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## Smell in Covid-19 and Efficacy of Nasal Theophylline (SCENT 2)

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## A Introduction

### A1 Study Abstract

Evidence of COVID-19 related anosmia and dysgeusia continues to accumulate daily. Currently, up to 80% of patients report subjective olfactory dysfunction (OD), and prevalence using objective olfactory testing could be even higher. Anosmia and dysgeusia are often comorbid in this disease. Preliminary results from the COVID-19 Anosmia Reporting tool developed by the American Academy of Otolaryngology-Head and Neck Surgery suggests that 27% of patients had some improvement in OD with a mean of 7.2 days. Prevalence of permanent anosmia from COVID-19 has yet to be elucidated, however preliminary studies suggest over a third of patients may not recover for over two months since acute infection. Post-viral OD has numerous known adverse effects such as loss of cortical gray matter and decrease in quality of life. Intranasal and oral corticosteroids as well as olfactory training are currently used to treat post-viral OD; however they have demonstrated limited efficacy and there is no current gold standard of care. There is no current consensus on the pathogenesis of COVID-related anosmia; however evidence for post-viral olfactory dysfunction suggests sensory axonal regeneration and olfactory signaling may rely on elevated levels of secondary messengers *cAMP* and *cGMP*, a known effect of theophylline. Therefore, we propose a phase II single-site, double-blinded, placebo-controlled randomized clinical trial to test the use of nasal irrigation with intranasal theophylline, a known phosphodiesterase inhibitor in the treatment of asthma, to treat COVID-19 related OD. Theophylline has shown benefit in similar clinical trials for post-viral OD.

### A2 Primary Hypothesis

We hypothesize that theophylline irrigation will be more effective than placebo saline irrigation for COVID-19 related OD treatment, and that intranasal theophylline use will have minimal adverse effects due to limited systemic absorption.

### A3 Purpose of the Study Protocol

To elucidate the efficacy and safety of intranasal theophylline irrigation in the treatment of COVID-19 related OD in comparison to placebo saline irrigation.

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## B Background

### B1 Prior Literature and Studies

**COVID-19 Pandemic.** In December 2019, a novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was identified in association with pneumonia in Wuhan China.<sup>1-3</sup> As of August 1<sup>st</sup>, 2020, over 17.5 million people around the world have been infected with the resulting illness, termed coronavirus disease 2019 (COVID-19). The United States has more cases than any other country, at over 5 million. The numbers continue to grow exponentially.<sup>4</sup> The CDC has listed the following key

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symptoms suggestive of illness with COVID-19: cough, shortness of breath or difficulty breathing, fever, chills, muscle pain, sore throat, and new loss of smell or taste.<sup>5</sup>

**Anosmia Prevalence in COVID-19.** New olfactory dysfunction (OD) has been reported in up to 80% of patients with COVID-19. Prevalence using objective olfactory testing could be even higher.<sup>6</sup> One study in Iran showed that 59 of 60 COVID-19 patients reported some degree of objective olfactory dysfunction, as reported by the validated University of Pennsylvania Smell Identification Test (UPSIT).<sup>7</sup> Using a smartphone-based app (COVID Symptom Tracker), another study gathered self-reported symptoms from patients in the UK and the US. Their study reported 65% of patients who tested positive for COVID-19 had loss of smell or taste, and for 16%, there was no associated fever or cough. Using data from over 70,000 patients, they concluded the predictive ability of olfactory dysfunction for COVID-19 was higher than the predictive ability of either cough or fever, and that the median duration of anosmia was about 5 days.<sup>8</sup> Preliminary results from the COVID-19 Anosmia Reporting tool developed by the American Academy of Otolaryngology-Head and Neck Surgery suggests that, out of 237 initial entries, 27% reported olfactory dysfunction as their initial symptom, and 27% of patients had some improvement in OD with a mean of 7.2 days.<sup>1</sup> A recent study of 143 patients in Italy assessed persistent symptoms of COVID-19 after about 60 days since onset of a patient's first COVID-19 symptom. About 45% of patients presented with anosmia in the acute setting, and about 17% of patients continued to report anosmia 60 days later.<sup>9</sup> This data suggests anosmia can persist beyond two months in over a third of cases. Based on a conservative estimate in which 50% of new daily cases will experience anosmia (average of 215,000 new daily cases in the first week of January 2021 in the US), and that 10% will experience permanent anosmia, we conclude that almost 968,000 patients may suffer from permanent olfactory dysfunction by April 2021.<sup>4</sup> This estimate does not take into account those that already suffer from long-term OD currently or those that will continue to be infected after April 2021.

**Anosmia and Dysgeusia in COVID-19.** Current research studies report both anosmia (loss of smell) and dysgeusia (loss of taste) related to COVID-19 interchangeably. While it may be possible that SARS-CoV-2 directly affects olfactory and gustatory symptoms, our current understanding of olfactory dysfunction suggests that dysgeusia is related to impaired retronasal olfaction (flavor) rather than gustatory sensations (sweet, salty, sour, bitter).<sup>10</sup> Therefore, primarily focusing on treatment for olfactory dysfunction may treat both anosmia and dysgeusia.

It is well established that the nasal cavity and the nasolacrimal duct are key entry points for SARS-CoV-2;<sup>11-13</sup> however there is yet to be a consensus on the exact mechanism that leads to COVID-related anosmia.<sup>2</sup> It is believed that the virus enters a cell using spike protein S1 to adhere to a host ACE2 receptor. ACE2 receptors are expressed throughout the nervous system, which may explain the virus's neurological manifestations.<sup>2,14</sup> A bulk sequencing study showed expression of both ACE2 and TMPRSS2 genes, both thought to facilitate SARS-CoV-2 viral entry, in the olfactory mucosa of humans. A single cell sequencing study, confirmed by immunostaining, further suggested higher expression of ACE2 in sustentacular cells, basal stem cells, and in pericytes as opposed to olfactory neural cells.<sup>15</sup> There is, however, ultrastructural evidence that SARS-CoV-2 enters the central nervous system via direct viral damage to the olfactory complex as seen via nasal endoscopic dissection at autopsy.<sup>16</sup> A case study using MRI in a 25-year-old female with COVID-associated anosmia and dysgeusia

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demonstrated signal alteration, suggesting viral brain invasion into the posterior gyrus rectus, which is associated with olfaction. The resolution of the anosmia correlated with resolution in that signal alteration as well.<sup>17</sup> Therefore, preliminary evidence exists for COVID-related anosmia affecting nasal epithelial cells, the olfactory neural complex, and/or the cortex directly. The resolution of COVID-related anosmia in the majority of patients may be related to the unique neuroplasticity the olfactory system exhibits both centrally and peripherally.<sup>18-20</sup> However for those in whom symptoms persist, it may be beneficial to rely on our current understanding of non-COVID-19 post-viral olfactory dysfunction to treat COVID-related anosmia. This research into treatments could retroactively support our understanding of the exact pathogenesis of the disease as well.

