each day (number of sprays and time of use)

Subjects will complete end of the study questions (in appendix).

The local investigator/designee will record any relevant medical and surgical history, including allergies or drug sensitivity, and adverse events. The local investigator/designee will also record use of any current medications/treatments, including prescription and non-prescription drugs, dietary supplements, and herbal remedies.

10 ADVERSE EVENT AND SERIOUS ADVERSE EVENTS

The local PI is responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE and remain responsible for following up on AEs that are serious, considered related to the study product or the study, or that caused the subject to discontinue the study product or study.

10.1 Definition of an Adverse Event (AE)

An AE is any untoward medical occurrence in a clinical study subject, temporally associated with the use of a study product including any washout or lead-in product (or

medical device), whether or not considered related to the study product, including any washout or lead-in product (or medical device).

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 the use of a study product including any washout or lead-in product (or medical device).

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 (i.e., not related to progression of underlying disease).
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study product administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study product or 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 (if applicable) 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 subject'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 subject's condition.
- Medical or surgical procedure (e.g., endoscopy, appendectomy) is not the AE. The condition that leads to the procedure is an AE (e.g., appendicitis).
- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.2 Definition of a Serious Adverse Event (SAE)

A SAE is a particular category of an adverse event where the adverse outcome is serious. 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).

A serious adverse event is any untoward medical occurrence at any dose that:

- **Results in death**
- **Is life threatening**
  - The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
- **Requires inpatient hospitalization or prolongation of existing hospitalization**
  - In general, hospitalization signifies that the subject 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 pre-existing condition that did not worsen from baseline is not considered an AE.
- **Results in persistent or significant 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.
- **Results in congenital anomaly/birth defect**
- **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 subject 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.

Note: Classification of an AE as 'serious' is based on the outcome of the event and is a factor in determining reporting requirements.

10.3 Time Period and Frequency for Collecting AE and SAE Information

Any AEs the subject experiences immediately after they provide consent to participate in the study, by the completion (signature) of the eIC, but prior to the use of the study product will be reported as Medical History by the investigator/designee.

Any events experienced from the first use of study product until last day of the study will be recorded as AEs. All SAEs will be collected immediately after a subject provides consent signature until last administration of the study product.

Details recorded by the subject on the study app that meet the definition of an AE must also be discussed with the subject.

All SAEs will be recorded and reported to GSK CH immediately and under no circumstance should this exceed 24 hours. CCI or it's designated representative will submit any updated SAE data to GSK CH within 24 hours of it being available.

CCI or its designated representative is not obligated to actively seek AEs or SAEs after the conclusion of the study participation. However, if CCI or its designated representative learns of any SAE, including a death, at any time after a subject has been discharged from the study, and considers the event to be reasonably related to the study product or study participation, CCI or it's designated representative must promptly notify GSK CH by emailing the information to the GSK CH Clinical Operations Safety Reporting email box PPD The GSK CH Study Manager or designee will be responsible for forwarding the information to the Case Management Group, Global Safety group mailbox at GSK PPD

CCI or it's designated representative will submit any updated SAE data to GSK CH within the designated reporting time frames.

10.4 Reporting Procedures

The investigator or a medically qualified designee is responsible for detecting, documenting and reporting events that meet the definition of an AE and remain responsible for following up on AEs that are serious, considered related to the study product(s), participation in the study or a study procedure, or that caused the subject to discontinue the study product or study.

Spontaneous reporting of adverse events and those elicited by asking subjects to respond to non-leading such as "How do you feel" will be assessed, recorded in the eCRF and reported appropriately.

The investigator or medically qualified designee is to report all directly observed AEs and all AEs spontaneously reported by the study subject. In addition, each study subject will be questioned about AEs.

Each AE is to be assessed to determine if it meets the criteria for a SAE. If an SAE occurs, expedited reporting will follow local and international regulations, as appropriate.

When an AE occurs, it is the responsibility of the investigator (or medically qualified designee) to review all documentation (e.g. hospital progress notes, laboratory, and diagnostics reports) related to the event.

The investigator or medically qualified designee will then record all relevant information regarding an AE in the eCRF and all details relating to a SAE in the SAE Form provided to be emailed to GSK CH.

It is not acceptable for the investigator or medically qualified designee to send photocopies of the subject's medical records to GSK CH in lieu of completion of the AE eCRF page/SAE form.

There may be instances when copies of medical records for certain cases are requested by GSK CH. In this instance, all subject identifiers, except for the subject number, will be redacted on the copies of the medical records prior to submission to GSK CH.

The investigator or medically qualified designee will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. The diagnosis will be the documented as the AE/SAE where known and not the individual signs/symptoms. (e.g. upper respiratory tract infection, seasonal allergy, etc. instead of runny nose).

AEs elicited by the investigator or medically qualified designee in a standard manner should also be recorded in the AE section of the eCRF and/or using the SAE form (subject to the classification of the AE). Care will be taken not to introduce bias when questioning a subject about any changes in their health. Open-ended and non-leading verbal questioning should be used.

10.4.1 Reporting of an Adverse Event

Spontaneous reporting of AEs will be recorded in the CCI app and reported appropriately. Care will be taken not to introduce bias when questioning a subject about any changes in their health.

Subjects will have the ability to report changes to their health via the CCI app through the Health Change Form or chat function. Subject may also choose to communicate with the virtual site study team via email or phone call to report a change to their health. Upon reporting of health change by the subject through these methodologies,

the study doctor or designee will be alerted to reach out to the subject to follow-up for a possible AE and document their findings within the CCI study portal.

All AEs will be recorded within study portal. It is not acceptable for CCI to share any subject's medical records to GSK CH in lieu of completion of the AE form. Each AE is to be assessed by the local PI to determine if it meets the criteria for a SAE. If a SAE occurs, expedited reporting will follow local and international regulations, as appropriate.

10.4.2 Reporting of a Serious Adverse Event

Following completion of the subject AE page within study app, the local PI will review the self-reported information and assess if the AE meets the definition of an SAE. The local PI will enter available information into the SAE form and will forward the completed SAE form to GSK CMG within 24 hours of receiving the questionnaire data.

If additional details are required from the subject in order to determine if the reported AE meets SAE criteria, the investigator/designee will re-contact the subject to query the AE details. If it is not possible to re-contact the subject within 24 hours, the local PI will complete the SAE form to the extent possible with the available information and will send to GSK CMG within the 24-hour time frame. The investigator/designee will contact the subject on a further 3 occasions to attempt to collect further details and will share additional information with GSK CMG.

The SAEs will be recorded within study portal. It is not acceptable for CCI to share any subject's medical records to GSK CH in lieu of completion of the AE form.

In addition to the subject recording the event on the study app, all SAEs will be reported to Case Management Group (CMG), Global Safety at GSK CH (GSK CMG).

It is essential to enter the following information:

- Protocol and subject identifiers
- Subject demography
- Description of events, with diagnosis if available
- Investigator opinion of relationship to study product (or study procedure, if appropriate)
- Criterion for seriousness

The following are desirable and are of particular relevance for local PI and GSK CH assessment of the SAE report:

- Date of onset of AE
- Date AE stopped, if relevant
- Study product start date
- Study product end date if relevant

- Action taken in relation to the study product
- Outcome if known

All collected SAE-related data should be sent to GSK CMG PPD, GSK CH Clinical Operations Safety Reporting email box PPD and the GSK clinical study manager associated with the present study.

