HALEON

CLINICAL PROTOCOL

A Real-World Evidence study evaluating Quality of Life parameters following treatment with Robitussin

Protocol Number:	300233
Compound/Product Names:	- Robitussin Maximum Strength Cough and Chest Congestion DM (Dextromethorphan HBr, USP 20 mg and Guaifenesin, USP 400 mg) - Robitussin Maximum Strength Nighttime Cough DM (Dextromethorphan HBr, USP 30 mg and Doxylamine Succinate, USP 12.5 mg)
Phase:	IV

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Document History

Document	Version	Summary of Changes
Original protocol	1.0	Not applicable (N/A)

Principal Investigator Protocol Agreement Page

- I confirm agreement to conduct the study in compliance with the protocol and any amendments according to the current Good Clinical Practice guidelines (GCP).
- 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 receives 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 ethical principles that have their origin in the Declaration of Helsinki.

Investigator Name:	PPD
Investigator Qualifications:	PPD
Investigator Signature:	PPD
Date of Signature/Agreement:	PPD

Table of Contents

List of in text tables

1 INTRODUCTION

1.1 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 controlled trials (RCTs), that do not always reflect real-world patient populations, limiting their generalizability and external validity (Sherman et al., 2016).

This decentralized study is designed to generate real world data from subjects with cough associated with the common cold, evaluating the effects in two arms with commercially available cough syrups on health-related quality of life. Arm 1 includes one cough syrup (which can be used day or night) and Arm 2 includes the daytime cough syrup and a nighttime cough syrup.

Robitussin Maximum Strength Cough and Chest Congestion DM (Dextromethorphan HBr, USP 20 mg; Guaifenesin, USP 400 mg) and Robitussin Maximum Strength Cough and Chest Congestion DM + Robitussin Maximum Strength Nighttime Cough DM (Dextromethorphan HBr, USP 30 mg; Doxylamine Succinate, USP 12.5 mg) are marketed cough and congestion syrups used for treatment of cough 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), Cough was the most common cold symptom (73.1%) and had a delayed onset (typically 1–5 days after cold onset) and a long duration (>6 days in 35.2%). Nasal congestion and cough were the most bothersome symptoms (Blaiss et al., 2015). Overall, 93% of survey participants reported sleep difficulty (slight to extreme) during a cough/cold. Among all respondents, 57% reported cough or nasal congestion as the symptoms making sleep difficult (Dicpinigaitis et al., 2015). In a similar RWE study, it was demonstrated that associated cold symptoms like blocked nose can impact overall quality of life and also that treatment can provide clinically meaningful improvements in QoL.

This study will generate data to support the effectiveness of the Robitussin syrups in the real-world setting to suppress cough among individuals with common cold to understand how the effect can influence their quality of life.

1.2 Background

Dextromethorphan, guaifenesin, and doxylamine are included in the FDA OTC Drug Monograph for Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products, which ensures their safety and efficacy as non-prescription medications. Dextromethorphan is an antitussive that works by suppressing the cough reflex in the brain, making it effective for temporary relief of coughs due to minor throat and bronchial irritation, such as from the common cold. Doxylamine, an antihistamine, blocks histamine H1 receptors to relieve symptoms like sneezing, runny nose, and itchy eyes associated with hay fever, allergic rhinitis, and the common cold. Guaifenesin, an expectorant, helps thin and loosen mucus in the airways, making it easier to clear congestion through productive coughing. The FDA monograph provides clear usage guidelines, ensuring safe access to these medications for both adults and children without a prescription.

Dextromethorphan's clinical efficacy has been demonstrated in several studies. In Parvez (Parvez, 1996), three successive trials involving 451 adults showed that a single 30 mg dose significantly reduced cough counts compared to placebo, with differences ranging from 19% to 36% ($P < 0.05$). Cough counts were measured using cough acoustic signals, and the studies reported a net difference of 8-10 coughing bouts every 30 minutes. In a meta-analysis (Pavesi, 2001) of 710 subjects, a single 30 mg dose of dextromethorphan was tested using continuous cough recording over three hours. This study measured cough bouts, components, effort, intensity, and latency. The average treatment difference was 12% to 17% in favor of dextromethorphan for cough bouts (P value = 0.004), cough components (P value = 0.003) and cough effort (P value = 0.001), with an increase in cough latency (P value = 0.002). These studies reflect dextromethorphan’s long-standing reputation as a reliable, non-prescription treatment for acute cough, complementing its well-established role in OTC medications.

The efficacy of guaifenesin as an expectorant has been demonstrated in studies involving both acute upper respiratory tract infections (URTIs) and chronic respiratory conditions such as chronic bronchitis. In a study by Robinson and colleagues (Robinson, 1977), guaifenesin was shown to significantly improve symptoms in patients with acute URTIs based on subjective patient assessments. Compared to placebo, guaifenesin reduced cough frequency and intensity at 48 and 72 hours ($p < 0.01$), and it also decreased chest discomfort at 24, 48, and 72 hours ($p < 0.01$). Additionally, in patients with productive coughs, guaifenesin increased sputum volume at 48 hours ($p < 0.01$) and made it easier to raise sputum at 24, 48, and 72 hours ($p < 0.01$). Given its proven efficacy, guaifenesin holds a well-established position as an OTC expectorant, offering consumers an accessible and effective treatment for chest congestion.

The efficacy of doxylamine in alleviating symptoms of runny nose and sneezing associated with the common cold was demonstrated in a clinical study involving cold sufferers (Eccles, 1995). The study involved 688 patients with cold symptoms who were randomized to receive either doxylamine succinate 7.5 mg four times daily ($n = 345$) or a placebo ($n = 343$). Results showed that doxylamine significantly reduced runny nose scores ($P < 0.01$) and sneezing scores ($P < 0.001$) compared to placebo. These findings suggest that doxylamine is an effective antihistamine in managing cold-related symptoms.

Cough is a common symptom associated with upper respiratory infections, particularly those caused by the common cold, which is predominantly viral in origin. The common cold affects millions of individuals worldwide, leading to significant morbidity and healthcare resource utilization. While cough serves as a protective reflex, persistent or bothersome cough can adversely impact quality of life, sleep, and daily activities.

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.

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.

1.3 Mechanism of Action/Indication

Dextromethorphan is a centrally acting cough suppressant, and its primary mechanism of action involves inhibiting the activity of the medullary cough center in the brainstem, which reduces the cough reflex.

Guaifenesin is an expectorant and its primary mechanism of action is to help loosen and thin mucus in the airways, making it easier to cough up and clear from the respiratory tract. It reduces sputum viscosity by increasing the volume and water content of the bronchial secretions, thereby facilitating the expectoration of sputum.

Doxylamine is an antihistamine, and its primary mechanism of action involves blocking histamine H1 receptors. By inhibiting these receptors, doxylamine reduces the effects of histamine, a chemical in the body that causes symptoms such as sneezing, runny nose, itching, and watery eyes as may occur with hay fever or other respiratory allergies.

Robitussin Maximum Strength Cough and Chest Congestion DM	**Robitussin Maximum Strength Nighttime Cough DM**
Active ingredients (in each 20 ml) and purposes Dextromethorphan HBr, USP 20 mg - Cough suppressant Guaifenesin, USP 400 mg - Expectorant	*Active ingredients (in each 20 mL) and purposes* Dextromethorphan HBr, USP 30 mg - Cough suppressant Doxylamine Succinate, USP 12.5 mg - Antihistamine
Uses ● Temporarily relieves cough due to minor throat and bronchial irritation as may occur with a cold ● Helps loosen phlegm (mucus) and thin bronchial secretions to drain bronchial tubes	*Uses* ● Temporarily relieves cough due to minor throat and bronchial irritation as may occur with a cold ● Temporarily relieves these symptoms due to hay fever or other upper respiratory allergies: ○ runny nose ○ sneezing ○ itchy, watery eyes ○ itching of the nose or throat ○ controls the impulse to cough to help you sleep

2 STUDY OBJECTIVES AND ENDPOINTS

Table 2-1 Study Objectives and Endpoints

Each of the treatment groups will be analyzed separately; there is no comparison between the study groups (daytime product only and daytime/nighttime product combination).

Objectives	Endpoints
Primary	
To evaluate the over-time effects of Robitussin on QoL factors and common cold symptoms among individuals experiencing cough associated with common cold, following up to 8 days of treatment using WURSS-21.	Score change from Baseline to each treatment day in: ● WURSS-21 total score ● WURSS-21 total symptom domain score ● WURSS-21 total QoL domain score ● Each of the WURSS-21 symptom scores (10 items in total) ● Each of the WURSS-21 QoL scores (9 items in total)
Secondary	
To evaluate the over-time effects of Robitussin on QoL factors among individuals experiencing cough associated with common cold, following up to 8 days of treatment, using specific QoL questions.	Score change from Baseline to each treatment day in: ● social activities ● feeling self-conscious around people ● coughing in public ● falling asleep ● sleeping through the night ● energy ● motivation
To evaluate the over-time effects of Robitussin on specific QoL questions among individuals experiencing cough associated with common cold, following up to 8 days of treatment, using categorized QoL factors.	Score change from Baseline to each treatment day in: ● Sleep quality ● Vitality ● Physical activities ● Social activities
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
Exploratory	
Subgroup analysis for primary and secondary endpoints	Subgroups: ● Excluding subjects who took concomitant medications that are known to have an impact on common cold symptoms

3 STUDY DESIGN

3.1 Overall Design

This is a longitudinal, randomized, decentralized, open-label study evaluating the effect on QoL factors in subjects with cough associated with the common cold in two arms using Robitussin Maximum Strength in a real-world setting. A sufficient number of adults (approx. 372) aged 18 and over with symptoms of common cold will be screened for eligibility. The study expects to enroll approximately 260 eligible subjects across the United States with a total of 200 subjects expected to complete the study, approximately 100 in each study group. Subjects will be randomized into one of two study groups (at a 1:1 ratio):

- Group 1 will take Robitussin Maximum Strength Cough and Chest Congestion DM
- Group 2 will take Robitussin Maximum Strength Cough and Chest Congestion DM + Robitussin Maximum Strength Nighttime Cough DM.