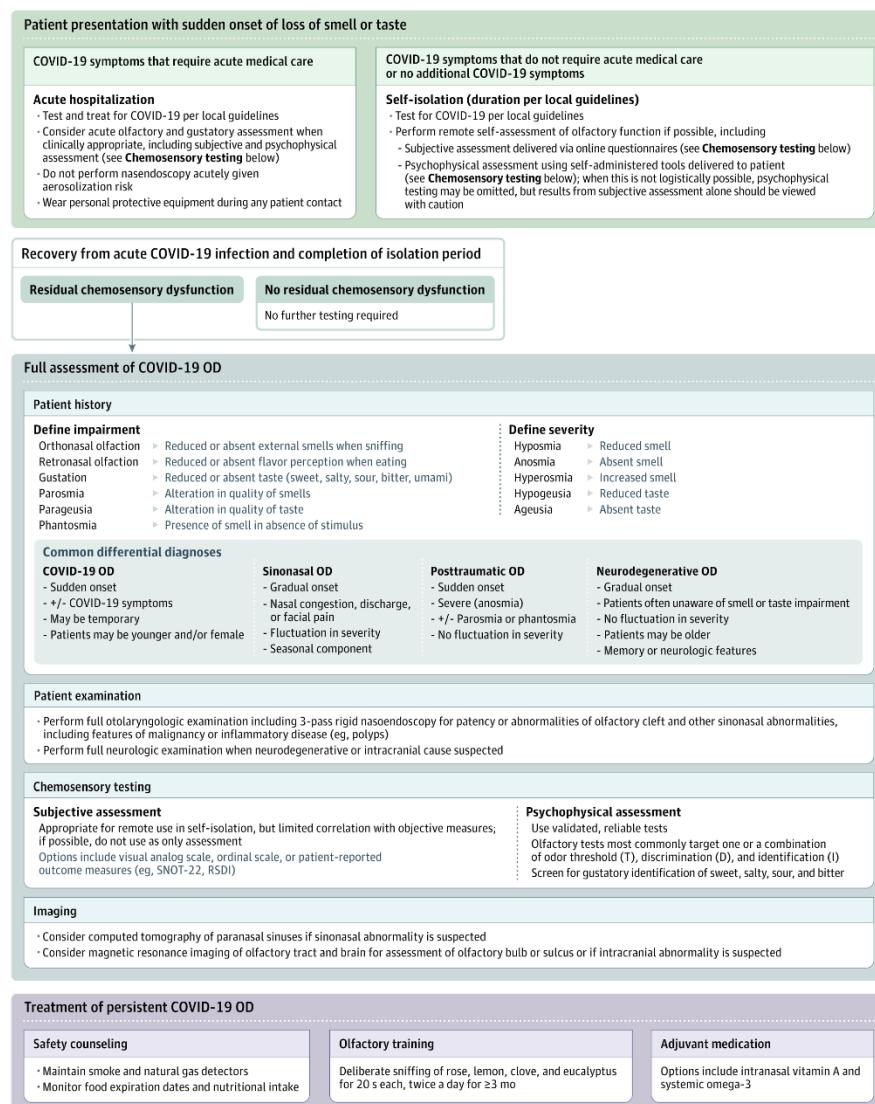
**Significance and Management of Olfactory Dysfunction.** As of 2016 before COVID-19, about 13 million or 1 in 8 Americans over the age of 40 suffered from a measurable smell dysfunction. In total, 3% of all Americans had anosmia or hyposmia, with post-viral olfactory dysfunction (PVOD) being the leading cause.<sup>21</sup> While often considered a benign or innocuous condition, in recent years olfactory loss has in fact been associated with an increased 5-year mortality rate, even after accounting for neurologic disease or weight loss. Anosmia has even been shown to be more predictive of 5-year mortality than cardiovascular disease, cerebrovascular accident, diabetes, heart failure, or cancer in older adults.<sup>22-25</sup> Olfactory dysfunction is known to cause loss of cortical gray matter as well as significantly decreased quality of life due to its inherent importance in taste and flavor, memory, and emotion.<sup>18,26</sup> OD affected up to 25% of persons over the age of 50, and evidence also suggests it may be associated with depression and contribute to the anorexia of aging.<sup>27-29</sup> While spontaneous recovery is possible in up to one-third of patients with post-viral OD, the recovery is often incomplete.<sup>30,31</sup>

Because of our limited understanding of the exact pathophysiology of permanent anosmia, treatment options have been difficult to develop. In the past, oral and intranasal corticosteroids were considered a possible treatment to target nasal mucosal inflammation; however they are not currently recommended due to lack of clear benefit and a number of adverse effects.<sup>3,10</sup> Moreover, systemic corticosteroids (particularly dexamethasone) are only recommended for acute COVID-19 infection if supplemental oxygen is needed, and it is unclear what the effect of steroids would be for COVID-related anosmia.<sup>32</sup> Other medications such as intranasal sodium citrate, intranasal vitamin A, or systemic omega-3 fatty acids have shown potential benefit and negligible adverse effects in treating olfactory dysfunction; however more research is needed to ascertain their use.<sup>3</sup>

It is well established that the olfactory system exhibits unique neuroplasticity both centrally and peripherally. Neurogenesis in the olfactory tract continues throughout our lifetime, leading experts to conduct research on olfactory training to modulate neural olfactory function. The current first-line treatment for post-viral OD is olfactory training, in which a patient is repeatedly exposed to four different odors in an attempt to regenerate olfactory receptor cells and recreate the signaling pathway to the olfactory cortex.<sup>18</sup> Olfactory training has shown significant improvements in odor discrimination and identification scores in comparison to controls; however treatment is still not definitive.<sup>18,33</sup>