In order to maintain compliance with international and national regulatory bodies, the subject will be notified in the eIC that they may be further contacted in order to collect additional information required to evaluate the potential event.

AEs/SAEs will be reported to local and regional health authorities by GSK CH, when appropriate, in accordance with applicable local and regional regulations. Prompt notification of SAEs by the local PI to GSK CH is essential so that legal obligations and ethical responsibilities towards the safety of subjects are met.

GSK CH will comply with country specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/EC, etc. The local PI and GSK CH will comply with all local medical device reporting requirements. Safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy.

10.5 Evaluating Adverse Events

10.5.1 Assessment of Intensity

The local PI will make an assessment of intensity for each AE reported during the study and will assign it to one of the following categories:

- Mild: An event that is easily tolerated by the subject, causing minimal discomfort, and not interfering with everyday activities.
- Moderate: An event that is sufficiently discomforting to interfere with normal everyday activities
- Severe: An event that prevents normal everyday activities.

NOTE: 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 non-serious AEs and SAEs can be assessed as severe. For example, a headache may be severe (interferes significantly with the subject's usual function) but would not be classified as serious unless it met one of the criteria for SAEs, listed above. 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.

10.5.2 Assessment of Causality

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

For each AE (serious and non-serious), the local PI **must** provide an assessment of causality on the AE eCRF page and the SAE form (subject to the classification of the AE). The local PI will also document in the medical notes that he/she has reviewed the AE and assessed causality, where applicable.

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. Generally, the facts (evidence) or arguments to suggest a causal relationship should be provided.

The local PI will use clinical judgment to determine the relationship and will also consult the Product Information, for marketed products, in the determination of his/her assessment. Alternative causes, such as underlying disease(s), concomitant therapy, other risk factors, and the temporal relationship of the event to the study product will be considered and investigated.

For each AE/SAE, the local PI must document in the subject record notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.

The local PI or assessment of causality must be provided for all AEs (serious and non-serious); the local PI must record the causal relationship in the study app, as appropriate, and report such an assessment in accordance with the SAE reporting requirements if applicable.

There may be situations when an SAE has occurred, and the local PI has minimal information to include in the initial report to GSK. **However, it is very important that the local PI always make an assessment of causality for every event prior to the initial transmission of the SAE data to GSK CH.** The local PI may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.

10.6 Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator/designee is required to proactively follow up with each subject and provide further information on the subject's condition.

All AEs (serious and non-serious) will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the subject is lost to follow-up. For non-serious events, if the event remains unresolved upon study exit, the local PI will mark the event as unresolved and provide a referral to the subject for further care, if applicable.

The local PI is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as may be indicated or as requested by GSK CH to

elucidate as fully as possible the nature and/or causality of the AE. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

New or updated information will be recorded on the AE eCRF page and on the SAE form (subject to the classification of the AE).

The local PI will submit any updated SAE data to GSK CH within 24 hours of receipt of the information.

Investigators/designees are not obliged to actively seek AEs in former subjects. However, if the investigator/designee or virtual site study team learns of a SAE, including death, at any time after a subject has been discharged from the study, and considers the event reasonably related to the study product or study participation, the local PI will promptly notify GSK CH by emailing the information to the GSK CH Clinical Operations Safety Reporting email box PPD The GSK CH Study Manager or designee will be responsible for forwarding the information to the Case Management Group, Global Clinical Safety and Pharmacovigilance group mailbox at GSK PPD

The local PI or virtual site study team will submit any updated SAE data to GSK CH within the designated reporting time frames.

10.7 Withdrawal Due to an Adverse Event

Withdrawal due to AEs should be distinguished from withdrawal due to other causes, according to the definition of an AE noted earlier, and recorded on the appropriate AE study app page.

When a subject withdraws because of an SAE, the SAE must be reported in accordance with the reporting requirements defined.

10.8 Regulatory Reporting Requirements for SAEs

GSK CH has a legal responsibility to notify, as appropriate, the local regulatory authority and other regulatory authorities about the safety of a product under clinical investigation. Prompt notification of SAEs by the PI to GSK CH is essential so that legal obligations and ethical responsibilities towards the safety of subjects are met.

GSK CH will comply with country specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/EC, and investigators.

PI safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator safety report which describes an SAE or other specific safety information e.g., summary or listing of SAEs from the sponsor will be reviewed by the PI and then filed in the investigator study master file. The PI or designee will notify the IRB/IEC, if appropriate according to local requirements.

10.9 Pregnancy

10.9.1 Time Period for Collecting Pregnancy Information

As per Summary of Product Characteristics, no fetal toxicity or fertility studies have been carried out in animals. In view of its potential systemic vasoconstrictor effect, it is advisable to take the precaution of not using Otrivine during pregnancy.

No evidence of any adverse effect on the breast-fed infant. However, it is not known if xylometazoline hydrochloride is excreted in breast milk, therefore caution should be exercised and Otrivine should be used only on the advice of a doctor whilst breastfeeding.

Although study product use is not recommended during pregnancy, and this is an exclusion criterion for participating in the study, pregnancy information will be collected on all pregnancies reported while a female subject is participating in the study from the signing of informed consent until 1 day after last administration of study product.

10.9.2 Action to be Taken if Pregnancy Occurs

The local PI will record pregnancy information on the appropriate form scan and e-mail it to the GSK CH Clinical Operations Safety Reporting email box PPD PPD within 24 hours of learning of the subject becoming pregnant. The GSK CH Study Manager or designee will be responsible for forwarding the pregnancy form to the Case Management Group, Global Clinical Safety and Pharmacovigilance mailbox PPD Original pregnancy information forms will be retained in the investigator study master file.

The subject will be followed to determine the outcome of the pregnancy. Information on the status of the mother and infant / neonate (including concomitant medications taken by the mother during the pregnancy) will be forwarded by the local PI or virtual site study team to the GSK CH Clinical Operations Safety Reporting email box and the GSK CH Study Manager or designee will forward this information to the Case Management Group, Global Clinical Safety and Pharmacovigilance group mailbox at GSK PPD Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported.

While pregnancy itself is not considered to be an AE, abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are, and should be recorded as an SAE.

Any female subject who becomes pregnant while participating will discontinue study treatment and be withdrawn from the study.

The investigator/designee will collect pregnancy information on any subject who becomes pregnant while participating in the study after administration of the investigational product. The local PI will record pregnancy information on the appropriate form and submit it to GSK CH within 24 hours of learning of the subject becoming pregnant. The subject will be followed to determine the outcome of the pregnancy. Information on the status of the mother and infant/neonate (including concomitant medications taken by the mother during the pregnancy) will be forwarded to GSK. Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported.

CCI will scan and email the pregnancy form to the Case Management Group, Global Clinical Safety and Pharmacovigilance group mailbox at GSK CH PPD with copy to the appropriate GSK CH Study Manager. Original pregnancy information forms will be retained in the investigator study master file.

11 DATA MANAGEMENT

As used in this protocol, the term eCRF is understood to refer to an electronic data record in the study portal.

