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Impact of eligibility criteria on participant enrollment for a randomized clinical trial of gonorrhea treatment

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Abstract

Background—High rates of failure to qualify for clinical trial participation increase time and cost required for study completion. Identification of remediable reasons for prescreen failure can help reduce prescreen failure rates and improve study cost effectiveness.

Methods—Reasons for prescreen failure to qualify for participation in a Phase 2 randomized clinical trial of treatment of uncomplicated urogenital gonorrhea were collected from prescreening logs. Reasons were categorized based on whether the reason was that the subject failed to meet eligibility criteria or declined participation. Subjects who failed prescreening but could have been enrolled under protocol amendments were used to estimate potential cost savings had enrollment completed sooner.

Results—Over 88% (1373/1554) of potential study candidates were not enrolled. The majority (68.8%) of non-enrolled subjects failed prescreening due to not meeting eligibility criteria, whereas 31.0% declined to participate. The most common reasons for failure to qualify were having only non-urogenital gonorrhea (16.4%), limited time (13.1%), and being on antiretroviral therapy (7.5%). Potential cost savings if protocol amendments affecting eligibility had been instituted earlier were estimated at \$127,500.

Conclusions—Careful attention to reasons for prescreen failure can inform clinical trial protocol development to address trial design features that may impact successful enrollment. More efficient subject enrollment can result in substantial cost savings.

Keywords

prescreen failure; eligibility; gonorrhea trials

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Declaration of conflicting interests

The authors have no conflicts of interest to declare.

Introduction

Neisseria gonorrhoeae (NG) infections are the second most common bacterial sexually transmitted infection (STI) worldwide (1). NG readily develops resistance to antibiotics, and in 2013, the Centers for Disease Control and Prevention (CDC) listed drug-resistant NG as an “Urgent Threat” to public health (2). The development of new antibiotics to combat drug resistant NG is one of the goals of the 2015 National Action Plan for Combating Antibiotic-Resistant Bacteria (3).

Clinical trials are essential and resource intensive steps for development of new therapies for gonorrhea and other STIs. Eligibility criteria for clinical trials directly impact the generalizability of study findings, the pace of study progress and study costs but often are not reported. In a recent trial of a new drug for gonorrhea treatment, we collected data on potential candidates for study enrollment and found that over 88% of potential participants could not be enrolled for a variety of reasons. While reports from clinical trials of cancer treatments cite non-enrollment rates of 63–82% amongst potential study candidates (4–5), no previous studies have reported on the enrollment rates or reasons for prescreen failure from a STI clinical trial. Discussions with other investigators suggest that relatively low enrollment compared to potential enrollment levels is not uncommon in gonorrhea treatment trials however. We now provide data on reasons for failure to enroll potential study participants and the impact of protocol amendments on the screened to enrolled ratio with the goal of assisting future investigators in the design of STI treatment trials.

Materials and Methods

These analyses utilize data from prescreening logs describing participant inclusion/exclusion criteria prospectively collected as part of a Phase 2 randomized clinical trial comparing treatment of uncomplicated urogenital gonorrhea with ceftriaxone to an investigational antibiotic (ClinicalTrials.gov Identifier: NCT02257918). The study intended to enroll 180 subjects from five Sexually Transmitted Disease (STD) Clinics. Study staff approached patients being seen for gonorrhea treatment to discuss potential enrollment in the clinical trial. Staff conducted “prescreening” to ascertain eligibility and interest in trial participation prior to seeking formal informed consent and completing enrollment. Study staff recorded reasons for prescreen failure via free text each week. The prescreening logs included all known reasons for prescreen failure but did not list each reason for prescreen failure by potential study candidate. No demographic data were recorded on subjects who failed prescreening because information on prescreen failure was collected prior to obtaining informed consent for study participation. The data were intended to inform whether specific eligibility criteria or trial features were impeding enrollment and not designed for analysis a priori.