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 platform using the subject's own mobile device, tablet, or computer.

Detailed study procedures can be found in Section 5 of the protocol.

3.2 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 gather information on participant quality of life from the target patient population.

The Wisconsin Upper Respiratory Symptom Survey (WURSS) is an evaluative illness-specific quality of life instrument, designed to assess daily the negative impact of acute upper respiratory infection, presumed viral (the common cold). WURSS-21 is the short version of this validated instrument. WURSS-21 includes a single question on a global severity score, a symptoms domain (10 items), a functional domain (9 items) and an overall question on improvement/deterioration since yesterday. While the WURSS-44 covers more symptoms, the WURSS-21 exhibits similar performance in terms of reliability, responsiveness, importance-to-patients, and convergence with other measures.

Subjects with cough associated with common cold, who seek to treat with study treatment (Robitussin) will complete WURSS-21 and a specific QoL questionnaire once per day. Study treatment use will be reported via electronic diaries (eDiary). These measures will provide information on the effects of Robitussin over the natural course of their cough associated with common cold. This supports evaluation of 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 and then cough.

Given the natural course of the disease, making sure subjects have access to treatment when cough 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. Subjects who report taking medication(s) known to have an impact on common cold symptoms will be excluded for subgroup analysis.

3.3 Justification for Dose

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

3.4 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 end of the treatment period per subject is tentatively defined as Day 7 but may vary based on the need/severity of cough (see section 5 for further details). At the end of study, each subject should complete an end of study survey including product satisfaction.

The end of study is defined as the last data collection from the last subject participating in the study.

4 STUDY POPULATION

4.1 Type and Planned Number of Subjects

Adult subjects aged 18 and over (inclusive), of any race/ethnicity, reporting symptoms of the common cold including cough and at least one other common cold symptom (scratchy throat, sore throat, nasal congestion or watery nasal discharge) onset within the previous 48 hours will be screened for enrollment into the study. No discrimination of any kind (e.g. social class, gender, skin color, ethnicity) should preclude eligible participants from participating in the study. The study will aim to recruit a diverse population representative of the US census.

Sufficient subjects will be screened in order to enroll approximately 260 eligible subjects (approximately 130 subjects per study group). This study assumes an approximate 30% drop out rate. A total of 200 subjects are expected to complete the study (approximately 100 subjects per study group, allowing for up to 30% dropouts). Potential participants will be recruited through targeted digital advertising campaigns.

4.2 Statistical Analysis:

Sample size:

The study will be sufficiently powered to demonstrate statistically significant differences between QoL parameters in changes from Baseline to each treatment day as measured by the WURSS-21 (primary objective). Further details on the sample size determination can be found in section 8.1.

This study can fulfill its objectives only if appropriate subjects are enrolled. All relevant medical and non-medical conditions should be taken into consideration when deciding whether a subject is suitable for this protocol. Subject eligibility to participate in the clinical study should be reviewed and documented by a delegated member of the investigator's study team before subjects are randomized in the study. The following eligibility criteria are designed to select subjects for whom participation in the study is considered appropriate.

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(s) and have at least one post-baseline QoL questionnaire data to support at least one of the primary endpoint assessments. Any subject who is randomized but discontinues without taking any study product will be replaced. 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(s). Adverse events will be summarized using the Safety population. Subgroup analysis is further defined in section 8.

4.3 Inclusion Criteria

An individual must meet all the following inclusion criteria to be eligible to be included into the study:

1. Individual provides a signed and dated electronic informed consent document indicating that the subject has been informed of and consents to all pertinent aspects of the study, before any assessment is performed and individual has reviewed and is willing to follow the product label.
2. Individual aged 18 years or older at the time of electronic consent, inclusive of all ethnicities, races and gender identities.
3. Individual reporting initiation of cough symptoms within 48 hours prior to initiation of the virtual visit.
4. Individual reporting a minimum score of 5 (moderate) for cough 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 symptom domains.
5. Individual reporting at least one night's sleep has been disrupted in the previous 2 nights due to the symptoms of common cold.
6. Individual who is willing to self-treat their cough using the study treatment.
7. Individual who is in good general and mental health.
8. Individual who resides in the United States (except for Hawaii and Alaska).
9. Individual who owns a mobile device with access to stable internet connection and is willing to use their device to complete study surveys and assessments per the schedule of events.
10. Individual who has not taken any cough products containing dextromethorphan, guaifenesin, or doxylamine (e.g. Robitussin, Delsym, Vicks, Mucinex), or cough

drops/lozenges containing benzocaine or menthol (e.g. Cepacol, Halls, Ricola) or any natural cough products during the study.

4.4 Exclusion Criteria

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

1. Have a history of allergies (e.g., rash, hives, difficulty breathing, swelling of face, lips, tongue, or throat) to any medication or any kind or sensitivity to ingredients in pain, cough, cold, and flu products; including the following active ingredients found in the Research products:
   - Active Ingredients – dextromethorphan, guaifenesin, doxylamine
   - Inactive Ingredients - anhydrous citric acid, carboxymethylcellulose sodium, FD&C blue no. 1, FD&C red no. 40, glycerin, liquid glucose, menthol, natural and artificial flavors, polyethylene glycol, propylene glycol, purified water, sodium benzoate, sodium citrate, sucralose, triacetin, xanthan gum
2. Individual who is currently taking medications that may interact with the study products.
3. Individual who is pregnant, lactating, or plans to be pregnant or lactating during the course of the study (self-report).
4. Individual who has taken any cough products containing dextromethorphan, guaifenesin, or doxylamine (e.g. Robitussin, Delsym, Vicks, Mucinex), or cough drops/lozenges containing benzocaine or menthol (e.g. Cepacol, Halls, Ricola) or any natural cough products within 7 days prior to the virtual visit.
5. Have previously been diagnosed with:
   - prostate gland enlargement or difficulty urinating
   - glaucoma (excessive pressure inside your eyes)
   - asthma, chronic bronchitis, chronic cough or chronic lung disease (difficulty in breathing and cough that won't go away).
   - Pneumonia (within the last 6 months)
   - COVID-19 (within the last month)
6. Are taking medication(s) to treat - psychiatric / mental health conditions (e.g. anxiety, depression) or Parkinson's disease. Medications such as:
   - MAOI (monoamine oxidase inhibitor) [e.g. Azilect, Emsam, Marplan, Nardil] or have stopped them within the last 2 weeks per your doctor's advice.
7. Are currently taking sedatives or tranquilizers (e.g. Ambien, Xanax, Klonopin)
8. Are taking drugs for heart problems such as quinidine, amiodarone or metoprolol, antidepressants such as fluoxetine and paroxetine, or antipsychotics such as haloperidol and thioridazine.
9. Individual who is currently experiencing:
   - cough accompanied by fever, rash, or persistent headache **OR**
   - cough with too much phlegm.
10. Individual who is an employee of CCI [redacted], either directly involved in the conduct of the study or a member of their immediate family; or a Haleon employee directly involved in the conduct of the study or a member of their immediate family.
11. Individual who has participated in other studies (including non-medicinal studies) involving investigational product(s) within 30 days prior to study entry.
12. Individual who has previously been enrolled in this study.
13. Individual sharing the same address as another individual who has been enrolled in this study.

14. Individual who, in the opinion of the investigator or delegate, should not participate in the study, including an individual who meets any of the "stop use" criteria recommended by the label.

4.5 Lifestyle Considerations

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

5 STUDY ASSESSMENTS

This section lists the procedures and assessments to be completed at each planned study time point. However, as per nature of RWE studies, if a subject fails to complete their daily questionnaire at any time point post-baseline, subjects will be permitted to continue in the study. The timing of each assessment is listed in the Table 5-1 Schedule of Activities section.

5.1 Schedule of Activities

The Schedule of Activities (Table 5-1) provides an overview of the subjects' virtual visit and study assessments. The investigator may schedule additional (unplanned) virtual visits to conduct additional evaluations or assessments required to protect the well-being of the subject.

Table 5-1 Schedule of Activities

All assessments are completed online. Subjects will receive links via email/text to complete questionnaires per the Schedule below.

	May occur same-day[a]									
Counterparty Assessments	**Pre-screening**	**Screening and Baseline (Virtual Visit) Day 0**	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Day 7**	**2 Days after Last Dose[j]**
Pre-screening Survey	X									
Informed consent (self-consent)	X									
Medical/Medication history[b]		X								
Demographics		X								
ID Verification		X								
WURSS–21 questionnaire[cf] (Baseline, pre-treatment)		X								
Specific QoL Questions (Baseline, pre-treatment)		X								
Eligibility Assessment		X								
Randomization		X								

Study product shipped[e]		X								
Study product use[eg]		X	X	X	X	X	X	X	X	
WURSS–21 questionnaire[f] **(post-treatment)**			X	X	X	X	X	X	X	
Specific QoL Questions (post-treatment)			X	X	X	X	X	X	X	
Product Usage eDiary[h]		X	X	X	X	X	X	X	X	
End of Study Survey[i]									X	
Concomitant Medication Check			X	X	X	X	X	X	X	
Adverse Event/Serious Adverse Event			X	X	X	X	X	X	X	X

QoL, quality of life; WURSS–21, Wisconsin Upper Respiratory Symptom Survey-21.

a Pre-screening, Screening and Baseline can occur same day if product is received by subject same-day

b Medical history including medication history will be self-reported by participant during the virtual visit.

c Participant eligibility to be confirmed through assessment of inclusion/exclusion criteria and cold symptoms of at least mild intensity reported on the Baseline WURSS-21 assessment at the time of Screening.

d Participant to confirm receipt of study product for study enrollment confirmation and read through detailed instructions regarding product dosing; Counterparty staff will be available to answer any queries regarding product use.

e Robitussin: Group 1: Subjects in Group 1 will be instructed to take up to 20 ml of Robitussin per label instructions for up to 8 days or until resolution of symptoms, whichever occurs first.
Group 2: Subjects in Group 2 will be instructed to take the following per label instructions for up to 8 days or until resolution of symptoms, whichever occurs first:
- up to 20 ml of Robitussin Maximum Strength Cough and Chest Congestion DM
- up to 20 ml of Robitussin Maximum Strength Nighttime Cough DM

f WURSS–21 to be completed at the time of Baseline/Screening to confirm eligibility as well as daily during treatment (from Day 1 up to Day 7).

g Study product (Robitussin) to be shipped only after screening/baseline assessments are completed and eligibility is confirmed; up to 8 days' worth of study product(s) will be shipped together to ensure there is no interruption in study timeline or treatment duration.

h Participant will complete an eDiary documenting Robitussin use each day directly through the Citrus ePRO module.

i Participant-reported End of Study Survey will be completed at the end of study directly through the Citrus ePRO module. Participants ending product use early will complete the survey one day after their last reported dose; participants dosing on Day 7 will complete the survey on Day 7.

j Participant-reported Change in Health will be recorded two days after last study product administration.

