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Early View

Study protocol

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Eradication of early MRSA infection in cystic fibrosis – a novel study design for "STAR-ter" trial

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Running title: STAR-ter trial

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Keywords: Methicillin resistant *S. aureus*; eradication; clinical trial; rare disease.

Take Home message: To accomplish an ethical and timely trial for incident infection in a rare disease we conduct a novel study design using the control group from our prior randomized study as comparator group.

INTRODUCTION

Cystic Fibrosis (CF), is an autosomal recessive disease that affects approximately 34,000 people in the U.S. Those living with CF produce abnormally viscous mucus, resulting in chronic bacterial lung infections [1]. Pulmonary infection and the resultant lung disease are the leading cause of death for CF patients [2]. Several bacteria are associated with higher mortality, including *P. aeruginosa*, *Burkholderia cepacia* and methicillin-resistant *Staphylococcus aureus* (MRSA)[3]. MRSA is also a risk for increased rates of hospitalization and failure to recover baseline lung function after IV antibiotics for pulmonary exacerbations [4]. Conversely, MRSA could be a marker of worse underlying disease. Within 2 years after MRSA acquisition there was no disease progression but was associated with more intense therapies [5, 6]. Of note, that all those studies were done before availability of highly effective modulator therapies (HEMT).

Similar to high rates of MRSA carriage and infections among the general population in the U.S., the prevalence of MRSA across U.S. CF care centers is high at ~25% [7] [8]. Chronic, but not intermittent MRSA infection is associated with lower survival when compared to those without MRSA [11]. This highlights the need for early intervention, prior to the development of chronic MRSA infection. Current CF care guidelines in the U.S. do not recommend prophylaxis against *S. aureus* and there are no guidelines for treating new or chronic MRSA [12].

Limited clinical trials have resulted in inconsistent treatment approaches for MRSA eradication. Several uncontrolled, retrospective series report variable rates of eradication with a multitude of treatment approaches [9, 13, 14]. To date, only two randomized controlled clinical trials have compared treatment of incident or early MRSA infection to no treatment [15, 16]. Both trials used complex dual antibiotic therapy, topical therapy, and environmental decontamination. Each trial showed a reduction in MRSA positivity in the treatment compared to the control arm, which achieved significance for the primary end-point in the STAR-too (***S****taph.* ***A****ureus* **R**esistance – **T**reat **O**r **O**bserve) study [15].

The STAR-too protocol (NCT01349192) was the first randomized trial of eradication treatment for early MRSA infection in CF [15]. The treatment arm received two weeks of oral trimethoprim-sulfamethoxazole (TMP-SMX) and rifampin, combined with nasal mupirocin and throat decontamination with chlorhexidine for five days and antiseptic skin washes for five days. Additionally, subjects performed intensified environmental cleaning in their homes for three weeks. The comparator was a no-treatment arm rather than a placebo arm as topical therapy and environmental contamination is difficult to conceal. The primary outcome was MRSA culture negativity on Day 28. Results showed that 82% of participants in the treatment arm were

MRSA negative at Day 28, compared to only 26% in the control arm. Adjusted for interim monitoring, this difference was 52% (95% CI 23% to 80%, p<0.001). STAR-too's aggressive approach to treatment yielded positive results but concerns over feasibility of a demanding treatment regime and the multiple drug interactions with rifampin led to the proposal and testing of a simpler regime described here.

The STAR-ter trial design represents a novel study design with an external, matched control group, enabling study completion in a rare disease (CF and incident MRSA) within a reasonable timeframe for STAR-ter (*Staph aureus* resistance – Treat Early and Repeat) (NCT03489629).

METHODS

Rationale and Study Design

A systematic study of incident events (MRSA infection) in a rare disease (CF) poses significant challenges to classical randomized controlled trials. As antibiotic treatment for incident MRSA has been shown to lead to lower infection rates, an untreated control group was no longer considered ethical by the study team and DSMB consistent with research standards despite use of no-treatment remaining an issue of discussion [17]. Use of an active comparator arm requires either a superiority or a non-inferiority trial design. Given the STAR-too trial results, one can anticipate a much smaller effect size in any additional comparator trial. Incident MRSA continues to be a relatively rare event in an orphan disease. Thus, follow-on studies comparing potentially better (superiority) or equal (equivalence or non-inferiority) treatment approaches would likely not be feasible given the available population (see **Analytic Approach**). These limitations led us to utilize a novel study design with an external comparator group, as has been done in other rare diseases [18]. Such an approach has increasing interest from regulatory bodies [19-21].

