Site Enrollment Success: Mixed Methods Evaluation and Modeling of an FDA-Approved Phase III Chronic Obstructive Pulmonary Disease Trial

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By

Raolat Abdulai, M.D.

Masters in Medical Science Candidate

ABSTRACT

The United States (U.S.) FDA mandates the use of multi-phase clinical trials to elucidate important information on drug safety and efficacy prior to approval and marketing. Since the Kefauver-Harris Drug Amendments of 1962, increasing regulations have focused on the mechanism by which these trials are conducted. Given the requirements for clinical trials, particularly randomized controlled trials, an expansive clinical research industry has emerged, led by contract research organizations (CROs). Consequently, by most estimates the cost to bring a drug to market is at least $2 billion, while the U.S. annual gross research and development (R&D) expenditure is approximately $400 billion and growing. A significant portion of these costs are due to site operations—site initiation activities (including IRB approval) and subject recruitment, amongst others. Despite these investments, the success rate is 11.8% and 13.4% for all new drugs and respiratory (COPD) drugs, respectively. Respiratory drug development is specifically challenging due to the increasing prevalence of diseases such as COPD and the complexities of inhaled therapies. Despite the prohibitive cost of such trials and low drug approval success rates, there are few publications or analysis of the metrics associated with the clinical trial process, or its' operational results and outcomes. Our study hypothesized that a mixed methods approach coupled with mathematical modeling can effectively analyze and produce evidence quantifying known and identifying unknown problematic operational steps which can then be used to develop probabilities for site enrollment success. An initial qualitative analysis revealed recruitment and study start up delays to be a common factor for concerns in clinical trials. Using data from a Phase III COPD study, we derived a model that includes the factors identified including season, site start-up timing, and competition from other COPD studies. This model allowed us to predict an important operational metric, site enrollment success, which can be incorporated into pre-trial planning utilizing simple clinical informatics tools.

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IMPORTANT ABBREVIATIONS AND DEFINITIONS

Abbreviations

AIC: Akaike Information Criterion
amonths: Active months
ARO: Academic contract research organization
COPD: Chronic obstructive pulmonary disease
CRF: Case report form
CRO: Contract research organization
DLSO: Days from first to last subject out (completed)
DSSI: Days between first subject to second subject in (enrolled)
DSSR: Days between first subject to second subject randomized
EDC: Electronic data capture
EHR: Electronic health record
EHR4CR: Electronic Health Records 4 Clinical Research
EU: European Union
FDA: Food and Drug Administration
FEV_1: Forced expiratory volume in 1 second
fsfailed: First screen failed subject
FSI: First subject in (enrolled)
IRB: Institutional review board
LSO: Last subject out
PSM: Patients per site per month
R&D: Research and Development
RCT: Randomized controlled trial
SFR: Screen failure rate
tmonths: Total months

Definitions

Clinical operations: Group (usually in pharmaceutical company) who executes the clinical project plan developed by the clinical study team; works closely with CROs

Clinical study/development: Group (usually in pharmaceutical company) who originates the project; involved in developing the clinical plan, study protocol, informed consent, and investigator brochure, amongst other tasks

Phase I: First-in-human or "first in man" trials, small studies that test for safety and usually performed in healthy volunteers

Phase II: Test for safety and usually performed in diseased population, efficacy also evaluated

Phase III: Large scale studies in diseases population that tests for safety, efficacy, and comparative efficacy

Phase IV: Post-marketing surveillance/observational studies, assessment of long term safety

Run-in: Period following enrollment and prior to randomization, allotted to further measure a study participant's eligibility and commitment to a study; to ensure that all subjects are clinically stable, non-study medications are adjusted or discontinued, and baseline lab & spirometric measurements are collected

Sponsor: Pharmaceutical company

Wash-out: Period during which subject stops use of either their regular medication (during run-in) or stops use of the experimental drug (end of trial treatment period) and "return to their baseline clinical state" including restarting their regular medications

INTRODUCTION

Clinical trials are complex exercises in the scientific, regulatory, and statistical processes that govern drug development. Initially meant to improve the safety and efficacy of pre-market medicines, clinical trials are now used for extensive post-marketing analysis and medical device development [1]. The number of trials registered on ClinicalTrials.gov have steadily increased over time. In 2010, approximately 83,400 studies were registered on the site, compared to the over 240,000 trials listed as of March 2017 [2]. While these findings may represent passage of the several legislative acts coupled with pre-publication disclosure requirements [3, 4], there is agreement that the number of clinical trials produced are on the rise [5]. Studies conducted as clinical trials for medicines in the U.S., regardless of listing on ClinicalTrials.gov, must ultimately provide results that meet the drug development standards of the Kefauver-Harris Drug Amendments passed in 1962 [6-8]. Thus, in addition to having a clearly stated objective and a good design, a well-controlled trial must also have methods for patient/subject selection, treatment assignments of patients/subjects with minimal bias, and measurement of an outcome [6].

To meet the standards put forth by the FDA, many of these drug studies must be outsourced to contract research organizations (CRO). CROs are tasked with conducting efficient clinical trials at the request of the pharmaceutical company (hereafter referred to as "Sponsor") or researcher [9]. The CROs are deeply involved in the current operation of clinical trials. Key operational components of a clinical trial include site start-up (i.e., site selection, protocol development, IRB approval), recruitment (i.e., enrollment, randomization, retention), data collection, and sample storage, amongst others [10]. In addition, these organizations often control the study site locations, facilitate contractual agreements between the Sponsor and site investigators, oversee institutional review board (IRB) interactions, and manage the study operational data output [9]. In fact, the CRO industry has grown from $10 billion in 2005 to > $25 billion in 2013, representing a large portion of the annual expenditures in the pharmaceutical industry [9]. Some

conclude that CROs may contribute to the structural inefficiency and lack of innovation seen in modern clinical trials [9, 11].

Drug development in chronic obstructive pulmonary disease (COPD) is not immune to the rigors of the FDA nor the complexities of the CRO system. COPD is a respiratory disease associated with smoking and biomass exposure which has an increasing worldwide prevalence, particularly in developing countries with emerging economies [12, 13]. Over a 20-year period, 1990-2010, there was a 68.9% increase in the worldwide prevalence of COPD [12]. In fact, for developed countries like the United States, the financial burden of COPD is high, costing an estimated $38.8-49.9 billion annually [14, 15]. While there may be new markets for COPD drugs, innovative treatment options are partly limited by the costs of drug development. These costs make it difficult to develop drugs for advanced stages of the disease, such as biologics and triple drug inhalers [14, 16, 17]. While current respiratory literature has focused on clinical outcomes, our work represents an evaluation of the operational results of an FDA-approved COPD study and predictive modeling of the site enrollment process.

The specific aims of our study were to: 1) conduct a diagnostic analysis of a clinical trial to identify and quantify operational barriers to the success of the trial, 2) develop a predictive model of barriers encountered in the clinical trial, and 3) use those quantitative differences to suggest adjustments to the optimal operational model for more effective clinical studies. To achieve these aims, we first completed a qualitative evaluation of the operational barriers in COPD drug development through semi-structured interviews of clinical research personnel at a multinational Sponsor. Then a diagnostic analysis of the complexities of an example Phase III COPD multinational clinical trial was performed using a dataset from the Sponsor. Each site and country was assessed for their operational trajectory and contribution to the study's overall success. To develop a model which quantifies the barriers and demonstrates the most important components to consider prior to study execution, we compared the actual operational outcome of the study to the pre-trial projected outcomes. These observations allowed us to determine the important

factors required in a model that addresses the operational efficacy of a COPD study. The use of similar models imbedded within existing informatics tools may facilitate effective planning and begin to address costly operational mistakes observed in COPD drug development.

BACKGROUND

The FDA regulates food, drugs (including biologics), medical devices, radiation-associated electronic devices, cosmetics, tobacco products, and alcohol amongst others [1]. The forerunner to the current FDA, the Division of Chemistry, was first created in 1862 under the presidency of Abraham Lincoln [1, 6-8]. This organization was later divided into two, where the FDA eventually became the regulating body we know today [8]. Since 1938, with the adoption of the Federal Food, Drug, and Cosmetics (FDC) Act, drugs have had to be proved safe for use prior to consumer marketing [1, 8]. Before the FDC was passed, untested drugs killed Americans at an alarming rate [1]. In fact, it was in response to the thalidomide tragedies that one of the most significant laws in drug development was passed—the Kefauver-Harris Drug Amendments of 1962. Thalidomide was a sedative used by expectant mothers, mostly in Europe and Japan, for morning sickness [7, 8, 18]. Unfortunately, it had the adverse effect of causing severe birth defects, most notably limb deformities. The Kefauver-Harris Drug Amendments required that companies prove efficacy in addition to stronger drug safety evaluations [1, 7, 8]. This law also ushered in the era of the randomized controlled trial (RCT) as the gold standard for drug development [8, 18]. RCTs required large number of patients, including a control group, to control for bias and error while meeting sample size requirements for the desired endpoint. Consequently, the high cost of such large, extensive studies likely contributes to the complex clinical trial industry seen today [18].

The requirements for drug approval outlined by the FDA, in addition to the adoption of the RCT, eventually led to the formation of the complicated three phase study structure [8, 19]. Phase I trials are the

"First In Man" studies which evaluate safety and dosing range (generally in healthy volunteers), but only after adequate animal toxicology studies have been completed. Phase II studies are used to determine safety *and* efficacy in healthy volunteers and/or patient populations. Phase III studies are even more complex trials for which long-term safety and efficacy are evaluated, requiring hundreds or even thousands of study subjects to meet an FDA-approvable endpoint. Finally, Phase IV studies are performed after drug approval to assess for potential safety issues [8, 19]. The significant number of studies and regulatory requirements for a new drug application (NDA) in effect led to the development of large, multicenter trials [6] and eventually a market for CROs [9]. Despite thousands of trials performed by various Sponsors, government entities, and academic researchers each year, little data was shared about these studies until 20 years ago. The FDA Modernization Act of 1997 (and later the FDA Amendments Act of 2007) provided additional guidance on the appropriate conduct of research and reporting of clinical trials [7, 20-22]. Fortunately, the FDA Modernization Act laid the groundwork for development of ClinicalTrials.gov, a web-based repository of regulatory-approved clinical studies from around the world [23, 24].

As noted earlier, to prove efficacy in controlled studies, a trial requires large sample sizes for the targeted endpoint. A solution to this issue has been the use of multicenter studies—trials with several investigators or clinics following a "common protocol with a common objective" [6]. Multiple center studies allow for accrual of large numbers of patients to meet these common objectives and demonstration of efficacy in a well-controlled setting. A center is defined as a unit which consist of a site or an investigator and sometimes a region [6]. Sites are usually chosen based on feasibility which includes, but is not limited to, the ability of the site to perform study related tests and the prevalence of the disease in the site location [10]. Also important are relationships between the site and study Sponsor, which may be based on previous trial experiences at the site. Sites can be evaluated using metrics such as cycle time, timeliness, efficacy, and quality [10]. Cycle times are the period from one event to another, such as from IRB approval to first enrolled subject. Timeliness refers to the completion of tasks in general, such as when a

site completes a budget evaluation [10]. Timeliness and cycle time are indicators of site efficiency and resources utilization. Finally, site quality metrics focus on the result of the tasks performed at the site, such as the number of enrolled subjects and the *appropriateness* of the subjects for the study [6, 10, 25].

Despite potential benefits of multinational multicenter studies, the results of such trials can sometimes fall short of expectations [10]. For instance, these trials can be costly due to the sheer number of sites and regulatory requirements across different regions and countries [10, 25-27]. In fact, the cost of drug development itself has skyrocketed in recent years [5, 28]. The estimated cost to bring a new drug to market is estimated between $161 million to approximately $2 billion with a timeline of over 7.5 years for clinical studies [5, 28]. Respiratory drug trials are one of the most expensive, costing an estimated $115.3 million per study [28]. Due to the chronicity of most respiratory diseases, longer treatment periods and event-centered endpoints (i.e., time to exacerbations) are required to prove safety and efficacy [14]. Therefore, respiratory clinical trials utilize larger sample sizes and are typically multicenter and multinational.

COPD, the focus of this scholarship, defined as persistent air flow obstruction due to chronic bronchitis or emphysema, is one area of respiratory drug development in need of newer therapies [29]. Symptoms include shortness of breath, increase in phlegm production, cough, and wheezing. COPD is associated with high morbidity including loss of function leading to decline in independent activities of daily living, cachexia, and eventually death. Despite aggressive management of the disease exacerbations are not infrequent. COPD exacerbations are defined as a change in COPD symptoms which require a change in medication, an ED visit, or hospitalization, are frequent and contribute to morbidity [30, 31]. The global prevalence of COPD is around 11.7% [12] with range of 6% (self-reported) to almost 20% (Uruguay) [29, 31]. Over the years many treatment modalities have been developed for COPD, however, the primary treatment for this illness are inhaled bronchodilators [29]. In addition to bronchodilators, inhaled and oral

corticosteroids, oxygen therapy, and pulmonary rehabilitation are being used to manage the disease [29, 32].

As mentioned above, one of the challenges faced by respiratory disease trials including those involving COPD patients, are the chronic nature of the disorders [28]. In fact, for COPD trials, the FDA recommends treatment periods of at least 3 months to 3 year treatment, depending on the ultimate clinical trial endpoint [33]. Further, inhaled drugs, are difficult to develop due to specific requirements for drug molecular weight and lipophilicity [34]. Even when a drug is developed, the clinical trial success rate (ability to advance from Phase I to market) for COPD drugs is only 13.4%, meaning approximately 6 out of 7 drugs will fail [14]. Given the challenges of COPD drug development couple with low success rates, it is imperative to strive for efficient and effective studies in this therapeutic area by understanding the how operational barriers effect outcomes.

As outlined in the introduction, the operational aspects of clinical trials are largely handled by CROs. Important operational tasks of a clinical trial include protocol development, IRB submission and approval, and study recruitment. There are few examples of studies evaluating the enrollment operational outcome of a clinical trial [10, 26, 35] and yet the Institute of Medicine (IOM) has identified clinical trial operations as an area in need of "disruptive innovation" [11]. One notable exception was the assessment of sites participating in the Altair HIV study by Berthon-Jones and colleagues in 2015 [10], which performed a thorough analysis of the operational outcomes of each clinical trial site. The study found that median days from protocol release to site opening was 250 days (range 188-266), with longer times found in Europe. The authors proposed strategies for evaluating sites based on parameters such as cycle times and more effective use of the data collection system. Our study builds upon this example by using a large-scale COPD trial to develop a model that predict success in clinical trial enrollment based on known and unknown operational barriers, aiming to fill an important gap in clinical trials operations research.