5.2 Pre-screening

Adult subjects reporting cough associated with common cold onset within the previous 48 hours who express interest in the study, via social media platform advertising, will be directed to complete an online pre-screening questionnaire assessing their eligibility to participate in the study. The information collected from the pre-screening questionnaire serves as the preliminary screening tool to isolate potentially eligible participants from ineligible subjects.

Subjects who successfully pass the pre-screening questionnaire are deemed potentially eligible for participation and are directed to complete an online electronic informed consent form (eICF).

5.2.1 Informed Consent

The Electronic Informed Consent Form (eICF) is a tool that assists in the consenting process by using multimedia components delivered by an electronic system. The eICF process for this study will be self-completed on the subject's mobile device following successful completion of the study pre-screening questionnaire. Informed consent must be obtained before any study-specific activity is performed. Once the eICF has been signed and dated by the subject, the subject will be provided with a copy via email. An additional copy of the signed eICF will be saved as a Portable Document Format (PDF) in the virtual site file.

If, during a subject's participation in the study, the eICF undergoes any changes, each ongoing subject should receive a copy of this new information and be re-consented into the study if applicable as determined by the IRB. Each subject should be provided with a copy of the signed and dated amended consent form.

Potentially eligible subjects who successfully complete the pre-screening questionnaire and execute the eICF will receive the following information: 1) a copy of the signed eICF, 2) an email/text invitation to complete the screening and baseline questionnaires and 3) an invitation to schedule the Screening & Baseline Virtual Visit.

5.3 Screening & Baseline Questionnaires

Pre-screening and Screening will most likely happen on the same day. After the informed consent is executed, subjects will receive links via email/text to complete questionnaires noted below.

5.3.1 Demographics

Subjects will self-report the following demographic information: year of birth and age, sex at birth, race, and ethnicity.

5.3.1.1 Smoking Status

Subjects will self-report their current smoking status, inclusive of cigarettes, e-cigarettes, vaping, etc.

5.3.2 Medical History and Prior Medication/Treatment

Relevant medical and/or surgical history (in the previous 12 months) will be self-reported, including allergies or drug sensitivity and prior medications/treatments, including prescription and non-prescription drugs, vaccines, dietary supplements and herbal remedies, that began before obtaining informed consent will be recorded as the Medical History/Current Medical Conditions.

Female subjects only:

- Female subjects who report being pregnant or confirm plans to become pregnant during the study will be excluded.

- Given the potential impact of pregnancy on study outcomes, female subjects of child-bearing potential will be reminded to inform the investigator site immediately if pregnancy is known or suspected.

5.4 Virtual Visit

The Virtual Visit may occur on the same day that the subject completes the Pre-screening.

5.4.1 Verification of Identity

During the virtual visit, a trained member of the study team will verify the subject's government-issued identification (i.e. photo ID such as driver's license or government issued passport) on camera at the beginning of the visit. Should the subject elect not to show a form of photo identification or is unable to provide a valid photo identification at the beginning of the virtual visit, the visit may be rescheduled, or the subject may be considered a screen failure.

5.4.2 Baseline Assessments

5.4.2.1 Baseline WURSS-21

After photo ID verification, the study team will trigger the Baseline WURSS-21 (in appendix section 14.3) for subject self-completion. The purpose of this assessment is to ensure potential participants meet the Inclusion criteria related to the WURSS-21 Symptom domain [minimum score of 5 (moderate) for cough associated with common cold symptoms and at least one other symptom of common cold (at least mild score of 3)]. The study team will review responses as related to determining subject eligibility.

This administration of the WURSS-21 at the Virtual Visit also develops the Baseline for eligible subjects.

5.4.2.2 Baseline Specific Quality of Life Questions

If the potential participant meets the Inclusion Criteria related to the WURSS-21 Symptom domain, the Baseline for Specific Quality of Life Questions (in appendix section 14.4) will be triggered for subject self-completion.

This administration of the Specific QoL Questions at the Virtual Visit also develops the Baseline for eligible subjects.

5.4.3 Eligibility Review

5.4.3.1 Inclusion/Exclusion Criteria

Inclusion and exclusion criteria as per Section 4.3 and 4.4 will be collected via pre-screening and screening surveys and confirmed during the virtual visit with a trained & delegated study team member.

5.4.3.2 Medical History & Prior Medications

A trained member of the study team will review the subject's medical history and prior medications to confirm subject eligibility to participate in the study.

Relevant medical and surgical history, including allergies or drug sensitivity can be documented by the investigator or designee in the medical history form.

Please refer to section 9 for further details on Adverse Event and Serious Adverse Event Monitoring.

5.4.4 Enrolled Subjects and Screen Failures

An enrolled subject is one who has agreed to participate in the clinical study following completion of the eICF and who has directly and successfully met eligibility criteria to proceed beyond the screening visit.

Screen failures are defined as subjects who consent to participate in the clinical study but do not meet study inclusion criteria.

To ensure transparent reporting of screen failure subjects, a minimal set of screen failure information will include demography and screen failure details (e.g., withdrawal of consent, eligibility criteria, any protocol deviations and any adverse events).

Individuals who do not meet the criteria for participation in this study (screen failure) will not be re-screened.

5.4.5 Randomization

If the subject successfully meets eligibility criteria, the subject will be considered enrolled. At enrollment, the following activities will occur:

- The subject will move forward to randomization into one of two study groups (on a 1:1 allocation) as follows:
    - Group 1: will be instructed to take the following per label instructions for up to 8 days or until resolution of symptoms, whichever occurs first:

Product	Dose
Robitussin Maximum Strength Cough and Chest Congestion DM	Up to 20 ml*
*Not to exceed 6 doses in any 24 hour period.	

    - Group 2: will be instructed to take the following per label instructions for up to 8 days or until resolution of symptoms, whichever occurs first:

Product	Dose
Robitussin Maximum Strength Cough and Chest Congestion DM	Up to 20 ml*
Robitussin Maximum Strength Nighttime Cough DM	Up to 20 ml*
*Not to exceed 4 doses of daytime + 1 dose of nighttime OR 3 doses of daytime + 2 doses of nighttime in any 24 hour period.	

- Upon group allocation, study team will arrange delivery of the study product(s).

- Once the delivery is successfully received, the subject will confirm receipt and usability of the product(s) via an online questionnaire directly entered into the EDC platform.
    - If unsuccessful (e.g. lost, damaged) study team will discuss with participant and arrange a new delivery if needed.

During the screening visit, subjects will be provided with dosing instructions and training on how to complete the assessment, questionnaires, and eDiaries. Subjects will be reminded to reach out to the study team with any questions or concerns.

5.5 Treatment Period

The number of days each subject will actively engage with the study will vary according to the resolution of their cough symptoms. Subjects will use the product(s) (as per label instructions) for up to 8 days unless they self-report that they are no longer seeking relief from their cough symptoms prior to that. If symptoms and subject reporting continues through Day 7 , subjects will complete the daily questionnaires for 7 days (Day 1 - Day 7). Subjects with cough symptoms resolved sufficiently to no longer warrant product use or those who determine they no longer wish to medicate for cough symptoms will complete daily forms from baseline through one day after the last dose of study product(s). This will complete their "study period".

The subject will receive links via text and email with instructions for completion of the study assessments. The subject will input their responses directly into the EDC platform during the study period:

- Subjects will report any changes in health, use of concomitant medications, or non-drug treatments/procedures
- Subjects will complete the WURSS-21 questionnaire, and specific QoL questions
- Subjects will complete an eDiary to record product use each day including:
    - product type taken
    - number of doses
- Subjects will self-report whether they are still seeking relief from their cough symptoms and answer end of the study questions prior to exiting the study.

5.6 End of Treatment Period

Robitussin product(s) may be used for up to 8 days (Day 0 - Day 7).

Subjects will have the option to discontinue treatment at their discretion. Subjects may choose to discontinue treatment if:

- they feel that their symptoms do not warrant further use of the study product(s), or
- their cough symptoms are considered resolved

Subjects that continue to use the study product(s) will be prompted to discontinue treatment after 8 consecutive days of use and seek advice from their general physician 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 Day 7), and will be asked to fill in an End of Study survey.

Subjects will be informed that a Change in Health survey will be sent 2 days after their last study product dose (day 9 at latest) and will be asked to report any changes in their health post-completion of the study.

5.7 Study Conclusion

The Study Conclusion page of the eCRF will be completed for all subjects by the study team.