The current approach to treating COVID-related anosmia relies on this past knowledge of post-viral OD, and has been outlined by Whitcroft, et al. (**Figure 1**).<sup>10</sup> This approach,

however, is continually evolving, and randomized control trials (RCT) on treatments for COVID-related anosmia are ongoing. One three-arm RCT for COVID-related anosmia treatments has been approved in which participants are randomized to olfactory training, budesonide nasal irrigation, or training with smelling household items (NCT04374474).<sup>34</sup> Another compares the use of omega-3 fatty acids or placebo (NCT04495816),<sup>35</sup> and one more uses mometasone nasal spray or placebo (NCT04484493).<sup>36</sup>



**Figure 1. Possible Approach for the Assessment and Management of Suspected Coronavirus Disease 2019 (COVID-19)-Related Olfactory Dysfunction<sup>10</sup>**

**Use of Theophylline in OD and COVID-related anosmia.** Prior *in vivo* and *in vitro* studies have demonstrated the importance of secondary messengers cAMP and cGMP in both olfactory signaling and sensory axonal regeneration.<sup>37-39</sup> When odorants attach to olfactory receptors, downward signal amplification leads to increases in cAMP and cGMP, which then instigate action potentials via sodium and calcium channels.<sup>40</sup> This results in our sense of olfaction.<sup>41</sup> cAMP promotes sensory axonal regeneration by blocking the inhibition of axonal regeneration by myelin and MAG, found in most adult

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axons.<sup>42</sup> Moreover, cAMP and cGMP levels in nasal mucus were significantly lower in hyposmic participants compared to normosmic controls,<sup>43</sup> and a stepwise increase in olfactory dysfunction was associated with a stepwise decrease in nasal mucus cAMP and cGMP levels.<sup>44</sup> The use of a phosphodiesterase inhibitor, such as theophylline, that prevents the breakdown of intracellular cAMP and cGMP, therefore, has been theorized to improve olfaction.<sup>45,46</sup> Moreover, two preliminary molecular docking studies showed potential affinity of theophylline derivatives to inhibit two important SARS-CoV-2 proteins, papain-like protease protein (PLpro) and 3-chymotrypsin-like protease (3CLpro), offering promise as a treatment of COVID-19. Further *in vivo* and *in vitro* studies are needed to evaluate clinical utility.<sup>47,48</sup>

Clinically, theophylline is an inexpensive drug with FDA approval for the treatment of both asthma and chronic obstructive pulmonary disease (COPD).<sup>39</sup> Theophylline is a methylxanthine that works by smooth muscle relaxation (bronchodilation) and suppression of tissue response to stimuli (anti-inflammatory).<sup>49</sup> While systemic theophylline has a narrow therapeutic index, the use of intranasal theophylline has recently been studied as a potential treatment for post-viral OD at doses that do not increase serum theophylline levels.<sup>50</sup> Two pilot studies of participants who had post-viral OD refractory to multiple treatments reported statistically significant improvement in quantitative subjective scores of smell.<sup>50,51</sup>

A study at our institution attempted to evaluate the role of intranasal theophylline nasal irrigation, as opposed to nasal spray, on post-viral OD. Delivery via nasal irrigation may improve penetration into the middle meatus and olfactory cleft compared to the nasal spray. This study was conducted at a particularly low dose of 12 mg twice a day and reported no clinically or statistically significant differences in olfactory function improvement between theophylline nasal irrigation and placebo.

A follow-up dose escalation trial tested higher doses up to 400mg twice daily for safety and reported minor side effects in 2 out of 10 participants at the maximum dose thus far. One patient reported pre-existing atrial fibrillation for all four weeks of the trial. 4 out of 10 participants also reported improvements in their sense of smell. Therefore, a study should be conducted to test the use of 800mg daily theophylline irrigation for the treatment of COVID-19 OD.

## **B2 Rationale for this Study**

COVID-related anosmia is a major symptom of infection with SARS-CoV-2, affecting up to 80% of those with COVID-19. While research on the pathogenesis is ongoing, a significant subset is expected to suffer from permanent olfactory dysfunction. We seek to test intranasal theophylline nasal irrigation as a potential therapeutic option for treatment of COVID-related anosmia lasting over 2 months. Theophylline has been shown to improve outcomes in post-viral OD in pilot studies, and the effects on placebo group for a similar study is already known. This phase II placebo-controlled, double-blinded RCT will provide us with the needed observed OD treatment effect for future phase III RCTs.

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## C Study Objectives

### C1 Primary Aim

*Evaluate the efficacy of intranasal theophylline irrigation on olfactory recovery and health-related quality of life in patients with COVID-19 related chronic olfactory dysfunction.* Participants will receive 6 weeks of either theophylline or placebo nasal saline irrigation. The primary outcome will be within- and between-subject changes in the subjective ratings of smell via the Clinical Global Impression Scale (CGI). Secondary measures include measurements of health-related quality of life via the 36-Item Short Form Health Survey, the clinically validated University of Pennsylvania Smell Identification Test (UPSIT), the Olfactory Dysfunction Outcomes Rating (ODOR) survey, and a Questionnaire for Olfactory Dysfunction survey (QOD).

### C2 Secondary Aim

*Describe the adverse effects of intranasal theophylline irrigation.* All participants will be monitored for adverse effects throughout the study. A subset of participants will be tested for systemic absorption via serum theophylline measurements after one week of therapy. Based on prior studies to safely escalate the intranasal theophylline dosage, we hypothesize that intranasal theophylline irrigation will have minimal systemic absorption and adverse effects.

### C3 Rationale for the Selection of Outcome Measures

In accordance with virtual research protocols, all measurement tests at baseline, at the 3-week mark, and at the 6-week mark will be administered via online HIPAA-compliant survey. The UPSIT strips will be mailed to participants in advance. The following outcome measures were chosen to evaluate our hypothesis.

Primary Outcome:

1. **Clinical Global Impression Scale (CGI)**- We will measure the response rate defined as the number of participants self reporting minimal change or larger in the Clinical Global Impression Scale (CGI) scale, divided by the number of participants in each group. The CGI has two components – the CGI-Severity and the CGI-Improvement. The CGI-Severity Scale from 1-7 (1 is Normal, 7 is Complete loss of smell) will provide us with subjective data on the patient's perceived severity of their dysfunction at baseline. The CGI-Improvement Scale from 1-7 (1 is Very Much Improved, 7 is Very Much Worsened) will allow us to measure changes at 4 weeks and post-treatment at 8 weeks. Each rating is well defined to minimize variability.<sup>52</sup> Participants reporting 3 as Minimally Improved, 2 as Much Improved, or 1 as Very Much Improved in the CGI-I will be deemed responders to treatment, and the number of responders to non-responders will be compared between the two arms.