STAR-ter is an open-label, multi-center interventional trial in patients with CF with new isolation of MRSA from the respiratory tract (oropharyngeal (OP) swab, sputum, or bronchoscopy) who are at their clinical baseline. The study investigates a cyclical and multi-faceted treatment protocol to eradicate incident MRSA. Over the course of six months subjects have four study visits and will receive two courses of antibiotic treatment (at start and repeated after a 2-week washout) targeting MRSA. Repeat OP-swabs and nasal swabs to monitor colonization will be collected at all visits; screening, day 28, day 56, day 168 (see **Figure 1**).

The primary endpoint will be the proportion of positive MRSA respiratory cultures at day 28 compared to the rate of MRSA positivity in the placebo group in STAR-too as an external comparator control group. We

hypothesize that short term microbiological efficacy of STAR-ter will be superior to an untreated control while accounting for a rare study population.

Novel Trial Design

An external control group broadly defines studies in which the control group is not part of the current randomized study and are discussed as part of FDA guidelines for industry studies [https://www.fda.gov/media/71349/download]. Often the control subjects are selected from the wider population of the disease to be studied. In our case, the control group is from a prior trial that had the same inclusion criteria, participants are well characterized in regard to characteristics relevant to the study questions, and the bias of inclusion is minimized due to the randomization in the STAR-too study. Further, the primary endpoint is objectively defined as the proportion of subjects with MRSA negative cultures and the 28-day observation period from the STAR-too trial provided carefully curated data regarding the short-term outcome of untreated incident MRSA in CF.

Ethical considerations strongly influenced the study design. Including a no-treatment arm would be unethical. Conducting a non-inferiority design would lead to an estimated sample size requirement of 366 incident MRSA cases assuming a non-inferiority margin of 10% [22]. Enrollment in STAR-too was around 1-2 patients/month across 10 CF centers. Given the rarity of such infection, a sample size of 366 was deemed unfeasible without including upwards of 69 CF centers or, at enrollment rates within the STAR-too trial, the trial would require 25 years to fully enroll. Such an approach would delay the answer to an important clinical question and have a negative impact on CF care. Given an increasingly crowded clinical space in CF with many competing studies for people with CF, such a large trial would also be challenging to justify. Thus the use of prior clinical trial observation arm as comparators matches criteria recommended by FDA and is the best method to allow for study of a rare infection in a rare disease population.

To allow comparisons between STAR-ter and STAR-too, STAR-ter was designed to mirror STAR-too as closely as possible. The studies use the same exclusion and inclusion criteria, except for a slightly expanded age range to better address the affected patient population as seen in STAR-too (**Table 1**).

The two trials recruited subjects from as many of the prior study sites as possible to minimize bias. Study design and procedures differ only in the medication of interest to the study, with STAR-ter not administering rifampin and not employing chlorhexidine body wipes for 5 days (see below for rational). Clinically stable

subjects with new MRSA infection will be enrolled and receive oral TMP-SMX for two weeks, and nasal mupirocin for 5 days (**Table 2**).

Choice of Study Medications and Optimization

Trimethoprim-sulfamethoxazole was chosen due to low rates of antibiotic resistance (~ 3%-12% in CF depending on strain type), its oral availability and its approval for children as young as 3 months of age with a good safety and tolerability profile [23]. The most common side effects are rash and nausea occurring in 2-4% of patients taking TMP-SMX. Further, TMP-SMX has good penetration into lung tissue with sputum levels close to those in serum and dose dependent between 2-4.5 ug/ml [24]. Dosage was based on recommendations and PK/PD studies in CF [25]. In case of known TMP-SMX or sulfa allergy, minocycline is used in both trials for patients age 8 years and older**.**

