09-17-2020

Reducing Adenoviral Patient Infected Days (RAPID)

https://clinicaltrials.gov/ct2/show/NCT02472223

Chapter 2 RAPID Protocol
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2.0 Study Design

Summary of Reducing Adenoviral Patient-Infected Days (RAPID) Study
This is a double-masked, randomized pilot study to estimate planning parameters for a definitive large scale trial. In the pilot study, we will randomize 50 participants with adenoviral conjunctivitis confirmed by qPCR in 1:1 ratio to either one-time, in-office treatment with artificial tears or povidone iodine 5% (5% PVP-I). Follow-up care in both groups after treatment at baseline will be standard of care with single-use artificial tears 4 times-a-day until resolution of symptoms. The pilot study is funded by a NIH R-34 Planning Grant.

Key Eligibility Criteria

1. Ability to provide written informed consent;
2. At least 18 years of age, male or female, of any race;
3. Self-reported onset of symptoms in first affected eye $\leq$ 4 days of presentation;
4. Adeno-viral conjunctivitis in study eye confirmed by RPS AdenoPlus™;
5. Females capable of becoming pregnant must have negative urine pregnancy testing.

Key Exclusion Criteria

1. History of hypersensitivity to iodine or Betadine™ or thyroid disease;
2. History of herpetic eye disease;
3. Ocular surgery in study eye within the past 3 months;
4. Presence of skin vesicles, corneal subepithelial infiltrates, corneal dendrites, traumatic corneal abrasion, corneal ulcer, foreign body, or conjunctival membrane/pseudomembranes, or anterior chamber cell or inflammation in study eye on slit lamp examination;
5. Females who are pregnant or lactating or have positive urine pregnancy test.

Study Visits
Screening/Baseline visit includes completion of RAPID symptom survey, a comprehensive eye examination including visual acuity, SLE, fluorescein staining, RPS AdenoPlus™ and tear sampling for molecular diagnosis.

Eligible patients are randomized to receive one-time, in-office dose of 5% PVP-I or artificial tears at baseline and complete 5 f/up visits (1-2, 4, 7, 14 and 21 days). Tear samples for molecular diagnosis are taken at each f/up visit and AdenoPlus™ testing continues til 2 consecutive negative tests.

Ineligible patients will receive standard of care outside of the RAPID study.

Unmasked clinician/technician administers randomized treatment.
Masked clinician/technician completes all follow-up visits.

2.1 Specific Aims

There are no published clinical trials evaluating the efficacy of one-time, in-office administration of 5% PVP-I against a control group. A definitive trial has the potential to alter clinical practice patterns whether 5% PVP-I is shown to be efficacious or not. Our long-term goal is to conduct a definitive, randomized clinical trial (under an NEI UG1 grant award) that evaluates whether or not a single, in-office application of 5% PVP-I is more effective than artificial tears alone at reducing viral load and improving symptoms in patients with Ad-Cs. To optimize the design of such a large-scale clinical trial, we are conducting this R34-planning study. We will use this planning study to address three specific aims that will yield information that is critical to the successful design of the UG1 RCT.

Aim 1: Evaluate the performance of the RPS AdenoPlusTM detector in determining study eligibility by comparing the RPS AdenoPlusTM case positive eyes in patients presenting with conjunctivitis to molecular diagnosis such as PCR testing.

While molecular diagnosis such as PCR is the gold standard for adenovirus detection, PCR is performed off-site and delays diagnosis by 24-48 hours. The inaccuracy of clinical diagnosis of Ad-Cs based on patient signs and symptoms has been extensively documented. We will use the RPS AdenoPlus^{TM}, a rapid in-office detection system, to screen for Ad-Cs and will adjust sample size of the future UG1-funded study to reflect the false-positive rate associated with this device.

Aim 2: Assess patient visit completion, change in patient-reported symptoms and PCR-determined viral load and masking during the 21 day follow-up period.

We will assess participants over six visits, baseline (treatment randomization) and follow-up at 1-2, 4-5, 7, 14 and 21 days. We will quantify rates of visit completion and changes in participant-reported symptoms and viral load by qPCR at these time-points. These data will be used to determine the necessity and feasibility of a shorter/longer follow-up period in the UG1 clinical trial. We will also assess participant-reported eye discomfort due to treatment using a 10 point visual analog scale to assess participant tolerance of 5% PVP-I. Masking of participants will be assessed at baseline and at visit day 4-5. Success of clinician masking will be assessed at baseline and day 14.

Aim 3: Correlate changes in PCR-determined viral load with changes in clinical signs and symptoms.

Improvement in clinical signs and symptoms is the most important outcome from the participant's perspective and a prerequisite for wide adoption of 5% PVP-I as Ad-Cs therapy. The data collected in this planning study at baseline, 1-2, 4-5, 7, 14 and 21 days will be used to start probing this relationship and to identify the key variables that could be more directly focused on and addressed fully in the larger UG1-funded Ad-Cs clinical trial.

These Aims will provide key planning parameters for the preparation of a Manual of Procedures for a national, multi-site clinical trial to test definitively whether or not a

single, in-office treatment of 5% PVP-I is more effective than artificial tears at reducing viral load and improving symptoms in participants with Ad-Cs. 2.2 Study Organization Steering Committee members include Clinical Center PI's and Coordinating Center Director:

1. Harthan, Jennifer O.D., FAAO Illinois College of Optometry
2. Hartwick, Andrew O.D., Ph.D, Ohio State University
3. Johnson, Spencer O.D., Northeastern State University
4. Migneco, Mary O.D., FAAO, Washington University School of Medicine
5. Shorter, Ellen O.D., University of Illinois
6. Than, Tammy O.D., M.S., (Study Chair), University of Alabama at Birmingham
7. Gordon, Mae Ph.D., (Director) Coordinating Center, Washington University School of Medicine

The Steering Committee will meet weekly by teleconference as it has done since the summer of 2012, and in person 1-2 months within study funding and at 12-14 months to develop the UG1 study protocol. The Steering Committee will be responsible for monitoring study progress semi-annually, completing planning studies, designing the UG1 collaborative study protocol, preparation of the Manual of Procedures, and UG1 collaborative studies grant application.

