RANDOMIZED TRIAL TO EVALUATE THE EFFICAY OF THE NANODROPPER DEVICE ON INTRAOCULAR PRESSURE IN PATIENTS WITH GLAUCOMA

Protocol Number:	20-32530
NCT Number:	NCT05273385
Document Date:	11/02/2020
Intervention:	Efficacy of the Nanodropper Device on Intraocular Pressure in Patients With Glaucoma

Nanodropper Glaucoma Trial Study Overview

Study Title: Efficacy of the Nanodropper Device on Pupillary Dilation in Clinic and Intraocular Pressure Reduction in Patients with Glaucoma. (Nanodropper Glaucoma trial)

Principal Investigator:	Julius Oatts, M.D., Associate Professor of Ophthalmology. UCSF, San Francisco, CA. Phone: 415.353.2800 e-mail: Julius.Oatts@ucsf.edu
Co-Investigator:	Ying Han, M.D.- Ph.D., Professor of Ophthalmology. UCSF, San Francisco, CA. Phone: 415.353.2800 e-mail: ying.han@ucsf.edu
Study Coordinator:	Mariko Costantini Phone: 510.646.2065 e-mail: mari.costantini@ucsf.edu

STUDY SUMMARY

Introduction: Nanodropper is an eye dropper adapter that dispenses smaller eye drops. Eye drops from standard of care (SOC) dropper bottles are up to 5x larger than what the human eye can absorb (7-10 µL). Therefore, every time a patient administers an eye drop, they lose approximately 80% of their medication to wasted overflow and/or systematic absorption. The Nanodropper device elutes 10.4 µL per drop, which may reduce medical waste and reduce systemic side effects while maintaining efficacy.

Purpose: To determine non-inferiority of the Nanodropper adaptor for intraocular pressure (IOP) control in glaucoma patients compared to SOC dropper bottles.

Study Design: The study will include four visits: recruitment visit, baseline visit following a wash-out period of 4-5 weeks (± 1 week), 1-month follow-up (± 1 week), and 3-month follow-up (± 1 week). A random sample of 80 participants from UCSF will be selected to participate in the "Nanodropper Glaucoma" study, which will entail use of Nanodropper to administer eyedrops and IOP measurements at follow-up visits.

Table 1: Schedule for examination and treatment

	Recruitment	**Baseline**	**1-Month Follow-Up (± 7 days)**	**3-Month Follow-Up (±7 days)**
Consent	**X**			
Randomization		**X**		
Nanodropper Instruction		**X**		
IOP Measurement	**X**	**X**	**X**	**X**
Conjunctival Grading		X		X
Survey				X

Page Break

Study Population:

Inclusion Criteria:

1. 18 years old or older
2. Diagnosis of open-angle glaucoma (OAG) or ocular hypertension (OHT)
3. Use of prostaglandin analogue (PGA) eye drop
4. Stable disease status (no visual field loss progression or increase in IOP-lowering medications in the last 6 months)

Exclusion Criteria:

1. Uncontrolled glaucoma
2. Have had eye surgery (including laser procedures) within the past six months
3. Have a diagnosis of acute angle-closure glaucoma and/or other retinal diseases
4. Use of non-PGA class of IOP-lowering medication

Randomization (40 patients per group):

Group 1: administer eyedrops with SOC dropper bottles for three months
Group 2: administer eyedrops using Nanodropper for three months

Participants will be supplied a Nanodropper device free of charge.

Outcomes:

Intraocular Pressure (IOP)

Goldman applanation tonometry will be performed at each study visit by a masked and experienced ophthalmologist. The time of IOP measurement will be also recorded. The tonometer will be calibrated monthly. Pneumotonometer application tonometry will also be performed at each study visit by a masked and experienced ophthalmologist. The time of IOP measurement will also be recorded and the Pneumotonometer will be calibrated monthly. *The order of testing will always be applanation right eye, applanation left eye; pneumotonometry right eye, pneumotonometry left eye*

