NYU School of Medicine
NYU LANGONE MEDICAL CENTER

A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL OF THE EFFICACY OF RETAPAMULIN AS A TOPICAL DECOLONIZING AGENT FOR MUPIROCIN-RESISTANT METHICILLIN-RESISTANT *STAPHYLOCOCCUS AUREUS* (MRSA)

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Statement of Compliance

This study will be conducted in accordance with the Code of Federal Regulations on the Protection of Human Subjects (45 CFR Part 46), 21 CFR Parts 50, 56, 312, and 812 as applicable, any other applicable US government research regulations, and institutional research policies and procedures. The International Conference on Harmonisation ("ICH") Guideline for Good Clinical Practice ("GCP") (sometimes referred to as "ICH-GCP" or "E6") will be applied only to the extent that it is compatible with FDA and DHHS regulations. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the sponsor and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection Training.

Table of Contents

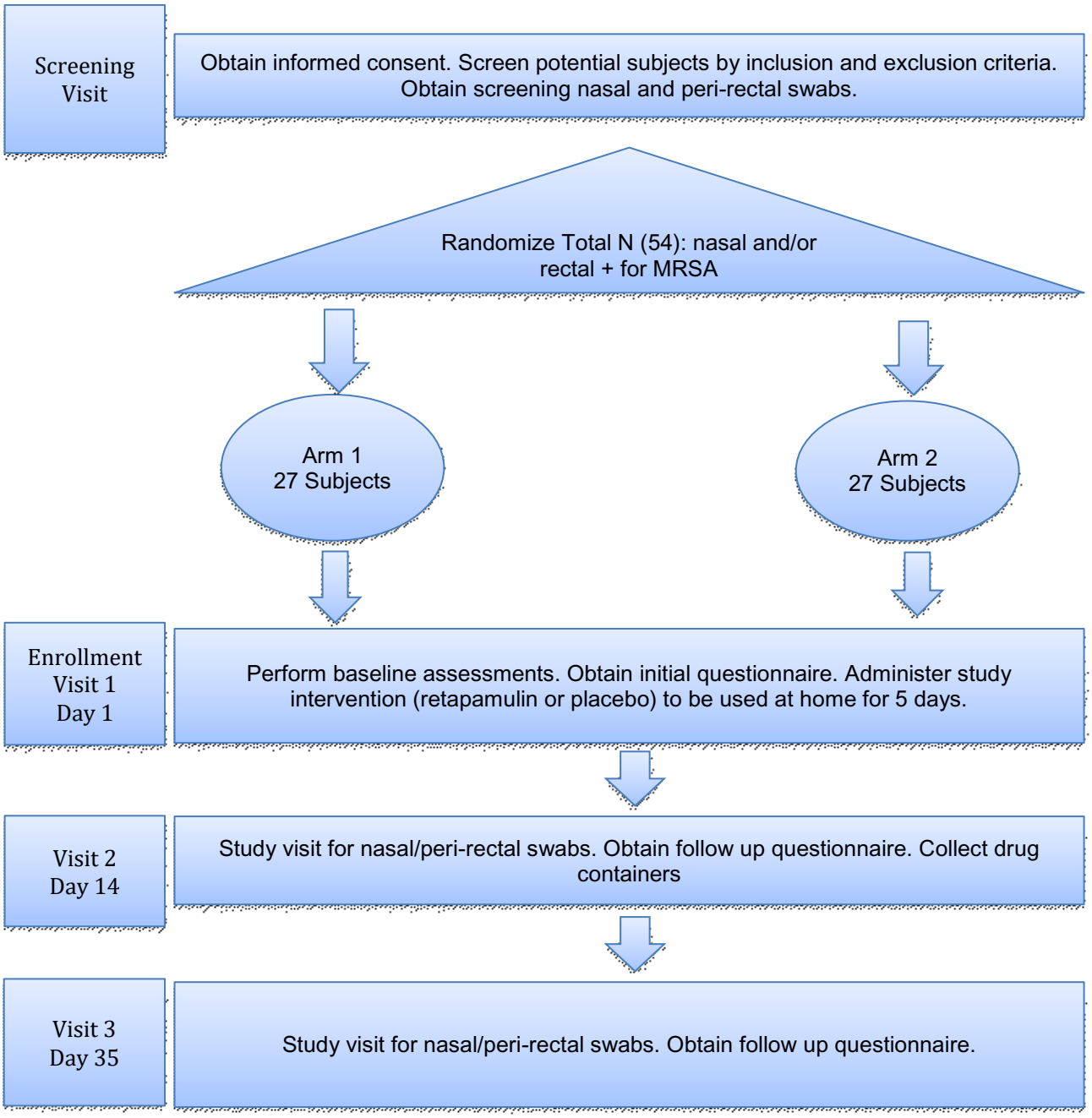
List of Abbreviations

AE	Adverse Event/Adverse Experience
CFR	Code of Federal Regulations
CRF	Case Report Form
CSOC	Clinical Study Oversight Committee
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DSMB	Data and Safety Monitoring Board
FFR	Federal Financial Report
FWA	Federalwide Assurance
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IDSA	Infectious Diseases Society of America
IRB	Institutional Review Board
ISM	Independent Safety Monitor
MOP	Manual of Procedures
MRSA	Methicillin-Resistant *Staphylococcus aureus*
N	Number (typically refers to participants)
NIH	National Institutes of Health
NYU	New York University
OHRP	Office for Human Research Protections
OHSR	Office of Human Subjects Research
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event/Serious Adverse Experience
SOP	Standard Operating Procedure
US	United States

Protocol Summary

Title	The Efficacy of Retapamulin as a Topical Decolonizing Agent for Mupirocin-Resistant Methicillin-Resistant *Staphylococcus aureus* (MRSA)
Short Title	Retapamulin as a Decolonizing Agent for MRSA
Brief Summary	A randomized, double-blind, placebo-controlled clinical trial to test the efficacy of retapamulin to decolonize MRSA in a high risk pediatric group aged 9 months-17 years. The sample size will include 27 subjects in each of the two arms of the study (retapamulin versus placebo) for a total of 54 subjects. Participants who are found to be nasal and/or rectal colonized with MRSA will be randomized to receive either retapamulin or placebo applied nasally and rectally for a total of 5 days. Nasal and rectal swabs will be collected at pre-defined time points during study duration (screening swab, swab one week after completion of topical therapy, swab 4 weeks after completion of topical therapy) to assess MRSA colonization status. The colonization rates of both groups will be assessed via Fisher's Exact Test.
Phase	Clinical study phase 3
Objectives	To investigate the efficacy of retapamulin to reduce carriage of MRSA via a randomized, double-blind, placebo-controlled clinical study testing retapamulin among patients with confirmed mupirocin-resistant nasal and/or rectal MRSA colonization.
Methodology	Randomized, double-blind, placebo-controlled clinical trial
Endpoint	Primary Endpoint: Nasal/Rectal MRSA carriage at 1 week following decolonization course Secondary Endpoint: Nasal/Rectal MRSA carriage at 4 weeks following decolonization course
Study Duration	2 years
Participant Duration	6 weeks
Duration of IP administration	5 days
Population	27 patients per the two arms of the study aged 9 months-17 years for a total of 54 participants, of both genders. Patients are required to be colonized with a mupirocin-resistant methicillin-resistant strain of Staphylococcus aureus of which there is currently an outbreak in a particular high risk geographical cluster (children living in Brooklyn NY of Orthodox Jewish descent). The patients will be sampled from admitted children who reside in Orthodox predominant neighborhoods in Brooklyn NY based on zip code of residence.
Study Sites	NYU Langone Medical Center - Tisch Hospital, ODA clinic in Brooklyn
Number of participants	54 participants across both arms of the study
Description of Study Agent/Procedure	Retapamulin is a topical antibiotic ointment. The study drug (and placebo) will be used topically in a thin layer to the nares and peri-rectal area twice a day for five consecutive days
Reference Therapy	Placebo (white petrolatum)
Key Procedures	Body surface swabs/cultures
Statistical Analysis	Statistical analysis will be performed using Fisher's exact test (non-parametric) to evaluate for significant difference in colonization between the two groups (retapamulin and placebo).

Schematic of Study Design



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2 Introduction, Background Information and Scientific Rationale

2.1 Background Information and Relevant Literature

Staphylococcus aureus (S. aureus) is a leading cause of superficial and invasive hospital and community-acquired infections. It is the most virulent of the Staphylococcus species and can produce systemic infections in otherwise healthy adults and children. The anterior nares are a natural reservoir for *S. aureus*, and colonization confers an increased risk of infection. [1] National data indicate that the prevalence of asymptomatic colonization with methicillin-sensitive *S. aureus* ranges from 18 to 38%, and with methicillin-resistant *S. aureus* (MRSA) from 0.8 to 6%.[1] Controlling MRSA colonization and preventing its spread is essential, as infection is associated with significant morbidity and mortality. Decolonization is an evidence-based intervention that can be used to reduce bacterial burden in order to prevent MRSA infections and transmission.[2] Standard decolonization regimens include mupirocin ointment to the nares and chlorhexidine wipes or baths for the body. Mupirocin is a topical antibacterial agent that is well established in clinical practice and is currently the gold standard therapy for MRSA nasal decolonization. [11] However, increasing resistance to mupirocin has been noted with some studies showing that MRSA mupirocin resistance (Mup-R) rates are as high as 24% in the US.[3] Emerging resistance to mupirocin highlights an urgent need for alternative approaches to MRSA decolonization.