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

5.8 Follow-Up Phone Call

The study team will contact a subject to follow up on any reported ongoing AE/SAE post-study completion/withdrawal to ensure any issues are resolved as soon as possible. The study team must make every effort to regain contact with the subject (where possible, 3 contacts).

Should the subject continue to be unreachable, the AE/SAE will be considered unresolved.

Consistent with the treatment period, any reports that are collected on the WURSS-21 symptom domain assessment are not to be considered as AEs.

Refer to section 9.8 Follow-up of AEs and SAEs for more information.

6 STUDY ASSESSMENTS

Every effort should be made to ensure that protocol-required assessments and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances outside the control of the investigator that may make it infeasible to complete an assessment. When a protocol-required assessment cannot be performed, the investigator (or designee) will document the reason for the missed assessment as a protocol deviation and any corrective and preventative actions that he or she has taken to ensure that required processes are adhered to as soon as possible. The Sponsor must be informed of any missed assessments.

6.1 Outcome Assessments

Assessments will be performed by delegated staff at the times, and in the order, defined in the Study Procedures section of this protocol.

The primary objective of the study is to evaluate the over-time effects of two Robitussin Maximum Strength products on QoL factors and common cold symptoms among individuals experiencing cough associated with common cold, following up to 8 days of treatment using WURSS-21.

Links will be sent to the subject daily for self-completion of the following quality of life tools from receipt of product to study conclusion.

- WURSS-21 Questionnaire (in appendix section 14.3)
- Additional QoL Questions (in appendix section 14.3)

6.2 Safety and Other Assessments

The following safety assessments will be performed by appropriately trained staff/clinical examiners, at the times and in the order defined in the Study Procedures section of this protocol.

6.2.1 Pregnancy Testing

There is no pregnancy warning on labeling, a pregnancy test will not be required.

Female subjects will provide verbal confirmation of pregnancy status at Screening (Virtual Visit) and will be asked to inform study staff immediately should this change at any point during the study. Female subjects who are pregnant or intending to become pregnant during the study (self-reported) will not participate further in the study.

7 STUDY PRODUCTS

For the purposes of this study, per International Conference on Harmonization (ICH) guidelines, and Haleon policy, study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol. This includes a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use.

As the study product(s) will be purchased from the local retailer, no study label will be required.

7.1 Study Product Supplies

Each subject will receive sufficient study product(s) to cover usage during the treatment period of the study. The following study products will be supplied by the CRO's preferred vendor (Table 7-1). Study product(s) usage instructions are consistent with the commercially available pack instructions. Subjects will not be required to return or destroy used/unused study products after treatment discontinuation, completion of study or withdrawal.

Table 7-1 Investigational/Study Product Supplies

	Group 1	Group 2 (Product 1 + Product2)
Product Name	Robitussin Maximum Strength Cough and Chest Congestion DM	Robitussin Maximum Strength Cough and Chest Congestion DM Robitussin Maximum Strength Nighttime Cough DM
Pack Design	Labeled commercial pack	Labeled commercial pack
Dispensing Details	Shipped to subject upon randomization	Shipped to subject upon randomization
Haleon formula codes:	CCI	CCI
Dose and usage Instructions	Up to 20 ml, not to exceed 6 doses in any 24-hour period.	Up to 20 ml per dose. Not to exceed 4 doses of daytime + 1 dose of nighttime

		OR 3 doses of daytime + 2 doses of nighttime in any 24-hour period.
Route of Administration	Oral	Oral
Return Requirements	All unused/used study products will not be returned	All unused/used study products will not be returned

*See dosing instructions in Section 5.4.5

7.2 Product Supplies, Product Storage, Accountability, Returns and Destruction

Study products are to be dispensed only to subjects enrolled in the study in accordance with the protocol, by delegated study staff. Enrolled/randomized subjects will be informed on product usage and storage and what to do in the event of product loss when the products are first dispensed.

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

Orders for study product(s) are to be placed immediately following randomization for delivery to subjects. Given this delivery model and the shelf stability of the product(s), a formal accountability form/record will not be maintained, however trained study staff will maintain an order and delivery tracker.

At the end of the study, subjects may retain any remaining/unused study product(s).

7.3 Blinding and Randomization

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

Qualifying subjects will be centrally randomized into one of two study groups using a 1:1 randomization list provided by Haleon Biostatistics. Subjects will be randomized into one of two study groups. Study Group 1 will take only the daytime Robitussin product and group 2 will take both the daytime and the nighttime Robitussin products. Before the study is initiated, training and directions for the randomization will be provided to the investigator study team. Study products will be dispensed in sequential order as per the randomization schedule. Only subjects who meet the study inclusion criteria will be randomized to a study product.

7.4 Breaking the Blind

Not applicable.

8 STATISTICAL CONSIDERATIONS AND DATA ANALYSES

8.1 Sample Size Determination

Sufficient individuals (approximately 372) will be screened to enroll approximately 260 eligible subjects assuming an estimated 23% drop out rate. It is believed that for this study, 200

completed subjects (100 per treatment group) are deemed sufficient to observe an improvement in the WURSS-21.

8.2 Populations for Analysis

8.2.1 Definitions of Analysis Populations

The following four study populations will be used for statistical 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. The safety population will be used for analysis of the 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.
- For the Exploratory Endpoint, the Non-Common-Cold-Med (NCCM) population will include all patients in the mITT population who have not used other medicinal products which might influence reported symptom severity. Reported concurrent medications will be assessed in a Blind Data Review (BDR) meeting to identify potentially interfering medications.

8.3 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 data analysis. All analyses will be carried out and reported without adjusting for multiple comparisons, reporting nominal p-values.

Each of the treatment groups will be analyzed separately for all endpoints; there is no comparison between the study groups (daytime product only and daytime/nighttime product combination).

Baseline WURSS-21 and the Specific QoL questions are completed at the Virtual Visit, prior to study product(s) shipment to the subject.

8.3.1 Exclusion of Data from Analysis

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

8.3.2 Primary Endpoint Analysis(es)

For the primary objective, measurements of health related QoL indicators and cold symptoms will be evaluated using daily WURSS-21 scores (total scores, total QoL domains scores, total symptom domains scores, and single symptom and QoL domains scores) change from baseline to each treatment day to determine the effectiveness of the two treatment groups (Daytime, Daytime+Nighttime).

Change from Baseline in mean WURSS-21 scores to each treatment day will be summarized and analyzed using a mixed-effects model for repeated measures (MMRM) with treatment, treatment day as a discrete variable, and applicable baseline WURSS-21 scores as fixed effect and a random intercept for each subject. Estimated marginal mean differences between baseline and each treatment day will be reported by treatment group including the mean difference on the original scale, standardized effect size including 95% confidence intervals (CI), and the respective p-value. The distribution of each outcome is assessed using Q-Q-plots by treatment group. In case of apparent deviations from the normal distribution, the changes from baseline are assessed using a Wilcoxon signed-rank test.

8.3.3 Secondary Endpoint Analysis(es)

For the secondary objective, measurements of health related QoL indicators will be evaluated using the specific QoL scores and categorized QoL scores change from baseline to each treatment day to determine the effectiveness of the two treatment groups (Daytime, Daytime+Nighttime).

Change from baseline in mean specific QoL scores and categorized QoL scores to each treatment day will be summarized and analyzed using a mixed-effects model for repeated measures (MMRM) with treatment, treatment day, as a discrete variable, and applicable baseline specific QoL scores or categorized QoL scores as fixed effect and a random intercept for each subject. Estimated marginal mean differences between baseline and each treatment day will be reported by treatment group including the mean difference on the original scale, standardized effect size including 95% confidence intervals (CI), and the respective p-value. The distribution of each outcome is assessed using Q-Q-plots by treatment group. In case of apparent deviations from the normal distribution, the changes from baseline are assessed using a Wilcoxon signed-rank test.

The QoL scores (sum of individual questions per category) will be categorized as below:

1. Sleep Quality
    - Sleep Well – WURSS-21 Q13
    - Falling asleep – QoL Q4
    - Sleep through the night – QoL Q5
2. Social Activities
    - Interact with others – WURSS-21 Q19
    - Less comfortable in social activities – QoL Q1
    - Self-conscious around others – QoL Q2
    - Coughing in public – QoL Q3
3. Physical Activities
    - Breathe easily - WURSS-21 Q14
    - Walk, climb stairs, exercise - WURSS-21 Q15
    - Accomplish daily activities - WURSS-21 Q16
4. Vitality
    - Energy – QoL Q6

- Motivation – QoL Q7
- Feel tired - WURSS-21 Q11

8.3.4 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 the number of subjects with AEs/SAEs will be listed and tabulated.

8.3.5 Exploratory Analysis(es)

For the exploratory objective, the NCCM population (defined in section 8.2.1) will be used to analyze the Primary and Secondary endpoints.

Additional exploratory analysis may be conducted as defined in the SAP.

8.3.6 Demographic and Baseline Characteristics

For each of the treatment groups, 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.

8.3.7 Study Product Compliance and Use of Other Therapies

8.3.7.1 Study 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.

8.3.7.2 Prior and Concomitant Medications

Prior medication use will be assessed during the Screening & Baseline Virtual visit. Prior medications/non-drug therapies and concomitant medications/significant non-drug therapies used prior to treatment initiation and in the treatment phase will be listed, including the frequency within each group, for the Safety population.

8.3.8 Handling of Dropouts and Missing Data

Missing values will not be imputed.

9 ADVERSE EVENT (AE) AND SERIOUS AE (SAE)

Adverse events can be reported / recorded by any member of the trial team. The investigator and their authorized safety designees are responsible for detecting, documenting and reporting events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to study product, a study procedure or study participation, or that caused the subject to discontinue use of a study product or study participation.

Any reports that are collected on the WURSS-21 symptom domain assessment are not to be considered as AEs.

All Adverse Events and Serious Adverse Events will be managed in line with the protocol and in line with the Site and Safety Management Plan.