For this study, subject data will be entered into the study app, which is a validated system. Data relating to SAEs, pregnancy and incidents will also be collected in the app.

CCI is responsible for verifying that data entries in the study app are accurate.

Each subject will be assigned and identified by a unique Screening Subject Number. Any reference made to an individual subject within the study must be done using their unique Screening Subject Number.

11.1 Case Report Form

A CRF is a printed, optical, or electronic document designed to record the protocol required information to be reported to the sponsor on each trial subject.

CCI must maintain accurate documentation (source data) that supports the information entered in the eCRF.

Management of clinical data will be performed in accordance with CCI applicable standards and data cleaning procedures with oversight by GSK CH to ensure integrity of the data, for example, to remove errors and inconsistencies in the data.

To protect the privacy of subjects, no personal information (including the subject's name or initials or full birth date) is to be recorded in the eCRF or as part of the query text.

All eCRF pages should be completed during a subject assessment when the eCRF has been designated as the source.

GSK CH will obtain and retain all eCRFs and associated study data as applicable at the completion of the study.

Identifiable data are isolated to a special team at CCI and these data will not be transferred/available to GSK CH.

11.2 Data Handling

Documentation of all data management activities should allow step-by-step retrospective assessment of data quality and study performance.

Any changes or corrections to data will be performed in the CCI Electronic Data Capture (EDC) Platform, and it will include rationale for changes. The EDC system has an audit trail, which will provide a complete record of the changes and corrections endorsed by the investigator/designee.

Adverse events will be coded using Medical Dictionary for Regulatory Activities (MedDRA) and any concomitant medications terms (if applicable) using a validated medication dictionary, WHODrug.

11.2.1 Data Queries

The CCI data management team will perform edit checks as the data are being entered into the system, and queries will be entered on a Data Issues Log for the decentralized site staff to address. CCI will raise queries as needed on safety data to code the terms (AEs and Drugs or concomitant medication) appropriately.

The study monitor will perform ongoing review the of the eCRFs in accordance with the monitoring plan, to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of subjects 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.

11.3 Processing Patient Reported Outcomes

Electronic Patient reported outcome (ePRO) data will be collected using electronic devices and transferred electronically to GSK CH or CCI

All ePRO source data should be reviewed by the study staff and the study monitor to ensure accurate transcription of data and that any potential AEs or concomitant medications reported on these documents are discussed with the subject and transcribed accurately to the eCRF and/or DMS. ePROs that are classed as source data will be retained by the investigator and true/certified copies may be sent to a designated vendor or GSK CH as

required. Any AEs or concomitant medications collected as ePRO will be reviewed and transcribed to the eCRF by a member of the study team.

To protect the privacy of subjects, no personal information (including the subject's name or initials or birth date) is to be recorded on any ePRO that will be forwarded to GSK CH or[redacted]

12 STATISTICAL CONSIDERATIONS AND DATA ANALYSES

12.1 Sample Size Determination

Sufficient individuals will be screened to enroll approximately 125 healthy eligible subjects assuming an estimated 20% drop out rate. It is believed that for this study 100 completed subjects are deemed sufficient to observe an improvement in QoL.

The sample size was based on a significance level (α) = 0.05, Power (1-β) = 80%, and a standardized effect size of 0.27. The effect size was chosen based on literature review to detect even mild improvement. “An effect magnitude between 0.2 and 0.5 indicates mild improvement, between 0.5 and 0.8 indicates moderate improvement, and greater than 0.8 indicates considerable improvement in symptoms and QoL”.

Literature review also indicated that QoL scores are not normally distributed. Subjects with worse baseline symptoms showed larger improvement in QoL scores. Therefore, a non-parametric Paired Wilcoxon sample size calculation was performed, using RStudio version 1.4.1103.

Using the above parameters, we obtain a sample size N =125 eligible subjects to retain 100 completed subjects.

12.2 Populations for Analysis

- The enrolled population will include all subjects who meet the inclusion/exclusion criteria.
- The safety population will include all subjects who use study product at least once. Safety population will be used of safety variables.
- The modified Intent-To-Treat (mITT) population will include all subjects who use study product at least once and have data from at least one post baseline QoL questionnaire to support at least one of the primary endpoint assessments. QoL and ePRO data will be summarized using the mITT population only.

12.3 Statistical Analyses

Additional details of the proposed statistical analysis will be documented in the statistical analysis plan (SAP), which will be written following finalization of the protocol and prior

to study analysis. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

12.3.1 Primary Analysis

For the primary objective, measurements of health related QoL indicators and cold symptoms will be evaluated using total scores, QoL domains scores, symptom domains scores and single domains scores using the WURSS-21 questionnaire pre and post treatment to determine the effect of Otrivine on QoL factors and cold symptoms. Change in mean WURSS-21 scores from pre and post treatment will be summarized for each study day and analyzed using a Student's paired t-test. If data are found to be non-normal a non-parametric Hodges-Lehmann test will be used.

12.3.2 Secondary Analysis

For the secondary objective, subjects' pre-treatment score will be used to determine the effect of Otrivine on additional QoL parameters. Median post-treatment scores will be presented for each day of treatment through Day 7 or until data are no longer provided due to nasal symptom resolution, whichever comes first.

12.3.3 Safety Analysis(es)

All AEs will be coded using MedDRA. AEs will be categorized as related, probable, unlikely, or unrelated by CCI prior to database lock. The number of AEs/SAEs and number of subjects with AEs/SAEs will be listed and tabulated.

12.3.4 Exploratory Analysis(es)

For the exploratory objective, time to resolution of symptoms will be evaluated using Kaplan-Meier curves of QoL factors. The median time to resolution of symptoms based on the Kaplan-Meier curve will be presented as well.

12.3.5 Exclusion of Data from Analysis

Exclusion of any data from the analyses will be determined during a Blind Data Review (BDR) Meeting prior to database lock. Any reasons for exclusion from an analysis population will be listed, if applicable.

12.3.6 Demographic and Baseline Characteristics

Age and other continuous demographic and baseline variables will be summarized using descriptive statistics such as mean, range, median and standard deviation. Gender and other categorical demographic and baseline variables will be summarized using frequency counts and percentages for the safety and mITT populations.

12.3.6 Study Drug/Product Compliance and Use of Other Therapies

12.3.6.1 Study Drug/Product Compliance

Study product compliance will be tabulated and summarized for the safety population. Summaries will include a simple yes/no frequency (and percent) count at each timepoint.

12.3.6.2 Prior and Concomitant Medications

Concomitant medications taken during the study will be listed for the safety population.

12.3.7 Handling of Dropouts and Missing Data

Missing data due to general dropout/withdrawals will be assessed on an ongoing basis during the study. Any further sensitivity analyses needed due to missing data will be reviewed at the time of data review. Additional details will be provided in the data management plan, and reporting and statistical analysis plan.

12.3.8 Interim Analysis

No interim analysis is planned for this study

13 STUDY GOVERNANCE CONSIDERATIONS

13.1 Quality Control

When reviewing data collection procedures, the discussion will include identification, agreement, and documentation of data items for which the eCRF will serve as the source document.

CCI will monitor the study data to verify that the:

- Data are authentic, accurate, and complete.
- Safety and rights of subjects are being protected.
- Study is conducted in accordance with the currently approved protocol and any other study agreements, GCP, and all applicable regulatory requirements.