In New York City (NYC), there is a high prevalence of MRSA infections. Over the past several years, pediatric clinicians at New York University Langone Medical Center (NYULMC) have observed an increased incidence of MRSA infections amongst the pediatric population, specifically among Orthodox Jewish children. These observations were confirmed in a 2015 prospective study conducted at NYULMC to better understand the epidemiology of Community Acquired MRSA (CA-MRSA) in the pediatric population. Children from the Orthodox Jewish community were identified as high risk compared to the general pediatric population. Children from the high-risk communities were identified via zip codes as described in a publication that determined Orthodox Jewish neighborhoods based on the concentration of Jewish establishments such as synagogues, yeshivas, and kosher food retailers.[12] Information was collected to ascertain MRSA infection and colonization rates among these two groups.

Interestingly, no difference in methicillin-susceptible *S. aureus* (MSSA) colonization prevalence was observed between children from high-risk and low-risk communities. However, children from these high-risk areas were 2.8 times as likely to be colonized with MRSA (prevalence 9% vs 3 % [p=0.04]). Likewise, the MRSA infection rate per 1,000 patient days was 36 for children from high-risk areas versus 3.9 in children from low-risk areas (p<0.0001). All isolates from patients in high-risk zip codes analyzed to date belong to genotype USA300, the predominant CA-MRSA clone in the US. This data suggests there is a geographically defined outbreak of CA-MRSA in children and these isolates form a distinct clade within the common USA300 MRSA lineage.

Moreover, the majority of the clinical strains from the outbreak cluster carry the plasmid encoding the *mupA* gene, which confers the mupirocin-resistant (Mup-R) phenotype. Phenotypic analysis confirmed mupirocin resistance in 84% (39/55) of the outbreak subclone isolates compared to none (0/17) in the USA300 CA-MRSA control isolates. This finding has significant clinical impact, as there are no validated approaches to decolonize these children and families, and many such patients are re-hospitalized with recurrent infections. In addition, CA-MRSA transmission in the community is ongoing and transmissions have been observed at our institution. Without an adequate way to decolonize Mup-R MRSA-positive patients, we risk expansion of the outbreak strain to lower risk patients and to communities outside the high risk geographic area.

Retapamulin is a novel topical bacteriostatic pleuromutilin antibiotic, currently used for the treatment of impetigo, which has been shown to be effective against *S. aureus* skin infections. It has excellent in vitro and in vivo activity against MRSA and methicillin-sensitive *S. aureus* (MSSA) strains. An in vitro study to determine the activity of retapamulin among 403 MRSA isolates found that 99% of the MRSA isolates were susceptible to retapamulin.[4] In a multicenter Global Surveillance Program, S. aureus isolates were collected from skin and soft tissue infections of adults and children in hospital and community settings. Among MRSA isolates, retapamulin was 128-fold more potent than mupirocin.[3]

Multiple in vitro studies have demonstrated that the likelihood of *S. aureus* developing resistance to retapamulin is low. This is in large part due to the antibiotic's mechanism of action, inhibition of bacterial protein synthesis by binding to and preventing formation of the 50S ribosomal unit. A multi-center study was performed by Biedenbach in outpatient dermatology centers to determine the rates of resistance of agents against *S. aureus* isolates collected from skin and soft tissue infections. The rate of mupirocin resistant *S. aureus* isolates was >10%, whereas retapamulin resistance was infrequent (1%). [5] Reduced susceptibility to retapamulin can occur via mutations in the cfr and rplC genes. [6, 7] The cfr (chloramphenicol-florfenicol resistance) gene encodes an rRNA methylase. The presence of this gene may lead to enhanced methylation, which is thought to prevent the antimicrobial from binding to the ribosome.[8] For the rplC (ribosomal protein L3) gene, the mechanism of resistance has been identified as first-, second-, and third- step rplC mutants of S. aureus. [9] The rplC gene encodes the L3 ribosomal protein which is essential for the formation of the peptidyl trasnferase center, the site where retapamulin binds. Three mutations are needed to have a notable effect; however each mutation confers a considerable fitness cost to the organism, leading to a low probability for the emergence of resistance in *S. aureus*. [10]

Evidence for retapamulin as an effective decolonizing agent against MRSA is sparse, with even more limited studies in the pediatric population. There is high prevalence of MRSA in New York City, specifically in a geographically defined outbreak of CA-MRSA in children that has resistance to mupirocin, the standard of nasal decolonization. This represents a unique opportunity to gain further insight into retapamulin susceptibility and its efficacy as an alternative decolonizing agent. We hypothesize that retapamulin will be an effective agent to decolonize children harboring mupirocin-resistant MRSA strain.

2.2 Name and Description of the Investigational Agent

Retapamulin is a topical 1% antibiotic ointment that consists of retapamulin and white petrolatum as the vehicle. Retapamulin is a white to pale yellow crystalline solid. It is a bacteriostatic pleuromutilin antibiotic which inhibits bacterial protein synthesis by binding to and preventing formation of the 50S ribosomal unit.

The recommended dose is a thin layer of ointment applied twice a day for five days. Systemic exposure following application to intact skin is generally very low.

It was FDA approved in 2007 for topical use in patients over 9 months of age. It is indicated for impetigo and mild secondary skin infections arising from lacerations, abrasions, sutured wounds, psoriasis or dermatitis. These infections are mainly caused by *Staphylococcus aureus*, but can also be due to *Streptococcus pyogenes*.

The drug meets IND exemption criteria as it meets all 6 criteria for IND Exemption in article 312.2(b) of the FDA Guidance and IND requirements. Please see attached IND appendix.

2.2.1 Preclinical Data

The study drug, retapamulin, was tested in the Shopsin laboratory at NYU by the study team to assess susceptibility to the isolates of the strain in question. The initial epidemiologic study in 2015-2016 conducted by Jennifer Lighter, MD and Bo Shopsin, MD, PhD described the outbreak of MRSA in this geographically defined high risk pediatric population. The genotypic and phenotypic analyses demonstrated that this MRSA strain is a subclone of the common USA 300 lineage and carries the *mupA* gene which confers resistance to mupirocin.

The isolates from the subjects in the above study were tested via broth dilution to determine minimum inhibitory concentration (MIC) of retapamulin to assess susceptibility. This in vitro data shows that all of these isolates are susceptible to the study drug, retapamulin.

2.2.2 Clinical Data to Date

Multiple in vitro and in vivo studies have been published to date that have demonstrated retapamulin activity against MRSA (a few referenced above in the background and listed in the reference section). Studies have tested retapamulin in vitro to determine susceptibility and MIC data and have found the drug to be effective against MRSA isolates. These studies have also compared these isolates to mupirocin, the standard of care in decolonization, to compare efficacy with retapamulin which was shown to be very efficacious.

A recent abstract/poster was presented at the Infectious Diseases Society of America (IDSA) 2016 ID week. The study was a randomized double-blinded placebo-controlled trial to assess effect of retapamulin for nasal decolonization of mupirocin-resistant MRSA nasal carriers. This trial found that nasal retapamulin reduced MRSA nasal carriage at 1 week following application of the study drug (84% reduction in odds of MRSA carriage compared to placebo) but reductions were not sustained at 6 weeks. This study found retapamulin was well tolerated when applied nasally with no reported side effects.[18]

2.2.3 Dose Rationale (if applicable)

The recommended dose for retapamulin is a thin layer of ointment applied twice a day for five days. This type of dosing is common for MRSA decolonization protocols and guidelines with other topical ointments.

2.3 Rationale

Methicillin resistant Staphylococcus aureus (MRSA) is an significant pathogen that causes a wide spectrum of superficial and invasive hospital and community-acquired infections. Controlling MRSA colonization is essential to prevent infections and transmission of the pathogen. At NYU Langone Medical Center there is a high prevalence of MRSA infections, specifically within a geographically defined community. Genotypic and phenotypic analysis of isolates from these patients demonstrates that the majority are resistant to mupirocin, the standard of care for decolonization. There is limited evidence of other alternative topical decolonizing strategies. In this study we will investigate the efficacy of decolonization in this pediatric population with a novel topical antibiotic, retapamulin which has been shown in a limited number of previous studies to be effective against MRSA.

Study Aim:
To investigate the efficacy of retapamulin to reduce carriage of MRSA via a randomized, double-blind, placebo-controlled clinical trial testing retapamulin among pediatric patients with confirmed mupirocin-resistant nasal and/or rectal MRSA colonization.

Hypothesis:
Retapamulin will be an effective way to decolonize children harboring mupirocin-resistant CA-MRSA strain compared to placebo at 1 week and 4 weeks post treatment. Specifically, we hypothesize retapamulin will reduce MRSA carriage by 60%.

2.4 Potential Risks & Benefits

2.4.1 Known Potential Risks

Known risks or adverse reactions from this drug use are minimal and include local application site irritation (pruritus, erythema, stinging). In clinical studies, this was found to occur in less than 2% of patients. Retapamulin has not yet been widely evaluated for use on mucosal surfaces. This information is listed in the package insert for retapamulin.

We do not anticipate that this research study will pose greater than minimal risk to participants. Side effects of Retapamulin not commonly expected and should subside with the discontinuation of the drug without expected long term risks. Serious side effects are rare and can include allergic reaction.