Secondary Outcomes:

1. **University of Pennsylvania Smell Identification Test (UPSIT)** – This test is a clinically validated 40-question forced-choice odor identification test where microencapsulated odorants on a strip are released by scratching. Out of a total of 40 points, normosmia is defined as  $\geq 34$  for males and  $\geq 35$  for females, and an increase in  $\geq 4$  points will be deemed a clinically significant improvement in

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symptoms.<sup>53</sup> While the primary outcome is subjective, this test allows for an objective measure of olfactory dysfunction and improvement.

2. **36-Item Short Form Health Survey (SF-36)** - The SF-36 is a well-established 36-item questionnaire evaluating physical functioning, bodily pain, role limitations due to physical health problems, role limitations due to personal or emotional problems, emotional well-being, social functioning, energy/fatigue, and general health perceptions.<sup>54</sup> This test allows us to study the overall quality of life changes for those suffering from COVID-19 related OD.
3. **Olfactory Dysfunction Outcomes Rating (ODOR)** – ODOR is a new disease-specific questionnaire that assesses for physical, functional, and emotional limitations in participants with olfactory dysfunction of any etiology. Based on the recurring impairments for participants with post-viral OD in eating/appetite, environmental safety, interpersonal relationships, hygiene, and mood, 28 items were generated to create the new patient reported outcome measure. This test is expected to be validated in Spring 2021.
4. **Questionnaire for Olfactory Dysfunction (QOD)** – QOD will measure changes in the health-related quality of life of participants based on four factors as outlined by Mattos, et al. This will qualify which factor (eating, mental health, social interactions, or fear of dysfunction) was affected most by the proposed intervention. The survey also includes questions on parosmia, a phenomena of COVID-related OD.<sup>55</sup>
5. **COVID-19 related questions** – Questions will be asked about the length of time since COVID-19 infection, severity of symptoms, previously attempted treatments for olfactory dysfunction, and presence of parosmia/phantosmia. This survey will help us determine whether the efficacy of theophylline therapy depends on any of those factors.

## D Investigational Agent

### D1 Preclinical Data

Theophylline is a methylxanthine that works by smooth muscle relaxation (bronchodilation) and suppression of tissue response to stimuli (anti-inflammatory). It non-selectively inhibits phosphodiesterase (PDE) III and IV, thereby increasing intracellular cAMP and cGMP levels.<sup>39</sup> These secondary messengers then result in bronchodilation, smooth muscle relaxation, and decreased inflammation. It also prevents the translocation of nuclear factor- $\kappa$ B (NF- $\kappa$ B), a pro-inflammatory transcription factor, into the nucleus and thus decreases inflammation even further.<sup>49</sup> We hypothesize that due to these mechanisms, theophylline could improve olfactory dysfunction by reducing inflammation in nasal epithelial cells as well.

There are two preliminary molecular docking studies that used derivatives of theophylline to test high-affinity inhibition of three SARS-CoV-2 proteins. Theophylline derivatives in particular showed potential affinity for inhibiting papain-like protease protein (PLpro) and 3-chymotrypsin-like protease (3CLpro); however *in vivo* and *in vitro* studies are needed to evaluate future clinical use.<sup>47,48</sup>

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## D2 Clinical Data to Date

Clinically, theophylline is an inexpensive drug with FDA approval for the treatment of both asthma and chronic obstructive pulmonary disease (COPD). Clinical studies show conflicting data for its use in acute asthma exacerbations; however in acute COPD exacerbations, theophylline may decrease dyspnea, air trapping, and the work of breathing.<sup>56</sup> It may also improve contractility of diaphragmatic muscles, but it does not improve pulmonary function measurements.<sup>57,58</sup> Theophylline may be efficacious in chronic asthma and exercise-induced bronchospasm, and is an alternative, but not preferred, treatment for mild persistent, moderate, and severe asthma.<sup>39</sup> Theophylline improves respiratory function in COPD in multiple ways and is recommended as daily maintenance therapy with beta2-agonists and anticholinergics. It has been shown to reduce hematocrit and improve symptoms from chronic hypoxemia and allow for greater bronchodilation and reduced diaphragmatic fatigue.<sup>39,58</sup> At serum concentrations approaching 17 mcg/mL, theophylline has been shown to improve peak flow, trapped gas volumes, vital capacity, distances walked, and breathlessness and fatigue.<sup>59</sup> Recent data suggests a goal serum concentration of 10-15 mcg/mL to achieve clinical efficacy without side effects commonly seen at concentrations >20 mcg/mL.<sup>39,60</sup> Non-FDA approved uses may include nocturnal asthma, newborn apnea, and post-dural punctural headache. It has been studied as prophylaxis for acute renal failure, seasonal allergic rhinitis, cerebral vasospasm, and more.<sup>60</sup>

Oral theophylline has also been studied in a single-arm longitudinal trial for the treatment of hyposmia in which 50% of patients (157/312) reported subjective improvement in smell and taste, and 11% of patients even (34/312) reported return of normal function of smell. Mean odor detection and recognition thresholds were also significantly improved.<sup>45</sup> Oral theophylline use has also been associated with increased brain activation signals on fMRI in response to odors.<sup>46</sup>

Systemic effects of theophylline suggest a relatively narrow therapeutic index.<sup>39</sup> These effects may be related to phosphodiesterase III inhibition in particular. Common adverse effects of theophylline known thus far include headache, nausea, vomiting, tremors, insomnia, lightheadedness, and restlessness. Serious adverse effects can include tachyarrhythmias, atrial fibrillation, Stevens Johnson syndrome, intracranial hemorrhage, and seizure.<sup>39,60</sup>

It was hypothesized that topical theophylline may be preferred for certain disease states. A pilot study of 10 participants who previously had submaximal responses or intolerance to oral theophylline were given intranasal theophylline for the treatment of hyposmia and hypogeusia. This study showed improved taste and smell acuity in 8 participants after 4 weeks of intranasal theophylline therapy, reporting a statistically significant mean increase of 28% in quantitative subjective scores for smell improvement in comparison with 14% for the oral theophylline group. Moreover, serum theophylline levels were undetectable in all participants.<sup>61</sup> Four of 8 patients with chronic anosmia and hyposmia who did not respond to prednisone had improvement of olfactory dysfunction in another study with intranasal theophylline spray.<sup>51</sup>