13.2 Quality Assurance

To ensure compliance with GCP and all applicable regulatory requirements, GSK CH may conduct a quality assurance assessment and/or audit of the site records, and the regulatory agencies may conduct a regulatory inspection at any time during or after completion of the study.

In the event of an assessment, audit, or inspection, CCI must agree to grant the advisor(s), auditor(s), and inspector(s) direct access to all relevant documents and to allocate their time and the time of their staff to discuss the conduct of the study, any

findings/relevant issues and to implement any corrective and/or preventative actions to address any findings/issues identified.

CCI will notify GSK CH or its agents immediately of any regulatory inspection notification in relation to the study.

The sponsor will be available to help CCI prepare for an inspection.

13.3 Regulatory and Ethical Considerations

13.3.1 Institutional Review Board/ Ethics Committee

It is the responsibility of CCI to have prospective approval of the study protocol, protocol amendments, informed consent documents, and other relevant documents, e.g., recruitment advertisements, if applicable, from the IRB/EC. All correspondence with the IRB/EC should be retained in the investigator file. Copies of IRB/EC approvals should be forwarded to GSK CH prior to the initiation of the study, and when subsequent amendments to the protocol are made.

The only circumstance in which an amendment may be initiated prior to IRB/EC approval is where the change is necessary to eliminate apparent immediate hazards to the subjects. In that event, the PI must notify the IRB/EC and GSK CH in writing immediately after the implementation.

13.3.2 Ethical Conduct of the Study

The study will be conducted in accordance with the protocol and legal and regulatory requirements, as well as the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002), International Ethical Guidelines for Health-Related Research Involving Humans (Council for International Organizations of Medical Sciences, 2016), guidelines for GCP (ICH 1996 and revision 2), and the Declaration of Helsinki (World Medical Association 2013).

In addition, the study will be conducted in accordance with the protocol, the ICH guideline on GCP, and applicable local regulatory requirements and laws.

13.3.3 Subject Information and Consent

All parties will ensure protection of subject personal data and will not include subject names or other identifiable data in any reports, publications, or other disclosures, except where required by laws.

When study data are compiled for transfer to GSK CH and other authorized parties, subject names, addresses, and other identifiable data will be replaced by numerical codes based on a numbering system provided by GSK CH in order to de-identify study subjects.

The study site will maintain a confidential list of subjects who participated in the study, linking each subject's numerical code to his or her actual identity. In case of data transfer,

GSK CH will maintain high standards of confidentiality and protection of subjects' personal data consistent with applicable privacy laws.

The informed consent document must be in compliance with ICH GCP, local regulatory requirements, and legal requirements, including applicable privacy laws.

The IC document used during the IC process must be reviewed and approved by the sponsor, approved by the IRB/EC before use, and available for inspection.

The investigator/designee must ensure that each study subject is fully informed about the nature and objectives of the study and possible risks associated with participation.

CCI will obtain eIC from each subject before any study specific activity is performed. The investigator will retain the original of each subject's signed eIC document.

13.3.4 Subject Recruitment

Advertisements approved by IRBs/ECs and investigator databases may be used as recruitment procedures. Use of ethics committee approved, generic, prescreening questionnaire to assess basic subject characteristics to determine general eligibility for this study is allowed.

GSK CH will have an opportunity to review and approve the content of any study recruitment materials directed to potential study subjects before such materials are used.

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

Within GSK CH a serious breach is defined as a breach likely to affect to a significant degree the safety and rights of a subject or the reliability and robustness of the data generated in GSK CH sponsored human subject research studies.

In the event of any prohibition or restriction imposed (i.e., clinical hold) by an applicable competent authority in any area of the world, or if CCI is aware of any new information that might influence the evaluation of the benefits and risks of the investigational product, GSK CH should be informed immediately.

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

13.4 Posting of Information on Publicly Available Clinical Trial Registers

Study information from this protocol will be posted on publicly available clinical trial registers before enrollment of subjects begins in accordance with applicable GSK CH processes.

GSK CH intends to make anonymized subject-level data from this trial available to external researchers for scientific analyses or to conduct further research that can help advance medical science or improve patient care. This helps ensure the data provided by trial subjects are used to maximum effect in the creation of knowledge and understanding

13.5 Provision of Study Results to Investigators

Where required by applicable regulatory requirements, a local PI signatory will be identified for the approval of the clinical study report. The local PI will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a GSK CH site or other mutually agreeable location.

GSK CH will also provide the local PI with the full summary of the study results. The local PI is encouraged to share the summary results with the study subjects, as appropriate.

The procedures and timing for public disclosure of the results summary and for development of a manuscript for publication will be in accordance with GSK CH Policy.

A manuscript will be progressed for publication in the scientific literature if the results provide important scientific or medical knowledge.

13.6 Records Retention

Following closure of the study, CCI must maintain all study records (except for those required by local regulations to be maintained elsewhere), in a safe and secure location.

The records (study/ site master file) must be maintained to allow easy and timely retrieval, when needed (e.g., for a GSK CH audit or regulatory inspection) and must be available for review in conjunction with assessment of the facility, supporting systems, and relevant site staff.

Where permitted by local laws/regulations or institutional policy, some or all of these records can be maintained in a format other than hard copy (e.g., microfiche, scanned, electronic); however, caution needs to be exercised before such action is taken.

CCI must ensure that all reproductions are legible and are a true and accurate copy of the original and meet accessibility and retrieval standards, including re-generating a hard copy, if required. Furthermore, the investigator must ensure there is an acceptable back-up of these reproductions and that an acceptable quality control process exists for making these reproductions.

CCI must assure that the subject's anonymity will be maintained. On eCRFs or other documents submitted to GSK CH, subjects should not be identified by their names or initials, but by an identification code. CCI should keep a separate log of subjects' codes, names, and addresses. Documents not for submission to GSK CH, e.g.,

subjects' written consent forms, should be maintained by the investigator in strict confidence.

Records and documents, including signed eIC, pertaining to the conduct of this study must be retained by the investigator as per the signed contractual agreement, from the issue of the final Clinical Study Report (CSR) or equivalent summary, unless local regulations or institutional policies require a longer retention period. The minimum retention time will meet the strictest standard applicable to that site for the study, as dictated by any institutional requirements or local laws or regulations, GSK CH standards/procedures, and/or institutional requirements.

No study document should be destroyed without a prior written agreement between GSK CH and the investigator. The investigator must notify GSK CH of any changes in the archival arrangements, including, but not limited to, archival at an off-site facility or transfer of ownership of the records in the event the investigator is no longer associated with the site.

13.7 Conditions for Terminating the Study

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/EC, or study product safety problems, or at the discretion of GSK CH.

If a study is prematurely terminated, GSK CH will promptly notify CCI After notification, CCI must promptly contact all participating subjects and should assure appropriate therapy/ follow-up for the subjects. As directed by GSK CH, all study materials must be collected and all eCRF's completed to the greatest extent possible. Where required by the applicable regulatory requirements, GSK CH should inform the regulatory authority(ies) and the investigator should promptly inform the IRB/EC and provide the IRB/EC a detailed written explanation of the termination or suspension.