METHODS

Qualitative Evaluation of the Planning and Execution of a Multicenter Multinational Phase III COPD Clinical Trial

Before commencing an extensive quantitative analysis on the operational efficacy of COPD clinical trials, and to ensure our scholarship was aimed appropriately, we performed a qualitative evaluation using semi-structured interviewing. We interviewed members of the clinical operations team, a medical director (part of the clinical study team), and a biostatistician (part of the clinical study team) at a large, multinational, Sponsor (Table 1). The interviews were conducted in both group and individual settings. As the clinical operations team members were located around the world, most of these interviews were performed via Skype™(video/teleconference). We will refer to a "study" as a group of clinical trials (and their entities) focused on the development of single drug.

Using open ended questions, we determined the extent of each participant's involvement in clinical trial operations, including number of years' experience. We asked a combination open-ended and discrete questions: "tell us about your last study," "what do you like least/most about clinical trials", "what areas need improvement", "what are the pain points in these areas." From these interviews, we developed a list of the main clinical trial 'pain points' according to each interviewee and arranged by role. Two common issue amongst all interviewees were patient/subject recruitment and site initiation. Recruitment is the process by which potential trial subjects are found and enrolled into the study. The site initiation ("start-up") period is a series of processes that occurs between the protocol approval and the declaration of site readiness to enroll subjects ("site ready"). This is often a period of significant delay due in part to contract negotiations and IRB evaluations, amongst others [27]. Poor recruitment, antiquated methods of recruitment, and complex trial eligibility (inclusion and exclusion) criteria, were the main pain points from the clinical operations team perspective. Strategies that the clinical operations team used to mitigate

recruitment issues include increasing the number of sites, increasing the payments for the investigators or subjects, or both. Similar methods were used for issues related to delays during the site initiation period, including increasing payments to the site and early activation of sites known for better enrollment based upon past performance. The medical director also felt that appropriate subject identification and stratification were significant concerns in clinical trials. Finally, the biostatistician related that statistical analysis of multicenter can be complex due to multiple levels of variability of each unique site utilized for the trial.

Using the results of our interviews, we developed a simplified process map which includes the activities, people, and outputs from the activities related to an FDA approved study from the perspective of a Sponsor (Figure 1). The process map starts during the planning phase of a clinical trial. The first activity is internal study approval (within the Sponsor or academic organization). The result of the study approval is a budget and initial working timeline, both of which can be modified further down the process. The second activity involves writing the protocol and informed consent form (ICF). This activity is completed by the clinical study team with support from the statistician and some input from the clinical operations team. The output is a final protocol which outlines the type of study, subject eligibility criteria, sample size, and endpoints (outcome measured). In addition, a completed ICF and other supporting documents such as the investigator brochure are generally completed at this point. The third activity is external, the regulatory approval process. The process in the United States involves the submission of the Investigational New Drug (IND) application to the FDA [36]. Outside of the U.S., there are various mechanisms for study regulatory approval. The fourth is site initiation, which includes finalizing the study protocol, site contracts (following pre-study site inspections and feasibility evaluations of the site), IRB approval, and site ready visit. Even after the regulatory body has approved the study, the protocol can be modified using the process of amendments which may require regulatory notification [37]. The site contracts and the IRB approval can be performed in parallel, as some countries have nation-wide IRB committees while others (like the US) have site specific- or regional IRB committees. The final output

from this activity is the declaration of site readiness as it marks the official start of the clinical trial at the site. The fifth activity is subject recruitment which results in accrual of study subjects, randomization to drug or placebo, and, eventually, study completion.

We presented this visualization to our interviewees to allow them to reassess their initial thoughts in the contexts of a process map. With this visualization, they reaffirmed their concerns regarding site readiness and subject recruitment as major pain points. However, there was additional consensus that the specifications of the study placed in the protocol (e.g., eligibility criteria) may contribute to these issues. Due to the heterogeneity of study protocol development process and the limited data we obtained for the quantitative stage of our evaluation, we focused our investigation on the non-regulatory post-protocol approval activities that lead to site readiness and enable subject recruitment (Figure 1).

Quantitative Evaluation of the Planning and Execution of a Multicenter Multinational Phase III COPD Clinical Trial

Step I: Search for appropriate data

As the qualitative evaluation was being completed, the quest began for an appropriate data source for the quantitative portion of the study. As stated earlier, operational data is often gathered and managed by CROs [38]. Academic institutions, if funding allows, can chose to work with academic CROs (ARO) which function similarly to industry CROs except for their expertise in the university system [39]. Therefore, it was important to find either a CRO that was willing to share this information or find a research study which was performed using in-house (non-CRO) resources to manage operational data. Several academic study groups specializing in respiratory diseases were approached for use of their operational data. The feedback from these academic institutions was that the partnering CRO/ARO either

did not keep significant operational data or that this data was unavailable for secondary analysis. For non-CRO studies, this data was not collected in a central location but rather in a series of proprietary databases, excel spreadsheets, or combination of both.

We then approached a large, multinational Sponsor for use of their operational data from a recently completed respiratory clinical trial. We identified several studies that was performed using in-house mechanisms, as the process of obtaining the data could be facilitated directly through the Sponsor. We found one COPD study that was recently completed and utilized this as our example study. The clinical operations and study teams from our qualitative analysis were not directly involved in this example study.

Step II: Understanding the COPD study

Our example study was a multinational multicenter, double-blind, Phase III COPD interventional trial. The goal of the study was to assess the effect of two types of inhalers, a new treatment and a control treatment, in COPD patients. The primary endpoint (outcome) was reduction in exacerbations. An exacerbation is defined by change in respiratory symptoms, medication usage, and/or use of health services (clinic visits or hospitalization). The final protocol for the study was approved on approximately April 1, 2014. The major inclusion criteria for this study was the diagnosis of COPD. The study consisted of a four-week run-in (period after enrollment and prior randomization) and a two-week washout (period following treatment completion) (Figure 2). The run-in period is a time "allotted to further measure a participant's eligibility and commitment to a study" prior to randomization to either treatment or control/placebo [40]. During the run-in period for this study, site clinical team ensures that all subjects are clinically stable, non-study medications are adjusted or discontinued, and baseline lab & spirometric measurements are collected. If subjects still meet the eligibility criteria at the end of this period, then they are randomized to a treatment group [41]. In the treatment period, the patient receives either the control inhaler or the treatment inhaler (or new therapy) for 26 weeks in total. During the two-week wash-out period (ending at Week 28), subjects "return to their baseline clinical state" [41] and any medications that

were stopped before the subject was randomized, are restarted. Subjects are also monitored for reversibility of the treatment effect and any potential adverse treatment effects [42, 43]. In terms of sample size, the study protocol recommended 1136 patients based on an assumption of a target reduction of 28% in rate of exacerbations, 0.6 exacerbations per subject years in control group, with a 90% power with 2.5% one-sided alpha and expectations of 10% subject attrition. The assumptions on exacerbation rate was also re-assessed by a blinded sample size review before recruitment was closed.

Step III: Creating an idealized timeline

Once we understood the structure and timeframe of our example clinical trial, we created an idealize timeline for a similar clinical trial (Figure 3). We developed this idealized timeline to understand the potential inefficiencies faced by our example COPD trial. The timeline also allowed us to visualize the pain points areas outlined earlier by the clinical operations team. Our estimates were partly based on findings from "The European Respiratory Society study on chronic obstructive pulmonary disease (EUROSCOP): recruitment methods and strategies" evaluation, a multinational, multicenter study which required 18 months for recruitment using only 20% of the sites in our example study [44]. In this idealized timeline, we placed a maximum of 5 months between the study protocol approval and the first IRB approval. We chose 5 months or 150 days based on our qualitative analysis. We placed a maximum of two months between the first IRB approval and the first site readiness declaration. We allowed for a maximum of one month between the site readiness declaration ("site ready") and the first subject in (FSI). Between the FSI and the last subject enrolled into the study, we felt that six months was sufficient time to recruit. The total study would run approximately 23 months, with 6 months dedicated to subject enrollment (Figure 3).

Step IV: Initial diagnostic analysis of complex phase III COPD multinational clinical trial

The operation data from the study was captured using Sponsor's proprietary software. The data was captured on three levels: site, country, and study. The study level components provided an overview of

the planning by the clinical operations and clinical study teams. Specifically, there was information on projected enrollment and recruitment into the study. The country level data provided similar analysis. Site level data included dates covering study enrollment, randomization, run-in, discontinuation, and completion. The data also included dates for the IRB approval, site readiness, and drug availability, amongst others. We made diagnostic plots for the total study reflecting monthly enrollment, randomization, and run-in. We performed the same evaluation for each country. In addition to performing a month by month analysis, we also assess the cumulative monthly rates of enrollment and randomization. For the purposes of analysis, we used cycle times rather than dates thus, allowing us to treat variables as either continuous or dichotomous (with a specified cut-off points). This also allowed us to assess any potential lag between major events within the trial. For instance, the time between IRB approval and FSI, was calculated and made into a cycle time. The same was done for the periods between protocol approval to site readiness, protocol approval to IRB approval, site readiness to FSI, and IRB approval to site readiness.

The dataset was complete with rare exceptions. Missing data were handled as to minimize bias. In the rare event that the IRB date was missing, we used the IRB date of another site within the country with a similar FSI date. If a site ready date was missing, we used the FSI date as the site ready date. If a site did not have an IRB date or FSI date, meaning the site did not participate in recruitment, then we excluded this site from analysis. We summarized the characteristics of the study sites within the countries, including the cycle times and competing studies (Table 2).

Step V: Qualitative feedback on data and initial model development

We re-interviewed the operational team to obtain their thoughts on the trajectory and outcome of the trial. From this interview, we determined that an enrollment outcome would be the most helpful information for a clinical trial due to the ubiquity of recruitment issues in trials. Specifically, the total number of patients that can be enrolled in a site for the duration of the study. To do this, we focused our evaluation on site level data.

Initially we performed simple linear regression using a mixture of continuous and categorical variables based on an initial univariate analysis. The variables we chose were screen failure rate (SFR), total months (tmonths), active months (amonths), interval between the first to second subjects enrolled (DSSI), number of enrolled patients per month (PSM), and cycle times (IRB approval to FSI [irb_fsi], site readiness to FSI [ready_fsi], days from the site ready to the first screen failure [ready_fsfailed]). We performed a scatter plot of our enrollment outcome to these various factors to assess for linear relationships (Figure 4). There were no observed linear relationships between our outcome and the chosen variables. However, the pattern of the cycle times, when compared to each other, posed concerns regarding collinearity.

Step VI: Selecting a model, Purposeful and Stepwise

Initially, we performed our regression assessment using purposeful selection for the first two models (site enrollment and site randomization). Meaning, that the variables discussed were selected based on our evaluation of the diagnostic plots and univariate analysis. A similar regression evaluation was performed for the outcome of site randomization. Variables used for the randomization model include SFR, total months, active months, IRB to FSI, site ready to FSI, IRB to ready, site ready to first screen failure, days to second subject in (DSSI), days to second subject randomize (DSSR), days from first to last patient out (DLSO), and PSM (Supplemental Figure 4a). Our third and fourth models used the outcome of site proportional contribution to enrollment and randomization, respectively. To obtain these values, we calculated the site contribution (or proportion) of subjects to a country's total subject enrollment or randomization. Again, we visualized these model variables with a scatterplot and acknowledged that there was a linear relationship between site enrollment and enrollment contribution and site randomization and randomization contribution but felt these variables were initially necessary for prediction (Supplemental Figure 4b-c). For this evaluation, we decided to use automated selection to provide an alternative model optimization pathway. Using the basic statistics package in R, a stepwise model selection was performed.

We selected our final model based on the Akaike Information Criterion (AIC), this included both backward and forward selection. The model with the lowest AIC was selected. Table 3 shows the models developed for site enrollment (model 1), site randomization (model 2), site enrollment contribution (model 3), and site randomization contribution (model 4), using the methods outlined above.

Step VII: Evaluation of Initial Models

When we re-evaluated our initial models, we discovered several potential issues. First and most importantly, we did not account for longitudinal data (enrollment over months) on multiple levels of data (site, country, and study). We had correlated data – longitudinal information with multiple observances that were related to each other and thus they broke the role of independence required for linear regression modeling. Second, the variation was different along the time points measured during the trial (lack of homoscedasticy). Third, data was not normally distributed (lack of normality). Furthermore, we utilized automated selection which can lead to model selection bias and over fitting of the model. Finally, we did not account for the fact that some sites might have been purposefully utilized more vigorously than others or activated later solely for planning reasons. Such information could only be known to the actual study and operations teams involved in the study and for whom we did not have access.

Step VIII: Addition of outside data, re-evaluation of the original outcome, and new model

Given the potential conflicts within our initial models, we felt that a more robust question and approach was required. Initially, it was our desire to predict total site enrollment and randomization for any given month based on findings from our qualitative research. However, these endpoints were difficult to crystallize given the multiple factors involved in the studies. Namely the fact that the clinical trial sites commenced at different times during the study period, likely due to planning efforts by the clinical operations team. In addition, we were attempting to model outcomes that would require an active ongoing trial. In fact, those initial models required knowledge of the SFR and PSM, both of which would be unknown prior to the trial. Such information could come from an already completed study, however

historical operational data is difficult to obtain. Therefore, we focused our outcome on site productivity as defined as meeting a goal enrollment of one (1) subject per month. The selection of 1 subject per month as a benchmark was made based on discussions from our qualitative analysis and observations from other COPD studies [44, 45]. This outcome would also allow us to develop a pre-enrollment model which would be more helpful for planning and independent of historical data. Finally, we decided to focus our evaluation solely on an enrollment-type outcome given the multiple factors involved in randomization and our limited dataset, rending any potential randomization model less robust.

To answer our new query, we first had to understand which pre-FSI factors have been shown to have impact efficiency in clinical trials. Thus, we required additional data to enrich our model. We chose to include in our model the various cycle times, season, and competitive COPD trials. We obtained data from ClinicalTrials.gov to determine the number of COPD studies occurring in each country within the same period as our example trial. Specifically, we searched for COPD studies starting within 150 days (or approximately 5 months) after our study was initiated. Ongoing studies and non-COPD studies were excluded. Seasonal observations for each month were made into a categorical variable. We included this variable as seasonal variations can affect COPD exacerbations, with the winter being noted as a high season for exacerbations due to viral illnesses [46-48]. Therefore, the loss of potential pool of subjects for enrollment may be impactful for a study. Scatterplots of this data were developed and we removed the variables which were collinear. This left us with only one cycle period – the time between the protocol approval to the site ready declaration. We dichotomized this variable into "early start," cycle time <150 days from the protocol approval to the site ready, and "late start," cycle time >150 days. We developed our model using generalized linear mixed model (GLMM) multilevel regression to account for the different levels of data with the trial.