A study at our institution attempted to evaluate the role of intranasal theophylline nasal irrigation, as opposed to nasal spray, on post-viral OD. Delivery via nasal irrigation may improve penetration into the middle meatus and olfactory cleft than the nasal spray. Patients with chronic OD were randomized to 12mg twice daily theophylline nasal

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irrigation (n=12) or placebo saline nasal irrigation (n=10). There was no statistical or clinical significant difference in olfaction outcomes, except for QOD-NS which favored the theophylline group, between the two groups; however a follow-up dose escalation trial was done recently to test the use of higher doses of intranasal theophylline delivered via nasal irrigation for hyposmia and hypogeusia. 7 out of 10 patients tolerated the maximum dose of 400mg twice daily without any reported side effects. One patient reported transient minor side effects that lasted for one day following increase in dose to 300mg twice daily and again at 400mg twice daily. An other patient reported continued tremors, anxiety, and abdominal pain after increasing dose to 300mg twice daily and discontinued the study. Abdominal pain is not currently a well-known side effect of theophylline use. The third patient reported pre-existing atrial fibrillation throughout the study.

There have been no current clinical studies on the use of theophylline in COVID-related anosmia and dysgeusia.

### ***D3 Dose Rationale and Risk/Benefits***

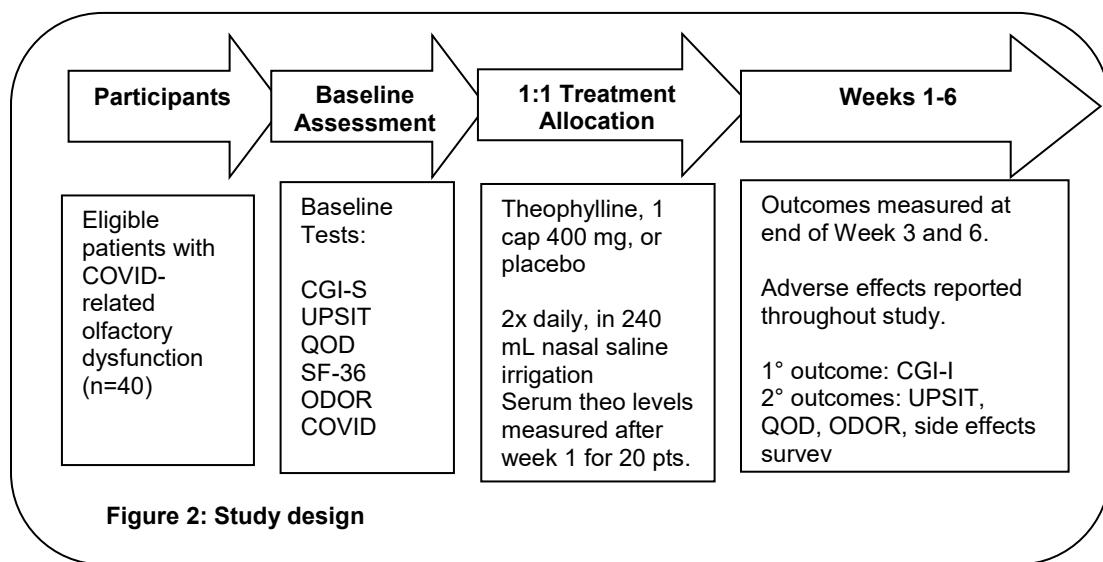
Previous data suggest a serum concentration between 10-15 mcg/mL will achieve the majority of the drug's potential benefit while minimizing adverse effects for asthma and COPD. Adverse effects significantly increase beyond a serum concentration of 20 mcg/mL, and severe symptoms (seizures, ventricular arrhythmias, and death) has been shown to occur in chronic concentrations of 40 mcg/mL or an acute concentration above 80 mcg/mL.<sup>39,60</sup>

The dose of oral theophylline used in the treatment trial of hyposmia and hypogeusia ranged from 200 mg up to 800 mg a day divided into two equivalent doses (breakfast and lunch).<sup>45</sup> Some patients only responded to theophylline in a dose-dependent manner, at a minimum of 600 to 800 mg, requiring further escalation of dosing and prolonged treatment duration. This escalation also meant exposing patients to further adverse events associated with theophylline such as headaches. Mean serum levels for patients on 800 mg oral theophylline daily was 11.2 +/- 0.8 mg/dL.<sup>45</sup> Dr. Jake Lee's low-dose theophylline nasal irrigation trial used 12 mg capsules of theophylline dissolved in 240 mL saline twice daily for six weeks, which was the equivalent converted dose from the intranasal theophylline spray open-label trial.<sup>45</sup> Dr. Lee's follow-up dose escalation trial used a maximum daily dose of 800 mg, which was increased from 200 mg daily in 200 mg increments like the earlier oral theophylline trial did with minimal side effects. Moreover the bioavailability of theophylline via nasal irrigation is expected to be lower than that of oral theophylline. Therefore, we propose the use of 400 mg theophylline nasal irrigation twice daily in comparison to placebo. Serum theophylline levels will be measured at one week for a subset of subjects. Results will be inspected immediately upon receipt of lab report, and appropriate action will be taken as defined in the Medical Monitoring section (Section 3.b).

### **E Study Design**

## **E1 Overview or Design Summary**

This study will be a single-site, double-blinded, placebo-controlled randomized clinical trial performed at a tertiary academic medical center. The purpose of this Phase II trial is to evaluate the efficacy of intranasal theophylline irrigation in treating COVID-related olfactory dysfunction. This study will also be used to describe adverse effects related to intranasal theophylline irrigation. Below is a diagram of the approach to a randomized control trial for achieving the specific aims (Figure 2):



This study will be conducted via virtual research guidelines and procedures. We will not require in-person patient participation or evaluation apart from one serum theophylline measurement after one week of the trial for up to the first twenty participants who enroll in the trial. Following initial evaluation to ensure patients meet all inclusion criteria and none of the exclusion criteria, the research study will be explained in full via phone call. Participants will then be randomized in a 1:1 allocation via permuted-block sequencing to the intranasal theophylline irrigation group or the intranasal placebo irrigation group. All assessments will be conducted through a HIPAA-compliant online survey form. Baseline assessments will help us determine subjective and objective rates of olfactory dysfunction. Assessments will be conducted again at 3 weeks and at 6 weeks, at which point the study will conclude. The primary objective of this study is to assess the efficacy of intranasal theophylline irrigation in improving COVID-related olfactory dysfunction.