All efforts will be made to minimize risk for participants in this study. Study staff have been trained in human subjects' research and protection. The subjects will be instructed on proper use (amount, technique, duration) of the study drugs and potential effects to monitor for. If a side effect were to occur or there are any concerns, the subjects will be advised to call the research staff immediately and guidance or treatment will be offered as needed. Immediate necessary care for adverse events will be provided at NYULMC. Subjects will be monitored for side effects at each study visit and check-in via telephone to parent/guardian. If subjects experience serious adverse events or side effects to the study drug they will be withdrawn from the study.

2.4.2 Known Potential Benefits

Successful decolonization with retapamulin may prevent future MRSA infections in subjects and transmission to family members. The findings will also advance our understanding of the efficacy of retapamulin as a novel decolonization strategy for mupirocin-resistant MRSA. If efficacious, this therapy will have a significant clinical impact upon general practice for control of MRSA colonization and infections within this outbreak community. This is especially important in the study group and strain we are investigating as it has been found to be resistant to the standard of care for decolonization.

3 Objectives and Purpose

3.1 Primary Objective

To assess the efficacy of retapamulin to reduce carriage of MRSA via a randomized, double-blind, placebo-controlled clinical trial testing retapamulin among pediatric patients with confirmed mupirocin-resistant nasal and/or rectal MRSA colonization. This study will investigate the efficacy of retapamulin to reduce MRSA colonization 1 week post therapy by 60% compared to placebo, assuming a 15% spontaneous decolonization rate.

3.2 Secondary Objectives (if applicable)

To assess the efficacy of retapamulin to reduce MRSA colonization 4 weeks post therapy.

4 Study Design and Endpoints

4.1 Description of Study Design

The proposed study will be a randomized, double-blind, placebo-controlled clinical trial. Subjects who are positive for mupirocin-resistant methicillin-resistant *Staphylococcus aureus* (MRSA) based on nasal or rectal culture will be recruited. They will be randomized into one of the two arms to the study – retapamulin or placebo. They will be advised to apply the study drug to the nares and peri-rectal area twice a day for 5 consecutive days. Nasal and rectal colonization of MRSA will be observed at pre-determined points within the study timeframe as described below via nasal and peri-rectal culture. The participants will be cultured before and after the interventional drug and a final culture to assess long-term decolonization status. The primary outcome measures are nasal and/or rectal MRSA carriage at 1 week and 4 weeks post decolonization with retapamulin.

The participants will be recruited from NYU Langone Medical Center, specifically from Hassenfeld Children's Hospital's general pediatric and pediatric intensive care units (PICU). Hassenfeld Children's Hospital at New York University Langone Health consists of 4 inpatient units totaling 109 beds within a larger 1069-bed tertiary care academic medical center. There are 33 beds in our general pediatric ward and 14 PICU beds. Patients admitted from zip codes that are classified as Orthodox-predominant neighborhoods in Brooklyn will be recruited. As described in the background, a reference identified neighborhoods in Brooklyn determined to be mainly Orthodox based on the number of Jewish establishments (synagogues, yeshivas, and kosher food retailers) in the area.[12] A report will be generated daily through the Infection Prevention database that identifies patients admitted from these zip codes. These patients, regardless of reason for admission except as noted in exclusion criteria, will be recruited by the study team.

Participants will also be recruited from the ODA clinic on Park Aveunue in Williamsburg Brooklyn. Study team members will be going to the clinic for scheduled visits where participants can be screened for inclusion into study. These participants will be referred by their pediatricians, the members of the clinic, or by word of mouth. Additionally, participants who are recruited at NYU Langone can come to the ODA clinic for follow up visits for ease to the participants.

4.2 Study Endpoints

4.2.1 Primary Study Endpoints

The primary endpoint is % change in nasal/rectal colonization of MRSA from baseline to 1 week after completion of decolonization protocol with retapamulin compared to placebo.

This endpoint is important to determine the short term efficacy of the study drug to decolonize patients with MRSA.

4.2.2 Secondary Study Endpoints

The secondary endpoint is % change in nasal/rectal colonization of MRSA from baseline to 4 weeks after completion of decolonization protocol with retapamulin compared to placebo.

This endpoint is important to determine the long term efficacy of the study drug to decolonize patients with MRSA.

4.2.3 Exploratory Endpoints

Exploratory endpoints include: efficacy of decolonization per body site (nasal versus rectal), adverse events related to retapamulin use, and MRSA infections while on study/decolonization protocol.

5 Study Enrollment and Withdrawal

5.1 Inclusion Criteria

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1. Admission to the general pediatric floor and pediatric intensive care units at NYU Langone Medical Center or visit to study team members at ODA clinic (Park Ave locations) in Williamsburg Brooklyn.
2. Ages 9 months to 17 years
3. Residing in the zip codes which reflect Orthodox Jewish neighborhoods where there is a current outbreak of this strain of MRSA.
4. Nasal and/or rectal culture positive for mupirocin-resistant methicillin-resistant *Staphylococcus aureus* (MRSA)

5.2 Exclusion Criteria

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

1. Pregnant or lactating
2. Unable to appropriately consent
3. Open sores in either of the study sites (nares or rectum)
4. Recent surgical procedure to either study site (nares or rectum)
5. Concurrent use of Rifampin or Trimethoprim/Sulfamethoxazole
6. Current active MRSA infection
7. Immunocompromised
8. Presence of endotracheal tube, tracheostomy tube or other foreign body in upper airway

5.3 Vulnerable Subjects

This study will enroll children as we have established that we have a unique high risk pediatric population that has a high prevalence of mupirocin-resistant MRSA colonization and infections. These are no current studies on the use of the study drug, retapamulin, in the pediatric population for this indication. Please see attached Appendix: Children.

5.4 Strategies for Recruitment and Retention

We will recruit 54 total participants from ages 9 months – 17 years of age from the inpatient pediatric units at Tisch Hospital or ODA clinic. Our sample size calculation determined 22 participants in each arm (drug vs placebo) of the study to see a 60% reduction in MRSA colonization at a power level of 80%. We anticipated a 20% drop out rate based on prior studies of retention and therefore an additional 5 patients were added per arm of study.

Patients admitted to the general inpatient or pediatric intensive care units at NYU Langone Medical Center Tisch hospital will be recruited if they reside in a pre-defined zip code that is identified as an Orthodox predominant neighborhood. A daily report will be generated for patients admitted from these zip codes and sent to the Infection Prevention and Control team (specifically the PI Jennifer Lighter). Recruitment will be conducted by either the PI and co-investigator or study team members. The children will not necessarily be under the care of the PI or co-investigators, or some instances they may be if they are admitted with an infection that requires a Pediatric Infectious Diseases consult and the PI and co-investigator are the physicians who are covering the service. Otherwise, when patients from the defined zip-codes are admitted, a report that captures these patients will be created and sent to the PI and co-investigator. The study team will approach the parent/guardian explaining how they were identified for the potential study. It will be explained that the research team is not aware of their current reason for admission and will not access their Epic chart for this reason. Once permission is obtained from the

parent/guardian, then the child will be approached to discuss the study. Participants will also be recruited at the ODA clinic (Park Ave location) In Brooklyn. These participants will be referred for screening by clinic members, pediatricians in the community, or by word of mouth.

After informed consent, and assent when appropriate is obtained, screening nasal and peri-rectal cultures will be performed on these participants to determine if they are eligible to enroll. Eligibility includes either nasal or rectal positive for MRSA. Informed consent will take place either at NYULMC on the inpatient ward while they are admitted, at ODA clinic during time of screening, or at Fink Children's Ambulatory Center when present for a routine follow up visit. Participants will be asked to fill out a study questionnaire which asks about medical history, medication use, history of MRSA infections and prior use of antibiotics and specific MRSA medications. The study team will ask participants for this information via questionnaire only; it will not be gathered from their medical records. They study team will not access medical records or charts for participants.

The participants will be required to follow up at pre-defined time points throughout the 6 weeks study period to obtain follow up swabs, complete questionnaires regarding interim change in medical history or side effects experienced, and to collect containers from study drugs. Retention will be enhanced through telephone reminders of study visit appointments as well as payments for participation in the study. In addition, follow up for study visits for the participants recruited at NYULMC will occur at NYU Pediatric Infectious Diseases outpatient clinic as per routine medical management,at NYU Langone Main Campus,Greenberg Hall, or at ODA clinic (Park Ave location) in Brooklyn.

5.4.1 Use of DataCore/Epic Information for Recruitment Purposes

DataCore/Epic will not be utilized for study purposes

5.5 Duration of Study Participation

The duration of study participation including screening, both intervention study and follow up is about 6 weeks.

5.6 Total Number of Participants and Sites

The total number of participants enrolled will be 54 subjects. 27 in each of the two arms of the study.

Recruitment will end when approximately 54 participants are enrolled and have completed the study protocol. It is expected that approximately 54 participants will be enrolled in order to produce 44 evaluable participants as we estimate a 20% drop out rate. The participants will be recruited at NYULMC Tisch Hospital or ODA clinic in Brooklyn.

5.7 Participant Withdrawal or Termination

5.7.1 Reasons for Withdrawal or Termination

Participants are free to withdraw from participation in the study at any time upon request. An investigator may terminate participation in the study if:

- Any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- The participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation

5.7.2 Handling of Participant Withdrawals or Termination

For patients who have withdrawn or terminated from the study, follow up telephone calls will be conducted to assess for side effects. One phone call two weeks after the patient has been declared

withdrawn or terminated will be conducted. For patients who remain in the study, but discontinue the study agent, they will be asked to complete the follow up questionnaire when they present for study visits to assess for adverse reactions or side effects. Adverse events from the drug are local at the site of application and should subside with the discontinuation of the product. Therefore, long term follow up for adverse events is deemed unnecessary.