If the IRB/EC terminates or suspends its approval/favorable opinion of a trial, the local PI or designee should promptly notify the GSK CH and provide GSK CH with a detailed written explanation of the termination or suspension.

Upon completion or premature discontinuation of the study, the GSK CH monitor will conduct site closure activities withCCI as appropriate, in accordance with applicable regulations including GCP, and GSK CH Standard Operating Procedures.

14 REFERENCES

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[Eccles R, Eriksson M, Garreffa S, et al. (2008)] The nasal decongestant effect of xylometazoline in the common cold. Am J Rhinol; 22(5): 491-6.

[Heikkinen T, Jarvinen A (2003)] The common cold. Lancet; 361(9351): 51-9.

[Hemila H (2017)] Vitamin C and Infections. Nutrients; 9(4).

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[Sherman RE, Anderson SA, Dal Pan GJ, et al. (2016)] Real-World Evidence - What Is It and What Can It Tell Us? N Engl J Med; 375(23): 2293-7.

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15 APPENDICIES

15.1 ABBREVIATIONS

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

Table 15-1 Abbreviations

Abbreviation	Term
AE	Adverse event
ANOVA	Analysis of variance
COACH	Clinical Oversight and Coordination Hub
CRF	Case report form
EC	Ethics committee
eCRF	Electronic Case Report Form
EudraCT	European Clinical Trials Database
FDA	Food and Drug Administration (United States)
GCP	Good Clinical Practice
HSI	Human Subject Information
IB	Investigator's brochure
ICH	International Conference on Harmonisation
ID	Identification
IEC	Independent Ethics Committee
IRB	Institutional review board
IRC	Internal review committee
MedDRA	Medical Dictionary for Regulatory Activities
N/A	Not applicable
OTC	Over the counter (reference to medications available without prescription)
PI	Principal investigator
QC	Quality control
QoL	Quality of Life
RCT	Randomized Clinical Trial
RWD	Real World Data
RWE	Real World Evidence
SAE	Serious adverse event
SOP	Standard operating procedure

15.2 STUDY QUESTIONNAIRES

15.2.1 Wisconsin Upper Respiratory Symptom Survey – 21 (WURSS-21)

Wisconsin Upper Respiratory Symptom Survey – 21 --- *Daily Symptom Report*

Day:	*Date:*	*Time:*	*ID:*

Please fill in one circle for each of the following items:

	Not sick	Very mildly		Mildly		Moderately		Severely
	0	1	2	3	4	5	6	7
How sick do you feel today?	o	o	o	o	o	o	o	o

Please rate the **average severity of your cold symptoms over the last 24 hours** for each symptom:

	Do not have this symptom	Very mild		Mild		Moderate		Severe
	0	1	2	3	4	5	6	7
Runny nose	o	o	o	o	o	o	o	o
Plugged nose	o	o	o	o	o	o	o	o
Sneezing	o	o	o	o	o	o	o	o
Sore throat	o	o	o	o	o	o	o	o
Scratchy throat	o	o	o	o	o	o	o	o
Cough	o	o	o	o	o	o	o	o
Hoarseness	o	o	o	o	o	o	o	o
Head congestion	o	o	o	o	o	o	o	o
Chest congestion	o	o	o	o	o	o	o	o
Feeling tired	o	o	o	o	o	o	o	o

Over the last 24 hours, how much has your cold interfered with your ability to:

	Not at all	Very mildly		Mildly		Moderately		Severely
	0	1	2	3	4	5	6	7
Think clearly	o	o	o	o	o	o	o	o
Sleep well	o	o	o	o	o	o	o	o
Breathe easily	o	o	o	o	o	o	o	o
Walk, climb stairs, exercise	o	o	o	o	o	o	o	o
Accomplish daily activities	o	o	o	o	o	o	o	o
Work outside the home	o	o	o	o	o	o	o	o
Work inside the home	o	o	o	o	o	o	o	o
Interact with others	o	o	o	o	o	o	o	o
Live your personal life	o	o	o	o	o	o	o	o

Compared to yesterday, I feel that my cold is…

Very much better	Somewhat better	A little better	The same	A little worse	Somewhat worse	Very much worse
o	o	o	o	o	o	o

WURSS -21® (Wisconsin Upper Respiratory Symptom Survey) 2004
Created by Bruce Barrett MD PhD et al., UW Department of Family Medicine, 777 S. Mills St. Madison, WI 53715, USA

15.2.2 Additional QoL Questions

Baseline Questions (pre-treatment):

Instructions: Considering the last 24 hours, please read each question and choose the answer that best reflects your experience with your nasal congestion before the use of Otrivine.

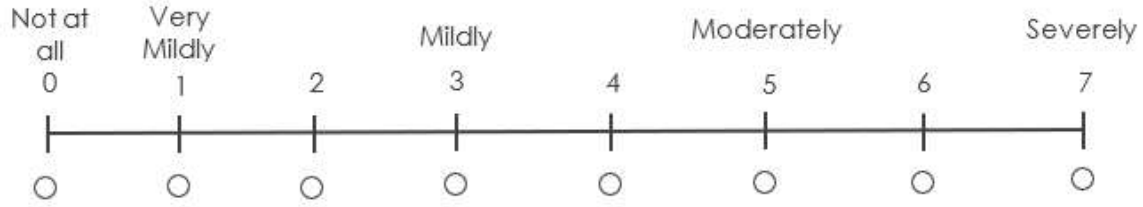
- Before using Otrivine, is your nasal congestion/cold making you snore during the night? (*For those with sleeping partners only)
- Before using Otrivine, is your nasal congestion/cold making you slow in your responses?
- Before using Otrivine, is your nasal congestion/cold making you self-conscious about how you sound?
- Before using Otrivine, is your nasal congestion/cold affecting your sense of smell?
- Before using Otrivine, is your nasal congestion/cold affecting your sense of taste?
- Before using Otrivine, is your nasal congestion/cold making you self-conscious around people?
- Before using Otrivine, is your nasal congestion/cold making you less energetic than usual?
- Before using Otrivine, is your nasal congestion/cold making you less motivated than usual?

Post treatment Questions (asked every day in the morning)

Instructions: Considering the past 24 hours, please read each question and choose the answer that best reflects your experience with Otrivine use and your nasal congestion.

- After using Otrivine, is your nasal congestion/cold making you snore during the night? (*For those with sleeping partners only)
- After using Otrivine, is your nasal congestion/cold making you slow in your responses?
- After using Otrivine, is your nasal congestion/cold making you self-conscious about how you sound?
- After using Otrivine, is your nasal congestion/cold affecting your sense of smell?
- After using Otrivine, is your nasal congestion/cold affecting your sense of taste?
- After using Otrivine, is your nasal congestion/cold making you self-conscious around people?
- After using Otrivine, is your nasal congestion/cold making you less energetic than usual?
- After using Otrivine, is your nasal congestion/cold making you less motivated than usual?