Additionally, topical decontamination of nares and throat is included in each trial **(Table 2)**. An exception will be children ages 2-4 years who may be too young to reliable gargle and are not receiving throat decolonization. The number of subjects enrolled into the trial in this age range is unclear and sensitivity analyses will be done with and without inclusion of this age group. The initial study (STAR-too) also included skin decontamination with chlorhexidine based on the high rates of skin and soft tissue infections in non-CF patients. Yet, there was only a single occurrence of MRSA positive axilla/groin swab out of 44 subjects in the STAR-too study, leading us to not include this procedure in STAR-ter. As MRSA skin colonization was very low in the prior trial with the difference between study groups at enrollment being 4% (-12%, 20%), p=1.00 and all subsequent axilla/groin cultures were MRSA negative in both arms an impact of such colonization status was deemed unlikely to affect outcomes. In contract, nasal colonization was present in 14 (32%) of subjects at enrollment and decolonization is included in this protocol and analyses.

The key difference between studies was the use of rifampin in the STAR-too study; rifampin was initially included based on its excellent penetration into respiratory secretions, the pharynx, and reports on effectively reducing nasal carriage in asymptomatic persons [26]. Yet, given high rates of GI-side effects and drug-drug interactions with agents often used in CF, this trial tests a more tolerable regimen.

Optimization in relation to recurrence

Although STAR-too showed significant rates of eradication at day 28, the differences in culture status decreased over time with 62% in the treatment and 41% of the placebo arm remaining MRSA negative on day 84 (Difference = -21% (-47%, 10%) p=0.328). Such apparent recurrence could be persistence in other

body sites [27] or true reinfection either from environmental sources in the household or other household members. The repeat cycle of eradication treatment using the same regimen as the initial one after a 2-week wash-out period will assess this as an exploratory endpoint. Microbiologically, the MRSA at incident and any recurrent isolates will be sequenced to establish relatedness of the MRSA isolates.

Contemporaneous Clinical Care Comparison Arm

A descriptive study component of STAR-ter is the inclusion of subjects who meet inclusion criteria but decline to participate in the intervention. This study arm is termed the Contemporaneous Clinical Care Comparison Arm (CCCCA). Data collected on these patients includes if and which treatment regimens were chosen, complications and outcomes for the same duration as for the interventional arm. This design allows evaluation of clinical practices and data collection on early interventions without influencing the patient's treatment plan to capture additional detailed data in this rare disease population.

Analytic Approach

The primary endpoint, the proportion of subjects with a negative culture for MRSA at Day 28, will be descriptively summarized with a corresponding 95% confidence interval. The primary analysis population will be composed of all subjects with culture results available at baseline and Day 28 as defined by the ITT-E population. The primary efficacy analyses will also be performed on a per-protocol efficacy (PPE) population consisting of protocol-defined compliant subjects. The proportion of subjects with a negative respiratory culture for MRSA at Day 28 will be compared to the treatment arm of the STAR-too trial using Fisher's exact test, with corresponding 95% CI derived using the Newcombe-Wilson method. Event rate comparisons will be performed using Poisson regression.

To evaluate the robustness of primary study results, multiple sensitivity analyses for the primary endpoint will be conducted; e.g. restricting the analysis to patients who were positive for MRSA at the screening visit. As several subjects in the prior observational control group were treated with TMP-SMX prior to Day 28 sensitivity analyses will assess the robustness of study results by restricting the analysis to patients who do not require treatment for MRSA prior to Day 28. We will also compare the eradication proportion achieved in the STAR-ter trial to our CCCCA arm at follow up – assessing both patients treated and not treated for incident MRSA. However, no sample size estimate was conducted as the goal is to primarily enroll into the interventional arm and that heterogeneity of therapeutic approach may exist.

Secondary clinical efficacy endpoints are identical in both STAR-too and STAR-ter with addition of monitoring for small-colony variants *S. aureus* as a potential effect of repeat use of TMP-SMX. See **Table 3** for all secondary endpoints (clinical and microbiologic).

Adverse events will be monitored per standard research protocols [28]. Compliance and Adherence will be defined as the proportion of subjects with >80% compliance for study drug during the first 28 days.