A participant will be stated as lost to follow-up (and therefore withdrawn/terminated) if: they have missed all three study visits, the study team has attempted weekly phone calls to parent/guardian for three weeks without answer or success of having the participant return for study visit.

5.8 Premature Termination or Suspension of Study

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the study investigators to the study team members, partnering sites, industry partner, and the IRB. If the study is prematurely terminated or suspended, the PI will promptly inform the IRB and will provide the reason(s) for the termination or suspension.
Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination of futility

Study may resume once concerns about safety, protocol compliance, data quality are addressed and satisfy the sponsor, IRB and/or FDA.

6 Study Agent (Study drug, device, biologic, vaccine etc.) and/or Procedural Intervention

6.1 Study Agent(s) and Control Description

Retapamulin is a topical antibiotic ointment. The ingredients include retapamulin and white petrolatum as the vehicle. The composition is 10mg retapamulin per 1g of ointment (1%). The placebo that will be used is triple-purified pharmaceutical-grade petrolatum.

The study is IND exempt as it meets all 6 criteria for IND Exemption in article 312.2(b) of the FDA Guidance and IND requirements listed below. Please see attached Appendix: IND Recruitments Exemption.

1. The drug product is lawfully marketed in the United States.
2. The investigation is not intended to be reported to FDA as a well-controlled study in support of a new indication and there is no intent to use it to support any other significant change in the labeling of the drug.
3. In the case of a prescription drug, the investigation is not intended to support a significant change in the advertising for the drug.
4. The investigation does not involve a route of administration, dose, patient population, or other factor that significantly increases the risk (or decreases the acceptability of the risk) associated with the use of the drug product (21 CFR 312.2(b)(1)(iii)).
5. The investigation is conducted in compliance with the requirements for review by an IRB (21 CFR part 56) and with the requirements for informed consent (21 CFR part 50).
6. The investigation is conducted in compliance with the requirements of § 312.7 (i.e., the investigation is not intended to promote or commercialize the drug product).

6.1.1 Acquisition

The study drug will be acquired directly from the drugs distributor, Aqua Pharmaceuticals. Aqua Pharmaceuticals will ship the drug directly to the NYU Investigational Research Pharmacy.

The placebo control will be acquired from the distributor and also shipped directly to the NYU Investigational Research Pharmacy.

6.1.2 Formulation, Appearance, Packaging, and Labeling

Retapamulin is a 1% ointment that consists of retapamulin and white petrolatum as the vehicle. Retapamulin is a white to pale yellow crystalline solid that is packaged by the manufacturer in 15g/30g tubes and commercially available for human use in this form.

GlaxoSmithKline (GSK) is the manufacturer of the study agent, Aqua Pharmaceuticals is the distributor of the study agent and acquired its US rights in 2015. As supplied, it is labeled under the brand name Altabax.The package insert of the product is attached in the appendix.

The placebo used will be a triple purified pharmaceutical grade white petrolatum. White petrolatum is the vehicle in the Altabax ointment which consists of retapamulin and white petrolatum. The petrolatum is Ultimate EP White PET UP (code: 130985), Product Code: PEN1702-02-C-DR, manufactured by Calumet Specialty Products. It is a topical ointment that is colorless to white ointment. It will be purchased in bulk in jar containers or tubes but will be distributed to the subjects weighed into unlabeled containers.

6.1.3 Product Storage and Stability

The study agents are stored at room temperature. Per package insert - store at 25°C (77°F) with excursions permitted to 15°-30°C (59°-86°F). The product can be used after opening or further dispensed after seal is broken until the expiration date on package.

6.1.4 Preparation

The study drug and placebo will be dispensed by the NYULMC Investigational Research Pharmacy. Both will be handled in the same manner. The drug (retapamulin) and placebo (white petrolatum) will be removed from their original packaging and packaged into standard unlabeled containers for the blinding process. The drug and placebo will be aliquoted and distributed in 15g amounts throughout the study. The study agents are ready for use from the package and do not require additional preparation. The NYULMC Investigational Research Pharmacy will receive, store, and dispense all study drug and placebo for this study's use. The contact for the NYULMC Investigational Research Pharmacy is Kanika Ballani, Pharm.D, Assistant Director of Pharmacy, Clinical Trials, 212-263-5039.

6.1.5 Dosing and Administration

Retapamulin is a topical drug. Each participant will be advised to apply a thin layer of the ointment using a cotton swab or finger to both nares and peri-rectal area twice a day (morning and evening) for 5 consecutive days.

6.1.6 Route of Administration

Topical

6.1.7 Starting Dose and Dose Escalation Schedule

Not applicable. Each participant will receive the same drug concentration and dose. 15g of ointment will be distributed and the subjects will be instructed to apply a small pea size layer topically using a cotton swab or tip of finger to both nares and peri-rectal area.

6.1.8 Dose Adjustments/Modifications/Delays

Not applicable

6.1.9 Duration of Therapy

Each ointment will be applied for five consecutive days. The five days is necessary for an 'evaluable' participant

6.1.10 Tracking of Dose

Participants will be advised on correct application and dosing at each study visit. They will be required to return the containers were dispensed in to monitor use. Participants will be asked to fill a questionnaire at each visit regarding the use of the medications (frequency of application, doses/days missed, etc).

6.1.11 Device Specific Considerations

Not applicable

6.2 Study Agent Accountability Procedures

The study agents will be allocated and dispensed by the NYULMC Investigational Research Pharmacy. The pharmacy and research pharmacist will receive shipment of the agents, allocated into individual un-identifiable container and be responsible for the blinding of the agents. The dispensed drugs will be given to the PI or co-investigator in blinded fashion by the Investigational Pharmacy for enrolled patients at the time of enrollment visit. The PI/co-investigator will distribute the agents to the participants at study visit 1. The handling and distribution will be documented by the PI/co-investigator in locked and de-identified official study records. The participants will be asked to return containers at study visit 2 after completing the 5 day decolonization process at home. This will allow for drug reconciliation checks to document drug assigned, drug consumed and drug remaining. This reconciliation will be logged on the drug reconciliation form and signed and date by the study team. The returned containers will be collected by the study team and then returned to the NYULMC Investigational Research Pharmacy for final reconciliation and destruction on site.

7 Study Procedures and Schedule

7.1 Study Procedures/Evaluations

7.1.1 Study Specific Procedures

- History
    - Medical history: list of chronic medical conditions, history of MRSA infections to be obtained from initial study questionnaire
    - Medication history: list of daily medications use, antibiotic use in the past 6 months, as well as interim antibiotic use while on study. This will be obtained from study questionnaires. Medication use does not affect assessment of eligibility.
- Physical Exam
    - A physical exam of the nares and peri-rectal area will be conducted at screening, enrollment and each follow up visit to assess area, integrity of skin/mucosa and evaluate for side effects. The exam will be documented by study team in the subject's study chart.
- Biological specimen collection and laboratory evaluations:
    - Specimen collection: Nasal and peri-rectal cultures via cotton swab will be obtained at screening visit and each subsequent study visit to assess MRSA colonization. Samples will be collected by surface swabs for MRSA culture using cotton swabs. Swabs will be collected from both of the anterior nares. Separate swabs will be collected from the peri-rectal area.
    - Specimen processing: Samples will all be processed in Shopsin laboratory at NYU by the study investigators. Cultures of the swabs will be performed within one day of collection on chromagar MRSA culture plates to identify MRSA positive isolates. The initial screening isolates will them undergo susceptibility testing via E-test to determine

mupirocin resistance. Rapid MRSA identification will also be performed via PCR testing. Specimens collected at follow up visits post decolonization that are positive for MRSA will also be analyzed via PCR to determine if resistance mutations (specifically in the *rplC* gene) are present after use of the drug.

- Study Drug Agent
  - Study drug monitoring: The study drug will be prepared by the Investigational Pharmacy at NYU. The medications will be weighed, aliquoted and prepared for distribution by the research pharmacist. The subjects will be required to return all left over medication and containers to the researchers. The research pharmacist at the Investigational Pharmacy will verify amount and contents prior to discarding the drug.
  - Assessment of study agent adherence will occur at each study visit based on questionnaires completed by the participants and assessment of study drug containers returned by participants to study team members after use.
- Decolonization: Subjects will all be instructed to performed the following decolonization protocol at home:
  - Apply the study drug topically to their nares and peri-rectal area twice daily (morning and night) for 5 consecutive days.
  - Perform environmental procedures to help eradicate MRSA from the home and prevent recolonization which includes washing all towels and linens with hot water and cleaning all frequently touched surfaces with bleach.
- Administration of questionnaires will occur at each study visit to assess change in medical history, change in infectious history, use of antibiotics, adherence to study drug agents and assessments of side effects
- A discussion of results of any study specific procedures will be provided to participant at the end of the study period after blinding has been lifted.

7.1.2 Standard of Care Study Procedures

All planned procedures completed during the study are investigational. The environmental procedures to be completed at home by participants to aid in eradication of MRSA in the home is regular standard to care for decolonization protocols.

7.2 Laboratory Procedures/Evaluations

7.2.1 Clinical Laboratory Evaluations

Screening and post enrollment microbiology evaluations: Nasal and peri-rectal culturesand PCR testing to determine MRSA colonization. All samples will be processed by the study team at Shopsin Laboratory.