RESULTS

The sample size estimation in the final protocol was 1136 subjects. The study enrolled 2026 and randomized 1221, with 1104 subjects completing the study (Table 2). There was a total of 10 countries including the U.S., Argentina, Bulgaria, Chile, Czech Republic, Germany, Mexico, Poland, South Africa, and Spain. The first IRB for the study was approved on May 5, 2014 in Argentina. The first subject was enrolled (FSI) in the study on June 27, 2014 and the final subject enrolled (LSI) in the study was on June 8, 2015, both in the United States. The last subject visit (last subject out, LSO) for this study was on February 8, 2016. In the end only 204 of the projected 242 confirmed sites participated in the clinical trial (Table 2; Figure 5). Over half 119 (58.3%) of the sites in the study were in the United States. The next largest site contributor to the study was Poland, with 17 (8.3%). All confirmed study sites in Germany, Mexico, and South Africa were utilized in the study. There was no information on site location within the country, principle investigator background, or years of facility experience in clinical trials.

Overall, the United States contributed the most subjects through each stage of the study (Figure 6)—enrollment (1010/2016, 50%), randomization (502/1221, 41.1%), and completion, (419/1104, 38%). The study had a SFR of 39.7%, which is in-line with limited published reports of 7-42% in COPD studies [49, 50]. High SFRs were observed for the US (50.3%) and Spain (43%) (Table 2). Completion rates for studies were high in most countries: Bulgaria (98.7%), Czech Republic (97.4%), Mexico (97.3%), Poland (96.9%), and South Africa (93%). The United States and Spain were the only countries not to achieve a completion rate of at least 90%. Notably, the Czech Republic had the best combination of SFR (23.8%) and completion rates (97.4%). The slopes of the subject enrollment to subject randomization demonstrate a linear and positive relationship, as expected for a study that progresses (Figure 7a). This relationship is also seen in the subject randomization to subject completion plot (Figure 7b).

We also evaluated the cycle times – periods between times between important events. Figure 8a focuses on the protocol approval to IRB cycle time. The United States and South African were the only two countries to have a median of under 100 days for this cycle time. The IRB approval to site ready cycle

time (Figure 8b) was a median of 27 days for all countries, the shortest duration cycle time. Site ready to FSI (Figure 8c) was consistent across most countries (median = 39 days), with the exception of Spain (median = 92 days) and South Africa (median = 0 days). South Africa was the only country without a site ready date listed, therefore the FSI was used to estimate the site ready date. Finally, we assessed the protocol approval to site ready cycle time (Figure 8d), which encompasses a large swath of the time. The median cycle times for this parameter were shortest in the United States, Czech Republic, and Germany, and longest in the South American countries.

A plot of the cumulative enrollment and randomization over the course of the study reveals that the United States was the only country accumulating patient for the first 4 months of the study. After this period, additional countries and sites we added. The last country to start enrolling subjects was Mexico (May 2015). The randomization plot (Figure 9b) revealed a similar study trajectory. Examining the non-US sites deeper (10a-b), we find that three countries did not achieve their enrollment and randomization predictions: Czech Republic, Germany, and Spain. Despite the low SFR and higher study completion rate, the Czech Republic was overall less effective in reaching its recruitment goals. In fact, as a whole, the study lagged behind in its enrollment and randomization goals for almost the entire active period recruitment. However, this pattern reversed in the last 3 months of the study, indicating a time of significant activity. Further evaluation of each country's individual effort to enrollment and randomization, including projected targets is available in the appendix (Supplemental Figures 10e-p).

Enrollment predictions with conditional logistic regression and modification of variables

Our new outcome variable for our fifth and ultimate model was site enrollment success, defined as a site recruiting at least one patient in any given month. We included the following variables: season (fall as indicator variable for "season"), competing studies starting within 150 months after our model study began ("competition"), and start time ("start," late start defined as >150 days between the protocol approval to site readiness vs an early start as the indicator variable). Interaction terms were placed in the

model to assess if early vs late site start modified the enrollment success outcome in each season. Our simplified regression equation:

$$Site\ Enrollment\ Success = \log(p_\iota/1-p_\iota) = \beta 0 + \beta 1 * competition_{\iota,j} + \beta 2 * start_j + B3 * season_{\iota,j} + B4 * start_j * season_{\iota,j} + b_{0,\iota} + e_{\iota,j}$$

This simplified equation is interpreted as the log odds of site enrollment success, defined as recruiting at least one subject per month, is accounted for by factors that include the intercept, the outside competition, season, start timing, and an interaction between the season and the start timing. We chose a multilevel analysis to account for longitudinal data with correlated outcomes. Our levels were sites (j) and observations within sites (ι). In this equation, $b_{0,\iota}$ represents the random effect of site (all of the observations within a site are related) and $e_{\iota,j}$ is the residual error. The "start" variable has only a j notation because a site can either have an early start or late start. This equation implies that there are differences between sites *and* the observations within a site also has inherent residual error. Using GLM function in lme4 package (R software), we obtained our final regression equation with coefficients for the generalized multilevel model:

$$Site\ Enrollment\ Success = 0.83 - 0.04competition - 0.52startlate - 0.07spring - 1.08summer - 0.07winter + 0.80startlate{:}spring + 0.31startlate{:}summer + 0.18startlate{:}winter$$

The model showed a negative effect of competition and the summer season on the site enrollment success. In addition, there was a significant interaction between a late starting site (protocol approval to site ready >150 days) and spring time enrollment (Table 4). Performing an ANOVA on this model confirmed that indeed these were significant factors (Table 5). The odds of site enrollment success in the

summer were 0.34 times of the odds of successful enrollment in the fall (Table 6). Interestingly, for a site with a starting late and attempting to enrolling in the spring time, the odds of site enrollment success was 2.23 (CI 1.27-3.93) times higher when compared to a late starting site in the fall season. The odds of success with increasing outside competition were significant (0.96, CI 0.94-0.98), though to a lesser extent than the seasonal effects (Table 6).

Predicting outcomes using the model, an example

For competing trials and its effect on the site enrollment success of a study, we developed a table of predicted probabilities (Table 7a; Figure 11). A hypothetical site in X country hoping to enroll a single subject during a given month and has 7 competitors also performing COPD studies would expect to have between 45-68% chance of enrolling at least one subject. This probability drops to between 40% and 62% when competition doubles. If 25 competitor studies are also recruiting COPD patients, then the site can expect ≤50% chance of enrolling a single subject. The predicted probability of success between starting early or starting late were not significantly different, 45.5% and 42%, respectively (Figure 12), as indicated by our model analysis testing (Table 5). However, the predictions for the interaction between the site start timing and the site enrollment success showed a variable pattern (Table 7b; Figure 13). For example, a site that was late start and enrolling in the spring, had a 57% chance of achieving the recruitment of one subject that month. This was slightly better than the 50% chance for a site with an early start in the study and enrolling subjects in the spring. However, if the enrollment for an early or late starting site occurred in the summer, the chances of site enrollment success dropped to 27% and 23%, respectively (Figure 13). Finally, we assessed the interaction between site start timing and competing studies (Figure 14). This revealed slightly lower predicted success for a site with a late start compared to a site with an early start. However, there were overlapping intervals and this interaction was not formally tested for significance.

DISCUSSION

From our qualitative analysis, we learned that a multicenter trial had several pain points. Namely, recruitment of patients into the study to ensure enrollment, randomization, and eventual completion required for adequate statistical power. Additionally, the site start-up delay was a notable concern from all the professionals interviewed. These interviews allowed us to develop a timeline of the ideal events from a clinical study on COPD. Furthermore, using our data, we could process these concerns into quantifiable parameters, such as cycle times. While our initial approach lacked the capacity to account for the complexity of correlated longitudinal data, the simple linear regression models allowed us to understand the relationship between the variables in our data and potential outcomes. In fact, it was the process of working through the initial models that we understood the difficulties related to developing a model around a simple enrollment or randomization outcome. The process enabled us to rule out the possibility of developing a model for randomization due our limited dataset. The results of our model showing the impact of competition, summer months, and an interaction between enrolling in the spring time after a late start, was revealing. Examining each of these entities separately may provide some insight.

Competition and Multicenter Multinational Trials

The predictions from our model reveals that the impact of ≤7 competing COPD studies is relatively small, with only a 5% decline in site success enrollment success. However, in more competitive environments (>13 studies), the average chance of enrollment drop to below 50%. Competition between sites for subjects, and even investigators, has been identified as a problem by the United States Health and Human Services in their study on barriers to drug development [28]. In our example, the majority of sites were in the United States. The U.S. is a robust drug development environment with annual gross R&D expenditure approximately $400 billion [51], surpassing all other developed countries. Thus, the fact that most sites and most patients in this study came from the U.S. was not surprising and likely a strategic move given the advanced clinical trial infrastructure. However, the U.S. sites also faced the most outside

competition – 25 active COPD trials. In the U.S., the R&D cost per approved drug can range from $2.5 to $2.8 billion yet only about 11.8% of drugs make it through clinical approval [5]. The rising cost of drug development in the United States and emergence of technological innovation in developing countries has opened the door for a shift in locations of clinical trials [51]. At least 25% of trials registered on ClinicalTrials.gov are being conducted in regions with emerging economies such in South America, Eastern Europe, Asia, and Sub-Saharan Africa [52]. This finding does not necessarily mean drug development will be reduced in the U.S. and Western Europe, but that the future may bring increased interconnectedness of the global clinical research system [53]. Thus, countries with fewer competitive trials such as South Africa or the Czech Republic, may play larger roles in subject recruitment in future clinical trials. Finally, as noted previously, multinational multicenter sites can also have less than optimal results [44]. The EUROSCOP study used 39 sites and required 18 months, rather than the projected 12 months, to obtain 2,147 subjects for their study and only accomplished this after a change in the eligibility criteria for easier enrollment [44]. While our study was successful in recruiting the appropriate number of subjects, this was done with a much large number of sites, likely leading to higher operational costs.

Start Timing and Cycle Times

From our qualitative research, we learned that site activation delays were a concern for all those involved in clinical research. The strategies used to mitigate included activating additional sites, increasing compensation to the sites, or combination of both. One of the most important mitigation actions was the strategic early activation of best enrolling sites based on historical knowledge of site performance. This may explain the activity seen only in the U.S. four months before the next group of countries (Germany, Poland, and the Czech Republic). It may also explain the activation of countries in South America later in the trial. Thus, the cycle times, including the start timing, must be taken in context. With this noted, our model did not detect a significant difference between those sites that were ready early vs late in terms of their site enrollment success (Table 2). However, there seemed to be a seasonal interaction with start timing which we will discuss shortly. The protocol approval to site ready cycle time was longer in our

study than those seen in the Berthon-Jones evaluation of the Altair HIV study [10]. These differences may be attributed to the type of diseases study (COPD vs HIV) and the number of sites (204 vs 36).

Start Timing and Competition

The interaction between start timing and competition was not formally tested in our model (as an interaction term), however, we were able to use our model to study this relationship. We found slight differences in enrollment success in sites with an early start vs those with a late start when faced with outside competition for subjects (Figure 14). The late start sites had a 37.5% chance of success with up to 25 competing trials while early sites had a slightly better chance of enrollment with similar competition, approximately 40%. This interaction was not formally tested for significance in our model and may be due to chance.

Seasonality

Seasonality was a factor on its own and as an interaction. Our results revealed that the summer season had a negative impact on successful enrollment. In general, the summer months are vacation times in most countries thereby reducing the pool of subjects eligible for enrollment. In our study, winter months did not appear to have a lower rate of enrollment than the fall or spring despite the loss of a pool of patients who may experience an exacerbation [47]. For this study, the timing of the first and last subjects into the trial may provide a clue. The first subject was enrolled in June 2014 and the last subject enrolled was in early June 2015, covering each season once. In the northern hemisphere, the first summer season was at a disadvantage because this is the period when the study was opening. Likewise, the last summer season (where only a few days in June 2015 are represented) marked the end of enrollment as seen by a plateau in cumulative rates (Figure 9a). The opposite would true in the southern hemisphere, where the winter months would have been affected by the difference. Thus, the effect of the summer season on site enrollment success is real and it is significant. The spring season's enrollment success was likely the result of increased efforts to enroll patients in order to meet the internal success metrics. Thus, the

seasonal findings may be due to factors related to the calendar timing of the trial but given what is known about vacation patterns, we would not be surprised if enrollment in the summer season is difficult.

Seasonality and Start Timing

While start timing itself was not an indicator for site enrollment success, the interaction with season was a factor. When a site is a late starter, there is evidence that the site will generally underperform compared to early starting sites during most seasons (except for the spring). Our model interaction term shows that the spring time conferred a benefit to those sites activated late in the study. As discussed above, the spring time was a period of major recruitment efforts on the part of the sites, therefore the significant increase in enrollment towards the end of the study may be attributed to late starting sites. Given that some sites in the United States also started late, it is difficult to detect if there is a country difference in this interaction.

Solutions

Based on preliminary literature review, we determined that poor recruitment was a major issue for single and multicenter clinical trials and thus a major barrier to clinical trial enrollment success [26, 44, 54, 55]. In their study using ClinicalTrials.gov, Williams and colleagues found that 57% of trials terminated for non-scientific reasons were done so because of insufficient recruitment of subjects [56]. There have been many solutions suggested, including use of electronic medical records, community-based methods, and use of social media tools [57-62]. Our study provided some insights on the patterns of enrollment that may be helpful in pre-trial planning. There is an indication that avoiding the summer months would be a good strategy for clinical study operations teams. However, further validation in other COPD and respiratory studies may help determine if this effect was unique to the example used in this paper.

Understanding the competitive landscape is an important learning from this study. Competition played an impactful role on the ability to successfully enroll subjects. ClinicalTrials.gov would be an important tool for researchers and Sponsors during the planning of their study. In addition to completed studies, actively

recruiting and upcoming trials can also be viewed on this site. However, there may be a registration bias towards the United States, given disclosure regulations [63]. Utilizing trial sites in different countries and those in emerging economies may be of benefit to clinical research teams as clinical trials are becoming globalized [51, 53, 64]. Each country's regulatory requirements and technological capabilities should be assessed before embarking on a multinational study to ensure they are aligned with the complex U.S. regulatory system [64].

The use of informatics tools in clinical research should be further explored to facilitate multicenter multinational studies. Despite their flaws, CROs are important contributors in the development of clinical informatics tools used within the clinical trial. These tools include the electronic data capture (EDC) and case report form (CRF), systems that study results during the trial [11, 65]. And while these tools are helpful for trial management, they do not address the issue of low accrual that plague many clinical studies [56, 66, 67]. In the last few years, studies have focused on newer informatics-based tools and mechanisms utilizing the electronic health records (EHR) to help with the planning of clinical trials [61, 68]. Electronic Health Records 4 Clinical Research (EHR4CR), is newer effort using big data to facilitate multinational clinical research EHR data [68]. This venture is supported by the European Union (E.U.) and aims to connect hospital EHR systems within the E.U. to improve clinical research and trial enrollment. Despite this, the field of clinical research and clinical trial informatics has room for growth.