2.2 Study Organization

Clinic Personnel

To attain the overall target sample of 50 randomized participants who are qPCR positive, at least 200 patients who present with pink eye will need to be screened. Thus, each clinic is expected to screen at least 50 patients and randomize at least 8-9 eligible patients who are qPCR positive by February 2018. Each clinic must have at least one study certified person in each of the following positions: 1. unmasked treating clinician/technician, 2. masked clinician/technician and 3. study coordinator. Supplies are distributed to clinics by the Coordinating Center. Participants receive a retention incentive of $20 by gift card or check for each follow-up visit completed.

Data Safety and Monitoring Committee

NIH does not require a Data Safety and Monitoring Committee for R-34 planning studies. However, in this R-34 planning study, an external, unmasked committee will be needed to review interim outcome data to make timely interim protocol changes because clinicians are masked. The Data Safety and Monitoring Committee will convene annually. Its members include: Sally Atherton, Ph.D, (Regents Professor Emeritus, Medical College of Georgia) specializing in the pathogenesis of herpes virus infections of the eye and brain and routes of virus spread, James Chodosh, M.D., M.P.H. (Massachusetts Eye and Ear Infirmary) a clinician scientist specializing in clinical and pre-clinical adenovirus research; Thomas Freddo, O.D., Ph.D., (New England College of Optometry, Boston), an internationally recognized expert in ocular pathology; Thomas Leitman, M.D., clinician scientist specializing in community strategies for trachoma control and corneal ulcer prevention programs. Dr. William Mather (2015-2016) withdrew upon retirement from Oregon Health and Science University.

Ex Officio members include Mae Gordon, Ph.D., Washington University, Director Coordinating Center, Mr. Donald Everett, National Eye Institute and Dr. Israel Goldberg, consultant.

The Coordinating Center will monitor safety and efficacy in an ongoing fashion and generate semi-annual reports on study progress for review by the Steering Committee. Death and selected other serious adverse events will be reported to the local IRB and the Coordinating Center within 24 hours of notification. The Coordinating Center will notify the Steering Committee and Data Monitoring and Oversight Committee within 24 hours of its notification.

2.3 Schedule of Visits, Tests and Measures

Procedure	**Screening/Baseline Exam Pts.≥ 18 yrs. presenting w pink eye**	**Follow-up Exam Randomized Pts. at 1-2, 4-5, 7, 14, 21 days**
	Unmasked or Masked Clinician/Technician	**Masked Clinician or Masked Technician**
Pt. washes hands upon entering exam rm.	X	X
Written Informed Consent	X	n/a
Examiner-Administered Symptom Survey	X	X
Medical and Ocular History	*X*	*X*
Snellen Visual Acuity **Pinhole if VA worse than 20/20**	X	X
Slit Lamp Examination	X	X
Grading of Ocular Signs	X	X
Subepithelial Infiltrate Check	X	X
Lymph Node Palpation	X	X
Pregnancy testing for women of childbearing age	X	n/a
AdenoPlus™ Testing and photograph RPS test display	X	Continue RPS testing until 2 negative results
Tear sample for molecular diagnosis	X	X
Fluorescein Grading	X	X
Clinician Prediction of Cause of Pink Eye	X	n/a
	Randomization of Study Eye of Eligible Patients	
Randomization to artificial tears or 5% PVP-I (Betadine™5%)	Unmasked Clinician/Technician Administers Randomized treatment	n/a
Repeat Fluorescein Grading	X	n/a
Pt. receives artificial tears for 21 days	X	X
Staff gives gift card to pt. & completes check voucher for $20	n/a	X
Complete disinfection protocol	X	X

2.4 Recruitment of Patients with "Pink Eye"
(Appendix 2-A "Recruitment Screening Script")
Participants who present with "pink eye" will be ushered directly to a designated "red eye" examination room. If a designated room is not available, the patient will be ushered to a designated "red eye" chair in the waiting area. Magazines adjacent to chair will be disposed of afterwards in a red biohazard bag. The chair surface will be disinfected with hypochlorite bleach or cavicide wipes.

Participants, who are ≥ 18 years of age and report symptom in the first affected eye onset ≤ 4 days, will be informed of the study by Clinical Center personnel and asked if they would be interested in learning more. Patients expressing interest in the study will discuss study participation with a study certified clinician/coordinator in a specially designated "Red Eye" examination room. **(Appendix 2-B, "Sample Consent Form")**

Upon entering the "red eye" examination room, the study certified clinician/technician will request the patient to wash their hands. The clinician/technician will turn on the water and dispense soap. The patient dries hands with paper and disposes of paper towels in red biohazard bag.

The study certified clinician/coordinator will explain the study to the patient, answer all questions and provide a brochure (Appendix 2-C "RAPID Recruitment Brochure"). The brochure will include information about adenoviral conjunctivitis (public health impact and proper hygiene to reduce infection and diagnosis) and describe the RAPID study and provide Clinical Center contact information.

Patients who decline study participation will be treated according to the standard of care with artificial tears as recommended by the American Academy of Optometry and American Ophthalmology Academy. Patients who decline participation will not be assigned a study ID code. The patient EXITS the study and no more questions need to be completed. The visit date and gender of patients who decline participation will be maintained on a screening log. No other data is retrieved on patients who decline participation.

Patients who agree to study participation and will sign two copies of the consent form and will be assigned a study ID code. The clinic files one in a red folder indicating biohazard. The other copy is given to the patient along with the pen used to sign.

All research data are identified only by study ID code. No personal identifying data are collected as research data. All subsequent study forms are completed by study personnel to reduce risk of infection transmission.

2.5 Recruitment, Consent and Tear Sampling in Control Patients
Approximately 50 normal, healthy adult controls (age ≥ 18) at each clinic will be invited to provide a one-time tear sample for immunoassay and molecular diagnosis to describe ocular microbiome in the normal eye. Control eyes will provide a baseline against which to compare microbiome in eyes that present with "pink eye" infected with

adenovirus and/or other infectious agents including co-infection by bacteria. A high prevalence of adenovirus co-infection with bacteria causing conjunctivitis could favor the use of a broad spectrum anti-microbial agent such as betadine rather than an anti-viral agent.

A study certified clinician/technician will explain the study to healthy adults and answer all questions. Individuals who agree to possible participation will sign a copy of a consent form for healthy, adult volunteers. They will be assigned a study ID code and be asked to complete a form asking age, gender, race/ethnicity and if they have taken prescription medications for an ocular condition in the last 2 months. Those who answer "yes" are excluded. No other data will be collected from controls. There is no follow-up beyond the day of presentation and there is no payment for participation. The control volunteer receives a photocopy of the consent form and the original is filed at the clinic in a HIPAA compliant office.