7.2.2 Other Assays or Procedures

The assay includes bacterial cultures and PCR testing on the samples. MRSA will be determined via chromagar MRSA culture plates to identify MRSA positive isolates. MRSA PCR testing will be performed if rapid MRSA detection is needed. In addition, follow up specimens that are positive for MRSA after decolonization will undergo PCR testing to detect acquisition of resistant mutations. All will be processed at Shopsin Laboratory by study team members.

7.2.3 Specimen Preparation, Handling, and Storage

Specimens will be obtained from participants at each study visit. These include nasal specimen using cotton culture swabs and peri-rectal specimen using separate cotton culture swabs. These specimens will be stored at room temperature and then processed within one day of collection. Storage and processing of the specimen will occur by the study investigators at Shopsin Laboratory. Processing of the specimens includes culturing on chromagar MRSA culture plates and/or PCR testing. Originally cotton swabs and plates will be labeled with the participants study code number. Original cotton swabs will be discarded after processing. If culture plates are positive for MRSA, the isolates will be stored in -80C freezer in Shopsin Laboratory for further testing as needed. The stored isolates will be labeled with the study code number, not with patient identifier.

7.2.4 Specimen Shipment

The cotton swab specimens will be transported by hand by study investigators at room temperature from site of collection (NYULMC) to Shopin Laboratory on day of collection.

7.3 Study Schedule

7.3.1 Screening

Screening

- Admitted patients from an Orthodox predominant neighborhood based on zip code of residence will be approached regarding the study for recruitment
- Informed consent (and assent when appropriate) of a potential participant will be obtained and verified by signature on written informed consent form
- Review eligibility based on inclusion/exclusion criteria
- Perform physical examination
- Collect and nasal peri-rectal culture specimens
- Schedule study visits for participants who are eligible and available for the duration of the study.

7.3.2 Enrollment/Baseline

Enrollment/Baseline Visit (Visit 1, Day 0)

- Verify inclusion/exclusion criteria.
- Obtain demographic information, medical history, medication history, infection history from initial study questionnaire.
- Perform physical examination
- Subject randomization
- Provide study drug at this visit for home use.
- Instructions provided to the participants: The subjects will apply study drug topically inside the anterior nares and peri-rectal area twice a day (morning and night) for five consecutive days. They will also follow the environmental procedures in the attached instructions to help eradicate MRSA from the home.

7.3.3 Intermediate Visits

7.3.3.1 Visit 2

Visit 2 (Day 14 +/- 5)

- This visit will occur about one week after completion of 5 days of the study drug
- Record adverse events as reported by participant on follow up study questionnaire
- Record change in medical history, recent infections or antibiotic use on follow up study questionnaire
- Record participant's adherence to protocol via follow-up study questionnaire
- Perform physical examination
- Collect samples for MRSA culture using cotton swabs to culture the anterior nares and peri-rectal area
- Collect study drug containers from participants

7.3.4 Final Study Visit

Final Study Visit (Visit 3, Day 35 +/- 15)

- This visit will occur about four weeks after completion of the study agent
- Record adverse events as reported by participant on follow up study questionnaire

- Record change in medical history, recent infections or antibiotic use on follow up study questionnaire
- Perform physical examination
- Collect samples for MRSA culture using cotton swabs to culture the anterior nares and peri-rectal area

7.3.5 Withdrawal/Early Termination Visit

If a participant withdraws from the study or early termination occurs, a final nasal and peri-rectal swab will attempted to be collected. The participant will also be asked to fill out one final follow up questionnaire to assess use of the study agents and any adverse reactions. Participants will be asked to return all study agents containers at the time of withdrawal.

7.3.6 Unscheduled Visit

Unscheduled visits are not anticipated. If an unscheduled visit is required for unanticipated or serious adverse reaction, the participant will meet with a study team member and appropriate care will be offered. The study visit will be documented in the participants study chart and adverse reaction reported to the IRB. Any other unscheduled visit will be documented accordingly in the patients study chart.

7.4 Concomitant Medications, Treatments, and Procedures

All concomitant antibiotic use during study participation will be obtained via study questionnaires and recorded in the participant's study charts. No concomitant medications, treatment, and/or procedures are restricted while on study. Information about concomitant antibiotic use will be collected at each study visit via questionnaire. Concomitant antibiotic use information is collected to assess if the antibiotic is being used to treat a MRSA infection or could potentially impact colonization with MRSA.

7.5 Justification for Sensitive Procedures

A placebo is used to assess the true efficacy of retapamulin compared to no medication or spontaneous decolonization. The study is blinded to both the researchers and the participants to minimize any bias with study drug use.

7.5.1 Precautionary Medications, Treatments, and Procedures

There are no medication precautions, interactions or toxicities known with the study agent. Therefore, there are no instructions for medication or therapy avoidance or modification as part of this protocol.

7.6 Prohibited Medications, Treatments, and Procedures

There are no medications, treatments or procedures that are not permitted on study

7.7 Prophylactic Medications, Treatments, and Procedures

There will be no prophylactic medications, treatments or procedures provided as prophylaxis on study

7.8 Rescue Medications, Treatments, and Procedures

There will be no rescue medications, treatments or procedures provided as rescue on study

7.9 Participant Access to Study Agent at Study Closure

Participants who remain positive for MRSA colonization after their completion of study related procedures will be offered access to the study agent via open label through the NYU Investigational Pharmacy.. Once subjects have completed study visit #3 and the follow up cultures one month post decolonization are collected, if they remain positive the researchers will offer the study agent directly via the NYU Investigational Pharmacy The participants that remain positive for colonization will be advised to use the ointment again twice a day for 5 days to the nares and peri-rectal area.

After the final study closure has been completed, there will not be continued access to study agent. The study drug is commercially available through physician prescription.

8 Assessment of Safety

8.1 Specification of Safety Parameters

Safety parameters and adverse reactions/side effects will be recorded in the participants chart in the study database. No more than minimal adverse effects (local application site irritation) are anticipated from using the study agent. If adverse effects are encountered by participants and considered to be more than minimal affect it would be considered a study endpoint and adverse effects should subside with withdrawal of study agent. If more than minimal adverse effect is experienced (eg anaphylaxis or allergic reaction) it will be reported to the industry partner and the IRB.

If subject develops MRSA active clinical infection while on study protocol, they will be cared for per routine medical management for such infections. This is anticipated to be rare. This development of disease while on protocol will be reported to the IRB and industry sponsor. If available, the isolates from these cases of active disease will be collected and analyzed by study team members and Shopsin laboratory to assess the bacterium and resistance determinants. Bacterial strain isolates will be stored. No material containing subject DNA will be collected or stored.

8.1.1 Definition of Adverse Events (AE)

An ***adverse event*** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

8.1.2 Definition of Serious Adverse Events (SAE)

Serious Adverse Event
Adverse events are classified as serious or non-serious. A ***serious adverse event*** is any AE that is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- an important medical event

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above..

All adverse events that do not meet any of the criteria for serious should be regarded as ***non-serious adverse events***.

8.1.3 Definition of Unanticipated Problems (UP)

Unanticipated Problems Involving Risk to Subjects or Others
Any incident, experience, or outcome that meets <u>all</u> of the following criteria:

- Unexpected in nature, severity, or frequency (i.e. not described in study-related documents such as the IRB-approved protocol or consent form, the investigators brochure, etc)
- Related or possibly related to participation in the research (i.e. possibly related means there is a reasonable possibility that the incident experience, or outcome may have been caused by the procedures involved in the research)
- Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, or social harm).

8.2 Classification of an Adverse Event

8.2.1 Severity of Event

For AEs not included in the protocol defined grading system, the following guidelines will be used to describe severity.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating.

8.2.2 Relationship to Study Agent

The clinician's assessment of an AE's relationship to study agent is part of the documentation process, but it is not a factor in determining what is or is not reported in the study. If there is any doubt as to whether a clinical observation is an AE, the event should be reported. All AEs must have their relationship to study agent assessed. In a clinical trial, the study product must always be suspect. To help assess, the following guidelines are used.

- **Related** – The AE is known to occur with the study agent, there is a reasonable possibility that the study agent caused the AE, or there is a temporal relationship between the study agent and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study agent and the AE.
- **Not Related** – There is not a reasonable possibility that the administration of the study agent caused the event, there is no temporal relationship between the study agent and event onset, or an alternate etiology has been established.

8.2.3 Expectedness

The PI and essential study team members will be responsible for determining whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study agent.

8.3 Time Period and Frequency for Event Assessment and Follow-Up

The occurrence of an AE or SAE may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor. All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate RF. Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on

study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE. UPs will be recorded in the data collection system throughout the study.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

The PI will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

All unresolved adverse events should be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the investigator should instruct each subject to report any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study. The investigator should notify the study sponsor of any death or adverse event occurring at any time after a subject has discontinued or terminated study participation that may reasonably be related to this study. The sponsor should also be notified if the investigator should become aware of the development of cancer or of a congenital anomaly in a subsequently conceived offspring of a subject that has participated in this study.

8.4 Reporting Procedures – Notifying the IRB

8.4.1 Adverse Event Reporting

Adverse Events will be reported by the PI/co-investigator to the IRB and industry partner (Aqua Pharmaceuticals). Serious adverse events will be reported within 7 days. Minor/minimal adverse events (local application site irritation) will be reported at the completion of the study.