Finally, we developed an application called the Clinical Operations Probability of Enrollment Reporter (COOPER) which can be easily incorporated into the clinical trial work stream (Figure 15). Using the variables in our model—competition, start timing, and seasons – we can determine the probability of site enrollment success. The app provides a bar graph visualization and an outcomes table. Potential uses for COOPER include integration into an EDC system or as an open-source tool to facilitate evaluation of a clinical trials in their early stages.

Limitations

The major limitations for the qualitative analysis were the small sample size of clinical research professionals interviewed and applicability to other disease areas. The factors that were listed as pain points in our quantitative analysis, may be less relevant for a non-respiratory or even non-COPD study. The process map we developed may also be specific to the Sponsor of the example study. The process map may vary in smaller or non-US companies, and within academic centers.

A major limitation for the quantitative evaluation was our dataset. The data was limited in the degree of information it provided thus, limiting our model to enrollment predictions only. An ideal dataset would include the following: subjects' demographics, specific location of site (rural versus urban), clinical outcomes of the study, and budget/contract information. A subject's demographics would inform us of characteristics such as age, gender, and race—all of which can affect enrollment and alter clinical findings [69]. Understanding location of the sites would facilitate modeling of the dynamics of a site well-connected to a public transportation system compared to a site that may be difficult for patients to reach. Transportation has been identified as an important issue for clinical trial participation [70, 71]. Having the clinical outcomes data would allow us to evaluate whether site enrollment success impacted the clinic endpoint of the trial. In other words, we would learn if the enrolled subjects appropriate for the trial and the impact on the clinical outcome. Finally, understanding the site budget constraints helps to determine whether finances have an impact in facilitating enrollment success, particularly for late starting sites and sites in lower income countries.

Future studies should address if subject and site location variables impact site enrollment success. As we were unable to validate our study given lack of additional clinical trials operational data, further validation of the findings of this thesis should be assessed with other COPD, respiratory, and non-respiratory studies in various phases of development.

CONCLUSION

The clinical trial is a fundamental aspect of drug development with a history of regulatory necessity. Barriers to clinical trial enrollment have been extensively evaluated in the literature but few solutions are offered. Modern statistical techniques can be used to model the enrollment process. These findings can be incorporated into the planning period of a clinical study to improve site enrollment outcomes. The use of clinical research informatics has the potential to make the planning process for clinical trials, and thus, predictions for enrollment success readily accessible to professionals involved in multicenter multinational studies.

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FIGURES AND TABLES

Table 1. Pain Points in Multicenter Clinical Trials.

The groups represented with the clinical operation team and clinical development team (medical director) and study analysis/clinical development (biostatistician). In semi-structured interviews, they provided background on their work at industry and their perceptions of the major ”pain points” in clinical studies.

Interview Questions	Stakeholders		
	Clinical Operations (5)	Medical Director (1)	Biostatistician (1)
Average Number of Years in Industry	10	8	5
Area of Expertise	Feasibility& Recruitment	Clinical Development	Study Analysis
Pain Points	Site start-up delay Regulatory approval delay Recruitment of subjects poor Antiquated methods of recruitment PI with multiple studies Complex eligibility criteria	Site start-up delay Recruitment of subjects poor Subject identification/ stratification	Site start-up delay Recruitment of subjects poor Multicenter analysis/site variability

Figure 1. Clinical Study Process Map.

This process map shows the activities, people, and output from the activities required to bring a study to fruition. This is a simplified view with 5 major activities: 1) internal study approval, 2) protocol and informed consent form (ICF) development, 3) external approval by a regulating body, 4) site start-up activities, and 5) subject recruitment.

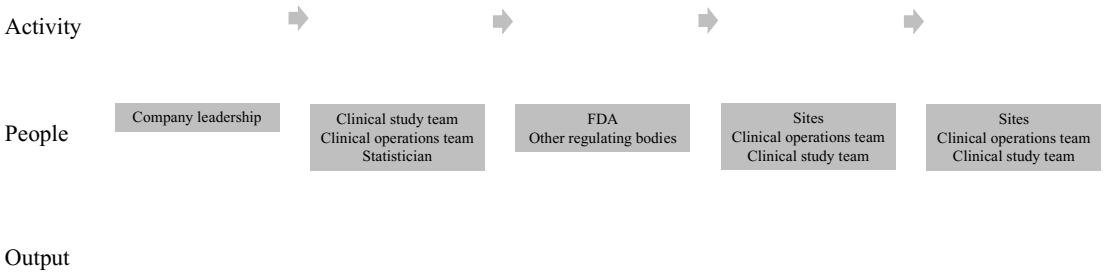


Figure 2. Sample Layout of the Sample Phase III COPD Trial.

After enrollment into the study, the subjects underwent a 4 week run-in period (Week -4 to Week 0). During the run-in period the study team ensures that all subjects are clinically stable, non-study medications are adjusted or discontinued, and baseline lab/spirometric measurements collected. If subjects still meet the eligibility criteria at the end of this period, then they are randomized to a treatment group. In the treatment period, the patient receives either placebo or drug (until end of Week 26). During the two week wash-out period (ending at Week 28), the subject is monitored for any adverse treatment effects. Any medications that were stopped before the study are restarted.

Figure 3. Idealized Timeline for a COPD Clinical Trial.

This timeline was created using working knowledge on clinical trials and feedback from the clinical operations and clinical study teams.

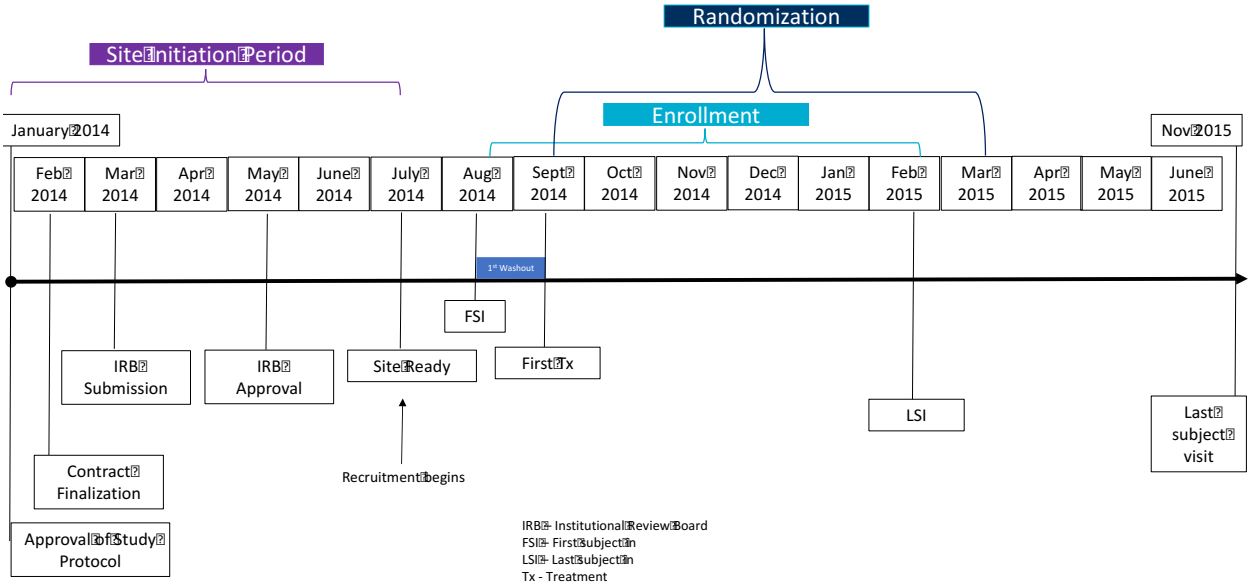


Table 2. Characteristics of Countries Used in Example Phase III COPD Trial

Characteristics of Countries Used in Example Phase III COPD Trial											
		All	USA	Argentina	Bulgaria	Chile	Czech Republic	Germany	Mexico	Poland	South Africa	Spain
	Sites	204	119	8	16	3	12	11	6	17	8	4
	Enrolled	2026	1010	128	236	60	101	106	57	226	81	21
	Randomized	1221	502	87	159	47	77	84	37	159	57	12
	Completed	1104	419 (83.5%)	79 (97.5%)	157 (98.7%)	43 (91.5%)	75 (97.4%)	78 (92.9%)	36 (97.3%)	154 (96.9%)	53 (93.0%)	10 (83.3%)
	SFR‡	39.7%	50.3%	32.0%	32.6%	21.7%	23.8%	20.7%	35.1%	29.6%	29.6%	42.9%
Cycle Times*	Pro-IRB	111 (84-148)	90 (76-121)	167 (114-167)	225 (225-225)	192 (126-223)	148 (148-148)	134 (134-134)	112 (105-119)	112 (112-168)	87 (87-87)	196 (196-196)
	Pro-Ready	139 (101-195)	121 (87-143)	353 (261-360)	289 (287-300)	329 (292-369)	167 (167-182)	181 (160-188)	367 (364-384)	195 (174-213)	210 (197-219)	226 (223-288)
	IRB-Ready	27 (13-47)	23 (9-32)	174 (147-224)	62 (62-66)	156 (100-203)	19 (19-26)	40 (26-47)	258 (248-272)	60 (55-83)	122 (97-129)	30 (27-35)
	IRB-FSI	81 (48-125)	77 (44-125)	224 (212.5-266)	85 (77-97)	170 (139-213)	49 (36-61)	70 (61-104)	266 (261-281)	81 (57-97)	129 (122-132)	127 (115-131)
	Ready-FSI	39 (17-83)	51 (26-90)	21 (3-119)	21 (16-35)	14 (10-39)	26 (8-32)	23 (10-64)	8.5 (3-13)	17 (3-24)	0 (0-94)	92 (88-97)
	Competition	18.7 (9.6)*	25	3	2	1	5	13	2	3	2	4

‡ SFR = Screen Failure Rate (%, Randomized/Enrolled). *Cycle times represented as median days (IQR). *Represented as mean (SD). FSI – First Subject In. IRB – Institutional Review Board.

Figure 4. Step V – Initial Model: Enrollment Outcome - Variables Scatterplot

The variables did not show significant correlation with enrollment, despite the slide trend in enrollment total and PSM.

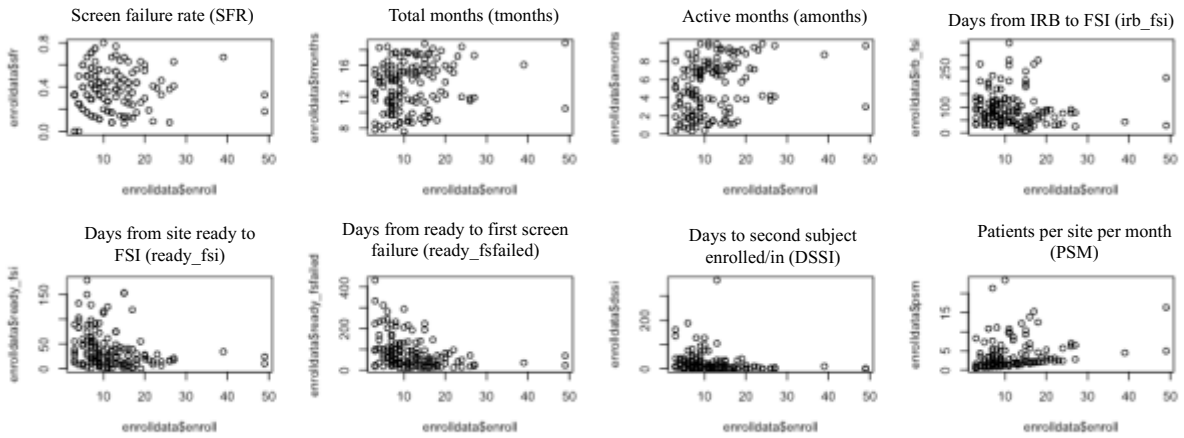


Table 3. Initial Models.

Model outcomes, approaches and full models with coefficients.

Outcome	Model Approach	Model with Coefficients
Site Enrollment	Purposeful	$Site\ Enrollment\ = -3.74 - 2.24\text{SFR} + 0.4\text{tmonths} + 1.7\text{amonths} + 0.01\text{irb}_{\text{fsi}} - 0.01\text{ready}_{\text{fsi}} - 0.02\text{ready}_{\text{fsfailed}} - 0.02\text{dssi} - 1.15\text{psm}$
Site Enrollment Contribution	Stepwise *Lowest AIC for model that includes only enrollment total, SFR, total months, and two cycle times (IRB to FSI and site ready to FSI)*	$Site\ Enrollment\ Contribution\ = 0.06 + 0.005\text{enroll} + 0.006\text{irb}_{\text{fsi}} - 0.0004\text{ready}_{\text{fsi}} - 0.09\text{sfr} - 0.02\text{tmonths}$
Site Randomization	Purposeful	$Site\ Randomization = 1.95 - 11.81\text{SFR} + 0.15\text{tmonths} + 1.2\text{amonths} + 0.01\text{irb}_{\text{fsi}} - 0.01\text{ready}_{\text{fsi}} - 0.021 - 0.01\text{dssi} - 0.02\text{dssr} + 0.76\text{psm}$
Site Randomization Contribution	Stepwise *Lowest AIC for model that includes only randomization total, SFR, and two cycle times (IRB to FSI and site ready to FSI)*	$Site\ Randomization\ Contribution = 0.04 - 0.1\text{SFR} + 0.0005\text{irb}_{\text{fsi}} - 0.0005\text{ready}_{\text{fsi}} - 0.003\text{randomize}$

Cycle times: IRB to FSI (irb_{fsi}), site ready to FSI ($\text{ready}_{\text{fsi}}$), and site ready to first screen failure ($\text{ready}_{\text{fsfailed}}$); SFR: screen failure rate; PSM: patients per site per month; DSSI: Days to second subject enrolled/in; DSSR: Days to second subject randomized; tmonths: total months; amonths: active months (months which the site was actively recruiting subjects)

Figure 5. Sites Utilized Per Country.

This shows the sites used per country. The United States accounted for over half the sites used in the study. Of the project 242 sites, only 203 enrolled subjects at anytime during the trial.