A study certified clinician/technician will instill a drop of 0.5% of proparacaine anesthetic to numb one eye. After 5 minutes, a tear sample will be taken from the lower lid with an RPS flock for immunoassay and swab for molecular diagnosis.

Potential adult controls who decline study participation will be treated according to the original purpose of their visit. No patients will be specifically called in to serve as an ocular control.

2.6 Screening Examination for Patients with "Pink Eye"
(Appendix 2-D "Screening/Baseline Form")

Re-Confirm age ≥ 18 years
Study certified personnel will confirm patient age (≥ 18). If age is less than 18, the patient EXITS the study, the examination stops here and no more questions need to be completed.

Ocular Symptom Survey
Study certified personnel will read ocular symptom questions in quotes "word-for-word". Duration of symptoms (again) in first affected eye (≤4 days) will be asked again as confirmation. If symptom duration is greater than 4 days, the patient is ineligible but will complete the screening examination, but will not complete the Screening/Baseline Form for eligible patients.

History and Eye Examination
Study certified personnel will complete:

1. Case history to determine history of allergy to iodine or Betadine, eye surgery within 3 months, thyroid disease, herpes related eye infection, pregnancy status;
2. Snellen visual acuity-corrected or uncorrected, pinhole if < 20/20;
3. Lymph node palpation;
4. Skin vesicles;
5. Slit lamp examination;

a. grading of eyelid edema
b. eye lid matting
c. tearing
d. purulent discharge
e. bulbar conjunctival edema
f. bulbar redness
g. hemorrhage
h. conjunctival papillary response
i. conjunctival follicular response
j. conjunctival membrane
k. corneal subepithelial infiltrates
l. corneal ulcer
m. presence of foreign body
n. corneal dendrites
o. anterior chamber flare
p. anterior chamber cell

6. AdenoPlus™ testing;
7. Tear Sample for molecular diagnosis
8. Fluorescein staining.
9. Urine pregnancy test for females of childbearing age who are eligible

2.7 RPS AdenoPlus™ and Tear Samples for Molecular Diagnosis

All patients ≥ 18 years of age who present with "pink eye" and consent to study participation will be tested with AdenoPlus™ (Rapid Pathogen Screening, Sarasota FL). After a 5 minute interval to replenish tears, a tear sample will be taken for molecular diagnosis. The first affected eye will be tested and defined as the "study eye".

If both eyes are clinically eligible and both eyes developed symptoms at the same time, the study eye will be selected randomly by coin toss. Data from both eligible and ineligible patients will to enable exploration of the relationship between symptoms, clinical signs and Ad-Cs.

2.8 RPS AdenoPlus™ Testing

1. If patient is wearing contact lens in study eye, remove CL's;
2. Place disposable Chux pad on the counter;
3. Instill 1 drop of proparacaine 0.5% in study eye;
4. Instruct the patient to look up and expose the inferior palpebral conjunctiva by lowering the eyelid;
5. Dab and drag the sampling fleece along the inferior palpebral conjunctiva 8 times; begin temporally moving nasally with each dab/drag movement;
6. Rest fleece against nasal palpebral conjunctiva for 5 additional seconds;
7. Assemble the test by firmly placing the sample collector into the test cassette body;
8. Remove the protective cap from the test cassette and place the absorbent tip into the buffer for 20 seconds;

9. Remove the tip from the buffer, replace the protective cap and lay horizontally on a flat surface for 10 minutes, but not more than 1 hour; Set timer for 10 minutes and record time in military time.
10. Write ID & date on cassette next to display window, photograph cassette with standard color chip with smart phone within 4 hours under ambient exam room lighting.

2.9 Tear Sample for Molecular Diagnosis

1. 5 minutes after AdenoPlus sampling, take tear sample with flocked swab for molecular diagnosis.
2. Remove flocked-swab and vial of Universal Viral Transport Medium from sterile packaging.
3. Confirm that it has been 5 min since 1 drop of proparacaine 0.5% was instilled in study eye.

Tear Sample Collection

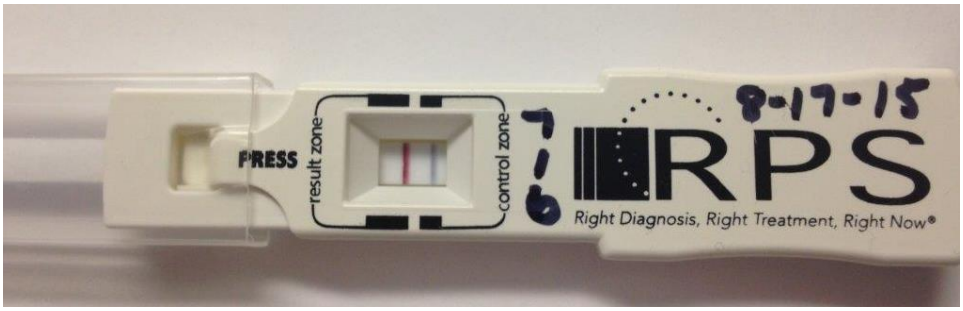
4. Pull down lower lid and hold swab approximately parallel to conjunctival fornix, with handle of swab pointing temporally.
5. Place swab on nasal palpebral conjunctiva and pull swab across palpebral conjunctiva until it reaches temporal angle.
6. Rotate the swab 180° and then slide swab back across the palpebral conjunctiva going from temporal to nasal side.
7. Hold the swab flat along the nasal palpebral conjunctival for 5 seconds.

Storage

8. Open vial and place swab in vial so that flocks are immersed in the medium.
9. Snap off the excess handle by pulling the swab against the vial at the scored line.
10. Screw cap tightly.

Labeling

11. Record date & participant ID# on label. Affix bar code label. Do not enter name or date of birth.
12. Sample can be stored at room temperature until transport to -20 or -80 degree freezer within 4 hours of collection.



10 minutes after RPS AdenoPlus test, Interpret RPS AdenoPlus™

No Blue Line – Invalid result

If a blue line is not visible, then the test is not valid. The test must be repeated.