9.1 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 an acclimatization product whether or not considered related to the study product, including an acclimatization product **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 an acclimatization product (or medical device).

Events <u>Meeting</u> the AE Definition:

- Any abnormal laboratory test results (hematology, clinical chemistry or urinalysis) or other safety assessments (e.g., electrocardiogram, 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.
- 'Lack of efficacy' or 'failure of expected pharmacological action' per se will not be reported as an AE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms and/or clinical sequelae resulting from lack of efficacy will be reported as an AE if they fulfill the definition of an AE.

Events <u>NOT</u> 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.
- A medical or surgical procedure (e.g., endoscopy, appendectomy) is not an AE. The condition that leads to the procedure is an AE (e.g., appendicitis). Planned medical or surgical procedures for preexisting illnesses are not an adverse event.
- 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.

9.2 Definition of a Serious Adverse Event

An SAE is a particular category of AE where the 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 prolonged 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 more than would be expected under the normal progression of the disease 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.

Events exempt from immediate reporting as SAEs

Hospitalization for a pre-existing condition, including elective procedures planned prior to trial entry, which has not worsened, does not constitute an SAE.

9.3 Time Period and Frequency for Collecting AE and SAE Information

All AEs, and therefore all SAEs (except from those exempt from recording, as described in section 9.1 and section 9.2) will be collected from immediately after a subject is randomized within the trial and until 2 days following the last administration of study product.

A change in health survey will be released to subjects 2 days after their last study product(s) dose. If a subject reports a change in health, a member of the study team will reach out to record the relevant details.

Medical occurrences that began before randomisation will be recorded in the Medical History/Current Medical Conditions section of the Electronic Case Report Form (eCRF), not the AE section.

Details recorded by the subject that meet the definition of a serious AE must be discussed with the subjects and transcribed into the SAE section of the eCRF

All SAEs will be recorded and reported to the sponsor or designee immediately, and under no circumstance should this exceed 24 hours. The investigator will submit updated SAE data to the sponsor within 24 hours of it being available.

9.4 Reporting Procedures

The investigator and study delegated designees are responsible for detecting, documenting and reporting events that meet the definition of an AE and remain responsible for following up AEs that are serious, considered related to study product, a study procedure or study participation, or that caused the subject to discontinue use of study product or study participation, until stabilization, resolution, trial completion or loss to follow up, whichever comes sooner.

The investigator and their authorized trial designees are to report all AEs at study visits and all AEs spontaneously reported by study subjects.

Study subjects will be questioned about AEs. 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.

AEs spontaneously reported by study subjects and those elicited by asking subjects to respond to non-leading questions (such as ‘how do you feel?’) will be assessed, recorded in the eCRF and reported, as appropriate.

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 their medically qualified designee to assess the severity of the event, which may require a review of additional documentation (e.g., hospital progress notes, laboratory and diagnostics reports) related to the event. The investigator or study staff will then record all relevant information relating to the event in the SAE section of the eCRF. In addition, all details relating to an SAE will be recorded electronically within Citrus using the SAE eCRF provided.

It is **not** acceptable for the investigator or their authorized safety designee to send photocopies of a subject’s medical records to the sponsor in lieu of completion of the AE section of the

eCRF/paper SAE form. There may be instances when copies of medical records for certain cases are requested by the sponsor. 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 the sponsor.

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

9.5 Reporting an AE

AEs will be reported by the investigator, their authorized trial designee or investigator staff in the AE section of the eCRF. These are collected throughout the study at each follow-up visit. Additionally, the subject will have the option to report any AEs to the study staff at any point during the study. Where an SAE is recorded the electronic SAE form should be utilized and reported within 24 hours of awareness. AEs/SAEs will be recorded based on information from the participant. The event terms will then be coded by a qualified member of the research team (see Section 11.2 for further details).

9.6 Reporting an SAE

In addition to recording the details of each SAE in the AE section of the eCRF, an SAE form should be completed, as fully as possible. All SAE reporting will utilize the eCRF in Citrus.

It is essential to record the following information for each SAE:

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

The following are desirable and are of particular relevance for investigator and sponsor assessment of the SAE report:

- Date of onset of SAE
- Date SAE stopped, if relevant
- Study product start date
- Study product end date, if relevant
- Action taken in relation to study product
- Outcome, if known

The SAE form, completed as fully as possible, must be exported from Citrus, e-mailed to the sponsor's Case Management Group mailbox CCI [redacted], with the appropriate sponsor Study Manager in copy, with the study number and subject number in the subject line of the email **immediately after investigator staff learn of the event, and under no circumstances should this exceed 24 hours**. The investigator will submit any updated SAE data to the sponsor, **immediately once it becomes available, and under no circumstance should this exceed 24 hours of it being available**.

The initial report will be followed up with more information as relevant, or as requested by the sponsor's Study Manager. The sponsor's Study Manager will be responsible for forwarding the SAE form to other sponsor personnel as appropriate.

9.7 Evaluating AEs

Assessment of Intensity

The investigator or their medically qualified designee 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 assessed as 'severe' should not be confused with an SAE. 'Severe' is a category utilized for rating the intensity of an event. Both non-serious AEs and SAEs can be assessed as severe, e.g., a headache may be severe (significantly interferes with the subject's usual function) but would not be classified as serious unless it met one of the criteria for SAEs listed in Section 9.2. An event is defined as 'serious' when it meets at least one of the pre-defined outcomes described in the definition of an SAE (section 9.2), **not** when it is rated as 'severe'.

Assessment of Causality

For each AE (non-serious and serious), the investigator or their medically qualified designee **must** provide an assessment of causality in the AE section of the eCRF and on the SAE form (as appropriate, subject to classification of the AE). Causality is one of the criteria used to determine regulatory reporting requirements.

A 'reasonable possibility' of a relationship conveys 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 in the AE/SAE report.

The investigator or their medically qualified designee will use clinical judgment to determine causality and will also consult the Product Label, as appropriate, when making their assessment. Alternative causes, such as underlying disease(s), concomitant therapy, other risk factors and the temporal relationship of the event to study product use will be considered and investigated.

Documentation of the (S)AE assessment will be recorded in the trial database, including the assessment of causality.Where applicable, the investigator or their medically qualified designee must document in the medical notes they have reviewed the AE/SAE and provided an assessment of causality.

There may be situations, when an SAE has occurred, where the investigator or their medically qualified designee has minimal information to include in the initial SAE report. **However, it is very important that the investigator or their medically qualified designee always makes an assessment of causality for every event prior to initial transmission of the SAE data to the sponsor.** The investigator may change their opinion of causality, in light of follow-up information, and send an SAE follow-up report with an updated causality assessment.

9.8 Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator or their authorized safety designee is required to proactively follow up all ongoing serious and severe AE with each subject and provide further information on the subject's condition, as available.

All severe AEs (non-serious and serious) should be followed until resolution, until the condition stabilizes, until the event is otherwise explained or until the subject is lost to follow-up.

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

New or updated information will be recorded in the AE section of the eCRF and on the SAE form (as appropriate, subject to classification of the AE). The investigator or their authorized safety designee will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

The investigator and their authorized safety designees are not obligated to actively seek AEs or SAEs after the conclusion of study participation. However, if the investigator or their medically qualified designee learns of an SAE, including a death, at any time after a subject has been discharged from the study, and they consider the event to be reasonably related to study product or study participation, they must promptly notify the sponsor by emailing the information to the sponsor's Case Management Group mailbox CCI [redacted], with the appropriate sponsor Study Manager in copy.

The investigator or their authorized trial designee will submit any updated SAE data to the sponsor within the designated reporting time frames.

9.9 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 provided (Section 9.1) and recorded in the withdrawal AE section of the eCRF.

When a subject withdraws due to an SAE, the SAE must be reported in accordance with the reporting requirements defined in this protocol.

9.10 Regulatory Reporting Requirements for SAEs

The sponsor 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 investigator to the sponsor is essential so that legal obligations and ethical responsibilities towards the safety of subjects are met.

The sponsor will comply with country specific regulatory requirements relating to safety reporting to the regulatory authority, the Institutional Review Board (IRB) and the investigator.

Investigator safety reports must be prepared for suspected Unexpected Serious Related Event (USRE) according to local regulatory requirements and sponsor policy, and forwarded to the investigator, as appropriate.

If the investigator receives an investigator safety report describing a SAE or other specific safety information (e.g., a summary or listing of SAEs) from the sponsor, they will review it, file it with other safety information (e.g., the IB) in the investigator site file and notify the REC, if appropriate, according to local requirements.

9.11 Pregnancy

9.11.1 Time Period for Collecting Pregnancy Information

Pregnancy information will be collected on all pregnancies reported while a female subject is participating in the study from the date/time of signing the informed consent until 5 days after the last administration of the study product.

9.11.2 Action to be Taken if Pregnancy Occurs

The investigator or their authorized trial designee will record pregnancy information on the appropriate eCRF and e-mail it to the Case Management Group mailbox CCI within 24 hours, with the appropriate sponsor Study Manager in copy. Original completed pregnancy information forms will be retained in the investigator site file.

The female subject will not be followed to determine the outcome of the pregnancy. Any female subject who becomes pregnant while participating will be withdrawn.

10 DISCONTINUATION OF STUDY INTERVENTION AND SUBJECT DISCONTINUATION/WITHDRAWAL

If a subject is discontinued early from the study product (Section 10.1) or discontinued or prematurely withdraws from the study (Section 10.1.1), the reason(s) for intervention discontinuation or withdrawal and the associated date must be documented in the relevant section(s) of the eCRF. If a subject is discontinued early from the study product, the subject should stay in the study and complete the remaining assessments unless they need to be withdrawn (see Section 10.1.1).