Over the course of the study, the study team implemented two protocol amendments to address specific issues thought to negatively impact successful enrollment. One amendment eliminated a blanket exclusion of persons with HIV from study participation initially present because of concern for potential drug-drug interactions with anti-retroviral medications and the new therapeutic under investigation. A second amendment addressed the fact that the

protocol initially excluded all subjects who had received any antibiotics within 30 days of enrollment. This amendment changed the protocol to exclude only subjects who received antibiotics with activity against NG within 30 days, allowing subjects who recently had received metronidazole to be enrolled.

The authors reviewed prescreening logs to tabulate reported reasons for prescreen failure for each clinical site. Reported reasons for prescreen failure were categorized based on whether the exclusion was related to the subject not meeting eligibility criteria or to declining participation, as listed in Table 1. The authors enumerated and tabulated each reason for prescreen failure and the three types and categories within each type by week both overall and by clinical site.

To calculate potential time and cost savings if protocol amendments had been instituted sooner, we counted subjects whose reason for prescreen failure was subsequently addressed in an amendment, i.e. HIV status or having received metronidazole, towards an enrollment on the date that the protocol amendment was approved at the respective site. Using these data we calculated the date on which 180 enrollments would have been met based on adding the “missed” enrollments related to amendments to the actual weekly enrollment numbers. We based the estimate of additional days required to complete the enrollment period on the time from this earlier date until the date enrollment actually completed.

The funding for the trial was based on a contract awarded to the University of Alabama at Birmingham in 2014 totaling \$1,255,296 (NIAID Contract No. HHSN2722013000121-HHSN27200003). The cost for the recruitment, enrollment, and follow-up period was estimated to amount to approximately \$850,000 of the total award, to be completed in 496 days. The percentage of the contract amount that could have been saved from an earlier completion of enrollment date was calculated.

IRB review of the current analyses was not required as the research involved study of existing data that was not individually identifiable, in accordance with 45 CFR 46.101(b)(4). Statistical analyses were performed using RStudio (version 0.99.896, RStudio, Inc., Boston, MA).

Results

Of 1554 potential subjects considered for enrollment, 181 (11.6%) were enrolled (one screen failure) and 1373 (88.4%) were not enrolled due to elimination during the prescreening process (Figure 1). Among the non-enrolled subjects, 48 reasons for prescreen failure were documented including two subjects with unknown reasons for prescreen failure. The most common reasons for prescreen failure were having only non-urogenital (pharyngeal or rectal) gonorrhea (16.4%), limited time for study participation including return visits (13.1%), and being on antiretroviral therapy (for HIV or Pre-exposure prophylaxis (PrEP)) (7.5%). The majority (68.8%) of non-enrolled subjects failed prescreening due to not meeting eligibility criteria. The most common exclusion categories included not meeting the case definition (22.4%), having required or received additional antibiotics (17.7%), and HIV (8.5%). Thirty-one percent of prescreen failures declined to participate. The categories of

reasons for declining to participate included time constraints (18.4%), personal concerns (8.2%), and trial concerns (4.3%).

The total prescreen failure rates were driven by the site with the largest number of prescreened subjects (Site 5). Overall, the enrollment rate per subject prescreened was 11.6% (181/1554). As depicted in Figure 2, the enrollment rate per site varied from 8.5% (12/141) – 28.8% (46/160). The enrollment rate at Site 2 was significantly higher than the rate at the other sites ($P < 0.001$).

The number of subjects that failed prescreening related to protocol amendments included 14 persons with HIV and 14 who had recently received metronidazole. Incorporating all of these subjects to the weekly enrollment totals would have resulted in a revised date of reaching full enrollment 74 days sooner than the actual date when enrollment completed. Additional trial costs related to the later enrollment completion date were estimated at \$127,500 (\$129,606 adjusted to 2016 dollars), 15% of the amount estimated for the recruitment, enrollment, and follow-up period (6).