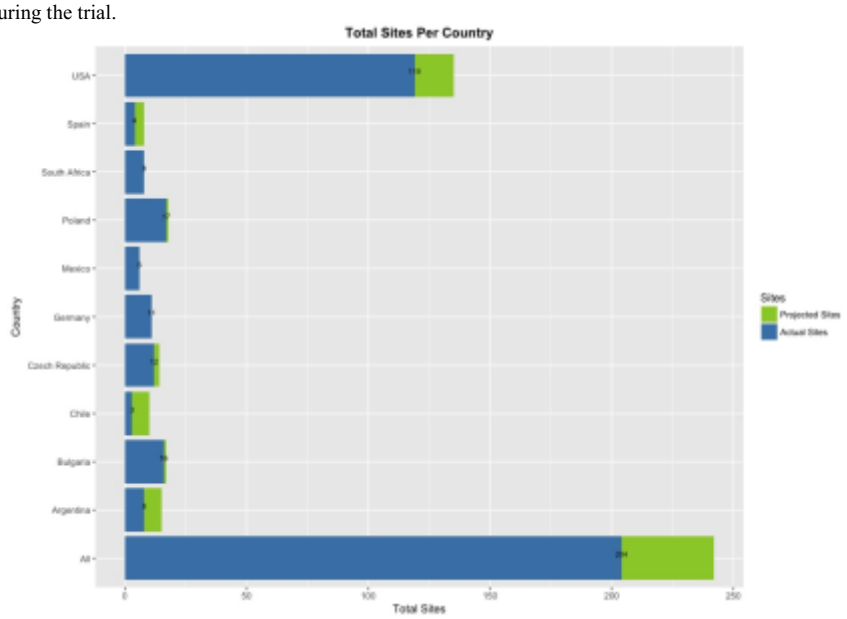


Figure 6. Total Subjects By Stage in Each Country.

This shows the subjects per stage. Stages are "Enrolled," "Randomized," and "Completed." The United States accounted for the majority of subjects entering and completing the study completing.

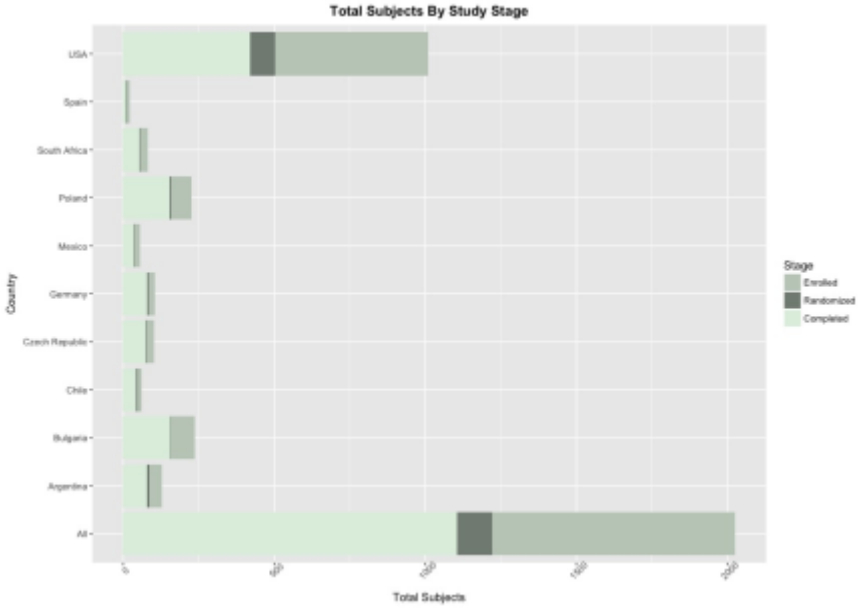


Figure 7a. Subjects enrolled vs randomized in the study by country.
These series of figures show the relationship between enrolling and randomizing subjects by country. The slope, linear and positive, can be used to extrapolate the screen failure rate.

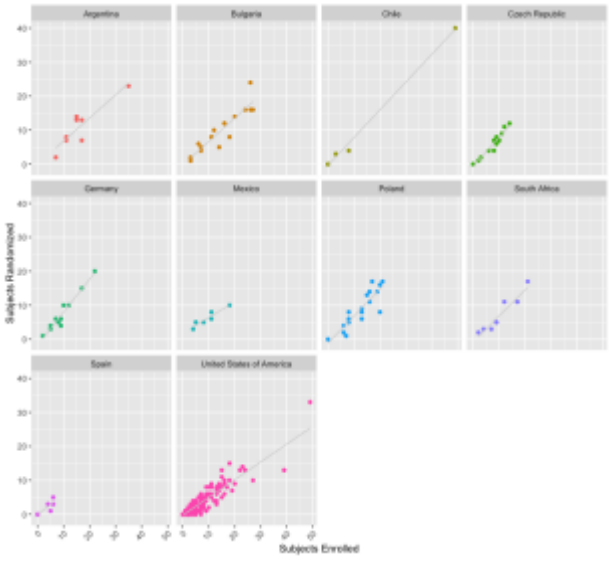


Figure 7b. Subjects randomized vs completing the study by country.
These series of figures show the relationship between randomizing subjects and subject completion of the country arranged by country. The slope, linear and positive, can be used to extrapolate the treatment completion rate.

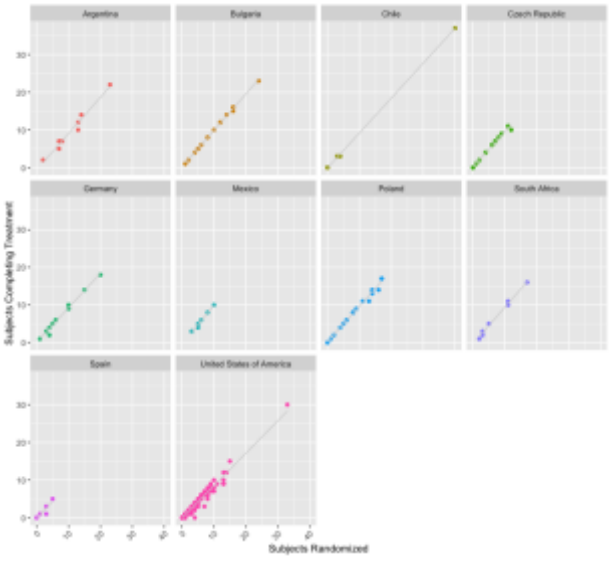
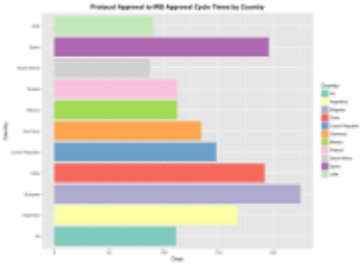
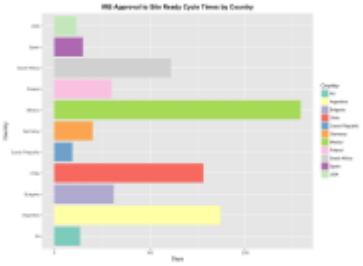


Figure 8a-d. Cycles Times by Country

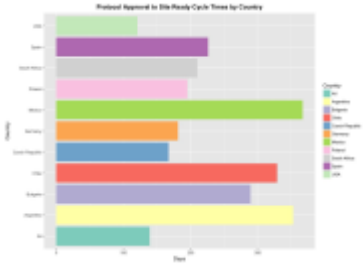
a. Protocol approval to IRB approval cycle time



b. IRB approval to site ready cycle time



d. Protocol approval to site ready cycle time



c. Site Ready to FSI approval cycle time

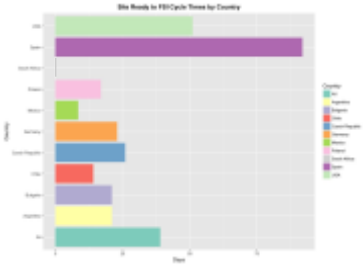


Figure 9a. Cumulative Enrollment – All Countries.
Underperformance can be observed when a country's dashed line (Original enrollment projects) is above the solid line (Actual enrollment projections).

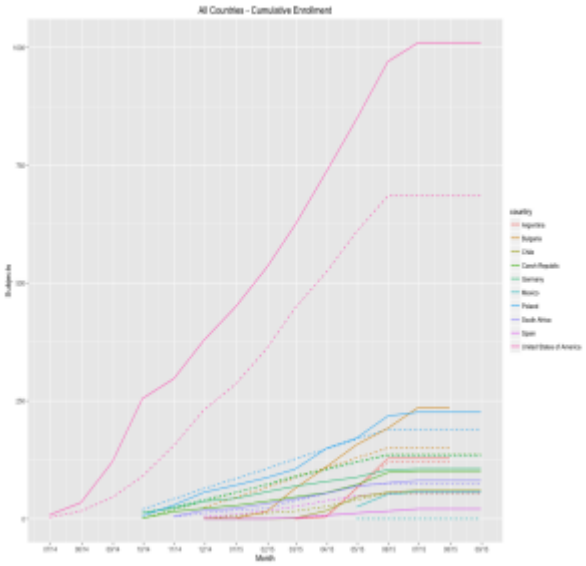


Figure 9b. Cumulative Randomization– All Countries.
Underperformance can be observed when a country's dashed line (Original enrollment projects) is above the solid line (Actual enrollment projections).

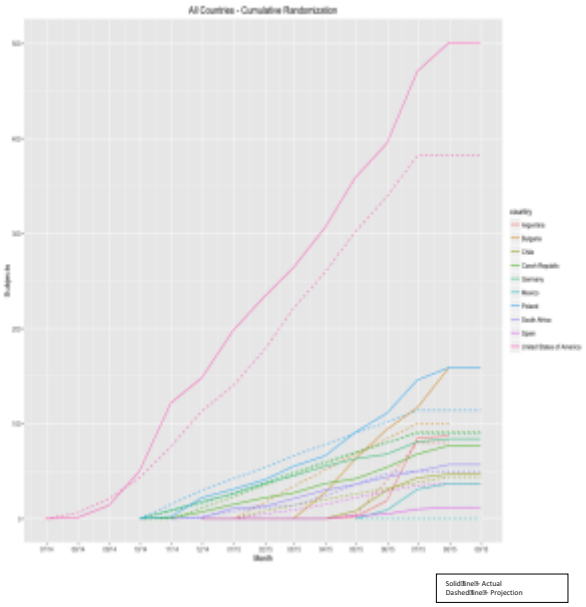


Figure 10a-b. Cumulative Enrollment & Randomization – Non-US Sites.
Underperformance can be observed when a country's dashed line (Original enrollment projects) is above the solid line (Actual enrollment projections).

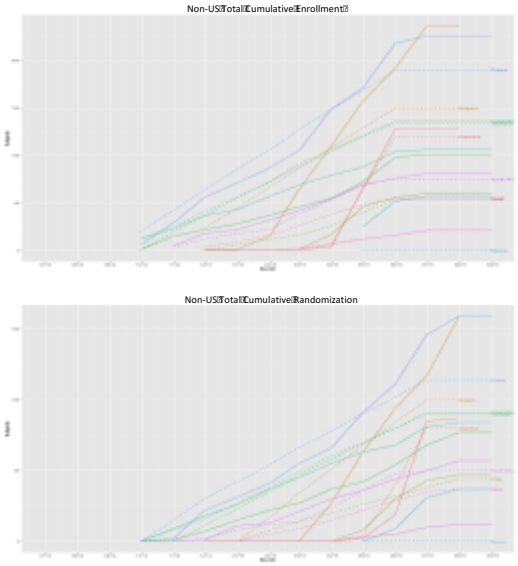


Figure 10c-d. Cumulative Enrollment & Randomization –US vs Total Sites.
Underperformance can be observed when a country's dashed line (Original enrollment projects) is above the solid line (Actual enrollment projections).

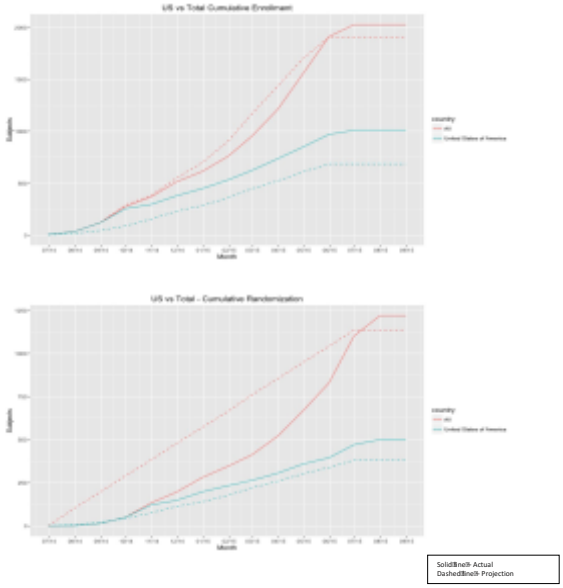


Table 4. Generalized linear mixed multilevel model.

Using a binary outcome for site enrollment success, we used logistic regression in a generalized linear mixed model with two levels and site as the random factor. The results of this evaluation showed a reduction in site enrollment success with competition, in the summer season, and in studies starting late and recruiting in the spring time.

Generalized Linear Mixed Model: Site Enrollment Success				
	Estimate	SE	z value	p value
(Intercept)	0.83	0.29	2.89	0.004*
competition	-0.04	0.01	-4.14	3.44E-05*
start late	-0.52	0.28	-1.89	0.059
spring	-0.07	0.19	-0.37	0.709
summer	-1.08	0.21	-5.23	1.66E-07*
winter	-0.07	0.19	-0.38	0.702
start late:spring	0.80	0.29	2.80	0.005*
start late:summer	0.31	0.35	0.89	0.375
start late:winter	0.18	0.29	0.61	0.541

Table 5. Analysis of the GLMM Multilevel Model.

We evaluated the model using a Type III ANOVA. This revealed significant in terms of site enrollment success outcome and competition, season. There was also a significant interaction between starting enrollment later in the study and season.

Analysis of Deviance Table (ANOVA, Type III)			
	Chisq	Df	p value
(Intercept)	8.33	1	0.003894**
competition	17.16	1	3.44E-05***
start late	3.56	1	0.059221
season	35.25	3	1.08E-07***
start late:season	9.54	3	0.022868*

Table 6. Odds ratios for Site Enrollment Success.

	Odds Ratio	95% CI
(Intercept)	2.30	1.31-4.05
competition	0.96	0.94-0.98
start late	0.59	0.35-1.02
spring	0.93	0.64-1.35
summer	0.34	0.22-0.51
winter	0.92	0.64-1.35
start late:spring	2.23	1.27-3.93
start late:summer	1.36	0.69-2.70
start late:winter	1.20	0.67-2.13

Table 7a. Predicted Probabilities of Success in Enrollment Presence of Competition.

Predictions in Presence of Competition			
Competitor Trials	**Predicted Probability**	**Lower**	**Upper**
1	0.61	0.51	0.73
2	0.60	0.50	0.72
4	0.58	0.48	0.70
5	0.57	0.47	0.69
7	0.56	0.45	0.68
13	0.50	0.39	0.62
19	0.44	0.33	0.56
25	0.39	0.28	0.50

Table 7b. Predicted Probabilities of Success in Enrollment Based on Interaction Between Start and Season.