10.1 Discontinuation of Study Product

A subject may be discontinued from the study product at any time whilst still in the study at the discretion of the investigator related to safety, subject consent or a potential worsening of the risk / benefit assessment from the subject of remaining on the intervention for the following reasons:

- Adverse Event
- Lack of efficacy from the intervention
- Subject request
- Subject to be withdrawn from the study (see Section 10.1.1)

10.1.1 Subject Discontinuation/Withdrawal

A subject may withdraw from the study at any time at his or her own request or may be withdrawn at any time at the discretion of the investigator or sponsor for safety, behavioral reasons, or the inability of the subject to comply with the protocol-required schedule of study visits or procedures.

Inclusion/Exclusion criteria are assessed at Baseline. Any participant who develops exclusionary symptoms during the course of the trial can be withdrawn at the discretion of the investigator.

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
- Unblinding of the subject
- Pregnancy
- Investigator withdrawal due to worsening severity of health condition

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.

10.1.2 Lost to Follow up

If a subject fails to complete two consecutive days of e-diaries, the investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls or emails or local equivalent methods) and counsel the subject on the importance of maintaining the assigned activity schedule and ascertain whether the subject wishes to and/or should continue in the study.

A subject will be considered lost to follow up and withdrawn from the study if he or she repeatedly fails to complete scheduled activities and is unable to be contacted following the 3 contact attempts by the study team.

If contact is made with the subject, the investigator should inquire about the reason for withdrawal and if appropriate request that the subject attend a final virtual visit and follow-up with the subject regarding any unresolved adverse events (AEs).

11 DATA MANAGEMENT

11.1 Case Report Form

An eCRF is an electronic document designed to record the protocol required information to be reported to the sponsor on each trial subject.

For each subject who has given informed consent the eCRF must be completed and signed by the Principal Investigator (or authorized designee) to certify that the data are complete and correct. The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.

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 Electronic Data Capture (EDC) System, 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.

Adverse events will be coded using Medical Dictionary for Regulatory Activities (MedDRA) and any concomitant medications terms (if applicable) using an internal validated medication dictionary. The MedDRA dictionary version will be documented within the Data Management Plan (DMP).

11.2.1 Data Queries

Programmed edit checks will be generated automatically, as the data are being entered into the system. Reports and listings on the CRF data will also be run, in addition to the queries already programmed and generated by the system, to raise manual queries as needed for site clarification or correction. The Clinical Dictionary Development and Management Group 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 of the CRFs in accordance with the monitoring plan, to confirm that data entered into the CRF by authorized site personnel are accurate and complete; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Any queries will be generated in the EDC System to the Investigator or designee, enabling the errors to be addressed in parallel with Data Management review. The study monitor can also run reports and listings on the CRFs, to raise manual queries as needed for site clarification or correction.

11.3 Processing Patient Reported Outcomes and Data Collection from Internet of Medical Things

Electronic Patient reported outcome (ePRO) that are measured by Internet of Medical Things (IoMT) devices (i.e., wearables, patches, sensors, and mobile data collection units such as smartphones and tablets) will be transferred in the protocol-specified aggregated and/or raw form electronically to Haleon or Third-party data management vendor.

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 Haleon as required. Any AEs or concomitant medications collected as ePRO will be reviewed and transcribed to the eCRF by the site.

To protect the privacy of subjects, no Personal Information (PI) (including the subject's name or initials or birth date) is to be recorded on any PRO/ePRO/IoMT Devices Data that will be forwarded to Haleon or Third-Party Vendor.

12 STUDY GOVERNANCE CONSIDERATIONS

Electronic Patient reported outcome (ePRO) that are measured by Internet of Medical Things (IoMT) devices (i.e., wearables, patches, sensors, and mobile data collection units such as smartphones and tablets) will be transferred in the protocol-specified aggregated and/or raw form electronically to Haleon or Third-party DM vendor.

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 Haleon as required. Any AEs or concomitant medications collected as ePRO will be reviewed and transcribed to the eCRF by the site.

To protect the privacy of subjects, no Personal Information (PI) (including the subject's name or initials or birth date) is to be recorded on any PRO/ePRO/IoMT Devices Data that will be forwarded to Haleon or Third-Party Vendor.

12.1 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.

12.2 Quality Assurance

To ensure compliance with GCP and all applicable regulatory requirements, Haleon 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 Haleon 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.

12.3 Regulatory and Ethical Considerations

12.4 Institutional Review Board/ Ethics Committee

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, informed consent document, safety statement (including any updates) 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 Haleon prior to the initiation of the study, and also 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 investigator must notify the IRB/EC and Haleon in writing immediately after the implementation.

12.5 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 ethical principles that have their origin in 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.

12.6 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 Haleon and other authorized parties, subject names, addresses, and other identifiable data will be replaced by numerical codes based on a numbering system provided by Haleon 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, Haleon will maintain high standards of confidentiality and protection of subjects' personal data consistent with applicable privacy laws.

12.7 Subject Recruitment

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

Haleon 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.

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

Within Haleon 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 Haleon 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, Haleon should be informed immediately.

In addition, CCI will inform Haleon 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.

12.9 Oversight Committees

Due to the low-risk nature of the trial, no oversight committees will be utilized. Monitoring will occur as per the study-specific risk-based monitoring plan.

12.10 Disclosure and Publication Policy

Study information from this protocol may be posted on publicly available clinical trial registers before enrollment of subjects begins in accordance with applicable Haleon policies.

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

The procedures and timing for public disclosure of the results summary and for development of a manuscript for publication will be in accordance with sponsor policy and as per the country specific requirements for disclosure.

12.11 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 Haleon site or other mutually agreeable location.

Haleon 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 Haleon Policy.

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

12.12 Records Retention

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

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.

The investigator must notify Haleon 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.

12.13 Conditions for Terminating the Study

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

If a study is prematurely terminated, Haleon 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 Haleon, all study materials must be collected and all eCRF's completed to the greatest extent possible. Where required by the applicable regulatory requirements, Haleon should inform the regulatory authority(ies) and the investigator should promptly inform the IRB and provide the IRB a detailed written explanation of the termination or suspension.

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

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

13 REFERENCES

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Parvez L, Vaidya M, Sakhardande A, Subburaj S, Rajagopalan TG. Evaluation of antitussive agents in man. Pulmonary Pharmacology 1996;9(5-6):299-308.

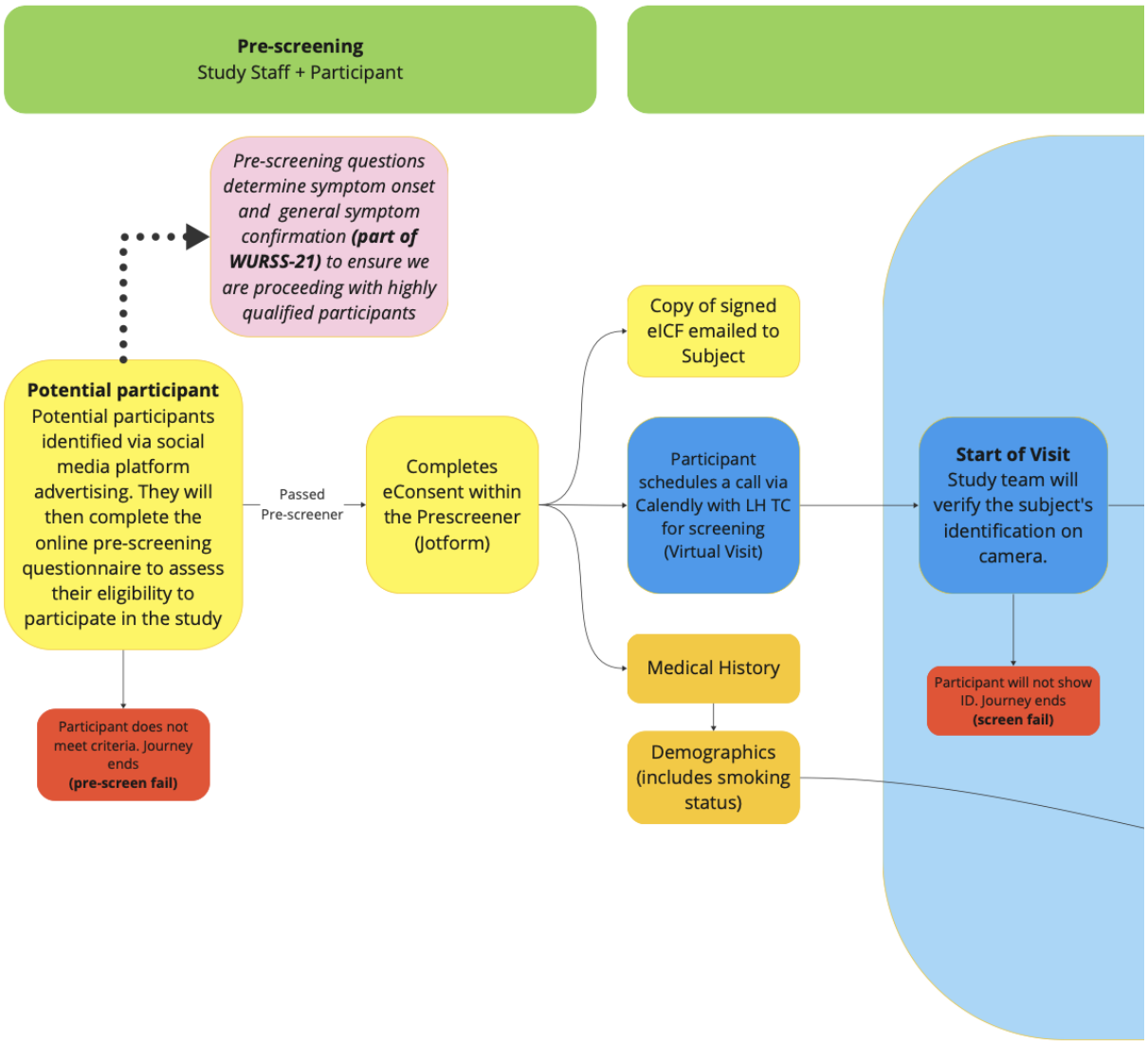
Pavesi L, Subburaj S, Porter-Shaw K. Application and validation of a computerized cough acquisition system for objective monitoring of acute cough: a meta-analysis. Chest 2001;120:1121-8.