8.4.2 Serious Adverse Event Reporting

Serious Adverse Events will be reported in written format by the PI/co-investigator to the IRB and the industry partner within 7 days. The PI will be responsible for completing and signing off on the SAE reports.

8.4.3 Unanticipated Problem Reporting

Incidents or events that meet the OHRP criteria for UPs require the creation and completion of an UP report form. It is the site investigator's responsibility to report UPs to their IRB and to the DCC/study sponsor. The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are SAEs will be reported to the IRB and to the DCC/study sponsor within 7 days of the investigator becoming aware of the event.
- Any other UP will be reported to the IRB and to the DCC/study sponsor within 30 days of the investigator becoming aware of the problem.
- All UPs should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and OHRP within 30 days of the IR's receipt of the report of the problem from the investigator.

8.4.4 Reporting of Pregnancy

If pregnancy were to occur while participants are on study protocol, they will be withdrawn from the study and study drug use will be discontinued. The pregnancy will be reported in written format to the IRB and the industry partner by the PI.

8.5 Reporting Procedures – Notifying the Study Sponsor

The study clinician will complete a SAE Form within the following timelines:

- All deaths and immediately life-threatening events, whether related or unrelated, will be recorded on the SAE Form and submitted to the DCC/study sponsor within 24 hours of site awareness. See Section 1, Key Roles for contact information.
- Other SAEs regardless of relationship will be submitted to the DCC/study sponsor within 72 hours of site awareness.

All SAEs will be followed until satisfactory resolution or until the site investigator deems the event to be chronic or the adherence to be stable. Other supporting documentation of the event may be requested by the DCC/study sponsor and should be provided as soon as possible.

As a follow-up to the initial report, within the following 48 hours of awareness of the event, the investigator shall provide further information, as applicable, on the unanticipated event or the unanticipated problem in the form of a written narrative. This should include a copy of the completed Unanticipated Problem form, and any other diagnostic information that will assist the understanding of the event. Significant new information on ongoing unanticipated adverse effects shall be provided promptly to the study sponsor.

8.6 Study Halting Rules

Administration of study agent will be halted when three grade 3 AEs determined to be "probably related" are reported to the DCC. In the case of this study agent, retapamulin, that would likely be serious allergic reaction or anaphylaxis. The DCC will notify the study sponsor and investigators immediately when the third grade 3 event is reported and enrollment screens will stop accepting new study participants. The study sponsor will inform the DSMB members within 24 hours of this occurrence and will provide the DSMB with AE listing reports. The DSMB will convene an ad hoc meeting by teleconference or in writing as soon as possible. The DSMB will provide recommendations for proceeding with the study to the study sponsor/NIH. The study sponsor will inform the FDA of the temporary halt and the disposition of the study.

8.7 Safety Oversight

It is the responsibility of the Principal Investigator to oversee the safety of the study. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a site data and safety-monitoring plan. Medical monitoring will include a regular assessment of the number and type of serious adverse events. The safety oversight will be conducted via a single medical monitor. It is felt that this is sufficient for this trial as the overall risk to the subjects is very low based on the number of subjects to be recruited, the type of non-invasive monitoring to be performed, and the safety profile of the drug to be studied.

Safety oversight will be under the direction of a medical monitor with appropriate expertise, Adam Ratner, MD, MPH. Dr Ratner is a Pediatric Infectious Diseases physician and Microbiologist at NYU with expertise in both of these fields. The medical monitor will meet with the PI and co-investigator at least semiannually to assess safety and efficacy data on each arm of the study. Data collected to date will be reviewed including participants' demographics, any significant history or illnesses, % change in colonization for nose and peri-rectal area, and answers to questionnaires. Safety data will also be reviewed including any adverse effects that have occurred, side effects reports and retention/dropout rate. The medical monitor will provide its input to the PI, IRB and industry partner.

9 Clinical Monitoring

Clinical site monitoring is conducted to ensure that the rights and well-being of human subjects are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with GCP, and with applicable regulatory requirement(s).

- Monitoring for this study will be performed by Adam Ratner, MD, MPH.
- Monitoring will be centralized at NYULMC and will occur at the initiation of the study and semi-annually throughout the duration of the study. On-site monitoring of Tisch Hospital will occur once at the initiation of the study. Targeted, random review of data collection, data recording, data handling, data analysis, study-related procedures, and safety monitoring will be performed. The monitoring reports will be distributed to the PI, co-investigators and the IRB within 30 days.
- Independent audits will not be conducted at this trial does not involve numerous sites
- Internal quality management of study conduct, data collection, documentation and completion will be performed centrally.

10 Statistical Considerations

10.1 Statistical and Analytical Plans (SAP)

There will be a formal Statistical and Analytical Plan (SAP). Partial details as outlined in the below sections, with full SAP created by study biostatistician being part of a stand-alone document. Key elements of the analysis plan are described below.

10.2 Statistical Hypotheses

Primary endpoint

The percent change in nasal/rectal colonization of MRSA from baseline to 1 week after completion of decolonization protocol with retapamulin compared to placebo

Null hypothesis: There will be no difference in reduction of nasal/rectal colonization of MRSA from baseline to 1 week after completion of decolonization protocol between retapamulin compared to placebo

Alternative hypothesis: There will be a 45% difference in reduction in nasal/rectal colonization of MRSA from baseline to 1 week after completion of decolonization protocol with retapamulin compared to placebo

Secondary endpoint

The percent change in nasal/rectal colonization of MRSA from baseline to 4 weeks after completion of decolonization protocol with retapamulin compared to placebo

Null hypothesis: There will be no difference in reduction of nasal/rectal colonization of MRSA from baseline to 4 weeks after completion of decolonization protocol between retapamulin compared to placebo

Alternative hypothesis: There will be a 45% difference in reduction in nasal/rectal colonization of MRSA from baseline to 4 weeks after completion of decolonization protocol with retapamulin compared to placebo

This analysis will be a superiority trial.

10.3 Analysis Datasets

This will be a triple-blinded randomized Intent to Treat (ITT) clinical trial to assess the effectiveness of retapamulin in children colonized with MRSA under the age of 18 from a pre-specified community in Brooklyn. Participants living in the following zip codes will be eligible: 11024, 11205, 11206, 11211, 11213, 11214, 11218, 11219, 11225, 11230, 11249. Neither the treatment team nor the subject will know the treatment assignments. The outcome will be a dichotomous variable (1 = Yes, patient's swab negative for MRSA, 0 = No, Patient's swab positive for MRSA). We will analyze additional co-variables collected on the data collection form such as age, gender, history of MRSA infections, history of chronic medical conditions/chronic skin conditions, etc. (see Data Collection Form in appendix uploaded into study-related documents).

Information from the data collection form will be entered into an Access database designed for this study to provide a readily electronic version dataset to analyze. The following variables will be included: Assigned group (blinded treatment arm, A/B), age, gender, side effects, application day 1 (Y/N), application day 2 (Y/N), application day 3 (Y/N), application day 4 (Y/N), application day 5 (Y/N), environmental clean (Y/N), history of medical conditions or chronic skin conditions, history of MRSA, history of MRSA in family, recent or concomitant antibiotic use, prior retapamulin use etc. Variables related to safety will also be recorded in the database.

In addition to the ITT analysis, we will conduct a per-protocol analysis of those who completed 4 or 5 days of treatment and analyze similar to the ITT analysis.

10.4 Description of Statistical Methods

10.4.1 General Approach

The design of the study is a randomized, double-blind, placebo-controlled clinical trial. Schematic of Study design on page 2 of this document illustrates further.

This will be a double-blinded randomized Intent to Treat (ITT) clinical trial to assess the effectiveness of retapamulin in children colonized with MRSA under the age of 18 from a pre-specified community in Brooklyn. The outcome will be a dichotomous variable (1 = Yes, patient's swab negative for MRSA, 0 = No, Patient's swab positive for MRSA). We will analyze additional co-variables collected on the data collection form such as age, gender, history of MRSA infections, history of chronic medical conditions/chronic skin conditions, etc. (see Data Collection Form in appendix uploaded into study-related documents).These will be presented as descriptive statistics between Retapamulin and Placebo groups and assessed for potential statistical differences between the groups. Chi-square will be used for dichotomous variables and a T-test will be used for continuous variables (if normally distributed otherwise Mann-Whitney).

10.4.2 Analysis of the Primary Efficacy Endpoint(s)

To assess the primary dichotomous endpoint, the change in nasal/rectal colonization of MRSA from baseline to 1 week after completion of decolonization protocol with retapamulin compared to placebo, we will use a fisher exact (non-parametric) to evaluate for significant difference in colonization after 1 week between the two groups. We will provide the difference in decolonization rates with an odd ratio, 95% confidence interval and p-value. Participants will be selected to treatment group at random, therefore baseline characteristics should not significantly differ. However if the two treatment groups have covariates that are significantly different, we will consider a logistic regression to adjust for the difference

in population. Before we analyze with a logistic regression, we will test for normality to assure that all apriori statistical assumptions are met.

10.4.3 Analysis of the Secondary Endpoint(s)

To assess the secondary dichotomous endpoint, the change in nasal/rectal colonization of MRSA from baseline to 4 week after completion of decolonization protocol with retapamulin compared to placebo, we will use a fisher exact (non-parametric) to evaluate for significant difference in colonization after 4 week between the two groups. We will provide the difference in decolonization rates with an odd ratio, 95% confidence interval and p-value. Participants will be selected to treatment group at random, therefore baseline characteristics should not significantly differ. However if the two treatment groups have covariates that are significantly different, we will consider a logistic regression to adjust for the difference in population. Before we analyze with a logistic regression, we will test for normality to assure that all apriori statistical assumptions are met.