Only Blue Line – Negative
If there is only a blue line, then AdenoPlus™ is negative for Ad-Cs. Complete the eye examination, fluorescein staining grading and manage the patient according to the standard of care with artificial tears. Patient EXITS the study at this point and no additional questions need to be completed.

Red Line (Solid or partial) – Positive
If there is partial or solid red line in addition to the blue line, then AdenoPlus™ is positive for Ad-Cs.

Pregnancy Testing
Female patients who are clinically eligible and RPS positive must complete urine pregnancy test to rule out pregnancy.

Negative pregnancy test: If the pregnancy test is negative, and the female patient is clinically eligible and RPS positive, will complete the "Randomization" Form for eligible patients, qPCR and treatment randomization.
Positive pregnancy test: if the pregnancy test is positive, the female patient is ineligible. Complete the eye examination, fluorescein staining grading and manage the patient according to the standard of care with artificial tears. Patient EXITS the study at this point and no additional questions need to be completed.

Shipping of Tear Sample to Washington University

- Sample can be stored at room temperature until transport to -40 or -80 degree freezer within 4 hours of collection.
- All specimens for a participant should be sent in the same shipment using the shipping carton provided by the Coordinating Center with a shipping manifest. Follow shipping instructions for biohazard specimens for molecular testing at your institution.

2.10 Randomization (Appendix 2-F, Randomization Form)
Participants who meet eligibility criteria including an AdenoPlus positive test are eligible for randomization. Randomization will be performed using a coded, sequentially numbered sealed envelope kept in the examination room. Randomization plan will be stratified by clinic and use a permuted block design with small random sized blocks. Treating (UNMASKED) clinician or technician administers the randomized treatment packet which includes the randomization assignment and one bottle of treatment-artificial tears or 5% PVP-I.

Treatment Protocol
Participant will not be informed of the treatment assignment. If the fellow eye presents with symptoms of Ad-Cs, it will be treated according to the standard of care with artificial tears.

Treating (UNMASKED) clinician or technician opens the randomization packet, completes randomization form and administers the randomized treatment - one bottle of either -artificial tears or 5% PVP-I.

1. Instill 1 drop of proparacaine 0.5% in study eye.
2. Open randomization package.
3. Instill 4 to 5 drops of assigned treatment (either artificial tears or 5% Betadine™) in inferior fornix.
4. Instruct participant to gently close his or her eyes and set timer for 2 minutes.
5. Gently place gloved finger on closed treated eye.
6. Ask participant to look up/down and left/right.
7. With the participant's eye closed, use 2x2 gauze moistened with assigned treatment and dab along the eyelid margins.
8. Make a dam with Kleenex around treated eye.
9. Lavage the ocular tissues with sterile saline irrigation solution.
10. Take another 2x2 gauze moistened with sterile saline and dab along lid margins to remove all residual treatment solution and dispose in a red bag.
11. Dispense in each eye 8-10 preservative-free, single use artificial tears q.i.d. for 2 days.

2.11 Discharge Instructions (Appendix 2-G, Discharge Instructions)
Upon completion of the Baseline Visit, the participant will receive "Discharge Instructions" for eye care and prevention of adenovirus transmission.

2.12 Follow-Up Visits (Appendix 2-H, Follow-up Visit Form)
The **masked** clinician or **masked** technician, **not** the treating clinician/technician will perform follow-up examinations.

Five follow-up visits should be scheduled ± 3 days of the target date and at least 4 days apart as follows:

1. 1-2 days (± 1);
2. 4-5 days (± 1);
3. 7 days (± 3);
4. 14 days (± 3);
5. 21 days (± 3). If symptoms have not resolved by day 21, clinician will continue to follow the participant for further assessment.

The masked clinician/technician completes follow-up visits as follows:

1. Ocular symptom survey;
2. Visual acuity;
3. Lymph Node Palpation;
4. Slit lamp examination;
5. Tear sampling for qPCR.
   Conjunctival swabs for qPCR will be placed in a cooler immediately and stored in a -40 or -80 freezer. When the participant has completed all follow-up visits, all swabs from baseline and follow-up visits will be batched and sent to Washington University (Dr. Sarah Chavez) for storage in a -80 freezer. When samples for 6-10 participants (6 samples per participant) have been received, the samples will be walked to the Washington University pediatrics virology laboratory (Dr. Richard Buller) for DNA extraction and molecular diagnosis including qPCR with

the Focus Diagnostics cycler. Samples of DNA and unprocessed samples will be returned to the Chavez lab for long-term storage.

6. RPS testing of study eye until 2 consecutive negative test results. Photograph RPS display window labeled with ID/date along w standard color chip in ambient exam room lighting. RPS is done <u>after</u> tear sampling for molecular diagnosis because molecular diagnosis provides quantitative measure of viral burden and is the primary outcome of the study. Repeat RPS testing is done to determine consistency of RPS results and to identify sensitivity compared to molecular diagnosis.

2.13 Missed Visits
If participant misses a follow-up appointment, participant should be immediately rescheduled.

If the participant is unable to be rescheduled, the participant should complete the RAPID survey by telephone or by a password protected REDCap link to the HIPAA compliant RAPID website. Participant will receive $10 for completion of the RAPID survey.

2.14 Participant Withdrawal (Appendix 2-I, Withdrawal Form)
Participants will be free to withdraw from the study at any time with no penalty.

Participants may be withdrawn from the study if the study clinician determines it is not in the best interest of the participant to continue.

Participant may be withdrawn from the study if clinical features of the conjunctival infection change during follow-up in a manner to indicate a non-adenoviral infection (e.g. bacterial, herpetic). Participants who develop known complications of adenoviral infections including corneal subepithelial infiltrates decreasing visual acuity two lines or more, a conjunctival pseudomembrane or a conjunctival membrane, will continue in the study and will be managed according to standard clinical care with the most appropriate therapy.

2.15 Infection Control Protocol
In compliance with the findings from the 2006 Rutala et al study and the CDC Guideline for Disinfection and Sterilization in Healthcare Facilities",[66] hypochlorite bleach wipes (1:10 dilution) will be used to disinfect all counter-tops, chair surfaces, handled equipment, chin and forehead rests, and door knobs. All surfaces will be disinfected immediately following each visit. The 1:10 dilution complies with the CDC guidelines.