Robinson RE, Cummings WB, DeDenbaugh ER. EDectiveness of guaifenesin as an expectorant: a cooperative double-blind study. Current Therapeutic Research 1977;22(2):284-96.

14 APPENDICES

14.1 Schedule of Assessments Schematic

Pre-screening, Screening & Baseline (continues on next page)



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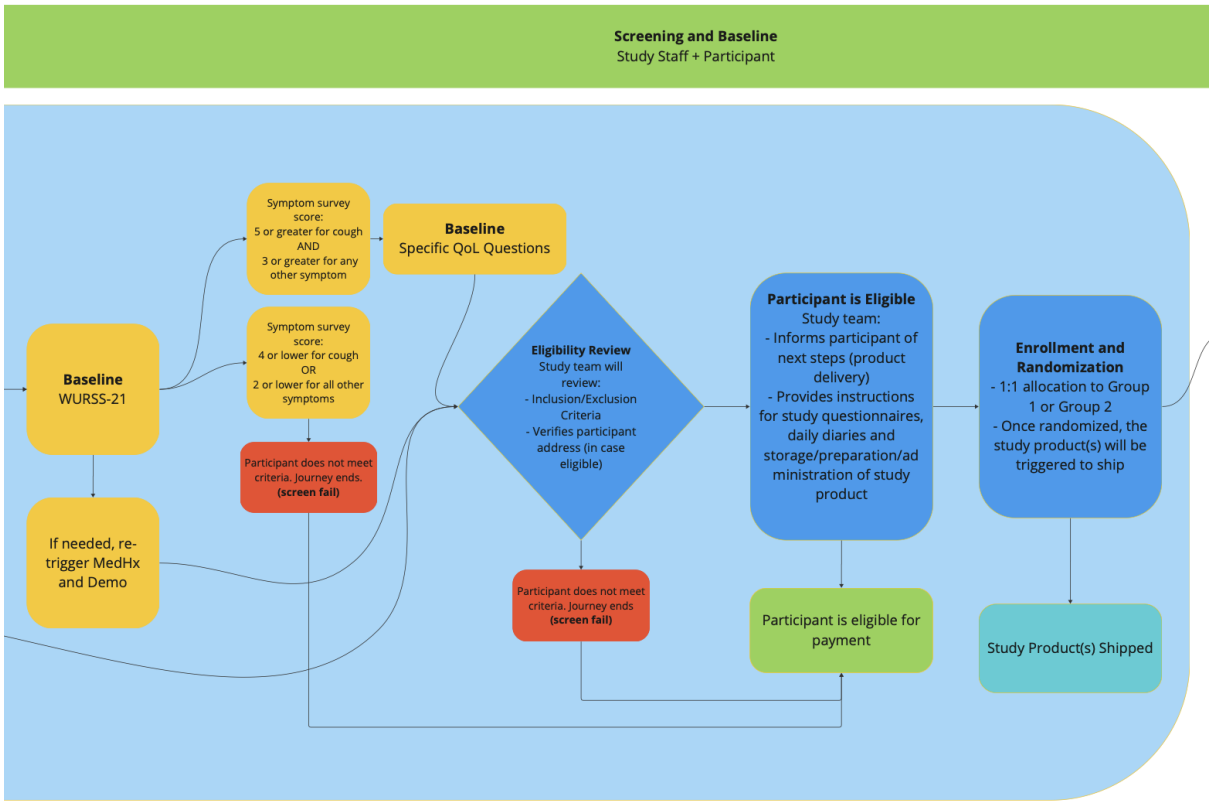

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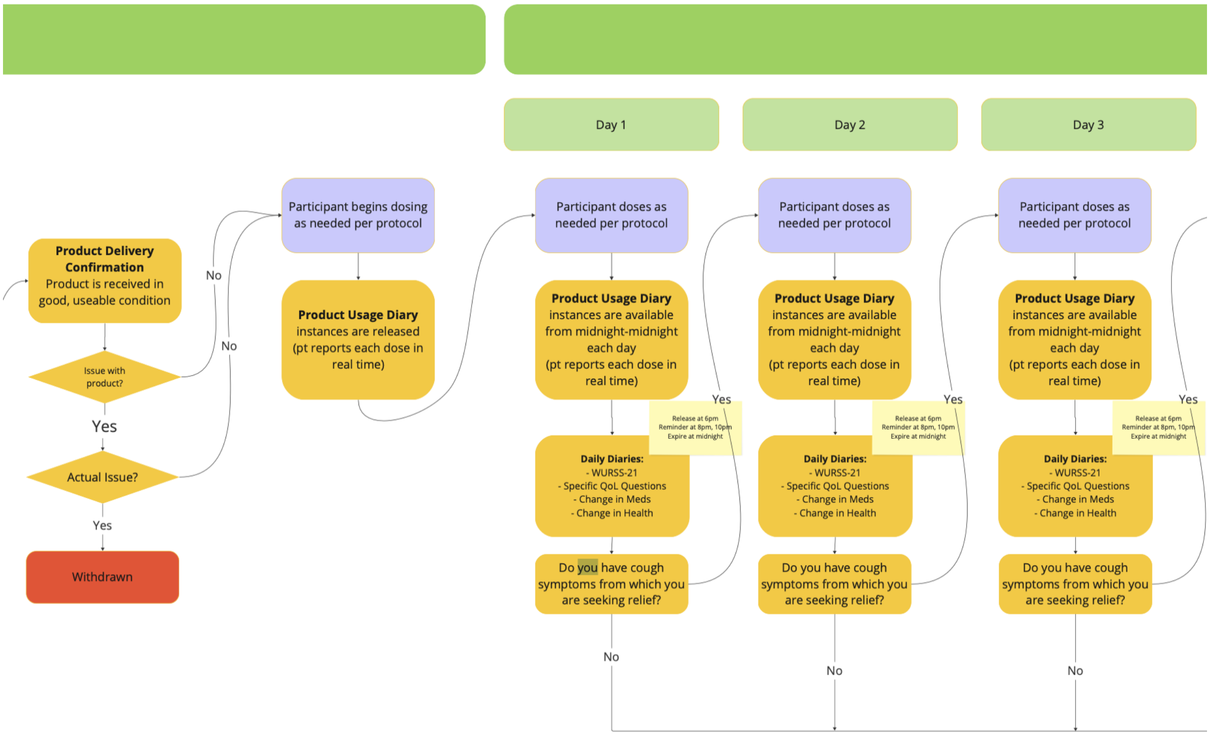