10.4.4 Safety Analyses

Patients will be monitored for the occurrence of possible adverse events using a standardized data collection form prior to hospital discharge. All serious events which many potentially be adverse reactions (anaphylaxis, serious rash or death) will be assessed by the primary investigator. The study team and the NYU SOM Institutional Review Board will be notified within one day of identification of the event by study personnel.

10.4.5 Adherence and Retention Analyses

Adherence to the protocol will be collected and documented using the data collection form (in appendix uploaded into study-related documents). Subjects will be asked to report the use of the provided ointment in follow-up questionnaire which will be administered at the follow-up study visit conducted one week after completion of study decolonization protocol. The subjects will receive phone calls from study team members as reminders to use the study drug provided. Additionally, containers from the drug provided will be collected at the same follow-up study visit to assess use. Subject retention/follow up will be assessed via phone call when subject fails to return for study visit within three weeks of completion of decolonization protocol. Additional comments due to loss to follow-up will be recorded after scheduled phone call. Discontinuation of intervention will occur if serious side effect (anaphylaxis) occurs.

10.4.6 Baseline Descriptive Statistics

We will assess differences in baseline descriptive statistics between the intervention groups. These variables include age, sex, history of MRSA infections, history of chronic skin conditions, and recent antibiotic use.

10.4.7 Planned Interim Analysis

Not applicable

10.4.7.1 Safety Review

Study enrollment and administration of study drug will be halted if serious adverse events are noted across multiple participants. If it was deemed that enrollment and administration of drug needed to be stopped, it would pertain to the entire study including participants in both arms.

10.4.7.2 Efficacy Review

Study enrollment and administration of study drug will be halted if serious adverse events are noted across multiple participants. If it was deemed that enrollment and administration of drug needed to be stopped, it would pertain to the entire study including participants in both arms. Interim analysis is not planned for efficacy review.

10.4.8 Additional Sub-Group Analyses

We will assess differences in baseline descriptive statistics between the intervention groups. These variables include age, gender, history of MRSA infections, history of chronic skin conditions, and recent antibiotic use.

10.4.9 Multiple Comparison/Multiplicity

Not applicable

10.4.10 Tabulation of Individual Response Data

De-identified patient data will be listed measure (blinded) and pre-defined study follow up time points as illustrated in the Schematic of Study design on page 2 of this document. .

10.4.11 Exploratory Analyses

None planned

10.5 Sample Size

The table below presents ranges of the required sample size based on the primary trial endpoint of the change in nasal/rectal colonization of MRSA from baseline to 1 week after completion of decolonization protocol at approximately 80% power. It provides a range of sample size depending on the potential effectiveness of retapamulin.

Computed N Per Group

Proportion Diff	Actual Power	N Per Group
0.30	0.809	42
0.35	0.801	32
0.40	0.807	26
0.45	0.822	22
0.50	0.811	18
0.55	0.802	15
0.60	0.808	13
0.65	0.841	12

The sample size calculation was based on prior literature indicating a 60% decolonization rate; a 45% difference in decolonization between groups (60% retapamulin vs 15% placebo/spontaneous decolonization) at 80% power. This is taken into account a 15% spontaneous decolonization rate as reported in the literature. Power calculation analyses were performed in SAS 9.3 (SAS Institute, Cary NC) using fisher's exact conditional test for two proportions (Walters normal approximation with exact conditional distribution). A 20% lost to follow up was estimated and added to the final sample size number. Therefore, the total number of participants enrolled will be 54 subjects – 27 in each of the two arms of the study.

It is estimated that 0.8-6% of the general population is colonized with MRSA. Colonization in persons with previous infection is estimated to be 20%. We suspect this percent is higher in the particular population we aim to study as it is a high risk population for MRSA colonization and infection. Therefore we estimate screening 500 participants to meet the sample size goal of our study.

We will use fisher exact test at alpha .05 to determine a significant difference between treatment groups (retapamulin vs placebo). Participants who withdraw before the 1 week primary endpoint will be excluded from analysis as the primary end point will not be recorded.

10.6 Measures to Minimize Bias

10.6.1 Enrollment/Randomization/Masking Procedures

In order to produce treatment groups in which the distributions of prognostic factors, known and unknown, are similar and minimize bias, we will randomize participants to treatment groups. We will generate a randomization schedule using SAS 9.3 (SAS Institute, Cary NC). Additionally, participants, investigator, treatment team and analyst will be blinded to treatment group. The generated randomization schedule will be provided to the research pharmacy who will assign which arm is the treatment groups and reveal assignment after analysis is complete. The pharmacy will carry out the blinding as the drugs (ointments) will be aliquoted into unmarked containers labeled with the arm (A or B). The research pharmacy will provided drug to the investigators when a subject is enrolled in blinded form. The A/B group identifier (retapamulin vs placebo) will not be revealed until the study is completed and data analyzed. There are no anticipated obvious drug effects from the retapamulin or placebo that would imperfect blinding.

10.6.2 Evaluation of Success of Blinding

If treatment group assignment is unknown to all subjects, investigators, treatment team and analyst for the duration of the study, blinding will be considered a success.

10.6.3 Breaking the Study Blind/Participant Code

Criteria to break the study blind for an individual include serious adverse events such as anaphylaxis in the particular patient. Study blind would be broken for all participants if recurrent serious adverse events are observed among numerous participants. Serious adverse effects are not expected with the use of this study drug. Intentional and unintentional breaking of the blind will be reported by the PI/co-investigator to all members of the study team, the IRB, and the industry sponsor.

11 Source Documents and Access to Source Data/Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial. It is acceptable to use CRFs as source documents. If this is the case, it should be stated in this section what data will be collected on CRFs and what data will be collected from other sources.

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write "N/D". If the item is not applicable to the individual case, write "N/A". All entries should be printed legibly in black ink. If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialed and dated. DO NOT ERASE OR WHITE OUT ERRORS. For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it.

Access to study records will be limited to IRB-approved members of the study team. The investigator will permit study-related monitoring, audits, and inspections by the IRB/EC, the sponsor, government

regulatory bodies, and University compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable University compliance and quality assurance offices.

12 Quality Assurance and Quality Control

QA/QC will be monitored by Adam Ratner, MD, MPH. All planned study related procedures, data handling and analysis will be assessed at the initiation of the trial and semiannually to ensure the trial is performed and data is generated, documented and reported in compliance with GCP and the applicable regulatory requirements. QC procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the PI for clarification/resolution.

Following written SOPs, the monitors will verify that the clinical trial is conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing.

13 Ethics/Protection of Human Subjects

13.1 Ethical Standard

The investigator will ensure that this study is conducted in full conformity with Regulations for the Protection of Human Subjects of Research codified in 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, and/or the ICH E6.

13.2 Institutional Review Board

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether previously consented participants need to be re-consented.

13.3 Informed Consent Process

13.3.1 Consent/Assent and Other Informational Documents Provided to Participants

Consent forms describing in detail the study agent, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting intervention/administering study product.

The following consent materials are submitted with this protocol in the appendix:

Informed Consent
Assent (Age 7-11)

Assent (Age 12-14)
Assent (Age 15-17)

13.3.2 Consent Procedures and Documentation

Informed consent and assent will be obtained from all subjects by the PI and trained study co-investigators. The consent forms (informed consent, and age specific assents) are included in the appendix. Informed consent will be obtained from the participant's parent/legal guardian and assent will be obtained if able from the participant. The study staff will explain the study rationale, procedures, risks and benefits. Subjects will be given ample time to read and review the consent/assent forms and to ask questions to ensure comprehension of the consent/assent, the scientific background of the study, and the procedures required of them.

Since the population being studied may not be able to provide informed consent in English, the informed consent and assent forms will be translated into the subject's preferred language and submitted to the IRB for review before a non-English speaking subject is enrolled. A translator will be used when a non-English speaking subject is taken through the informed consent and assent process. For non-English speaking children capable of providing assent, assent will be obtained verbally and documented accordingly in the research record. For English speaking children capable of providing assent, the age-appropriate assent will be signed.

The following individuals are authorized to obtain consent:
Ami Patel, M.D.,M.P.H. – Co-investigator
Jennifer Lighter, M.D. – Principal Investigator
Israel Rosman, MBA
Rebecca Rosenberg, MD, MPH

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Extensive discussion of risks and possible benefits of participation will be provided to the participants and their families. Consent forms will be IRB-approved and the subject's parent/guardian will be asked to read and review the document while children will be asked to review the age-appropriate assent form. The investigator will explain the research study to the participant and the parent/guardian and answer any questions that may arise. All participants and parent/guardians will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants' parents/guardians will have the opportunity to carefully review the written consent form and ask questions prior to signing and the children will in turn have the opportunity to review the assent form and ask questions. The participants and their parent/guardian should have the opportunity to discuss the study with their families or doctors or think about it prior to agreeing to participate. The participants' parent/guardian will sign the informed consent document prior to any procedures being done specifically for the study and the children will sign the appropriate assent form. The participants' parent/guardian may withdraw consent at any time throughout the course of the trial. A copy of the signed informed consent and assent document will be given to the participants' parent/guardian for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

A copy of the signed informed consent document and assent form will be stored in the subject's research record. The consent and assent process, including the name of the individual obtaining consent and assent, will be thoroughly documented in the subject's research record. Any alteration to the standard consent process (e.g. use of a translator, consent document presented orally, etc.) and the justification for such alteration will likewise be documented.