Predictions Based on Interaction Between Start and Season					
Start	**Season**	**Predicted Probability**	**SE**	**Lower**	**upper**
early	fall	0.52	0.16	0.44	0.60
late	fall	0.39	0.20	0.30	0.49
early	spring	0.50	0.16	0.42	0.58
late	spring	0.57	0.15	0.50	0.64
early	summer	0.27	0.18	0.20	0.34
late	summer	0.23	0.24	0.16	0.32
early	winter	0.50	0.17	0.42	0.58
late	winter	0.42	0.17	0.34	0.50

Figure 11. Model Prediction for Probability of Success When Competing with Outside Studies.

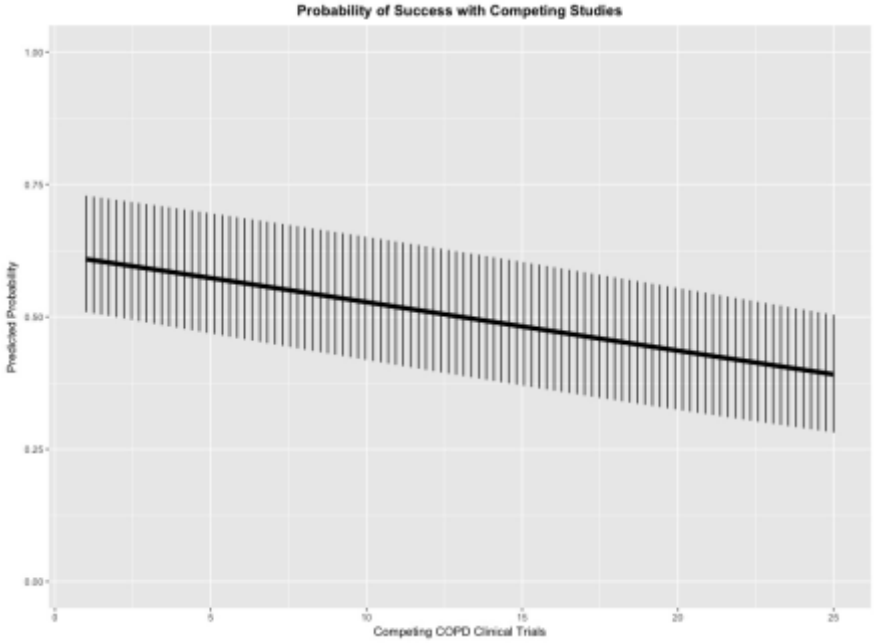


Figure 12. Probability of Success Based on Early vs Late Start Period.

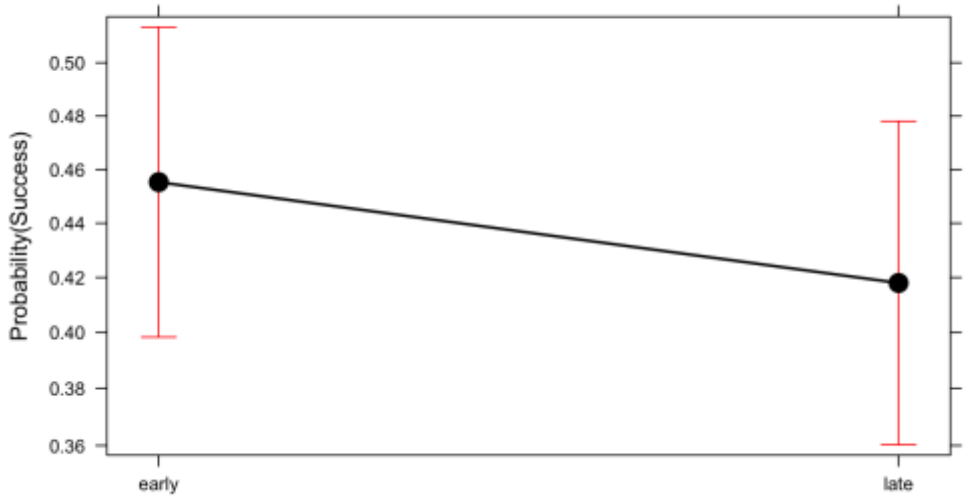


Figure 13. Model Prediction by Start (Early vs Late) and Seasonality.

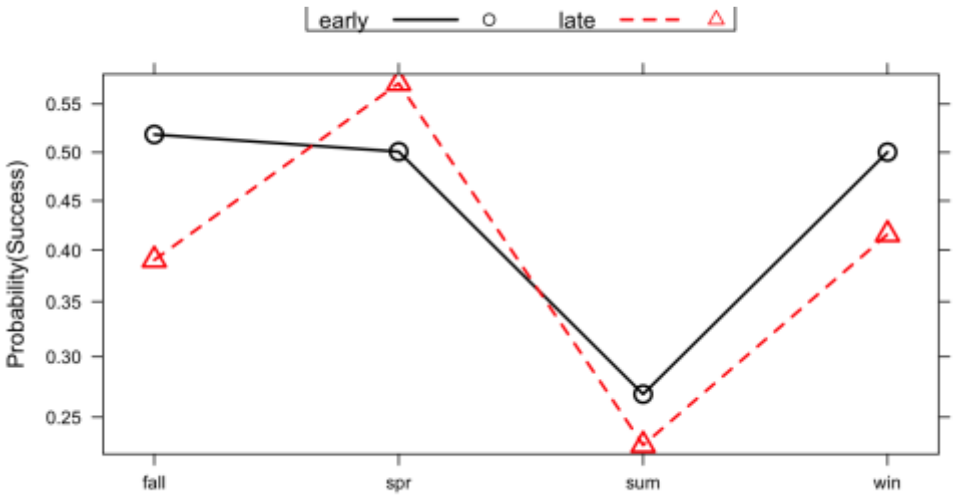


Figure 14. Model Prediction by Start (Early vs Late) and Competing Studies.

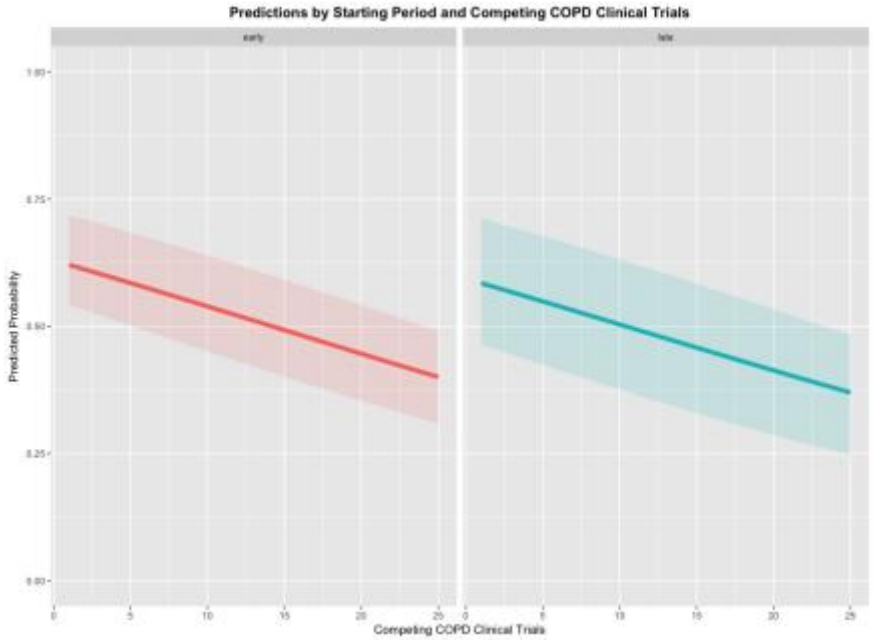
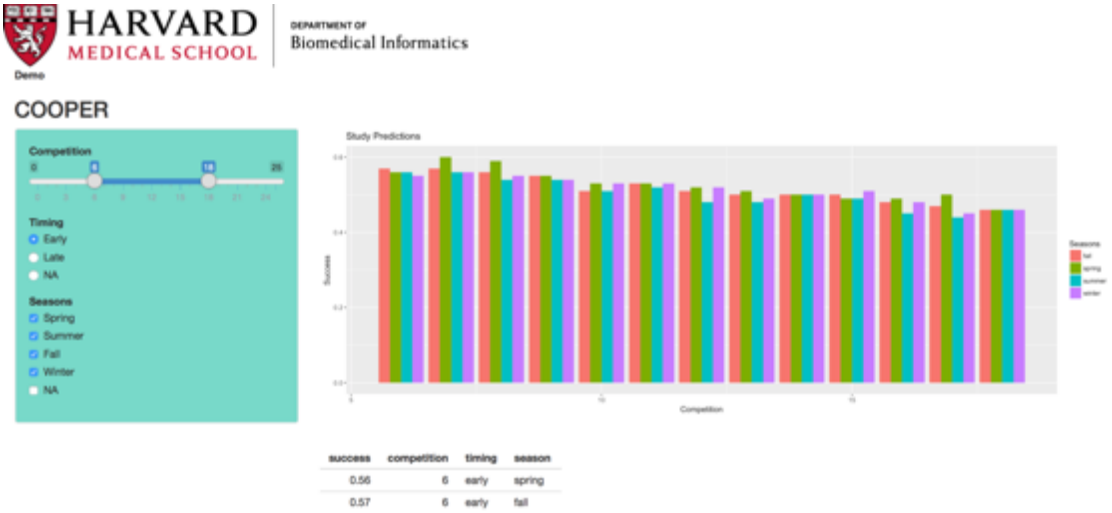
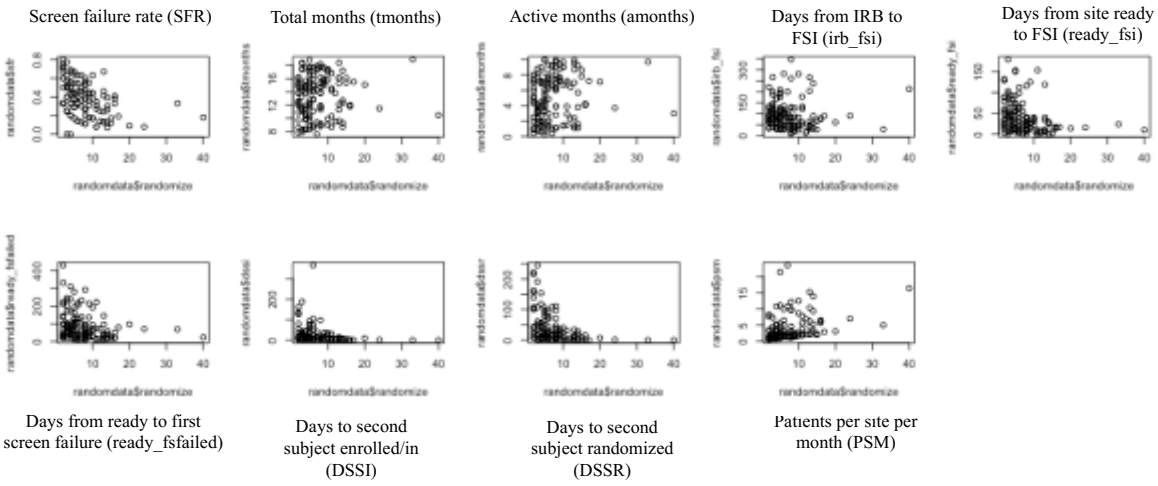


Figure 15. Clinical Output Operations Probability of Enrollment Reporter (COOPER) app.

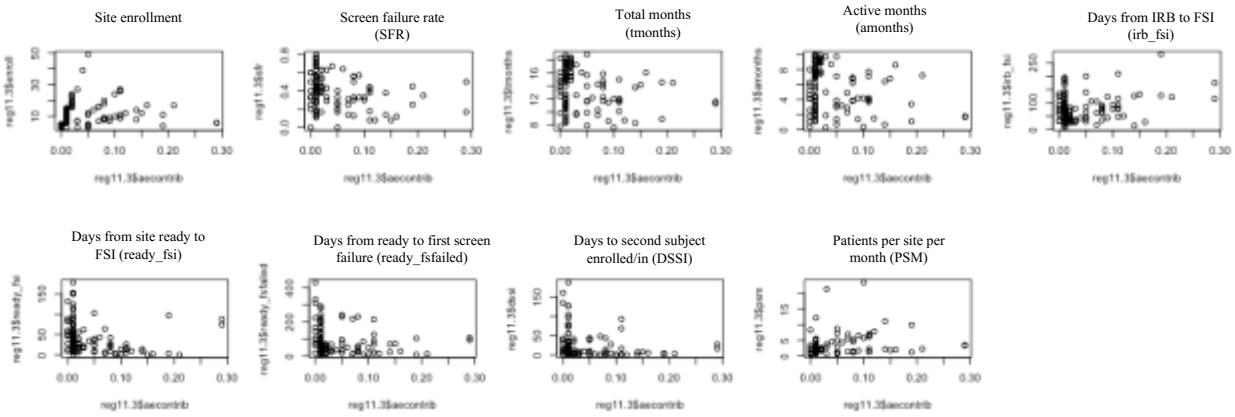


Appendix

Supplemental Figure 4a. Step V – Initial Model: Randomization Outcome - Variables Scatterplot
Left: Scatterplot of variables. Right: Listing of Variables.



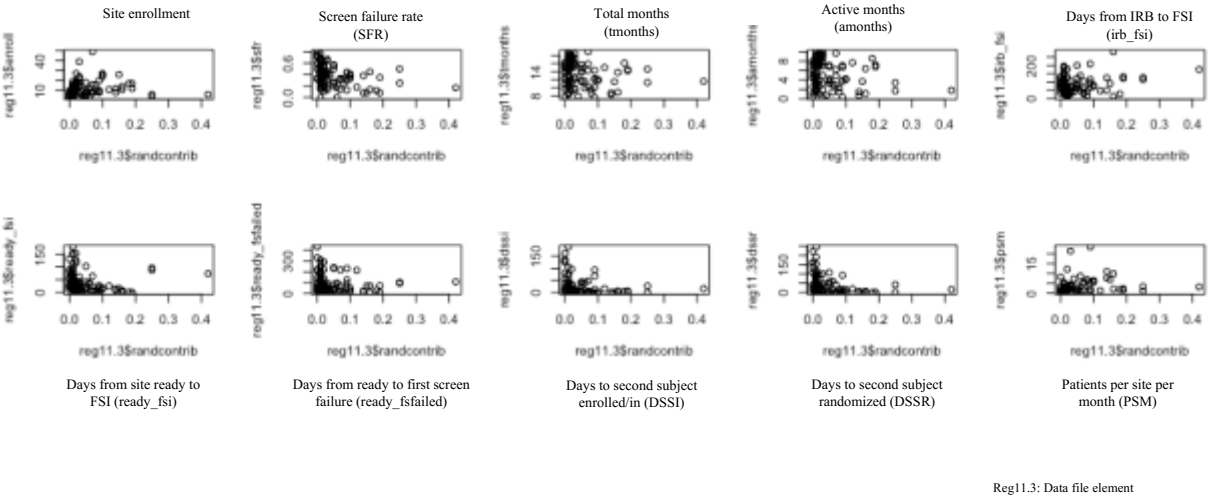
Supplemental Figure 4b. Step VI – Initial Model: Site Contribution to Total Enrollment Outcome - Variables Scatterplot
The site contribution to total enrollment ("aecontrib") was assessed against the variables in the model. Not surprisingly, there was a linear relationship with site enrollment.