1. Participants who present with "pink eye" will be ushered directly to a designated "red eye" examination room. If one is not available, the patient will be ushered to a designated "red eye" chair in the waiting room.
2. Magazines adjacent to chair will be disposed of afterwards in red biohazard bag. The chair surface will be disinfected with hypochlorite bleach or cavicide wipes.
3. Upon entering the "red eye" examination room, the study certified clinician/technician will request the patient to wash their hands. The clinician/technician will turn on the water and dispense soap. The patient dries hands and disposes of paper towels in red biohazard bag.
4. Two copies of the consent form are signed. The clinic files one in a red folder indicating biohazard. The other copy is given to the patient along with the pen used to sign.
5. Label vial of Universal Viral Transport Medium and apply barcode prior to beginning examination. Write patient ID and visit date on RPS test cassette with Sharpie® permanent marker prior to beginning examination.
6. The clinician/technician dons gloves.
7. After the examination is completed, the clinician/technician disposes of their gloves in the red biohazard bag and will request the patient to wash their hands again. The clinician/technician will turn on the water and dispense soap. The patient dries hands and disposes of paper towels in red biohazard bag.
8. The clinician/technician disinfects all surfaces with hypochlorite bleach or cavicide wipes including:
    Chair
    Slit lamp microscope
    Handheld occluder
    Proparacaine bottle and paint chip

2.16 Reporting of Adverse Events (AE) (Appendix 2-J, Adverse Events Form)
Participants will be instructed to contact the study investigator immediately should an AE occur. All AE's will be documented on AE forms and entered into a computer-based log. The masked clinician grades AE severity: 1) minimal discomfort 2) moderate discomfort limiting daily activities, or 3) major discomfort requiring medical care and judges "relatedness" of AE to treatment as "Definitely not related" "Possibly related", "Definitely related".

Serious adverse events will be reviewed electronically within 24 hours of notification of the Coordinating Center by the Steering Committee and the Data Monitoring and Oversight Committee. Routine review of AE's will be done weekly by the Steering Committee and quarterly by the Data Monitoring and Oversight Committee.

2.17.1 Participant Reimbursement

Participants completing 5 F/U visits at 1-2 days, 4, 7, 14 and 21 days will be reimbursed $20 per completed visit for $100 total. Parking costs, if applicable, will also be reimbursed. Participants who miss a visit but complete RAPID survey questions on the follow-up form by phone or on the HIPAA compliant study website will be reimbursed $10 as well. Clinical staff will complete reimbursement voucher for each completed visit within 3 working days and transmit the form via REDCap to the Coordinating Center. Reimbursement will be by a gift card in the amount of $20 or a check mailed directly to the participant for $10 for completion of the survey and/or $20 for each completed visit.

2.17.2 Clinic Reimbursement

Clinics may elect to forego or, if necessary, can request to receive up to $50 per follow-up research visit to cover some of the costs of participant follow-up, data collection and data entry. Clinic reimbursement does not include the screening/baseline visit nor follow-up visits that are considered standard of care. Some clinics will charge off follow-up research visits as "research" and not charge the study.

2.18 Methods to Minimize Bias

The following measures will be undertaken to reduce potential bias:

1. Masked, centralized randomization;
2. With the exception of the one-time, in-office application of artificial tears or 5% PVP-I at baseline, all participants will undergo the same follow-up treatment (artificial tears), measures and procedures during the follow-up visits;
3. Study entry requires a positive AdenoPlus™ test, an unbiased and objective criteria compared to signs/symptoms assessed by clinicians;
4. Separation of treating clinician/technician from the masked clinician/technician who conducts follow-up visits and records post-treatment clinical outcome measures;
5. All eyes are lavaged with saline to reduce residual staining that could unmask participants who receive 5% PVP-I;
6. The primary outcome is change in viral titers as measured by qPCR which is standardized, quantitative, performed by an independent laboratory and not subject to examiner bias.

Missed visits will be minimized by giving participants the clinic contact information (telephone number, cell number of PI, e-m address), List of dates/times of F/U visits and by remuneration of $20 for each completed follow-up visit and $10 for completion of the survey by phone or by secure internet.

2.19 Data Entry Software

REDCap data entry system is a secure, web-based data capture and management system that is currently in use in over 1,311 active institutional partners involving over 149,000 projects worldwide. Data entry screens are customized for each project and study variables can be drawn from a large dictionary of standard clinical and demographic variables, names and formats. The Division of Biostatistics is the Informatics Core that manages the system for the entire Washington University system. DES is installed on the private zone of the cluster of Linux servers in the Division of

Biostatistics. The private network is protected from the rest of the University by a Linux firewall, and the University system is protected from the world by another firewall. The DES is password protected and uses a multi-level login system that regulates access corresponding to approval level.

2.20 Timeline

The Steering Committee has met by teleconference weekly since the fall of 2012 and will continue to do so.

< Month 1	February, 2015: Complete provisional protocol and operational description for R-34 planning study, case report forms, web data entry and randomization system, IRB submission/approvals.
Month 1-5	February-June 2015: Face-to-face Steering Committee meeting to finalize planning study and train/certify Clinical Center Clinicians, Coordinating Center completes programming for key progress and safety reports for monthly Steering Committee review, purchase & distribute supplies, clinics enroll patients.
Month 6-12	July-January 2016: Steering Committee will review pre-randomization data (recruitment, exclusions, baseline data, pre-post treatment fluorescein staining, treatment discomfort and masking at 4 days) and post-randomization data including retention, data quality and completeness. Data Monitoring and Oversight Committee will review masked data semi-annually by randomization assignment including qPCR, clinical and pt. reported outcome data and safety data. Continue enrolling patients and generate quarterly reports on study progress and safety.
Month 13-18	February-July 2016: Close enrollment, analyses of AdenoPlus™ specificity and differences in viral load and symptoms over time by randomization groups.
Month 18-24	August 2016-February 2017: Face-to-face Steering Committee meeting to finalize protocol for UG1 clinical trial and MOP chapters.

MEMORANDUM #1

TO: RAPID Study Clinicians

FROM: Tammy P. Than, MS, OD TPT

SUBJECT: Protocol Clarification

DATE: January 21, 2018

The purpose of this communication is to clarify when patients that do not meet the eligibility criteria are exited.