## **E2 Subject Selection and Withdrawal**

### **2.a Inclusion Criteria**

Participants will be recruited based on the following inclusion criteria:

- 1) males and females ages 18 to 70 years
- 2) residing within the states of Missouri or Illinois

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- 3) Olfactory dysfunction that has persisted for >3 months following suspected COVID-19 infection
- 4) initial score on the UPSIT consistent with decreased olfactory function (<= 34 in women, <=33 in men)
- 5) ability to read, write, and understand English.

## **2.a Exclusion Criteria**

Individuals will not be allowed to participate in this study if they meet one or more of the following exclusion criteria:

- 1) History of olfactory dysfunction prior to COVID-19 infection
- 2) Any use of concomitant therapies specifically for the treatment of olfactory dysfunction
- 3) History of olfactory dysfunction of longer than 12 months
- 4) Known existence of nasal polyps, prior sinonasal, or anterior skull-based surgery
- 5) Dependence on theophylline for comorbid conditions such as asthma and COPD
- 6) History of an allergic reaction to theophylline or other methylxanthines
- 7) History of neurodegenerative disease (ie. Alzheimer's dementia, Parkinson's disease, Lewy body dementia, frontotemporal dementia)
- 8) Pregnant or breastfeeding mothers.
- 9) Current use of medications with significant ( $\geq 40\%$ ) interactions with theophylline, which include cimetidine, ciprofloxacin, disulfiram, enoxacin, fluvoxamine, interferon-alpha, lithium, mexiletine, phenytoin, propafenone, propranolol, tacrine, thiabendazole, ticlopidine, and troleandomycin.
- 10) Pre-existing arrhythmias or seizures (at least until serum blood measurements show minimal systemic levels of theophylline or lower)

## **2.b Ethical Considerations**

This project relies on the participation of human subjects. To ensure their safety, we will prioritize obtaining informed consent, maximizing benefit and minimizing risk, and maintaining confidentiality. Participants will be evaluated by a medical professional during the first interaction via phone call. Participants will phone in data or submit online surveys at baseline, the 3<sup>rd</sup> week, and the 6<sup>th</sup> week. Intranasal theophylline has been proven to have a minimal side effect profile and results in no detectable serum theophylline concentrations to date. The study team will be available at all times in case of adverse events, and a patient may remove themselves from the trial at any point throughout the trial. No financial conflicts of interest.

## **2.c Subject Recruitment Plans and Consent Process**

Recruitment will be done at the Washington University Department of Otolaryngology-Head and Neck Surgery outpatient clinics. Advertisements will also be sent to all members of the St. Louis ENT Club, otolaryngologists whose practices are within 150 miles of Washington University Medical Center (WUMC), members of the Washington University Faculty Practice Plan, the BJH Medical Group, and otolaryngologists at nearby academic institutions. Recruitment of subjects will also be achieved by sending flyers through the Washington University Volunteers for Health Research Participant Registry (VFH), and the Otolaryngology Research Participant Registry. Study posters and flyers may be posted around the medical campus and on Facebook with the help of VFH. This recruitment strategy has been successful for Dr. Jake Lee's Smell Changes & Efficacy of Nasal Theophylline (SCENT) trial (NCT03990766). We may also attempt to

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recruit participants from past studies in our lab, such as Dr. Piccirillo's CODS trial (IRB #202004146) and Dr. Piccirillo's NASAL trial (IRB #202010228). Additionally, due to the focus on virtual research at this time, we will also post the flyer on websites and social media, including the WUSTL Clinical Outcomes Research lab website. We will also work with anosmia support groups such as AbScent and FifthSense to share the study flyer. Lastly, we may use ResearchMatch to recruit within Missouri and Illinois.

## **2.d Randomization Method and Blinding**

Subjects will be randomized in a 1:1 allocation via permuted-block sequencing to the intranasal theophylline irrigation group or the intranasal placebo irrigation group. This trial will be double-blinded, meaning neither the subjects nor the study team will be aware of the intervention received by any subject.

## **2.e Risks and Benefits**

The potential benefit to the participant is improvement of their smell and taste using this novel therapy. The potential benefit to the society is the use of the results to initiate a large phase III study to definitively determine efficacy of intranasal theophylline use for treatment of COVID-related olfactory dysfunction. If effective, intranasal theophylline would become a mainstay treatment of this disease, which currently has no effective treatment. The potential risk to the participant is an adverse event related to the use of intranasal theophylline. Common adverse effects of systemic theophylline known thus far include headache, nausea, vomiting, tremors, insomnia, lightheadedness, and restlessness. Serious adverse effects can include tachyarrhythmias, atrial fibrillation, Stevens Johnson syndrome, intracranial hemorrhage, and seizure. Intranasal theophylline has shown minimal adverse effects.

## **2.f Early Withdrawal of Subjects**

The consent process informs a volunteer about the study, indicates that participation is voluntary, and that he/she has the right to stop at any time. Risks are enumerated in the informed consent form and described orally during the consent process. Subjects will be allowed to end participation in the study at any point should they desire. If a participant must be withdrawn due to a drug-related serious adverse event, the study drug will be stopped immediately. They will have an exit interview to ascertain any adverse effects and discuss the reason for the ending participation. The study team will follow them for safety reasons up to 30 days after stopping use of the study drug.

If a subject has ended participation for any reason, the only data that will be collected are the data from the exit interview and the data collected prior to withdrawal within the 6-week time period. There will not be any other follow-up or data collected from these subjects.

A participant can withdraw consent for the study at any time. Data collected up to this point will not be used in the analysis, and further data will not be collected from these subjects.

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## **E3 Study Drug**

### **3.a Treatment Regimen**

Participants will dissolve the contents of the 400 mg theophylline capsules (experimental) or identical-appearing lactose capsules (control) into the sinus rinse bottle containing nasal saline. All participants will receive an 8-ounce sinus rinse bottle and a 6-week supply of USP Grade Sodium Chloride & Sodium Bicarbonate Mixture (pH balanced, Isotonic & Preservative & Iodine Free) commercially prepared packets.