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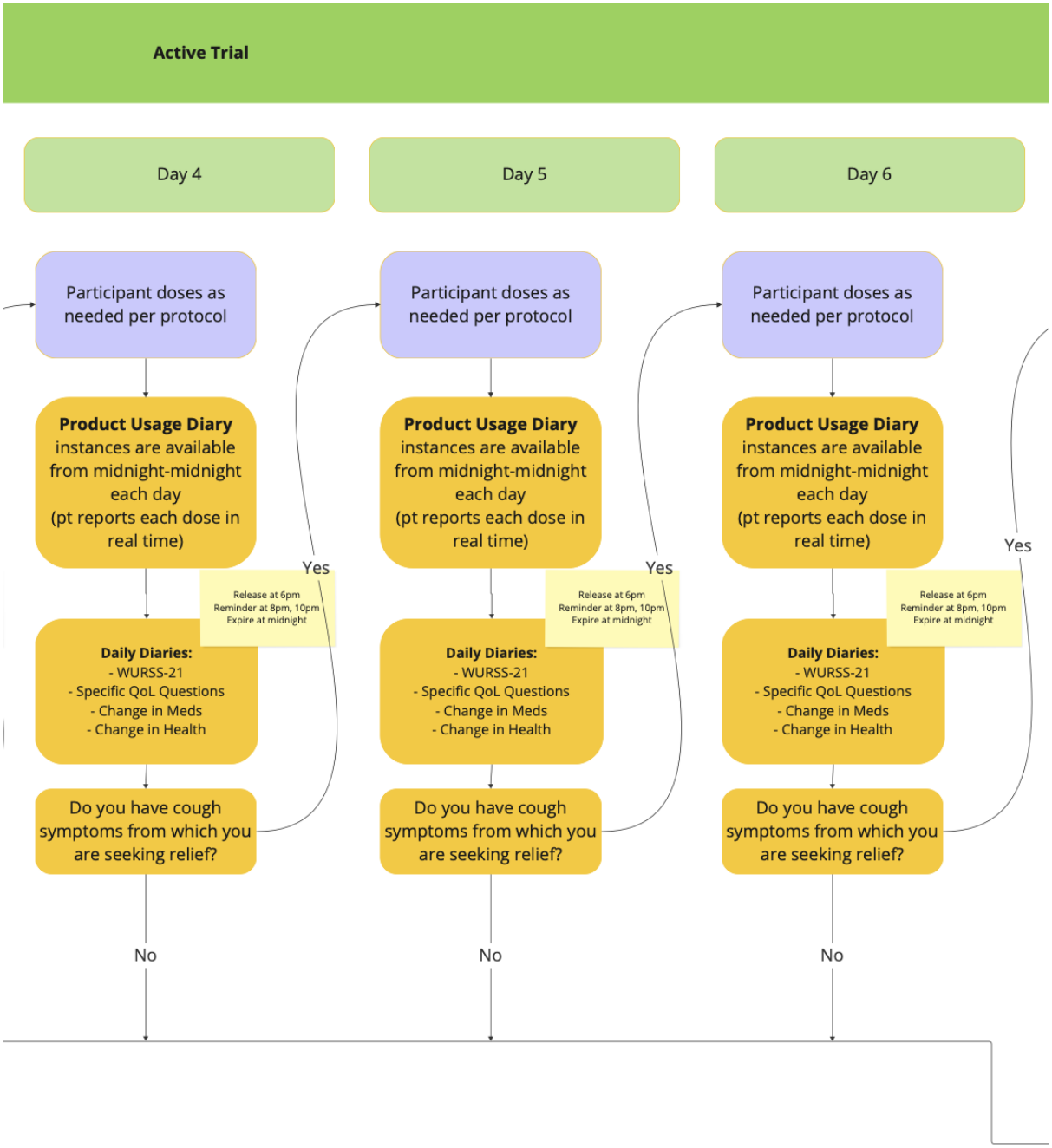
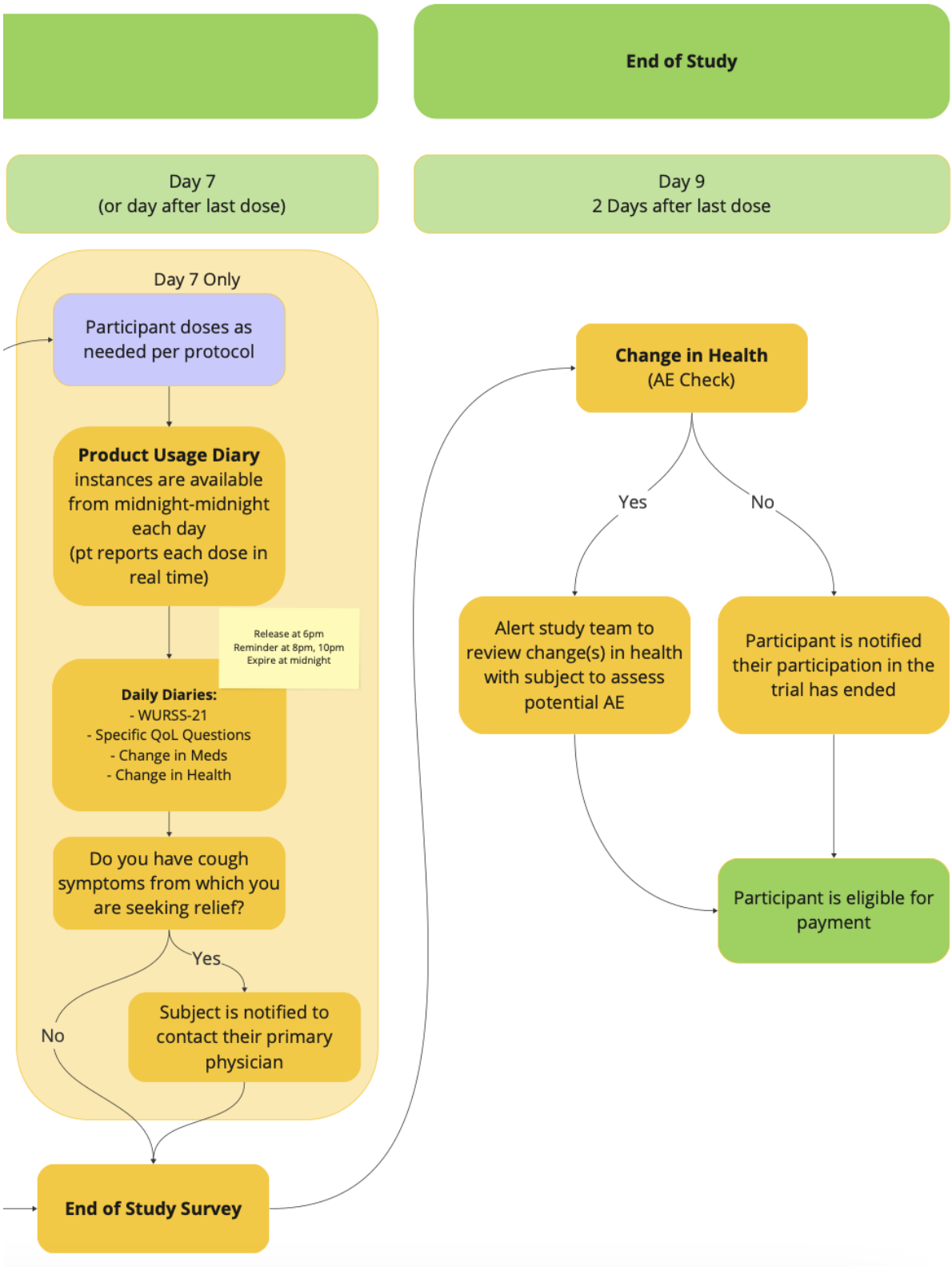


Active Trial (continued from previous page), End of Study



14.2 Study Assessments

14.2.1 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…

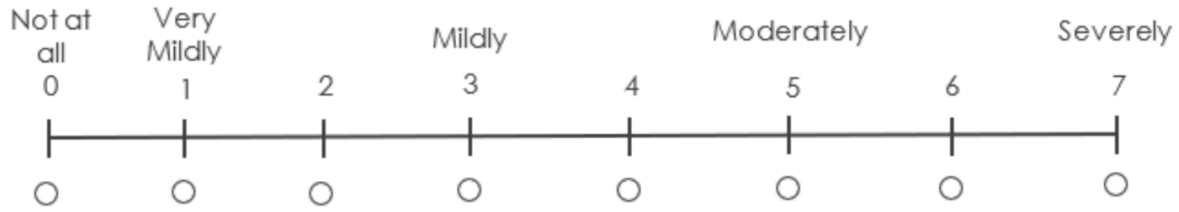
Very much better	Somewhat better	A little better	The same	A little worse	Somewhat worse	Very much worse
o	o	o	o	o	o	o

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

14.2.2 Specific Quality of Life (QoL)Questions

14.2.2.1 Baseline Questions (pre-treatment):

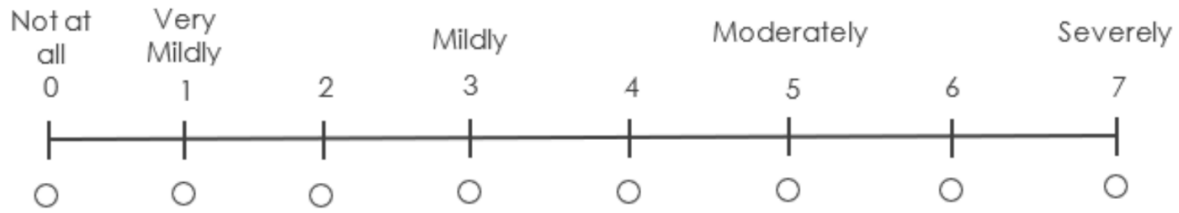
Please complete this questionnaire prior to your first dose of the study product(s). Considering the past 24 hours, please read each question and choose the answer that best reflects your experience with Robitussin use and your cough/cold:



1. Is your cough/cold making you less comfortable participating in social activities?
2. Is your cough making you self-conscious around people?
3. Are you worried about coughing in public?
4. Is your cough/cold making it more difficult for you to fall asleep?
5. Is your cough/cold making it more difficult to sleep through the night?
6. Is your cough/cold making you less energetic than usual?
7. Is your cough/cold making you less motivated than usual?

14.2.2.2 Post treatment Questions (asked every day in the morning):

Considering the past 24 hours, please read each question and choose the answer that best reflects your experience with Robitussin use and your cough/cold:



1. After using Robitussin, is your cough/cold making you less comfortable participating in social activities?
2. After using Robitussin, is your cough making you self-conscious around people?
3. After using Robitussin, are you worried about coughing in public?
4. After using Robitussin, is your cough/cold making it more difficult to fall asleep?
5. After using Robitussin, is your cough/cold making it more difficult to sleep through the night?
6. After using Robitussin, is your cough/cold making you less energetic than usual?
7. After using Robitussin, is your cough/cold making you less motivated than usual?

15 ABBREVIATIONS

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

Table 15-1 Abbreviations

Abbreviation	Term
AE	Adverse Event
BDR	Blinded Data Review
COVID-19	2019 Novel Coronavirus
CRO	Clinical Research Organization
DM	Data Manager
DM HBr	Dextromethorphan
DMP	Data Management Plan
EC	Ethics Committee
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
eDiary	Electronic Diary
e.g.	exempli gratia (for example)
eICF	Electronic Informed Consent Form
ePRO	Electronic Patient-Reported Outcome
FDA	Food and Drug Administration
GCP	Good Clinical Practice
H1	Histamine-1
ICH	International Conference on Harmonization
ID	Identification
IOMT	Internet of Medical Things
IRB	Insitutional Review Board
ITT	Intent to Treat
MAOI	Monoamine Oxidase Inhibitors
MD	Medical Doctor
MedDRA	Medical Dictionary for Regulatory Activities
mg	Miligranms
mITT	Modified Intent to Treat
ml	Mililiters
MMRM	Mixed Model with Repeated Mearures
N/A	Not Applicable
NCCM	Non-Common-Cold-Med
OTC	Over the Counter
PDF	Portable Document Format
PI	Personal Information
PI	Principal Investigator
PRO	Patient Reported Outcome
QoL	Quality of Life
RCT	Randomized-controlled Trial

Abbreviation	Term
RWD	Real World Data
RWE	Real World Evidence
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
UK	United Kingdom
URTI	Upper Respiratory tract Infection
US	United States
USA	United States of America
USD	United States Dollar
USP	United States Pharmacopeia
USRE	Unexpected Serious Related Event
Wi-Fi	Wireless Fidelity
WURSS	Wisconsin Upper Respiratory Symptom Survey

Signature Page for 300233 TMF-257976 v1.0

Reason for signing: Approved	Name: PPD Role: Approver ature: PPD PPD

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

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