Please rate each of the statements:



End of the study questions

- **How would you rate your satisfaction with the treatment?**

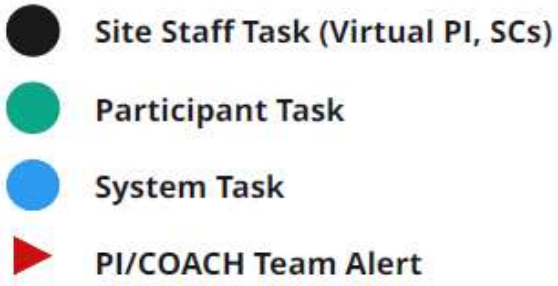
  Very Satisfied
  Satisfied
  Neutral
  Dissatisfied
  Very Dissatisfied
  Please explain why you chose Very Satisfied/Satisfied/Neutral/Dissatisfied/Very Dissatisfied?

- **Will you use this kind of treatment again?**

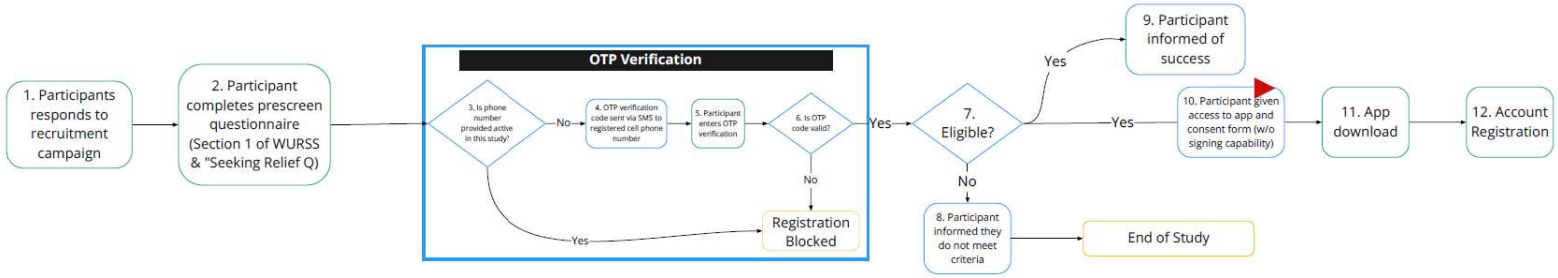
  Yes
  No
  Please explain why you would/would not use this product again

Happy Path

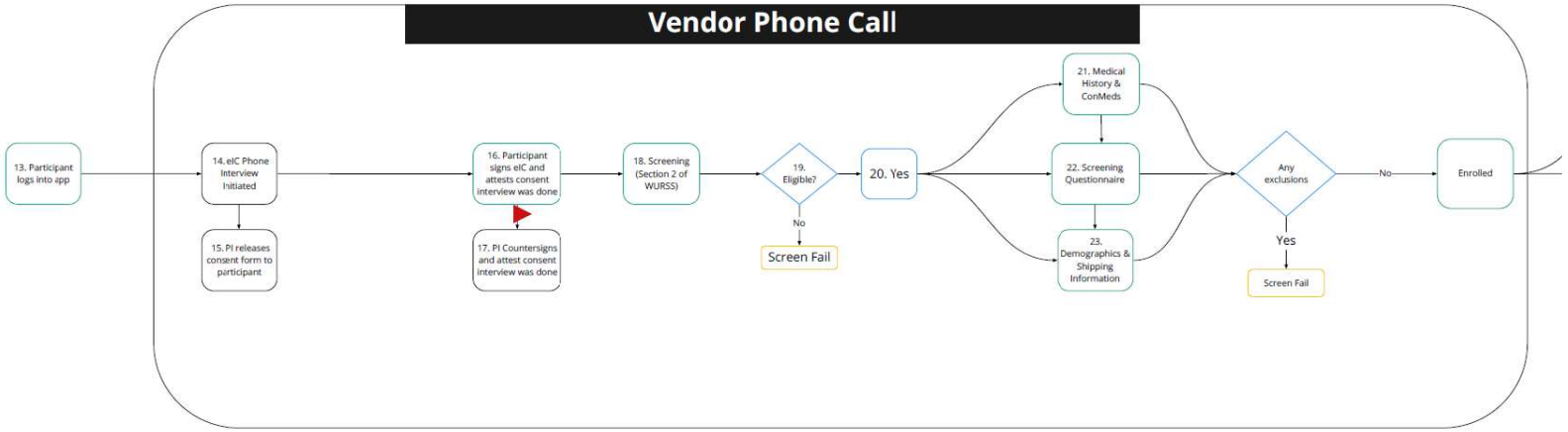
Key



[1] Recruitment & Onboarding



[2] Screening, Baselind & Product Dispensation (continued on next page)



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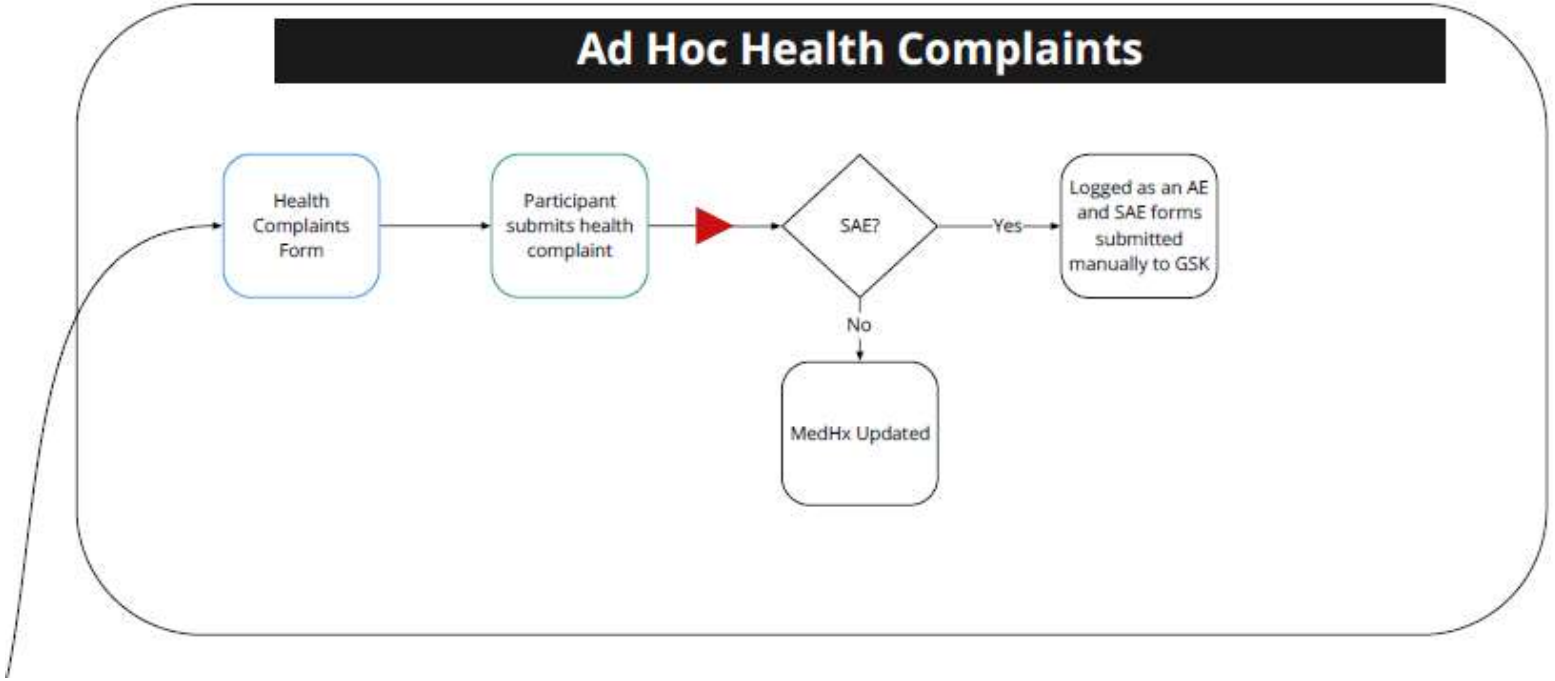