Participants will either need to purchase distilled water or boil tap water for five minutes for use with the saline irrigation. A member of the research team will instruct participants on how to irrigate each nasal cavity with one-half of the contents of the sinus rinse bottle. Written instructions and a video demonstration will also be provided to ensure proper technique. Because the half-life of theophylline in healthy adults (16-60 years) is 8.7 hours and 9.8 hours in the elderly (> 60 year), irrigations will be performed **twice daily** – once in the morning and once at night for all subjects,<sup>62</sup> for a total daily dose of 800mg theophylline nasal irrigation.

### **3.b Preparation and Administration of Study Drug**

After faxing a signed prescription, the compounding pharmacy will formulate and directly ship the study drug regimen to the patient's provided mailing address via FedEx or via the United States Postal Service if the patient only has a PO box. All packages in transit can be monitored via the tracking numbers.

### **3.c Subject Compliance Monitoring**

Patients will be evaluated at 3 weeks and at 6 weeks to ensure compliance with the study drug regimen as a self-reported measure. As a part of the REDCap surveys, patients will be asked whether they have been compliant with twice daily irrigations thus far, and what issues have arised, if any.

### **3.d Prior and Concomitant Therapy**

Patients receiving concomitant therapy specifically for the treatment of olfactory dysfunction will not be eligible for the trial unless they are able to stop taking those therapies. Patients who have tried previous therapies for their olfactory dysfunction (including over-the-counter treatments such as vitamin A or omega-3 fatty acids) will be eligible for the trial. Information will be gathered on their use of therapies, and if needed, a sensitivity or subgroup analysis may be considered.

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## **F Study Procedures**

### **F1 Screening for Eligibility**

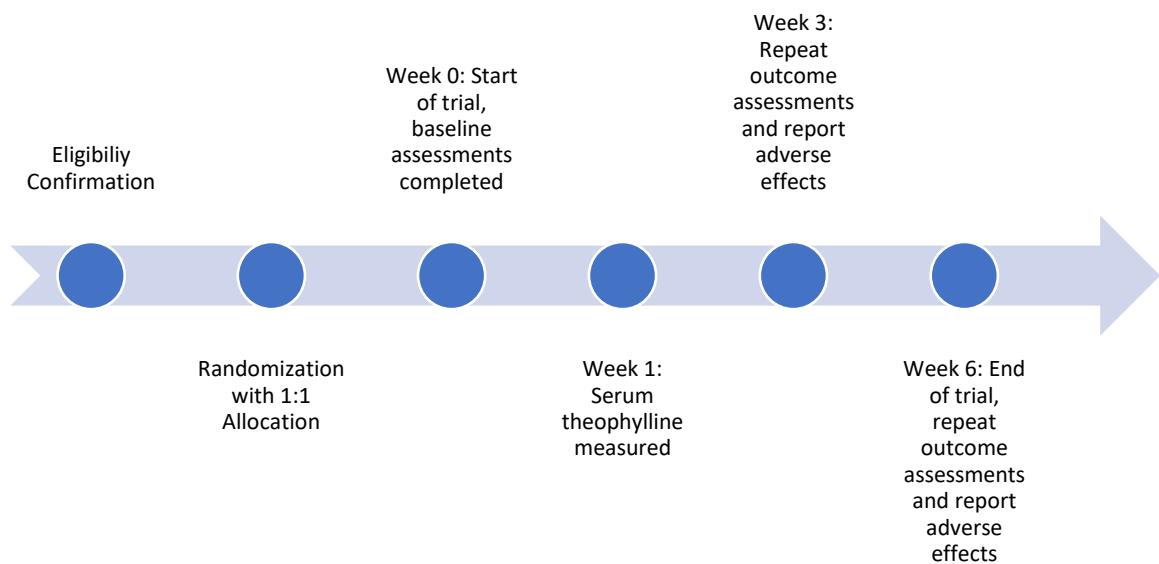
Identified patients through chart review as well as interested individuals who reach out after seeing the approved study flier will be contacted via phone call to introduce and explain the study. Interested individuals will be asked to complete an online screening questionnaire to ensure he or she meets all of the inclusion criteria and none of the

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exclusion criteria. Following eligibility confirmation, an informed e-consent will be acquired.

## **F2 Timeline of Measurements**

Following the recruitment period, randomization of subjects will occur one week prior to the start of the trial. The timeline of measurements can be seen in Figure 3.



**Figure 3. Timeline of measurements for SCENT2.**

### **2.a Start of trial**

Throughout the week before the first day of the trial, baseline tests will be administered as described in Figure 1. Participants will be mailed the UPSIT packet and will be required to complete all assessments prior to the first day of the trial through an online secure survey platform. A member of the study team will be available for any questions or concerns. Participants will also be provided instruction on how to properly conduct intranasal saline irrigation with theophylline or placebo. Participants will then receive the study drug by mail and will report their start date of nasal irrigation. One week following use of therapy, up to the first twenty participants will undergo a serum theophylline measurement, which marks the only in-person requirement for this trial.

### **2.b 3-week interaction**

At the 3<sup>rd</sup> week of the trial, participants will repeat assessments as according to Figure 2 and submit them via online secure survey platform. Efficacy of theophylline nasal irrigation for 3 weeks can then be measured to efficacy at 6 weeks. They will also be asked to report any adverse events.

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## **2.c End of trial**

At the 6<sup>th</sup> week of the trial, patients will repeat assessments as described in Figure 2 and submit them via online secure survey platform. They will also be asked to report any adverse events. This will conclude participation in the clinical trial.

## ***F3 Safety and Adverse Events***

### **3.a Safety and Compliance Monitoring**

The specific monitoring plan for this study is based on the potential risk of participation and size and complexity of the planned investigation. Based on these considerations, this study will have a monitoring board comprised of Dr. Piccirillo, Ms. Kukuljan, and Dr. Kallogjeri, the study biostatistician. The monitoring board will meet to review data at least every 6 months. All reports of a Serious Adverse Event (SAE) or an Unexpected Adverse Event (UAE) will be investigated by the monitoring team and reported to Washington University HRPO according to the reporting requirements.