Analyses of secondary endpoints will be descriptively summarized by study arm with corresponding 95% confidence intervals and tested using a two-sided 0.05 level chi square test. Time to first exacerbation over the 6-month study will be graphically displayed for each treatment group using Kaplan-Meier estimates, and a corresponding hazard ratio will be estimated using Cox proportional hazards regression. Longitudinal analyses for changes in lung function and weight will be done using longitudinal linear regression models to estimate differences between study arms. We will also do a stratified analysis by highly effective modulator therapy (HEMT) (ivacaftor or elexacaftor/tezacaftor/ivacaftor) to address changes in CF therapeutics. Although this analysis is not part of the a priori statistical analysis plan, it will be of interest to the community.

All descriptive statistics will be completed as done in STAR-too, with two additions. STAR-ter will also collect and analyze data on household member culture results, and small colony variant rates. A two-sided p value of less than or equal to 0.05 will be considered significant.

Sample size estimate

The STAR-too trial led to 82% of subjects with incident MRSA being MRSA negative at Day 28 as compared to 26% of those who receive standard of care (observation only) (56% treatment difference, 95% CI: 23% to 80%). The primary aim of STAR-ter is to determine whether a streamlined eradication protocol will produce comparable microbiologic efficacy at Day 28. Assuming that the streamlined treatment will be comparable at 80%, a sample size of 42 subjects leading to at least 38 evaluable patients will provide estimation of the proportion of subjects negative for MRSA at Day 28 to be 82% (31/38) with precision quantified by a confidence interval ranging from 66% to 92%. If we observe an 82% rate of success (31/38), then compared to the rate in STAR-too (82% [61,93]%), the 95% C.I. for the difference would be [-22, 19]%. Based on an estimate 10% attrition rate the study aims to recruit 42 subjects.

The lower bound of this confidence interval (66%) does not rule out non-inferiority to the aggressive MRSA eradication protocol and but would demonstrate superiority to the STAR-too observational control; the lower bound includes a range of values to be considered efficacious for administration of the treatment protocol.

Discussion

Research on early MRSA infection treatment for the CF population is limited, yet data support the importance of early intervention [29] [30]. The lack of any guidance in the U.S. leads to uncertainty and variation in treatment especially in patients who are asymptomatic at time of MRSA positive culture [31-33]. Therefore, further data are necessary to inform practice. Our initial MRSA eradication trial (STAR-too) provided data to support the need for a standardized approach to early MRSA intervention. However, STAR-too used a complex treatment and raised concerns for tolerance and drug interactions with rifampin. Case series report successful eradication of MRSA in CF with combination therapies of rifampin and fusidic acid [13, 14], yet given the side-effect profile, the fact that incident infection may require less intense therapy and to simplify the regimen we now test a single oral agent while keeping mucosal topical therapies the same. Such a simpler approach would increase patient adherence and allows a repeat cycle of therapy. However, research into rare disease populations can have reduced enrollment rates which affect the feasibility of randomized clinical controlled trials. Our prior trial required 11 study sites and 3.5 years for randomizing 47 participants. This is a known challenge in rare diseases. A search of ClinicalTrials.gov showed that 30% of trials in rare diseases conducted between 2010-2012 were discontinued with insufficient patient accrual being cited as the most frequent reason [34].

We thus take a novel approach to address low enrollment by using the placebo group from the previous randomized trial, STAR-too, as a comparator group thus allowing for lower enrollment rates while maintaining a clinical trial approach that includes a control arm. Schedule of events, study sites, and inclusion and exclusion criteria are highly similar between the studies. The differences being that STAR-ter has an expanded age (youngest age 2 instead of 4 years) group to increase generalizability. The unique trial design of STAR-ter allows us to further develop a treatment protocol for incident MRSA infection for CF patients. Increased interest in novel study designs also occurred by regulatory agencies in recent years with study designs aiming to minimize subject numbers yet providing rigorous results [35, 36]. Such trial designs may include n=1 design, cross-over trials or adaptive randomizations. None of these would be well suited to our outcome where the goal is to achieve continued eradication. These trial designs also emphasize the focus on continuous outcomes which is at odds with our dichotomous primary outcome.