End-of study Survey

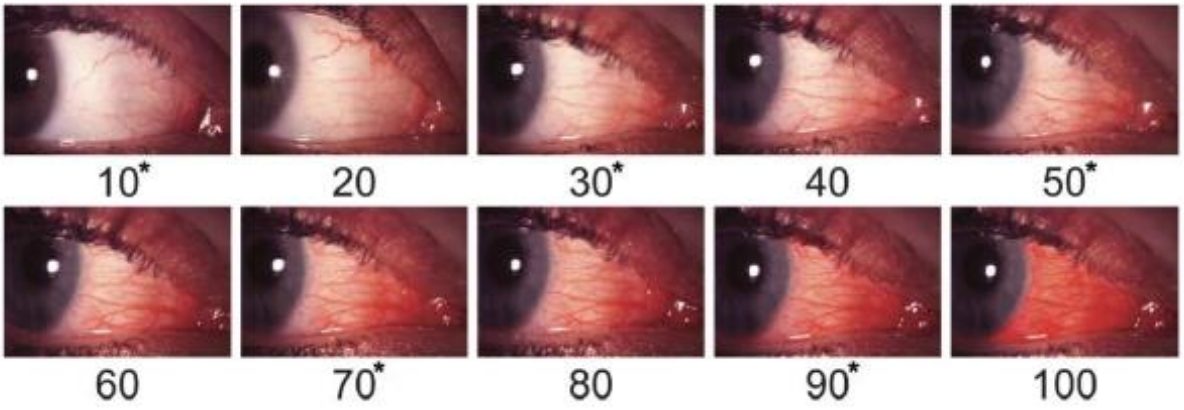
The following open-ended questions will be administered to participants randomized to the Nanodropper group at the end of the 3-month study.

1. Would you consider using the Nanodropper for your regular eye drop use in the future? (yes/no)
2. Did you find the Nanodropper easy to use? (yes/no)
3. Did using the Nanodropper cause more irritation compared to normal eye drop bottles? (yes/no)

Conjunctival Grading

Conjunctival grading will be performed by a masked ophthalmologist at the baseline and 3 month study visits. Grading will be performed as described in the following citation, with redness graded on a scale of 0-100 using the 5-picture validated scale (which will be printed on photographic paper in a size of 3.8x5.7 cmand used for

comparison). Time between grade and last eye drop administration at the 3 month end point will be measured as well.



Non-Inferiority of Nanodropper for Intraocular Pressure Control

Statistical Analysis Plan

1. Administrative Information

Trial registration:	ClinicalTrials.gov
Funder:	UCSF Internal Funding
SAP Version:	Version 1 A revision history for this document is included at the end.
Protocol Version:	Refers to Protocol Version
Contributors:	Statisticians responsible: Jeremy Keenan[1] Principal Investigators: Jeremy Keenan[1] Julius Oatts[2] Ying Han[2]

[1] Francis I. Proctor Foundation for Research in Ophthalmology, University of California, San Francisco, USA

[2]Department of Ophthalmology, University of California, San Francisco, USA

SAP Table of Contents

The content of this Statistical Analysis Plan meets the requirements stated by the US Food and Drug Administration and conforms to the American Statistical Association's Ethical Guidelines. This SAP was organized following guidelines proposed in:

Gamble C, Krishan A, Stocken D, Lewis S, Juszczak E, Doré C, et al. Guidelines for the Content of Statistical Analysis Plans in Clinical Trials. *JAMA*. 2017;318: 2337–2343. PMID: 29260229.

2. Introduction

2.1. Background and rationale

Topical ophthalmic medications in the form of eye drops are widely used for diagnostic and therapeutic purposes. The human eye can only absorb 7-10 μL of fluid, but the average volume dispensed from commercially available eye dropper bottles is approximately 50 μL. Given this, every time a patient administers an eye drop, they lose approximately 80% of their medication to wasted overflow and/or systemic absorption. Besides generating waste, larger eye dropper volumes may also increase the likelihood of local and systemic adverse medication effects, especially since topical medications that reach the nasolacrimal duct and nasopharynx can be absorbed systemically through the mucosa, avoiding first-pass metabolism. Major systemic side effects have been reported in children including bradycardia, hypotension, and asthma attacks after topical beta-blocker use and anticholinergic symptoms and psychosis following topical cycloplegia. Locally, preservatives found in eye drops are known to cause adverse eye symptoms and irritation.

Instillation of a smaller volume eye drop could limit medication waste and reduce systemic and local side effects, although the efficacy of smaller volume eye drops has not been well characterized. The aim of this study was to evaluate the effectiveness of a novel small volume eye drop adapter, Nanodropper, which administers 10.4 μL eye drops when used for pupillary dilation and cycloplegia in children.

2.2. Objectives

1: To determine if the use of Nanodropper eye adapter is non-inferior for intraocular pressure (IOP) control to standard of care (SOC) eye drop bottles.