If patients do not meet age or disease duration criteria, no further questioning or testing is performed. If it is determined on Page 1, Item #1 of the RAPID: Screening/Baseline Form that the patient is not at least 18 years of age, the patient is exited at this point. Ensure that the first affected eye has been symptomatic for no more than four days. This will be queried on Page 2, Item #5 (right eye) or Item #7 (left eye). If the patient reports a red eye in the first involved eye of more than four days, the patient is exited at this point and no further testing is performed.

If a patient is at least 18 years of age and the first affected eye has been symptomatic for no more than four days, complete the ENTIRE screening form asking all questions and performing all testing including RPS and qPCR tear sampling. Patients who do not meet all of the eligibility criteria (e.g. history of thyroid disease, allergy to Betadine, etc.) will not be randomized but it will still be useful for the study to collect all screening information on these patients who are eligible to be screened. The one testing exception is that patients who will not be randomized do NOT need to complete a pregnancy test.

This is not a change in the protocol, merely clarification. Please contact any member of the RAPID steering committee if you have any questions.

2.21 Statistical Analysis Plan: Primary Efficacy Outcome

RAPID is a National Eye Institute funded R-34 planning study. The target sample size of 40 (20 per group) is selected assuming a large effect size of 0.80, power = 0.80, and a nominal two-sided alpha of 0.05. To decrease the probability of failing to reject a null hypothesis, there is no correction for multiple comparisons.

The primary efficacy outcome is reduction from peak viral load defined as the percent reduction of DNA copies per ml from the participant's peak viral load. The Data and Safety Monitoring Committee approved a modified intention to treat analyses (mITT) to test efficacy outcomes in participants with detectable viral load by qPCR at baseline. The mITT analysis should not bias efficacy results because samples for qPCR were taken from all screened patients prior to randomization and qPCR results were never disclosed to participants or study personnel. Safety is assessed using all randomized participants per intention-to-treat.

The primary outcome and other quantitative variables including symptoms and signs will be analyzed using nonparametric Wilcoxon rank order tests. The exact p-value will be calculated by a computational network algorithm (Mehta and Patel, 1983) given that asymptotic results assuming a normal distribution cannot be assumed with small sample sizes. Nominal variables will be analyzed using Fisher's exact test. Treatment "effect size" (PVP-I mean minus AT mean divided by their standard deviation) will be calculated for the primary outcome to supplement p-values. Cohen has classified effect sizes of 0.2 as "small", 0.5 as "medium" and 0.8 as "large". (REF: Cohen J. Statistical Power Analysis for the Behavioural Sciences. 2nd ed. Hillsdale, NJ: Erlbaum Associates; 1988.)

Washington University in St. Louis

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INFORMED CONSENT DOCUMENT – Pink Eye

Project Title: Reducing Adenoviral Patient Infected Days (RAPID) Study

Principal Investigator: [redacted]

Research Team Contact: [redacted]

This consent form describes the research study and helps you decide if you want to participate. It provides important information about what you will be asked to do during the study, about the risks and benefits of the study, and about your rights and responsibilities as a research participant. By signing this form you are agreeing to participate in this study.

- You should read and understand the information in this document including the procedures, risks and potential benefits.
- If you have questions about anything in this form, you should ask the research team for more information before you agree to participate.
- You may also wish to talk to your family or friends about your participation in this study.
- Do not agree to participate in this study unless the research team has answered your questions and you decide that you want to be part of this study.

WHAT IS THE PURPOSE OF THIS STUDY?

This is a research study. We invite you to participate in this research study because you have had "pink eye" for 4 days or less and are 18 years of age or older.

The purpose of this pilot research study is to improve the treatment of "pink eye". Currently there is no U.S. Food and Drug Administration (FDA) approved treatment for "pink eye". Standard care recommended by the American Academy of Optometry and American Ophthalmology Academy is with artificial tears to relieve symptoms and to possibly reduce adenovirus in the eye. Another possible treatment is with Betadine 5%, an antiseptic ophthalmic solution used for over 50 years to prepare patient's eye and surrounding area for eye surgery and to clean minor wounds. Because Betadine 5% kills bacteria and viruses, it may be useful in treating adenoviral conjunctivitis. This study will be among the first to test Betadine 5% for "pink eye".

Betadine is approved by the U.S. Food and Drug Administration for prepping of the periocular region (lids, brow, and cheek) and irrigation of the ocular surface (cornea, conjunctiva, and palpebral fornices). However, the use of Betadine is considered investigational in this study.

WHAT WILL HAPPEN DURING THIS STUDY?

In order to determine if you are eligible for this investigational treatment you will need to do the following as part of the screening process:

- Complete questionnaires about symptoms of pink eye, lost days of work or school and transmission of "pink eye". You are free to skip questions that you would prefer not to answer.
- Receive a comprehensive eye examination. Give a sample of tears to confirm "pink eye" by genetic diagnosis and immunoassay.

- Ask a few questions about your past health history such as any allergies, problems with your thyroid and past eye conditions.
- We will conduct a urine pregnancy test if you are a woman that is capable of becoming pregnant.

TREATMENT
If after completing the screening process you are eligible to continue in the study, you will receive treatment that day. Steps in treatment are:

- First, you will receive a drop of a topical anesthetic (numbing drop) in the infected eye.
- 50% of the patients will receive a one-time, in-office dose of artificial tears and 50% of the patients will receive Betadine 5%.
- After approximately 2 minutes, the treatment will be flushed out of the eye with a sterile eye wash.

This will be a double-blind study. This means neither you nor your doctors conducting your follow up care will know whether you received Betadine 5% or not. If medically necessary, the doctor can find out whether you received artificial tears or Betadine 5%. Participants will be instructed to use one drop of artificial tears four times a day in the infected eye as long as symptoms persist.

FOLLOW-UP VISITS
It is important to know at what point in time you become free of pink eye symptoms and free of adenovirus. For this reason, your pink eye symptoms and adenovirus levels will be measured at each visit at day(s) 1, 4, 7, 14 and up to 21 after today. Each follow up visit is about 30 minutes. At each follow-up visit, you will:

- Complete a questionnaire about symptoms of pink eye, lost days of work or school and transmission of "pink eye." You are free to skip questions that you would prefer not to answer.
- A comprehensive eye examination.
- Give a sample of tears to measure adenovirus levels.
- If you miss a follow up visit you will be asked to complete the symptom checklist by telephone or by a secure data entry website.

HOW MANY PEOPLE WILL PARTICIPATE?
Approximately 20 patients with pink eye will take part in this study conducted by investigators at Washington University. Nationwide, there are 9 clinics that will enroll about 50 patients into the study.