The CCCCA further increases the size of the population to compare potential changes in baseline characteristics over time. Additionally, this pragmatic, observational approach contributes to understanding current clinical practices, which may be informative in regard to attitudes towards early treatment and preferences in medications. Results will need to be interpreted cautiously as those subjects are drawn from the same study sites limiting the generalizability.

External controls are being cautiously discussed by FDA, with emphasis however on the external control being as closely matched to the study population as possible, minimizing bias and having objective outcomes. We maximized these conditions as much as possible here. One limitation that was not foreseen at time of study design was the introduction of novel, better tolerated and highly effective cystic fibrosis transmembrane conductance regulatory (CFTR) modulators. This will potentially affect underlying disease severity in our population. On the other hand, STAR-too subjects were children with preserved lung function (3% had a $FEV_1 < 75\%$). The effect of CFTR modulators on microbiology and infections is still under investigations with several studies showing persistence of the patients' prior organisms [37, 38].

There are several key strengths and weaknesses to our approach. The strengths include marked improved feasibility to complete the study due to lower enrollment requirements. Another key strength is that our primary endpoint is objective and easy to assay. *S. aureus* is not a fastidious organism and does not require a lower airway specimen to understand its clinical implications. As for this study, our prior study accepted any respiratory source of *S. aureus*. In addition, a central laboratory will ensure confirmation of methicillin-resistance using CF culture guidelines. The weakness of our approach is that it cannot fully account for temporal changes in MRSA spontaneous clearance rates, e.g. with increased use of HEMT. The advent of HEMT may have unanticipated impacts on the study. This could be in part due to reduced sputum production in those with established CF lung disease. Recent data however notes that changes in microbiology may be more limited with HEMT that initially anticipated [39]. Our sensitivity analysis will be able to explore these effects. Our CCCCA analysis could provide data to assess enhanced clearance as a potential confounder and will also provide a comparator to use of anti-MRSA antibiotics prior to Day 28 as had occurred in several subjects previously. We will also not be able to fully address selection bias if the STAR-ter trial population is different in meaningful way (disease severity or age). We can create age and disease severity strata but this will not fully address this weakness.

In conclusion, we describe here an innovative approach to addressing a clinical question in a rare infection in an orphan disease, CF. Our study will support the current clinical evidence guiding CF care in relation to new MRSA infection and is designed with a focus on feasibility.

Table 1. **Similarities and Difference between STAR-ter and STAR-too Protocols**

	STAR-ter	**STAR-too**
Study Sites by Region	West: 2 Midwest: 6 South:1 North East: 0	West: 2 Midwest: 6 South: 3 North East: 0
Eligibility Age	**STAR-ter eligible age: ≥ 2 - ≤ 45**	**STAR-too eligible age: ≥ 4 - ≤ 45**
Drug Cycle	14 day oral antibiotic treatment cycle 14 day wash out period **Repeat treatment cycle***	14 day oral antibiotic treatment cycle
Primary endpoint	The proportion of subjects with MRSA eradicated from respiratory tract cultures at day 28 compared to the placebo arm in STAR-too.	The proportion of subjects with MRSA eradicated from respiratory tract cultures at day 28 compared to the placebo arm.
Inclusion	Incident or ≤ 2 positive MRSA cx	Incident or ≤ 2 positive MRSA cx
Exclusion	Receiving oral or IV anti-MRSA antibiotics within 28 days MRSA resistant to study drug Patient allergic to any of the study medications Abnormal renal of liver function or FEV_1 < 25% predicted Pregnancy, lactation or not using barrier-contraception. s/p transplant.	Receiving oral or IV anti-MRSA antibiotics within 28 days MRSA resistant to study drug Patient allergic to any of the study medications Abnormal renal of liver function or FEV_1 < 25% predicted Pregnancy, lactation or not using barrier-contraception. s/p transplant.

Footnotes: Text in bold highlights differences between studies. ***** This repeat cycle occurs past the primary end-point thus no direct comparison to STAR-too placebo will be done. Cx = culture.