3. Study Methods

3.1. Trial design

The study will be a randomized trial to evaluate the non-inferiority of Nanodropper eye drop adapter versus SOC eye drops.

3.2. Randomization

Participants (including both eyes for every participant) will be randomized 1:1 to two groups using RedCap with an imported allocation table from R with the following code. Note the important thing here is the seed, which will be chosen at random by non-masked study personnel. The person doing the randomization will not share the seed with anyone who is masked. The person doing the randomization will share the R script (and randomization list) with a member of the DSMC as a backup.

```
library(blockrand)
library(tidyverse)

set.seed(1234*** will be replaced with random number)
randomlist <- blockrand(n=90, num.levels=2, block.sizes = 4:6) %>%
  mutate(tx=case_when(treatment=="A" ~ "nanodropper",
                      treatment=="B" ~ "standard",
                      TRUE ~ NA_character_),
         redcap_copypaste=paste0(id, ", ", tx))
write_csv(randomlist, "randomlist_forpractice.csv")
```

Group 1: administer eyedrops with SOC bottles for three months
Group 2: administer eyedrops using Nanodropper for three months

3.3. Sample size

The trial's target enrollment will be 80 participants. Sample size was determined based on a power calculation to reach significance for one outcome at a p-value = 0.05 for 80% statistical power. R code for Power calculation included below:

```
Library(SampleSize4ClinicalTrials)
ssc_meancomp(design=3L, ratio=1, alpha=0.025, power=0.8, sd=3,
theta=0, delta=2)
```

Assuming 10% loss to follow up, 80 participants are needed.

3.4. Statistical framework

For the primary prespecified analysis, we propose a non-inferiority analysis with a margin of error of 2 mmHg.

3.5. Statistical interim analyses and stopping guidance

This is a small trial with four study visits to evaluate the non-inferiority of Nanodropper eye adapter. Interim analyses will not be performed.

3.6. Timing of the final analysis

The final analysis will take place when study data has been measured and collected on all study participants. If the trial is stopped for safety concerns or complications before the full sample, the final analysis will include all outcomes among patients who have been enrolled at the time the trial is stopped.

4. Statistical Principles

4.1. Confidence intervals and *P*-values

The trial will report 95% confidence intervals for the mean/pseudomedian of each group, together with boxplots and other descriptive statistics.

4.2. Missing data

We will report the number of individuals with missing outcomes, together with relevant covariates. The primary analysis will be a complete case analysis only including those who do not have missing data.

5. Trial Population

5.1. Screening data

We will report the number of patients screened and characteristics to the extent they are available to assess representativeness of the enrolled study population.

5.2. Eligibility

See the trial protocol for eligibility criteria.

5.3. Recruitment

We will report the number of participants screened, enrolled, randomized, and measured, along with reasons for exclusion at each step following CONSORT guidelines.

5.4. Withdrawal/follow-up

We will report the proportion of patients who withdraw from the trial, along with reasons. We will report this information in the trial's CONSORT flow chart.

5.5. Baseline patient characteristics

We will summarize patient characteristics by arm, including: age, sex, intraocular pressure (IOP), and ocular diagnoses at the time of enrollment.

6. Analysis

6.1. Outcome definitions and analysis methods

Outcome: The primary outcome will be intraocular pressure (IOP) at each follow-up time point.

Analysis: We propose to compare the mean IOP for SOC *vs* Nanodropper groups at each follow-up timepoint (1 and 3 month visits).

6.2. Additional analyses

Additional analyses may be added. If so, these analyses will be addended to the SAP prior to the analysis being performed.

6.3. Harms

Adverse events and serious adverse events (SAEs) will be reported to a Data and Safety Monitoring Board, with SAEs being reported within 24 hours. These events will be tabulated by study arm. The counts of adverse events and serious adverse events will be analyzed using chi-square tests between study and control eyes. However, we note that conservative statistical analyses are not necessarily appropriate in analysis of safety signals and that the DSMB may recommend discontinuation due to evidence of safety without achieving a 0.05 threshold for significance. In publication, we propose to not report statistical significance for these analyses.

6.4. Statistical software

Analyses will be conducted using R version 4 or later.

7. References

1. Non-Inferiority Clinical Trials to Establish Effectiveness Guidance for Industry. (2016). *U.S.Department of Health and Human Services Food and Drug Administration*. Retrieved from https://www.fda.gov/regulatory-information/search-fda-guidance-documents/non-inferiority-clinical-trials.