HOW LONG WILL I BE IN THIS STUDY?
If you agree to participate in this study, your involvement will last up to 21 days.

WHAT ARE THE RISKS OF THIS STUDY?
You may experience one or more of the risks indicated below from being in this study. In addition to these, there may be other unknown risks, or risks that we did not anticipate, associated with being in this study.

Use of temporary dye, topical anesthetic, betadine 5% may cause:
Less Likely / Less Common(less than 50% of patients will experience)

- Temporary stinging (for a few seconds to several minutes)

Use of artificial tears may cause:
Less Likely / Less Common(less than 50% of patients will experience)

- Blurred vision (for a few minutes)

Use of Betadine 5% may cause:
Rare (less that 2 % of patients will experience)

- Temporary discoloration (discoloration of the white part of your eye and eyelid)

A risk of participating in this study is that confidential information about you may be accidentally disclosed. We will use our best efforts to keep the information about you secure. Please see the section in this consent form titled *"How will you keep my information confidential?"* for more information.

There is a federal law called the Genetic Information Nondiscrimination Act (GINA). In general, this law makes it illegal for health insurance companies, group health plans and employers with greater than 15 employees to discriminate against you based on your genetic information. However, it does not protect you against discrimination by companies that sell life insurance, disability insurance or long term-care insurance.

WOMEN CAPABLE OF BECOMING PREGNANT
If you are a woman capable of becoming pregnant, we will ask you to have a pregnancy test before beginning this study. You must use effective birth control methods and try not to become pregnant while participating in this study. If you become pregnant, there may be unknown risks to your unborn child, or risks to your unborn child that we did not anticipate. There may be long-term effects of the treatment being studied that could increase the risk of harm to an unborn child. You must tell the doctor if your birth control method fails while you are on the study. If you believe or know you have become pregnant while participating in this research study, please contact the research team member identified at the top of this document as soon as possible. Please discuss with the research team how long you need to wait before becoming pregnant after completing the treatment or procedures on this study.

WHAT ARE THE BENEFITS OF THIS STUDY?

You may or may not benefit from being in this study.
However, we hope that, in the future, other people might benefit from this study because this study may help us better understand how to diagnose and treat adenoviral infections of the eye in the future.

WHAT OTHER TREATMENT OPTIONS ARE THERE?

Alternative therapies for the treatment of adenoviral conjunctivitis are available. These include topical steroids, topical non-steroidal anti-inflammatory drugs, or topical ganciclovir. None of these treatments have FDA approval for treatment of adenoviral conjunctivitis.

Before you decide whether or not to be in this study, your doctor will discuss the other options that are available to you. Instead of being in this study, you could be treated using artificial tears as recommended by the American Optometric Association and the American Academy of Ophthalmology.

WILL IT COST ME ANYTHING TO BE IN THIS STUDY?

As part of this study you will receive tests and procedures that are similar to what you would receive during routine clinical care of your condition. Your health plan/insurance company will be billed for some or all of these costs, and you will be responsible for any co-pays and deductibles that are normally required by your health plan/insurance. Not all insurance plans cover the costs associated with being in a study. Even if they do, you may be responsible for more out-of-pocket expenses, such as co-pays and deductibles, when there are more tests and procedures or more expensive tests and procedures involved in the study than if you were to receive routine clinical care outside the study.

If you wish to know whether there are more tests and procedures or more expensive tests and procedures in the study, you should ask your study doctor.

If you wish to know whether your insurance will pay, you should contact them directly, or speak with the study team about obtaining a financial pre-certification prior to enrolling in the study.

WILL I BE PAID FOR PARTICIPATING?

You will be paid $20 for each visit or up to a total of $100 for 5 visits in this research study. You will need to provide your social security number (SSN) in order for us to pay you. You may choose to participate without being paid if you do not wish to provide your social security number (SSN) for this purpose. If your social security number is obtained for payment purposes only, it will not be retained for research purposes.

WHO IS FUNDING THIS STUDY?

This research study is funded by the National Institutes of Health. This means that Washington University is receiving payments from the National Institutes of Health to support the activities that are required to conduct the study. No one on the research team will receive a direct payment or increase in salary for conducting this study.

WHAT IF I AM INJURED AS A RESULT OF THIS STUDY?

Washington University investigators and staff will try to reduce, control, and treat any complications from this research. If you feel you are injured because of the study, please contact the investigator at 314-362-6125, and/or the Human Research Protection Office at 1-(800)-438-0445.

Decisions about whether payment for medical treatment for injuries relating to your participation in research will be made by Washington University and the National Institute of Health**.** If you need to seek medical care for a research-related injury, please notify the investigator as soon as possible.

HOW WILL YOU KEEP MY INFORMATION CONFIDENTIAL?

We will keep your participation in this research study confidential to the extent permitted by law. However, it is possible that other people such as those indicated below may become aware of your participation in this study and may inspect and copy records pertaining to this research. Some of these records could contain information that personally identifies you.

- Government representatives, (including the Office for Human Research Protections) to complete federal or state responsibilities.
- The U.S. Food and Drug Administration.
- National Institutes of Health.

- Your primary care physician if a medical condition that needs urgent attention is discovered.
- Hospital or University representatives, to complete Hospital or University responsibilities.
- Information about your participation in this study may be documented in your health care records and be available to your health care providers who are not part of the research team.
- Washington University's Institutional Review Board (a committee that oversees the conduct of research involving human participants) and the Human Research Protection Office. The Institutional Review Board has reviewed and approved this study.

To help protect your confidentiality, research data are coded as to clinic site and patient numeric ID and do not include personal health data. Study examinations are conducted in private, closed-door "Red Eye" examination rooms. Only certified study personnel are authorized to conduct research measures or handle data. Research data are transmitted to Washington University on secure, web-based data management systems protected by firewalls and passwords.

If we write a report or article about this study or share the study data set with others, we will do so in such a way that you cannot be directly identified.

To further protect your privacy, this research is covered by a Certificate of Confidentiality from the federal government. This means that the researchers can refuse to disclose information that may identify you in any legal or court proceeding or to anyone who is not connected with the research except if:

- there is a law that requires disclosure, such as to report child abuse and neglect, or harm to self or others*;*
- you give permission to disclose your information, including as described in this consent form; or
- it is used for other scientific research allowed by federal law.