Table 2. Study Intervention STAR-ter and STAR-too

Drug	**STAR-ter**	**STAR-too**
Oral trimethoprim-sulfamethoxazole (TMP/SMX)	Body weight <40 kg: 8mg/kg TMP/40mg/kg SMX; BID x 14 days. BW ≥ 40 kg 320mg/1600mg BID x 14 days.	Body weight <40 kg: 8mg/kg TMP/40mg/kg SMX; BID x 14 days. BW ≥ 40 kg 320mg/1600mg BID x 14 days.
**Oral minocycline (if TMP-SMX allergy)	<50 kg : 2 mg/kg orally BID x 14 days; if ≥ 50kg 100 mg BID x 14 days	<50 kg : 2 mg/kg orally BID x 14 days; if ≥ 50kg 100 mg BID x 14 days
Oral rifampin	none	< 40 kg : 7 mg/kg (range 5-10mg) orally BID x 14 days. ≥ 40 kg: 300 mg BID
Nasal Mupirocin 2%	Apply into each nostril twice daily for the first 5 days	Apply into each nostril twice daily for the first 5 days
Oral Gurgle (0.12% chlorhexidine gluconate wash)[1]	Oral rinse twice daily for 14 days	Oral rinse twice daily for 14 days
Chlorhexidine 2% body wipes	none	Once daily for initial 5 days.

Footnotes: [1] for subjects old enough to gurgle.

Table 3: ***Secondary Clinical Endpoints***

Endpoint	**Descriptive details**
Pulmonary exacerbations (PEx)	Proportion of subjects with protocol defined Pex[1] overall and between Day 0 and Day 28. Number of PEx. Proportions of subjects receiving any additional antibiotics. Time to first PEx.
Patient reported outcomes	CFQ-R[2]; CFRSD; CRISS[3]
Other clinical endpoints	Change in forced expiratory volume in one second (FEV_1) from baseline to end of study. Change in weight and percentile from baseline to end of study.
Microbiology endpoints	Proportion of subjects who are negative at Day 28 and remain MRSA negative and/or are MRSA negative at 3 months and 6 months. Proportion of MRSA isolates developing resistance to any study medication. Emergence of *P aeruginosa* infection.
Adverse events	Frequency, by body system and severity.
Microbiologic adverse events	Emergence of small colony variant MRSA[4]

Footnotes: [1] per modified Fuchs criteria [40] [2] CF Quality of Life – Respiratory Domain symptom score. [3] CF-Respiratory Symptom Diary - Chronic Respiratory Infection Symptom Score. [4] differs between STAR-too and STAR-ter.

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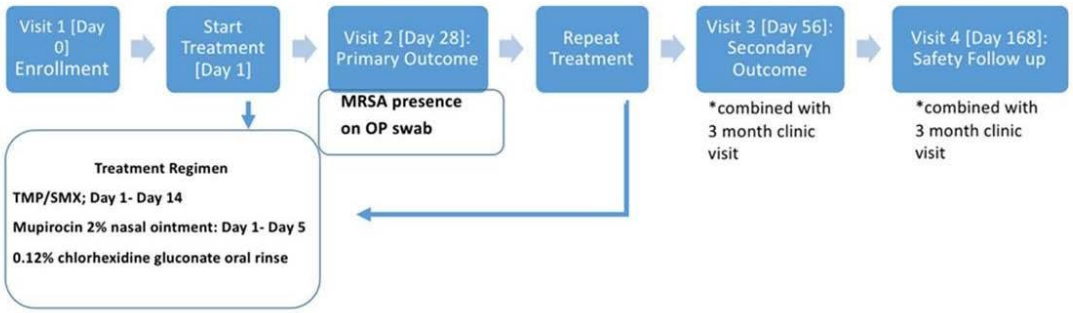
Figure 1


Visit 1 [Day 0] Enrollment
Start Treatment [Day 1]
Visit 2 [Day 28]: Primary Outcome
Repeat Treatment
Visit 3 [Day 56]: Secondary Outcome
Visit 4 [Day 168]: Safety Follow up
MRSA presence on OP swab
*combined with 3 month clinic visit
*combined with 3 month clinic visit
Treatment Regimen
TMP/SMX; Day 1- Day 14
Mupirocin 2% nasal ointment: Day 1- Day 5
0.12% chlorhexidine gluconate oral rinse