Reg11.1: Data file element

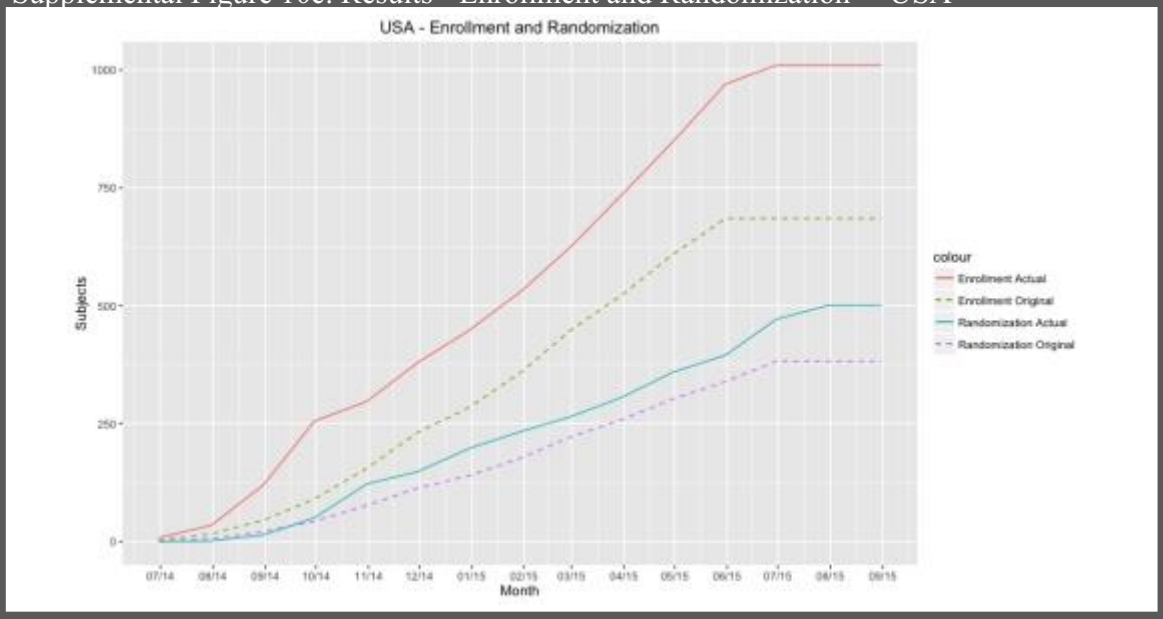
Supplemental Figure 4c. Step VI – Initial Model: Site Contribution to Total Randomization Outcome - Variables Scatterplot

The site contribution to total randomization ("randcontrib") was assessed against the variables in the model. Again, there was a linear relationship with site randomization.

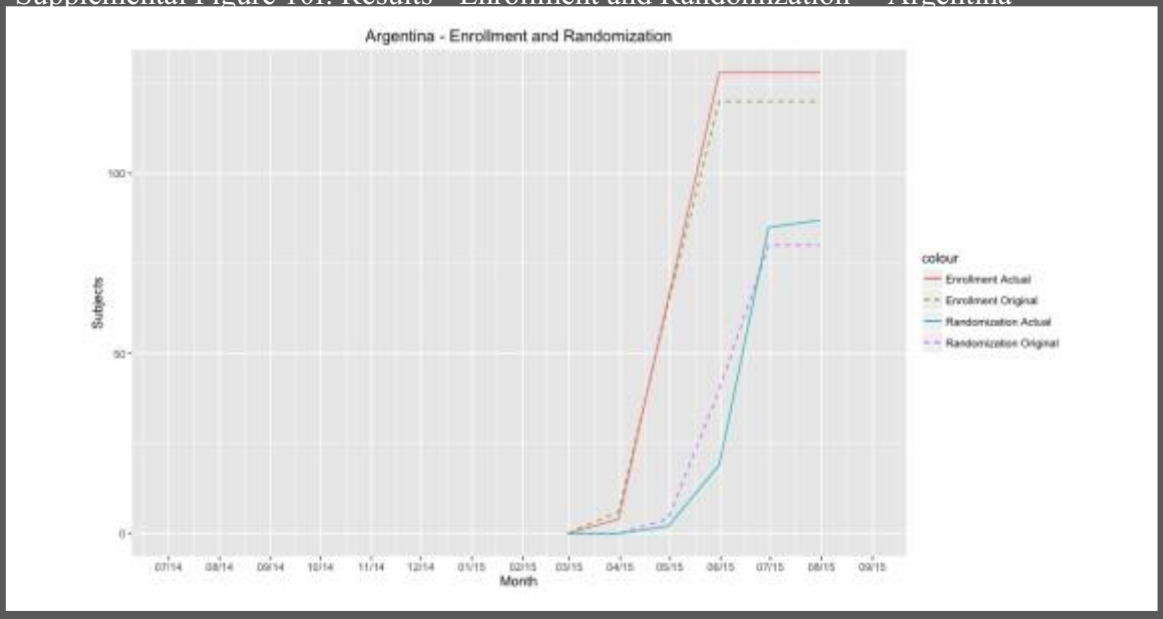


Reg11.3: Data file element

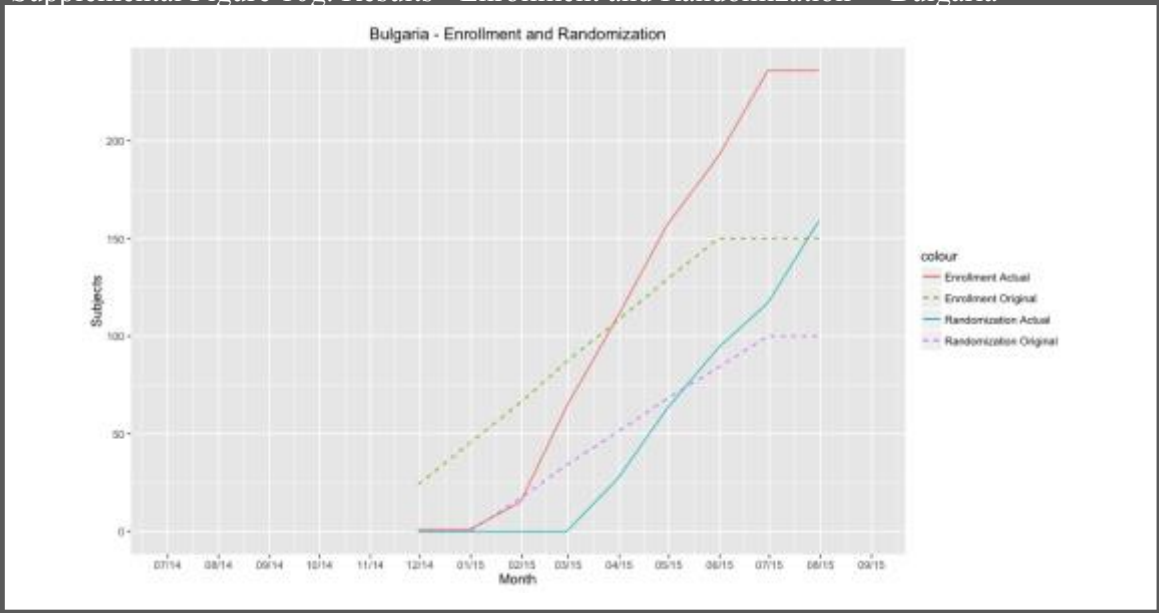
Supplemental Figure 10e. Results - Enrollment and Randomization – USA



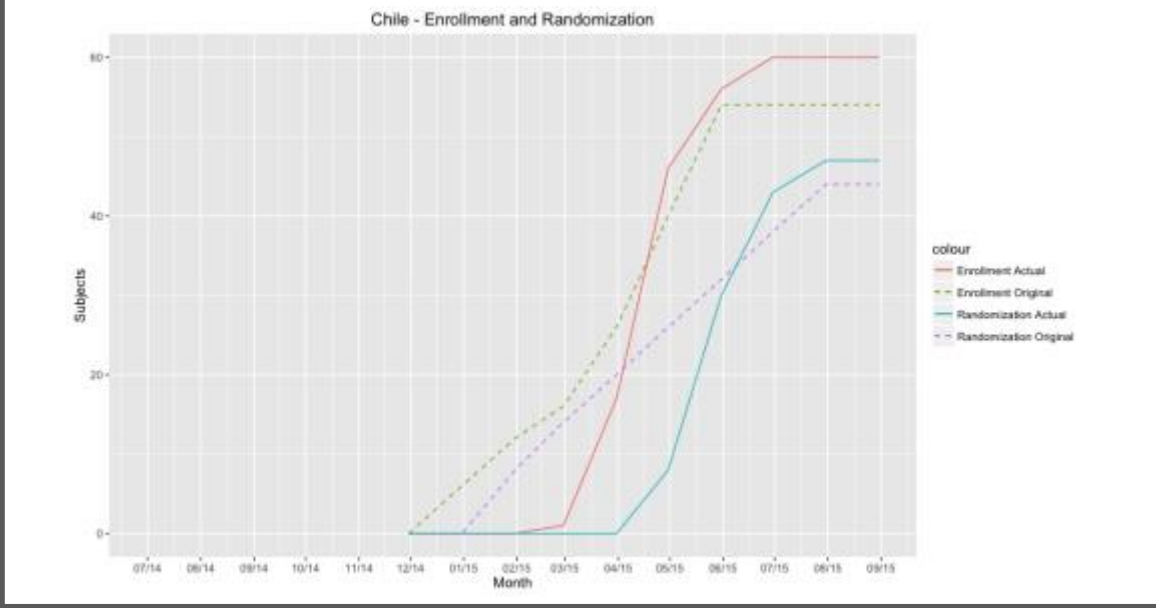
Supplemental Figure 10f. Results - Enrollment and Randomization – Argentina



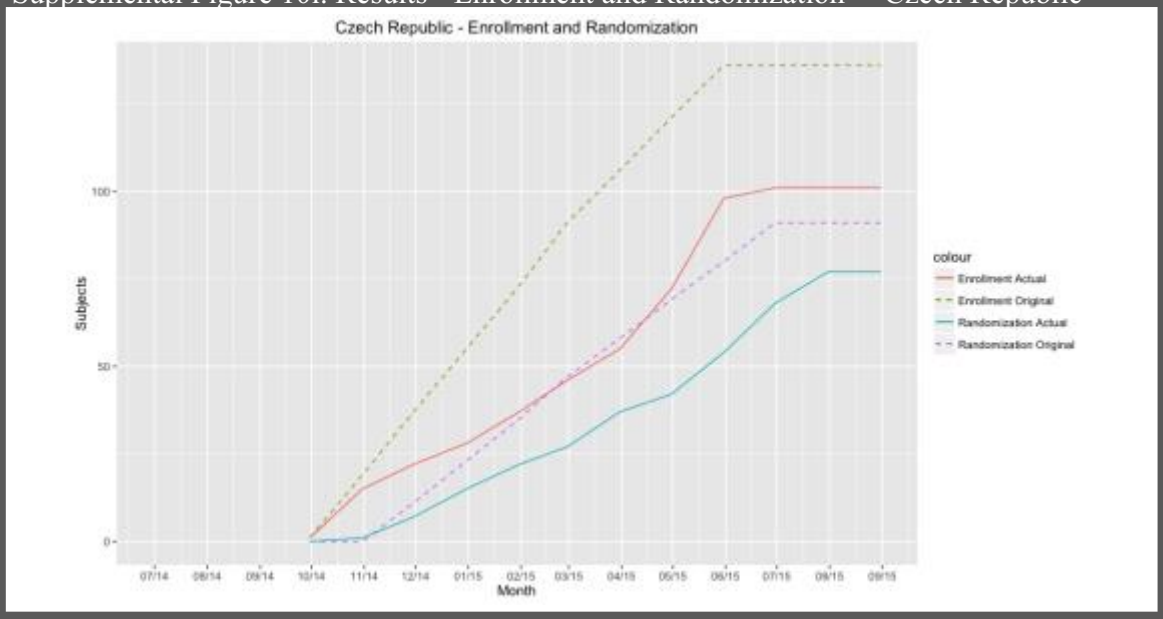
Supplemental Figure 10g. Results - Enrollment and Randomization – Bulgaria



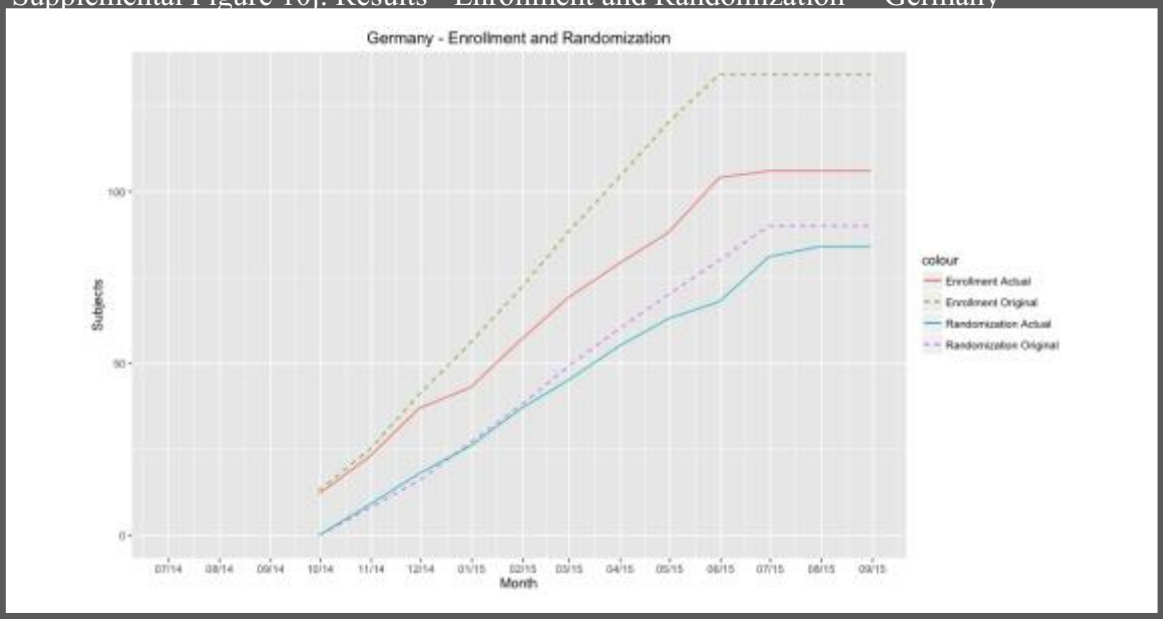
Supplemental Figure 10h. Results - Enrollment and Randomization – Chile