You have the right to share your information or involvement in this study with anyone at any time. You may also give the research team permission to disclose your information to a third party or any other person not connected with the research.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. You can search this Web site at any time.

Are there additional protections for my health information?

Protected Health Information (PHI) is health information that identifies you. PHI is protected by federal law under HIPAA (the Health Insurance Portability and Accountability Act). To take part in this research, you must give the research team permission to use and disclose (share) your PHI for the study as explained in this consent form. The research team will follow state and federal laws and may share your health information with the agencies and people listed under the previous section titled, "How will you keep my information confidential?"

Once your health information is shared with someone outside of the research team, it may no longer be protected by HIPAA.

The research team will only use and share your information as talked about in this form or as permitted or required by law. When possible, the research team will make sure information cannot be linked to

you (de-identified). Once information is de-identified, it may be used and shared for other purposes not discussed in this consent form. If you have questions or concerns about your privacy and the use of your PHI, please contact the University's Privacy Officer at 866-747-4975.

Although you will not be allowed to see the study information, you may be given access to your health care records by contacting your health care provider.

If you decide not to sign this form, it will not affect

- Your treatment or the care given by your health provider.
- Your insurance payment or enrollment in any health plans.
- Any benefits to which you are entitled.

However, it will not be possible for you to take part in the study.

If you sign this form:

- You authorize the use of your PHI for this research
- This authorization does not expire.
- You may later change your mind and not let the research team use or share your information (you may revoke your authorization).
    - To revoke your authorization, complete the withdrawal letter, found in the Participant section of the Human Research Protection Office website at https://hrpo.wustl.edu/participants/withdrawing-from-a-study/ or you may request that the investigator send you a copy of the letter.
        - **If you revoke your authorization:**
            - The research team may only use and share information already collected for the study.
            - Your information may still be used and shared as necessary to maintain the integrity of the research, for example, to account for a participant's withdrawal from the research study or for safety reasons.
            - You will not be allowed to continue to participate in the study.

CAN WE CONTACT YOU BY EMAIL?

We would like to contact you by email for the purposes listed below. Some of these emails may contain health information that identifies you.

- If you miss a visit, you can opt to complete the questionnaire about "pink eye" symptoms on a secure website.

Only the research team will have access to your email communications. We will only communicate by email to send you the information listed above. If you have any questions or need to contact us for an urgent or emergent situation, please contact the research team member identified at the top of this document.

You should be aware that there are risks associated with sending your health information via email.

- There is always a risk that the message could be intercepted or sent to the wrong email address. To avoid sending messages to the wrong email address, the first email we send you will be a test message to ensure we have the correct email address.
- When using any computer you should be careful to protect your username and password. Make sure you log-out before getting up from the computer.
- If you share a home computer with other family members, and do not want them to know you are participating in this study make sure you provide an email address that only you can access.
- Your employer will have access to any email communications sent or received on any electronic devices used for work or through a work server.

Do you agree to allow us to send your health information via email?

_____ **Yes** _____ **No**
Initials **Initials**

IS BEING IN THIS STUDY VOLUNTARY?

Taking part in this research study is completely voluntary. You may choose not to take part at all. If you decide to be in this study, you may stop participating at any time. Any data that was collected as part of your participation in the study will remain as part of the study records and cannot be removed.

If you decide not to be in this study, or if you stop participating at any time, you won't be penalized or lose any benefits for which you otherwise qualify.

WHAT IF I DECIDE TO WITHDRAW FROM THE STUDY?

You may withdraw by calling the study team [redacted] or e-mailing [redacted] that you are no longer interested in participating in the study or you may send in a withdrawal letter. A sample withdrawal letter can be found at https://hrpo.wustl.edu/participants/withdrawing-from-a-study/ under Withdrawing from a Research Study.

WILL I RECEIVE NEW INFORMATION ABOUT THE STUDY WHILE PARTICIPATING?

If we obtain any new information during this study that might affect your willingness to continue participating in the study, we'll promptly provide you with that information.

CAN SOMEONE ELSE END MY PARTICIPATION IN THIS STUDY?

Under certain circumstances, the investigator might decide to end your participation in this research study earlier than planned. This might happen because the study doctor decides it is not in the best interest of your health or because you became pregnant.

WHAT IF I HAVE QUESTIONS?

We encourage you to ask questions. If you have any questions, concerns, or complaints about the research or a research- related injury including available treatments, [redacted]. She will be glad to answer any of your questions. [redacted] can be reached during office hours at [redacted] can also be reached after hours at [redacted].

If you have questions, concerns, or complaints about your rights as a research participant, please contact the Human Research Protection Office at 660 South Euclid Avenue, Campus Box 8089, St. Louis, MO

63110, 1-(800)-438-0445, or email hrpo@wustl.edu. General information about being a research participant can be found on the Human Research Protection Office web site, http://hrpo.wustl.edu. To offer input about your experiences as a research participant or to speak to someone other than the research staff, call the Human Research Protection Office at the number above.

This consent form is not a contract. It is a written explanation of what will happen during the study if you decide to participate. You are not waiving any legal rights by agreeing to participate in this study. As a participant you have rights and responsibilities as described in this document and including:

- To be given enough time before signing below to weigh the risks and potential benefits and decide if you want to participate without any pressure from the research team or others.
- To understand all of the information included in the document, have your questions answered, and receive an explanation of anything you do not understand.
- To follow the procedures described in this document and the instructions of the research team to the best of your ability unless you choose to stop your participation in the research study.
- To give the research team accurate and complete information.
- To tell the research team promptly about any problems you have related to your participation, or if you are unable to continue and wish to stop participating in the research study.

Your signature indicates that this research study has been explained to you, that your questions have been answered, and that you agree to take part in this study. You will receive a signed and dated copy of this form.

Do not sign this form if today's date is after EXPIRATION DATE: 04/22/21.

_____ _____

(Signature of Participant) (Date)

_____

(Participant's name – printed)

STATEMENT OF PERSON WHO OBTAINED CONSENT

The information in this document has been discussed with the participant or, where appropriate, with the participant's legally authorized representative. The participant has indicated that he or she understands the risks, benefits, and procedures involved with participation in this research study.

_____ _____

(Signature of Person who Obtained Consent) (Date)

_____

(Name of Person who Obtained Consent - printed)