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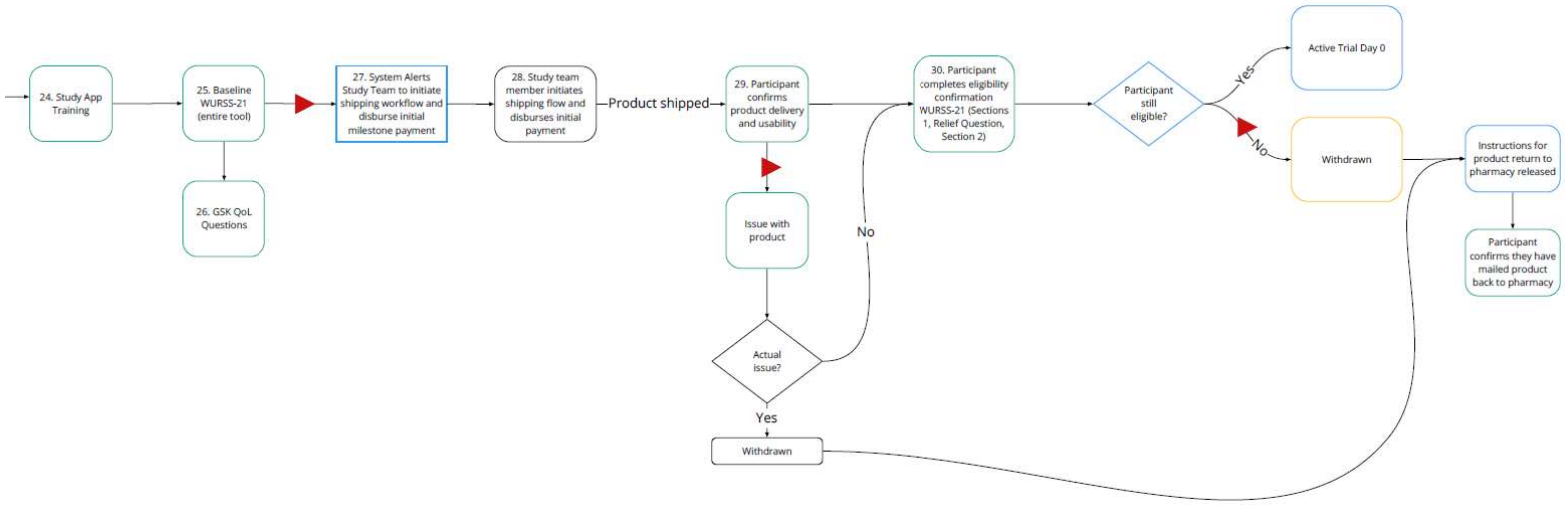
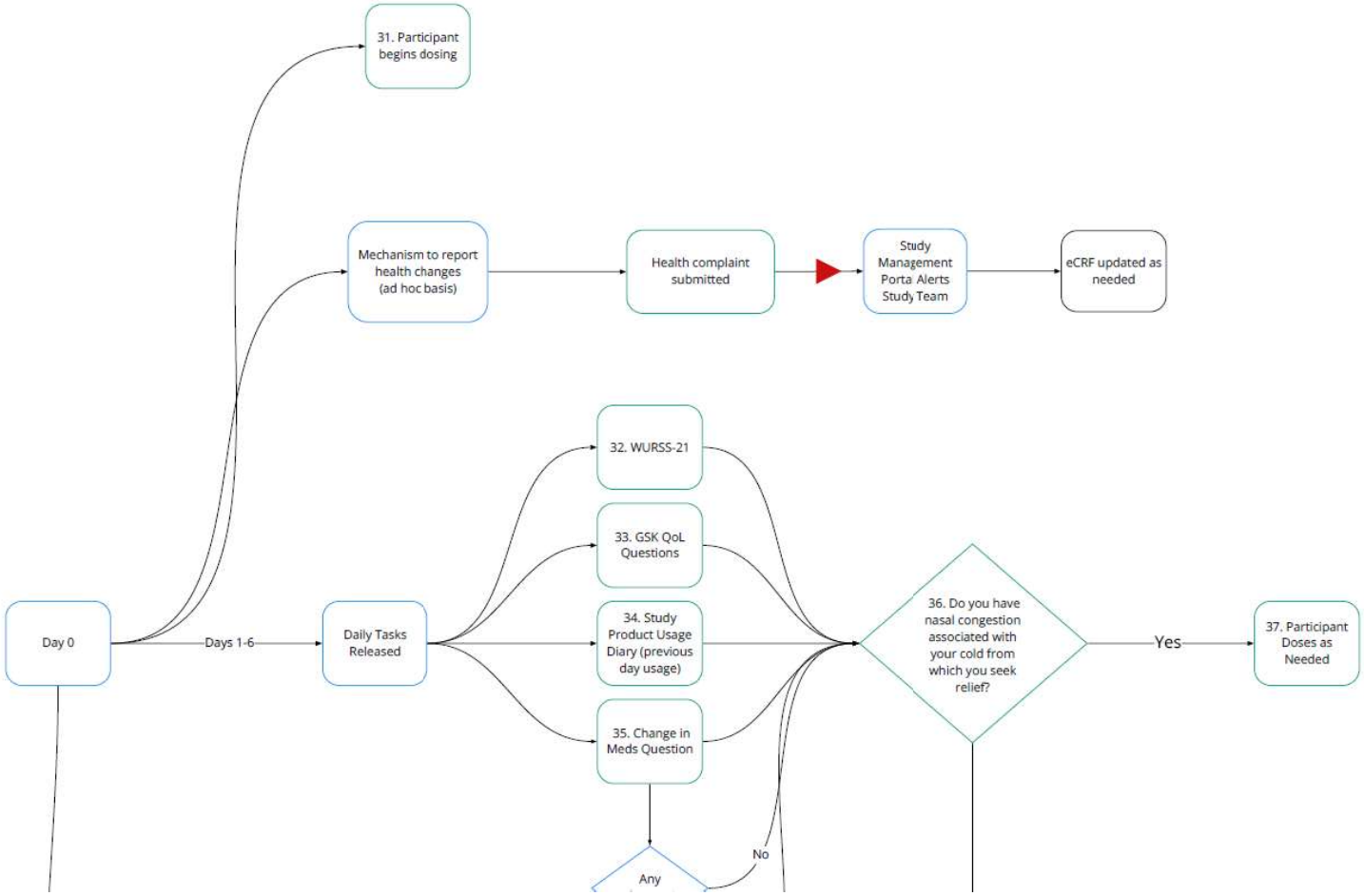