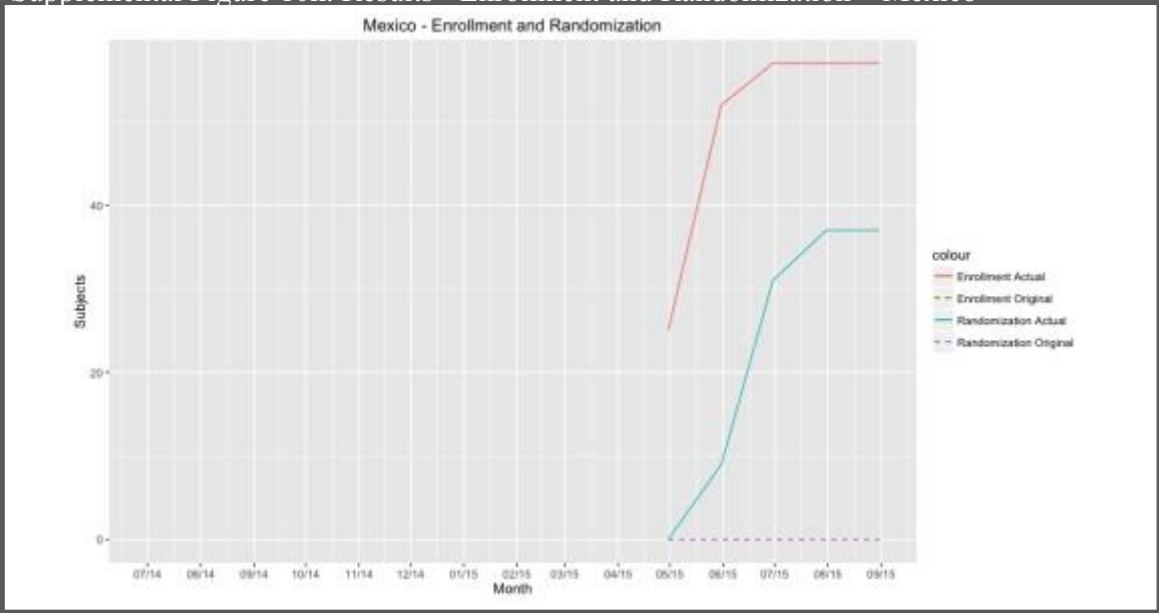
Supplemental Figure 10i. Results - Enrollment and Randomization – Czech Republic



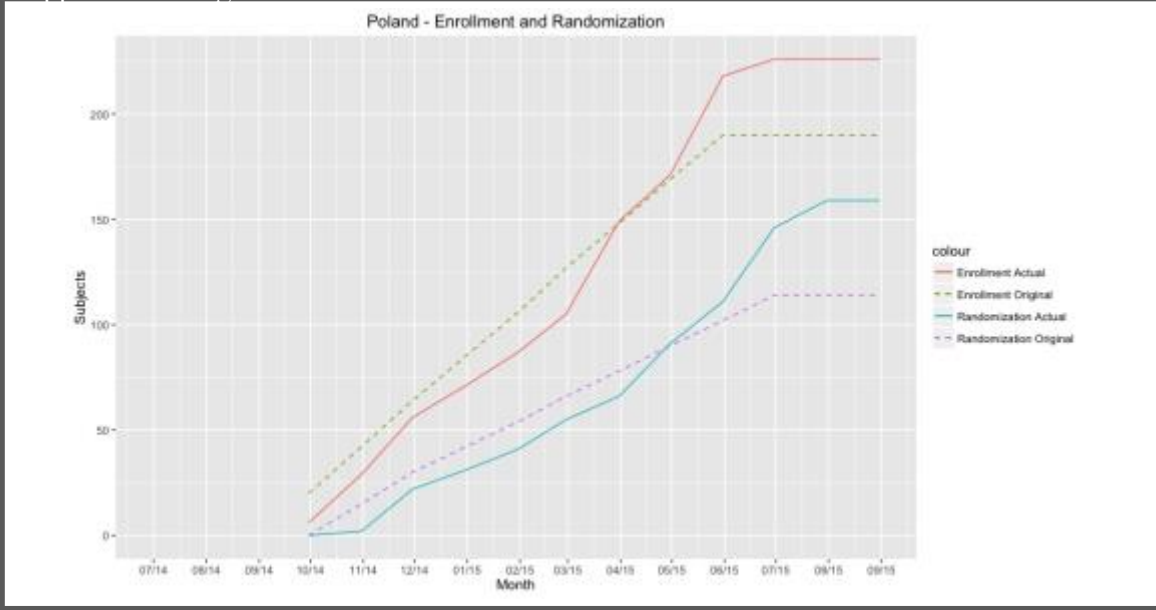
Supplemental Figure 10j. Results - Enrollment and Randomization – Germany



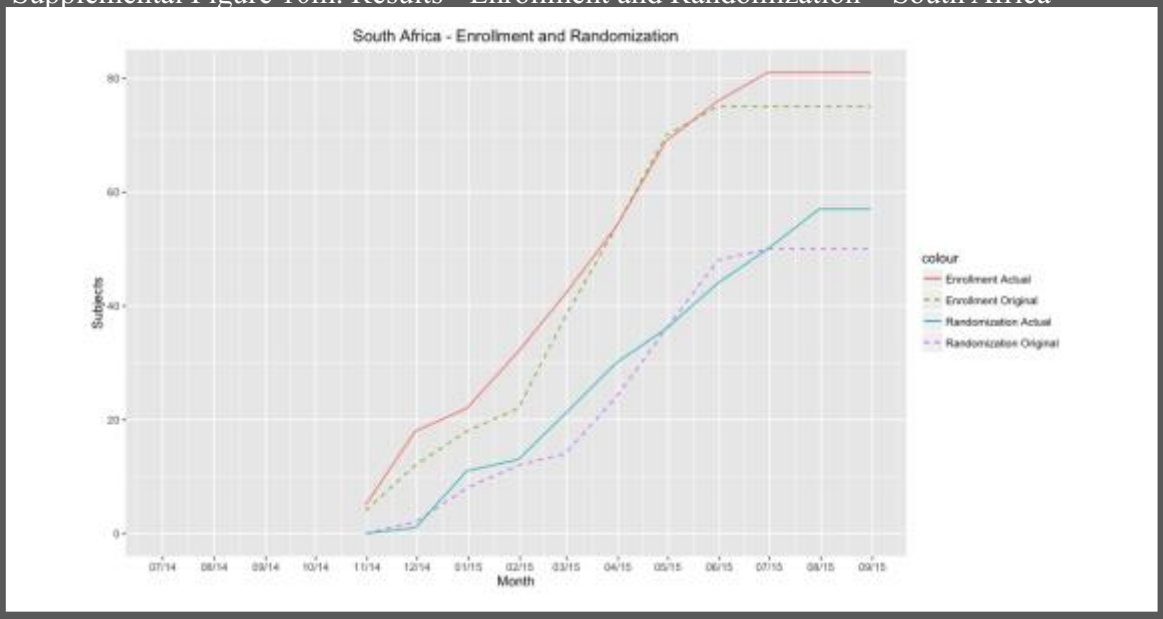
Supplemental Figure 10k. Results - Enrollment and Randomization – Mexico



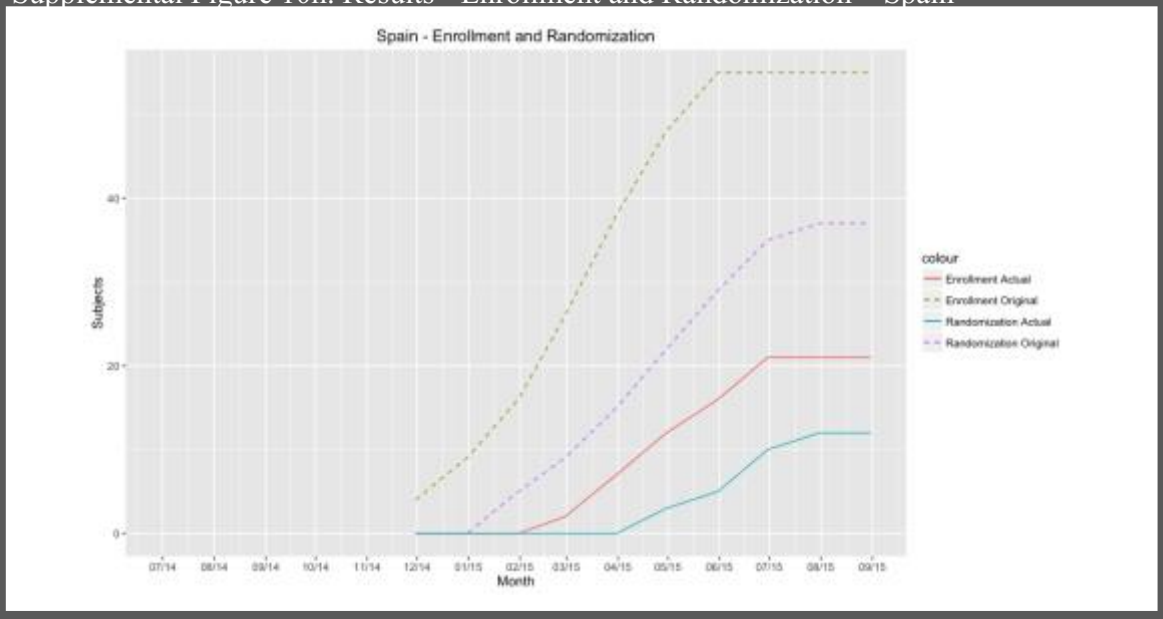
Supplemental Figure 10l. Results - Enrollment and Randomization – Poland



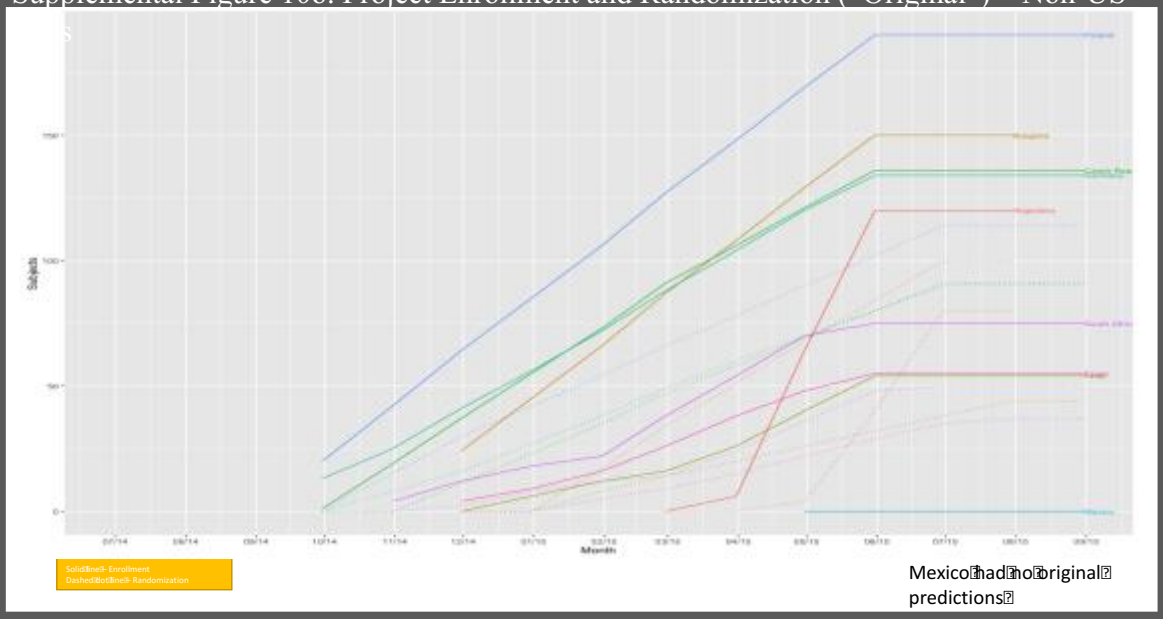
Supplemental Figure 10m. Results - Enrollment and Randomization – South Africa



Supplemental Figure 10n. Results - Enrollment and Randomization – Spain

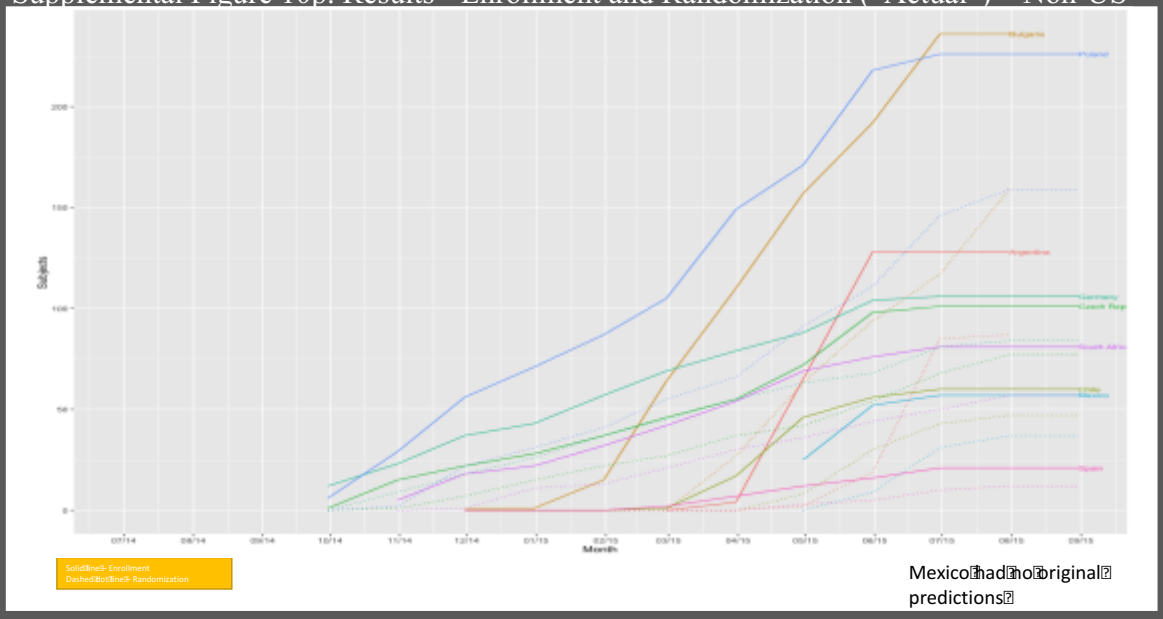


Supplemental Figure 10o. Project Enrollment and Randomization (“Original”) – Non-US



Mexico had no original predictions

Supplemental Figure 10p. Results - Enrollment and Randomization (“Actual”) – Non-US



Mexico had no original predictions