The PI and the study team will be monitoring patients for any safety concerns, such as SAE or UAE, in real time for the duration of the 6-week study. In addition, patients will be specifically asked about any adverse events at the 3-week and 6-week mark via REDCap. Participants will be able to get in touch with a member of the study team 24/7 via phone or pager for the duration of the 6-week clinical trial. The study statistician will hold the randomization codes, and in the event of an SAE or UAE in which the blind needs to be broken, the patient will receive immediate care and will be removed from the trial. A description of the event will be included in the report of adverse events for the clinical study.

Serum theophylline levels will be measured in the first ten participants of the trial. If any subject has a serum theophylline level greater than 20 mcg/mL,<sup>39,60</sup> the study will be discontinued. If serum theophylline levels are unable to be detected or very minimal (<5 mcg/mL), the study will continue with no modifications. If any subject has detectable serum theophylline levels >5 mcg/mL, ten more participants will undergo serum theophylline testing.

Participants who experience serious adverse effects with theophylline therapy will be removed from the study. Participants with serious adverse effects, such as arrhythmia and seizures, will be instructed to call 911, seek immediate medical care and discontinue all further theophylline treatment. If tolerated, all participants will complete a total of 6 weeks of treatment.

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## **G Statistical Plan**

### ***G1 Sample Size Determination and Power***

To date there have been no studies investigating efficacy of theophylline in COVID-19 related OD. Due to the lack of preliminary data and effect size, estimates of the sample

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size for this study will be determined based on feasibility. For this pilot study, we plan to enroll 50 subjects. The sample size of 50 subjects is feasible given the current numbers of new COVID-19 cases in Missouri (average of over 3,500 daily new cases in December 2020),<sup>63</sup> taking into account a conservative estimate of a 10% rate of permanent olfactory dysfunction. Using a 20% drop out rate we estimate that the sample size of 50 subjects will provide us with 40 evaluable cases.

A 50% rate of improvement with intranasal theophylline was reported in a pilot study for post-viral OD;<sup>51</sup> however discussion with Dr. Greg Davis, who prescribes nasal theophylline spray in his clinical practice, led Dr. Lee to estimate a more realistic response rate of 25%. In Dr. Lee's trial of participants with post-viral olfactory dysfunction, 30% of the participants randomized to placebo reported improvement at the end of the trial as compared to baseline. Assuming that this will be the response rate in the placebo group of our trial, the sample size of 20 subjects per group will provide us with a 95% Confidence Interval -5% to 55% around the desired proportion difference of 25% between theophylline and placebo groups. The upper limit of confidence interval suggests that there is real value in the response rate of theophylline in the population. The effect size calculated from this study will be used for sample size calculations for future fully powered studies.

We anticipate no more than a 20% drop-out or withdrawal rate, which is included in our calculation of sample size.

## **G2 Analysis Plan**

An intention-to-treat analysis will be used where all participants will be examined in the groups to which they were initially assigned regardless of the treatment actually received. Standard descriptive statistics will be used to assess the demographics, clinical characteristics, and olfactory test results of the study population. The **difference in rate of responders** at 6 weeks will estimate the effect size of the primary outcome measure, and the 95% CI around that point estimate will measure precision. In each group, the frequency and relative frequency of the participants' response to the global rating of smell change will be reported for each Likert category. Fisher's exact test will be used for comparing the responders' rates between the 2 groups at 3 weeks and at 6 weeks. Histograms and Shapiro-Wilks test will be used to test the normal distribution assumption of the continuously measured **UPSIT** scores and the differences pre-post treatment in each of the groups. Independent samples *t*-test or its nonparametric equivalent Mann-Whitney U test will be used to compare the change in UPSIT scores between the two groups. A mixed model analysis will be used to compare the change in outcomes through different study assessments between the study groups. Effect sizes with 95% CIs will be reported for each analysis. All statistical analyses will be conducted in SPSS 27 (IBM Corp., Armonk, NY).

## **G3 Missing Outcome Data**

Maximum efforts will be made to limit the number of missing values. Missing outcomes will be taken into consideration at the beginning of each analysis. Valid percents will be reported alongside overall percent for standard descriptive statistics, and data for participants who do not complete the full 6-week trial will be excluded for further analyses.

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## **H Data Handling and Record Keeping**

### ***H1 Confidentiality and Security***

Procedures that are in place to curb risks of breaches in confidentiality and privacy are 1) formal training protocols centered on the maintenance of confidentiality for all study team members; 2) de-identified databases using only the study ID numbers; 3) a password-protected computer file of a master list that contains the identity of subjects, corresponding ID numbers, and contact information but no clinical information; 4) secure storage for identified data forms such as completed questionnaires and UPSIT exams; and 5) communication with study team via secure email, phone line, or televideo call.

Only members of the study team will have access to the computer file and password for the master list. All research data files will be stored on secure Washington University servers with computer, network, and database-level passwords that will only be accessible to study team members. Accordingly, these mechanisms intend to limit access to information that can link clinical data to individual subjects. No subject identifying information will be revealed in any publications or presentations.

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## **I Study Monitoring, Auditing, and Inspecting**

### ***I1 Study Monitoring Plan***

The Principal Investigator (PI) will be responsible for ensuring participants' safety on a daily basis and for reporting Serious Adverse Events and Unanticipated Problems to his or her Institutional Review Board (IRB) as required.

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## **J Study Administration**

### ***J1 Subject Stipends or Payments***

Subjects will receive \$40 after the initial consultation and serum theophylline measurement at 1 week and \$40 at the completion of the 6-week study for a total of \$80.

### ***J2 Study Timetable***

January-February 2021: IRB approval process and acquisition of resources

February 2021: Rolling recruitment

February-April 2021 : 6-week clinical trial

May 2021: Statistical analysis and publication of results

## **K Publication Plan**

We plan to analyze the accumulated data throughout the months of March to May 2021 and publish results by the end of May 2021. This data includes an analysis of the results of the CGI-I, UPSIT, ODOR, and 36-SF questionnaires as well as a discussion of potential adverse effects related to intranasal theophylline irrigation for treatment of COVID-related olfactory dysfunction.

## **L Attachments**

### **L1 Informed consent documents**

### **L2 Questionnaires or surveys**

- Clinical Global Impression Scale (CGI)
- 36-Item Short Form Health Survey
- Olfactory Dysfunction Outcomes Rating (ODOR) survey
- Questionnaire for Olfactory Dysfunction survey (QOD)

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