[3] Active Trial (continued on next page)



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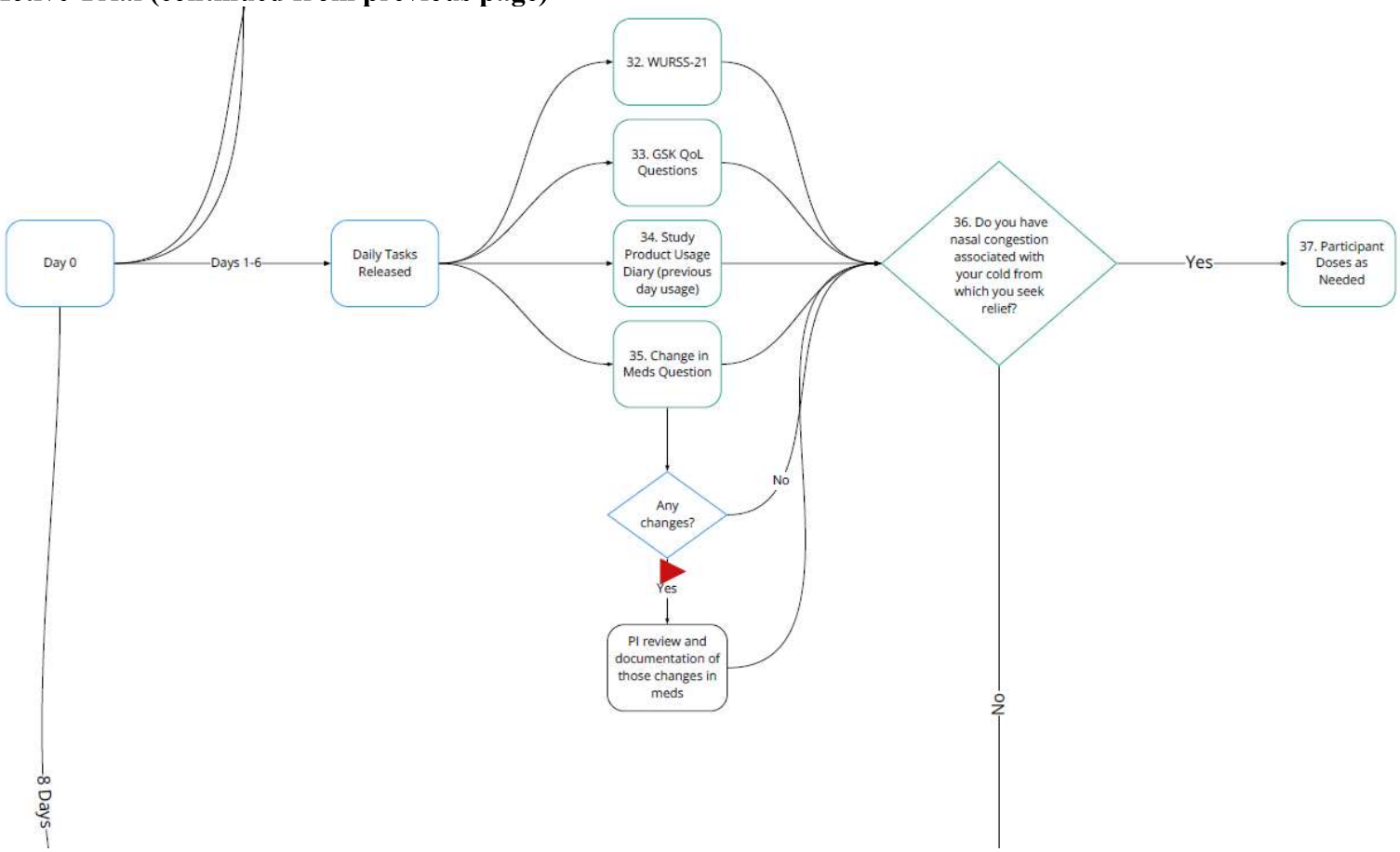

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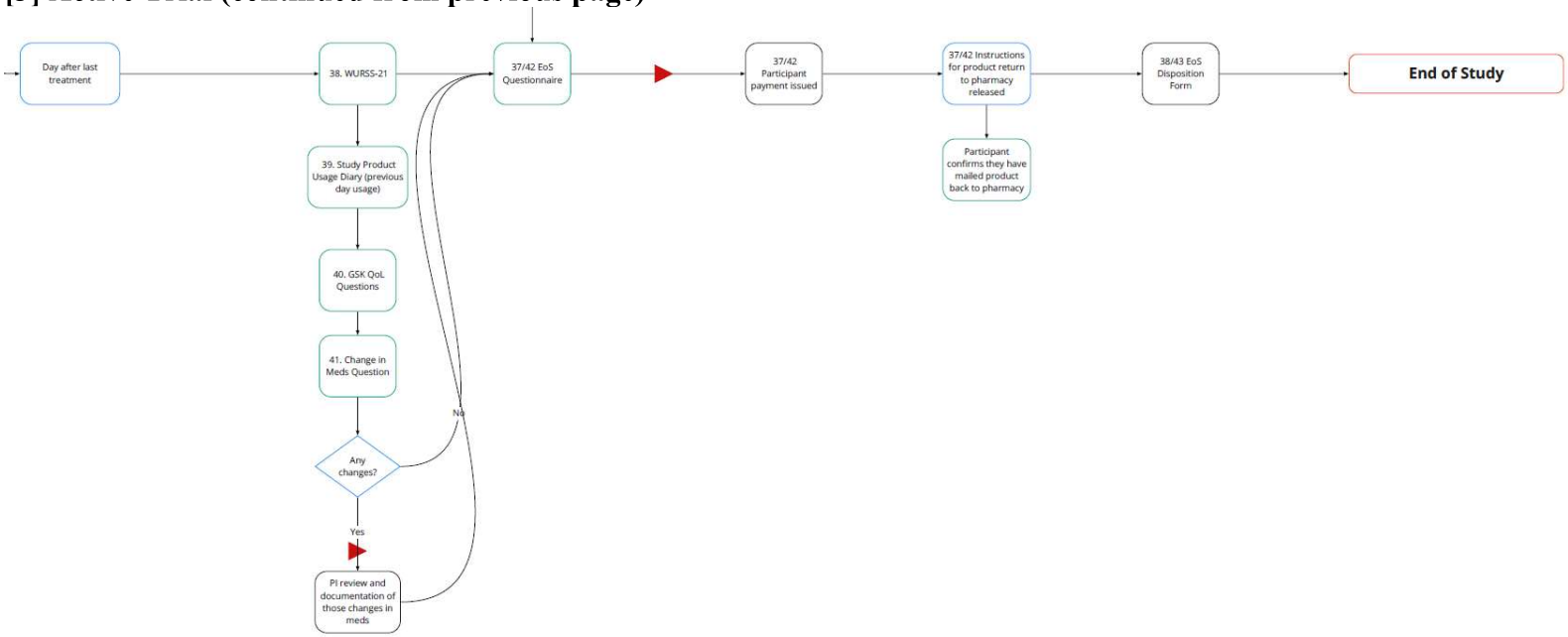

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Reason for signing: Approved	Name: PPD Role: Approver Date of signature: PPD GMT+0000

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