Discussion

Approximately two-thirds of prescreen failures did not meet eligibility criteria and one-third declined study participation. Of the subjects that did not meet eligibility criteria, approximately one-third did not meet the case definition for urogenital gonorrhea and one-fourth required or had received additional antibiotics. Careful consideration of the case definition and other eligibility criteria should be made to ensure that they are as broad as possible to capture potential subjects with the condition of interest. For example, with 16.4% of prescreen failures failing due to only having non-urogenital gonorrhea, the enrolled subject population may represent a different sexual risk profile than the overall population with uncomplicated gonorrhea. However, including subjects with extra-genital infections only presents an additional burden regarding potentially lower cure rates of pharyngeal and rectal infections and regulatory requirements for demonstrating microbiologic cure. Some exclusions, like having taken antibiotics with activity against NG within 30 days, are necessary to protect the integrity of study outcome measures. Others, like HIV infection, likely have no impact on outcomes of gonorrhea treatment. Since gonorrhea rates are currently higher in persons with HIV compared to the general population, understanding treatment outcomes in this population is particularly important. Age restriction for STI treatment trial participants is complicated as rates of most STIs are highest in adolescents; yet additional justifications and safeguards are required for clinical research involving minors. Given that over half of the potential subjects who declined to participate cited time constraints, streamlining the time required the informed consent process and for study procedures may also aid in successfully recruiting study subjects.

Our interpretation of the impact of protocol amendments on enrollment rates is limited by the assumption that potential subjects who failed prescreening for a reason related to a protocol amendment met all other eligibility criteria and would then have agreed to participate in the trial.

The prescreen failure data reported here is subject to several limitations. Some of the reasons for prescreening failure are subjective (e.g. subject did not have time) and are limited by the patient's honesty in disclosing his or her reason for not wanting to participate. As the reasons for prescreen failure were entered by free text, there was some interpretation required to categorize and collate the listed reasons. The prescreen failure data would have been more informative had demographic information been collected along with the reason for prescreen failure and if the data had described whether a study candidate had multiple reasons for prescreen failure.

The majority of the limitations of this study are due to the fact that the prescreen failure data was not designed a priori for analysis. Formalizing the collection of prescreen failure data, e.g. using prepopulated dropdown menus or pre-determined lists of reasons for prescreen failure, may aid in gathering more precise data to inform researchers as to clinical trial features that most significantly impact successful enrollment.

This study highlights the importance of careful attention to the eligibility criteria and time involved in participation in STI clinical trials to maximize successful enrollment and cost effectiveness. Prescreen failure rates of 88% may compromise larger scale trials required for Phase 3 pivotal clinical trials. At this prescreen failure rate, a Phase 3 trial in the range of 500 subjects would require prescreening more than 4,000 potential study candidates.

Including HIV infected subjects in STI clinical trials and only excluding subjects based on antibiotics that would interfere with the interpretation of study endpoints should be considered for these types of trials. Attention to these factors may have an important impact on overall study costs and timely completion of clinical trials required to bring new antimicrobials to market.

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Figure 1.
Disposition of Study Candidates

Figure 2. Enrollment and Prescreen Failure Numbers by Site and Total

The ratio of enrolled to prescreened subjects at each site is represented at the top of each bar. The enrollment rate at Site 2 was significantly higher than the rate at the other sites ($P < 0.001$).

Table 1

Type 1: Not eligible for study	
Categories	
Age restriction	
Antibiotics within 30 days	
Did not meet case definition (for example, non-urogenital or complicated gonorrhea)	
HIV	
Informed consent barrier	
Medical Exclusion (for example, subject on chemotherapy)	
Operational (for example, subject previously enrolled or no drug available)	
Requires additional antibiotics	
Safety Exclusion (for example, prohibitive allergy, pregnancy, or no birth control)	
Type 2: Declined participation	
Categories	
Personal concerns (for example, not reliable, too upset about gonorrhea diagnosis, or not interested)	
Time constraints	
Trial concerns (for example, declined rectal swabs, concerned about investigational drug, or did not want blood drawn)	
Type 3: Unknown/other	