13.4 Participant and Data Confidentiality

Data will be kept secure and minimal personal identification information will be collected which will then be de-identified in the study database. Each subject enrolled in the study will be assigned a unique code. All samples and data collected will be labeled with the subject's assigned code. No other names or identifiers will be on these samples or data. A file linking the study code to the patient will be maintained by the study PI and co--investigator to enable retrieval of additional information if needed. This file will be store in a locked cabinet and password protected database created specifically for this study. Only the PI and essential research personnel will have access to the cabinet and database. No individual identifiable information from the data collected will be published. Only aggregate data will be presented publicly to avoid identification of any individual subject. Project staff will verify that all research materials are collected before leaving a research site.

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

Participant confidentiality is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their agents. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

The study monitor, other authorized representatives of the sponsor, representatives of the IRB or pharmaceutical company supplying study product may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by local IRB and Institutional regulations.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at NYU Langone Medical Center. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by NYU Langone Medical Center research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at the NYU Langone Medical Center.

13.4.1 Research Use of Stored Human Samples, Specimens, or Data

- Intended Use: Samples and data collected under this protocol may be used to study MRSA infections, the bacterium, risk factors, complications, potential subsequent microbiome analysis, or potential therapies. No genetic testing will be performed.
- Storage: The isolates from the surface swabs will be retained at Shopsin laboratory. Access to stored samples will be limited to study team members. Samples and data will be stored using codes assigned by the investigators. Data will be kept in password-protected computers. Only investigators will have access to the samples and data.
- Tracking: Data will be tracked using basic electronic logging/tracking methods (Microsoft word and excel).
    - Disposition at the completion of the study: All stored samples will be stored at Shopsin Laboratory. Study participants who request destruction of samples will be notified of compliance with such request and all supporting details will be maintained for tracking.

13.5 Future Use of Stored Specimens

With the approval of the local IRB, de-identified biological samples of MRSA isolates will be stored at the Shopsin Laboratory in the Alexandria building at NYU for future research into MRSA and to improve treatment. Banking of the isolates is required indefinitely because if the patient/isolates develop resistance to the study drug, we would want to find the mechanistic basis of the resistance through genotypic and phenotypic analysis. This work can take years to accomplish. The sample from the swabs stored will be bacterial strain isolates, no material containing patient DNA is saved.

The banked isolates will be identified via a code. The PI will hold the code-link that will allow linking the biological specimens with the phenotypic data from each participant, maintaining the masking of the identity of the participant. If future studies are conducted with these isolates, they will be reviewed by the site's IRB under a new protocol or addendum to existing approved protocol.

14 Data Handling and Record Keeping

14.1 Data Collection and Management Responsibilities

Data collection is the responsibility of the clinical trial PI and co-investigator. The investigators are responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

Data capture will be paper (study related questionnaire, tracking of sample collection, results of sample processing, and tracking of study agents) and will be transferred to an electronic database in an ongoing fashion by study PI and co-investigator. These paper source documents will be kept in the participants study charts that will be kept in a locked cabinet accessible to PI and co-investigator.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. Black ink is required to ensure clarity of reproduced copies. When making changes or corrections, cross out the original entry with a single line, and initial and date the change. DO NOT ERASE, OVERWRITE, OR USE CORRECTION FLUID OR TAPE ON THE ORIGINAL.

Copies of the electronic CRF (eCRF) will be provided for use as source documents and maintained for recording data for each participant enrolled in the study. Data reported in the eCRF derived from source documents should be consistent with the source documents or the discrepancies should be explained and captured in a progress note and maintained in the participant's official electronic study record.

Clinical data (including AEs, concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into the subject's chart and Microsoft word or excel. The data system includes password protection and internal quality checks, such as automatic range checks, to identify

data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

14.2 Study Records Retention

Study documents will be retained for the longer of 3 years after close-out, 5 years after final reporting/publication, or 2 years after the last approval of a marketing application is approved for the drug for the indication for which it is being investigated or 2 years after the investigation is discontinued and FDA is notified if no application is to be filed or if the application has not been approved for such indication.

14.3 Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol, GCP, or Manual of Procedures (MOP) requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH E6:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

It is the responsibility of the site PI to use continuous vigilance to identify and report deviations within 14 working days of identification of the protocol deviation, or within 30 working days of the scheduled protocol-required activity.

All protocol deviations must be addressed in study source documents, reported to QA/QC and safety monitor Adam Ratner, MD, MPH and the IRB by the study PI.

14.4 Publication and Data Sharing Policy

This study will comply with the NIH Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

The PI and co-investigator will be responsible for developing publishing procedures and resolving authorship issues. The study will be registered and updated onto ClinicalTrials.gov.

The International Committee of Medical Journal Editors (ICMJE) member journals have adopted a clinical trials registration policy as a condition for publication. The ICMJE defines a clinical trial as any research project that prospectively assigns human subjects to intervention or concurrent comparison or control groups to study the cause-and-effect relationship between a medical intervention and a health outcome. Medical interventions include drugs, surgical procedures, devices, behavioral treatments, process-of-care changes, and the like. Health outcomes include any biomedical or health-related measures obtained in patients or participants, including pharmacokinetic measures and adverse events. The ICMJE policy, and the Section 801 of the Food and Drug Administration Amendments Act of 2007, requires that all clinical trials be registered in a public trials registry such as ClinicalTrials.gov, which is sponsored by the National Library of Medicine. Other biomedical journals are considering adopting similar policies. For interventional clinical trials performed under NIH IC grants and cooperative agreements, it is the grantee's responsibility to register the trial in an acceptable registry, so the research results may be considered for publication in ICMJE member journals. The ICMJE does not review specific studies to determine whether registration is

necessary; instead, the committee recommends that researchers who have questions about the need to register err on the side of registration or consult the editorial office of the journal in which they wish to publish.

FDAAA mandates that a "responsible party" (i.e., the sponsor or designated principal investigator) register and report results of certain "applicable clinical trials":

- Trials of Drugs and Biologics: Controlled, clinical investigations, other than Phase I investigations of a product subject to FDA regulation;
- Trials of Devices: Controlled trials with health outcomes of a product subject to FDA regulation (other than small feasibility studies) and pediatric postmarket surveillance studies.
- NIH grantees must take specific steps to ensure compliance with NIH implementation of FDAAA.

15 Study Finances

15.1 Funding Source

The study is partially financed through an investigator-initiated grant from Aqua Pharmaceuticals and a monetary donation made to the PI for academic/research purposes. The study drug is provided by Aqua Pharmaceuticals.

15.2 Costs to the Participant

There will be no cost to the subjects for participation in this study. The study is being sponsored by a grant from Aqua Pharmaceuticals, the company that distributes Retapamulin. All study related costs will be paid through this grant.

15.3 Participant Reimbursements or Payments

The subjects will receive $100 for their participation in this study. The full compensation will be provided upon completion of the study protocol. If subjects were to withdraw prior to the completion of the study, they will be eligible for $25 compensation per visit completed. The compensation will be provided to the parent/guardian of the participants.

16 Study Administration

16.1 Study Leadership

The study will be led by the PI (Jennifer Lighter) and co-investigator (Ami Patel). They are responsible for participant recruitment, consent, specimen collection and processing, data handling, data analysis, and safety monitoring. The main study decisions will be led by them. They will be in continuous communication during the duration of the study with weekly meetings.

Other study team members include: Israel Roman, Bo Shopin, MD PhD, Rebecca Rosenberg, MD, MPH who will provide guidance on details of study design, subject recruitment and retention, assistance with microbiologic procedures and provide general oversight. Anna Stachel, MPH will provide guidance on study design, data handling, and will conduct study related statistical analysis. Adam Ratner, MD, MPH will provide oversight to the study including QA/QC and safety and clinical monitoring.

All study team members will meet on a semi-annual basis and more frequently as needed to discuss study progress. Progress will be communicated and reported in both verbal and written formats.

17 Conflict of Interest Policy

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the trial. The study leadership has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by the NYU Langone Conflict of Interest Management Unit (CIMU) with a Committee-sanctioned conflict management plan that has been reviewed and approved by the study sponsor prior to participation in this study. All NYULMC investigators will follow the applicable conflict of interest policies.

18 References

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19 Attachments

These documents are relevant to the protocol, but they are not considered part of the protocol. They are stored and modified separately. As such, modifications to these documents do not require protocol amendments.

19.1 Informed Consent

19.2 Assent (Age 7-11)

19.3 Assent (Age 12-14)

19.4 Assent (Age 15-17)

19.5 Questionnaire - Initial

19.6 Questionnaire – Follow Up

19.7 Instructions on application of study drug and environmental decolonization protocol

19.8 Retapamulin Package Insert/Product Information

19.9 Data Collection Form

19.10 Study handout

20 Schedule of Events

	Screening	Visit 1	Decolonization at home	Visit 2	Visit 3
	Screening visit	Enrollment	Retapamulin vs placebo	1 week post-decolonization	4 weeks post-decolonization
Consent/ Assent	X				
Randomization		X			
Demographics		X			
Medical History		X		X	X
Physical Examination		X		X	X
Questionnaire		X		X	X
Nasal/Peri-rectal Swabs	X			X	X
Study drug dispensation		X			
Participant study drug compliance check				X	
Participant Adverse Events check				X	X